Sleep and Daytime Functioning In Chronic Stroke Patients with Hemiparesis

By

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ABSTRACT

Sleep is a critical modulator for daytime functioning, health and wellbeing and has a pivotal role in motor memory consolidation. It is for these reasons that sleep is a potentially important part of stroke care. However, this idea is severely under researched. It is necessary to explore sleep behaviour in stroke patients and the importance of healthy sleep for recovery and neurorehabilitation. More specifically, investigate the extent to which sleep may be a key modulator for motor neurorehabilitation success. It is the central aim of this thesis to contribute to the understanding of the sleep behaviour and daytime functioning in patients with chronic physical deficits after stroke and to explore the potential role of sleep for neurorehabilitation. Furthermore, this is the first known study to monitor sleep behaviour during a motor neurorehabilitation trial and assess outcome within this context. The research aimed to: 1) make a substantial contribution to the under researched field of post stroke sleep, 2) address some of the limitations imposed on previous studies, 3) focus on a specific cohort, 4) examine sleep in the context of a neurorehabilitation programme. The patient cohort employed in this research comprised chronic stroke patients (>12 months) with upper limb hemiparesis. It was found that sleep and daytime functioning disturbances were prevalent in approximately one third of patients. Interestingly, patients were not generally aware of the severity of their daytime functioning deficits. Sleep and daytime functioning were mildly related to motor recovery and neurorehabilitation. In conclusion, sleep clearly has a role in stroke patient quality of life, recovery and neurorehabilitation outcome, however further research using alternative assessments of sleep are necessary. The findings of this thesis have implications for post stroke management including increasing medical knowledge and adjustments in rehabilitation protocols that favour sleep.
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CHAPTER 1

Theoretical Perspective

1.1 Stroke Epidemiology, Consequences and Treatment ........................................... 26
1.1.1 What Is A Stroke? ...................................................................................... 26
1.1.2 Pathogenesis............................................................................................... 29
1.1.2 Consequences of Stoke .............................................................................. 33
1.1.3 Treatment Options for Post-Stroke Management ........................................ 40
1.2 What is sleep? ................................................................................................... 44
1.2.1 Physiological Biomarkers of Sleep-Wake Function .................................. 45
1.2.2 Sleep/Wake Regulation .............................................................................. 49
1.2.3 Measuring Sleep......................................................................................... 51
1.2.4 Disorders of Sleep and Daytime Functioning ............................................ 57
1.3 Function of Sleep .............................................................................................. 60
1.3.1 Maintaining Daytime Functioning and Cognitive Performance ............... 61
1.3.2 Memory Consolidation .............................................................................. 63
1.3.3 Maintaining Quality of Life ....................................................................... 67
1.4 The Role of Sleep For Post Stroke Recovery and Rehabilitation ..................... 70
1.4.1 Stroke Consequences Modulated By Sleep ............................................... 70
1.4.2 Sleep and Recovery Outcome After Stroke .............................................. 74
1.4.3 The Implication of Sleep For Post Stroke Neurorehabilitation Protocols . 76
1.4.4 Necessity For Research .............................................................................. 76
1.5 Putting Theory Into Applied Clinical Practice: Development of Research Aims
For This Thesis ........................................................................................................ 78
1.5.1 Limitations In Previous Studies ................................................................. 78
1.5.2 Addressing Limitations in Previous Studies .............................................. 79
1.5.3 Thesis Aims and Major Research Questions ............................................. 82

CHAPTER 2

Method Overview of All Studies
CHAPTER 3

Study 1: Characterising Perceived Sleep and Daytime Functioning in Chronic Stroke Patients

3.1 Introduction ................................................................. 125
3.1.1 Post Stroke Sleep and Daytime Functioning Alterations ... 126
3.1.2 Methodological Issues For Researching Post Stroke Sleep and Daytime Functioning ... 129
3.1.3 The Rationale For Study 1 ........................................... 131
3.1.4 The Current Study .................................................. 133
3.2 Method ........................................................................ 134
3.2.1 Design ................................................................... 134
3.2.2 Participants ........................................................... 135
3.2.3 Materials ............................................................... 136
3.3.4 Procedure .................................................................................................. 137
3.3.5 Analysis .................................................................................................... 137
3.3 Results ............................................................................................................. 139
3.3.1 Demographics .......................................................................................... 139
3.3.2 Sleep Behaviour Compared To Pre-Morbid Behaviour ........................... 141
3.3.3 Chronic Phase Nocturnal Sleep Questionnaires ....................................... 142
3.3.4 Dimensions of Daytime Functioning ....................................................... 146
3.3.5 Comparison With Published Data ............................................................ 147
3.3.6 Interaction Between Nocturnal Sleep and Daytime Functioning .......... 154
3.3.7 Psychological Disturbance, Perceived Health and Sleep ......................... 155
3.4 Discussion ....................................................................................................... 160
3.4.1 Overall Findings ....................................................................................... 160
3.4.2 Further Theoretical Considerations .......................................................... 166
3.4.3 Implications of The Findings ................................................................... 168
3.4.4 Methodological Limitations ..................................................................... 169
3.4.5 Future Research ........................................................................................ 171

CHAPTER 4 173

Study 2: Prospective Investigation of Longitudinal Sleep
Behaviour and Correlates of Residual Motor Recovery

4.1 Introduction ..................................................................................................... 173
4.1.1 Subjective and Objective Longitudinal Sleep Assessment ...................... 174
4.1.2 Sleep And Recovery Levels After Stroke ................................................ 179
4.1.3 Rationale For Study 2 .............................................................................. 183
4.1.4 Aims and Hypotheses ............................................................................... 185
4.2 Methods .......................................................................................................... 186
4.2.1 Design ...................................................................................................... 186
4.2.2 Participants ............................................................................................... 187
4.2.3 Materials ................................................................................................... 188
4.2.4 Procedure .................................................................................................. 188
4.2.5 Analysis .................................................................................................... 189
4.3 Results ............................................................................................................. 191
4.3.1 Demographics .......................................................................................... 191
4.3.2 Sleep Diary and Actigraphy Concordance ............................................... 193
4.3.3 Motor Recovery Level In The Context of Sleep ...................................... 201
4.4 Discussion ....................................................................................................... 203
4.4.1 Overall Findings ....................................................................................... 203
4.4.2 Implications of Findings .......................................................................... 207
4.4.3 Methodological Limitations ..................................................................... 208
4.4.4 Future Studies ........................................................................................ 210
CHAPTER 5  

Study 3: EEG-derived biomarkers for daytime sleepiness in patients with chronic stroke

5.1 Introduction
5.1.1 Definitions of Sleepiness In Research
5.1.2 Measuring Sleepiness
5.1.3 Sleepiness in Chronic Stroke
5.1.4 The Rationale For Study 3
5.1.5 The Current Study

5.2 Methods
5.2.1 Design
5.2.2 Participants
5.2.3 Materials
5.2.4 Procedure
5.2.5 Analysis

5.3 Results
5.3.1 Demographics
5.3.2 The Effects of Stroke On The EEG (Pre Task Data Only)
5.3.3 Motor Priming Task Effects

5.4 Discussion
5.4.1 Overall Findings
5.4.2 Mechanisms Behind Objective Sleepiness In Stroke Patients
5.4.2 Implications of Findings
5.4.3 Limitations of This Study
5.4.4 Future Studies

CHAPTER 6

Study 4: The Role of Sleep and Daytime Functioning in Neurorehabilitation

6.1 Introduction
6.1.1 Theoretical Underpinnings: Somatic, Behavioural, Cognitive, and Neural Evidence
6.1.2 Sleep and Rehabilitation Outcome
6.1.3 The Rationale For Study 4: Clinically Application of Sleep Research
Within CIT ........................................................................................................ 263
6.1.4 The Current Study .................................................................................... 265
6.2 Methods ........................................................................................................... 266
6.2.1 Design ...................................................................................................... 267
6.2.2 Participants ............................................................................................... 267
6.2.3 Materials ................................................................................................... 268
6.2.4 Procedure .................................................................................................. 269
6.2.5 Analysis .................................................................................................... 269
6.3 Results ............................................................................................................. 270
6.3.1 Demographics .......................................................................................... 270
6.3.2 CIT Outcome ............................................................................................ 272
6.3.3 Sleep and Daytime Functioning Per Phase .............................................. 272
6.3.4 Sleep, Daytime Functioning and CIT Outcome ....................................... 277
6.3.5 Laboratory Observations .......................................................................... 279
6.4 Discussion ....................................................................................................... 280
6.4.1 Overall Findings ....................................................................................... 281
6.4.2 Further Theoretical Considerations .......................................................... 283
6.4.3 Implications of Findings .......................................................................... 283
6.4.4 Limitations of the Study ........................................................................... 284
6.4.5 Further Studies ......................................................................................... 285

CHAPTER 7

General Discussion 288

7.1 Summary of The Findings............................................................................... 288
  7.1.1 Thesis Objectives ..................................................................................... 288
  7.1.2 The Findings ............................................................................................ 289
  7.1.3 Findings In Comparison To Previous Literature...................................... 292
7.2 Proposed Explanations For The Findings ................................................... 293
  7.2.1 Disturbed Sleep and Daytime Functioning In Chronic Stroke ................. 294
  7.2.2 Self Perceived Sleep and Daytime Functioning ....................................... 298
  7.2.3 Sleep, Daytime Functioning and Motor Ability ....................................... 299
7.3 Further Theoretical Considerations .............................................................. 301
  7.3.1 Sleep Dependent Learning Theory ........................................................... 301
  7.3.2 Patient Characteristics ............................................................................ 304
7.4 Limitations of Thesis Research ..................................................................... 307
  7.4.1 Constraints of The CIT Trial Protocol ..................................................... 307
  7.4.2 Subjective Assessments .......................................................................... 308
  7.4.3 Objective Assessment ............................................................................. 311
7.5 Implications and Practical Applications of The Findings............................ 313
  7.5.1 Informing The Medical Profession .......................................................... 314
7.5.2 Treatment Options For Post Brain Injury Sleep Disturbance ................................. 316
7.5.3 Implications For Further Research ........................................................................ 322
7.6 Future Studies ......................................................................................................... 324
7.6.1 Methodological Improvements To The Current Research .................................. 324
7.6.2 Exploring Other Stroke Cohorts ......................................................................... 325
7.6.3 Future Paradigms For Applied Clinical Research ............................................... 326

References ...................................................................................................................... 330

APPENDICES .................................................................................................................. 380

Appendix A: Study Consent Documents ......................................................................... 380
Appendix B: Materials Supplement for Chapter 2 .......................................................... 380
Appendix C: Case Tables For All Participants ............................................................... 429
Appendix D: Supplement For Study 2 ........................................................................... 437
Appendix E: Supplement For Study 3 ........................................................................... 443
Appendix F: List of Abbreviations .................................................................................. 453
List of Tables

Table 3.1. Study 1 questionnaires. Details include number of items, scoring range and cut off criteria scores above cut off criteria per questionnaire to indicate the following a) poor quality sleep on the PSQI, b) presence of a likely sleep disorder on the S50, c) vulnerability to sleep problems as a result of stress on the FIRST, d) excessive sleepiness on the ESS, e) high levels of fatigue on the FSS and f) clinically significant depression or anxiety on the HADS.................................180

Table 3.2. Demographic data for stroke patients and controls. Values presented as mean (+/- 1 SD and range) or percent valid where appropriate. The remaining 41% of stroke patients unlisted for employment status were classified as not working. Sleep medication was taken by one control participant (Zipiclone taken irregularly) and one stroke patient (Melatonin taken every evening). For individual case information for all participants is provided in Appendix C.................................................183

Table 3.3. PSQI parameters. Global score (GPSQI), sleep parameters and component scores for stroke patients (36 males, 24 female) and controls (28 male, 33 female). Mean (+/- 1 SD and range), Mann-Whitney U test statistic (Z) and significance value (p) is presented.......................................................187

Table 3.4. S50 sleep disorder category scores for stroke patients (37 males, 24 female) and (28 male, 33 female). Mean (+/- 1 SD and range), Mann-Whitney U test statistic (Z) between sleep disorder scores and significance value (p) are presented. The nightmare scoring system for the S50 only includes those who suffer nightmares,
therefore is reported as a percentage. Presence of hypersomnia is scored as a ‘yes’ or ‘no’, therefore is also presented as a percentage ........................................ 190

Table 3.5. ESS item scores and total score for stroke patients (37 males, 24 female) and (28 male, 33 female). Mean (+/- 1 SD and range) Mann-Whitney U test statistic (Z) and significance value (p) are presented ........................................ 192

Table 3.6. FSS item scores and total score for stroke patients (36 males, 22 female) and (27 male, 31 female). Data presented as mean (+/- 1 SD and range), Mann-Whitney U test statistic (Z) and significance value (p) are presented .......................... 193

Table 3.7. FIRST item data for stroke patients (37 males, 24 female) and (26 male, 29 female). Mean (+/- 1 SD and range), Mann-Whitney U test statistic (Z) and significance value (p) is presented. Trends indicated in bold ................ 203

Table 3.8. Three regression models are presented: a) sleep quality (GPSQI) as the dependent variable (DV), b) sleepiness (ESS) as the DV and c) fatigue (FSS) as the DV. The correlations between the variables, the unstandardised regression coefficients (B) with +/- 1 SE, and intercept, the standardised regression coefficients (β), R and R². Trends are indicated in bold. Note that group is categorical (1=stroke, 2=control). Where the p value is not reported, the degree of significant is indicated (*p>0.05 **p>0.01 ***p>0.001) ........................................ 204

Table 3.9. Standard multiple regression of contributing factors to overall perceived health as the dependent variable (SF-36) in stroke patients. The correlations between the variables, the unstandardised regression coefficients (B) with +/- 1 SE, and intercept, the standardised regression coefficients (β), the semipartial correlations
Where the p value is not reported, the degree of significant is indicated (*p≥0.05 **p≥0.01 ***p≥0.001) ................................................ 208

Table 4.1. Summary of the literature for chronic (≥12 months) stroke and mixed stroke and TBI samples. A full list of abbreviations is presented in Appendix F1...236

Table 4.2. Data presented as mean, +/- 1 SD and range or percent valid where appropriate. The remaining 35.71% of stroke patients unlisted for employment status were classified as not working. For individual case information for all participants, see Appendix C................................................................................ 251

Table 4.3. Mean (+/-1 SD) and range across 14 weekdays for matched parameters drawn from the sleep diary and actigraphy recordings. Test statistics include the Wilcoxon signed rank test (Z) and Spearman’s (r). *Significant values ............ 253

Table 4.4. Mean (+/-1 SD) and range across 4 weekend days for matched parameters drawn from the sleep diary and actigraphy recordings. Test statistics included the Wilcoxon signed ranks test (Z) and Spearman’s (r). *Significant values ............. 256

Table 4.5. Mean (+/-1 SD and range). All values represent the score across items on each test battery apart from WMFT RT which is median time taken to complete a task (ms)................................................................................................................. 263

Table 4.6. Spearman’s rank correlation coefficient of motor ability tests with sleep and daytime functioning. Significant values are indicated as *p≤0.05, **p≤0.01 and those in bold represent non-significant trends. The scatter plots for significant correlations are located in Appendix D3 ................................................... 263

Table 5.1. The ‘Left Group’. Data presented as mean, +/- 1 SD and range or percent valid where appropriate. The remaining 57.14% of stroke patients unlisted for
employment status were classified as not working. Sleep medication was taken by one control participant (Zipiclone taken irregularly). For individual case information for all participants, see Appendix C........................................................ 299

Table 5.2. The ‘Right Group’. Data presented as mean, +/- 1 SD and range or as percent valid where appropriate. The remaining 38.89% of stroke patients unlisted for employment status were classified as not working. Sleep medication was taken by one control participant (Zipiclone taken irregularly). For individual case information for all participants, see Appendix C........................................................ 300

Table 5.3. KSS ratings pre and post motor task. Data reported as mean, +/- 1 standard deviation. t and p values for left stroke and control (df13), and right stroke and control (df17) .................................................................................. 313

Table 5.4. Left group pre and post task mean raw power density values (±1 SE) and t values (df13) for ipsilateral (C3), contralateral (C4) hemispheres and right hemisphere (C4) for control. One tailed t-test completed on logged values of raw data .............................................................................................. 315

Table 5.5. Right group pre and post task mean raw power density values (±1 SE) and t values (df17) for ipsilateral (C4), contralateral (C3) hemispheres and right hemisphere (C3) for control. One tailed t-test completed on logged values of raw data .............................................................................................. 316

Table 5.6. Spearman’s Rho correlation coefficient for logged µV²/Hz per frequency band pre and post task and KSS score. Significance indicated (*p<0.01) ......................... 320

Table 6.1. Data presented as mean (+/- 1 SD and range) or percent valid where appropriate. The remaining 28.12% of stroke patients unlisted for employment status
were classified as not working. For individual case information for all participants, see Appendix C.
List of Figures

Figure 1.1. The framework for the theoretical perspective of this thesis, as described in this chapter. Grey ovals represent each section of this chapter and the white boxes describe the specific evidence presented within these sections. .................................................. 32

Figure 1.2. Reproduced from The Stroke Internet Center (1998-1999). ....................... 40

Figure 1.3. Adapted from Aminoff, Simon and Davis (2005) p. 289............................ 41

Figure 1.4. The Sleep Histogram, based on Carskadon and Rechtschaffen (2005). Diagram of one night of sleep shows sleep stages across time.............................................. 62

Figure 1.5. Adapted from Jones (2005, p.137 and 139). The diagram highlights the main brain areas involves in sleep/wake regulations. The faint lines show the pathways for projection of neurons to other structures associated with wake and sleep promoting systems. ........................................................................................................ 64

Figure 1.6. Two Process Model. Adapted from Borbely and Acherman (2005). As S (homeostatic sleep drive) increases, the need for sleep increases during wakefulness and then declines during sleep. C describes the circadian rhythm cycle (measured by body temperature). The greatest point of sleep propensity occurs during the trough of body temperature and when S is at its peak. .................................................................................. 65

Figure 1.7. Waking EEG traces for 33 channels across a 10 second segment of recording drawn from data used for Chapter 5 of this thesis. Each trace represents the recording of a particular electrode. The EEG presents mixed, dysynchronised frequencies which defines wake. The black arrow shows an eye blink event......... 69

Figure 1.8. Actiwatch Mini ®’ (CamNtech Ltd., © 2009). Various actigraphy devices have been developed and the device name is specific to the manufacturer............. 71
Figure 1.9. Dimensions of memory. Based on Gabrieli (1998) and Stickgold and Walker (2005 – trends in neurosciences) ................................................................. 83

Figure 1.10. The consequences of stroke are displayed. Evidence suggests that these same consequences are modulated by sleep .................................................. 92

Figure 2.1. The CIT trial framework and the data capture sections for studies 1 to 4 conducted for this thesis. Full completion of the CIT trial involved screening, three test points, an EEG and long term sleep monitoring during baseline, CIT and Post CIT phases. The same patient may appear in one of more of the four studies. ....... 114

Figure 2.2. This flow chart presents the number of stroke patients recruited for each process of the CIT trial from January 2007 ................................................….. 122

Figure 2.3. Electrode positions are displayed, labeled according to underlying brain areas: FP for frontal pole, F for frontal, P for parietal, C for central, T for temporal, and O for occipital. Sites are numerically sequenced from midline, which is set as zero or Z, with odd numbers on the left hemisphere alternating with even numbers on the right. ........................................................................................................ 146

Figure 2.4. Presentation of stimuli for one trial within the motor task. One of four pre-cues and corresponding actual cue for each trial are presented 12 times at random per block ........................................................................................................ 148

Figure 2.5. Power spectra of a waking EEG. Data from a non-brain injured participant drawn from Chapter Five. Although the peak within the delta band (coloured as orange) indicates a presence of slower waves in the EEG, this is also suggestive of artefact in the recording, known as spectral leakage ........................................ 158
Figure 2.6. A topographical map of the power spectra within the beta range (13-30 Hz) of a healthy participant focusing on a spot on a screen (no task). The red indicates increased power of the beta waves in the frontal areas.

Figure 3.1. Design of CIT trial, The highlighted section indicates time point from which data for this study was collected.

Figure 3.2. Box plots are displayed for PSQI habitual sleep items 1 to 4 for stroke patients and controls. Median values are demonstrated centrally in the box. The top and bottom values of the box represent the upper and lower interquartile range (H-spread) containing 50% of cases. The whiskers represent highest and lowest scores which lie within 1.5 times the H-spread. Values more than 1.5 times the H-spread are considered outliers, represented by circles. Extreme cases within the patient (CP) and control group (C) cases are labelled.

Figure 3.3. Bar charts to display mean (+1 SD where available) GPSQI scores between studies. The dashed line indicates the cut off criteria for poor sleep (>5).

Figure 3.4. Bar charts to display mean (+1 SD where available) time in bed and sleep duration between studies.

Figure 3.5. Bar charts to display mean (+1 SD) ESS between studies. The dashed line indicates the cut off criteria (>9).

Figure 3.6. Bar charts to display mean (+1 SD) FSS between studies. The dashed line indicates the cut off criteria (>4).

Figure 3.7. Bar charts to display mean (+1 SD) overall health, mental and physical health dimensions on the SF-36 for the following groups of patients: a) those with (GPSQI >5) and without sleep disturbances (GPSQI ≤5), b) those with high (total
FSS >35) and low (total FSS ≤35) levels of fatigue and c) those with (>9) and without excessive sleepiness (≤9). Significant differences are indicated (*p≥0.05, ***p≥0.001).

Figure 4.1. Model of post stroke recovery over time. Based on the findings of (McHale, 1998, Lesniak, et al., 2008; Rasquin et al., 2004; et al., 2008; Horgan et al., 2009; Donnan, Bladin, Berkovic, Longley, & Saling, 1991; Duncan, Goldstein, Matchar, Divine, & Feussner, 1992; Jorgensen et al., 1995) which show that recovery stabilises after 12 months.

Figure 4.2. Design of CIT trial. The highlighted section indicates time point from which data for this study was collected.

Figure 4.3. Correlations of sleep diary and actigraphy including regression line for weekday results only.

Figure 4.4. Correlations of sleep diary and actigraphy including regression line for weekday results only.

Figure 4.5. Mean (+/-1 SD) KSS and D-FIS scores for the morning and evening. Significant differences between morning and evening scores are indicated as *p≤0.05, **p≤0.01, *** p≤0.001.

Figure 5.1. Design of CIT trial, The highlighted section indicates time point from which data for this study was collected.

Figure 5.2.

Figure 5.3. a) logged power density (µV²/Hz) per 1 Hz bin, pink line=ipsilateral hemisphere (left, C3), blue line=contralateral hemisphere (right, C4), dashed black line (100%)=controls and left stroke EEG expressed as a percentage of controls.
Figure 5.1 b) t values ($d/26$) and corresponding one tailed p values of left stroke vs control. See Appendix E1 for the corresponding data tables.

Figure 5.4. a) logged power density ($\mu V^2/Hz$) per 1 Hz bin, pink line=ipsilateral hemisphere (right, C4), blue line=contralateral hemisphere (left, C3), dashed black line (100%)=controls and right stroke EEG expressed as a percentage of controls.

Figure 5.4 b) t values ($df/34$) and corresponding one tailed p values of right stroke vs control. See Appendix E2 for the corresponding data tables.

Figure 5.5. Topographical map of p values of one tailed t test for power density ($\mu V^2/Hz$) across all electrodes ($df/26$) per frequency band left stroke vs controls. See Appendix E3 for values for each value per electrode within the map. Values between electrodes were interpolated using spherical splines.

Figure 5.6. Topographical maps of the p values calculated for tests of difference between $\mu V^2/Hz$ of right stroke vs controls across all electrodes ($df/34$) per frequency band right stroke vs controls. See Appendix E4 for values for each value per electrode. Values between electrodes were interpolated using spherical splines.

Figure 5.7. a) logged power density ($\mu V^2/Hz$) per 1 Hz bin, pink line=left hemisphere or contralateral to stroke (C3), solid black line= control left hemisphere (C3), dashed black line (100%)=ipsilateral hemisphere for left stroke or right hemisphere for controls (C4). Figure 5.5 b) t values ($df/13$) and corresponding one tailed p values. See Appendix E5 for corresponding data table.

Figure 5.8. a) logged power density ($\mu V^2/Hz$) per 1 Hz bin, pink line=right hemisphere or contralateral to stroke (C4), solid black line= control right hemisphere (C4), dashed black line (100%)=ipsilateral hemisphere for left stroke or right
hemisphere for controls (C3). Figure 5.6 b) $t$ values ($d/17$) and corresponding one
tailed $p$ values. See Appendix E5 for corresponding data table.......................... 311
Figure 5.9. Left stroke pre and post task mean log power density values ($\pm 1$ SE) for
ipsilateral (C3), contralateral (C4) hemispheres and right hemisphere (C4) for control.
* in corresponding colour denotes a significant difference pre and post task ($p \leq 0.05$).
................................................................................................................................... 315
Figure 5.10. Right stroke pre and post task mean log power density values ($\pm 1$ SE) for
ipsilateral (C4), contralateral (C3) hemispheres and left hemisphere (C3) for control.
* in corresponding colour denotes a significant difference pre and post task ($p \leq 0.05$).
................................................................................................................................... 316
Figure 5.11. Scatter plots for left stroke KSS and $\mu V^2$/Hz per frequency band. 1a)
C3= ipsilateral/left hemisphere and 1b) C4=contralateral/right hemisphere. 2a and 2b
display C3 and C4 sites as described for 1a and b however present post task data.
Linear regression fit lines as indicated per group. .................................................. 321
Figure 5.12. Scatter plots for right stroke KSS and $\mu V^2$/Hz per frequency band. 1a)
C4= ipsilateral/left hemisphere for control 1b) C3=contralateral/right hemisphere for
control. 2a and 2b display C4 and C3 sites as described for 1a and b however present
post task data. Linear regression fit lines as indicated per group.......................... 323
Figure 5.13. Mean change in KSS (post minus pre) and performance measures on the
motor task; reaction time (RT) and percent correct (%). Linear regression fit lines as
indicated per group................................................................. 325
Figure 6.1. Design of CIT trial, The highlighted section indicates time point from
which data for this study was collected........................................................... 353
Figure 6.2. Pre and post CIT mean scores (+/-1 SD and range) for all motor. Pre and post significant differences are indicated (*p<0.05) ................................................................. 361

Figure 6.3. Mean (+/-1 SD and range) nocturnal sleep data drawn from the sleep diary per phase. Friedman test statistic ($X^2$) and significance value (p) is presented (df/2). Significant values are indicated (*p<0.05) ................................................................ 362

Figure 6.4. Mean (+/-1 SD and range) nocturnal sleep data drawn from actigraphy recordings per phase. Friedman test statistic ($X^2$) and significance value (p) is presented (df/2). Significant values are indicated (*p<0.05) ................................................................. 363

Figure 6.5. Mean (+/-1 SD and range) KSS and D-FIS scores. Friedman test statistic ($X^2$) and significance value (p) is presented. Significant values indicated (*p<0.05). ................................................................................................................................... 364

Figure 6.6. Mean (+/-1 SD and range) daytime functioning data drawn from actigraphy recordings per phase. Friedman test statistic ($X^2$) and significance value (p) is presented. Significant values indicated (*p<0.05) ................................................................. 365

Figure 6.7. Significant correlations of CIT outcome and sleep as recorded by actigraphy recorded during the CIT phase ................................................................. 367

Figure 6.8. Significant correlations of CIT outcome and napping as recorded by actigraphy during the CIT phase ................................................................. 369

Figure 7.1. Reproduced from Zafonte et al. (1996) Neurorehabilitation, p.192...... 422
CHAPTER 1: Theoretical Perspective

Chapter 1 Overview

Stroke is one of the leading causes of disability, associated with a range of acute and long term somatic, behavioural, cognitive and motor consequences. Treatment intends to alleviate and manage these characteristics of the stroke sequelae through pharmacological, psychological and rehabilitative interventions. These treatments primarily focus on waking behaviour and consequently neglect sleep. It is well documented in the literature that sleep is a critical mediator of wellbeing, daytime functioning and learning. Therefore, healthy sleep may be highly important for stroke treatment provisions. More research into the potentially crucial role of sleep in stroke recovery and management is essential for recovering patients.

The objective of Chapter 1 is to present the theoretical perspective from which the research for this thesis evolved (Figure 1.1).
Firstly, the clinical definition and epistemology of stroke is described followed by the endured consequences and a summary of current treatments available to manage the condition. Secondly, a paradigm shift in the approach to stroke treatment is proposed and the field of sleep is introduced. The physiology of sleep is explained as well as how it is measured and the disorders of sleep. The third section of this chapter continues to discuss sleep with regard its overall function for the body, brain and quality of life. The fourth section proposes the importance of sleep for recovering stroke patients and presents the overall working model for this thesis. The final section describes the development of the research design for the four studies carried out for this thesis.
1.1 Stroke Epidemiology, Consequences and Treatment

Stroke is a form of cardiovascular disease that manifests itself as an acquired brain injury. It presents a multitude of acute and chronic consequences that severely impact the quality of life of patients. Current service provisions offer a range of rehabilitative treatments to support acute stroke however there are fewer regimes in place for chronic sufferers. Further research is required to generate a greater understanding of the stroke sequelae and improve levels of care for both short and long term consequences.

1.1.1 What Is A Stroke?

Clinical Definition
A stroke is characterised by the rapid deterioration of neurological function as a result of interrupted blood supply to the brain, lasting more than 24 hours (World Health Organisation, 1998). Blood supply to the brain can be affected by either a blockage or haemorrhage which immediately initiates focal neuronal damage (Lipton, 1999; Sugawara et al., 2004). This impacts those functions controlled by the affected brain regions. Motor control, language and comprehension, vision and cognitive function are typically impaired by stroke (American Heart Association, 2009). However, severe strokes within critical brain areas, such as the midbrain and brain stem, may result in coma or death. A stroke event begins as an acute medical emergency requiring immediate medical attention and, depending on the extent of the damage, may cause long-term disability in patients.

Types of Stroke
There are two main types of stroke: ischemic and haemorrhagic (Caplan, 2005, p.10). Ischemic stroke accounts for 67–80% of all stroke events (Feigin, Lawes, Bennett, & Anderson, 2003; Leoo, Lindgren, Petersson, & von Arbin, 2008). This form of stroke...
is caused by a blockage that restricts blood flow to a specific area of the brain, known as an infarct (Aminoff, Simon, & Greenberg, 2005, p.290). Blockages may occur as a result of a thrombus or collection of debris such as plaques, fat, air or cancerous cells. Infarcts may originate from within the brain or a result of travelling debris from another part of the body, known as an embolism. Haemorrhagic strokes occur when a blood vessel in the brain ruptures. A bleeding blood vessel can no longer carry blood to its target tissue, therefore causes cell damage, similarly to ischemia. Haemorrhagic strokes may also occur due to a burst aneurysm. Accumulating blood not only increases intracranial pressure but irritates brain tissue causing cell damage (Caplan, 2005, p.13).

A transient ischemic attack (TIA) is a less severe form of stroke. A TIA is defined as “a brief episode of neurologic dysfunction caused by focal brain or retinal ischemia, with clinical symptoms typically lasting less than one hour, and without evidence of acute infarction” (Albers et al., 2002, p. 1713-1716). Blood supply is interrupted from a few minutes up to 24 hours, however, full recovery is achieved post event (Aminoff, Simon and Davis, 2005, p.286). A TIA is sometimes considered a warning for a stroke. Eight to fifteen percent of people who experience a TIA, have a stroke within a year (Hankey & 1996; Lovett et al., 2003; Weimar et al., 2009).

**Incidence**

Stroke affects approximately 100,000 people per year in England and Wales, and 30,000 of those people suffer further strokes (Department of Health, 2001). Although risk increases with age, 10,000 sufferers are under 55 years old and 1,000 of those persons are under 30 (Office of National Statistics UK, 1998). Stroke mortality has declined in recent years (Bonita, Stewart, & Beaglehole, 1990; Feigin, Lawes, Bennett, Barker-Collo, & Parag, 2009; Sarti, Rastenyte, Cepaitis, & Tuomilehto, 2000). Therefore, an increasing amount of people are surviving and living with the consequences (Bonita, Beaglehole, & Asplund, 1994; Elneihoum, Goransson, Falke, & Janzon, 1998).
**Causes and Risk Factors**

For some patients, strokes have a clear cause, e.g. as a result of vascular injury after an accident or due to complications during brain surgery (Gerlach et al., 2002; Norris, Beletsky, Nadareishvili, & Consortium, 2000; Wong et al., 2000), however the cause of some strokes are not identified. Several patients have an increased vulnerability to stroke due to several well known risk factors. This includes demographical risks such as increasing age and being male (Gafarov, Gromova, Gagulin, & Pilipenko, 2005; Goldstein et al., 2008). Presence of congenital heart diseases, such as arrhythmia, diseases of the blood and atrial fibrillation, are associated with stroke (American Heart Association, 2001). Chronic conditions including diabetes mellitus, high cholesterol and hypertension, are also associated with stroke (American Heart Association, 2001; Goldstein et al., 2008; Leoo et al., 2008). Unhealthy lifestyle such as obesity, smoking and high levels of stress are also prominent risk factors (Office of Population Censuses and Statistics UK, 1995; Gafarov et al., 2005). A link has been identified between a stroke event and existence of sleep breathing disorders (described in Section 1.2.4), even when controlling for other stroke risks such as smoking and obesity (Bradley & Floras, 2009; Drager, Bortolotto, Krieger, & Lorenzi-Filho, 2009; Portela, Fumado, Garcia, & Borrego, 2009; Spriggs et al., 1992b; Yaggi et al., 2005). Successful treatment of sleep breathing disorders using Continuous Positive Airway Pressure (CPAP) is associated with a reduced risk of cardiovascular disease, including stroke (Drager, Bortolotto, Figueiredo, Krieger, & Lorenzi, 2007; Marin, Carrizo, Vicente, & Agusti, 2005). Also regarding sleep, those who sleep more than eight hours a night and have excessive daytime sleepiness are more likely to experience a stroke (Qureshi, Giles, Croft, & Bliwise, 1997).

**Stroke In The Wider Context of Acquired Brain Injury and Chronicity**

Within the stroke literature, patient samples normally include only those who have experienced a brain injury of a vascular origin. In the wider context of brain injury, some studies use mixed samples of both stroke and patients with traumatic brain injury (TBI). TBI refers to acquired brain damage caused by an external force, e.g. automobile accident (Maas, Stocchetti, & Bullock, 2008). Only patients who
experienced stroke (excluding TIA) were included for the research carried out for this thesis.

The stages of injury, as defined by time since injury, or chronicity, is subject to different interpretations in literature (Sullivan, 2007). Some studies refer to chronicities less than six months as acute stroke, whereas some studies define acute as less than three months. Some researchers describe the three to six month post brain injury phase as sub acute. To confuse this issue further, several studies report that patients at three to six months post injury have reached a plateau in their recovery and are therefore considered chronic (Sullivan, 2007). However, the long term consequences of stroke, both physical and psychological, are unlikely to remain stable until 12 months after injury (Donnan, Bladin, Berkovic, Longley, & Saling, 1991; Duncan, Goldstein, Matchar, Divine, & Feussner, 1992; Horgan, O'Regan, Cunningham, & Finn, 2009; Jorgensen et al., 1995; Kotila, Waltimo, Niemi, Laaksonen, & Lempinen, 1984; Lesniak, Bak, Czepiel, Seniow, & Czlonkowska, 2008; MacHale, O'Rourke, Wardlaw, & Dennis, 1998; Rasquin, Lodder, & Verhey, 2005). Based on this evidence, this thesis will use the term acute to refer to patients with chronicities of less than 12 months, whereas chronic will describe those beyond this time. Those at 12 months post stroke and beyond are more likely to be in a chronic state regarding their recovery levels, and critically, are stable in terms of their psychological adjustment to the disease.

1.1.2 Pathogenesis

Blood supply to the brain is vital for maintaining normal brain function and to sustain life. Restricted blood supply or haemorrhaging within the brain facilitates a complex cascade of cellular, structural and behavioural alterations.

Brain Blood Supply

29
Brain metabolism is an energy consuming process (aerobic) that requires a constant supply of oxygen and glucose carried by the blood (Amonoff, Simon and Davis, 2005, p.289). Cerebral blood flow (CBF) is the main homeostatic factor for maintaining adequate oxygen and is tightly regulated to meet metabolic demands (Walters, 1998). CBF also serves a purpose to remove waste products such as free radicals that are harmful to cells. Furthermore, CBF is important for maintaining intracranial pressure levels (Walters, 1998).

Blood is supplied to the brain via two main pairs of arteries: the common carotid and vertebral (Figure 1.2; The Internet Stroke Centre, 1998-1999). The carotid divides into two major terminal branches, known as the internal and external carotid arteries. The external carotid artery supplies blood to the face and scalp whereas the internal carotid supplies blood to most of the brain. The vertebral artery carries blood to parts of the cerebrum, cerebellum and brain stem. The common carotid and vertebral both feed into the circle of willis located at the base of the brain (Aminoff, Simon and Davis, 2005, p288). The circle of willis supplies blood to discrete brain regions via the anterior, middle and posterior cerebral arteries. Interruption of blood flow deprives neurons of energy, and, unless normal blood flow is promptly restored, leads to cell death (Aminoff, Simon and Davis, 2005, p286-290). Too much blood as a result of haemorrhage can raise intracranial pressure which can compress and damage delicate brain tissue. Lack of blood, also known as ischemia, causes cell damage.
Figure 1.2. Reproduced from The Stroke Internet Center (1998-1999).

**Stroke In Evolution**

Figure 1.3 presents the biological cascade at stroke onset which may last from minutes to hours (Aminoff, Simon and Davis, p.289; Pulsinelli, 1992). Disruption of the energy supply to cells causes depolarisation. Cell membrane permeability becomes increased, leading to an inability to maintain potential. This results in a neurotransmitter imbalance, most notably an increase in glutamate. An abundance of glutamate stimulates an influx of sodium or calcium that causes cells to swell and break down (mitochondria injury). Furthermore, increased sodium and calcium lead to the activation harmful enzymes and release of reactive free radicals. Haemorrhagic strokes generate toxic by-products which may also release free radicals (Thanvi, Treadwell, & Robinson, 2008). Additionally, continuing haemorrhagic strokes facilitate an accumulation of fluid; blood or endema. This results in cell swelling and an increase in intracranial pressure (Rincon & Mayer, 2008). Continuation of this cascade eventually leads to cell damage or death, causing a focal deterioration in neural function. A fully completed stroke event is defined by “the presence of
residual deficits, and this can include those that are stable or improving” (Aminoff, Simon and Davis, p.287).

The Stroke Cascade

![The Stroke Cascade diagram]

The longer the time since stroke onset, the greater the severity of injury (Hacke et al., 2004; Hacke, Kaste, Skyhøj Olsen, Orgogozo, & Bogousslavsky, 2000; Ringleb, Schellinger, Schranz, & Hacke, 2002). Cell damage may occur at three levels (Aminoff, Simon and Davis, p.288): 1) preferential loss whereby only certain neuronal populations are affected, 2) further selective damage but more severe however some parts of the cell are preserved, e.g. glial (support cells), which have the capacity to regenerate as part of recovery (Butefisch, 2006; Cramer & Bastings, 2000) and, 3) permanent ischemia as a result of gross cell damage (Aminoff, Simon and Davis, p.288).
Stroke produces focal symptoms that correlate with the area of the brain tissue affected by the ischemia or haemorrhage (Davis, 2005). Strokes within the cerebral cortex are associated with aphasia, apraxia, visual deficits, memory difficulties, hemineglect and confusion. Damage to the cortex may also produce muscle weakness in limbs and face, numbness, poor coordination and poor sensation. Cerebellum and brain stem strokes are associated with motor and sensory loss, nystagmus, amnesia, altered senses, ocular weakness, decreased reflexes, balance problems, altered breathing and heart rate, poor control of the tongue. Increased intracranial pressure as a result of stroke can cause vomiting, headache and eventually loss of consciousness (Aminoff, Simon and Davis, p.315).

Early recognition and treatment is critical to minimise the extent of brain damage. Treatment windows beyond three to six hours after onset are less favourable for stroke outcome (Hacke et al., 2004; Hacke et al., 2000; Ringleb et al., 2002). Pharmacological treatments are commonly applied to reduced blockages (The National Institute of Neurological Disorders and Stroke, 1995). For example, anticoagulant medications are used to thin the blood in the event of a clot (Lip & Edwards, 2006). For haemorrhagic stroke, neurosurgery is required to contain bleeding (Rincon & Mayer, 2008). Only 10% of stroke survivors achieve a full recovery, 25% have minor impairments, 40% have moderate to server impairment, 10% require long-term care and 15% die shortly after stroke (National Stroke Association, 2009).

1.1.2 Consequences of Stoke

Survivors of stroke endure a multitude of somatic, behavioural, psychological, cognitive and motor movement consequences. Deficits in these areas considerably affect the quality of life of sufferers and their families (de Haan, Limburg, Van der Meulen, Jacobs, & Aaronson, 1995; Duncan, 1997; Gokkaya, Aras, & Cakci, 2005; Hop, Rinkel, Algra, & van Gijn, 1998).
Somatic

Stroke is associated with various comorbid medical conditions including pain, seizures, hypertension, incontinence and vision problems. These medical ailments are most prominent within the acute phase of stroke however some somatic concerns become chronic (Sisson, 1995).

Post stroke pain may include headaches as well musculoskeletal, joint and neuropathic pain (Gamble, Barberan, Bowsher, & Tyrrell, 2000; Kong, Woon, & Yang, 2004; Widar, Ek, & Ahlstrom, 2004). Long term pain interferes with activities of daily living, quality of life, mood and sleep (Iolascon, Gimigliano, & Gimigliano, 2006; Widar et al., 2004). Pain also adversely affects motor rehabilitation processes as patients struggle with physical endurance (Griffin, 1986; Roy, Sands, Hill, Harrison, & Marshall, 1995). Successful post stroke pain treatment is associated with better functioning and quality of life (Zorowitz, Smout, Gassaway, & Horn, 2005).

Increased stroke severity is associated with a high risk of seizures (Reith, Jorgensen, Nakayama, Raaschou, & Olsen, 1997). Eight to twelve percent of stroke survivors experience seizures and a small proportion may develop epilepsy (Bentes, Pimentel, & Ferro, 2001; Bladin et al., 2000). While seizures can be controlled with medication, patients still experience difficulties (Strine et al., 2005). Epilepsy is associated with increased psychological stress and cognitive deficits (Moore & Baker, 2002; Motamedi & Meador, 2003). Furthermore, the side effects of anti-epileptic medication can cause severe drowsiness (Hoepchner, Garron, & Cartwright, 1984; Legros & Bazil, 2003).

Hypertension is not only a risk factor of stroke (Lewington, Clarke, Qizilbash, Peto, & Collins, 2002) but is also a consequence (Carlberg, Asplund, & Hagg, 1990). Post stroke psychological stresses (Carlberg et al., 1990; Morfis, Schwartz, Poulos, & Howes, 1997) and increased sympathetic activity within the nervous system (Naredi et al., 2000) can cause high blood pressure. This is normally controlled with
medication which also reduces risk of further strokes (Cook et al., 2007; Rashid, Leonard-Bee, & Bath, 2003). Hypertension and blood pressure variability have been mildly associated with poorer stroke outcome (Ahmed & Wahlgren, 2001; Potter et al., 2009) however this may also be related to initial stroke severity.

Weakened bladder and bowel control is commonly reported in acute and to a lesser degree, chronic stroke (Barrett, 2002). Incontinence may be directly related to brain damage to the neural pathways that control the bladder, pudendal nerve and pelvic floor muscle (Sakakibara, Hattori, Yasuda, & Yamanishi, 1996). In addition, incontinence can be caused by cognitive deficits or is a side effect of medication (Gelber, Good, Laven, & Verhulst, 1993). The social consequences and inconvenience of incontinence is severely disturbing for patients (Brittain, 2001; Burney, Senapati, Desai, Choudhary, & Badlani, 1996). Incontinence reflects the severity of the stroke and is associated with poorer recovery (Brittain, 2001) and rehabilitation outcome (Ween, Alexander, D'Esposito, & Roberts, 1996).

In the acute phase of stroke, the visual system is affected in 92% of patients (Rowe, 2009). More specifically, 8.4% of patients have eye movement difficulties, 46.1% have visual field impairments, 25.1% have low vision and 20.5% have perception problems (Rowe, 2009). Peripheral field loss may persist in chronic patients (Cassidy, Bruce, & Gray, 2001). Some patients even report hallucinations as a directly related to brain damage after stroke, rather than presence of psychoses (Ashwin & Tsaloumas, 2007). Problematic vision is associated with poorer functioning on activities that require vision (Gall, Lucklum, Sabel, & Franke, 2008; Jones & Shinton, 2006; Rowe, 2009) and may impede rehabilitative treatment (Johansen, White, & Waraisch, 2003).

**Behavioural**

Nocturnal sleep disturbance and poor daytime functioning, such as increased sleepiness and fatigue, are common co-morbidities of acute stroke (Annoni, Staub, Bogousslavsky, & Brioschi, 2008; Bassetti, 2005a; Bassetti & Valko, 2006).
Maladaptive sleep/wake behaviour may be caused by a multitude of factors including the physical and psychological consequences of stroke (Schepers, Visser-Keily, Ketelaar, & Lindeman, 2006; Van Zandvoort, Kappelle, Algra, & De Haan, 1998) or as a direct result of brain damage per se (Ingles, Eskes, & Phillips, 1999; van der Werf, van den Broek, Anten, & Bleijenberg, 2001), particularly disruptions to those mechanisms involved in sleep regulation and arousal (Bassetti & Valko, 2006; Evans, 2002). Poor sleep and daytime functioning evolves into a chronic condition in 25-67% of patients (Cadilhac et al., 2005; Campos et al., 2005; Masel, Scheibel, Kimbark, & Kuna, 2001; Palomaki et al., 2003; Schuiling, Rinkel, Walchenbach, & de Weerd, 2005; Sterr, Herron, Dijk, & Ellis, 2008; Van Zandvoort et al., 1998; Worthington & Melia, 2006). Post stroke sleep and daytime functioning difficulties not only impact quality of life of patients (Schuiling et al., 2005) but have implications for recovery outcome (Choi-Kwon, Han, Kwon, & Kim, 2005; Glader, Stegmayr, & Asplund, 2002; Ingles et al., 1999; Naess, Nyland, Thomassen, Aarseth, & Myhr, 2005) and adversely affect participation in rehabilitation (Barker-Collo, Feigin, & Dudley, 2007; Morley, Jackson, & Mead, 2005; Terzoudi et al., 2009; Worthington & Melia, 2006).

**Psychological Disturbance**

Stroke is associated with a wide range of psychological disturbances, which may have psychiatric connotations (Carota & Bogousslavsky, 2002), as defined by the Fourth revision of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; 1994) or 10th revision of International Classification of Diseases (ICD-10; 1992). Such disturbances stem from a complex array of etiologies including lesion characteristics, functional impairment, cognitive difficulties, medications, support, resources and ability to cope (Carota & Bogousslavsky, 2002). Depression and anxiety are among the most commonly experienced psychological difficulties after stroke (Clarke & Currie, 2009).

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¹ Mixed stroke and TBI sample.
The DSM-IV identifies major and minor post stroke depression. Major depression is characterised by a presence of depressed mood, apathy, mania, or a mixture of these features for two weeks. In addition, patients must experience four other symptoms for including a significant changes in appetite or weight, sleep difficulties, daytime tiredness, psychomotor agitation, feelings of worthlessness or guilt, loss of concentration, and recurrent suicidal ideation. Patients diagnosed with minor depression typically have a depressed mood or loss of interest with at least two but fewer than four symptoms of major depression. It is important to note that studies examining post stroke depression do not necessarily utilise the DSM-IV conceptualisation (Whyte & Mulsant, 2002).

Within the first few weeks after stroke, 6-27% of patients fulfil DSM criteria for major depression (Whyte & Mulsant, 2002) and approximately 30-50% experience minor depression (Paolucci, 2008; Robinson, 1997). Acute depression may evolve into a chronic condition, with 19-29% of patients having major depression (Astrom, Adolfsson, & Asplund, 1993a; Robinson, Bolduc, & Price, 1987; Whyte & Mulsant, 2002) and 30-40% with minor depression (Robinson et al., 1987). Depression is a strong predictor of poorer quality of life after stroke (Jonkman, de Weerd, & Vrijens, 1998; Kim, Warren, Madill, & Hadley, 1999; Neau et al., 1998) and has been linked to increased morbidity and mortality (Morris, Raphael, & Robinson, 1992; Morris, Robinson, Andrzejewski, Samuels, & Price, 1993). Post stroke depression is associated with poorer long term functional outcome (Herrmann, Black, Lawrence, Szekely, & Szalai, 1998; Pohjasvaara, Vataja, Leppavuori, Kaste, & Erkinjuntti, 2001; Sisson, 1995), cognitive impairment (Kauhanen et al., 1999), daytime sleepiness and fatigue (Ingles et al., 1999; LaChapelle & Finlayson, 1998; Naess et al., 2005; Van Zandvoort et al., 1998), worse rehabilitation outcome (Gillen, Tennen, McKee, Gernert-Dott, & Affleck, 2001; Paolucci et al., 2001) and impacts ability to return to work in younger survivors (Neau et al., 1998).

Anxiety describes a psychological state involving a summation of cognitive, somatic, emotional, and behavioural components which create feelings of uneasiness, distress,
catastrophic thinking and heightened physiological arousal (Davidson & Neale, 2001, p.127). Although anxiety is a normal reaction to a stressful situation, persistent or non-specific anxiety may evolve into a chronic condition, i.e. Generalised Anxiety Disorder (GAD). The DSM-IV categorizes post stroke GAD as “anxiety disorder due to stroke, with generalized anxiety”. More specifically, GAD is accompanied with restlessness, decreased energy, difficulty in concentration, irritability, muscle tension, and sleep disturbance (DSM-IV, 1994).

Approximately 24-28% of patients will develop acute GAD (Astrom, 1996; Castillo, Starkstein, Fedoroff, Price, & Robinson, 1993; Leppavuori, Pohjasvaara, Vataja, Kaste, & Erkinjuntti, 2003), however, this becomes chronic in 20.6% (Astrom, 1996; Leppavuori et al., 2003; Sharpe et al., 1990). Fourteen percent of patients experience mild anxiety symptoms but do not fulfil DSM-IV criteria (Castillo et al., 1993). Moreover, 74% of GAD suffers will also experience depression (Castillo et al., 1993). The existence of post stroke anxiety substantially has negative implications for health, social life, functional recovery and rehabilitation (Astrom, 1996; Leppavuori et al., 2003; Shimoda & Robinson, 1998; Visser-Meily, van Heugten, Post, Schepers, & Lindeman, 2005).

Stroke is also associated with psychological conditions other than depression and anxiety. Eleven to twenty-one percent of patients report apathy (Santa et al., 2008; Starkstein, Fedoroff, Price, Leiguarda, & Robinson, 1993), a condition characterised by lack of emotion, interest, motivation or concern. Apathy can exist independently of depression (Marin & Wilkosz, 2005; Starkstein et al., 1993) and is associated with increased daytime naps (Muller, Czymmek, Thone-Otto, & Von Cramon, 2006), fatigue (Sisson, 1998) and reduced work capacity (Bassetti, Mathis, Gugger, Lovblad, & Hess, 1996). It has also been attributed to poorer functional outcome and may hinder rehabilitation participation (Santa et al., 2008; Starkstein et al., 1993). Fifteen to 25% of patients experience emotionalism within the first six months of stroke, (MacHale et al., 1998) which describes sudden or easily provoked episodes of crying or laughing precipitated by seemingly minor stimuli. These symptoms usually decline
within the first year of stroke (MacHale et al., 1998). Emotionalism has been linked to poorer motor dysfunction (Kim & Choi-Kwon, 2000) and severely impairs social contact (Allman, Hope, & Fairburn, 1992). A small number of patients may develop post stroke psychotic disorder (Chemerinski & Robinson, 2000). This disorder reflects the severity of stroke and is associated with greater mortality (Almeida & Xiao, 2007).

Cognitive Disruption
The brain damage sustained after stroke usually disrupts cognitive functioning. Focal damage may lead to selective cognitive deficits whereas diffuse neural dysfunction may produce global impairments such as a reduction in processing speed, memory and executive functioning difficulties, e.g. planning and problem solving (de Haan, Nys, & Van Zandvoort, 2006; Mori, Sadoshima, Ibayashi, Lino, & Fujishima, 1994). Seventy-eight percent of patients may be impaired on one or more cognitive domain (Lesniak et al., 2008), most notably attention, language, short-term memory and executive functioning (Lesniak et al., 2008). Left stroke is associated with language and comprehension difficulties, affecting 38% of acute patients and 18% of chronic patients (Pedersen, Jorgensen, Nakayama, Raaschou, & Olsen, 1995). Deficits in cognitive functioning can improve, particularly within the first six months (Lesniak et al., 2008; Rasquin et al., 2005; Siccoli & Bassetti, 2008). Overall, poorer cognitive functioning after stroke is associated with lower quality of life (Kwa, Limburg, & de Haan, 1996; Paolucci et al., 1998), poorer social functioning (Hommel, Trabucco-Miguel, Naegele, Gonnert, & Jaillard, 2009; McDowd, Filion, Pohl, Richards, & Stiers, 2003), functional ability (McDowd et al., 2003; Sisson, 1995; Van Zandvoort et al., 1998) and response to rehabilitation (Galski, Bruno, Zorowitz, & Walker, 1993; Mokler, Sandstrom, Griffin, Farris, & Jones, 2000; Sandra Zinn et al., 2004).

Motor Deficit
Hemiplegia describes full paralysis of one side of the body whereas hemiparesis refers to partial paralysis (Schmahmann, Ko, & MacMore, 2004). Paralysis affects the side of the body that is contralateral to the lesion, where damage affects motor areas
of the brain including the corticospinal tract (Jang, 2009; Schaechter, Perdue, & Wang, 2008). Patients experience problems with balance, walking and functioning of the affected limbs. Activities of daily living such as cooking, eating, personal care, attending work and social activities are challenging tasks in stroke patients. Moreover, degree of motor loss was reported as the single biggest predictor of overall physical recovery and independence (Lincoln et al., 1989). Thirty-three percent of survivors to rely on 24 hour care and 71% are unable to work primarily due to motor function incapacity (American Heart Association, 2009).

1.1.3 Treatment Options for Post-Stroke Management

The consequences of stroke are managed through coordinated intervention. Recovery can occur spontaneously and as a result of multifaceted support including pharmacological, psychological, cognitive and motor neurorehabilitative interventions. Motor neurorehabilitation is by and large, the primary focus of post stroke treatment as successful outcome enables greater independence of the patient, therefore lower care requirement (Laidler, 2000, p.83).

Pharmacological, Psychological and Cognitive Interventions

Stroke survivors are normally prescribed life long medications, such as anticoagulants, antiplatelets and blood pressure reducing drugs to reduce the likelihood of further strokes (Aminoff, Simon and Davis, 2005, p.308-312; PROGRESS Collaborative Group, 2001). Other medications may be applied to manage co-morbid conditions including anti-epileptic drugs (Ryvlin, Montavont, & Nighoghossian, 2006) and pain control (Kumar, Kalita, Kumar, & Misra, 2009; Zorowitz et al., 2005). Furthermore, sleep medication is sometimes prescribed to patients suffering from sleeping difficulties (Palomaki et al., 2003). Approximately twenty percent of stroke patients remain on sleep medications at three to four months after stroke (Palomaki et al., 2003).
Post stroke depression is normally treated with anti-depressant medication (Clarke & Currie, 2009; Paolucci et al., 2001). Emotionalism also responds well to antidepressants (Robinson, 1997). Anti-depressants are commonly prescribed to patients to help them cope and psychologically adjust to the consequences of stroke (Paolucci, 2008). Alternative non-pharmacological therapies are also beneficial for patients (Paolucci, 2008). For example, counselling and cognitive behavioural therapy have shown high efficacy for post stroke depression and anxiety (Clark, Rubenach, & Winsor, 2003; Kendall et al., 2007; Kneebone & Dunmore, 2000; Thompson, 2000).

Cognitive impairment can be treated with a range of cognitive training therapies including cognitive exercises, computer-assisted training, communication skill training and physical exercise (Jordan, 2000; Pyun et al., 2009). Speech and language therapy is also beneficial for those with communication difficulties (Bhogal, Teasell, & Speechley, 2003; Marshall, 2000).

**Motor Neurorehabilitation**

Motor neurorehabilitation is a vital part of post-stroke treatment to enable the patient regain previously lost motor skills. After stroke, the brain holds the capacity to regain some lost motor functions via neuroplasticity, i.e. the ability to adapt and reorganise in response to injury (Matthews, Johansen-Berg, & Reddy, 2004; Mulder & Hochstenbach, 2001; Platz, Kim, Engel, Kieselbach, & Mauritz, 2002).

After the stroke event, tissue damage to the motor areas, including the pre-motor cortex, the primary motor cortex and the supplementary motor area (SMA), results in impairment or even cessation of motor function (Lukacs, Vecsei, & Beniczky, 2008). The neuroplastic properties of the brain allow some motor skills to be, at least in part, regained (Carey, Abbott, Egan, Bernhardt, & Donnan, 2005; Mark Hallett, 2001; Matthews et al., 2004; Platz et al., 2002). Neuroplasticity involves the interaction of neural and behavioural inputs which enable the brain to reorganise and adapt. As neural pathways have a larger region of anatomical connectivity than their usual...
territory of functional influence, the brain can remap itself to reinstate some motor ability after stroke (Butefisch, 2006; Cramer & Bastings, 2000). Neuroplasticity is facilitated in three ways: 1) through self organisation, i.e. spontaneous recovery, 2) exercise, i.e. treatment induced recovery and 3) lack of input which may lead to shrinkage of a specific neural net therefore reduce functionality (Hallett, 2001; Nudo, 2006). Early neuroplasticity mechanisms originate from emerging activity of latent synapses whereas changes over longer periods of time involve cell regeneration and recruitment of connections from other areas (Chen, Cohen, & Hallett, 2002; Jang, 2007). Re-learning motor skills intensifies connectivity between neurons and the co-activation of connected cells causes modifications in demand upon these areas (Hallett, 2001; Kopp et al., 1999; Sunderland & Tuke, 2005). This process allows the brain to form alternative motor pathways which ultimately leads to an increase of motor movement in patients with hemiparesis. The behavioural demands of motor neurorehabilitation, including skill, strength and endurance, facilitate structural and functional reorganisation of the motor system (Adkins, Boychuk, Remple, & Kleim, 2006).

The majority of UK neurorehabilitative service provisions use neurodevelopmental treatments (NDTs), most typically, Bobath approaches (Davidson & Waters, 2000; Lennon & Ashburn, 2000). Such treatments aim to reduce muscle spasticity by focusing on normal patterns of movement and adaptation to the environment and to gain a better range and quality of functional skills. NDT approaches introduce physiotherapeutic strategies and exercises early after injury. However NDTs alone, are largely ineffective due to the lack of emphasis on task orientated motor learning (Langhammer & Stanghelle, 2000) and focus on compensatory strategies rather than restitution of motor function (Duncan, 1997). One form of treatment uses alternative strategies that are specifically based on to the theory of motor learning and neuroplasticity, i.e. ‘Constraint-Induced Movement Therapy’ (CIT; Taub et al., 1993). CIT aims to maximise use of the paretic limbs and mass practice of newly learned skills. Extensive clinical trials reveal high efficacy of CIT over other forms of motor neurorehabilitation (Wolf et al., 2006).
Current Issues In Stroke Medical Care and Management

Although existing rehabilitation strategies are of some benefit for patients, current treatment options and rehabilitation strategies are deemed unsatisfactory (Rodgers & Thomson, 2008; Wilkinson et al., 1997). Increased independence, motor and cognitive performance are typically found between discharge from acute care and one year however levels begin to plateau, or even decline, between three to five years (Leonard, Miller, Griffiths, McClatchie, & Wherry, 1998). Many survivors remain chronically disabled, require full time care, cannot work and have a reduced quality of life as promotion of long term functional recovery remains largely ignored (Murray, Ashworth, Forster, & Young, 2003; Neau et al., 1998; Wolf, 1997). Despite the large burden of stroke, substantially less is spent on stroke research than that of heart disease and cancer (Rothwell, 2001). Therefore, it is highly necessary to research and explore other strategies to improve current treatment and long term care protocols and consider alternative avenues which may influence the post-stroke recovery process. Recent evidence suggests that one such avenue is the field of sleep.

→ Proposed Paradigm Shift In Stroke Medical Care, Management and Neurorehabilitation

Evidence within the field of sleep has highlighted a new direction in the approach to post-stroke treatment, including medical care, management and motor neurorehabilitative strategies. It is well established that the consequences of stroke including somatic complaints, behavioural changes, cognitive deficits, and psychological disturbance are all influenced by sleep (Bassetti & Aldrich, 1999; Bassetti & Valko, 2006; Bassetti & Aldrich, 2001; Gamble et al., 2000; Kong et al., 2004; Schepers et al., 2006; Siengsukon & Boyd, 2008a, 2009a; Siengsukon & Boyd, 2008b; Van Zandvoort et al., 1998; Widar et al., 2004). With particular relevance to neurorehabilitation, several studies have revealed compelling evidence that supports the role of sleep for consolidation of motor learning (Siengsukon & Boyd, 2009b), and more specifically, neuroplasticitic processes in response to motor learning (Hoffman & McNaughton, 2002; Walker & Stickgold, 2006). Although, there is
strong theoretical reason to predict a relationship between the consequences of stroke and sleep, the evidence-base for research and support provisions for patients is primarily focused on daytime behaviour, and largely neglects sleep. The central argument within this thesis is that sleep may be a critical element to the post stroke sequelae with regard to quality of life, recovery and treatment efficacy. Therefore, a paradigm shift in the direction of sleep in the context of stroke will have great implications, not only within care provisions, but future research and rehabilitation related fields.

The next section of this chapter aims to introduce the field of sleep, including neural mechanisms, how sleep is measured, sleep disorders and the function of sleep. The remaining sections of this chapter aim to merge the fields of stroke and sleep literature and introduce the thesis concept.

1.2 What is sleep?

“Sleep is a reversible behavioural state of perceptual disengagement from and unresponsiveness to the environment” (Carskadon & Dement, 2005, p.13) characterised by changes in behavioural and physiological processes that are distinct from waking behaviour. Sleep is manifested in mammalian and, to some extent, non-mammalian species (Siegel, 2008). However, scientists have only recently begun to understand the overall function of sleep. Sleep is by no means a passive state, it is an active process involving several brain mechanisms, including the forebrain, mid-brain and brainstem (Hirshkowitz, Moore, & Minhoto, 1997; Jones, 2005).

The sleep process has distinct physiological biomarkers that define a sleep period, sleep architecture and sleep/wake regulation. These processes can be measured via several methods including objective techniques and by examining an individuals
perception of sleep. Persons with poor sleep may exhibit a sleep disorder which impairs daytime functioning and requires medical attention.

1.2.1 Physiological Biomarkers of Sleep-Wake Function

Sleep is easily recognisable in humans based on behavioural observations which include closed eyes, postural recumbrance, and a heightened threshold for responding to external stimuli (Carskadon & Dement, 2005, p.13). However, it is the physiological mechanisms behind sleep that truly defines the process. Transition to and from wakefulness, as well as the sleep period per se, is accompanied by a complex array of brain activity alterations.

Neurological Correlates of Sleep

Electroencephalography (EEG) is the main form of neurophysiological measurement used to describe the distinct characteristics of sleep (the method is described in Section 1.2.3). Standard criteria for defining sleep and sleep stages are based on characteristics within the sleep EEG (Carskadon & Rechtschaffen, 2005, p.1362-1368). Additional physiological signals are also used to define sleep including eye movement (electrooculogram; EOG) and muscle movement (electromyogram; EMG). Respiratory function, oxygen saturation and heart rate (electrocardiogram; ECG) may also be measured but are not typically part of the criteria for defining sleep. Global patterns of simultaneous synchronisation and disruption (desynchronisation) of EEG rhythms not only identify sleep/wake states, but sleep architecture (Steriade, McCormick, & Sejnowski, 1993).

EEG measures brain activity which oscillates at varying frequencies. With regard to sleep/wake function, frequencies are conventionally subdivided into four main bands: beta (13-30 Hz), alpha (12-8 Hz), theta (4-7 Hz) and delta (1-3 Hz). Sleep architecture comprises two states: non-rapid eye movement (NREM) and rapid eye movement (REM). Non-REM and REM alternate throughout the night as part of the
normal sleep cycle (Figure 1.4; Carskadon & Dement, 2005; Hirshkowitz et al., 1997). Non-rapid eye movement (NREM) sleep comprises four stages, individually characterised by a set of criteria (Carskadon & Dement, 2005; Hirshkowitz et al., 1997). Stage 1 contains rolling eye movements, an increased presence of synchronised theta, slower heart rate, and a lower arousal threshold. Stage 2 consists largely of theta with regular bursts of spindles (12-14 Hz) and k-complexes (a high voltage peak). Stages 3 and 4 are deeper aspects of the sleep cycle, characterised by synchronised slow waves within the delta range, collectively known as slow wave sleep (SWS). During SWS, heart, breathing and metabolic rate is slower.

REM is sometimes referred to as ‘paradoxical sleep’ as the EEG rhythm becomes mixed in frequency, generally faster, and desynchronized as observed during wakefulness (Siegel, 2005). Similarly to wake, heart and breathing rates are increased as well as blood flow to the brain (Geyer & Dillard, 2005, p.77). However unlike wake, REM sleep comprises muscle atonia, saccadic eye motion and is associated with dreaming. Peripheral muscle activity is disabled so that the active brain state does not influence bodily behaviour. This is coordinated by the release of neurotransmitters, glycine and gamma-aminobutyric acid (GABA) which inhibit motor neurons (Chase & Morales, 2005).

Although NREM and REM alternate in approximately 90 minute cycles, the make up of these cycles changes across the night where a greater proportion of SWS occurs during the first third of the night and REM predominantly occurs within the final third of the night (Figure 1.4; Carskadon & Rechtschaffen, 2005). The typically reported optimum sleep duration is eights hours (Van Dongen, Maislin, Mullington, & Dinges, 2003) however this largely varies between individuals due to circadian timing (Wyatt, Ritz-De Cecco, Czeisler, & Dijk, 1999), lifestyle (Groeger, Zijlstra, & Dijk, 2004; Krueger & Friedman, 2009), presence of a sleep disorder (Vaughn, Neill, & D'Cruz, 2005) and ill health (Ferrie et al., 2007).
Neural Mechanisms Behind Neurological Correlates

Several regions within the forebrain, mid-brain and brainstem are simultaneously involved in sleep/wake activity (Hirshkowitz et al., 1997; Jones, 2005). Damage to these areas is likely to result in abnormal sleep and wakefulness regulation (Evans, 2002). More specifically, key neuronal populations and pathways (Figure 1.5) have been identified as mechanisms for co-ordinating sleep transition from wakefulness and vice versa (Jones, 2005; Nofzinger, 2005). Neural projections from the brain stem to the thalamus, hypothalamus and basal forebrain facilitate sleep (Figure 1.5). Additional pathways from the mid-brain directly to the hippocampus and cortex are also involved in this process (Figure 1.5).

Sleep promoting systems act antagonistically with wake promoting systems forming a ‘sleep switch’ which results in stable wakefulness and sleep (Saper, Chou, & Scammell, 2001). Mutual inhibition between the arousal and sleep promoting chemical messengers result in switching processes that define discrete wake and sleep
states (Saper, Scammell, & Lu, 2005). Sleep antagonists include those mechanisms within the recticular activating system which are important for controlling arousal levels (Culebras, 1999, p.38). The recticular activating system is network of neurons within the brain stem up towards the upper border of mid brain. Ascending projections from the reticular activating system are involved in the modulation of arousal (Jones, 2005). The activated reticular formation arouses the cerebral cortex via two routes: dorsal route which projects to nonspecific thalamic nuclei and cerebral cortex; and the ventral route which projects to the hypothalamus, basal forebrain, eventually reaches the cerebral cortex and hippocampus (Figure 1.5).
1.2.2 Sleep/Wake Regulation

The amount, timing and quality of sleep are combined effects of two processes: 1) the homeostatic sleep debt and, 2) the circadian rhythm phase. The haemostat is determined by prior sleep and waking. It aims to balance the sleep/wake schedule by driving sleep need in response to prolonged wakefulness (Borbely & Acherman, 2005). Circadian rhythm is pertained to a biological clock which is in approximation with the 24-hour clock and is independent of prior sleep or wakefulness (Borbely &
Acherman, 2005). Homeostatic drive and circadian rhythm are integrated which form an overall model for the sleep-wake cycle, known as the ‘Two Process Model’ (Figure 1.6; Borbely, 1982). An essential determinant of these systems is the influence of social factors which is not included in the model (Dijk & Franken, 2005, p. 421).

![Two Process Model](image)

Figure 1.6. Two Process Model. Adapted from Borbely and Acherman (2005). As S (homeostatic sleep drive) increases, the need for sleep increases during wakefulness and then declines during sleep. C describes the circadian rhythm cycle (measured by body temperature). The greatest point of sleep propensity occurs during the trough of body temperature and when S is at its peak.

**The Homeostatic Drive**

The homeostatic drive reflects pressure for sleep, similar to that of hunger and thirst. These motivational states direct behavioural systems to perform actions which reduce this drive. Prolonged wakefulness reliably induces sleep, and failure to obtain at least a core amount (sleep deprivation) leads to impaired function. As well as regulating sleep/wake cycles, homeostatic mechanisms also regulate sleep stages. Amount of
slow wave sleep corresponds to amount of hours of wakefulness previously, independent of circadian phase (Dijk, Brunner, Beersma, & Borbely, 1990). This may explain why the majority of slow wave sleep occurs at the beginning of the night and exhibits an immediate rebound after sleep deprivation (Borbely and Acherman, 2005, p.407-408).

**Circadian Rhythm**

Circadian rhythm is an endogenous biological timing system that oscillates over approximately a 24 hour period (Czeisler, Buxton, & Khalsa, 2005). Hormonal output, core body temperature, rest and activity, sleep and wakefulness, and cellular process are mediated by the circadian timing system (Campbell, 2000). The circadian component of sleep enables behavioural states to adapt to day and night. The mechanism that maintains the circadian clock for sleep is located within the suprachiasmatic nucleus (SCN) of the hypothalamus (Zlomanczuk & Schwartz, 1999). The SCN has its own internal momentum and acts as a central convergence point for both the sleep agonists and the sleep antagonists. The SCN is made up of a cluster of neurons which receive both photic cues from the retinal ganglion cells and nonphotic information from hormones and neurotransmitters (Culebras, 1999, p.46-48). The SCN facilitates regularity in the sleep wake cycle pertaining to the 24 hour clock, however can be entrained by exogenous factors (Campbell, 2000), e.g. when adjusting to a different time zone.

**1.2.3 Measuring Sleep**

Sleep, as well as wake, can be assessed using objective and subjective techniques. The gold standard objective technique for measuring sleep is polysomnography (PSG). Actigraphy is an alternative objective assessment of sleep which uses a less intrusive technique compared to PSG. However, actigraphy is limited to measuring behavioural measures and cannot measure sleep architecture. Subjective measures of sleep are typically in the form of sleep diaries and questionnaires. Criteria derived
from these methods can be used to characterise sleep behaviour, define a sleep
disorder or indicate general sleep and daytime functioning disturbance.

**PSG**

PSG involves measuring physiological signals by means of electrode sensors that
record the EEG, EOG, EMG, respiratory function, oxygen saturation and ECG. Some
researchers use a variety of physiological signals whereas others measure EEG only.
PSG is typically recorded in a purpose built laboratory however recent developments
have simplified this technique to be used in participant homes. The PSG technique
requires four main processes: 1) electrode placement, 2) data recording, 3)
observation and processing and 4) offline pre-processing and quantitative analysis.

Electrode sensors are applied to predefined sites on the scalp (EEG) and on the body
for the remaining signals. The electrodes are plugged into a receiving device that
record sleep behaviour and amplifies the signal for technician viewing and analysis.
PSG traces are viewed on a computer monitor in real time. Figure 1.7 provides an
eexample of a waking EEG trace.
Figure 1.7. Waking EEG traces for 33 channels across a 10 second segment of recording drawn from data used for Chapter 5 of this thesis. Each trace represents the recording of a particular electrode. The EEG presents mixed, dysynchronised frequencies which defines wake. The black arrow shows an eye blink event.

The EEG trace can be used to detect clinical abnormalities after brain injury (Finnigan, Walsh, Rose, & Chalk, 2007; Lukashevich et al., 1999; Sainio, Stenberg, Keskimaki, Muuronen, & Kaste, 1983). It also enables of sleep propensity to be performed such as the Multiple Sleep Latency Test (MSLT; Carskadon, 1994, p962-96, 1994) or Maintenance of Wakefulness Test (MWT; (Miltner, Carskadon, & Hirshkowitz, 2005; Mitler, Gujavarty, & Browman, 1982, 2005, p.1420).

In order to derive sleep behaviour parameters and determine feature of sleep architecture including proportions of sleep stages, off line analyses is required. Offline analysis allows the study of the frequency composition within the EEG. Frequency can also be used to determine level of arousal during wakefulness. More
specifically, daytime sleepiness can be detected by the EEG increased sleepiness is associated greater presence of theta waves (Gillberg, Kecklund, & Åkerstedt, 1994; Marzano et al., 2007; Torsvall & Akerstedt, 1988).

The PSG technique holds several disadvantages. In particular, it is an expensive and lengthy procedure, and imposes great intrusion on natural sleep behaviour (Reynolds et al., 1992; Richards, O'Sullivan, & Phillips, 2000). Critics therefore argue that the methodological rigor of PSG comes at the expense of ecological validity (Reynolds et al., 1992; Richards et al., 2000). Alternative modes of monitoring sleep have been designed to address these issues, e.g. actigraphy.

**Actigraphy**

Actigraphy is considered a favourable objective method for measuring sleep in situations where PSG is not feasible and can be applied to a range of research protocols (Ancoli-Israel et al., 2003). Furthermore, actigraphy also provides an estimate of daytime functioning through the identification of naps. This is done by calculating sleep/wake states of an individual based on their activity every 24 hours as monitored by a wrist worn device (Figure 1.8).
The device contains a piezo-electric accelerometer which produces an electrical signal when distorted. The corresponding voltage is then converted into an activity count using an algorithm set by the manufacture. Activity counts are an integration of the amount and duration of movement. Sensitivity of this algorithm can be adjusted by the researcher. This information is downloaded telemetrically and stored on a computer. Actigraphy software packages are able to derive behavioural sleep parameters from the raw activity data. This is done by examining the data in terms of pre-set epoch lengths, e.g. one minute. The software determines if each epoch is sleep or wake by either utilising an algorithm that detects the number of zero crossings (i.e. the number of times the activity count is zero) or the number of counts above a set threshold. These algorithms are limited to calculating sleep/wake distinctions and cannot determine sleep stages. The software allows the extraction of sleep parameters including bed time, get up time, wake time, time in bed, sleep duration, sleep onset latency, sleep efficiency, night time awakening frequency and duration. Furthermore, daytime napping parameters can also be calculated by actigraphy.
A significant benefit of actigraphy is that it enables quantification of sleep/wake cycles over days, weeks and months under natural conditions. Actigraphy is increasingly recognised as a valid measure of long term sleep behaviour (Ancoli-Israel et al., 2003; Littner et al., 2003; Sadeh & Acebo, 2002). The technique has shown good concordance with PSG measures in healthy (Cole, Kripke, Gruen, Mullaney, & Gillin, 1992; Sadeh, Hauri, Kripke, & Lavie, 1995) and clinical samples including those disordered sleep (Jean-Louis et al., 1996; Kushida et al., 2001; Lichstein et al., 2006).

**Sleep Diaries**
Sleep diaries involve the collection of subjective sleep variables, such as bed time, sleep duration, number of night awakenings, for a specified number of days. Sleep diaries may also request daytime functioning information such as number of naps, level of sleepiness and caffeine intake. Sleep diaries rely on self inspection and therefore provide an account of the subjective perception of sleep rather than a direct measure. In this respect, it is considered less accurate than objective methods, particularly regarding those parameters that rely on night awakening reports (Fontaine, 1989; Kushida et al., 2001; Means, Edinger, Glenn, & Fins, 2003; Vanable, Aikens, Tadimeti, Caruana-Montaldo, & Mendelson, 2000). Sleep diaries are vulnerable to under or overestimation of sleep parameters (Fontaine, 1989; Kushida et al., 2001) and lack of compliance (Stone, Shiffman, Schwartz, Broderick, & Hufford, 2002). However, sleep diaries contribute clinically useful information by providing important insights into the perception of sleep behaviour (Chesson et al., 2000) as well as serving a complimentary function to other objective methods (Sadeh & Acebo, 2002).

**Questionnaires**
Similarly to sleep diaries, questionnaires capture the subjective perspective of how an individual rates their sleep in retrospect. One time questionnaires are commonly used as they are relatively simple and quick to administer, measure a range of sleep and daytime functioning behaviour and are easily applied to a range of cohorts including
those with sleep disorders, chronically ill, brain injured and psychiatric patients. Retrospective questionnaires may be used to determine habitual sleep traits, such as the Pittsburgh Sleep Quality Index (PSQI). This measure is sensitive to identifying good or poor quality sleep and is useful for highlighting those persons likely to experience a sleep disorder (Buysse et al., 2008; Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). Questionnaires may also be used to capture daytime functioning at a particular point in time (e.g. current level of sleepiness). A commonly used assessment of daytime sleepiness is the Karolinska Sleepiness Scale (KSS; Akerstedt & Gillberg, 1990). This form of assessment is short and can be used over several intervals during the day (Akerstedt & Gillberg, 1990; Kosuke Kaida, Torbjörn Akerstedt, Göran Kecklund, Nilsson, & John Axelsson, 2007). Moreover, this method is cheap, does not require specialist equipment or sophisticated data processing. However, the results of subjective assessments should be interpreted with caution due to possible inaccuracies for several reasons as a result of experimenter bias and poor introspection of personal behaviour (Elsenbruch, Harnish, & Orr, 1999; Harvey, Stinson, Whitaker, Moskovitz, & Virk, 2008; Robert & Zadra, 2008).

1.2.4 Disorders of Sleep and Daytime Functioning

Sleeping difficulties are common in the general population (Anderson & Horne, 2006; Groeger et al., 2004) and may occur as a result of ill health, psychological disturbance, lifestyle, environmental cues, and for some, the causes may remain unknown (Basner, Muller, Elmenhorst, Kluge, & Griefahn, 2008; Foley, Ancoli-Israel, Britz, & Walsh, 2004; Groeger et al., 2004; Ohayon, 2005; Parish, 2009; Pressman, Gollomp, Benz, & Peterson, 2000). Although sleep problems are often transient, they can evolve into a severe and chronic disorder. Sleep disorders can occur as a primary condition or are secondary to ill health. Clinical diagnoses of sleep disorders typically apply criteria provided by the International Classification of Sleep Disorders (ICSDI; American Academy of Sleep Medicine, 2001) or Diagnostic and Statistical Manual of Mental Disorders (DSM-IV, 1994). The ICSD classifies sleep
disorders into: 1) dyssomnias, 2) parasomnias and 3) sleep disorders associated with mental, neurologic and other medical disorders. A range of pharmacological and non-pharmacological treatments have been implemented in sleep medicine to alleviate such disorders.

**Dyssomnias**

Dyssomnias describe those sleep disorders where the main symptom is related to initiating or maintaining sleep or excessive daytime sleepiness. Such disorders include insomnia, sleep disordered breathing (e.g. sleep apnoea), periodic limb movement disorder (PLMD), restless leg syndrome (RLS), circadian rhythm disorder, narcolepsy and hypersomnia.

Insomnia refers to a complaint of insufficient or non-restorative sleep as a result of difficulty getting to sleep or problems staying asleep for at least one month with marked impairment on functioning (ICSD, 2001). Insomnia affects approximately 30% of the population (Roth, 2007). Sleep disordered breathing refers to abnormal respiratory function during sleep such as frequent snoring and apnoeas. Sleep apnoeas is a syndrome characterised by recurrent episodes of partial or complete obstruction of the upper airway during sleep, result in oxygen desaturation which causes frequent arousals from sleep. The prevalence of sleep apnoea ranges from 2-19% in the general population (Duran, Esnaola, Rubio, & Iztueta, 2001; Young et al., 1993) whereas snoring occurrence is higher (35%; Duran et al., 2001). PLMD sufferers experience unintentionally initiated movements in one or both legs frequently throughout the night, more than 15 times an hour (ICSD, 2001). These movements are substantial enough to cause an awakening and severely disrupt sleep (Hornyak, Feige, Riemann, & Voderholzer, 2006). PLMD affects approximately 8% of the general population (Scofield, Roth, & Drake, 2008). RLS describes abnormal sensations in the legs with an increasing urge to move, particularly during times of rest such as lying in bed (Allen et al., 2003). The symptoms of RLS prolong sleep onset and lower quality of sleep (Hornyak, Feige, Voderholzer, Philipsen, &
RLS affects approximately 7-10% of the general population (Allen et al., 2005; Phillips et al., 2000).

Dyssomnias may also be manifested during wakefulness. The most severe of these disorders is invariably narcolepsy. Persons with narcolepsy experience frequent ‘sleep attacks’ during the day, characterised by a rapid onset of REM sleep (Overeem, Mignot, van Dijk, & Lammers, 2001). Narcolepsy is one of the least common dyssomnias, affecting 0.05% of the general population (Ohayon, Priest, Zulley, Smirne, & Paiva, 2002). A more commonly experienced wakefulness syndrome is hypersomnia which is a disorder of excessive sleepiness and increased sleep needs.

**Parasomnias**

Parasomnia refers to those sleep disorders which intrude on the normal sleep/wake cycle, characterised by arousals and abnormal sleep stage transition. Parasomnias include sleep walking, sleep talking, nightmares, snoring and sleep paralysis (ICSD). Parasomnias are particularly distressing for sufferers and their partners. These problems occur commonly in children (Petit, Touchette, Tremblay, Boivin, & Montplaisir, 2007) and up to approximately 4% of adults exhibit some form of parasomnia (Ohayon, Guilleminault, & Priest, 1999).

**Sleep Disorders Associated with Medical, Mental and Neurologic Disorders**

Some of the above sleep disorders develop as a result of a medical condition, mental health disorder or abnormal neurological function (e.g. after brain damage). Symptoms of medical conditions including pain, fever, increased bed rest and general ill health are associated with increased sleep disturbance (Dogan, Ertekin, & Dogan, 2005; Katz & McHorney, 1998; Lautenbacher, Kundermann, & Krieg, 2006; Widar et al., 2004). Mental health are also strongly associated with disturbed sleep including schizophrenia, depression, anxiety and post traumatic stress disorder (Green, 2003; Hofstetter, Lysaker, & Mayeda, 2005; McCall, Reboissin, & Cohen, 2000; Ware & Morin, 2000; Wirz-Justice, Haug, & Cajochen, 2001). Given that the mechanisms driving sleep and arousal are located in the brain, it is not surprising that neurological...
disease; such as dementia, Parkinsonism, epilepsy, and acquired brain injury; such as stroke and TBI, are associated with sleep/wake disturbance (Bassetti & Valko, 2006; Foley et al., 2004; Happe, 2003; Happe et al., 2005; Vitiello & Borson, 2001). Post-traumatic hypersomnia refers to excessive sleepiness after a traumatic event, including brain injury (ICSD, 2005).

**Treatment of Sleep Disorders**

Recent advances in sleep medicine have drastically improved treatment options for those with sleep disorders, including pharmacological and non-pharmacological interventions. For insomnia related problems, pharmacological treatments, also referred to as hypnotics, typically involve medications which act on neurotransmitters, normally GABA, in order to initiate sleep (Dundar et al., 2004; Mendelson, 2005). Medications may also be prescribed to achieve the opposite for disorders of excessive sleepiness where arousal promoting mechanisms are driven by stimulants (Boutrel & Koob, 2004). Parasomnias can be treated by medication (Schenck & Mahowald, 1996) and some approaches use psychological techniques if the origins are believed to have stemmed from anxiety (Hauri, Silber, & Boeve, 2007). Sleep disordered breathing can be treated medications that act on the neural mechanisms that control respiratory function (Hedner, Grote, & Zou, 2008) however devices to aid breathing (e.g. Continuous Positive Airway Pressure; CPAP) are used to reduce frequency of respiratory malfunction (Gay, Weaver, Loube, & Iber, 2006). Studies have shown that modifying behaviour to accommodate healthy sleep hygiene can largely improve sleep disorders (Edinger & Wohlgemuth, 1999; Espie, 1993; Stepanski & Wyatt, 2003).

**1.3 Function of Sleep**
Sleep is an active process that subserves daytime functioning and performance, memory consolidation as well as being a critical mediator of health and wellbeing. In order to understand the importance of sleep for these functions, experiments have examined sleep loss under laboratory based sleep deprivation conditions or sleep disturbance in the natural environment.

1.3.1 Maintaining Daytime Functioning and Cognitive Performance

Daytime Functioning

Sleepiness describes an increased need to sleep and is typically experienced after prolonged wakefulness. Experimental paradigms involving total or partial sleep deprivation have shown increased objective sleepiness in the waking EEG (Akerstedt & Gillberg, 1990; Franzen, Siegle, & Buysse, 2008; Ikegami et al., 2009; Marzano et al., 2007; Strijkstra, Beersma, Drayer, Halbesma, & Daan, 2003; Torsvall & Akerstedt, 1987, 1988) as well as subjective reports of sleepiness (Franzen, Siegle et al., 2008). Furthermore, increased sleepiness is experienced as a result of sleep loss in naturalistic settings including those who endure shift work (Drake, Roehrs, Richardson, Walsh, & Roth, 2004; Gold et al., 1992; Harma, Sallinen, Ranta, Mutanen, & Muller, 2002; Papp et al., 2004; Torsvall & Akerstedt, 1987) and those that live in environments that are not conductive to sleep, e.g. near airports (Basner et al., 2008). Sleepiness may also be caused by poor health (Kapur et al., 2002; Parish, 2009) and brain injury (Bassetti & Valko, 2006). Increased sleepiness has repercussions for mood (Dinges et al., 1997; Ikegami et al., 2009), cognitive performance (Pilcher & Huffcutt, 1996) and social activity (Drake et al., 2004; Papp et al., 2004). Importantly, the presence of excessive sleepiness is extremely dangerous for everyday tasks. For example, driving whilst sleep deprived has been likened to driving under the influence of alcohol (Powell et al., 2001). Therefore efforts to minimise sleepiness is essential for daytime functioning as well as reducing risk of injury from accidents (Dinges, 1995; Gold et al., 1992; Kaida, Akerstedt, Kecklund, Nilsson, & Axelsson, 2007).
Fatigue is another dimension of poorer daytime functioning, which shares some overlap with sleepiness, despite being a distinct entity (Hossain et al., 2005; Mahowald & Mahowald, 2000). Fatigue is clinically defined as "a reversible decrease or loss of abilities associated with a heightened sensation of physical or mental strain, even without conspicuous effort, an overwhelming feeling of exhaustion, which leads to inability or difficulty to sustain even routine activities and which are commonly expressed verbally or a loss of drive" (Staub & Bogousslavsky, 2001). Sleepiness and fatigue are often poorly defined in the literature and used interchangeably (Hossain et al., 2005; Mahowald & Mahowald, 2000; Pigeon, Sateia, & Ferguson, 2003). Like sleepiness, fatigue is associated with poor sleep at night (Chervin, 2000; Hossain et al., 2005; Lichstein, Means, Noe, & Aguillard, 1997) and sleep deprivation (Akerstedt & Gillberg, 1990; Akerstedt et al., 2004; Franzen, Siegle et al., 2008; Ikegami et al., 2009; Marzano et al., 2007). Severe fatigue is a disease itself, known as chronic fatigue syndrome., but fatigue is also a commonly reported symptoms of poor health (Akerstedt et al., 2004; Pawlikowska et al., 1994) and after brain injury (Choi-Kwon et al., 2005; Ingles et al., 1999; Park et al., 2009; Schepers et al., 2006; Valko, Bassetti, Bloch, Held, & Baumann, 2008; van der Werf et al., 2001; Van Zandvoort et al., 1998). Similarly to sleepiness, fatigue can occur despite sleeping well at night (Nijrolder, van der Windt, & van der Horst, 2008).

**Cognitive Performance**

Meta-analyses have shown that sleep deprivation, even partial, impairs cognitive performance (Pilcher, Ginter, & Sadowsky, 1997; Samkoff & Jacques, 1991). Reaction time, correct responses and attention to tasks under laboratory conditions are affected by both short and long term sleep deprivation (Dinges et al., 1997; Ikegami et al., 2009; Van Dongen et al., 2003). Furthermore, sleep loss under natural conditions, such as shift work, working to deadlines and sleep disorders are associated with decrements in cognitive functioning (Durmer & Dinges, 2005; Kobbeltvedt, Brun, & Laberg, 2005; Robbins & Gottlieb, 1990).
Cognitive functioning is impaired after sleep loss due to the reduced capacity of the brain to perform cognitive tasks. Neuroimaging studies have shown brain deactivation, or low level activity, in response to sleep loss (Thomas et al., 2000; Thomas et al., 2003). Recent evidence has shown that particular brain regions are affected by sleep deprivation which selectively impairs facets of cognitive function (Drummond & Brown, 2001; Drummond et al., 1999; Harrison & Horne, 1998; Thomas et al., 2000; Thomas et al., 2003). For example, sleep loss particularly affects the frontal lobe with repercussions for executive functioning, such as problem solving and decision making (Harrison & Horne, 1999; Killgore et al., 2007; McKenna, Dicjinson, Orff, & Drummond, 2007).

1.3.2 Memory Consolidation

Recent behavioural and neural evidence has shown that a period of sleep is linked to stabilisation of a memory or enhancement of skill, i.e. consolidation. More specifically, neural processes during sleep may selectively enhance learning (Cohen, Pascual-Leone, Press, & Robertson, 2005; Fischer, Hallschmid, Elsner, & Born, 2002; Gaab, Paetzold, Becker, Walker, & Schlaug, 2004; Karni, Tanne, Rubenstein, Askenasy, & Sagii, 1994; Kuriyama, Stickgold, & Walker, 2004; Robertson, Press, & Pascual-Leone, 2005; Wagner, Gais, Haider, Verleger, & Born, 2004; Walker, Brakefield, Hobson, & Stickgold, 2003a; Walker, Brakefield, Morgan, Hobson, & Stickgold, 2002a). This discovery has been described as a “renaissance in sleep research” (Walker & Stickgold, 2006). The modulatory processes of sleep for learning is commonly referred to as offline learning or sleep dependent consolidation (Robertson, Pascual-Leone, & Miall, 2004). Memories are encoded during wake and then enhanced by sleep (Walker et al., 2003a) via “dynamic stabilisation through reactivation of the corresponding neuronal assemblies which cannot be done during wake due to incoming stimuli with waking behaviour” (Krueger & Obal, 1993, cited in Maquet, Smith, & Stickgold, 2003, p.2). As learning new skills is an important part
of neurorehabilitation after stroke, this theory holds particular relevance for this thesis.

**Types of Learning and Memory**

Experiments have investigated the two major dimensions of memory; declarative and non-declarative (Gabrieli, 1998; Figure 1.9). Declarative memories comprise the knowledge of facts (semantic) and events (episodic). Semantic and episodic memories are usually explicitly acquired, i.e. with awareness (Tulving, 1972, p.10). Non-declarative memories refer to a learned skill involving motor function such as walking, riding a bike and playing a musical instrument. Non-declarative memories are acquired by procedural learning, an explicit set of rules to complete a motor task or skills acquired without awareness (implicit) such as habituation, priming and emotional learning (Robertson & Cohen, 2006).

![Figure 1.9. Dimensions of memory. Based on Gabrieli (1998) and Stickgold and Walker (2005).](image)

Learning involves six main processes: 1) encoding (forming memory trace), 2) consolidation (becoming permanent, involving stabilization and enhancement or...
improvement of a skill), 3) storage (maintenance over time), 4) retrieval (ability to use the memory) and 5) reconsolidation (reusing the memory and further modifying it) (Kandel, Kupfermann, & Iversen, 2000; Robert Stickgold & Walker, 2005; Walker et al., 2003a). Evidence suggests that processes 2 to 5 beyond the initial encoding of a memory are modulated by sleep.

**Empirical Evidence**

Experimental learning paradigms show that skills acquired during the initial learning phase remain stabilised for several hours, indicative of memory or skill consolidation over time (Brashers-Krug, Shadmehr, & Bizzi, 1996; Donchin, Sawaki, Madupu, Cohen, & Shadmehr, 2002; Karni & Sagi, 1993; Shadmehr & Brashers-Krug, 1997). Evidence suggests that the consolidation process may occur during a sleep period, however to a greater degree. Greater level of consolidation, demonstrated by greatest amount of improvement on a task, was observed post sleep compared to the same amount of time awake (Fischer et al., 2002; Gaab et al., 2004; Karni et al., 1994; Wagner et al., 2004; Wagner, Hallschmid, Verleger, & Born, 2003; Walker et al., 2002a; Walker et al., 2003b; Walker, Liston, Hobson, & Stickgold, 2002b). Furthermore, a period of sleep is associated with learning complex skills, including fine motor dexterity (Kuriyama et al., 2004).

Particular sleep stages are associated with consolidation of certain types of memory. This effect is typically identified through a correlation between proportion of a sleep stage and greater level of learning. REM sleep is associated with the consolidation of declarative memory (De Koninck, Lorrain, Christ, Proulx, & Coulombe, 1989; Gaab et al., 2004; Karni et al., 1994; Stickgold, Scott, Rittenhouse, & Hobson, 1999; Walker et al., 2002b). Both REM and slow wave sleep have been implicated in the consolidation of procedural or skill based memory, such as motor learning (Fischer et al., 2002; Smith & MacNeill, 1994; Walker et al., 2003a; Walker et al., 2002b). Relationships between stage two sleep and motor learning has also been observed (Nishida & Walker, 2007; Smith & MacNeill, 1994; Walker et al., 2002a).
Several studies have demonstrated that a daytime nap may also enhance memory consolidation (Atienza, Mednick, Cantero, Nakayama, & Stickgold, 2001; Cote, Milner, Baxter, Ray, & Osip, 2001; M Hayashi & Hori, 1998; Mitsuo Hayashi, Ito, & Hori, 1999; Hofer-Tinguely et al., 2005; Milner, Fogel, & Cote, 2006). In particular, it has been shown that short periods of day time sleep have enhanced motor skills (Backhaus & Junghanns, 2006; Mednick, Nakayama, & Stickgold, 2003; Milner et al., 2006; Nishida & Walker, 2007) and declarative learning (Tucker et al., 2006).

**Mechanisms Behind Sleep Dependent Consolidation**

Research has shown that sleep facilitates memory consolidation due to plasticity mechanisms which are triggered during sleep. "Sleep per se enables mechanisms of cortical plasticity [and] could be part of a more global process of memory consolidation [which has a] potentially crucial link in our understanding of how long-term memories are encoded in the brain" (Hoffman & McNaughton, 2002).

The behavioural changes associated with sleep dependent learning, including enhancement and improving retention have been attributed to key cellular events during stage 2, SWS and REM sleep. The consistently observed relationship between stage two sleep and motor learning (Fogel, Smith, & Cote, 2007; Nishida & Walker, 2007; Smith & MacNeill, 1994; Walker et al., 2002a) may be explained by the presence of spindles. Increased spindle density has been associated with motor learning (Fogel et al., 2007; Nishida & Walker, 2007). The slow oscillatory process of stages 3 and 4 sleep have also been implicated in brain plasticity and learning. Huber & Ghilardi (2004) found that slow wave activity during sleep was more pronounced in those same brain regions activated during motor skill learning during wake. It was theorised that sleep reflected local synaptic changes triggered by motor learning involving a specific brain region. Other studies have shown that waking brain activity expressed during a motor task was also replayed during REM (Maquet et al., 2000; Peigneux et al., 2003).
The evidence presented above strongly suggests that sleep may be a critical modulator for memory consolidation. With regard to motor learning in particular, the research has great implications for skill learning professions such as musicians, performance in sport, refining surgical skills and speech articulation (Kuriyama et al., 2004; Walker et al., 2002a). Furthermore, several authors have concluded that sleep may benefit neurorehabilitation for recovering stroke patients with motor damage (Gomez Beldarrain, Astorgano, Gonzalez, & Garcia-Monco, 2008; Kuriyama et al., 2004; Robertson & Cohen, 2006; Siengsukon & Boyd, 2009b; Walker et al., 2003a).

### 1.3.3 Maintaining Quality of Life

Quality of life is a term used to describe the subjective and multidimensional concept of physical, psychological and social wellbeing, particularly regarding vulnerable groups receiving medical care (Cella, 1994). Assessment of sleep is an important component of general medical care and quality of life (Strine & Chapman, 2005). A large population study of 12 million people found that those who suffered from poor sleep also had poorer quality of life (Strine & Chapman, 2005). Furthermore, those with clinical sleep disorders also report poor quality of life (Flemons & Tsai, 1997; Totterdell, Reynolds, Parkinson, & Briner, 1994). Such associations occur because poor sleep has adverse physiological effects, associated with poorer health and interacts with long term chronic conditions.

**Physiological Impact of Sleep Loss**

Sleep loss alters hormone and immune function which affects the body’s ability to fight disease (Bryant, Trinder, & Curtis, 2004; Moldofsky, 1995). Sleep deprivation further increases vulnerability to viral and bacterial pathogens (Benca & Quintas, 1997). It has also been shown that sleep deprivation lowers the immunity response to vaccinations (Spiegel, Leproult, & Van Cauter, 1999). Research has shown that sleep deprivation adversely impacts cardiac function by increasing in blood pressure and key inflammatory markers of cardiac disease (Carrington & Trinder, 2008; Meier-
Ewert et al., 2004). This evidence may explain why poor sleep is associated with an increased risk of cardiovascular disease including stroke (American Academy of Sleep Medicine, 1999; Ayas, Pittman, MacDonald, & White, 2003; Ayas et al., 2003; Bradley & Floras, 2009; Drager et al., 2009; Portela et al., 2009; Spiggs et al., 1992b; Yaggi et al., 2005). Other studies have shown that partial sleep restriction severely alters metabolic processes required to synthesise carbohydrate (Spiegel et al., 1999). It was postulated that maintained impairment of carbohydrate synthesis as a result of chronic sleep loss may increase risk of diabetes, obesity and hypertension (Spiegel et al., 1999).

**Ill Health Risk and Development**

The incurred physiological alterations as a result of sleep loss may increase risk of chronic poor health and disease (Rogers, Szuba, Staab, Evans, & Dinges, 2001). Long term sleep disturbance presents a premorbid risk for somatic health decline (Ayas et al., 2003; Nijrolder et al., 2008; Wingard & Berkman, 1983). This may be due to the adverse effects of sleep deprivation on the immune system and ability to fight disease (Benca & Quintas, 1997; Bryant et al., 2004; Moldofsky, 1995).

It is well established that sleep loss has a profound effect on psychological health (Ayas et al., 2003; Nijrolder et al., 2008; Wingard & Berkman, 1983). Laboratory based sleep deprivation studies have consistently shown decrements in mood (Dinges et al., 1997; Franzen, Siegle et al., 2008; Pilcher & Huffcatt, 1996). Large population studies revealed a strong link between sleep disturbances and poorer psychological health (Manocchia, Keller, & Ware, 2001; Reid et al., 2006; Strine & Chapman, 2005). This relationship is further confirmed by evidence which suggests that consistently good sleep may actually prevent the development of a psychological illness (Ford & Kamerow, 1989; Steptoe, O'Donnell, Marmot, & Wardle, 2008). Poorer psychological functioning as a result of sleep loss is typically due to increased sleepiness and fatigue (Breslau, Roth, Rosenthal, & Andreski, 1997). Moreover, anxiety and depression are associated with difficulty getting to sleep and maintain sleep (Morin, Rodrigue, & Ivers, 2003).
Long Term Health Conditions

Normal sleep patterns are commonly altered in those suffering from chronic disease. Illnesses such as cancer, diabetes, heart disease, arthritis, osteoporosis, lung disease, infections, breathing disorders, gastroesophageal reflux, chronic pain, renal disease are associated with sleep disturbance (Foley et al., 2004; Goldsmith & Levin, 1993; Kapur et al., 2002; Katz & McHorney, 1998; Parish, 2009; Pressman et al., 2000). Furthermore, increased prevalence of sleep problems have been observed in a range of neurological conditions including Parkinson’s, multiple sclerosis, epilepsy, migraine, traumatic brain injury and stroke (Benca, Obermeyer, Thisted, & Gillin, 1992; Pressman et al., 2000). Chronic psychiatric illness is also associated with co-morbid sleep disorders (Benca et al., 1992; Ohayon, 2005). Either as a result of poor sleep or the disease per se, daytime functioning is disrupted by the presence of sleepiness, fatigue and increased napping behaviour (Briones et al., 1996; Muller et al., 2006; Parish, 2009). Dysfunctional sleep and daytime functioning may be a result of the symptoms of the disease however may also arise from medication side effects (Legros & Bazil, 2003; Novak & Shapiro, 1997; Obermeyer & Benca, 1996) and change in sleeping environment (Dogan et al., 2005; Southwell & Wistow, 1995). A large population study revealed that patients with co-morbid sleeping problems utilised more health care services than those without sleep problems (Manocchia et al., 2001).

Sleep has a reciprocal relationship with health. Poor sleep patterns during the course of illness may contribute to the worsening of symptoms and unnecessarily prolong the disease if left untreated (Briones et al., 1996). Furthermore, increased sleep and daytime functioning problems interact with treatment interventions including musculoskeletal rehabilitation (Hyypä & Kronholm, 1995) and post brain injury neurorehabilitation (Barker-Collo et al., 2007; Morley et al., 2005; Muller et al., 2006; Worthington & Melia, 2006).
The evidence presented above demonstrates that sleep is highly influential on health. Poor sleep is associated with the development of a range of conditions, including cardiovascular, as well as exacerbating symptoms present within an existing condition. Furthermore, prioritising healthy sleep may be of benefit for management and treatment of chronic conditions, including stroke. It is therefore necessary to specifically examine the role of sleep for stroke recovery and rehabilitation programmes.

1.4 The Role of Sleep For Post Stroke Recovery and Rehabilitation

There is strong theoretical reason to predict that sleep has a critical role for post stroke recovery and rehabilitation programmes for several reasons: 1) there is evidence to suggest that the consequences of stroke are partly modulated by sleep (Figure 1.5), 2) sleep supports brain plasticity, a vital process for functional recovery, 3) sleep disturbance is associated with poorer stroke outcome, 4) poor daytime functioning affects rehabilitation participation which may indirectly affect treatment outcome.

1.5.1 Stroke Consequences Modulated By Sleep

The consequences of stroke are largely somatic, psychological, behavioural, cognitive and motor movement related. Evidence shows that sleep is a likely mediator of these aspects of the stroke sequelae (Figure 1.10). The modulatory processes of sleep for stroke symptoms may also be bidirectional, i.e. sleep may impact the consequences of stroke and vice versa (Figure 1.10). However, the majority of evidence that shows the role of sleep for these factors stems from non-stroke populations (as described in Section 1.3). Some studies have begun to explore this idea in stroke patient
populations however the evidence base is still relatively sparse and requires further investigation.

Figure 1.10. The consequences of stroke are displayed. Evidence suggests that these same consequences are modulated by sleep as well as being influenced by poor sleep.

*Somatic*

The range of post stroke somatic complications, including seizures, infections, mobility deficits and pain (Langhorne et al., 2000), may further comprise sleep (Bassetti & Aldrich, 2001; Gamble et al., 2000; Kong et al., 2004; Krachman, D'Alonzo, & Criner, 1995; Widar et al., 2004). In addition, prescribed medications pose sedating or hypnotic side effects and also alter the sleep EEG (Bourne & Mills, 2004; Holshoe, 2009; Lowson & Sawh, 1999; Mayers & Baldwin, 2005; Novak &
Shapiro, 1997; Obermeyer & Benca, 1996). Pain and cardiac complications after stroke are particularly relevant to sleep.

Stroke is associated with long term pain (Gamble et al., 2000; Kong et al., 2004; Widar et al., 2004). Post stroke pain is associated with disturbed sleep as well as increased fatigue (Widar et al., 2004). Evidence further suggests that sleep disturbances may exacerbate acute and chronic pain in a reciprocal manner (Lautenbacher et al., 2006). Therefore it is important to address sleep as treating sleep problems may help alleviate post stroke pain (Smith & Hawthornewaite, 2003).

Cardiac problems are a common somatic effect of stroke as well as a premorbid risk (American Heart Association, 2001). Poor sleep is associated with poorer cardiac health (American Academy of Sleep Medicine, 1999; Ayas et al., 2003). Although post stroke cardiac problems are typically controlled using medication, sleep loss may be detrimental to cardiac function after stroke. However, this notion has not yet been investigated. It may be important to minimise sleep loss in order to maintain cardiac health as post-stroke cardiac disease increases risk of further strokes (Hankey, 2003). This association may also occur as initial evidence suggests that sleep modulates blood pressure and essential protein regulation for maintaining cardiac health (Carrington & Trinder, 2008; Meier-Ewert et al., 2004).

**Psychological**

The debilitating effects of stroke require dramatic lifestyle alterations which pose a major strain on psychological adjustment (Brittain, 2002; Strine & Chapman, 2005; Zorowitz et al., 2005). Patients who experience poor psychological health may experience disturbed sleep and increased sleepiness and fatigue (Bassetti & Valko, 2006; Leegaard, 1983; Schepers et al., 2006; Staub & Bogousslavsky, 2001). Treating sleep disorders may promote psychological health and well being in stroke patients. Although this has not been demonstrated in a stroke sample at present, there is ample research in non-brain injured persons which shows that sleep treatment also improves mental health including anxiety and depression (Menza, Marin, & Opper, 2003;
Thase, 2006; Uhde, Cortese, & Venediapin, 2009). Given that the relationship between sleep and psychological disturbance is reciprocal (Ellis, Hampson, & Cropley, 2007; Jansson & Linton, 2006; Steptoe et al., 2008), alleviating the psychological stresses of patients may be of benefit to for sleep (Khan, 2004).

**Behavioural and Cognitive**

Increased sleepiness, fatigue and daytime napping are commonly experienced deficits of daytime functioning after stroke (Bassetti & Valko, 2006). In stroke patients, poor daytime functioning is associated with worse cognitive performance (Leegaard, 1983; Van Zandvoort et al., 1998), less active participation in neurorehabilitation (Barker-Collo et al., 2007; Morley et al., 2005; Muller et al., 2006; Worthington & Melia, 2006), increased risk of accidents (Lundqvist, Alinder, & Ronnberg, 2008; Michael, Allen, & Macko, 2006; Sagberg, 2006) and contributes to poorer overall quality of life (Ingles et al., 1999; LaChapelle & Finlayson, 1998; Naess, Waje-Andreassen, Thomassen, Nyland, & Myhr, 2006b; Schuiling et al., 2005; Van Zandvoort et al., 1998). Sleep is a key modulator of daytime functioning therefore improving sleep may help resolve daytime functioning difficulties in stroke patients (Worthington & Melia, 2006). Those who sleep well, however, still experience excessive daytime sleepiness or fatigue and may require additional forms of treatment such as stimulant medication (Black, Duntley, Bogan, & O'Malley, 2007; Schneerson, 2005; Bassetti, 2005a). Furthermore, addressing depression may particularly be of benefit for sleepiness and fatigue.

Increased sleepiness adversely affects cognitive performance in non-brain injured participants (Pilcher & Huffcutt, 1996; Samkoff & Jacques, 1991). Although laboratory based sleep deprivation studies have not been carried out in stroke patients samples, poor quality sleep and sleepiness in this cohort has known affects on cognitive functioning, particularly attention capacity and (Hermann et al., 2008; Van Zandvoort et al., 1998). Moreover, such cognitive deficits negatively impact rehabilitation participation and outcome (Galski et al., 1993; Sandra Zinn et al., 2004).
Motor

Motor neurorehabilitation is an essential component to stroke treatment and management to promote independence of patients with motor deficits (Laidler, 2000, p.83). There is strong evidence that sleep may be a modulator for motor learning (Walker et al., 2002a; Walker, Stickgold, Alsop, Gaab, & Schlaug, 2005). This evidence has led several authors to postulate that sleep has a crucial role in motor recovery after brain damage (Gomez Beldarrain, Astorgano, Gonzalez, & Garcia-Monco, 2008; Kuriyama et al., 2004; Robertson & Cohen, 2006; Siensukon & Boyd, 2009; Walker et al., 2003a).

The only known research that has explored sleep and motor learning in chronic stroke patients is the work of Seingsukon and Boyd (Siensukon & Boyd, 2008a, 2009a; Siensukon & Boyd, 2008b). Their research involved laboratory based motor learning in patients and retesting one group after a period of sleep and one group after the same amount of time awake. Patients who slept between learning and retesting demonstrated greatest improvement. The authors of these studies concluded that sleep has important implications for motor neurorehabilitation protocols. However, this postulation requires further investigation.

1.4.2 Sleep and Recovery Outcome After Stroke

Given that sleep is related to a range of post stroke consequences, presumably poorer sleep is related to poorer recovery after stroke. Several studies have investigated this potential relationship by measuring sleep and stroke outcome in patients. Stroke outcome is assessed in terms of survival or general disability levels. Other studies have used validated tests that measure general level of functioning, including activities of daily living, motor ability and level of independence, such as the Barthel Index (Mahoney & Barthel, 1965) or Rankin Scale (Bonita & Beaglehole, 1988).
**Stroke Outcome Studies**

Evidence shows that sleep is related to stroke outcome during the acute (<6 months) and chronic (>12 months) phase of recovery. Acute patients with poor sleep quality, a sleep disorder or abnormal circadian rhythm were associated with increased mortality (Dyken, Somers, Yamada, Ren, & Zimmerman, 1996; Hachinski, Mamelak, & Morris, 1987) and worse recovery outcome (Claudio Bassetti, Aldrich, & Quint, 1997; Bassetti & Aldrich, 2001; Good, Henkle, Gelber, Welsh, & Verhulst, 1996; Hachinski et al., 1987; Kaneko, Hajek, Zivanovic, Raboud, & Bradley, 2003b; Leppävuori, Pohjasvaara, Vataja, Kaste, & Erkinjuntti, 2002; Sandberg, Franklin, Bucht, sta, & Gustafson, 2001; Spriggs et al., 1992a; Takekawa, Miyamoto, Miyamoto, & Hirata, 2007). Furthermore, Hachinski et al., (1987) found that the relationship between sleep and recovery were independent of age and lesion location. A study of closed head injury patients revealed that for every unit of improvement in the functional independence measure, patients had a 4% decrease of risk of having disturbed sleep (Makley et al., 2008). Those with sleep apnoea spent longer in hospital after the stroke event (Kaneko et al., 2003b). Valente et al. (2002) reported that the presence of organised sleep patterns rather than the Glasgow Coma Scale was more predictive of better outcome, in terms of survival and functional recovery, in those with sub-acute coma after brain injury (classed as severe brain injury including stroke and TBI). It was concluded that sleep patterns may be a prognostic marker for recovery Sleep disturbance during the acute phase was also predictive of poorer long term outcome of stroke in the chronic phase (Good et al., 1996; Hermann et al., 2008; Vock et al., 2002). Chronic patients with poor sleep and daytime functioning also exhibited poorer recovery level (Cadilhac et al., 2005; Worthington & Melia, 2006).

As the above studies show that sleep is related to general stroke recovery, it is plausible to suggest that sleep may also be specifically related to neurorehabilitation outcome and have implications for treatment protocols. Neurorehabilitation aims to facilitate recovery level after stroke and increase motor movement and control.
1.4.3 The Implication of Sleep For Post Stroke Neurorehabilitation Protocols

Several authors have addressed sleep in brain injured patients, including stroke and TBI, and commented on the crucial implications sleep may hold for rehabilitative treatment (Cohen, Oksenberg, Snir, Stern, & Groswasser, 1992; Masel et al., 2001; Parcell, Ponsford, Rajaratnam, & Redman, 2006; Terzoudi et al., 2009; Uomoto, 2008). However, at present, this idea remains severely under researched. Several studies have monitored sleep and daytime functioning behaviour during rehabilitation. It was found that sleep disturbance and increased daytime sleepiness hampered rehabilitation sessions and affected day to day functioning of patients (Barker-Collo et al., 2007; Morley et al., 2005; Muller et al., 2006; Worthington & Melia, 2006). Surprisingly, these studies did not measure rehabilitation outcome. Only one known study has measure sleep in a rehabilitation context and addressed outcome at the same time. Alessi et al. (2008) monitored a large sample of older patients (≥65 years) with a range of conditions (10% of which experienced stroke, the majority had orthopaedic problems) admitted to a post acute rehabilitation facility. They found that increased napping was associated with poorer rehabilitation outcome across all patients. However the above studies did not control for amount and type of rehabilitation patients received.

Based on the evidence presented above, further research examining sleep behaviour in a rehabilitation context is necessary. More specifically, such research should refine sample selection, including the recruitment of stroke only samples, and utilise carefully controlled conditions to help identify possible causal relationships and therapeutic interventions (Terzoudi et al., 2009).

1.4.4 Necessity For Research

Sleep disturbance and poor daytime functioning is highly prevalent after stroke however is not always recognised by medical staff or the patients themselves
(Bassetti & Valko, 2006; Castriotta & Lai, 2001; Castriotta et al., 2007; Makley et al., 2008; Parcell et al., 2006; Wessendorf, Teschler, Wang, Konietzko, & Thilmann, 2000). Although The National Stroke Association (based in USA) recently published patient guidelines regarding the importance of healthy sleep during recovery and rehabilitation (National Stroke Association, 2006), there is little applied clinical research in the context of sleep and stroke rehabilitation to establish a scientific link. The National Clinical Guidelines For Stroke (2nd Ed, 2004; UK based) does not list sleep disturbance treatment or management of healthy sleep within the guidelines. This lack of knowledge and awareness may cause unnecessary suffering of sleep disorders of which may be treatable. Furthermore, it is possible that the initial disturbance of the sleep/wake cycle by the stroke (e.g. coma) develops into a chronic sleep problem if left untreated.

Based on the evidence presented in this chapter, it is hypothesised that sleep may be a modifiable aspect of behaviour that may benefit stroke recovery and rehabilitation, and benefit general well being and quality of life. Therefore maintaining healthy sleep after stroke might be critical. One potential avenue is devising a 24 hour approach to rehabilitation whereby behaviour wake and sleep are equally considered as part of the treatment process.

It is essential to further investigate sleep in the context of stroke for several important reasons: 1) sleep disturbance is highly prevalent after stroke, 2) sleep is largely ignored as part of the post stroke treatment process, and 3) sleep may be a crucial modulator of recovery and rehabilitation outcome. Therefore a paradigm shift is necessary to increase awareness and improve quality of life of patients.
1.5 Putting Theory Into Applied Clinical Practice: Development of Research Aims For This Thesis

Evidence from non-stroke populations presents a strong theoretical argument in that sleep may have critical role within the post stroke sequelae, including quality of life of patients and rehabilitative treatment. It is the prerogative of this thesis to build upon the limited evidence within brain injured cohorts that has suggested a relationship between sleep and stroke recovery and rehabilitation. In order to form a substantial evidence base from which further research can continue, there is a need to resolve the apparent limitations in previous studies, design an appropriate protocol that employs a highly controlled rehabilitation model. The research for this thesis was carried out within the framework of a motor neurorehabilitation trial, more specifically, Constraint Induced Movement Therapy (CIT). The CIT trial framework allowed the limitations from previous work to be addressed and further explore sleep in chronic stroke patients with residual motor deficits. Within the CIT framework, four individual studies were carried out to address sleep in chronic stroke patients with hemiparesis.

1.5.1 Limitations In Previous Studies

The existing literature on stroke and sleep presents several limitations which are yet to be addressed. Firstly, the majority of studies focus on acute stroke ranging from one day to six months after the event. The chronic evolution of sleep behaviour for long term stroke recovery remains poorly studied. Critically, time since injury is a modulating factor of physical and psychological recovery after stroke (Sullivan, 2007). Stroke presents a complex multitude of consequences which develop, change or evolve over time, such as psychological adjustment and motor functioning (Donnan et al., 1991; Duncan, 1997; Horgan et al., 2009; Jorgensen et al., 1995; Lesniak et al., 2008; Rasquin et al., 2005). For some patients, sleep problems may
resolve as time since injured increases (Hermann et al., 2008; Vock et al., 2002). Should these factors remain uncontrolled or in an unstable state, the sample is vulnerable to extraneous factors on results, for example uncontrolled co-morbid conditions. Therefore, chronicity is an important variable that should be controlled. Some studies do not take time since stroke into account and recruit a broad range of chronicities from several weeks to years within the same sample.

Although previous studies suggest that sleep is related to stroke recovery, the term 'recovery' or 'stroke outcome' is poorly defined in these studies. Moreover, medical and rehabilitative treatment may vary between patients, therefore 'residual recovery' (independent of treatment) and 'treatment induced recovery' (facilitated by treatment) cannot be distinguished. Furthermore, studies measuring stroke recovery utilise a general measure of recovery, e.g. Barthel Index. These measures may overlook particular deficits (Ashford, Slade, Malaprade, & Turner-Stokes, 2008; Duncan, 1997; Lai, Studenski, Duncan, & Perera, 2002; Van Zandvoort et al., 1998) such feature of motor recovery including upper limb speed and quality. With regard to the potential role that sleep may holds for motor learning, it would be advantageous to incorporate measures which conceptualise the spectrum of residual motor ability, e.g. The Wolf Motor Function Test.

1.5.2 Addressing Limitations in Previous Studies

The studies carried out for this thesis aimed to address the limitations. The studies were designed around a highly controlled rehabilitation trial, time point of recovery was beyond one year and patients were carefully selected based on their physical and psychological adjustment.

*The Model Neurorehabilitation Context: Constraint Induction Movement Therapy (CIT)*
For this thesis, research was completed within the context a CIT clinical trial. CIT is a form of treatment for stroke patients that specifically targets upper limb hemiparesis. This intervention comprises a strong motor learning component as patients re-learn how to use the affected upper limb through of the affected arm shaping combined with restriction of the non-affected arm, therefore, increasing affected arm use. In addition, motor learning is incorporated as part of intense training of the affected arm using real world based tasks (Taub et al., 1994). CIT sessions are disturbed equally per day across two weeks and administered in carefully controlled conditions. CIT is designed to capitalise on the adaptive capacity of the brain and promotes plasticity after brain injury.

Evidence shows that CIT facilitates motor learning determined by behavioural outcome measures (Taub et al., 1993; Taub, Ramey, DeLuca, & Echols, 2004; Taub & Uswatte, 2003; Taub, Uswatte, & Pidikiti, 1999; van der Lee, 2003; Wolf et al., 2006). Importantly, CIT has also facilitates neuroplastic changes within those brain regions required to prepare and execute movement (Kim, Park, Ko, Jang, & Lee, 2004; Liepert, Bauder, Miltner, Taub, & Weiller, 2000). If sleep indeed facilitates motor learning (Kuriyama et al., 2004; Walker et al., 2002a; Walker et al., 2005), sleep may be a vital process in demanding learning situations such as CIT.

CIT has shown lasting benefits beyond one year after treatment (Taub et al., 1993; Taub et al., 2006) however there is a need for further studies to develop advanced treatment protocols in order to maximise CIT success. One potential avenue is developing a 24 hour approach to CIT whereby improved outcome may be further facilitated by offline learning processes, i.e. sleep. No known studies have exclusively examined sleep within a motor neurorehabilitation context such as CIT, however several authors have stressed a need for applied clinical research of this nature (Hyypä & Kronholm, 1995; Makley et al., 2008; Masel et al., 2001; Siengsukon & Boyd, 2009b; Terzoudi et al., 2009). Such research will have implications for rehabilitation protocols as promotion of healthy sleep after brain injury, i.e. a 24 hour approach to rehabilitation might be crucial for improving service provisions.
Patients

The sampling method employed by the CIT trial utilized a highly selective inclusion/exclusion criteria. Firstly, patients were selected at least one year after stroke. This chronicity length is considered a sufficient time from which patients are stable with regard to their physical and psychological recovery (Donnan et al., 1991; Duncan et al., 1992; Horgan et al., 2009; Jorgensen et al., 1995; Lesniak et al., 2008; Rasquin et al., 2005). Secondly, patients with uncontrolled co-morbid conditions, including psychological were excluded. Finally patients were selected based on a narrow range of motor ability. These criteria formed a more homogenous group in comparison to existing studies in the sleep and stroke literature. By employing this selection criteria, patients are more likely to be in stable state with regard to their recovery. The results are then more representative of normalised stroke rather than the unstable trajectory of symptoms during the acute phase.

Methods of Assessment

The research for this thesis also aimed to address these poorly studied aspects of post stroke sleep behaviour in the chronic phase of injury. Firstly, both subjective and objective measures were used. This included a comprehensive battery of questionnaires and actigraphy. Actigraphy in particular has not yet been largely incorporated into studies regarding post stroke sleep. This method provides a favourable alternative to PSG, particularly when observing sleep in brain injured patients for several reasons: 1) there is little disruption to sleep, i.e. no electrode placement, 2) recordings can be completed at home, 3) recordings can continue for several weeks, 4) recently developed waterproof actiwatches do not need to be removed. Secondly, sleep was monitored over a longer period, i.e. longer than one week, to ensure adequate capture of normal sleep behaviour.

Furthermore, the current research aimed to specifically measure motor recovery after stroke, rather than general stroke outcome as used in the majority of sleep and stroke studies. For example, The Wolf Motor Function Test was employed as a fine grained
motor assessment. This test not only scores upper limb motor ability but also measures reaction time in carefully controlled laboratory conditions. Furthermore, this test is useful for evaluating motor neurorehabilitation outcome.

1.5.3 Thesis Aims and Major Research Questions

This thesis comprises four main studies presented in Chapters 3 to 6. The general methodological approach is described in detail in Chapter 2 and the reader is directed to the appropriate sections of this Chapter for specific methods regarding each study.

The research for this thesis aimed to characterise sleep and daytime functioning behaviour, address the relationship between sleep and residual motor recovery, and the potential link between sleep and CIT outcome in a group of chronic stroke patients with hemiparesis. This involved the collection of habitual sleep data, long term subjective sleep diaries, actigraphy and high density waking EEG recordings in those patients volunteering for the current CIT trial.

It is the aim of the following four studies presented in Chapters 3 to 6 to answer these main research questions:

1) How does a chronic stroke population sleep and function during the day in comparison non-brain injured persons from a subjective point of view?

2) How do chronic stroke patients sleep as determined by objective methods?

3) Can chronic stroke patients accurately perceive their own sleep behaviour and daytime functioning levels?

4) Is sleep and daytime functioning related to levels of residual motor recovery after stroke?
5) How does sleep and daytime functioning change during a motor neurorehabilitation programme and is it related to treatment outcome?

**Conclusion to Chapter 1**

- More and more people are surviving stroke and living with the consequences. Stroke is associated with a range of somatic, behavioural, cognitive, psychological and motor deficits, including poor sleep and daytime functioning. Current treatment provisions for patients are unsatisfactory. Further research is required to explore new ways to improve stroke support. One potential area is that of sleep.

- Damage to mechanisms responsible for sleep and waking results in an instability in the sleep wake cycle, therefore it is not surprising that sleep problems are common after stroke. For some patients, this evolves into a sleep disorder. Sleep is responsible for a variety of functions including maintaining health, daytime functioning cognitive performance, important for the well being of stroke patients. Furthermore, sleep may be a critical modulator for motor learning with important repercussions for motor neurorehabilitation after stroke.

- There is evidence to suggest that sleep is related to stroke outcome however this notion is poorly studied in chronic patients. Moreover, there is research which points towards a potential relationship between sleep and motor neurorehabilitation after stroke. No know study has investigated this notion, therefore it is the aim of the present thesis to contribute to the sleep and stroke literature by researching this potential link.
This thesis is unique in comparison to previous studies as each study emphasises three important factors when exploring the research aims. These factors are chronicity, level of recovery and a controlled setting. Moreover, this research specifically focused on upper limb motor ability in a group of chronic stroke patients with hemiparesis. No known research has examined sleep in this context. Such research has important implications for patients, their carers, clinicians, other researchers and the overall development of care systems for post stroke management.
CHAPTER 2
Method Overview of All Studies

Chapter 2 Overview

This chapter describes the research methods used for each of the four studies carried out for this thesis, including the design, sample of participants, materials, procedure and analysis techniques. Data for all studies was collected from an opportunity sample of patients with chronic hemiparesis who attended screening and/or participated in a neurorehabilitation trial.

Using the described methodology, the following four studies were carried out to investigate sleep behaviour in these patients: 1) Characterising perceived sleep and daytime functioning in chronic stroke patients 2) Prospective investigation of longitudinal sleep behaviour and correlates of residual motor recovery, 3) EEG-derived biomarkers for daytime sleepiness in patients with chronic stroke, and, 4) The role of sleep and daytime functioning in neurorehabilitation. Each of these studies are presented in Chapters 3 to 6 respectively. Specific design and analysis techniques for each study will be described within the corresponding results chapter.

2.1 Design

The research carried out for this thesis was designed to be fully integrated within the framework of a five year clinical trial entitled: "Clinical benefits and neural correlates of Constraint-Induced Movement Therapy (CIT): An investigation using behavioural outcome measures, functional magnetic resonance imaging and event
related brain potentials” which commenced in January 2004. The trial specifically investigated modified protocols of CIT in stroke patients with chronic upper limb hemiparesis. These modifications included reducing the traditional CIT session length from 6 hours of therapy per day to 1.5 and 3 hours with or without constraining the non-affected arm, and introducing a constraint only group with no therapy sessions. CIT participants were randomised into one of four groups: a) 1.5 hours of CIT with constraint, b) 1.5 hours of CIT without constraint, c) 3 hours with constraint and d) 3 hours without constraint. Those patients who demonstrated high functioning upper limb motor ability by exceeding the maximum motor movement criteria formed group e) ‘Home CIT’ group. This group did not attend laboratory CIT sessions however wore a constraint on the non-affected limb at home. The research design for this thesis was subsequently implemented within the CIT trial in October 2005. Ethical approval was granted in December 2006 and data collection began in January 2007.

Laboratory observations suggested that sleep and daytime functioning problems were frequent complications of stroke patients enrolled onto the CIT trial. Furthermore, the emerging evidence in the literature postulates that sleep may have a critical role in motor recovery after stroke provided good theoretical reason to research sleep in stroke patients. Following these notions, an investigation of sleep in patients enrolled onto the CIT trial was carried out. Crucial to the current research, patients involved in the CIT trial provided an opportunity sample for exploratory sleep and daytime functioning research on: 1) patients with chronic hemiparesis and 2) patients undergoing neurorehabilitation.

The research methods used for the present studies were partly determined by the fundamental design parameters specified in the CIT protocol. The CIT trial utilises a randomised baseline controlled repeated measures design. The trial consists of three phases: baseline (2 weeks), CIT (2 weeks) and post (2 weeks). Motor ability testing and questionnaire based assessments were carried out at three test points: baseline (T1), pre-CIT (T2) and post CIT (T3). From this framework, the protocol for each of
the four studies was introduced which subsequently yielded four individual data sets within the trial presented in Chapters 3 to 6 (Figure 2.1). Control samples were implemented for the current study only, and not the CIT trial. The specific experimental design and participant grouping for each data set is described below.

Figure 2.1. The CIT trial framework and the data capture sections for studies 1 to 4 conducted for this thesis. Full completion of the CIT trial involved screening, three test points, an EEG and long term sleep monitoring during baseline, CIT and Post CIT phases. The same patient may appear in one of more of the four studies.

2.1.1 Study 1 (Presented in Chapter 3): Characterising perceived sleep and daytime functioning in chronic stroke patients.

Study 1 Research Aims
Study 1 was a cross sectional investigation which aimed to examine post stroke sleep and daytime functioning in comparison to pre-morbid behaviour. The data collected in patients was also compared to that of healthy populations and published norms. The relationship between sleep, psychological functioning and perceived health of stroke patients was also examined.
Experimental Design

A between groups design was implemented to compare habitual subjective sleep and daytime functioning in patients and a matched group of non-brain injured healthy controls. In addition, the results collated for this study was compared with data published in other studies using chronic stroke patients and that of other control groups using varying sampling methods.

Data Collection

Subjective habitual sleep data for this study comprised the results of a battery of nocturnal sleep and daytime functioning questionnaires. To further address psychological and health related variables upon sleep behaviour, questionnaires regarding psychological disturbance and perceived health were also administered.

Sample

Study 1 included all stroke patients invited to the laboratory to attend a screening session for CIT participation. This group included those who were subsequently invited to participate in the CIT trial, those who did not meet the CIT inclusion requirements and those who decided to withdraw from the CIT programme. Healthy non-brain injured control participants were recruited from the general population. They completed the same sleep questionnaires as patients. Published results for comparison with results of the current study were drawn from other chronic stroke cohorts. Published control samples used for comparison included those of good health and no sleep disorders, and large population studies where sleep disorders and health were not part of the inclusion/exclusion criteria.

2.1.2 Study 2 (Presented in Chapter 4): Prospective investigation of longitudinal sleep behaviour and correlates of residual motor recovery.

Study 2 Research Aim)
Following the subjective sleep data collected in Study 1, this study collected objective data in patients. Study 2 had three main aims. The first aim was, to assess the agreement between subjective sleep perception and actigraphy. Secondly, this study intended to describe prospective longitudinal sleep behaviour using subjective and objective parameters. Thirdly, this study aimed to assess the relationship between sleep behaviour and residual upper limb motor recovery after stroke.

**Experimental Design**

Prospective sleep data was collected over two weeks during the baseline phase for study 2 in stroke patients. A within groups design was implemented for these data whereby matched indices drawn from subjective and objective sleep reports were compared. Subjective parameters additionally included daytime functioning measures which were tested for an association with nocturnal measures. This study also investigated the relationship between sleep behaviour parameters and residual motor recovery, independent of CIT as assessed during the pre-CIT (T2) test point.

**Data Collection**

Subjective sleep monitoring data was collected using a sleep diary which comprised nocturnal and diurnal sleep parameters as well as daytime functioning scales. Objective sleep and daytime activity was measured by actigraphy. Residual motor functioning was assessed by a battery of upper limb ability tests.

**Sample**

The data capture for this study included all patients randomised into groups a) to e) recruited to undergo CIT intervention who completed a sleep diary and continued 24 hour actigraphy monitoring for the baseline phase. This group included those that attended test points T1 and T2 (Figure 2.1).
2.1.3 Study 3 (presented in Chapter 5): EEG-derived biomarkers for daytime sleepiness in patients with chronic stroke

**Study 3 Research Aim**

Study 2 investigated objective sleep whereas study 3 focused on objective daytime functioning. The aim of this study was to use EEG as an indicator of sleepiness in patients and controls. The main research question was to determine if patients could perceive their current level of arousal as depicted in the EEG.

**Experimental Design**

An EEG protocol was carried out in stroke patients prior to the CIT trial at T2. In between groups comparison of the EEG data was applied to stroke patients and controls. A within groups comparison was also applied to examine hemispheric differences in the EEG. Furthermore, the EEG was used as physiological indication of sleepiness levels which was addressed in the context of a motor preparation and execution task. A within subject, repeated measures design, pre and post of the motor task, was implemented to assess changes in subjective sleepiness state and objective sleepiness as indicated by the EEG in both stroke patients and controls. Additionally, within groups correlation analyses were carried out to examine the relationship between subjective and objective sleepiness in stroke patients and controls.

**Data Collection**

Frequency composition of the EEG provided a marker of objective sleepiness and a sleepiness state questionnaire was employed to measure this subjectively.

**Sample**

Study 3 comprised those patients from groups a) to e) who had an EEG recording prior to CIT therapy and healthy non-brain injured controls, matched for age and gender, drawn from the general population.
2.1.4 Study 4 (presented in Chapter 6): The role of sleep and daytime functioning in neurorehabilitation

Study 4 Research Aim
The previous studies aimed to provide an in depth assessment of sleep and daytime functioning in chronic stroke patients and how this relates to psychological health, quality of life and residual motor recovery. The final study aimed to examine to what extent sleep and daytime functioning has a role in neurorehabilitation. Study 4 aimed to explore the role of sleep and daytime functioning in those patients undergoing CIT. This study focused on the effects that different sessions length of CIT had on sleep. Furthermore, the relationship between sleep and CIT outcome was examined.

Experimental Design
Twenty-four hour subjective and objective monitoring of sleep and daytime functioning were recorded throughout baseline, CIT and post phases for a total of six weeks forming a repeated measures design. The relationship between sleep, daytime functioning behaviour, activity and CIT outcome were examined.

Data Collection
Sleep and daytime functioning was measured using sleep diaries and actigraphy. CIT outcome was assessed by the level of change between T2 and T3 on upper limb motor ability tests.

Sample
This sample involved only those who completed the laboratory based CIT, groups a) to d). This particular sample was highly selective as it comprises a very specific cohort of ability and all participants attended CIT in a controlled setting of either 1.5 or 3 hours of CIT per day.
2.2 Participants

The thesis reports data from stroke patient and control cohorts: 1) those who have experienced a stroke (Stroke Patient Sample) and 2) non brain-injured matched controls (Control Sample). A case table for all participants involved in this thesis, including both stroke patients and controls, is provided in Appendix C. The selection criteria employed for recruitment of these two cohorts is specified below.

2.2.1 Stroke Patient Sample

Recruitment

The stroke patient cohort comprised an opportunity sample of community dwelling persons with chronic upper limb hemiparesis, recruited directly from the CIT trial. Advertisements for volunteers were posted in local GP practices, National Health Service (NHS) clinics, newspapers and relevant websites. The advert specified that volunteers must be between 18-75 and have experienced hemiparesis for at least a year as a consequence of stroke. Critically, this recruitment strategy resulted in a positive selection of highly motivated patients.

Eighty-two potentially suitable participants for the CIT trial were telescreened, 61 of these volunteers were invited for laboratory screening (Figure 2.2). Within the study period, 61 participants that were screened and agreed to participate in the sleep related research for this thesis. Specific participant numbers for studies 1 to 4 including details of exclusions, are described in the relevant result chapters.
**Inclusion/Exclusion Criteria**

Volunteers of the CIT trial were subjected to strict inclusion/exclusion criteria outlined by the CIT protocol:

*Inclusion Criteria*

1) Hemiparesis$^2$ >12 months after insult.

2) Minimum of 5 degrees wrist extension and 10 degrees finger extension against gravity in the affected limb.

4) Maximum of 20 degrees wrist and 10 degrees finger extension against gravity in the affected limb.

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$^2$ The majority of patients experienced contralateral hemiparesis as result of unilateral stroke. Two patients experienced bilateral strokes therefore presented both ipsilateral and contralateral hemiparesis. These patients were only included in Study One.
5) Generally fit to attend the study schedule.
6) GP approval.

*Exclusion Criteria*

6) Serious co-morbid conditions.
7) Uncontrolled psychological disturbance.
8) Cognitive difficulties (<20 Mini Mental State Exam\(^3\), Folstein & Folstein, 1975, described in more detail under ‘Materials’).
9) Insufficient ability to understand instructions.
10) Seizure event within the past six months.
11) Balance difficulties.
12) Uncorrected visual impairment.
13) Motor Activity Log score > 2.5 on each item (described in more detail under ‘Materials’).

### 2.2.2 Control Sample

**Recruitment**

All control samples used in this study comprised non-brain injured healthy participants drawn from the general population. Control participants were recruited via flyers and poster advertisements in local community services.

**Inclusion/Exclusion Criteria**

In order to gain a relatively healthy, representative sample of the general population, the only exclusion criteria employed was absence of brain injury, a diagnosed sleep disorder, excessive daytime sleepiness, participants must be in generally good health. Importantly, the control cohort was not selective for sleep problems.

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\(^3\) Patients who experienced expressive aphasia completed the 3-step command on the MSE only.
2.2.3 Ethical Approval

The CIT trial, including the EEG recordings, received ethical approval from The Thames Valley Multi-centre Research Ethics Committee. As the addition of sleep related research was implemented after the CIT trial commenced, a separate ethics application was submitted and approved by the Surrey Research Ethics Committee (NHS) specifically for sleep questionnaires (stroke patients and controls), sleep diaries and actigraphy data collection (stroke patients). The University of Surrey Research Ethics Committee approved all protocols for stroke patients and EEG protocols for control participants. Experimental procedures adhered to The Declaration of Helsinki (World Medical Association, 2000). All participants gave their informed consent prior to participation in this study. The ethically approved information sheets give to participants prior to the study and consent forms are provided in Appendix A1 to A4.

2.3 Measures and Assessments

The section describes the assessments and equipment used for data collection employed in studies 1 to 4. This includes those materials used at each stage of the protocol including telescreening, laboratory screening, motor testing, sleep assessment, sleep monitoring and the EEG recording protocol.

2.3.1 Telescreening (stroke patients only)

Interested volunteers, or family members on their behalf, were asked a brief set of questions to avoid the inconvenience of attending laboratory screening for those likely to be excluded. The requested information during telescreening included: age
of potential volunteer, date of brain injury, current living situation, cognitive and language difficulties, visual impairment, secondary conditions, current rehabilitation, level of health care assistance required and ability to cope with a challenging situation. In addition, physical impairment details were asked such as: level of hemiparesis details including severity and ability to carry out tasks using the affected limb, mobility and balance control.

2.3.2 Laboratory Screening

The purpose of the laboratory screening assessment was to examine eligibility of potential CIT volunteers. This procedure also provided an opportunity to collect habitual sleep data on a large group of stroke patients regardless of CIT participation.

General Screening Form

The general screening form was designed to collate information from stroke patients regarding medical history, motor ability assessment, rehabilitation history and living situation. An example of this form is provided in Appendix B1.

Patients were asked to describe to the best of their knowledge, the details of their stroke experience including: date, circumstance, type of injury (e.g. bleed, blood clot), location of lesion, side of body affected by hemiparesis and possible cause of stroke. Should the patient have experienced multiple strokes, these details were also reported. Patients were asked to report the presence of secondary conditions as a result of the stroke, as well as current medication and levels of pain or discomfort. In some cases patients, nor their families, could provide all these details. GP approval was provided for all stroke patients recruited for the CIT trial.

The minimal and maximum motor criterion was assessed by examining the patient’s ability to perform the following motor tasks: lifting the wrist and returning to resting position, raising each digit, bending and straightening the elbow and lifting the
shoulder. Patients were also asked to report the degree to which spasm influences their affected limb use. Additionally, general use of the affected limb outside the laboratory was measured using a tool developed for the measurement of real world rehabilitation outcome, known as the Motor Activity Log (MAL; Taub et al., 1993; Taub et al., 1993). A detailed description of the MAL is provided in section 2.3.3. This assessment formed part of the exclusion criteria to excluded those patients who were too high functioning in terms of their real world motor activity in the home environment.

Information regarding previous and current rehabilitation treatment was collected including type, amount and provider, e.g. UK NHS. Patients were also asked to describe their current goals for prospective rehabilitation and what they hope to achieve as a result of CIT treatment. Current living situation, marital status, previous and current employment position was also requested on this form.

**Cognitive Functioning and Education**

Cognitive functioning was assessed using the Mini-Mental State Exam (MMS) (Folstein & Folstein, 1975) which was used to indicate the presence of cognitive impairment. This test was implemented as part of the exclusion criteria as those with cognitive problems may struggle with the demands of the CIT trial. The assessment involved asking a series of questions to assess orientation, immediate and short-term memory, attention, calculation, language and spatial awareness (See Appendix B2). A summed score between 25 and 30 (maximum) is considered normal. Patients with expressive language difficulties were considered for CIT as understanding of instructions may remain intact (Grodzinsky, 2000). Aphasic patients were therefore asked to complete the 3-step item on the MMS only. This item required patients to follow a 3-step command, “place the index finger of your non-affected hand on your nose, and then on your left ear”. Failure to complete this item resulted in exclusion for CIT participation. This method has been used in previous studies requiring cognitive demand from stroke patients (Siengsukon & Boyd, 2008a, 2009a; Siengsukon & Boyd, 2008b). Validity and reliability of the MMS is well established.
in population based studies (Crum, Anthony, Bassett, & Folstein, 1993) as well as sensitivity to moderate and severe cognitive impairment (Tombaugh & McIntyre, 1992). It is a recommended tool for indicating cognitive status for screening purposes, rather than diagnosis, in those with neurological disease (Appelros, 2005; Dick et al., 1984).

Patients were also asked to report their highest educational degree and to complete the National Adult Reading Test (NART; Nelson, 1982) to allow assessment of pre-morbid IQ. The NART requires participants to read aloud 50 words of irregular grapheme-phoneme correspondence within increasing difficulty. From the number of incorrect pronunciations, IQ score was estimated based on population norms. The NART was not applied to those with expressive aphasia. It is important to note that this test did not form part of the inclusion/exclusion criteria for the CIT trial.

_Sleep Questionnaires_

Sleep questionnaires were also carried out during laboratory screening. Controls also completed the same questionnaires. All assessments asked participants to report how they have felt/behaved during the past month. A description of the each questionnaire within sleep interview is described below:

**In House Sleep Questionnaire.** The validated scales were complemented by an in house questionnaire to obtain further information. The in house questionnaire comprised a series of fixed and open ended questions regarding sleep medication history, caffeine, alcohol and nicotine intake, and description of any night time disturbances other than their own sleep, e.g. traffic noise. In order to document specific sleep behaviour changes as a result of stroke, an adjusted version (Version 1a; See Appendix B3) of the in house questionnaire was applied to the stroke patient sample only. Patients were asked to report the nature of their pre-morbid habitual sleep and daytime functioning behaviour. Most critically, the questionnaire asked for post-morbid changes during the acute (1 month) and chronic phase (>1 year). The version for control participants (Version 1b: See Appendix B4) included
demographical questions, such as age, gender, height, weight and highest degree, as they did not complete the screening protocol carried out by the patient group.

The Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989) is a widely used screening tool (See Appendix B4) chosen to classify subjective levels of sleep quality. The PSQI contains 19 items which require a factual response, e.g. time of day, or a rating using four-point Likert scale ranging from 0 to 3. From these items, seven component scores, ranging from 0 to 3, are generated: subjective sleep quality (1 item), sleep latency (2 items), sleep duration (1 item), habitual sleep efficiency (3 items), sleep disturbance (9 items), use of sleep medication (1 item), and daytime dysfunction (2 items). The summation of all component scores, termed the PSQI global score (GPSQI), indicates overall level of sleep quality. GPSQI scores range from 0 (good sleeper) to 21 (poor sleeper) where a score >5 is applied as the cut off criterion to classify poor quality sleep (Buysse et al., 1989). In addition, PSQI items 1-4 provide informative habitual sleep parameters including bed time (24 hour clock), get up time (24 hour clock), time in bed (mins), sleep duration (mins) and sleep onset latency (mins).

The PSQI has shown high validity and reliability in a number of studies including healthy individuals, those with sleep disorders and elderly samples (Backhaus, Junghanns, Broocks, Riemann, & Hohagen, 2002; Carpenter & Andrykowski, 1998; Gentili, Weiner, Kuchibhatla, & Edinger, 1995). However one study reported an inconsistency between poor quality sleep as reported on the PSQI an objective measures of sleep (Buysse et al., 2008). For this reason, it must be noted that the PSQI is not suitable for clinical diagnosis of a sleep disorder, however is a useful screening tool for sleep abnormalities with potentially clinical significance (Buysse et al., 2008). The PSQI has also been widely used in chronically brain injured cohorts including stroke (Fictenberg, Putnam, Mann, Zafonte, & Millard, 2001; Mahmood, Rapport, Hanks, & Fictenberg, 2004; Masel et al., 2001).
The Sleep-50 (S50; Spoormaker, Verbeek, van den Bout, & Klip, 2005) is a relatively new sleep disorder screening tool. The S50 utilises DSM-IV criteria to screen for clinically significant sleep disorders and was incorporated in this study as an additional measure to assess the presence of likely sleep disorder cases. This questionnaire comprises 50 items from which participants rate on a four-point Likert scale from 1 (not at all) to 4 (very much), how often they experience symptoms of a sleep disorder (See Appendix B6). Varying numbers of items are summed for each of the 12 sleep disorder categories and the following cut off criteria is applied: sleep apnoea (>14 on 8 items), insomnia (>18 on 8 items), affective disorder (>11 on items 10, 11, 43 and 44 out of 4), sleep state misperception (>18 insomnia category and estimated amount of hours slept >4), narcolepsy (>6 on 5 items), restless legs syndrome/periodic leg movements (>6 on 4 items), circadian rhythm disorder (>7 on 3 items), sleep walking (>6 on 3 items) and nightmares (>2 on item 32 and >8 on items 33-35). Overall, a sleep disorder is likely if participants score above the cut-off criteria within a category and score >14 within the ‘impact of sleep complaints upon daily functioning’ category. If participants do not obtain scores above the criteria for any of the above sleep disorders, however a score >14 is obtained within the ‘impact of sleep complaints upon daily functioning’ category (7 items), hypersomnia is classified. A ‘factors influencing sleep’ category is also included in the S50 however this is for reference purposes only and does not employ cut-off criterion.

Reliability and validity of the S50 has only been tested in one study by the developers of the instrument (Spoormaker et al., 2005). High internal consistency and good test-retest reliability was found in healthy and sleep disordered samples (Spoormaker et al., 2005). The S50 is a recommended screening tool as it holds predictive validity for sleep apnea, insomnia, restless legs syndrome and periodic leg movement disorder and mild preliminary predictions for sleep state misinterpretation, narcolepsy, sleep walking and hypersomnia. It must be noted that the S50 has not yet been fully validated in brain injured populations. Use of this form of assessment for the current study provided an opportunity to test the usefulness of the S50 in stroke patients and matched controls.
The **Ford Insomnia Response to Stress Test** (FIRST; Drake, Richardson, & Roehrs, 2004) is designed to measure predisposed vulnerability to insomnia precipitated by environmental and psychological stressors (See Appendix B7). This questionnaire was developed in accordance with research revealed that pre-sleep cognitive and physical arousal has greater impact upon those with insomnia compared to controls (Bonnet & Arand, 1995; Perlis, Giles, Mendelson, Bootzin, & Wyatt, 1997; Vgontzas et al., 2001). Therefore items within this questionnaire aimed to identify typically precipitating factors which influence subsequent sleep (Speilman, Caruso, & Glovinsky, 1987). This type of assessment was chosen for this study to distinguish those with sleep disturbance as a result of likely psychological origins. The FIRST contains nine hypothetical situations that are emotionally stressful from which participants rate on a four-point Likert scale, how likely their sleep may be disrupted should they encounter this situation. Possible ratings range from 1 (not likely) to 4 (very likely). Scores for each item are summed together to give one overall score. The FIRST does not currently provide a cut-off criterion score. To determine high and low scores, a median score split has previously been used (Drake et al., 2004; Fornal-Pawlowska, Skalski, & Szelenberger, 2007). Initial evidence has suggested that high scores on the FIRST was associated with longer sleep latency and poorer sleep efficiency and greater hyperarousal as determined by objective methods, and poor mood (Fornal-Pawlowska et al., 2007). This data has highlighted that the FIRST may be useful for detecting persons who are vulnerable to stress related sleep disturbance. However, the long term reliability of this assessment in relation to chronic sleep problems remain unknown (Fornal-Pawlowska et al., 2007). The FIRST, like the S-50, is also a recently devised scale and has not yet been widely used in brain injured or other clinical populations.

The **Epworth Sleepiness Scale** (ESS; Johns, 1991) is a widely used questionnaire designed to assess daytime sleep propensity. The ESS was employed to identify individuals with high levels of daytime sleepiness. It is important to note that the ESS measures habitual sleepiness rather than current state sleepiness which is typically
assessed by the Karolinska Sleepiness Scale (discussed in section 2.3.4). The ESS comprises eight hypothetical situations (See Appendix B8). Participants are asked to rate how likely they would fall asleep if placed in those situations during the day using a four-point Likert scale ranging from 0 (no chance of dozing) to 3 (high chance of dozing). These eight items are summed to give an overall score to indicate the degree of general sleep propensity during the day. Scores between 0-6 indicate low sleepiness, 7-9 is average and 10-24 indicate severe sleepiness with potential clinical implications.

Previous studies have shown that the ESS is a valid and reliable measure of daytime sleepiness (Ronald D. Chervin, Aldrich, Pickett, & Christian Guilleminault, 1997; Johns, 1991, 1992). Moreover, strong correlations with ESS and objective sleepiness have been demonstrated in sleep disordered and healthy participants (Johns, 1991). It has also been widely used in clinical samples (Kumru, Santamaria, & Belcher, 2004), including those with sleep disorders and daytime functioning difficulties (Violani et al., 2003), those with psychiatric conditions (Lundt, 2005), chronic brain injured patients (Bassetti & Aldrich, 1999; Cadilhac et al., 2005; Fictenberg et al., 2001; Masel et al., 2001; Parcell et al., 2006; Vock et al., 2002). Although the ESS provides important information regarding levels of daytime sleepiness, it is important to note that it is a subjective measure and should be used in conjunction with objective measures for diagnostic purposes of disorders of excessive sleepiness (Miletin & Hanly, 2003).

The Fatigue Severity Scale (FSS; Krupp, LaRocca, Muir-Nash, & Steinberg, 1989) was used for this thesis to measure fatigue, independent to the dimension of sleepiness. For the purposes of this study, fatigue is defined as physical or mental weariness as a result of excursion. In contrast, sleepiness refers to the likelihood of falling asleep during the day. The FSS is one of the most commonly used questionnaires to measure general fatigue (Dittner, Wessely, & Brown, 2004). It is specifically designed to assess the degree to which post-morbid fatigue impacts daily life. Due to the lack of the operationalisation of fatigue between studies measuring
fatigue (Hossain et al., 2005), additional information was given to participants of this study to ensure clarification of fatigue (See Appendix B9). The FSS comprises nine statements relating to the impact of fatigue on daily living from which participants rate on a seven-point Likert scale how much they agree or disagree, from 0 (disagree) to 7 (agree) that the statement applies to them (See Appendix A.7). Summed item scores form an overall score from which a cut off criterion of >35 indicates high levels of fatigue (Flachenecker et al., 2002). In addition, the mean score across all items can also be used where an average score >4 suggests a moderate to high impact of fatigue (Mathiowetz, Matuska, & Murphy, 2001).

The FSS has been widely used in a range of clinical populations, showing high reliability and validity (Kleinman et al., 2000; Merkies, Schmitz, Samijn, van der Meche, & van Doorn, 1999; Taylor, Jason, & Torres, 2000). It has also been used in chronic brain injuries samples (Choi-Kwon et al., 2005; Michael et al., 2006; Naess et al., 2005; Schepers et al., 2006) and demonstrated high internal consistency and reliability within these cohorts (Valko et al., 2008). The FSS is also considered a useful tool for distinguishing fatigue as a result of brain injury compared to control participants (LaChapelle & Finlayson, 1998).

2.3.3 CIT Test Point Assessments

The following tests were employed to assess ‘residual motor recovery’ (pre CIT; assessed during T1 and T2) and ‘CIT induced motor recovery’, otherwise known as ‘CIT outcome’, (post CIT; assessed during T3) in terms of motor ability in the affected upper limb. In addition to the quality of life assessments were incorporated to assess subjective perception of health and psychological functions. All assessments carefully selected to be sensitive to CIT related change.

Quality of Life Questionnaires
The Medical Outcome Study Short Form 36 (SF-36; Ware & Sherbourne, 1992) was used to assess perception of physical and mental health status. Participants were asked to rate the current status of their health in comparison with a year ago and the past 4 weeks (See Appendix B.10). Thirty-six items contribute to eight individual dimension scores: physical functioning, physical role limitations, bodily pain, vitality, social functioning, emotional role limitations, mental health and general health (See Appendix A.8). Items 1, 2, 4a-d, 5a-c, 6-8, 9a-i, 10, 11a-d are scored using a five-point Likert scale, and items 3a-3j are scored on a three-point Likert scale. A score of 1 corresponds to poorer health on all items however a reversed Likert-scale is used for items 7, 1, 6, 8, 9a, 9d, 9e, 9h, 11b and 11d. For the purpose of this study, individual item scores were transformed to a scale of 0 (poor health) to 100 (good health) using the following algorithm:

\[
\text{Transformed Score} = \left[\frac{(\text{Actual raw score} - \text{lowest possible raw score})}{\text{Possible raw score range}}\right] \times 100
\]

Transformed item values for each of the 36 items were assigned to one of the eight domains to which they contribute and then subsequently averaged to give a single score per domain. Overall physical (5 domains) and mental health (5 domains) dimensions can be calculated, where vitality and general health domains contributed to both dimensions (Kalantar-Zadeh, Kopple, Block, & Humphreys, 2001). The average of all eight domains forms an overall health score. Transformed scores between 0-50 suggests below average and 51-100 indicates above average health.

The SF-36 is a well known and widely used assessment for health across several scientific disciplines and in clinical practice. It has shown sensitivity to health changes in large population studies (Garratt, Ruta, Abdalla, & Russell, 1994; Hemingway, Stafford, Stansfeld, Shipley, & Marmot, 1997), and has high reliability and validity in healthy (Jenkinson, Wright, & Coulter, 1994), and clinical samples (Fajlde & Ramos, 2000; Ruta, Abdalla, Garratt, Coutts, & Russell, 1994), including...
chronic stroke (Anderson, Laubscher, & Burns, 1996; Buck, Jacoby, Massey, & Ford, 2000; Schuiling et al., 2005).

The Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983). The HADS was developed as a screening tool to indicate possible cases of depression and generalized anxiety in clinical populations. It was employed in this study to highlight the presence of psychological disturbance, i.e. anxiety and depression, present in stroke patients and controls. This instrument was also used to examine the impact of CIT on psychological functioning. As the questionnaire refers to feelings experienced in the past week, it is sensitive to changing mood states rather than enduring traits, therefore can be re-administered over short time intervals (Snaith, 2003). The HADS (See Appendix B 11) is a self-report questionnaire containing 14 items contributing to two subscales, anxiety (seven items) and depression (seven items). Participants rate the extent to which each item is a problem using a four-point Likert scale, ranging from 0 to 3, where a lower score corresponds to increased anxiety or depression. Scores for each subscale are summed, ranging between 0 and 21. Scores >10 are suggestive of a clinically significant condition whereas scores between 8-10 are considered borderline.

It is important to note that the HADS is a screening tool and should not be used for diagnostic purposes (Snaith, 2003). The HADS has demonstrated high validity and reliability (Bjelland, Dahl, Haug, & Neckelmann, 2002; Flint & Rifat, 2002; Stafford, Berk, & Jackson, 2007), also in a variety of clinical populations, including chronic stroke (Johnston, Pollard, & Hennessey, 2000; O'Rourke, MacHale, Signorini, & Dennis, 1998).

Affected Upper Limb Motor Testing

The Wolf Motor Function Test (WMFT; Wolf, Lecraw, Barton, & Jann, 1989) was employed as a laboratory based motor assessment, specifically designed for CIT motor outcome. The test evaluates the affected upper limb in terms of reaction time and functional ability through a series of 13 tasks based on standardised gross and
dexterous motor movements (See Appendix B12 and B13). Such tasks include lifting the arm and hand onto the table, extending the elbow to a 28cm distance (with and without 1.35kg weight), lifting arm and hand onto a box, lifting several objects, turning on a light switch, placing cotton wool into a pot and lifting a basket containing a 1.35kg weight onto a higher table. Tasks are arranged in order of complexity. Time to complete each task is recorded in seconds and rated for quality on a 8-point functional ability scale from 0 (unable to perform task) to 7 (same as before stroke). In instances where the patient cannot perform a task, the task is aborted and a maximum reaction time of 120 seconds and functional ability score of 0 is recorded (See Appendix B13).

Research has shown that the WMFT has high inter-rater reliability, internal consistency, test-retest reliability, construct validity, criterion validity, has preference over other forms of assessments and is sensitive to changes over time (Morris, Uswatte, Crago, Cook, & Taub, 2001; Wolf et al., 2001). This assessment has also shown good discrimination between high and low functioning patients (Wolf et al., 2005). The WMFT has also been consistently used in CIT research protocols (Dettmers et al., 2005; Morris, Crago, DeLuca, Pidikity, & Taub, 1997; Sterr et al., 2002b; Taub et al., 1993; Wolf et al., 2006).

The Motor Activity Log (MAL; Taub et al., 1993) is designed to measure subjective affected limb use in their home environment. The MAL utilises semi-structured interview format to assess the amount and quality of affected limb functional use (with reference to pre-stroke levels) based on 12 activities of daily living, including eating, dressing and washing (See Appendix B14 and B15). Amount of use scores range from 0 (no use of affected arm) to 5 (always use affected arm). Quality of use scores range from 0 (unable to complete task using affected arm) to 5 (able to use affected arm as well as the non-affected arm). Half points may be applied if the participant feels it best fits their functioning.
The MAL is a reliable and valid instrument for assessing real world arm use (Uswatte, Taub, Morris, Vignolo, & McCulloch, 2005; van der Lee, Beckerman, Knol, de Vet, & Bouter, 2004). The MAL has demonstrated particular sensitivity to changes post CIT intervention, and at follow-up, in both acute and in chronic stroke patients with various levels of motor ability (Bonifer, Anderson, & Arciniegas, 2005; Dettmers et al., 2005; Liepert, Bauder, Miltner et al., 2000; Miltner, Bauder, Sommer, Dettmers, & Taub, 1999; Stephen J. Page, Levine, Leonard, Szaflarski, & Kissela, 2008; Rijntjes et al., 2005; Taub et al., 1993; Wolf et al., 2008). The MAL is a widely used assessment paired with other objective assessments of motor function in research and rehabilitation outcome studies (Ashford et al., 2008).

2.3.4 Long Term Sleep Monitoring (CIT participants only)

Sleep and daytime functioning behaviour was monitored every 24 hours for six weeks during the CIT trial using the following methods:

Subjective Sleep Diary

An in house daily sleep diary was designed to yield sleep indices typically used for subjective sleep assessment. The sleep diary (See Appendix B16) contained questions regarding the patient’s perception of the previous night’s sleep including sleep quality and refreshment using visual analogue scales (0-100mm). The following parameters were also requested: bed time (24 hour clock), get up time (24 hour clock), wake time (24 hour clock), time in bed (mins), sleep onset latency (mins), sleep duration (mins), sleep efficiency\(^4\) (%) and frequency and duration (mins) of night awakenings. In addition, the sleep diaries incorporated daytime sleep measures including nap frequency and length (mins).

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\(^4\) Sleep efficiency determined by calculating the percentage of sleep duration per time in bed. This calculation was performed by the author of this thesis.
In addition, twice daily (morning and evening), Karolinska Sleepiness Scale (KSS) (Akerstedt & Gillberg, 1990) and Daily Fatigue Scale (D-FIS) (Fisk & Doble, 2002) were obtained. This KSS is a one-dimensional scale to assess state sleepiness at a particular time point rather than in general like the ESS. Current state sleepiness rated on a scale of 1 (very alert) to 9 (very sleepy). The KSS has provided good correlation with objective measures of alertness including EEG and vigilance tests (Kaida et al., 2006) and sleep deprivation paradigms (Akerstedt & Gillberg, 1990; Gillberg et al., 1994; Johannes van den Berg, Gregory Neely, Leif Nilsson, Anders Knutsson, & Ulf Landstrom, 2005). There is no known research which has used repeated KSS measures in chronically brain injured patients. The D-FIS measures the impact of fatigue on different areas of daytime functioning including cognitive, physical and psychosocial. The D-FIS is based on the Fatigue Impact Scale (FIS) (Fisk et al., 1994) from which this modified version has been specifically created to address daily fatigue rather than general fatigue like the FSS used in this study. Furthermore, it has been used to assess changes as a result of interventions within clinical trials (Prince, James, Holland, & Jones, 2000). The D-FIS comprises eight fatigue related problems from which participants rate the extent of this problem using a scale of 0 (no problem) to 4 (extreme problem). The overall score comprised the sum of all eight items as well independent scores which distinguished mental (D-FIS Mental) and physical (D-FIS Physical) fatigue. The D-FIS holds good validity, is useful for long term assessment and is related to other general health ratings (Fisk & Doble, 2002). The FIS is considered an accurate and valid measure of fatigue within a brain injured sample in comparison to controls (Ingles et al., 1999; La Chapelle & Finlayson, 1998) however the use of the modified D-FIS within brain injured samples has not yet been examined.

Sleep diaries are considered reliable for collecting data regarding sleep/wake patterns however this measure should be used with caution in participants with frequent fluctuations of daytime vigilance (Evans & Rogers, 1994; Rogers, Caruso, & Aldrich, 1993). Furthermore, the use of daily diaries in clinical cohorts gives rise to some concerns regarding compliance as long term monitoring may result in completing
several days of the diary towards the end of the experiment (Stone et al., 2002). Although this issue cannot be avoided, all patients in the current study were asked to bring back the diaries prior to each study phase for inspection and reminded of the importance of accurate responses per day. Albeit various concerns, sleep diaries are useful for documenting long term sleep and daytime behaviour as well as examining treatment progress (Douglass, Carskadon, & Houser, 1990). Several studies have successfully used the sleep diary method in brain injured cohorts (Campos et al., 2005; Fichtenberg et al., 2001; Parcell et al., 2006) which have demonstrated associations with objective measures (Baumann, Werth, Stocker, Ludwig, & Bassetti, 2007). Furthermore, pairing sleep diaries with other methods such as actigraphy is considered accurate in providing information concerning long term sleep behaviour (Lockley, Skene, & Arendt, 1999; Sadeh & Acebo, 2002).

**Actigraphy**

Twenty-four hour actigraphy was used to monitor sleep/wake behaviour, for up to six weeks, to determine daytime napping, activity levels and nocturnal sleep indices. Actigraphy was recorded via a watch-like device known as an ‘Actiwatch Mini ®’ (CamNtech Ltd., © 2009), worn on the non-affected wrist. The device detected all movement exceeding 0.05g, sampled at 32 Hz (3-11 Hz bandpass filtering) which stored data in 1 minute epochs. The final activity score was calculated using the algorithm

\[ A = 0.04E_2 + 0.20E_1 + E_0 + 0.20E_{r1} + 0.04E_{r2} \]

(A=final activity score, E=epoch). The data was downloaded onto a computer and analysed using Actiwatch Sleep Analysis Software (version 7.22, CamNtech Ltd, © 2009). A medium sensitivity algorithm was set for analysis, where an activity count ≥40 defined wake, and the software calculated nocturnal sleep parameters using sleep or wake epoch detection. Diurnal sleep behaviour was measured using the nap analysis function whereby <10 (medium sensitivity) activity counts per minute epoch defined sleep within a pre-defined napping period. The Actiwatch Mini ® model is waterproof, therefore did not need to be removed for the duration of the study.
It is important to highlight here that the algorithm used in the present study was developed for those with normal movement and specific algorithms have not yet been developed for hemiparetic patients. Sadeh, & Acebo (2002) advised that actigraphy should not be used in those with motor movement difficulties due to artefact however the authors did not report the degree to which increasing severity of motor handicaps affects actigraphy recordings. Laakso, Leinonen, Lindblom, Joutsiniemi, & Kaski (2004) compared actigraphy with PSG in those with a range of motor handicaps and concluded that the method was reliable in such a sample, apart from those with very severe handicaps. This is a common result found in healthy and clinical populations (Ancoli-Israel et al., 2003) regardless of motor ability. The actiwatches were worn on the non-affected wrist to reduce the possibility of movement artefact. Furthermore, other studies have successfully used actigraphy in acute and chronically brain injured populations with varying recovery levels (Baumann et al., 2007; Hermann et al., 2008; Muller et al., 2006; Schuiling et al., 2005; Takekawa et al., 2007; Takekawa, Miyamoto, Miyamoto, Yokota, & Hirata, 2002) and in those undergoing rehabilitation (Alessi et al., 2008) which has revealed important insights with regard to the natural sleep-wake cycle in these patients. The validity of the actigraphy method is discussed in more detail within chapter 4.

2.3.5 The EEG Protocol

The CIT trial employed a protocol involving EEG recordings that were carried out during a highly controlled motor priming task. The data collected during this protocol was used for the current study as a physiological biomarker for daytime sleepiness. EEG recording equipment and a description of the motor task is provided below.

**EEG**

Qualitative EEG (qEEG) allowed for both frequency and topographical analyses of the resting brain state in CIT and control participants.
The raw data for qEEG analysis was drawn from high density waking EEG recordings. Sixty-four Ag/AgCl electrodes were positioned and labelled according to the internationally standardised 10-10 system (Chatrian, Lettich, & Nelson, 1985) which divides the skull into proportional distances based on four prominent landmarks: dent of the nose (nasion), protrusion in the back of the head (inion), and preauricular points directly in front of each ear (Figure 2.3). To ensure accurate positioning, electrodes were slotted into predefined sites using the 'BrainCap', placed on the head.

Figure 2.3. Electrode positions are displayed, labelled according to underlying brain areas: FP for frontal pole, F for frontal, P for parietal, C for central, T for temporal, and O for occipital. Sites are numerically sequenced from midline, which is set as zero or Z, with odd numbers on the left hemisphere alternating with even numbers on the right.

Vertical (VEOG) and horizontal (HEOG) electrooculographic signals were recorded bipolarly using electrodes 1cm above and below the left eye and from the left and
right outer canthi, respectively. The ground electrode was placed on the forehead in order to record and subsequently remove external electrical noise from the raw trace. Electrode impedances were kept below 5kOhm. Electrodes were recorded against an average reference calculated by the amplifier hardware (QuickAmp amplifier). EEG and EOG signals were continuously recorded in DC mode using Brain Vision Recorder. The data was digitally filtered using 0.5 Hz low-pass and 30Hz high pass phase shift-free Butterworth filter as well as a 50Hz notch filter. Recordings were sampled and stored at 500Hz. Raw EEG data was transferred to Brain Vision Analyser software for offline frequency analysis (See Section 2.5.1). All hard/software for EEG recordings and analyses was provided by Brain Products GmbH ©. Further qEEG analyses is described in more detail within Chapter 5.

**Motor Preparation Task**

The motor task aimed to elicit motor preparation and execution related activity in response to stimuli on a computer screen (Figure 2.4; Neurobehavioural Systems Presentation Software). Pre-cue (preparatory) primes consisted of two directional arrows and response (execution) cues of a white semi-circle displayed on a black background (Figure 2.4).
Font size was controlled for all stimuli (1.15° wide by 0.92° tall). Stimuli were shown in the centre of the screen to prevent horizontal eye movements. Participants were asked to respond as quickly and accurately as possible by pressing the response pad using the left or right index finger. Responses provided two performance measures including reaction time (ms) and percent correct (correct responses to the pre-cue). These indices are especially useful as they are known to be sensitive to sleepiness in sleep deprived healthy persons (Miccoli, Versace, Koterle, & Cavallero, 2008; van den Berg, Neely, Nilsson, Knutsson, & Landstrom, 2005), non-sleep deprived healthy persons (Peiris, Jones, Davidson, & Bones, 2006), those with sleep disorders (Edinger, Means, Carney, & Krystal, 2008; Sforza, Haba-Rubio, De Bilbao, Rochat, & Ibanez, 2004) and brain injured patients (Castriotta et al., 2007; Gomez-Beldarrain, Astorgano, Gonzalez, & Garcia-Monco, 2008). To avoid levels of motor ability affecting performance levels on the motor task, only responses from the non-affected arm were used for analyses.
2.4 Procedure

2.4.1 Researcher Roles: The Clinical Neuroscience Research Team (CNRT)

The CIT trial was carried out by CNRT, headed by Professor Annette Sterr, and comprised one laboratory manager, one project manager, two post-doctoral researchers (fMRI research only) and one PhD student (author of this thesis). The PhD student acted as a supportive team member by sharing several responsibilities within the team, including recruitment, administering CIT to patients, motor testing, data entry, general administration and training new staff members. The author of this thesis was the sole researcher for all sleep and daytime functioning questionnaires, sleep diaries and actigraphy collected for this thesis. The waking EEGs were recorded with the assistance of the laboratory manager. All data analysis, including EEG data, was carried out by the author of this thesis.

2.4.2 Stroke Patients Procedure

Telescreening
Respondents of CIT trial advertisements were mailed a comprehensive information pack providing details of the trial. The information pack contained the sleep related research information sheet (for the current study) but did not contain the CIT trial information sheet as this was only presented to those who attended screening. Interested participants, or a close relative on their behalf, telephoned the laboratory to undergo the telescreening process as a brief screening procedure. Suitable participants for the CIT trial were then invited for laboratory screening.

Laboratory Screening
During laboratory screening, suitability for the CIT trial was assessed, using the methods described in Section 2.3.2 of this chapter, including general screening and motor ability assessment, cognitive functioning and education, and then the sleep questionnaires. Prior to the sleep questionnaires, consent regarding sleep related research was taken as all potential participants were sent the information sheet previously. Therefore, data collected during screening could be used with the participant’s permission regardless of participating in CIT trial. The in house sleep questionnaire was completed first, followed by the sleep validated scales, administered in the following order: PSQI, S-50, FIRST, ESS and FSS. Next, the CIT trial was explained to the participants and CIT trial information sheet was provided. Laboratory screening duration was approximately two hours. Successfully recruited CIT participants were provided with a study schedule to inform them in advance of all testing sessions and assessment phases.

**Baseline Test Point (T1)**
Firstly participants attended T1 where informed consent for the CIT trial was taken. During T1, patients complete the motor test battery, quality of life questionnaires and were provided with sleep monitoring materials.

**Quality of Life Questionnaires.** Participants were asked to complete the HADS and SF-36 in any order. All questionnaires took approximately 30 minutes to complete. Assistance was provided where necessary should the participants required any clarification regarding the questionnaires.

**Motor Movement Testing.** Standardised instructions were read to the patients for all motor movement assessments. Firstly, the WMFT was carried out. A standardised map was secured to the table to enable accurate positioning of the equipment required for each task. Chair and table positions for each item were recorded which is then used as a reference for repeated test points. Prior to each task, the patient was instructed not to begin these tasks until the researcher says ‘ready, set, go’. It is at this point where the timer is started and the patient performed the task. All tasks were
videotaped and performances were re-timed and scored for functional ability. Next, the MAL was carried out by giving the participant two rating sheets from which to select their response for each activity. Ratings were recorded during the test. The total time for the entire motor assessment battery was approximately 60 minutes depending on level of motor ability.

Sleep Monitoring. During this test point, patients were given sleep diary instructions. To ensure patients were clear in completing the sleep diary, they filled in an example page with the assistance of the researcher. Patients were also fitted with the actiwatches and given specific instructions to record in the sleep diary, any instances when the watches were removed.

Baseline Phase (Two weeks)
Patients completed part one of the sleep diary, relating to the previous night sleep and morning sleepiness/fatigue levels, 30 minutes after waking and part two, relating to evening sleepiness/fatigue, two hours before retiring to bed everyday for six consecutive weeks. Actiwatches were continuously worn for 24 hours a day. If the actiwatch was removed for any reason, participants were asked to report this in the sleep diary. No CIT was administered during the baseline phase.

Pre CIT Test Point (T2)
Patients returned to the laboratory, one to three days before the beginning of the CIT phase, to repeat the motor movement test battery and quality of life questionnaires as described in T1. In addition, patients’ completed the EEG protocol. The EEG was conducted in a recording booth (2.5 x 3.5m). Participants sat at a viewing distance of 50cm from a 19” computer screen which presented all experimental stimuli. After application of electrodes (approximately 45 minutes), participants were asked to rate their current sleepiness level using the KSS. The a clean (no task) EEG during wakefulness with eyes open was recorded whilst participants focused on a solid black circle (8mm in diameter) against a white screen for 2 minutes. After a short break,
motor task instructions were provided on screen as well as clarification by the researcher.

For the motor task, participants were presented with an empty white circle against a black screen (See Figure 2.4). Next a white pre-cue in the form of two arrows flashes in the centre. The pre-cue enabled participants to 'prepare' their next movement in accordance with the direction of the pre-cue. One of four pre-cues were presented: ‘<< prepare left’, ‘>> prepare right’, ‘< > prepare for either direction’ and ‘>< don’t respond’. Next, the actual cue was presented where one half of the circle becomes white from which the participant has to respond with a left or right button press, or no response. Once the response has been registered or the time window to respond has expired, feedback was provided. This was followed by a grey blank screen preceding the next trial.

Each pre-cue and corresponding cue were presented randomly 12 times which equates to 60 trials in one approximately four minute block. The response window was extended for those patients who had difficulty pressing the button. Cues are 100% predictive of actual cue. Participants responded to the actual cue (circle) by pressing the corresponding left or right button. The ideal button press is to use the index finger which is achievable for control and patient responses on their non-affected side. Some patients were able to press the button using the index finger of their affected limb, however lower functioning patients may use the palm of their hand, or fist. For some lower functioning patients, the button required to be pressed by the affected hand is attached to the table to stop the button from moving.

Firstly, a training session lasting two blocks was administered. During training participants were presented with a series of trials of each type in fixed order to familiarise themselves with the trial sequence. These training trials were repeated until participants gave six correct responses for each trial. Following training, electrodes were applied (45 minutes) and the main experimental session began comprising eight blocks. The motor task lasted approximately 45 minutes. Between
blocks the experiment was paused automatically and resumed by the participant when instructed.

Immediately following the motor task, a second KSS measure was recorded followed a second two minute resting EEG, following the same procedure as prior to the motor task. The duration for the pre-CIT (T2) test point was approximately two hours for motor testing, followed by a break, and two hours to carry out the EEG protocol. The order of motor testing session and EEG was counterbalanced to examine time of day effects in the EEG.

**CIT Phase (Two weeks)**

During the treatment period CIT was administered to groups a) to d). Within CIT sessions, patients practiced a range of motor tasks, similar to those carried out in everyday life, with the affected upper limb with the supervision and encouragement of the therapist. Training was given on a one-to-one basis. The shaping technique is used to elicit the desired movement from the affected limb by gradually increasing task difficulty. Tasks involved upper limb movements (e.g., using a spoon uses the elbow, wrist, and grip) and dexterous activities (e.g., concerning individual fingers), which are repetitively practiced using tangible feedback on task performance from the therapist. For those in the constraint condition (groups a and c), the unaffected arm was restrained using a forearm splint, worn for a target of 90% of waking hours. However the constraint was removed when safety may be compromised. Participants were also encouraged to employ their affected arm within functional tasks at home.

Patients attended 10 consecutive daily CIT sessions (excluding weekends) for 1.5 or 3 hours depending on group randomisation. Patients in the home CIT group (e) did not attend CIT sessions, however wore the constraint and were coached at home. During the CIT phase, patients continued to complete the sleep diary and wore the actiwatches as described for the Baseline Phase.
**POST CIT Test Point (T3)**

One to three days after the CIT phase, patients repeated the exact procedure described in T1.

**Post Phase (Two weeks)**

During the post phase, the patients continued the sleep diary and wore the actiwatches as described during for the Baseline Phase. At the end of the post phase, patients posted the final sleep diary and actiwatches using the pre-paid envelope provided. Patients were also asked to complete the debriefing interview by telephone or post at the end of this phase.

**2.4.3 Control Participants**

Control participants recruited to complete the habitual sleep interview and the HADS, did so by post or within the laboratory. Those recruited for an EEG recording followed the exact procedure undertaken by the stroke patients during T1. One EEG is recorded per control participant.

**2.5 Analyses**

This section describes the analyses theory and techniques used for QEEQ and general statistics throughout Studies 1 to 4. Specific analytical methods for the studies are described within the method section in each chapter.

**2.5.1 qEEG Analyses Theory**
**Frequency Analysis**

In order to perform qEEG analysis, this thesis used the Fast Fourier Transformation (FFT) to quantify the power within different EEG frequencies (Thakor & Tong, 2004). FFT is an algorithm used to transform EEG data from the time-domain (wave form) to frequency (stationary) domain by expanding the time signal into a sum of infinite waves. In other words, the FFT synthesises the moving wave forms into a single frequency spectrum at a single point in time. The output reflects the frequency content of the signal which allows examination the distribution of signal power over frequency. FFT gives estimation of power spectral density within one block of stationary data (Duhamel & Vetterli, 1990).

**Frequency Analysis Data Output and Presentation**

The “Power spectrum” of a signal refers to the amplitude of the Fourier transform (Figure 2.5). This is typically expressed as the ‘power (µV²)’ within a frequency bin (e.g. 1 Hz) or summed within a frequency band (e.g. alpha). As sampling rates, i.e. the amount of data points collected per second, vary per study, the power can be divided by the sampling rate to make the data more comparable between studies. This measure is termed ‘power density (µV²/Hz). Frequencies are typically summed into four frequency bands according to the Hz range: beta (13-30Hz), alpha (8-12Hz), theta (7-4Hz) and delta (1-3Hz). Normal wakefulness is characterised by dominance of a mixture of beta and alpha although the presence of some lower frequencies may also be observed (Figure 2.5). Increased power in the lower frequencies (<10 Hz) during wakefulness is indicative of an abnormality and is commonly manifested after brain injury (Finnigan et al., 2007; Lukashevich et al., 1999; Sainio et al., 1983).
Figure 2.5. Power spectra of a waking EEG. Data from a non-brain injured participant drawn from Chapter Five. Although the peak within the delta band (coloured as orange) indicates a presence of slower waves in the EEG, this is also suggestive of artefact in the recording, known as spectral leakage.

Additional analysis techniques were applied to reduced common limitations with respect to the resolution and leakage of noise that remains present in the EEG recording (Muthuswamy & Thakor, 1998). Spectral leakage (Figure 2.5) can be reduced by applying a tapering function known the ‘hanning window’ (Nuwer, 1988b) which was applied to all EEG data for this study. Application of the hanning window increases resolution by reducing the appearance of weak waves, i.e. those that are not meaningful, in the data.

For representational details, mapping techniques were employed by expressing the multi-electrode output in the form a topographical EEG map (Figure 2.6). This method enables visualisation of the distribution varying EEG outputs including power within a frequency band and statistical values. Topographical maps created within this thesis utilise an interpolation approach between electrodes in order to produce a
set of smooth gradients that are mapped over the surface of the scalp. This method encompasses all electrode positions and the intervening spaces between electrodes. Each pixel between electrodes is interpolated using an algorithm based on the spherical splines technique (Perrin, Pernier, Bertrand, & Echallier, 1989).

Figure 2.6. A topographical map of the power spectra within the beta range (13-30 Hz) of a healthy participant focusing on a spot on a screen (no task). The red indicates increased power of the beta waves in the frontal areas

2.5.2 Statistical Analyses

All statistical analyses for this thesis were performed using Statistical Package for the Social Sciences, version 15.0 for Windows (SPSS Inc., Chicago, USA). The result sections of studies 1 to 4 present data in frequencies, percentages for larger samples, mean, median, +/-1 standard deviation (+/-1 SD) or (+/-1 SE) where appropriate. All time of day related data is presented in 24 hour clock format. Alpha (p) was set to p≤0.05 for determining significance. The bonferroni correction was applied where appropriate.
Preliminary assumption testing was conducted to check for normality, linearity, univariate and multivariate outliers and homogeneity. Should any violations have occurred, alternative procedures were incorporated. In instances where the data were not normally distributed, non-parametric alternatives were applied. For the Mann-Whitney U Test, the Z approximation (corrected for ties in the data) statistic will be reported in place of the U value as the Z-score is recommended for samples sizes larger than 30 (Pallent, 2005, p.292). However, samples are lower than 30 for some analyses therefore the U value was reported. Abbreviations for other statistics are t values (t), F ratio (F), partial eta squared (n_p^2), degrees of freedom (df), unadjusted regression (R), R squared (R^2).

Specifically for the highly skewed data from EEG recordings, log transformations were applied to enable the application of parametric statistical tests. More specifically, the current investigation utilised a base 10 logarithmic transformation (Lg10). This approach is useful as it allows more robust statistical tests to be used. (Thatcher et al., 2001) and has been used in previous waking EEG studies (Lockley et al., 2006; Viola, James, Archer, & Dijk, 2008). The raw data is presented in table form as this is more meaningful when comparing with findings from other studies. Regression analyses were only performed for larger samples where N>50 (Tabachnick & Fidell, 2000, p.117). For purposes of comparison with published work, the magnitude of difference between the results studies was examined using the Cohen’s d statistic. The mean of one group (M_1) is subtracted from another (M_2) and divided by the standard deviation:

\[ d = \frac{M_1 - M_2}{SD} \]

The strength of the calculated effect sizes were interpreted based on the following: \( \geq 0.20 = \) small effect, \( \geq 0.50 \) and \( \leq 0.80 = \) medium effect and \( \geq 0.80 = \) large effect (Cohen, 1988).
Conclusion to Chapter 2

- The overall methodology for the research carried out for this thesis was designed within the framework of a neurorehabilitation trail investigating the efficacy of CIT.
- Four studies using chronic patients with upper limb hemiparesis were implemented in the current thesis research. Control participants were employed for Study 1 and 3.
- The studies collected data on a broad range of life style factors and aspects of the post stroke sequelae. This included demographical information, stroke details, co-morbid conditions, cognitive functioning, education, health, psychological adjustment, sleep, daytime functioning, and motor ability. This information was assessed or monitored using a range of subject questionnaires and semistructured interviews. Additionally, objective measures were implemented for longitudinal sleep monitoring, daytime sleepiness and upper limb motor ability.

Specific methodological details for Study 1 to 4 are described within the corresponding chapters.
CHAPTER 3

Study 1: Characterising Perceived Sleep and Daytime Functioning in Chronic Stroke Patients

Chapter 3 Overview

The aim of this study was to characterise perceived sleep and levels of daytime functioning chronic stroke patients with residual motor deficits. Sixty-one patients and 61 healthy non-brain injured controls drawn from the general population completed a battery of in house questionnaires and validated scales. Prevalence of sleep difficulties, sleepiness and fatigue were compared to published data from other chronic stroke cohorts and non-brain injured control samples. Furthermore, the relationship between sleep, psychological functioning and health was examined. The results have important implications for gaining a greater understanding of how self reported sleep behaviour of stroke patients compares with non-brain injured persons and the impact of sleep on the quality of life of patients.

3.1 Introduction

Chronic health conditions, including physical and psychological, are commonly associated with adverse alterations in normal sleep patterns (Foley et al., 2004; Katz & McHorney, 1998; Manocchia et al., 2001; Ohayon, 2005; Parish, 2009). As a result of poor sleep or the disease per se, chronically ill patients may experience increased sleepiness, fatigue and frequent napping (Kapur et al., 2002; Parish, 2009). Furthermore, poor sleep and disrupted daytime functioning contributes to poorer quality of life and may inhibit recovery (Briones et al., 1996; Hyypää & Kronholm,
1995; Manocchia et al., 2001). Despite this knowledge, sleep remains poorly studied in patients with chronic neurological conditions, more specifically stroke, associated with both physical and psychological consequences (Duncan et al., 1997). Although several studies have reported that stroke often manifests behavioural and neural alterations in sleep and daytime functioning, the long term evolution of perceived sleep and daytime functioning has not yet been characterised.

3.1.1 Post Stroke Sleep and Daytime Functioning Alterations

Prevalence of Nocturnal Sleep Problems
Sleep disturbances are experienced in 20-57% of stroke patients within the first six months of injury (acute), including difficulties getting to sleep, increased night awakenings, reduced sleep duration, reduced sleep efficiency and poor sleep/wake cycle based on objective reports (Bassetti & Aldrich, 1999; Bassetti & Aldrich, 2001; Giubilei et al., 1992; Gottselig, Bassetti, & Achermann, 2002; Hermann et al., 2008; Iranzo, Santamaria, Berenguer, Sanchez, & Chamorro, 2002; Müller et al., 2002; Santamaria et al., 2000; Siccoli & Bassetti, 2008; Takekawa et al., 2007; Takekawa et al., 2002; Terzoudi et al., 2009; Vock et al., 2002). These disturbances are also reflected subjectively (Leppävuori et al., 2002; Van Zandvoort et al., 1998) however less is known about perceived sleep behaviour in patients.

Critically, prevalence of clinically diagnosed sleep disorders is high in stroke patient populations. Insomnia occurs in approximately 37-68% of acute patients (Leppävuori et al., 2002; Palomaki et al., 2003). Sleep disordered breathing is highly common after stroke as reported prevalence ranges from 45 to 95% (Bassetti & Aldrich, 1999; Good et al., 1996; Iranzo et al., 2002; Parra et al., 2000; Rola et al., 2007; Wessendorf et al., 2000). Fifty-five to 72% of such patients are diagnosed with sleep apnoea (Broadley et al., 2007; Kaneko, Hajek, Zivanovic, Raboud, & Bradley, 2003a; Sandberg et al., 2001). Parasomnias have also been reported in acute stroke including
periodic leg movements and restless leg syndromes (Lee et al., 2009; Schuiling et al., 2005; Sechi et al., 2008) as well as frequent nightmares (Leppävuori et al., 2002).

Few studies have addressed long term sleep behaviour in chronic stroke, i.e. at least 12 months after injury. Of the existing small number of studies, it has been shown that persisting objective sleep disturbances exist in 34% of patients beyond one year (Schuiling et al., 2005). In addition, subjectively problematic sleep is reported in 34 to 67% of patients (Campos et al., 2005; Masel et al., 20015; Schuiling et al., 2005; Sterr et al., 2008). Carer observations have also confirmed the presence of post stroke sleep and daytime functioning disturbance (Worthington & Melia, 20066). Palomaki et al. (2003) reported that at 18 months post injury, 48% of patients fulfilled DSM-IV criteria for insomnia. Persisting sleep breathing problems have been reported in up to 81% of chronic stroke patients whereas 20% fulfilled diagnosis for sleep apnoea (Cadilhac et al., 2005). Parasomnias may also persist beyond one year in 16.9% of patients (Masel et al., 2001). For those studies that employed a control group, the reported prevalence rates of sleep disturbance were greater than in non-brain injured controls (Campos et al., 2005; Muller et al., 2006).

In addition to sleep behaviour changes, alterations in sleep architecture have been reported. These changes are characterised by an increase or reduction of a particular sleep stage in comparison to a normal sleep cycle. In acute stroke, increased stage 1 (Hermann et al., 2008; Korner et al., 1986), reduced stage 2 (Bassetti & Aldrich, 1999; Bassetti & Aldrich, 2001; Hachinski et al., 1987; Santamaria et al., 2000; Terzoudi et al., 2009) and reduced REM sleep (Giubilei et al., 1992; Hachinski, Mamelak, & Norris, 1990; Korner et al., 1986; Mohsenin & Valor, 1995; Siccoli & Bassetti, 2008; Vock et al., 2002) have been reported. Alterations in slow wave sleep are inconsistent as increased (Culebras & Miller, 1983; Santamaria et al., 2000) and decreased proportions of slow wave have been described (Bassetti & Aldrich, 1999; Bassetti & Aldrich, 2001; Mohsenin & Valor, 1995; Müller et al., 2002). Sleep

5 Mixed stroke and TBI sample.
6 Mixed stroke and TBI sample.
abnormalities observed in the acute phase improved with no abnormal proportions of sleep stages observed after one year (Gottselig et al., 2002; Hachinski et al., 1987; Müller et al., 2002; Vock et al., 2002). In contrast, Herman et al. (2008) showed sleep EEG alterations remained despite improved subjective sleep. This demonstrates that more research is required to clarify the extent to which sleep disturbance evolves into a chronic problem after stroke.

**Prevalence of Daytime Functioning Problems**

While excessive sleepiness is commonly experienced during the acute phase of stroke (Bliwise, Rye, Dihenia, & Gurecki, 2002; Davies, Rodgers, Walshaw, James, & Gibson, 2003; Good et al., 1996), persisting subjective and objective sleepiness remains in 17 to 34% of chronic patients (Campos et al., 2005; Masel et al., 2001; Schuiling et al., 2005; Vock et al., 2002; Worthington & Melia, 2006). Cases of hypersomnia and narcolepsy are also apparent in some chronic patients (Bassetti & Aldrich, 1999; Masel et al., 2001). Seventy to 92% chronic stroke patients regularly nap to compensate for sleepiness (Campos et al., 2005; Muller et al., 2006; Schuiling et al., 2005). Surprisingly, none of these studies utilised a control group. Published norms have indicated that excessive sleepiness occurs in 19.55% in the general UK population (Anderson, Platten, & Horne, 2009). Therefore some sleepiness s to be expected irrespective of stroke, however further research is required to examine stroke specific changes in daytime functioning.

Another dimension of daytime functioning, independent of sleepiness, is fatigue. Fatigue refers to physical or mental exhaustion as a result of exertion and is usually measured using subjective questionnaires. Thirty to 69% of chronic stroke patients complain of fatigue (Choi-Kwon et al., 2005; Ingles et al., 1999; Park et al., 2009; Schepers et al., 2006; Valko et al., 2008; van der Werf et al., 2001). Post stroke fatigue is considerably more prevalent than reported rates in controls which range from 12 to 36% (Ingles et al., 1999; Park et al., 2009; Valko et al., 2008; van der Werf et al., 2001). Furthermore, fatigue may evolve over the course of stroke (Schepers et al., 2006; Valko et al., 2008). It is common for patients to report that
fatigue is their worst symptom after suffering a stroke (Ingles et al., 1999; van der Werf et al., 2001).

**Mechanisms Subserving Post Stroke Sleep Alterations**

It is postulated that a stroke event is directly related to the observed changes in sleep behaviour due to neural damage of sleep and arousal mechanisms (Bassetti & Valko, 2006; Evans, 2002). Some studies suggest that particular stroke topographies are associated with selective sleep deficits. For example, reduced sleep stages 2 and 4 has been attributed to supratentorial stroke (Bassetti & Aldrich, 2001). Furthermore, thalamic stroke is highly associated with increased sleepiness (Autret et al., 2001; Catsman-Berrevoets & Harskamp, 1988; Christian Guilleminault, Quera-Salva, & Goldberg, 1993). Although some brain mechanisms have been identified in modulating fatigue (Naess et al., 2005; Staub & Bogousslavsky, 2001), further investigation is required to establish this link.

In contrast, there is not always a direct association between lesion location and sleep and daytime functioning disturbance (Autret et al., 2001; Baumann et al., 2007; Parra et al., 2000). Also, Choi-Kwon et al., (2005) and Ingles et al., (1999) found no relation between fatigue and lesion location in chronic stroke patients. This suggests that other non-neurological factors are likely to subserve post stroke sleep disturbance. For example, concomitant medications, lifestyle alterations and psychological consequences have been attributed to the development of sleep disturbance in acute patients (Bassetti, 2005b). Such relationships have not yet been fully addressed in the context of chronic stroke.

### 3.1.2 Methodological Issues For Researching Post Stroke Sleep and Daytime Functioning

Although previous studies have begun to describe sleep and daytime functioning in chronic stroke, several limitations arising from previous work highlights that more
research is required to fully address this aspect of the post stroke sequelae. It is the intention of the current study to resolve some of these issues.

**Conceptualising and Measuring Sleep and Daytime Functioning**

The prevalence of post stroke sleep disturbance may be subject to bias due to the conceptualisation of sleep problems. Some studies use strict clinical criteria as listed within the DSM-IV or the International Classification of Sleep Disorders whereas others use healthy controls as a normative comparison. It is also important to consider the type of assessment being used. Objective and subjective measures may not be in concordance or measure different aspects of sleep (Buysse et al., 2008; Masel et al., 2001). Therefore the inferences drawn from other studies should take into account the inter-study variance in criteria and type of assessment.

Another commonly occurring conceptualisation problem is the lack operationalisation of sleepiness and fatigue. These concepts are distinct dimensions of daytime functioning and can be assessed independently (Hossain et al., 2005). It is possible to derive empirically separate sleepiness and fatigue scales from existing self report instruments (Bailes et al., 2006) which is necessary to explore post stroke daytime functioning.

**Patient Group Selection**

The majority of studies address post stroke sleep behaviour during the acute phase of recovery with chronicities ranging from several hours or weeks. Acute patients are exposed to critical factors which impose upon sleep. For example, during the first few months after stroke, patients are subject to changes in sleeping environment, biological and psychological stress, increased bed rest, medications, fever, pain and other complications (Bassetti and Aldrich, 2001, p.191). Studies addressing stroke within 6 months are also at risk for confounds upon sleep as patients may not yet be discharged from the rehabilitation facility and are not yet fully adjusted to the long term consequences of stroke (Jorgensen et al., 1995; Sullivan, 2007). More studies are required to characterise sleep in patients who are in a stable state with regard to
their recovery, i.e. at least 12 months post stroke (Donnan et al., 1991; Duncan et al., 1992; Horgan et al., 2009; Jorgensen et al., 1995; Kotila et al., 1984; Lesniak et al., 2008; Rasquin et al., 2005).

Control Group Selection
The reported literature presents some concerns over the lack of, or choice of control group. The choice of control group is highly varied between studies. Some studies make comparisons based on published norms, whereas others choose strictly healthy controls. Other studies have examined alternative neurological conditions including transient ischemic attack (TIA) or non-brain injured persons in a hospitalised status. The varied choice of control group is highly influential for data interpretation. For example, positive selection of strictly healthy controls will contain less sleep disordered participants than general populations. Therefore comparing sleep behaviour between stroke patients and strictly healthy populations may result in an overestimation of post stroke sleep problems.

3.1.3 The Rationale For Study 1
There is a strong rationale to explore sleep behaviour in chronic stroke. Firstly, initial evidence suggests that post stroke sleep disturbance impacts quality of life. Secondly, long term outcome as well as the success of neurorehabilitation efforts is influenced by sleep and deficits in daytime functioning. Thirdly, post stroke sleep problems have been attributed to greater family burden and increased medical costs.

Impact Sleep on Psychological Adjustment and Quality Of Life
Quality of life construct refers to both physical and mental health, typically from the subjective perspective (Cella, 1994). It is well established that sleep disturbance, and the associated sleepiness and fatigue, contributes to poorer quality of life. This has been shown in healthy persons and those with chronic illness (Baldwin et al., 2001; Briones et al., 1996; Finn, Young, Palta, & Fryback, 1998; Flemons & Tsai, 1997;
Katz & McHorney, 1998; Manocchia et al., 2001; Redeker, Ruggiero, & Hedges, 2004; Reid et al., 2006; Strine, Chapman, Balluz, Moriarty, & Mokdad, 2008; Totterdell et al., 1994). With regard to chronic stroke, only one study has assessed sleep and quality of life. Schuiling et al. (2005) investigated the relationship between post stroke sleep disturbance and quality of life using the SF-36. In this study, chronic stroke patients with sleep problems had lower quality of life compared to patients with no sleep problems. Although this study combined daytime functioning and nocturnal sleep as one variable. Specifically regarding sleepiness and fatigue, increased levels are associated with poorer post stroke quality of life (Ingles et al., 1999; Naess et al., 2006b).

Post stroke psychological conditions, including depression and anxiety, are associated with increased sleep disturbance, sleepiness and fatigue (Bassetti & Valko, 2006; Leegaard, 1983; Schepers et al., 2006; Fabienne Staub & Julien Bogousslavsky, 2001). Few studies have examined this relationship in chronic patients, particularly examining both perceived sleep disturbances and daytime functioning. This is important to examine as psychological adjustment after stroke is an important contributor to quality of life after stroke (Strine & Chapman, 2005) and this is unlikely to stabilised until the chronic phase of stroke (Horgan et al., 2009; Kotila et al., 1984).

**Stroke Outcome and Rehabilitation**

Sleep problems, in addition to the physical and mental consequences of chronic disease, may aggravate disability and functional impairment (Parish, 2009; Stein, Belik, Jacobi, & Sareen, 2008). More specifically, several studies have found an association between sleep problems and the level of acute (Claudio Bassetti et al., 1997; Bassetti & Aldrich, 2001; Good et al., 1996; Hachinski et al., 1987; Kaneko et al., 2003b; Leppävuori et al., 2002; Sandberg et al., 2001; Spriggs et al., 1992a; Takekawa et al., 2007) and chronic (Good et al., 1996; Hermann et al., 2008; Vock et al., 2002) stroke recovery outcome. Furthermore, there is evidence to suggest that rehabilitation participation is interrupted by sleepiness and fatigue (Barker-Collo et
al., 2007; Morley et al., 2005; Muller et al., 2006; Palomaki et al., 1999; Worthington & Melia, 2006).

**Medical and Family resources**

Not only is stroke a serious medical condition, it places great financial burden upon patients and their families as well as the healthcare system (Kapur et al., 2002). Moreover, high levels of sleep problems in chronically ill patients are associated with increased use of health care services (Manocchia et al., 2001). Treating sleep disorders in addition to primary chronic conditions may reduce length of stay in hospital therefore limit the medical burden associated with stroke (Kaneko et al., 2003b).

### 3.1.4 The Current Study

The above studies have shown that sleep problems are especially prominent during the acute phase of stroke in the form of poor sleep quality or more serious sleep conditions including insomnia and sleep apnoea. However there are inconsistencies in the methodology and findings across studies. Furthermore, there is a lack of research considering: 1) the patients experience of post stroke sleep and daytime functioning disturbance and 2) the post stroke evolution of sleep disturbances in the context of psychological adjustment and quality of life. Moreover, patients recruited for this study were in the chronic state of injury, therefore more like to be in a stable state with regard to physical and psychological recovery. No known study has incorporated a battery of assessments to address subjective nocturnal sleep, addressing sleepiness and fatigue as separate entities, and measure psychological adjustment and quality of life in chronic patients compared to controls.

**Research Aims**

The aim of the current study was to characterise habitual sleep and daytime functioning and the potential relationship with psychological disturbance and quality
of life within a chronic stroke population. Crucially, the study aimed to expand the existing literature by providing an in depth study of perceived sleep and daytime functioning in patients with chronic residual motor deficits.

Based review of the literature, the following research questions were addressed:

1. How is sleep and daytime functioning affected after stroke in comparison to pre-morbid behaviour in acute and chronic patients?

2. Is sleep and daytime functioning in chronic stroke patients different to that observed within healthy populations and published norms?

3. To what degree does the stroke event per se and psychological functioning contribute to the manifestation of poorer sleep behaviour?

4. Is nocturnal sleep and daytime functioning related to the perceived health of stroke patients?

3.2 Method

3.2.1 Design

A cross-sectional design was employed to address subjective sleep and daytime functioning in a chronic sample of patients with hemiparesis. Habitual sleep behaviour data was collected during the screening session for the CIT trial (Figure 3.1). A between groups design was employed whereby stroke patients were compared to a group of non-brain injured healthy controls. Furthermore, data from the current study was compared to stroke patient and control data from published studies. A
within group design was applied in order to make comparisons between questionnaires. Stroke patients and controls were combined into one group for the regression analyses examining predictors of sleep behaviour. A second regression analyses was conducted to examine perceived health, sleep and daytime functioning involving stroke patients only.

Figure 3.1. Design of CIT trial, The highlighted section indicates time point from which data for this study was collected

3.2.2 Participants

Sixty-one community dwelling chronic stroke patients with residual motor deficits were included in the analysis for the current study. All participants fulfilled the inclusion/exclusion criteria as described in Section 2.2.1, Chapter 2.

In addition, 61 non-brain injured control participants drawn from the general population were recruited for. Participants with clinically diagnosable sleep disorders were excluded, however the sample is likely to contain what would be classified as poor sleepers (a sampling method used by Lichstein, Taylor, Bush, Reidel, &
Durrence, 2004, p.73). Furthermore, the data of the current study was compared to that of published subjective data from non-brain injured populations and other comparable samples involving chronic stroke cohorts (Clare Anderson & Horne, 2008; Bassetti & Valko, 2006; Buysse et al., 1989; Choi-Kwon et al., 2005; Groeger et al., 2004; Johns, 1991; Lichstein et al., 2004; Magee, Caputi, Iverson, & Huang, 2008; Masel et al., 2001; Monk, Buysse, Rose, Hall, & Kupfer, 2000; Motohashi et al., 1999; Naess et al., 2005; Park et al., 2009; Schepers et al., 2006; Siengsukon & Boyd, 2009a; Valko et al., 2008; Vock et al., 2002; Ziino & Ponsford, 2005).

3.2.3 Materials

All stroke patients completed a screening interview comprising medical history, motor ability, rehabilitation history, life style, cognitive functioning and education details. Patients also completed a battery of sleep and daytime functioning questionnaires including: the in house sleep questionnaire (Version 1a), The Pittsburg Sleep Quality Index (PSQI; Buysee et al., 1989), The Sleep 50 (S50; Spoormaker & van den Bout, 2005), The Ford Insomnia Response To Stress Test (FIRST; Drake et al., 2004), The Epworth Sleepiness Scale (ESS; Johns, 1991) and The Fatigue Severity Scale (FSS; Krupp et al., 1989). The cut off criterion employed within this study to indicate a noteworthy sleep of daytime functioning difficulty is also provided in Table 3.1. Presence of psychological disturbance was assessed in stroke patients using the Hospital Depression and Anxiety Scale (HADS; Zigmond & Snaith, 1983). The SF-36 was administered as a measure of perceived health. Control participants recruited for this study completed the in house sleep questionnaire (Version 1b), PSQI, S50, FIRST, ESS, FSS and the HADS only. See Section 2.3.2 (Chapter 2) and Appendix B for a sample of all questionnaires.
Table 3.1. Study I questionnaires. Details include number of items, scoring range and cut off criteria scores above cut off criteria per questionnaire to indicate the following: a) poor quality sleep on the PSQI, b) presence of a likely sleep disorder on the S50, c) vulnerability to sleep problems as a result of stress on the FIRST, d) excessive sleepiness on the ESS, e) high levels of fatigue on the FSS and f) clinically significant depression or anxiety on the HADS.

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>No. of Items</th>
<th>Score Range</th>
<th>Cut off Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSQI</td>
<td>19</td>
<td>0-21</td>
<td>&gt;5</td>
</tr>
<tr>
<td>S50: Insomnia</td>
<td>50</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sleep Apnea</td>
<td>8</td>
<td>0-32</td>
<td>&gt;14</td>
</tr>
<tr>
<td>Insomnia</td>
<td>6</td>
<td>0-32</td>
<td>&gt;18</td>
</tr>
<tr>
<td>Affective Disorder</td>
<td>8</td>
<td>4-16</td>
<td>&gt;11</td>
</tr>
<tr>
<td>Sleep state misperception</td>
<td>8 + sleep duration</td>
<td>- 18 insomnia score and &gt; 4 hours sleep duration</td>
<td></td>
</tr>
<tr>
<td>Narcolepsy</td>
<td>5</td>
<td>5-20</td>
<td>&gt;6</td>
</tr>
<tr>
<td>Restless legs syndrome/periodic leg movements</td>
<td>4</td>
<td>4-16</td>
<td>&gt;6</td>
</tr>
<tr>
<td>Circadian rhythm disorder</td>
<td>3</td>
<td>3-12</td>
<td>&gt;7</td>
</tr>
<tr>
<td>Sleep walking</td>
<td>3</td>
<td>3-12</td>
<td>&gt;6</td>
</tr>
<tr>
<td>Nightmares</td>
<td>4</td>
<td>4-16</td>
<td>&gt;2 on 1 item 32 and &gt; 6 on items 33-35</td>
</tr>
<tr>
<td>Hypersomnia</td>
<td>7</td>
<td>7-28</td>
<td>&gt;14</td>
</tr>
<tr>
<td>FIRST</td>
<td>9</td>
<td>1-36</td>
<td>&gt;median group score</td>
</tr>
<tr>
<td>ESS</td>
<td>8</td>
<td>0-24</td>
<td>&gt;9</td>
</tr>
<tr>
<td>FSS</td>
<td>9</td>
<td>0-63</td>
<td>&gt;35 (total score) or &gt;4 mean across items</td>
</tr>
<tr>
<td>HADS: Depression</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Anxiety</td>
<td>7</td>
<td>0-21</td>
<td>&gt;10</td>
</tr>
<tr>
<td>SF-36</td>
<td>36</td>
<td>0-100</td>
<td>&gt;50</td>
</tr>
</tbody>
</table>

3.3.4 Procedure

All stroke patients completed screening and the questionnaires, during the laboratory screening session. HADS and SF-36 questionnaires were completed by those stroke patients who attended baseline testing (T1) as part of the CIT trial. These questionnaires were not included during screening due to increased timing constraints in order to accommodate the necessary assessments. Control participants completed the questionnaires in the laboratory or by post.

3.3.5 Analysis
Statistical analysis was performed on item score, component scores, total score or calculated index for the PSQI (GPSQI), FIRST (FIRST Total) ESS (ESS Total), FSS (FSS Total), HADS (Anxiety and Depression) and SF-36 (Mental, Physical and Overall Health). See Section 2.3.3, Chapter 2 for a description of the calculation steps for questionnaire scoring. Furthermore, items 1 to 4 on the PSQI were used to provide the following habitual sleep parameters: bed time (24 hour clock), get up time (24 hour clock), time in bed (minutes), sleep duration (minutes), sleep onset latency (minutes) and sleep efficiency (% sleep duration per time in bed). The sum of PSQI items 5b-j was used to calculate level of sleep disturbance. Between group comparisons were conducted between patients, control data from participants of the current study and published data. Furthermore, within group analysis of nocturnal sleep and daytime functioning was examined. In instances where participants did not complete the full sleep interview and questionnaire battery, the final number of patients or controls was listed where appropriate.

Due to the non-normal distribution of the data, all tests of group differences were calculated using Mann Whitney U Tests and tests of association used Spearman’s Rank Correlation Coefficient. To address the magnitude of difference as well as statistically comparing data of the current investigation with other published data, effect sizes were calculated using Cohen’s d (see Section 2.5.5, Chapter 2). Effect sizes could not be calculated for those studies which did not provide a standard deviation. A standard multiple regression was performed to assess the degree to which demographic and psychological factors contributed to sleep and daytime functioning difficulties. A second regression analysis was applied to stroke patients who completed the SF-36 to examine factors contributing to perceived health. All statistical tests were one tailed and the alpha value was set to p≤0.05.
3.3 Results

3.3.1 Demographics

The demographics for both stroke patients and healthy controls are presented in Table 3.2. There were marginally more male stroke patients (60%) who took part in this study compared to female. Gender balance was relatively similar for controls (46% male). Several co-morbid conditions were apparent amongst the stroke patients, most notably psychological and cardiac related, all of which, were medically controlled.
Table 3.2. Demographic data for stroke patients and controls. Values presented as mean (+/- 1 SD and range) or percent valid where appropriate. The remaining 41% of stroke patients unlisted for employment status were classified as not working. Sleep medication was taken by one control participant (Zipiclone taken irregularly) and one stroke patient (Melatonin taken every evening). For individual case information for all participants is provided in Appendix C.

<table>
<thead>
<tr>
<th>Demographical Variables</th>
<th>Stroke Patients (n=61)</th>
<th>Controls (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M: F)</td>
<td>37:24</td>
<td>28:33</td>
</tr>
<tr>
<td>Age (Years)</td>
<td>53.72 ± 12.63 (20-73)</td>
<td>52.13 ± 12.88 (24-72)</td>
</tr>
<tr>
<td>BMI</td>
<td>24.59 ± 3.49 (18-20:38:30)</td>
<td>25.28 ± 3.91 (18-00-38:90)</td>
</tr>
<tr>
<td>NART (IQ)</td>
<td>115.89 ± 6.94 (06:126)</td>
<td>-</td>
</tr>
<tr>
<td>Mini Mental State Exam*</td>
<td>28.96 ± 1.41 (23-30)</td>
<td>-</td>
</tr>
<tr>
<td>Education Level:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>School Leavers Certificate</td>
<td>33.80%</td>
<td>27.08%</td>
</tr>
<tr>
<td>Further Study</td>
<td>28.96%</td>
<td>14.58%</td>
</tr>
<tr>
<td>Higher Education</td>
<td>27.12%</td>
<td>58.33%</td>
</tr>
<tr>
<td>Employment Status:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full Time</td>
<td>11.48%</td>
<td>-</td>
</tr>
<tr>
<td>Part Time</td>
<td>14.75%</td>
<td>-</td>
</tr>
<tr>
<td>Retired</td>
<td>29.51%</td>
<td>-</td>
</tr>
<tr>
<td>Studying</td>
<td>3.28%</td>
<td>-</td>
</tr>
<tr>
<td>Living Support:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Living Alone</td>
<td>21.31%</td>
<td>-</td>
</tr>
<tr>
<td>Living With Family</td>
<td>78.67%</td>
<td>-</td>
</tr>
<tr>
<td>Chronicity (Months)</td>
<td>59.74 ± 50.41 (11-252)</td>
<td>n/a</td>
</tr>
<tr>
<td>Type of Stroke:†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>61.76%</td>
<td>n/a</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>29.41%</td>
<td>n/a</td>
</tr>
<tr>
<td>Both</td>
<td>8.82%</td>
<td>n/a</td>
</tr>
<tr>
<td>Lesion Hemisphere</td>
<td>30 Left, 31 Right</td>
<td>n/a</td>
</tr>
<tr>
<td>Co-morbid Conditions:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychological</td>
<td>24.59%</td>
<td>None</td>
</tr>
<tr>
<td>Muscular</td>
<td>4.91%</td>
<td>None</td>
</tr>
<tr>
<td>Neurological†</td>
<td>14.75%</td>
<td>None</td>
</tr>
<tr>
<td>Cardiac</td>
<td>37.71%</td>
<td>None</td>
</tr>
<tr>
<td>Cancer</td>
<td>3.27%</td>
<td>None</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.63%</td>
<td>None</td>
</tr>
<tr>
<td>Pain</td>
<td>1.63%</td>
<td>None</td>
</tr>
<tr>
<td>Dysphasia</td>
<td>22.95%</td>
<td>None</td>
</tr>
<tr>
<td>Medication:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-depressant</td>
<td>6.50%</td>
<td>None</td>
</tr>
<tr>
<td>Pain Relief</td>
<td>1.64%</td>
<td>None</td>
</tr>
<tr>
<td>Cardiac Control</td>
<td>4.92%</td>
<td>None</td>
</tr>
<tr>
<td>Anti-epileptic</td>
<td>11.48%</td>
<td>None</td>
</tr>
<tr>
<td>Sleep Hypnotics</td>
<td>1.64%</td>
<td>None</td>
</tr>
<tr>
<td>Alcohol (Units per week)</td>
<td>7.89 ± 9.05 (6.45)</td>
<td>5.83 ± 6.86 (6.35)</td>
</tr>
<tr>
<td>Caffeine (Cups per day)</td>
<td>4.80 ± 2.91 (0.12)</td>
<td>3.67 ± 2.71 (0.10)</td>
</tr>
<tr>
<td>Nicotine (Cigarettes Per Day)</td>
<td>1.11 ± 3.99 (0.20)</td>
<td>0.41 ± 1.68 (0.10)</td>
</tr>
</tbody>
</table>

(-) not required or recorded as part of this study.

* 22.95% of the patients experienced expressive dysphasia therefore only completed the 3-step command on the MSE and were not included in the total mean score. These patients also did not complete the NART.

† Value included only those patients who could report type of stroke.

‡ Neurological conditions other than stroke.
There were no significant differences between the stroke patients and controls for any demographic variables presented in Table 3.2 apart from caffeine consumption where the stroke patients consumed significantly more per day compared to controls ($Z = -2.08$, $p=0.0373$).

### 3.3.2 Sleep Behaviour Compared To Pre-Morbid Behaviour

**Acute Phase (>1 month Post Stroke)**

All patients were in hospital within the acute phase. During this time, 19% of patients recalled sleeping deeper compared to their pre-morbid habitual sleep behaviour. 41% of patients reported disturbed sleep and 82% felt sleepy and/or fatigued. Of those who felt sleepy or fatigued, 70% regularly took daytime naps. Interestingly, 40.54% of patients felt that the hospital did not maintain a supportive environment for healthy sleep schedules as they were often disturbed by loud noises or awoken too early in the morning for rehabilitation or medication dosing during the night. Only 11% were prescribed sleep medication during this time despite the high levels of sleep disturbance.

**Chronic Phase (>1 Year Post Stroke)**

The majority of patients (85%) reported a persistent change in their nocturnal sleep behaviour after their stroke. Of these patients, 39% felt that this change had a negative impact upon their daily life. The reminder of these patients felt their sleep was deeper, longer and more regulated than prior to the stroke. 25% of patients habitually napped prior to the stroke whereas 61% now nap more frequently compared to before the stroke. Furthermore, 25% reported feeling persistently tired or fatigued.
3.3.3 Chronic Phase Nocturnal Sleep Questionnaires

*PSQI*

There were no significant difference between groups for GPSQI scores (Table 3.3). There was also little difference between the proportion of those classified as poor sleepers using the GPSQI cut off criteria (GPSQI>5) within the stroke group (32%) compared controls (38%).

When examining PSQI individual items, significant differences emerged for several sleep parameters (Table 3.3). Stroke patients reported going to bed 24 minutes earlier, getting up 30 minutes later and spending approximately an hour longer in bed compared to controls. Stroke patients on average slept 36 minutes longer than controls although it took patients longer to fall asleep (9.28 minutes). Patient sleep efficiency was 3% lower for stroke patients compared to controls by near significant trend. Analysis of the component scores revealed a significant difference for Component Two (Sleep Latency) and Six (Sleep Medication). Regarding the component scores, stroke patients scored significantly higher for the sleep latency component whereas controls scored higher for sleep medication.
Table 3.3. PSQI parameters. Global score (GPSQI), sleep parameters and component scores for stroke patients (36 males, 24 female) and controls (28 male, 33 female). Mean (+/- 1 SD and range), Mann-Whitney U test statistic (Z) and significance value (p) is presented.

<table>
<thead>
<tr>
<th>PSQI Variables</th>
<th>Stroke Patients (n=60)</th>
<th>Controls (n=61)</th>
<th>Z</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>GPSQI</td>
<td>5.18 ± 3.45 (1-14)</td>
<td>4.90 ± 3.54 (0-13)</td>
<td>-0.51</td>
<td>0.30</td>
</tr>
<tr>
<td>Habitual Sleep Parameters:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bed Time (24 Hour Clock)</td>
<td>22:45 ± 00:57 (19:30-02:00)</td>
<td>23:09 ± 00:56 (22:00-02:00)</td>
<td>-2.05</td>
<td>0.0201*</td>
</tr>
<tr>
<td>Get Up Time (24 Hour Clock)</td>
<td>07:36 ± 01:44 (03:00-12:50)</td>
<td>7:06 ± 00:53 (05:00-09:00)</td>
<td>2.24</td>
<td>0.0127*</td>
</tr>
<tr>
<td>Time in Bed (mins)</td>
<td>541.50 ± 82.61 (360-795)</td>
<td>480.00 ± 54.87 (360-600)</td>
<td>-4.39</td>
<td>0.0000*</td>
</tr>
<tr>
<td>Sleep Duration (mins)</td>
<td>452.55 ± 100.16 (180-750)</td>
<td>416.41 ± 68.60 (190-570)</td>
<td>-2.23</td>
<td>0.0123*</td>
</tr>
<tr>
<td>Sleep Onset Latency (mins)</td>
<td>22.62 ± 21.32 (1-90)</td>
<td>13.34 ± 12.56 (1-80)</td>
<td>-2.08</td>
<td>0.0189*</td>
</tr>
<tr>
<td>Sleep Efficiency (%)</td>
<td>83.76 ± 14.77 (34.80-99.80)</td>
<td>87.18 ± 12.01 (45.20-100)</td>
<td>-1.34</td>
<td>0.09</td>
</tr>
<tr>
<td>Sleep Disturbances</td>
<td>7.32 ± 3.71 (0-15)</td>
<td>7.64 ± 5.14 (0-25)</td>
<td>-0.16</td>
<td>0.0470*</td>
</tr>
<tr>
<td>PSQI Component Score:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Sleep Quality</td>
<td>0.70 ± 0.74 (0-3)</td>
<td>0.82 ± 0.67 (0-2)</td>
<td>-1.22</td>
<td>0.11</td>
</tr>
<tr>
<td>2 Sleep Latency</td>
<td>1.28 ± 1.01 (0-3)</td>
<td>0.75 ± 0.79 (0-3)</td>
<td>3.01</td>
<td>0.0013*</td>
</tr>
<tr>
<td>3 Sleep Duration</td>
<td>0.56 ± 0.67 (0-3)</td>
<td>0.61 ± 0.76 (0-3)</td>
<td>-0.48</td>
<td>0.32</td>
</tr>
<tr>
<td>4 Sleep Efficiency</td>
<td>0.70 ± 1.06 (0-3)</td>
<td>0.57 ± 0.88 (0-3)</td>
<td>-0.36</td>
<td>0.36</td>
</tr>
<tr>
<td>5 Sleep Disturbances</td>
<td>1.20 ± 0.51 (0-2)</td>
<td>1.28 ± 0.66 (0-3)</td>
<td>-0.50</td>
<td>0.31</td>
</tr>
<tr>
<td>6 Sleep Medication</td>
<td>0.13 ± 0.57 (0-3)</td>
<td>0.25 ± 0.62 (0-3)</td>
<td>-1.62</td>
<td>0.0531*</td>
</tr>
<tr>
<td>7 Daytime Dysfunction</td>
<td>0.63 ± 0.74 (0-3)</td>
<td>0.66 ± 0.83 (0-3)</td>
<td>0.12</td>
<td>0.45</td>
</tr>
</tbody>
</table>

*Significant values

The stroke group consisted of four cases (CP1 to 4) who presented extreme scores on several parameters (Figure 3.2a to g). The greater spread of scores observed for bed time, get up time and time in bed for the stroke patients may reflect that the majority of the sample no longer worked therefore were not restricted to a sleep schedule (Figure 3.2a to c). CP1 reported an extremely early bed time (19:30), later getting up time (12:30), longer sleep duration (750 minutes) and time in bed (800 minutes), however this patient did not report disturbed sleep (Figure 3.1g). CP2 described an early get up time (3am), long sleep latency (71 minutes), very short sleep duration (180 minutes) and low sleep efficiency (42%), demonstrating severely poor sleep that was not receiving medical attention. Figure 3.2d also shows that the majority of sleep latency reports fall within the upper limits of box plot, i.e. more patients take longer to compared to controls. This effect is reflected in the significant difference observed for Component Two (Sleep Latency) on the PSQI between patients and controls.
Another two patients had severely low sleep efficiencies of 35% (CP3) and 47% (CP4; Figure 3.2f). Considering that healthy sleep efficiency should be at least 85% (Morin and Espie, 2003, p.16) these patients are severely below a healthy level. One control case (C1) had a severely low sleep efficiency (45%; Figure 3.2f).

Figure 3.2. Box plots are displayed for PSQI habitual sleep items 1 to 4 for stroke patients and controls. Median values are demonstrated centrally in the box. The top and bottom values of the box represent the upper and lower interquartile range (H-spread) containing 50% of cases. The whiskers represent highest and lowest scores which lie within 1.5 times the H-spread. Values more than 1.5 times the H-spread are considered outliers, represented by circles. Extreme cases within the patient (CP) and control group (C) cases are labelled.

**S50**

The S50 scoring criteria for insomnia revealed increased presence of cases within the stroke group (13%) compared to controls (7%). Although the S50 detected more
cases of restless leg syndrome/periodic leg movement disorder in the stroke patients (10%) compared to controls (5%), the total score was significantly higher in control participants (Table 3.4). Furthermore, the control group had significantly higher scores for circadian rhythm disorder compared to stroke patients however no controls fit the criteria for this disorder. The control group also experienced significantly more symptoms of narcolepsy with 5% being classified as having the disorder compared to patients. Crucially, no control participants had been diagnosed with narcolepsy nor did they display any behavioural characteristics of the condition. Patients reported greater level of nightmares. Anecdotally, several patients reported recurring and vivid dreams regarding their physical disability which often awoken them during the night and was particularly distressing. This may reflect the high psychological impact of stroke.

Table 3.4. S50 sleep disorder category scores for stroke patients (37 males, 24 female) and (28 male, 33 female). Mean (+/- 1 SD and range), Mann-Whitney U test statistic (Z) between sleep disorder scores and significance value (p) are presented. The nightmare scoring system for the S50 only includes those who suffer nightmares, therefore is reported as a percentage. Presence of hypersomnia is scored as a ‘yes’ or ‘no’, therefore is also presented as a percentage.

<table>
<thead>
<tr>
<th>S50 Variables</th>
<th>Stroke Patients (n=61)</th>
<th>% Stroke Patients With Disorder</th>
<th>Controls (n=61)</th>
<th>% Controls With Disorder</th>
<th>Z</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep Apnea</td>
<td>10.67 ± 2.36 (8-18)</td>
<td>3.28%</td>
<td>10.66 ± 2.34 (3-7)</td>
<td>0%</td>
<td>-0.39</td>
<td>0.35</td>
</tr>
<tr>
<td>Insomnia</td>
<td>14.60 ± 5.27 (8-32)</td>
<td>13.11%</td>
<td>13.66 ± 4.65 (8-26)</td>
<td>6.86%</td>
<td>-0.95</td>
<td>0.17</td>
</tr>
<tr>
<td>Affective Disorder</td>
<td>6.79 ± 2.55 (4-13)</td>
<td>6.56%</td>
<td>6.44 ± 2.01 (4-12)</td>
<td>3.28%</td>
<td>-0.28</td>
<td>0.39</td>
</tr>
<tr>
<td>Sleep State Misperception</td>
<td>-</td>
<td>19%</td>
<td>-</td>
<td>8.2%</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Narcolepsy</td>
<td>5.33 ± 1.02 (5-11)</td>
<td>0%</td>
<td>5.77 ± 1.15 (3-9)</td>
<td>4.92%</td>
<td>-3.25.</td>
<td>&lt;0.0005'</td>
</tr>
<tr>
<td>RLS/PLMD</td>
<td>4.72 ± 1.53 (4-12)</td>
<td>9.64%</td>
<td>5.08 ± 1.56 (4-11)</td>
<td>4.92%</td>
<td>-2.01.</td>
<td>&lt;0.0220'</td>
</tr>
<tr>
<td>Circadian Rhythm Disorder</td>
<td>3.40 ± 0.82 (3-6)</td>
<td>0%</td>
<td>3.04 ± 1.44 (3-9)</td>
<td>0%</td>
<td>-1.85.</td>
<td>&lt;0.0321'</td>
</tr>
<tr>
<td>Sleep Walking</td>
<td>3.09 ± 0.47 (3-6)</td>
<td>0%</td>
<td>3.11 ± 0.78 (3-9)</td>
<td>1.64%</td>
<td>-0.5</td>
<td>0.46</td>
</tr>
<tr>
<td>Nightmares</td>
<td>-</td>
<td>18.96%</td>
<td>-</td>
<td>8.20%</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Hypersomnia</td>
<td>-</td>
<td>6.89%</td>
<td>-</td>
<td>8.20%</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Influences</td>
<td>9.40 ± 2.34 (6-19)</td>
<td>-</td>
<td>9.26 ± 1.91 (7-16)</td>
<td>-</td>
<td>-0.4</td>
<td>0.49</td>
</tr>
<tr>
<td>Impact</td>
<td>12.17 ± 4.05 (7-24)</td>
<td>-</td>
<td>11.25 ± 3.83 (7-25)</td>
<td>-</td>
<td>-1.41.</td>
<td>&lt;0.08</td>
</tr>
</tbody>
</table>
3.3.4 Dimensions of Daytime Functioning

**ESS**

In the stroke group, 28% had high levels of sleepiness as defined by ESS cut off criteria (>9). Marginally, more controls were classified as having high levels of sleepiness (31%) compared to patients. Total EES scores for the stroke patients were no different from control participants which suggest that stroke patients and controls have similar levels of perceived overall daytime sleepiness. There were differences for individual item scores including the ‘sitting and reading’ situation where controls felt they were more likely to doze off (Table 3.5). Furthermore, by non-significant trend, controls were more likely to fall asleep in a public place.

<table>
<thead>
<tr>
<th>Table 3.5. ESS item scores and total score for stroke patients (37 males, 24 female) and (28 male, 33 female). Mean (+/- 1 SD and range) Mann-Whitney U test statistic (Z) and significance value (p) are presented.</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESS Variables</td>
</tr>
<tr>
<td>ESS Total Score</td>
</tr>
<tr>
<td>Sitting and Reading</td>
</tr>
<tr>
<td>Watching TV</td>
</tr>
<tr>
<td>Sitting inactive in a public place</td>
</tr>
<tr>
<td>As a passenger in a car for an hour without a break</td>
</tr>
<tr>
<td>Lying down to rest in the afternoon</td>
</tr>
<tr>
<td>Sitting and talking to someone</td>
</tr>
<tr>
<td>Sitting quietly after lunch without alcohol</td>
</tr>
<tr>
<td>In a car, while stopped for a few minutes in traffic</td>
</tr>
</tbody>
</table>

*Significant values

**FSS**

There are two well used cut off criterion for classifying high levels of fatigue when using the FSS, either total FSS score (>35) or mean FSS (>4). According to total FSS score, 26% of the stroke patients reported high levels fatigue compared to 17% of controls, an increase of 9%. Mean score across items (>4) was similar, 25% of stroke patients were above the criteria compared to 16% of controls, a difference of 8%.
Only FSS mean score across items revealed a near significant difference between patients reported and controls (Table 3.6). Individual item analysis showed that patients reported significantly increased fatigue as a result of the following instances: 'exercise increases fatigue', 'fatigue prevents sustained physical functioning' and 'interferes carrying out certain duties and responsibilities'.

Table 3.6. FSS item scores and total score for stroke patients (36 males, 22 female) and (27 male, 31 female). Data presented as mean (+/- 1 SD and range), Mann-Whitney U test statistic (Z) and significance value (p) are presented.

<table>
<thead>
<tr>
<th>FSS Variables</th>
<th>Stroke Patients (n=58)</th>
<th>Controls (n=58)</th>
<th>Z</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSS Total Score</td>
<td>26.26 ± 16.56 (3-63)</td>
<td>21.98 ± 14.30 (0-51)</td>
<td>-1.24</td>
<td>0.11</td>
</tr>
<tr>
<td>My motivation is lower when I am fatigued</td>
<td>4.23 ± 2.24 (0-7)</td>
<td>4.16 ± 2.28 (0-7)</td>
<td>-0.05</td>
<td>0.48</td>
</tr>
<tr>
<td>Exercise brings on my fatigue</td>
<td>3.41 ± 2.41 (0-7)</td>
<td>2.62 ± 2.05 (0-7)</td>
<td>-1.65</td>
<td>0.0496*</td>
</tr>
<tr>
<td>I am easily fatigued</td>
<td>2.59 ± 2.36 (0-7)</td>
<td>2.62 ± 1.96 (0-7)</td>
<td>-0.39</td>
<td>0.35</td>
</tr>
<tr>
<td>Fatigue interferes with my physical functioning</td>
<td>3.44 ± 2.35 (0-7)</td>
<td>2.93 ± 2.08 (0-7)</td>
<td>-1.09</td>
<td>0.14</td>
</tr>
<tr>
<td>Fatigue causes frequent problems for me</td>
<td>1.78 ± 2.13 (0-7)</td>
<td>1.86 ± 1.79 (0-5)</td>
<td>-0.98</td>
<td>0.16</td>
</tr>
<tr>
<td>My fatigue prevents sustained physical</td>
<td>3.19 ± 2.45 (0-7)</td>
<td>2.19 ± 2.01 (0-5)</td>
<td>-2.02</td>
<td>0.0219*</td>
</tr>
<tr>
<td>Fatigue interferes with carrying out certain</td>
<td>3.05 ± 2.35 (0-7)</td>
<td>1.91 ± 1.80 (0-9)</td>
<td>-0.25</td>
<td>0.0061*</td>
</tr>
<tr>
<td>Fatigue is among my three most disabling</td>
<td>2.57 ± 2.60 (0-7)</td>
<td>1.78 ± 2.09 (0-6)</td>
<td>-1.27</td>
<td>0.10</td>
</tr>
<tr>
<td>Fatigue interferes with my work, family or</td>
<td>2.09 ± 2.90 (0-7)</td>
<td>1.84 ± 1.91 (0-5)</td>
<td>-0.18</td>
<td>0.43</td>
</tr>
<tr>
<td>FSS Mean Across Items</td>
<td>2.96 ± 1.84 (0.33-7)</td>
<td>2.43 ± 1.59 (0.5-87)</td>
<td>-1.29</td>
<td>0.099</td>
</tr>
</tbody>
</table>

*Significant values (trends in bold).

3.3.5 Comparison With Published Data

The following analysis was carried out in order to compare results of the current study with results reported in other studies using the following samples: 1) stroke patients of varying chronicities beyond 12 months (Bassetti & Valko, 2006; Choi-Kwon et al., 2005; Masel et al., 2001; Motohashi et al., 1999; Naess et al., 2005; Park et al., 2009; Scheipers et al., 2006; Siengsukon & Boyd, 2009a; Valko et al., 2008; Vock et al., 2002), 2) healthy samples, classified as good sleepers (Buysee et al., 1989; Monk et al., 2000), 3) generally healthy samples (Johns, 1991; Siengsukon & Boyd, 2009a; Ziino & Ponsford, 2005), 4) community samples which may contain less healthy persons (Magee et al., 2008) and 5) large samples derived from the
general population (Anderson & Horne, 2008; Groeger et al., 2004; Lichstein et al., 2004; Valko et al., 2008). Figures 3.2 to 3.5 present comparisons of mean GPSQI scores, time in bed, sleep duration, sleep onset latency, sleep efficiency, ESS and FSS scores with other published data. Effect sizes (Cohen’s $d$) were calculated to determine the magnitude of difference between the current study and that of other studies. At present, there is currently no known published subjective sleep onset latency or sleep efficiency data in chronic stroke cohorts. Furthermore, the FIRST and S50 has not yet been used in stroke cohorts. Therefore these parameters were omitted from the following analyses. In instances where studies did not report the standard deviation, effect sizes could not be calculated.

**GPSQI Comparisons (Figure 3.3)**

There were no significant effect sizes between stroke patients of the current study in comparison with controls ($d=0.08$) and the community sample ($d=0.07$) as provided by Magee et al. (2008). When GPSQI scores of the current study were compared to healthy controls who were classified as good sleepers (Buysee et al., 1989), a significant effect size was observed ($d=0.86$). These results showed that stroke patients drawn from the current study experienced significantly more sleep problems compared to a healthy sample who were also healthy sleepers. However, in comparison to control samples who were not subjected to sleep complaints as an exclusion criteria, stroke patients have similar GPSQI scores.
Comparison of Habitual Sleep Parameters Derived From The PSQI (Figure 3.4)

For comparisons involving time in bed, effect size could only calculated between stroke patients and controls of the current study. A large effect size ($d=0.88$) was observed. Upon further inspection of Figure 3.3a, it is clear that stroke patients, from the current study and those patients from Motohashi et al. (1999), spend longer in bed compared to other non-brain injured controls (Groeger et al., 2004). A medium effect size was found for sleep duration between stroke patients and controls of the current study ($d=0.43$). A small effect ($d=0.33$) was found between stroke patients of the current study and the general population (Groeger et al., 2000). According to Figure
3.4b, stroke patients appeared to sleep marginally longer than non-brain injured persons. Figures 3.4c and 3.4d clearly indicated that stroke patients have longer sleep onset latency and lower sleep efficiency compared to all control groups, indicative of poorer quality sleep in patients.
Figure 3.4. Bar charts to display mean (+1 SD where available) time in bed and sleep duration between studies.

*data from the present study
† Motohashi et al. 1999.
‡ Groeger et al. (2004)
§ Siengsukon and Boyd (2009)
** Lichenstien et al. (2004)
†† Monk et al. (2000)
‡‡ Anderson and Horne (2008)
ESS Comparisons (Figure 3.5)
The ESS scores derived from patients of the current study were similar, even compared to those patients diagnosed hypersomnia (Bassetti and Valko, 2006). The scores drawn from Vock et al.’s (2002) study could not be statistically compared to this study however, mean ESS scores differed by approximately 2 points on the scale which suggested the scores of this study are reasonably increased. A medium effect ($d=0.50$) was observed between the stroke patients of the current study and the community controls, where the controls appeared to have greater sleepiness than stroke patients. Interestingly, the non-brain injury community sample (Buysse et al. 2008) had the highest ESS scores compared to all other groups.

![ESS Score Derived From the Current Study, Other Chronic Stroke Samples and Mixed Control Groups](image)

*data from the present study
† Vock et al. (2002)
‡ Bassetti and Valko (2006) (n=22 with hypersomnia; n=78 without hypersomnia)
§ Buysse et al. (2008)
** Johns (1991)
†† Anderson and Horne (2008)

Figure 3.5. Bar charts to display mean (+1 SD) ESS between studies. The dashed line indicates the cut of criteria (>9).
**FSS Comparison (Figure 3.6)**

The majority of studies examining chronic stroke use the mean FSS score across items rather than mean total score, therefore the effect size calculations utilised the former method of scoring the FSS. FSS scores for controls are lower than those individual stroke groups, apart from Choi-Kwon (2005). Figure 3.6 shows that those stroke patients with the shortest chronicity (12 months) has the highest levels of fatigue (Schepers et al., 2006). This difference is further reflected in the very large effect size ($d=1.18$) found between these patients and those involved in the current study. Medium effects ($d=0.69$) were found between stroke patients of the current study and the stroke cohort with a longer chronicity of 72 months (Naess et al. (2005). The FSS scores of the Naess et al. (2005) study might be higher due to the less stringent sampling criteria. A medium effect ($d=0.50$) was also found between stroke patients of the current study and those patients at 14.4 months chronicity (Valko et al., 2008). A small effect ($d=0.37$) was found between the stroke patients of the current study and those at 32.7 months chronicity (Park et al., 2009). These results suggest that fatigue levels may change over the course of stroke, however those at only 15 months chronicity (Choi-Kwon et al., 2005) had a lower FSS. There was a small effect between the stroke patients and controls derived from the current study ($d=0.32$). A small effect ($d=0.24$) between stroke patients of the current study and controls reported in Zino and Ponsford (2005) was observed.
3.3.6 Interaction Between Nocturnal Sleep and Daytime Functioning

The degree to which nocturnal sleep (GPSQI) and daytime functioning (ESS and FSS) were associated was examined via correlation analyses. For the stroke group, GPSQI scores were not associated with ESS scores \((r=0.10, p=0.45)\). Increasing GPSQI scores were weakly associated with higher FSS total scores \((r=0.24, p=0.0548)\) in stroke patients. For controls, increased GPSQI scores correlated with increased FSS \((r=0.31, p=0.0185)\) but were not related to ESS score \((r=0.19, p=0.14)\). ESS and FSS scores correlated \((r=0.28, p=0.0358)\) within the stroke group however this effect was not observed within the control group \((r=0.16, p=0.25)\).
3.3.7 Psychological Disturbance, Perceived Health and Sleep

The relationship between sleep and levels of psychological disturbance was examined in both stroke and control groups. The FIRST questionnaire allowed classification of those more vulnerable to sleep disturbance as a result of psychological stress. As only those patients who completed the baseline motor testing (T1) were administered the HADS and SF-36. Fifty-five stroke patients and 55 controls were included in analyses involving the HADS. Fifty-five patients completed the SF-36 whereas controls did not. A regression models were developed in accordance with the observed relationships between questionnaires to determine parameters predictive of a) poor sleep (GPSQI), b) sleepiness (ESS) and c) fatigue (FSS). The degree to which psychological disturbance, perceived health and sleep behaviour parameters interact was also examined in stroke patient only. A second regression model was employed to determine the influence sleep, daytime functioning, and psychological adjustment on perceived health in stroke patients only.

Psychological Disturbance (HADS) and Sleep

Mean anxiety was significantly increased ($Z = -4.25$, $p=0.0000$) for the stroke group (5.40, SD 3.45) compared to the control group 2.60 (SD 2.23). Mean depression was not significantly different between stroke (5.70, SD 3.18, 1-16) and controls (5.40; SD, 3.28; $Z=-0.56$, $p=0.57$). No participants within the control group scored above the criteria for anxiety where as 10% of patient were above this threshold. Even though uncontrolled depression was part of the exclusion criteria for this study, 12% of the stroke sample were above the criteria for presence of depression. 9.09% of controls were also above the threshold for depression.

The median of FIRST scores was used as cut off criterion determine those more likely have their sleep affected by stress relative to the group in question (Drake et al., 2004). As the median score for both stroke patients and controls was 18, scores above
this value were used as a cut off in each group. 58.18% of stroke patients were above the median compared to 49.09% of controls. Although this suggests that more patients reported that their sleep is affected by stress compared to controls, this was not reflected in item scores or total score of the FIRST (Table 3.7). Patient anxiety was associated with FIRST scores ($r=0.35$, $p=0.0169$) which is also indicative of psychological vulnerability to sleep problems. Also, higher levels of depression were associated with the FIRST ($r=0.30$, $p=0.0254$) in patients.

Table 3.7. FIRST item data for stroke patients (37 males, 24 female) and (26 male, 29 female). Mean (+/- 1 SD and range), Mann-Whitney U test statistic (Z) and significance value (p) is presented. Trends indicated in bold.

<table>
<thead>
<tr>
<th>FIRST Variables</th>
<th>Stroke Patients (n=56)</th>
<th>Controls (n=55)</th>
<th>Z</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before an important meeting the next day</td>
<td>2.15 ± 1.16 (1-4)</td>
<td>2.07 ± 0.96 (1-4)</td>
<td>-0.03</td>
<td>0.49</td>
</tr>
<tr>
<td>After a stressful experience during the day</td>
<td>2.07 ± 1.09 (1-4)</td>
<td>2.07 ± 0.92 (1-4)</td>
<td>-0.29</td>
<td>0.39</td>
</tr>
<tr>
<td>After a stressful experience in the evening</td>
<td>2.16 ± 1.13 (1-4)</td>
<td>2.27 ± 0.91 (1-4)</td>
<td>-0.82</td>
<td>0.21</td>
</tr>
<tr>
<td>After getting bad news during the day</td>
<td>2.53 ± 1.14 (1-4)</td>
<td>2.32 ± 1.00 (1-4)</td>
<td>-0.96</td>
<td>0.17</td>
</tr>
<tr>
<td>After watching a frightening movie or TV show</td>
<td>1.36 ± 0.82 (1-4)</td>
<td>1.44 ± 0.81 (1-4)</td>
<td>-0.80</td>
<td>0.21</td>
</tr>
<tr>
<td>After having a bad day at work</td>
<td>1.93 ± 0.98 (1-4)</td>
<td>1.63 ± 0.73 (1-4)</td>
<td>-1.41</td>
<td>0.08</td>
</tr>
<tr>
<td>After an argument</td>
<td>2.27 ± 1.11 (1-4)</td>
<td>2.21 ± 0.96 (1-4)</td>
<td>-0.14</td>
<td>0.45</td>
</tr>
<tr>
<td>Before having to speak in public</td>
<td>2.35 ± 1.27 (1-4)</td>
<td>2.30 ± 1.17 (1-4)</td>
<td>-0.08</td>
<td>0.47</td>
</tr>
<tr>
<td>Before going on vacation the next day</td>
<td>2.00 ± 1.09 (1-4)</td>
<td>2.05 ± 1.03 (1-4)</td>
<td>-0.41</td>
<td>0.34</td>
</tr>
<tr>
<td>FIRST Total Score</td>
<td>18.44 ± 6.99 (9-36)</td>
<td>18.34 ± 6.23 (9-33)</td>
<td>-0.01</td>
<td>0.50</td>
</tr>
</tbody>
</table>

Predictors of Poor Sleep, Sleepiness and Fatigue (Stroke Patients and Controls)

Three multiple regression models were devised to assess to what degree having a stroke and the associated psychological disturbance contributed to the existence of a sleep or daytime functioning problem. Each of the three models had a separate dependent variable Table 3.8: a) GPSQI, b) ESS and c) FSS. Predictor variables included age, group (stroke or control), depression (HADS) and anxiety (HADS). Due to the relationship between nocturnal sleep and daytime functioning, the GPSQI was included as a predictor variable in model b) and c). Although there are well known links between caffeine, alcohol and nicotine affects upon day time functioning (Roehrs and Roth, 2008; Roehrs and Roth, 2001), there was no correlation between these life style drugs with GPSQI, ESS or FSS. Furthermore, there were no gender
differences in sleep or psychological disturbance in both stroke and controls. Therefore these parameters were not included in the model.

Table 3.8. Three regression models are presented: a) sleep quality (GPSQI) as the dependent variable (DV), b) sleepiness (ESS) as the DV and c) fatigue (FSS) as the DV. The correlations between the variables, the unstandardised regression coefficients (B) with +/-1 SE, and intercept, the standardised regression coefficients (β). R and R². Trends are indicated in bold. Note that group is categorical (1=stroke, 2=control). Where the p value is not reported, the degree of significant is indicated (*p>0.05 **p>0.01 ***p>0.001).

For sleep quality, as indicated by the GPSQI (Table 3.8a), the R for regression was significantly different from zero, $F(4, 100) = 7.53$, $p=0.0000$. In this model, only
anxiety significantly contributed to the prediction of GPSQI scores. Semipartial correlation analyses revealed that anxiety contributed 10% to the model ($sr^2=0.10$).

Table 3.8b presents the regression model with sleepiness (ESS) as the DV. R for regression was different from zero by near-significant trend, $F(5, 99) = 2.10$, $p=0.0716$). Only depression significantly contributed to prediction of ESS scores, depression, however only contributed 4% ($sr^2= 0.04$) to the variance. Table 3.8c presents the regression model for fatigue (FSS) as the DV. R for regression within the fatigue model was significantly different from zero, $F(5, 97) = 6.36$, $p=0.0000$. Depression significantly contributed 13% of the variance ($sr^2=0.13$).

**Perceived Health (Stroke Patients Only)**

Overall perceived health on the SF-36 was 65.40 (SD 15.72) which is suggestive of above average health, although scores ranged from 30 to 91.09. Twenty four percent in patients reported below average health. Within the overall health dimension, mean mental health was 60.30 (SD 16.03) with 26% of scores falling below average. Mean physical health was 69.19 (SD 17.00) with 16% of scores below average. This indicates that despite the physical disability sustained during chronic stroke, mental health is rated more poorly than physical health.
Figure 3.7. Bar charts to display mean (+ 1 SD) overall health, mental and physical health dimensions on the SF-36 for the following groups of patients: a) those with (GPSQI >5) and without sleep disturbances (GPSQI ≤5), b) those with high (total FSS >35) and low (total FSS ≤35) levels of fatigue and c) those with (>9) and without excessive sleepiness (≤9). Significant differences are indicated (*p>0.05, ***p≥0.001).

Figure 3.7a clearly demonstrates that those with greater sleep disturbance have poorer mental (Z=-3.28, p=0.0011), physical (Z=-3.43, p=0.0006) and overall health (Z=-3.21, p=0.0013) compared to those patients without these problems. Furthermore, those with greater fatigue (Figure 3.7b) had poorer mental (Z=-3.72, p=0.0002), physical (Z=-3.21, p=0.0013) and overall health (Z=-3.27, p=0.0011). Those with excessive sleepiness (Figure 3.7c) did not demonstrate significantly poorer mental (Z=-1.57, p=0.12), physical (Z=-1.17.43, p=0.24) or overall health (Z=3.21, p=0.0013).

Table 3.9 presents the regression model of contributing factors, including age, depression (HADS), anxiety (HADS), GPSQI, ESS and FSS, to overall perceived health as reported on the SF-36. R for regression was significantly different from zero, F(6, 41) = 15.56, p=0.0000). Three IVs contributed significantly to prediction of SF-36 scores, depression (sr²= 0.19), anxiety (sr²= 0.03) and fatigue (sr²= 0.03) contributing 19% and both 3% respectively.
Table 3.9. Standard multiple regression of contributing factors to overall perceived health as the dependent variable (SF-36) in stroke patients. The correlations between the variables, the unstandardised regression coefficients (B) with +/-1 SE, and intercept, the standardised regression coefficients (β), the semipartial correlations (sr²), R and R². Where the p value is not reported, the degree of significant is indicated (*p>0.05 **p>0.01 ***p>0.001).

<table>
<thead>
<tr>
<th>Variables</th>
<th>SF-36 (DV)</th>
<th>Age</th>
<th>Depression</th>
<th>Anxiety</th>
<th>GPSQI</th>
<th>ESS</th>
<th>FSS</th>
<th>B (SE)</th>
<th>β</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.03</td>
<td>-</td>
<td>-0.00</td>
<td>-0.23*</td>
<td>-0.15</td>
<td>0.13</td>
<td>-0.12</td>
<td>-0.12</td>
<td>-0.09</td>
<td>0.30</td>
</tr>
<tr>
<td>Depression</td>
<td>-0.80***</td>
<td>-0.00</td>
<td>-0.49***</td>
<td>0.49***</td>
<td>0.40**</td>
<td>0.19</td>
<td>-0.48**</td>
<td>-2.68</td>
<td>-0.60</td>
<td>0.0000***</td>
</tr>
<tr>
<td>Anxiety</td>
<td>-0.53***</td>
<td>-0.23*</td>
<td>0.49***</td>
<td>-0.56**</td>
<td>0.01</td>
<td>-0.20</td>
<td>-1.15</td>
<td>-0.23</td>
<td>0.0400***</td>
<td></td>
</tr>
<tr>
<td>GPSQI</td>
<td>-0.38*</td>
<td>-0.15</td>
<td>0.40**</td>
<td>0.56***</td>
<td>-</td>
<td>0.06</td>
<td>0.25*</td>
<td>0.10</td>
<td>0.02</td>
<td>0.83</td>
</tr>
<tr>
<td>ESS</td>
<td>-0.21</td>
<td>-0.13</td>
<td>0.19</td>
<td>0.01</td>
<td>0.06</td>
<td>-</td>
<td>0.28*</td>
<td>-0.10</td>
<td>-0.03</td>
<td>0.77</td>
</tr>
<tr>
<td>FSS</td>
<td>-0.52***</td>
<td>0.12</td>
<td>0.48**</td>
<td>0.20</td>
<td>0.25*</td>
<td>0.28*</td>
<td>-</td>
<td>-0.19</td>
<td>-0.20</td>
<td>0.0545</td>
</tr>
</tbody>
</table>

Mean       65.40  53.72  5.40  5.70  5.18  6.20  
SD         15.72  12.63  3.45  3.18  3.45  4.28  

R²=0.70 R=0.83***

3.4 Discussion

3.4.1 Overall Findings

The present study aimed to characterise sleep and daytime functioning behaviour in a group of chronic stroke patients with residual motor deficits. This was addressed by employing a battery of subjective assessments and comparing the results with those of healthy controls. The findings revealed that sleep and daytime functioning is disrupted in some patients after stroke and that control group selection is critical for determining prevalence of sleep problems in stroke patient groups. It was also found that psychological functioning has a strong influence upon sleep and daytime functioning in both stroke patients and controls. Furthermore, poorer sleep and daytime functioning was related to perception of poorer overall perceived health.
**Perceived Sleep After Stroke**

The in-house questionnaire showed that 41% of patients felt their sleep was generally disturbed one month after stroke compared to pre-morbid sleep behaviour. Furthermore, post-morbid sleep disturbance evolved into a chronic problem in 39% of patients. These results confirm previous findings where subjectively poorer sleep, as reported using a range of questionnaires, occurred in 34 to 67% of patients beyond one year (Campos et al., 2005; Masel et al., 2001; Schuiling et al., 2005; Sterr et al., 2008). Critically, no patients for this study were receiving medical attention with regard to their sleep. The individual case who reported taking melatonin (a hormone that perpetuates sleep), did so under their own prerogative rather than that of a clinician.

Stroke patients reported similar levels of sleep quality compared to controls according to the GPSQI scores. According to the GPSQI index, approximately a third of both stroke patients and controls were classified as poor sleepers. This result is considerably lower than the number of patients classified as poorer sleepers (67%) reported in Campos et al. (2005) using the same criteria. One explanation for this difference may be that the sample recruited for Campos et al. (2005) were not subjected the strict levels of exclusion criteria as employed in the current study. Therefore comorbidities and confounds of stroke recovery may be reflected in the increased sleep disturbance. PSQI results of this study were comparable with those findings reported by Masel et al. (2001) who found in a mixed group of stroke and TBI patients that 32% scored above PSQI cut off criterion. Effect size calculations however, revealed a significant difference in GPSQI scores between patients from this study and healthy controls from Buysee et al. (1989). It is important to note that the controls employed in Buysee et al.’s (1989) study were positively selected based on the absence of sleep problems. No differences were observed between stroke patients from this study and control samples drawn from the general population. Closer examination of PSQI factual sleep items that patients spent considerably longer in bed, had longer sleep duration, less sleep disturbance and longer sleep onset latency compared to controls. A similar pattern was observed when comparing stroke
patients data of the current study with other control groups ranging from healthy cohort to general population samples (Anderson & Horne, 2008; Groeger et al., 2004; Lichstein et al., 2004; Monk et al., 2000).

According to S50 scoring criteria for insomnia, 13.11% of patients were likely insomnia cases compared to only 6.56% of controls. However this result is considerably lower than prevalence rates of insomnia in patients was 48% (Leppävuori et al., 2002). This discrepancy may have occurred due to the detailed clinical assessment based on DSM-IV criteria of insomnia employed by the Leppävuori et al. (2002) study. The S50 also revealed increased presence of the following sleep disorders within the control group in comparison to patients: narcolepsy, restless leg/periodic limb movement and circadian rhythm disorder. However no control participant had been diagnosed with such conditions and did not display behavioural characteristics of narcolepsy. These findings may have arisen due to different administration procedures for patients and controls. The control participants completed the questionnaires independently whereas the questionnaires were administered by a researcher for the stroke patients where there was greater opportunity for clarification of S50 items.

**Perceived Daytime Functioning After Stroke**

According to the in house questionnaire, 81% of patients reported high sleepiness and fatigue within the first month of stroke compared to before the stroke. This was further demonstrated by frequent napping behaviour. Poor daytime functioning was less prevalent one year after stroke (25%). Similar findings have also been reported in other studies where the prevalence of a general daytime dysfunction ranged from 17-34% in chronic patients (Campos et al., 2005; Masel et al., 2001; Schuiling et al., 2005; Worthington & Melia, 2006).

To further explore dimensions of daytime functioning, the ESS and FSS was applied to address sleepiness and fatigue independently. Twenty-eight percent of patients were excessively sleepy according to ESS criteria. Patient scores were slightly
increased compared to those reported in Masel et al.’s (2001) study (20.7%). Mean ESS score was comparable with chronic stroke patients in other studies (Bassetti and Valko, 2006), however was considerably higher than those patients reported in Vock et al. (2002). Patients’ sleepiness levels were similar compared to that of controls employed in this study. Thirty-one percent of controls were excessively sleepy however this is considerably higher than that reported in the general population (19.55%; Anderson and Horne, 2008). Effect size calculations revealed that mean patient ESS scores in this study were similar to healthy controls (Johns, 1991), and in fact less, than those in community sample reported in (Buysse et al., 2008). Although patients did not report more sleepiness than controls, this finding is in contrast to previous literature which suggests that sleepiness is more prevalent after stroke based on clinical observation and objective assessments (Bassetti et al., 1996; Bassetti & Valko, 2006; Masel et al., 2001).

Interestingly, half of the patient group regularly napped during the day despite just over a quarter reporting excessive sleepiness. Increased napping has also been observed in other chronic stroke patients in comparison to controls (Campos et al., 2005; Muller et al., 2006). It is difficult to determine within this study the extent to which increased napping is due to the increased opportunity for a non-working population or the possibility that patients underestimate their sleepiness. One way of addressing this issue is to employ an objective measure of sleepiness. Masel et al. (2001) compared objective sleepiness (Multiple Sleep Latency Test; MSLT; See Section 1.2.3, Chapter 1) with the ESS. It was concluded that brain injured patients do not perceive their own sleepiness as there was a dissociation between MSLT results and the ESS. Other authors have also commented on the risk of under reporting of sleepiness in brain injured patients (Bassetti et al., 1996; Bassetti & Valko, 2006; Castriotta et al., 2007; Makley et al., 2008; Parcell et al., 2006).

This study found that almost a quarter of stroke patients demonstrated high levels of fatigue compared to 16.39% of controls. The prevalence of fatigue in chronic stroke patients ranges from 30-69.5% (Choi-Kwon et al., 2005; Ingles et al., 1999; Park et
Therefore, the results of this study are slightly under this range. This may be due to the positive selection criteria employed by the current study. Effect size calculations revealed significant differences between FSS scores of patients in this study and those of other chronic stroke samples. The high variance between scores may represent differences in sampling or chronicity as fatigue may evolve after stroke (Schepers et al., 2006; Valko et al., 2008). Schepers et al. (2006) postulated that the impact of fatigue becomes more relevant when stroke victims attempt to resume a normal lifestyle including work and social activities therefore fatigue may be increasingly noticeable during this time. This then suggests that patients would have higher FSS scores.

A dissociation between GPSQI scores and sleepiness ratings on the ESS was observed as these measures did not correlate in both patients and controls. Furthermore, only mild associations were found between GPSQI and fatigue in both groups. The model of normal sleep assumes that poorer quality sleep results in decrements of daytime functioning in laboratory investigations (Akerstedt, Torsvall, & Gillberg, 1987; Franzen, Siegle et al., 2008; Marzano et al., 2007; Philip et al., 2005; Torsvall & Akerstedt, 1987, 1988; Wilhelm, Widmann, Durst, Heine, & Otto, 2009) and in naturalistic settings (Martikainen, Hasan, Urponen, Vuori, & Partinen, 1992; Pilcher & Huffcutt, 1996). However, subjective reports do not always follow this pattern, observed in non-brain injured controls (Anderson & Horne, 2008; Anderson et al., 2009; Buysse et al., 2008) and chronic stroke samples (Park et al., 2009; Masel et al., 2001). Perception of sleep and daytime functioning can be affected by a multitude factors, including laboratory conditions and type of assessment (Akerstedt, Kecklund, & Axelsson, 2008; Balkin, Rupp, Picchioni, & Wesensten, 2008; Kosuke Kaida et al., 2007), psychological state (Anderson et al., 2009; Urponen, Vuori, Hasan, & Partinen, 1988), presence of a sleep disorder (Edinger et al., 2008) and general health status (Briones et al., 1996; Elsenbruch, Harnish, & Orr, 1999). Therefore increased sleepiness and fatigue is not necessarily due to poor sleep at night.
The Influence of Control Group Selection

One of the striking findings of this study is the apparent similarity of sleep in patients and matched controls. As these results contradict previous literature, a secondary analysis was conducted to eliminate the potential influence of the chosen control group by examining varying types of control samples. Strong differences in GPSQI scores were observed when comparing stroke patient data with that of a strictly healthy control samples with no sleep disorders (Buysee et al., 1989). Crucially, no differences were found when comparing subjective data of stroke patients to controls drawn from general populations or community samples. This highlights the large impact that control sample selection can have upon the interpretation of results. Therefore control samples should be chosen carefully and interpreted appropriately.

Control sampling had less influence over daytime functioning differences. Subjective fatigue was reported as generally higher than controls in other published studies. In contrast, sleepiness was generally comparable or lower than published controls. Overall, the results suggest that sleep problems in chronic stroke are at least as prevalent as found in the general population. However, the impact of poor sleep is likely to be more severe in patients in comparison to a healthy person.

The Role of Psychological Disturbance For Sleep and Daytime Functioning

The results clearly show that greater psychological disturbance (HADS anxiety and depression) is largely associated with poorer nocturnal sleep, including longer sleep latency, shorter sleep duration, reduced sleep efficiency and increased GPSQI in patients and controls. For daytime functioning parameters, depression was associated with greater fatigue in stroke patients which is in line with previous literature (Astrom et al., 1993a; Choi-Kwon et al., 2005; Ingles et al., 1999; Naess et al., 2005; Staub & Bogousslavsky, 2001). Furthermore, according to the FIRST, stroke patients were more vulnerable to sleeping problems as a result of stress compared to controls. Results of the regression models further showed that anxiety had the greatest impact upon GPSQI scores, independent of a stroke event. Increased depression was associated with both daytime functioning variables, ESS and FSS, over all other..
predictors in the model, including having a stroke. Overall, these findings suggest that psychological functioning has greater influence on sleep and daytime functioning than stroke per se.

The Impact of Sleep and Daytime Functioning Behaviour Upon Perceived Health

Poor sleep and increased fatigue levels were significantly associated with poorer perceived health as reported on the SF-36, including mental and physical health dimensions. Regression analyses revealed that fatigue and psychological disturbance (HADS) explained the majority of the variance in perceived health, rather than nocturnal sleep problems. Schuiling et al. (2005) reported that sleep disturbance contributed to poorer health in stroke patients, however sleep disturbance and excessive sleepiness was characterized as a single variable. The present study confirms the findings of other studies which have shown fatigue is related to poorer quality of life after stroke (de Groot, Phillips, & Eskes, 2003).

3.4.2 Further Theoretical Considerations

The regression models did not fully account for the existence of sleep problems and daytime functioning difficulties. The literature suggests that the development of post stroke sleep and daytime functioning problems are likely to stem from a complex myriad of factors, including the direct impact of brain damage and age, as well as, the physical consequences, life style alterations of stroke recovery and personality factors which this study did not directly address.

Recovery Factors

The influence of brain damage per se may have differential effects upon the sleep regulation (Evans, 2002) and arousal centres of the brain (Bassetti & Valko, 2006; Cantor et al., 2008). For example, thalamic strokes are largely associated with excessive daytime sleepiness (Bassetti et al., 1996). Therefore varying lesion sites between patients may differentially influence subjective reports of sleep behaviour.
The physical consequences of stroke further compromise sleep (Bassetti, 2005a). The mobility restrictions imposed upon stroke patients suffering from hemiparesis may impact sleep in terms of comfort and ease of returning to bed after toileting. Post brain injury pain, such as neuropathic, headaches, nerve, musculoskeletal and joint pain (Gamble et al., 2000; Kong et al., 2004; Langhorne et al., 2000; Widar et al., 2004), and has also been attributed to frequent sleep disturbance (Fictenberg et al., 2001; Widar et al., 2004). Furthermore, this relationship may be reciprocal as the presence of sleep disturbances may to exacerbate acute and chronic pain (Lautenbacher et al., 2006).

**Pharmacological Agents**

Recovering patients are typically prescribed medications to control post stroke complications of stroke such as hypertension, pain and seizures. These medications may manifest sedating or hypnotic side effects that impact daytime functioning and also affect brain activity (Bourne & Mills, 2004; Lowson & Sawh, 1999; Novak & Shapiro, 1997; Obermeyer & Benca, 1996). Furthermore, antidepressants are commonly prescribed to stroke patients (Paolucci, 2008; Whyte & Mulsant, 2002) and are known to alter sleep architecture and reduce sleep efficiency (Holshoe, 2009; Mayers & Baldwin, 2005).

Both patients and controls regularly consumed caffeine and alcohol which may have impinged on sleep and daytime functioning levels. Increased amounts of caffeine have known affects upon sleep including delayed sleep onset latency, reduced sleep length and increase amounts of stage I sleep (Roehrs & Roth, 2008). Furthermore, increased alcohol consumption shortens sleep latency, and has profound effects upon sleep continuity and architecture (Roehrs & Roth, 2001). For the current study, no relationships were found between any of the above lifestyle drugs and subjective sleep. However stroke patients consumed significantly more caffeine in compared to controls which may reflect increased tiredness.
3.4.3 Implications of The Findings

Service Improvement
Approximately 40% of patients felt that healthy sleep was not a priority during hospital stay. Patients commented on the poor sleeping environments and lack of specific sleep treatment. In addition, the results highlighted several severely poor sleepers in the stroke group, exhibiting likely clinical sleep disorders. Alarmingly, these patients were not receiving medical attention regarding their sleep problems. Untreated sleep disorders are associated with poorer vocational outcome, increased behavioural and cognitive problems, and greater psychological disturbance in brain injured patients (Burke, Shah, Schneider, Ahangar, & Aladai, 2004). Therefore sleep is vital to address in addition to other post stroke complications. The present study highlights a lack of service/neglect of major health problems in stroke.

As psychological adjustment was largely associated with sleep and daytime functioning disturbances, addressing underlying psychological distress may alleviate sleeping difficulties and improve sleepiness and fatigue levels. Bowen, Knapp, Hoffman, & Lowe (2005) reported the results of a large scale audit of UK stroke services and only 50% of services were adequately addressing psychological health. The results of this chapter further highlight the need to increase access to psychological therapies for stroke patients as well as managing sleep. Moreover, improving sleep wake cycles is a possible non-pharmacological option for those with post stroke depression (Khan, Leung, & Jay, 2008). Furthermore, early recognition of sleep problems may actually act as a buffer for developing psychological illness (Steptoe et al., 2008).

Increase Clinical Knowledge
The results of this study contribute important information to clinicians by enhancing knowledge of post stroke sleep behaviour. At present, sleep disorders and the importance of healthy sleep are poorly covered in medical education (Stores, 2007)
and, as the results of this study suggest, are entirely lacking in stroke medicine. Post brain injury sleep disorders often remain unrecognised by medical staff (Richard J. Castriotta & Lai, 2001; Wessendorf et al., 2000), who have been known to overestimate the amount of sleep patients achieve (Aurell & Elmqvist, 1985). Improvements in post brain injury education for medical staff and the patients themselves is urgently required. Critically, clinicians should also promote the role of healthy sleep to patients and their carers (Parcell et al., 2006). In particular, patients should be warned of the difficulties associated with sleepiness and fatigue which negatively impact activities of daily living (Schepers et al., 2006) and impose safety risks including falls and driving (Lundqvist et al., 2008; Michael et al., 2006; Sagberg, 2006).

**Implications Upon Recovery and Rehabilitation**

Recent evidence suggests a potential link between sleep and stroke recovery outcome (Bassetti & Aldrich, 2001; Cadilhac et al., 2005; Choi-Kwon et al., 2005; Giubilei et al., 1992; Glader et al., 2002; Good et al., 1996; Herrmann et al., 2008; Ingles et al., 1999; Kaneko et al., 2003b; Rola et al., 2007; Sandberg et al., 2001; Vock et al., 2002; Winward, Sackley, Metha, & Rothwell, 2009). Furthermore, several studies have reported that excessive sleepiness and fatigue disrupt rehabilitation sessions (Barker-Collo et al., 2007; Morley et al., 2005; Worthington & Melia, 2006). It is therefore conceivable that treating sleep disorders and alleviating daytime functioning problems may potentially enhance stroke recovery and the efficacy of rehabilitation efforts. However, further investigation is required to establish this potential link. These issues are addressed further in Chapters 4 and 6 of this thesis.

**3.4.4 Methodological Limitations**

**Subjective Assessments**

Several authors have concluded that subjective sleep and daytime functioning reports in brain injured samples are subject to inaccuracies when compared to objective
assessments (Castriotta et al., 2007; Makley et al., 2008; Masel et al., 2001). As results of the current study were in contrast to some studies which show that objective sleep problems (Masel et al., 2001; Schuiling et al., 2005; Vock et al., 2002), and excessive sleepiness (Bassetti et al., 1996; Masel et al., 2001). With regard to fatigue, which is highly prevalent in stroke patients through self reports (Choi-Kwon et al., 2005; Ingles et al., 1999; Park et al., 2009; Schepers et al., 2006; Valko et al., 2008; van der Werf et al., 2001), the results of this study suggest subjective fatigue in was not as high. It is possible that patient reports in this study were underestimated as patients are either unaware of sleep changes or influenced by experimenter bias. For example, recruitment of a highly motivated sample may include those more likely to alter their responses in order to be accepted onto the rehabilitation programme (CIT). Another explanation may be that the threshold for what is considered a ‘problem’ changes after stroke. What is considered sleepy for someone who has had a brain injury may be different to a non-brain injured person. Stroke patients may accept that sleepiness and fatigue are normal manifestations of the stroke sequelae. For example, Bassetti et al. (1996) commented on the surprising lack of concern in the view of the patients with hypersomnia. Other subjective findings have shown no difference in ESS score between those with and without hypersomnia (Bassetti and Valko, 2006).

**Choice of Questionnaires**

Classification of sleep disorders as determined by the S50 should be interpreted carefully as additional objective measures are necessary for confirmatory diagnosis of a sleep disorder. For example, studies have shown that sleep apnoea is present in 20% of chronic stroke patients (Cadilhac et al., 2005), and sleep disordered breathing is present in 81% (Schuiling et al., 2005). However, the S50 scoring criteria classified only 3.28% of stroke patients in the current study. Furthermore, the S50 considered 4.92% of controls as having narcolepsy although these participants had not been diagnosed nor displayed behavioural characteristics of the disorder, a trait that is largely noticeable in narcoleptic patients (Guilleminault & Fromherz, 2005, p. 550).
3.4.5 Future Research

Further studies are required to characterise post stroke sleep behaviour. In particular, studies using alternative measures of sleep will supplement data provided by the current study. More specifically, it has been suggested that prospective investigations of sleep, e.g. using sleep diaries, are more accurate than retrospective questionnaires as used in the current study (Babkoff, Weller, & Lavidor, 1996). Furthermore, employing objective assessments of sleep behaviour will greatly build upon the findings presented in this chapter. Subsequent studies presented in the following chapters of this thesis aim to use alternative methods to further investigate sleep and daytime functioning in stroke patients.

Conclusion of Study 1

After careful consideration of the methodological influences upon interpretation of the data, the following main points were concluded from this study:

- Perceived sleep problems are present in approximately 30% of chronic stroke patients with residual motor deficits.
- The surprising similarity of sleep quality, sleepiness and fatigue between stroke patients and controls gave rise to the idea that patients may not hold reliable introspection of these behaviours. The results confirm previous findings, that subjective measures may not be accurate.
- Subjective excessive sleepiness is present in these patients however do not appear affect patients any worse than non-brain injured persons from the general population.
- High levels of fatigue are present in stroke patients compared to varied types of control samples.
• The selection procedure and exclusion criteria chosen for control groups is critical when collating incident rates of sleep problems after stroke.
• Current service provisions to not adequately address sleep which leaves some patients suffering with severely disturbed sleep, and perhaps even undiagnosed sleep disorders.
• Psychological adjustment is an important factor in the existence of sleep and daytime functioning problems.
• Fatigue and psychological stress greatly contributed to perceived health.

The results of the current study have implications for clinicians, patients and future studies with regard to subjective data collection. In particular, caution should be taken with regard to questionnaire choice and the control group selection. Study 4 presented in the following chapter aims to build on these results by using other modes of sleep assessment and to further examine how sleep is related to other aspects of the patients quality of life; specifically motor recovery.
CHAPTER 4
Study 2: Prospective Investigation of Longitudinal Sleep Behaviour and Correlates of Residual Motor Recovery

Chapter 4 Overview

The current study comprised two main aims: a) examine the concordance between subjective and objective measures of sleep, b) to prospectively explore sleep and daytime functioning using objective and subjective measures, and c) examine the relationship between sleep behaviour and level of motor functioning after stroke in a group of 42 chronic stroke patients with chronic motor deficits. By utilising a prospective study design, this study monitored sleep and daytime functioning over a two week period. Sleep monitoring was conducted using actigraphy and sleep diaries which provided objective and subjective data respectively. No known study has measured sleep and daytime functioning using this method of assessing sleep chronic stroke patients. Level of motor functioning was addressed in terms of residual upper limb motor ability. This was measured using a test battery comprising a fine grained motor assessment that measure functional ability, reaction time. In addition, real word affected arm use was examined. This study has clinical implications for post stroke sleep behaviour as well as future research protocols using actigraphy and sleep diaries in patients.

4.1Introduction
Sleep disturbances are evident in stroke patients as detected via PSG methods of assessment (Bassetti, 2005b). To some extent, these disturbances are perceived by patients (Campos et al., 2005; Leppävuori et al., 2002; Masel et al., 2001; Schuiling et al., 2005) however few studies have compared both objective and subjective measures. Furthermore, virtually no known studies have used a combination of both methods in chronic stroke patients with residual motor deficits. This may partly be due to the inconvenience and cost of PSG paradigms. In response to these the methodological issues with PSG, actigraphy is a favourable mode of sleep assessment for vulnerable groups.

4.1.1 Subjective and Objective Longitudinal Sleep Assessment

Technological advancements in actigraphy equipment and software have improved sensitivity of this method which has great advantages for sleep research. Actigraphy is becoming increasingly recognised as a valid assessment of sleep in various healthy and clinical cohorts, including brain injury.

Actigraphy

Retrospective subjective assessments are a useful screening tool to characterise a person's perception of their own sleep and daytime functioning behaviour (Buysse et al., 1989; Johns, 1991, 1994). However in order to fully describe how a person sleeps, it is useful to prospectively monitor sleep longitudinally, over several days, to characterise sleep more accurately (Babkoff et al., 1996). Longitudinal sleep monitoring is typically conducted through sleep diaries. However, perceived sleep estimations when benchmarked against to objective measures, give rise to an underestimation of night time awakenings (Fontaine, 1989; Kushida et al., 2001). Furthermore, some participants carrying out sleep diaries for longer periods of time become less motivated to complete the diaries accurately or forget to complete the

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7 Mixed stroke and TBI sample.
diary (Stone et al., 2002). Furthermore, those with sleep disorders are often inaccurate in reporting their own sleep behaviour (Means et al., 2003; Vanable et al., 2000). In order to avoid such methodological limitations, researchers often incorporate an objective measure of sleep. Although polysomnography (PSG) is the gold standard for measuring sleep, its uses in longitudinal sleep assessment are limited. As well as being expensive and typically limited to only several days of recording, PSG is intrusive upon a person's sleep due to electrode placement and unnatural sleeping conditions (Reynolds et al., 1992; Richards et al., 2000). Actigraphy has provided a favourable alternative to PSG in longitudinal sleep research as an attempt to resolve some of PSG limitations.

Actigraphy is widely used in sleep research and provides a range of sleep parameters such as sleep duration, sleep onset latency and night awakenings as well as napping behaviour, daytime activity levels and circadian rhythm patterns. Actigraphic information is recorded via a wrist worn device similar to a watch. The device records the intensity and duration of activity, and stores this information in the form of an activity count (this process is described in more detail in Section 1.2.3, Chapter 1). Activity counts are subsequently converted into sleep or wake epochs using a threshold based algorithm. These sleep and wake epochs are digitised for analysis whereby a range of sleep parameters can be extracted. Actigraphy, has a range of benefits; it is inexpensive, the devices can record and store data for up to three months, and it causes little, or no, disruption to natural sleep behaviour. The actigraphy method allows the longitudinal study of sleep and daytime functioning in a wide variety of research cohorts for up to several months and requires minimal supervision (Ancoli-Israel et al., 2003).

Sleep diaries are often used in conjunction with actigraphy, either as a complementary measure for manual input of bed time and get up time for analysis, or for examination of concordance between methods. The combination of methods also

\[8\) Algorithms vary depending on manufacturer.\]
enables detection of artefact within the actigraphy recordings, for example if the
watch was removed for any reason, then this can be reported in the sleep diary (Avi
Sadeh & Acebo, 2002).

**Actigraphy in Healthy Populations**

Studies have reported between 91% and 93% agreement between actigraphy and PSG
in healthy participants for sleep variables including sleep efficiency and duration
(Jean-Louis, Kripke, Mason, Elliott, & Youngstedt, 2001). More specifically,
actigraphy has correctly classified sleep from wake 88-90% of the time in comparison
to PSG (Cole et al., 1992; Sadeh et al., 1995). However, some studies have
highlighted that actigraphy is less accurate for determining night awakenings and may
over estimate total sleep time in comparison to PSG (Ancoli-Israel et al., 2003;
Paquet, Kawinska, & Carrier, 2007). Improved sensitivity of actigraphy devices and
software have greatly enhanced the calculations for sleep scoring and studies have
shown good correlations with PSG measures in a range of populations (Littner et al.,
2003).

**Actigraphy in Populations With Sleep Disturbances and Daytime Sleepiness**

Actigraphy has been widely used in a range of sleep disordered cohorts however
some authors emphasise the accuracy of actigraphy is reduced in these patients
(Sadeh & Acebo, 2002). Several studies have successfully used actigraphy in
insomnia groups, however an over estimation of sleep time is commonly observed
(Chambers, 1994; Guilleminault et al., 1995; Hauri, 1992). However, it is important
to note that these studies used sleep diaries as a comparison rather than PSG. Few
studies have validated actigraphy using PSG in insomnia cohorts, however two
studies have shown good correlation for sleep duration (Jean-Louis, Zizi, von
Gizycki, & Hauri, 1999; Lichstein et al., 2006). Actigraphy was also sensitive to mild
sleep disturbances in the non-sleep disordered population (Horne, Pankhurst, Reyner,
Hume, & Diamond, 1994).
Actigraphy is considered less sensitive to sleep disordered cohorts, other than insomnia. Although, Kushida et al. (2001) showed that a combination of subjective reports and actigraphy was able to successfully detect sleep duration and sleep efficiency in comparison to PSG in those with sleep disordered breathing. Furthermore, in this study, actigraphy was also useful for detecting night awakenings in comparison with PSG (Kushida et al., 2001). Some studies have also shown good correlation between actigraphy and PSG in those with restless leg syndrome (Collado-Seidel et al., 1999; Trenkwalder et al., 1995) and less success for periodic limb movement disorder (Gschliesser, Brandauer, Ulmer, Poewe, & Hogl, 2006; Sforza, Zamagni, Petiav, & Krieger, 1999).

Daytime actigraphy is sensitive to daytime sleepiness, inferred by a reduction in activity counts (Bruck, Kennedy, Cooper, & Apel, 2005; Littner et al., 2003; Roehrs, Turner, & Roth, 2000). Actigraphy can also be used to determine daytime nap frequency and duration (Lockley et al., 1999). However, the recordings are vulnerable to the possibility of falsely identify times of low activity as naps (Hauri, 1992; Paquet et al., 2007). Therefore, a combination of sleep diaries and actigraphy is advised to enable removal of artefact such as watch removal (Goldman et al., 2008; Pollak, Stokes, & Wagner, 1998; Sadeh & Acebo, 2002). It is important to note that actigraphy has also demonstrated sensitivity to napping which was not reported in sleep diaries (Evans & Rogers, 1994).

**Chronically Ill Populations (non-neurological)**

Actigraphy studies have provided crucial information regarding sleep and daytime functioning of chronically ill patients within hospital, institutional and home environments. Good concordance has been reported between actigraphy and medical staff observations of waking activity in hospitalised patients who were critically ill (Winkelman, Higgins, & Chen, 2005). The acquisition of specific sleep parameters, including sleep duration, in chronically ill patients has also shown good concordance with PSG measures (Ancoli-Israel, Clopton, Klauber, Fell, & Mason, 1997a). Actigraphy is further sensitive to lower levels of activity in those with chronic pain...
(Long, Palermo, & Manees, 2008), fatigue (Friedberg & Sohl, 2009) and cancer patients (Minors et al., 1996; Mormont et al., 2002).

Furthermore, studies have also examined actigraphy in the context of recovery levels in chronically ill patients. Improved sleep-wake cycles correlate with better quality of life and survival of cancer patients (Mormont et al., 2000). Normal circadian rhythm patterns as recorded by actigraphy correlated with better recovery after cardiac surgery patients (Redeker, Tamburri, & Howland, 1998).

**Actigraphy In Populations With Neurological Conditions**

Actigraphy has been useful for monitoring sleep/wake cycles in patients with neurological disease such as multiple sclerosis (Attarian, Brown, Duntley, Carter, & Cross, 2004), spinal injury (Spivak, Oksenberg, & Catz, 2007) and Alzheimer’s disease (Ancoli-Israel et al., 2003). Actigraphy has also been applied to patients with acquired brain injury including stroke (Bassetti & Valko, 2006; Hermann et al., 2008; Masel et al., 2001; Schuiling et al., 2005) and TBI (Baumann et al., 2007; Makley et al., 2009). Specifically within chronic stroke, actigraphy revealed sleep disturbances that were confirmed by PSG (Schuiling et al., 2005). Actigraphy reports of sleep duration have also correlated well with subjective sleep needs in chronic stroke patients (Hermann et al., 2008). However, there is no known study that has addressed the concordance between sleep diaries and actigraphy in a brain injured cohort.

Actigraphy has also been useful for determining daytime activity in patients in a group of chronic mixed stroke and traumatic brain injury (TBI) sample where naps correlated with less activity (Muller et al., 2006). Less activity also correlates with the degree of post stroke hypersomnia (Bassetti & Valko, 2006). One study used actigraphy to monitor ambulatory activity in a group of community dwelling stroke patients with chronic motor deficits (Haeuber, Shaughnessy, Forrester, Coleman, & Macko, 2004). It was concluded that this method was useful for quantifying daytime activity levels in these patients, however sleep behaviour was not addressed in this study. Another study used actigraphy to assess nocturnal and diurnal sleep in a group
of older patients with a range of rehabilitative needs including stroke, osteoporosis, cardiac problems and pulmonary problems (Alessi et al., 2008). The study found good concordance between actigraphy and staff observations of daytime sleep. A daily sleep diary was not completed by patients during this study however retrospective sleep disturbance was confirmed by actigraphy.

Actigraphy and subjective sleep diary measures are extremely useful for characterising sleep and daytime behaviour in stroke patients in situations where PSG is not feasible. Therefore further research can explore the role of sleep in the context of stroke recovery.

4.1.2 Sleep And Recovery Levels After Stroke

Previous literature and the findings from Study 1 of this thesis have shown that sleep and daytime functioning is persistently disturbed in some patients after stroke (Cadilhac et al., 2005; Campos et al., 2005; Choi-Kwon et al., 2005; Ingles et al., 1999; Muller et al., 2006; Park et al., 2009; Valko et al., 2008; van der Werf et al., 2001; Vock et al., 2002). Furthermore, the findings of Study 1 and the results of Schuiling et al., (2005) revealed that poor sleep is also related to poorer perceived health after stroke. In addition to poor health, several studies have identified a link between poorer sleep and poorer recovery levels after stroke, including independence and ability to perform activities of daily living, often referred to as outcome. A key parameter in the context of sleep and stroke recovery is that of the time since injury. Generally, two phases have been identified: acute (<12 months) and chronic (≥12 months). The majority of studies have examined sleep and recovery within the acute phase, whereas follow-up investigations focusing on chronic cohorts are presently limited.

Acute Outcome
A relationship between poor sleep and poorer stroke outcome is commonly observed in the acute phase of stroke (Bassetti & Aldrich, 2001; Hachinski et al., 1987; Leppävuori et al., 2002; Siccoli & Bassetti, 2008; Takekawa et al., 2007). In particular, several studies have shown that sleep disordered breathing is associated with poorer levels of stroke recovery (Bassetti & Aldrich, 1999; Good et al., 1996; Kaneko et al., 2003b; Sandberg et al., 2001; Spriggs et al., 1992a). Furthermore, disrupted sleep architecture has also been associated with poorer outcome after stroke (Bassetti & Aldrich, 2001; Giubilei et al., 1992; Hachinski et al., 1987; Valente et al., 2002). Improvement in sleep EEG correlates with improvement of stroke recovery over time (Giubilei et al., 1992; Gottselig et al., 2002). The authors postulated that, better sleep is suggestive of good brain function, perhaps even having a supportive role in stroke recovery (Gottselig et al., 2002; Vock et al., 2002).

**Chronic Outcome**

The relationship between sleep and stroke recovery is less clear in the chronic phase. Table 4.1 presents existing studies that have examined sleep and residual recovery in chronic stroke patients. Although a link was observed between sleep disordered breathing and poorer outcome in acute stroke, this pattern has only been reported in one study for chronic patients (Cadilhac et al., 2005). Another study observed found that those patients with poor levels of functioning also had disturbed sleep (Worthington & Melia, 2006). The authors suggested that the observed poorer functioning in patients was a result of increased daytime performance deficits as a result of poor sleep at night.

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9 Mixed stroke and TBI sample.
Table 4.1. Summary of the literature for chronic (≥12 months\textsuperscript{10}) stroke and mixed stroke and TBI samples. A full list of abbreviations is presented in Appendix F1.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Type of Brain Injury</th>
<th>n</th>
<th>Age</th>
<th>Chronicity</th>
<th>PSG</th>
<th>Subjective</th>
<th>AW</th>
<th>Health</th>
<th>Outcome</th>
<th>Chronic Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cadiha et al.</td>
<td>2005</td>
<td>Mixed Stroke</td>
<td>78</td>
<td>64</td>
<td>3 yrs ✓</td>
<td>ESS</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>mRS</td>
<td>Stroke severity was independently associated with sleep disordered breathing</td>
</tr>
<tr>
<td>Choi-Kwon et al.</td>
<td>2005</td>
<td>Mixed Stroke</td>
<td>220</td>
<td>60</td>
<td>15 mins</td>
<td>Fatigue (VAS), FSS, FIS</td>
<td>-</td>
<td>GCS</td>
<td>MRCMD, mRS</td>
<td>Post stroke fatigue was related to poorer mRS</td>
<td></td>
</tr>
<tr>
<td>Gleder et al.</td>
<td>2002</td>
<td>Mixed Stroke</td>
<td>4023</td>
<td>71.8</td>
<td>30.4 mins</td>
<td>“Do you feel tired?”</td>
<td>-</td>
<td>In house health interview</td>
<td>In house ADLs</td>
<td>Increased fatigue was associated with poorer ADLs, health, anxiety, pain and depression</td>
<td></td>
</tr>
<tr>
<td>Hermann et al.</td>
<td>2007</td>
<td>Paramedian Thalamic Stroke</td>
<td>31</td>
<td>48.4</td>
<td>9.7 days, 12, 24 mins ✓</td>
<td>Sleep needs ✓</td>
<td>-</td>
<td>GDS, in house quest.</td>
<td>SSS, mRS, BI</td>
<td>Increased sleep needs were associated with poorer recovery</td>
<td></td>
</tr>
<tr>
<td>Ingels et al.</td>
<td>1999</td>
<td>Mixed Stroke</td>
<td>88</td>
<td>66.6</td>
<td>212 days</td>
<td>FIS, PSQI ✓</td>
<td>-</td>
<td>-</td>
<td>SSS, BI, OHS</td>
<td>Fatigue was not related to functional recovery but negatively affected physical abilities</td>
<td></td>
</tr>
<tr>
<td>Masel et al.</td>
<td>2001</td>
<td>Mixed TBI and Stroke</td>
<td>71</td>
<td>32</td>
<td>38 mins ✓</td>
<td>PSQI, ESS ✓</td>
<td>-</td>
<td>-</td>
<td>MCMII</td>
<td>No relationship between sleep and psychological/cognitive functioning</td>
<td></td>
</tr>
<tr>
<td>Muller et al.</td>
<td>2006</td>
<td>Mixed TBI and Stroke</td>
<td>24</td>
<td>47.6</td>
<td>22 mins</td>
<td>-</td>
<td>✓</td>
<td>AES, BDI</td>
<td>BADL</td>
<td>Lower activity, increased napping and cognitive difficulty observed in those with high apathy</td>
<td></td>
</tr>
<tr>
<td>Naess et al.</td>
<td>2005</td>
<td>Cerebral Infarction</td>
<td>192</td>
<td>47.8</td>
<td>6 years</td>
<td>FSS</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>mRS</td>
<td>Fatigue associated with poorer outcome</td>
</tr>
<tr>
<td>Park et al.</td>
<td>2009</td>
<td>Mixed Stroke</td>
<td>40</td>
<td>59.9</td>
<td>32.7 mins</td>
<td>FSS</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>BI, MI</td>
<td>Fatigue was not associated with outcome but correlated with sleep disturbance</td>
</tr>
<tr>
<td>Schepers et al.</td>
<td>2006</td>
<td>Mixed Stroke</td>
<td>167</td>
<td>56.4</td>
<td>&lt;1 day, 6mm, 1 yr ✓</td>
<td>FSS</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>MHLC</td>
<td>Increased fatigue was not associated with motor ability</td>
</tr>
<tr>
<td>Worthington &amp; Mella</td>
<td>2006</td>
<td>Mixed TBI and Stroke</td>
<td>135</td>
<td>38</td>
<td>1 wk, 2wks ✓</td>
<td>Nursing staff reports</td>
<td>-</td>
<td>-</td>
<td>Response to rehabilitation</td>
<td>Arousal disturbance disrupted rehabilitation, daily activities, recovery and social relationships</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{10} Ingels et al. (1999) included patients >9 months chronicity.
Prospective studies have shown that good quality sleep during acute phase was associated with good long term outcome (Vock et al., 2002). Presence of snoring was related to poorer prognosis at 6 months after stroke (Spriggs et al., 1992a). Other studies have reported that reduced sleep efficiency, reduced total sleep time, increased 24 hour sleep was predictive of poorer outcome at long term follow-up. (Bassetti & Aldrich, 2001; Giubilei et al., 1992; Hermann et al., 2008; Vock et al., 2002). These studies did not take into account other factors between initial sleep assessment and long term outcome measures which may have contributed to recovery outcome. Such factors may include levels of medical care and rehabilitation received by patients which may greatly vary between patients from acute to chronic phases of stroke.

In addition to sleep difficulties, fatigue is also associated with poorer recovery levels in chronic phase of stroke (Glader, B. Stegmayr, & K. Asplund, 2002; Ingles et al., 1999; Naess et al., 2005). Choi-Kwon et al. (2005) showed that chronic post stroke fatigue has a greater negative impact on physical functioning in comparison to cognitive and psychological disturbance (Choi-Kwon et al., 2005). Conversely, two studies found that fatigue did not correlate with specifically with physical function (Park et al., 2009; Schepers et al., 2006). No known studies have reported a correlation between increased chronic sleepiness and stroke outcome, however greater sleep need and increased napping was associated with poorer stroke outcome (Hermann et al., 2008; Muller et al., 2006).

Sleep and fatigue may be related to post stroke recovery as evidence suggests that sleep is a modulator for factors that influence recovery, such as sustaining good daytime functioning (Bassetti & Valko, 2006; Worthington & Melia, 2006), cognitive performance (Decary, Rouleau, & Montplaisir, 2000; Leegaard, 1983; Van Zandvoort et al., 1998), maintaining good psychological health (Khan, 2004; Schuiling et al., 2005) and generally modulating quality of life (Schuiling et al., 2005). Furthermore, studies show that sleep may facilitate brain plasticity (Walker & Stickgold, 2006), a vital process for stroke recovery (Matthews et al., 2004; Mulder & Hochstenbach,
These findings have led some researchers to theorise that sleep may enhance post stroke recovery (Barker-Collo et al., 2007; Robertson & Cohen, 2006; Siensukon & Boyd, 2009b; Fabienne Staub & Julien Bogousslavsky, 2001; Walker et al., 2003a). However this notion has not yet been fully explored in chronic patients.

4.1.3 Rationale For Study 2

The evidence that shows a link between sleep and stroke recovery is encouraging however more research is required to address the limitations in the existing studies. Particular areas that require attention are chronicity, sleep assessments and outcome measures.

Limitations of Previous Studies

Existing studies typically involve patients with either a wide range of chronicity or recruit those still within the acute phase of recovery. Figure 4.1 presents the complications that arise when using such cohorts thereby increases the heterogeneous nature of the sample which may affect interpretation of the data. Complications of acute stroke are highly influential upon results of an assessment of sleep and recovery during this time. Such factors include change in sleep environment, biological and psychological stress, increased bed rest, drugs, fever, pain, cognitive deficits and poor psychological adjustment (Bassetti & Aldrich, 1999; Hermann et al., 2008; McDowd et al., 2003; Pohjasvaara et al., 2001; Sisson, 1995; Van Zandvoort et al., 1998; Visser-Meily et al., 2005). These factors also contribute to poorer outcomes after stroke (Kotila et al., 1984). There is a need for more studies to examine sleep in homogenous samples to minimise potential confounding factors on results (Terzoudi et al., 2009; Vock et al., 2002). These post stroke complications are unlikely to become stable until 12 months after injury (Donnan et al., 1991; Duncan et al., 1992; Horgan et al., 2009; Jorgensen et al., 1995; Kotila et al., 1984; Lesniak et al., 2008; Rasquin, Verhey, Lousberg, Winkens, & Lodder, 2002). Based on the characteristics
of patients during the acute phase, examining patients in the chronic phase of recovery enables recruitment of a more homogenous group.

Figure 4.1. Model of post stroke recovery over time. Based on the findings of (Donnan et al., 1991; Duncan et al., 1992; Horgan et al., 2009; Jorgensen et al., 1995; Kotila et al., 1984; Lesniak et al., 2008; Rasquin et al., 2002) which show that recovery stabilises after 12 months.

Another prominent limitation in these studies is the substantial variation in the way stroke outcome or recovery is defined and measured. The reported studies use global assessments to measure stroke outcome such as the Barthel Index (Mahoney & Barthel, 1965) or Rankin Scale (Bonita & Beaglehole, 1988). These scales provide a measure of general recovery and are not sensitive enough to measure modest recovery. In particular, they are not fine grained enough to assess modest changes (Ashford et al., 2008; Duncan et al., 1997; Lai et al., 2002). Sensitivity of an instrument may be highly important when determining the relationship between sleep and levels of post stroke outcome.
Few studies have used actigraphy with acute or chronic stroke patients in terms of characterising post stroke sleep behaviour or how sleep relates to residual recovery levels. This may partly be due to the suggestion that actigraphy is vulnerable to artefact due to the lower levels of motor ability of brain injured patients (Laakso et al., 2004; Sadeh & Acebo, 2002). Careful selection of a homogenous sample that are recruited based on their motor ability levels, may reduce the influence of motor disability related artefact. For example, those with hemiparesis are only affected on one side of the body, therefore the actigraphy device can be worn on the non-affected wrist. Furthermore, sleep diaries are beneficial for addressing artifact issues of those with motor deficits with regard to daytime napping.

As research indicates that sleep and post stroke recovery is related, and even postulate that sleep may be a mechanism to promote recovery, it is important to fully explore this idea as an avenue within stroke rehabilitation. Therefore it is important to firstly fully characterise sleep behaviour in chronic stroke patients as sleep is often disturbed in the chronic phase of stroke. If good sleep is related to good recovery then it is imperative to fully explore this notion in all stages of recovery, in particular, chronic stroke patients. Richter et al. (1995) reported that assessment and treatment of sleep disorders in patients with mild brain injury which correlated with improved clinical outcomes and also reduced cognitive, somatic and emotional problems associated with injury. Therefore, treating sleep disturbance and maintaining healthy sleep should be top priority in neurorehabilitative medicine.

4.1.4 Aims and Hypotheses

The aim of this study was to: a) investigate the agreement between subjective sleep perception and actigraphy, b) describe prospective longitudinal sleep behaviour using subjective and objective parameters, and c) assess the relationship between sleep behaviour and residual upper limb motor recovery after stroke. Unlike previous
studies which have addressed sleep, daytime functioning in terms of stroke recovery, this current study incorporated a motor test battery which included fine grained assessment of upper arm function as well as real world arm use.

Based on review of the literature, the following research questions were formulated:

1) How well do subjective sleep diaries and actigraphy agree in stroke patients with chronic residual motor deficits?

2) Are sleep and daytime functioning disturbances present in chronic stroke patients as measured using subjective and objective longitudinal sleep monitoring?

3) Are reduced overall activity levels associated with increased sleepiness and fatigue?

4) Is sleep behaviour, daytime functioning, or activity levels related to residual motor recovery in the chronic phase after stroke?

4.2 Methods

4.2.1 Design

A prospective design was employed to monitor longitudinal sleep and daytime functioning behaviour for two weeks in a group of chronic stroke patients (Figure 4.2). Subjective and objective sleep was measured using sleep diaries and actigraphy respectively. Residual motor recovery was assessed at baseline (T1) and repeated at pre-CIT (T2). The data was subjected to a within groups design where matched sleep indices drawn from the sleep diary and actigraphy were compared (i.e. subjective
time in be compared with that same parameter recording by actigraphy). Weekday and weekend recordings were also compared. Furthermore, the degree of association between subjective sleepiness, fatigue and activity were examined. Sleep and daytime functioning were subsequently correlated with residual motor recovery levels.

Figure 4.2. Design of CIT trial. The highlighted section indicates time point from which data for this study was collected.

4.2.2 Participants

Forty-two community dwelling chronic stroke patients with residual motor deficits were recruited for the present study. All patients fulfilled the inclusion/exclusion criteria as described in Section 2.2.1, Chapter 2. All patients fulfilled the motor criteria employed by the CIT trial.

11 A total of 54 patients were eligible for CIT (section 2.2.1, chapter 2). Ten patients were not included in the analysis for this study. Two patients were excluded from this study as they presented of bilateral strokes which resulted in hemiparesis in both upper limbs. It was felt that this may interact with actigraphy recordings. Two patients were non-compliant regarding sleep diary completion. The data of two patients was not included due to actigraphy fault. Four patients did not complete full two week baseline sleep monitoring.
4.2.3 Materials

Subjective sleep behaviour was assessed using a pen and paper based sleep diary that required patients to report their perception of nocturnal sleep. The sleep diaries also contained twice daily Karolinska Sleepiness Scale (KSS) and Daily Fatigue Scales (D-FIS) to assess sleepiness and fatigue respectively during the morning and evening. Twenty-four hour actigraphy recordings were conducted using the ‘Actiwatch Mini ®’ (CamNtech Ltd., © 2009), worn on the non-affected arm. Sleep diaries and actigraphy recording materials are described in more detail within Section 2.3.4, Chapter 2. In addition, PSQI, ESS and FSS scores were used as a measure of retrospective habitual sleep and daytime functioning. Residual motor recovery was assessed using a battery of upper limb motor ability assessments including the Wolf Motor Function Test (WMFT; Wolf, Lecraw, Barton, & Jann, 1989) and Motor Activity Log (MAL; Taub et al., 1993). These tests are all fully described Section 2.3.3, Chapter 2.

4.2.4 Procedure

Patients attended the baseline test point (T1) which comprised the first administration of the motor test battery. Additionally during T1, patients were fitted with the actiwatches, given the sleep diary and provided with instructions. Participants were instructed to complete the sleep diaries as accurately as possible and to report any instances when the actiwatches were removed to avoid miscoding of a daytime sleep period. Sleep diaries and actigraphy recordings were continued for two weeks (baseline period). At the end of the two week baseline period, the pre-CIT motor testing (T2) was carried out. This test point repeated the procedure carried out during T1.
4.2.5 Analysis

Sleep diary and actigraphy data were aggregated across 10 weekdays and weekend days. Weekdays and weekends were analysed separately due to shifts in sleep schedules and behaviour observed in the general population (Groeger et al., 2004) and brain injured populations (Campos et al., 2005). Only weekday data was used for characterising sleep in these patients and for analysis in the context of motor recovery. Patient sleep schedules were also compared to published norms.

Sleep Diary

The following nocturnal sleep parameters were extracted from the sleep diary: bed time (24 hour clock), wake time (24 hour clock)\textsuperscript{12}, get up time (24 hour clock), time in bed (mins), sleep duration (mins), sleep onset latency (mins), sleep efficiency (%) and night awakenings (frequency and duration). Daytime functioning parameters were morning and evening KSS and D-FIS ratings as well as daytime nap reports including frequency and duration per day.

Actigraphy

Actigraphy recordings were analysed using Actiwatch Sleep Analysis Software (Version 7.22, CamNtech Ltd, © 2009). The following sleep parameters were calculated: bed Time (24 Hour Clock), wake time (24 Hour Clock)\textsuperscript{2}, get up time (24 Hour Clock), time in bed (mins), sleep duration (mins), sleep onset latency (mins), sleep efficiency (%) and night awakenings (frequency and duration). Bed time and get up time were entered manually into the software (using the sleep diary for guidance) whereas the remaining parameters were calculated using the sleep scoring function within the Actiwatch Sleep Analysis Software. Sleep scoring analysis was set using a medium sensitivity of ≤40 activity counts per minute to define wake. This level of sensitivity has shown good correlation with PSG and actigraphy settings of even greater sensitivity (Kushida et al., 2001).

\textsuperscript{12} time of final awakening.
Diurnal sleep behaviour was measured using the napping analysis function where a nap was defined as any sleep period between get up time and bed time for a minimum of 15 minutes. The sensitivity was set to $\leq 10$ activity counts per minute to define an epoch of daytime sleep. This threshold has been used previously in brain injured patients with chronic motor difficulties (Laakso et al., 2004). For activity analysis, raw data (activity count) was exported in one minute epochs between 0800 and 2200 hours for each day. Each epoch was averaged across the weekdays recorded per phase (10 days), and then summed into one hour time bins. A reduction in daytime activity considered an indication of fatigue or sleepiness as shown previously in healthy (Roehrs et al., 2000) and stroke cohorts (Bassetti & Valko, 2006; Muller, Czymmek, Thone-Otto, & Von Cramon, 2006).

**Motor Ability Test Battery**

The WMFT provided two measures of motor ability; median reaction time$^{13}$ (mins) and mean functional ability (score out of 7) averaged across all 15 tasks. Two measures of subjectively rated arm use outside of the laboratory including amount of use (AOU) and quality of use (QOU) were extracted from the MAL. Section 2.3.4, Chapter 2, provides a detailed description of scoring procedures for these tests. Due to the unfamiliarity of the motor test situation, residual motor ability data from T2 was used for analysis as recommended by Whitall (2004) for a more accurate representation of motor ability.

**Statistical Tests**

Due to the non-normal distribution of the data, all statistical tests were carried out using non-parametric alternatives. Within group tests of difference were calculated using the Wilcoxon signed ranks test. Tests of association were calculated using Spearman’s rank correlation coefficient. Statistical tests of difference and association were applied to matched indices of the sleep diary and actigraphy. This method has

---

$^{13}$ WMFT median reaction time is considered is more stable across repeated test sessions and less susceptible to outliers (Wolf et al, 1989; Morris 2001).
been recommended by Wicklow and Espie (2000b) as significant correlations found between sleep diaries and actigraphy may also significantly differ in terms of the mean. Activity levels were examined using a between groups analysis comparing those with and without fatigue or sleepiness using the Mann Whitney U test. All statistical tests were carried out using a one tailed analyses with an alpha level set to \( p \leq 0.05 \).

4.3 Results

4.3.1 Demographics

The demographics for all stroke patients are presented in Table 4.2.
Table 4.2. Data presented as mean, +/- 1 SD and range or percent valid where appropriate. The remaining 35.71% of stroke patients unlisted for employment status were classified as not working. For individual case information for all participants, see Appendix C.

<table>
<thead>
<tr>
<th>Demographical Variables</th>
<th>Stroke Patients (n=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender (M:F)</strong></td>
<td>24:18</td>
</tr>
<tr>
<td><strong>Age (Years)</strong></td>
<td>55.02 ± 10.41 (28.73)</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td>23.95 ± 2.44 (18.20-31)</td>
</tr>
<tr>
<td><strong>NART (IQ)</strong></td>
<td>116.63 ± 6.86 (96.12-126)</td>
</tr>
<tr>
<td><strong>Mini Mental State Exam</strong></td>
<td>29.15 ± 1.04 (20-30)</td>
</tr>
<tr>
<td><strong>GPSQI</strong></td>
<td>4.83 ± 3.64 (0-13)</td>
</tr>
<tr>
<td><strong>ESS</strong></td>
<td>6.51 ± 4.36 (0-18)</td>
</tr>
<tr>
<td><strong>FSS</strong></td>
<td>23.07 ± 14.87 (0-51)</td>
</tr>
<tr>
<td><strong>Education Level:</strong></td>
<td></td>
</tr>
<tr>
<td>School Leavers Certificate</td>
<td>29.27%</td>
</tr>
<tr>
<td>Further Study</td>
<td>41.46%</td>
</tr>
<tr>
<td>Higher Education</td>
<td>29.27%</td>
</tr>
<tr>
<td><strong>Employment Status:</strong></td>
<td></td>
</tr>
<tr>
<td>Full Time</td>
<td>14.29%</td>
</tr>
<tr>
<td>Part Time</td>
<td>16.67%</td>
</tr>
<tr>
<td>Retired</td>
<td>33.33%</td>
</tr>
<tr>
<td>Studying</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Living Support:</strong></td>
<td></td>
</tr>
<tr>
<td>Living Alone</td>
<td>14.29%</td>
</tr>
<tr>
<td>Living With Family</td>
<td>85.71%</td>
</tr>
<tr>
<td><strong>Chronicity (Months)</strong></td>
<td>57.93 ± 44.80 (11-210)</td>
</tr>
<tr>
<td><strong>Type of Stroke:</strong></td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>47.62%</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>19.05%</td>
</tr>
<tr>
<td>Both</td>
<td>23.8%</td>
</tr>
<tr>
<td><strong>Lesion Hemisphere</strong></td>
<td>19 Left, 23 Right</td>
</tr>
<tr>
<td><strong>Co-morbid Conditions:</strong></td>
<td></td>
</tr>
<tr>
<td>Psychological</td>
<td>23.81%</td>
</tr>
<tr>
<td>Muscular</td>
<td>7.14%</td>
</tr>
<tr>
<td>Neurological</td>
<td>19.05%</td>
</tr>
<tr>
<td>Cardiac</td>
<td>42.86%</td>
</tr>
<tr>
<td>Cancer</td>
<td>2.58%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.38%</td>
</tr>
<tr>
<td>Pain</td>
<td>2.38%</td>
</tr>
<tr>
<td>Dysphasia</td>
<td>23.8%</td>
</tr>
<tr>
<td><strong>Medication:</strong></td>
<td></td>
</tr>
<tr>
<td>Anti-depressant</td>
<td>14.29%</td>
</tr>
<tr>
<td>Pain Relief</td>
<td>2.38%</td>
</tr>
<tr>
<td>Cardiac Control</td>
<td>4.76%</td>
</tr>
<tr>
<td>Anti-epileptic</td>
<td>14.29%</td>
</tr>
<tr>
<td>Sleep Hypnotics</td>
<td>0%</td>
</tr>
<tr>
<td>Alcohol (Units per week)</td>
<td>7.9 ± 8.91 (0-32)</td>
</tr>
<tr>
<td>Caffeine (Cups per day)</td>
<td>5.03 ± 2.96 (0-12)</td>
</tr>
<tr>
<td>Nicotine (Cigarettes Per Day)</td>
<td>0.88 ± 3.48 (0-20)</td>
</tr>
</tbody>
</table>

(-) not required or not recorded as part of this study.
* 23.8% of the patients experienced expressive dysphasia therefore only completed the 3-step command on the MSE and were not included in the total mean score. These patients also did not complete the NART.
† Value included only those patients who could report type of stroke.
‡ Neurological conditions other than stroke.
4.3.2 Sleep Diary and Actigraphy Concordance

Concordance Between Sleep Diaries and Actigraphy

Correlations and tests of difference for matched nocturnal sleep and napping parameters are presented in Tables 4.3 and 4.4 for weekday and weekend day analyses respectively. For both weekdays and weekends, sleep diaries and actigraphy were in good concordance, ranging from 0.27 to 0.85, for the following parameters: bed time, get up time, time in bed, sleep duration, sleep onset latency and nap length. An exception to this pattern was observed for night awakenings.

Significant differences between the sleep diaries and actigraphy emerged for wake time, time in bed, sleep duration, sleep onset latency, sleep efficiency, night awakenings and nap frequency during the week (Table 4.3). Significant differences in wake time, frequency and duration of night awakenings, and nap frequency emerged at weekends (Table 4.4). Apart from night awakenings, these observed differences also demonstrate a degree of concordance (Figure 4.3 and 4.4). This suggests that some patients may have been more accurate in reporting their sleep compared to others. Moreover, 42.86% of patients reported they did not nap on any occasion however actigraphy showed that this was 19.05%. A similar effect was reflected at weekends. This large discrepancy between the two measures of napping behaviour suggest that either patients do not report naps or actigraphy is miscoding quiescence as sleep. This finding fully mapped out observations made in the laboratory where some patients were clearly tired and even falling asleep during testing.
Table 4.3. Mean (+/-1 SD) and range across 14 weekdays for matched parameters drawn from the sleep diary and actigraphy recordings. Test statistics include the Wilcoxon signed rank test (Z) and Spearman’s (r). *Significant values.

<table>
<thead>
<tr>
<th>Weekday</th>
<th>Sleep Diary</th>
<th>Actiwatch</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Range</td>
</tr>
<tr>
<td>Bed Time (24 Hr Clock)</td>
<td>22.45</td>
<td>01.15</td>
<td>18.03-01.11</td>
</tr>
<tr>
<td>Wake Time (24 Hr Clock)</td>
<td>07.32</td>
<td>01.03</td>
<td>05:24-09:48</td>
</tr>
<tr>
<td>Get Up Time (24 Hr Clock)</td>
<td>08.06</td>
<td>01.01</td>
<td>05:57-10:07</td>
</tr>
<tr>
<td>Time In Bed (mins)</td>
<td>546.07</td>
<td>59.75</td>
<td>428.33-720</td>
</tr>
<tr>
<td>Sleep Duration (mins)</td>
<td>409.05</td>
<td>62.4</td>
<td>295-591.07</td>
</tr>
<tr>
<td>Sleep Onset Latency (mins)</td>
<td>21.99</td>
<td>20.21</td>
<td>0-106</td>
</tr>
<tr>
<td>Sleep Efficiency (%)</td>
<td>86.24</td>
<td>7.59</td>
<td>69.25-97.69</td>
</tr>
<tr>
<td>No. of Night Awakenings (freq.)</td>
<td>1.07</td>
<td>0.64</td>
<td>0-3</td>
</tr>
<tr>
<td>Duration of Night Awakenings (mins)</td>
<td>19.92</td>
<td>19.09</td>
<td>0-73.57</td>
</tr>
<tr>
<td>Nap Frequency (Per Day)</td>
<td>0.37</td>
<td>0.50</td>
<td>0-2.43</td>
</tr>
<tr>
<td>Nap Length (mins)</td>
<td>16.61</td>
<td>24.74</td>
<td>0-118.57</td>
</tr>
</tbody>
</table>

194
Figure 4.3. Correlations of sleep diary and actigraphy including regression line for weekday results only.
Table 4.4. Mean (+/-1 SD) and range across 4 weekend days for matched parameters drawn from the sleep diary and actigraphy recordings. Test statistics included the Wilcoxon signed ranks test (Z) and Spearman’s (r). *Significant values

<table>
<thead>
<tr>
<th>Weekend</th>
<th>Sleep Diary</th>
<th>Actiwatch</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Range</td>
</tr>
<tr>
<td>Bed Time (24 Hr Clock)</td>
<td>23.03</td>
<td>01.15</td>
<td>19:26-01:40</td>
</tr>
<tr>
<td>Wake Time (24 Hr Clock)</td>
<td>07.37</td>
<td>00.59</td>
<td>05:22-10:10</td>
</tr>
<tr>
<td>Get Up Time (24 Hr Clock)</td>
<td>08.18</td>
<td>00.52</td>
<td>06:13-11:19</td>
</tr>
<tr>
<td>Time in Bed (mins)</td>
<td>550.35</td>
<td>62.98</td>
<td>425-690</td>
</tr>
<tr>
<td>Sleep Duration (mins)</td>
<td>459.76</td>
<td>81.15</td>
<td>327.5-642</td>
</tr>
<tr>
<td>Sleep Onset Latency (mins)</td>
<td>24.36</td>
<td>24.84</td>
<td>0-111.67</td>
</tr>
<tr>
<td>Sleep Efficiency (%)</td>
<td>63.6</td>
<td>9.3</td>
<td>62.44-96.15</td>
</tr>
<tr>
<td>No. of Night Awakenings (freq.)</td>
<td>1.01</td>
<td>0.73</td>
<td>0-3.67</td>
</tr>
<tr>
<td>Duration of Night Awakenings (mins)</td>
<td>23.06</td>
<td>29.24</td>
<td>0-135</td>
</tr>
<tr>
<td>Nap Frequency (Per Day)</td>
<td>0.34</td>
<td>0.4</td>
<td>0-1.5</td>
</tr>
<tr>
<td>Nap Length (mins)</td>
<td>24.54</td>
<td>34.28</td>
<td>0-135</td>
</tr>
</tbody>
</table>
Figure 4.4. Correlations of sleep diary and actigraphy including regression line for weekday results only.
Characterising Prospective Sleep and Daytime Functioning

Sleep

In comparison to published norms, patient sleep schedule was similar to that of the self reports in the general population (Monk et al., 2000). In this study bedtime and wake time was 23:48 and 07:23 respectively (Monk et al., 2000). Sleep efficiency as recorded by the sleep diaries, and more accurately, by actigraphy, is below the threshold which is considered healthy (85%; Morin and Espie, 2003, p.16). Subjective and objective sleep duration was >7 hours on average per night which suggests patients received a sufficient amount of sleep (Carskadon & Rechtschaffen, 2005; Van Dongen et al., 2003). However time in bed was considerably longer (>9 hours on average per night) than the UK average of 7.5 hours (Clare Anderson & Horne, 2008; Groeger et al., 2004). Furthermore, increased night time awakenings, both frequency and duration, also contribute to poorer sleep efficiency. Night time awakenings appear to be increased in comparison to other actigraphy studies in healthy persons where number of wake bouts$^{14}$ were less than 10 per night (Lockley et al., 1999; Paquet et al., 2007). The frequency of night awakenings in the stroke patients are comparable with the number of awakenings of sleep disordered patients who awoke 36.6 times a night (Kushida et al., 2001). Longer time in bed, in addition to increased night time awakenings, contribute to low sleep efficiency.

For the majority of patients, total napping duration did not exceed 45 minutes however six patients reported napping longer than 45 minutes during the week, also confirmed by actigraphy. One patient napped on average for approximately two hours a day during the week and at weekends. It was indicated in the UK survey by Groeger et al. (2004) that non-brain injured persons do not habitually nap longer than 15 minutes. This suggests that patients nap considerably longer than the general population and that this may be indicative of increased sleepiness.

Daytime Functioning

$^{14}$ The actual number of episodes of wakefulness (> 1 minute).
Figure 4.5 shows that patients experienced subjective increases in sleepiness (KSS) and fatigue (D-FIS Overall), including mental (DFIS Mental Fatigue) and physical fatigue (D-FIS Physical Fatigue), in the evening compared to the morning. For weekday analyses, there was a significant difference for KSS scores ($Z=-5.23$, $p=0.0000$), overall D-FIS ($Z=-2.98$, $p=0.0028$), mental D-FIS ($Z=-3.93$, $p=0.0000$) and physical D-FIS ($Z=-3.36$, $p=0.000$). This effect was also present at weekends, increased KSS ($Z=-3.09$, $p=0.0020$), overall D-FIS ($Z=-2.06$, $p=0.0392$), mental D-FIS ($Z=-3.07$, $p=0.0021$) and physical D-FIS ($Z=-2.56$, $p=0.0185$).
Figure 4.5. Mean (+/-1 SD) KSS and D-FIS scores for the morning and evening. Significant differences between morning and evening scores are indicated as *p<0.05, **p<0.01, *** p<0.001.

Relationship Between Nocturnal Actigraphy and Daytime Functioning

KSS scores were not associated with any sleep or napping parameters derived from actigraphy. Weekday morning (r=0.27, p=0.0395) and evening (r=0.35, p=0.0252) fatigue ratings were related to longer actigraphy sleep duration. During the weekend, increased evening fatigue correlated with increased actigraphy derived sleep
efficiency (r=0.32, p=0.0195). Increased fatigue was related to greater subjective and
objective napping during the weekday and weekend. Greater weekday morning
fatigue correlated with longer patient reports of napping duration (r=0.27, p=0.0393).
Evening weekday fatigue correlated with increased objective napping frequency
(r=0.38, p=0.0071) and duration (r=0.30, p=0.0278). For the weekend, increased
morning overall fatigue was significantly associated with nap duration (r=0.27,
p=0.0418).

4.3.3 Motor Recovery Level In The Context of Sleep

The data obtained from the motor test battery are summarised in Table 4.5. As
expected in a cohort of patients with upper limb hemiparesis, there are marked
difficulties in reaction time and level of ability in task performance.

<table>
<thead>
<tr>
<th>Upper Limb Motor Ability Tests</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>WMFT RT (ms)</td>
<td>26.27 ± 39.47 (1.41-120)</td>
</tr>
<tr>
<td>WMFT FA</td>
<td>4.16 ± 1.46 (1.42-6.54)</td>
</tr>
<tr>
<td>MAL AU</td>
<td>1.20 ± 1.14 (0-3.96)</td>
</tr>
<tr>
<td>MAL QOU</td>
<td>1.12 ± 0.99 (0-3.08)</td>
</tr>
</tbody>
</table>

Relationship Between Motor Deficits and Sleep
Correlations between all motor tests, nocturnal parameters as determined by
actigraphy and subjective ratings of sleepiness and fatigue are presented in Table 4.6.
Table 4.6. Spearman’s rank correlation coefficient of motor ability tests with sleep and daytime functioning. Significant values are indicated as *p<0.05, **p<0.01 and those in bold represent non-significant trends. The scatter plots for significant correlations are located in Appendix D3.

<table>
<thead>
<tr>
<th>Sleep and Daytime Functioning</th>
<th>Residual Motor Ability</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>WMF TRT</td>
</tr>
<tr>
<td><strong>Actigraphy:</strong></td>
<td></td>
</tr>
<tr>
<td>Time in Bed (mins)</td>
<td>0.18</td>
</tr>
<tr>
<td>Sleep Time (mins)</td>
<td>0.12</td>
</tr>
<tr>
<td>Sleep Efficiency (%)</td>
<td>0.11</td>
</tr>
<tr>
<td>Sleep Efficiency (%)</td>
<td>-0.17</td>
</tr>
<tr>
<td>No. of Night Awakenings (freq.)</td>
<td>0.06</td>
</tr>
<tr>
<td>Duration of Night Awakenings (mins)</td>
<td>0.19</td>
</tr>
<tr>
<td>Nap Frequency (Per Day)</td>
<td>-0.01</td>
</tr>
<tr>
<td>Nap Length (mins)</td>
<td>-0.02</td>
</tr>
<tr>
<td><strong>Subjective Daytime Functioning:</strong></td>
<td></td>
</tr>
<tr>
<td>AM KSS</td>
<td>-0.31*</td>
</tr>
<tr>
<td>PM KSS</td>
<td>-0.00</td>
</tr>
<tr>
<td>AM D-FIS Overall Fatigue</td>
<td>-0.31*</td>
</tr>
<tr>
<td>PM D-FIS Overall Fatigue</td>
<td>-0.32*</td>
</tr>
<tr>
<td>AM D-FIS Mental Fatigue</td>
<td>-0.17</td>
</tr>
<tr>
<td>PM D-FIS Mental Fatigue</td>
<td>-0.08</td>
</tr>
<tr>
<td>AM Physical Fatigue</td>
<td>-0.17</td>
</tr>
<tr>
<td>PM Physical Fatigue</td>
<td>-0.15</td>
</tr>
</tbody>
</table>

The observed increased time in bed was significantly associated with poorer scores on the MAL (amount and quality of use). Correlations between sleep and motor ability were mild ranging from 0.22 to 0.33. Systematic effects across several tests were found for reduced time in bed, night awakenings and better motor ability. These results suggest that time in bed and night time awakening parameters are mildly associated with poorer motor ability. Increased napping was only associated with self reported motor function (MAL). Other systematic effects across all tests, ranging
from 0.27 to 0.36, were found for increased overall fatigue (morning and evening) and better motor test scores. Only a small effect was found between sleepiness and motor ability, but this was not consistent across all tests.

4.4 Discussion

4.4.1 Overall Findings

The present study aimed to prospectively examine subjective and objective sleep to firstly characterise sleep and daytime functioning in chronic stroke. Furthermore, this study aimed to examine sleep behaviour in terms of residual motor recovery. This was achieved by recording activity and sleep diaries over two weeks and assessing residual motor recovery using a comprehensive battery. Patients were relatively accurate in detecting their own sleep behaviour, however less accurate at determining daytime functioning. It was revealed that sleep and daytime functioning is highly disturbed in some patients. Furthermore, better daytime functioning in particular was related to motor ability which was contradictive to the initial assumption.

Concordance Between Sleep Diaries and Actigraphy

Sleep diary and actigraphy were in good agreement for the majority of parameters including bed time, get up time, time in bed, sleep duration, sleep onset latency and nap length. Therefore patients were reasonably accurate in reporting their nocturnal sleep behaviour however less perceptive when reporting night time awakening information. This effect is commonly observed in healthy (Lockley et al., 1999) those with a range of sleep disorders (Kushida et al., 2001; Means et al., 2003; Vanable et al., 2000). Despite good concordance of the group, a small proportion of patients were largely inaccurate in self reporting.
A discrepancy between subjective and objective measures as 42.58% of patients napped according to the actigraphy however only half this amount of patients (19.05%) reported this in the sleep diary. A similar effect was also observed at weekends. Lockley et al. (1999) also found that nap frequency and duration were increased using actigraphy in comparison to sleep diaries, but in a healthy non-brain injured sample. Some authors have suggested that actigraphy has a tendency to miscode a period of quiescence as sleep therefore overestimate frequency of naps (Hauri, 1992; Paquet et al., 2007). For the present study, careful attention was paid to napping analysis to avoid this problem. The nap detection criteria was set to a minimum of 15 minutes. Therefore the likelihood of miscoded naps is reduced as patients are likely to move within a 15 minute period compared to a 5 minute period. In addition, patients were asked to report if the actiwatch was removed. The detection of long periods of zero activity suggested that the actiwatch may have being removed. Where possible, patients were queried upon these findings in order to clarify if that period was a likely nap. Given that brain injured patients are particularly associated with poor perception of their sleepiness (Bassetti et al., 1996; Bassetti & Valko, 2006; Masel et al., 2001), it seems more plausible to assume that actigraphy is more reliable than sleep dairies with regard to napping. In addition, laboratory observations showed patients were indeed very sleepy however did not appear to acknowledge this. In this instance, more research is required to address daytime functioning perception in this cohort.

**Characterising Sleep and Daytime Functioning**

Overall, patients had healthy sleep duration (>7 hours) during the week and at weekends. Sleep schedules, including mean bed time, wake time and get up time appeared relatively normal in comparison with the general UK population (Groeger et al., 2004). Even though sleep duration was healthy, patients spent, on average, two hours longer in bed. This may explain why sleep efficiency was below the healthy threshold of 85% (Morin and Espie, 2003, p. 16). Fifty-five percent of chronic stroke patients in another study had sleep efficiencies below 80% (Schuiling et al., 2005). Stroke patients may stay in bed for longer due to the physical disability associated
with stroke and lifestyle changes such a reduction in occupational and social activity. Furthermore, longer night time awakenings also contributed to the observed low sleep efficiency. Under normal conditions, researchers have observed less than 10 wake bouts in healthy non-brain injured participants using actigraphy (Lockley et al., 1999; Paquet et al., 2007). Patient in this study however awoke 27 to 28 times a night. This is also suggestive of poorer quality sleep in patients which, is fact, comparable with those diagnosed with a sleep disorder who awoke 36.6 times a night\(^{15}\) (Kushida et al., 2001). Schuiling et al. (2005) also found that 75% of stroke patients demonstrated sleep fragmentation due to increased level of night awakenings.

Forty-three percent of chronic stroke patients took naps during the week and at weekends. This finding is lower than those reports by Campos et al. (2005). In this study, 66.75% of chronic stroke patients napped during the week whereas 75% napped at weekends. This difference may be due to the positive selection employed by the current study as 39.96% worked. Therefore these patients may have had fewer opportunities to nap. Interestingly, subjective reports of napping on the sleep diary for the present study was less than half of those patients who napped as detected by actigraphy. Based on the knowledge from the previous chapter which highlighted that patients may underestimate their sleepiness and fatigue levels, as well as the findings presented in other studies (Bassetti et al., 1996; Bassetti & Valko, 2006; Masel et al., 2001), these results further show that patients underestimate napping. Furthermore, anecdotal evidence from the laboratory and family reports revealed that some patients napped regularly however the patients did not feel they had, therefore this was not recorded in the sleep diary. It remains unknown without the use of more objective measures such as MSLT or MWT tests to resolve this issue. However it is clear from this study that chronic stroke patients take multiple naps, which may be as long as two hours a day, considerably longer than napping behaviour reported in non-brain injured samples. A survey of 2000 UK adults showed that less than 10% of participants napped during the week and less that 35% napped at weekends (Groeger

\(^{15}\) Using the same wake bout criteria (number of episodes of wakefulness longer than 1 minute) used in this study and Lockley et al, 1999).
et al., 2004). Furthermore, those in the general population napped, on average, for 15 minutes (Groeger et al., 2004).

This study also found a shift in sleep and napping behaviour at weekends in comparison to weekdays. During the weekend, patients had a later subjective and objective bed time, a behaviour trait observed in non-brain injured (Groeger et al., 2004; Monk et al., 2000) and other stroke samples (Campos et al., 2005). An significant increase in duration for night awakenings may reflect alcohol consumption at weekends. Sleep duration also increased during the weekend which is typical of the general population (Groeger et al., 2004) and other stroke samples (Campos et al., 2005).

With regard to daytime functioning, patients reported increased sleepiness and fatigue during the evening compared to the morning. This follows the normal pattern the daily cycle of daytime functioning. As sleep need increases in conjunction with the homeostatic drive and circadian rhythm, feelings of sleepiness and fatigue increase (Borbely & Acherman, 2005). However, level of sleepiness was not related to the quality of sleep at night. Poorer sleep at night usually results in increased sleepiness and fatigue during the day, as shown under laboratory (Franzen, Siegle et al., 2008) and real world conditions (Drake et al., 2004; Gold et al., 1992; Harma et al., 2002; Papp et al., 2004; Torsvall & Akerstedt, 1987). The findings of this study, and those of other authors (Bassetti & Valko, 2006; Baumann et al., 2007), show that patients reports do not necessarily follow this model of sleep. This suggests that patients either experience sleepiness despite sleeping well at night or they do not report worse daytime functioning despite having poor quality sleep. Further research is required to fully address the extent to which patients can accurately report level of daytime functioning.

**Sleep and Motor Recovery**

This study revealed relationships between residual upper limb motor ability with sleep and daytime functioning. Patients with poorer motor ability tended to stay in
bed longer and experience longer and more frequent night awakenings. Furthermore, increased fatigue was associated with better motor ability across all tests. These findings do not agree with other studies in chronic stroke. Previous studies have shown that increased fatigue and sleepiness is associated with poorer functional recovery (Alessi et al., 2008; Choi-Kwon et al., 2005; Glader et al., 2002; Ingles et al., 1999; Muller et al., 2006; Naess et al., 2005; Worthington & Melia, 2006). In Park et al. (2009), fatigue was not related to motor function, or activity of daily living in chronic stroke patients whereas sleep disturbances were related to outcome. Schepers et al. (2006) also found that fatigue was not related to motor ability. However these studies measured motor ability using general assessments whereas the current study used a fine grained motor test and addressed real world arm use. There was also a mild effect of increased napping and improved subjective motor functioning as reported on the MAL. Therefore these results indicated that in a highly motivated chronic stroke sample, better upper limb motor ability is associated with poorer daytime functioning. Schepers et al. (2006) commented that "...in clinical practice, stroke patients who have made a good clinical recovery often have disabling fatigue problems", however this has not yet been shown scientifically. Furthermore, Schepers et al. (2006) direct attention to the findings of Van Zandvoort et al. (2006) who found that even high functioning patients still report high levels of fatigue. Another study revealed that patients with good physical recovery also had severe fatigue (Staub & Julien Bogousslavsky, 2001). One possibility for this may be that increased use of the upper limb requires greater efforts of patients which results in feelings of increased fatigue. Using a selection of patients with greater stamina, they may try to push themselves to perform well on motor tasks.

4.4.2 Implications of Findings

Prospective Sleep Monitoring
This study showed that sleep diaries are a useful tool for monitoring sleep over time, however should not be used without the aid of actigraphy as some patients were
largely inaccurate as outlier cases were found in the concordance analyses. Actigraphy was also useful for monitoring sleep and daytime functioning behaviour in chronic stroke patients with residual motor deficits.

**Clinical Application of Results**

The results of this study have greatly contributed to the characterisation of sleep and daytime functioning behaviour in chronic stroke patients. The noted sleep disturbances should be addressed in treatment regimes and perhaps prescribed napping to alleviate sleepiness and fatigue. As the findings this study and the others revealed sleep changes in chronic stroke patients at weekends, it is important to take in account which days of the week are used to record sleep. Furthermore, few studies examining daytime functioning in stroke patients take morning and evening changes into account. As the results of this study have shown significant differences in sleepiness and fatigue between morning and evening, the timing of these assessments is therefore critical for interpretation.

This study also contributes to the understanding of stroke recovery. Not only does it point towards a link between good quality nocturnal sleep and better motor ability, it highlights that those with better motor ability may be susceptible to increased fatigue. This shows that sleepiness and fatigue is not necessarily an indication of poorer recovery as other studies have shown (Choi-Kwon et al., 2005; Glader et al., 2002; Ingles et al., 1999; Naess et al., 2005). Moreover, these results may reflect the motivated personality type of patients recruited for this study. It is therefore critical to promote awareness of daytime functioning in stroke patients and make previsions for rest and promoting napping may help cope with the sleepiness and fatigue associated with stroke recovery.

4.4.3 Methodological Limitations
Actigraphy did not appear to be affected by the level of motor deficit in these patients. Furthermore, patients did not report any problems with wearing the watches for the two week duration. Therefore, actigraphy can be used in this sample for even longer periods of time to further investigate sleep within other protocols, i.e. during a phase where a change in sleep behaviour is expected.

**Actigraphy**

There is some concern over the use of actigraphy in clinical populations with fragmented sleep or in situations where the sleep cycle is challenged (Paquet et al., 2007). Sleep duration was overestimated in those with sleep disorders using actigraphy in comparison to PSG (Kushida et al., 2001; Laakso et al., 2004). Furthermore, increased wakefulness during the night reduces the overall accuracy of actigraphy recordings (Hauri, 1992). As some patients within the current study demonstrated sleep disturbance, the validity of actigraphy recordings may have been affected, however this cannot be directly addressed without the use of PSG. With regard to the patient group in question, the benefits of actigraphy, e.g. low cost less disruption to sleep and ability to record longitudinal sleep, outweighed the benefits of PSG for this particular study.

Due to the inconsistency between napping behaviour as recorded by actigraphy and KSS measures, it cannot yet be concluded if this is due to actigraphy or poor patient perception. Actigraphy based assessment of napping behaviour has been known to overestimate diurnal sleep behaviour by miscoding quiet wakefulness as sleep (P. Hauri, 1992). However, Roehrs et al. (2000) suggested that actigraphy is perhaps a more real world index of daytime sleepiness compared to MSLT methods. Previous studies have also indicated that stroke patients underestimate their own sleepiness (Bassetti et al., 1996; Bassetti & Valko, 2006; Masel et al., 2001). Further research using alternative objective measures of sleep is necessary to clarify this issue.

Some authors have suggested that use of actigraphy in brain injured patients with physical disabilities are subject to artefact. Basetti commented that the influence of
fatigue and hemiparesis may contaminate actigraphy recordings (C. Bassetti et al., 1996). Laakson et al (2004) examined the use of actigraphy in patients with varying motor handicaps and found actigraphy was useful in patients with mild to moderate disability whereas those with severe handicaps in this study, i.e. almost motionless, required a highly sensitive algorithm to detect sleep. The present study shows good overlap on actigraphy and sleep diaries which suggests that the findings of Laakson et al. (2004) can be extended to patients with low functioning hemiparesis. Another study used actigraphy to measure circadian rhythm (Takekawa et al., 2007). Actigraphy was considered a valid measure in this sample as this data coincided with other measures of circadian rhythm including body temperature.

Possible Confounds Upon Residual Motor Ability
Inter-patient variability is difficult to control in any study involving stroke patients. Motor recovery is a multi factorial process which may be influenced by factors beyond control of this study including, stroke pathogenesis, genetics, quality of medical care and rehabilitation resources as well as the patients own motivation and family support. However the current study used stringent selection criteria which has led to a homogenous group. It is also important to note that all patients received standard UK treatment and rehabilitation provided by the NHS whereas two patients received care overseas.

4.4.4 Future Studies
In order to ultimately characterise sleep in chronic stroke patients, it would additionally be useful to incorporate the gold standard measure of sleep, i.e. PSG recordings. However PSG is challenging in the laboratory environment for patients with motor deficits. Therefore the future way forward would be the use of home based PSG.
Activity was determined by actigraphy did not appear to be related to sleepiness or fatigue therefore alternative measures need to be employed to further examine the accuracy of subjective reports in these patients. Therefore using objective measures would be beneficial. One possible measure is employing a physiological biomarker to assess levels of alertness, i.e. waking EEG.

The findings of this study revealed that sleep and daytime functioning is related to upper affected limb motor ability. Therefore sleep and daytime functioning may have a role in patients undergoing rehabilitation which specifically aims to increase motor movement in the affected limb, such as CIT. It may be particularly useful to implement actigraphy and sleep diary monitoring in those patients undergoing rehabilitation to examine this link.

**Conclusion to Chapter 4**

This is the first known study to prospectively measure sleep and daytime functioning behaviour over two weeks in a group of chronic stroke patients with residual motor deficits. The findings have contributed important information regarding the characterisation of sleep, sleepiness, fatigue and activity levels. The results have also suggested a relationship between sleep and daytime functioning are related to residual motor ability. Critically, these findings were obtained through fine grained motor ability assessments.

- The majority of patients were reasonably accurate in reporting nocturnal sleep behaviour however were less accurate for indices pertaining to night time awakenings.
- Napping reports appeared to be underestimated in patients and when compared to actigraphy. Furthermore, napping was unrelated to subjective sleepiness and daytime activity levels.
• According to 24 hour objective assessments, some stroke patients in this study presented disturbed sleep, increased napping and a significant increase in sleepiness and fatigue in the evening compared to morning.
• Sleep and daytime functioning is associated with levels of residual motor functioning.
• This study presented a useful protocol for monitoring longitudinal sleep behaviour in chronic stroke patients with residual deficits therefore was continued to be used for the collection of data during the neurorehabilitation trial reported in Chapter 6 of this thesis.

Discussion of the current results highlighted a need for more objective measurements of daytime functioning in patients. Although few such measures exist for fatigue, several studies have indicated that waking EEG is sensitive to increasing sleepiness. It was therefore the prerogative of Study 3, presented in the following chapter, to further explore sleepiness in chronic stroke patients.
CHAPTER 5
Study 3: EEG-derived biomarkers for daytime sleepiness in patients with chronic stroke

Chapter 5 Overview

The objective measure of sleep employed in Study 4 revealed that stroke patients were reasonably accurate in reporting their sleep. However, the study lacked an objective measure of daytime sleepiness and it could not be determined if patients had good perception of their daytime functioning. Therefore, the current study aimed to specifically examine post stroke objective sleepiness using EEG in the context of a motor priming task recorded during wakefulness in a group of 32 stroke patients and matched controls. In addition, patient perception of sleepiness levels was assessed using a subjective rating. Few studies have objectively examined post stroke sleepiness, and of these few, none have used EEG to measure arousal levels. This study will further characterise daytime functioning as part of the post stroke sequelae and determine the degree to which patients are able to perceive sleepiness.

5.1 Introduction

Brief periods of increased sleepiness is a normal response to fluctuations of the homeostatic drive and circadian rhythm. However sleepiness in excess is considered abnormal and is recognised by the International Classification of Sleep Disorders (ICSD-10). Furthermore, sleepiness is severely under researched in chronically ill populations, particularly in chronic stroke. Of the few studies available, measures of sleepiness are normally limited to subjective reports with little comparison to
objective assessments. This is surprising as excessive sleepiness is a common observation within the post stroke sequelae and strongly contributes to poorer quality of life (Schuilling et al. 2005). Moreover, it is conceivable that sleepiness hinders the success of rehabilitation efforts in this population and hence outcome and recovery (Barker-Collo et al., 2007; Morley et al., 2005; Muller et al., 2006; Worthington & Melia, 2006). A greater understanding of post stroke sleepiness is necessary for post stroke treatment and management, particularly with regard to patient well being and safety.

5.1.1 Definitions of Sleepiness In Research

Sleepiness refers to sleep propensity or a readiness to fall asleep, in opposition to alertness or increased arousal (Dement & Roth, 2005). Feelings of sleepiness during the day are typically experienced as a result of circadian timing, soporific environments, due to tasks (e.g. monotony) or events (after exercise), ill health and medication side effects (Dement & Roth, 2005; Happe, 2003). Sleepiness becomes a clinical syndrome when it is recurrent, intense and affects daily functioning, sometimes referred to as excessive daytime sleepiness (EDS). The International Classification of Sleep Disorders (ICSD) recognises EDS as “the inability to stay awake and alert during the major waking episodes of the day, resulting in unintended lapses into drowsiness and sleep”. In instances where the sleepiness is not typically caused by poor sleep at night, and has another origin, it is termed ‘hypersomnia’. The ICSD specifically categorises hypersomnia due to a medical condition if the presence of sleepiness is not better explained by poor sleep at night, medication, mental health disturbance or substance abuse. Specifically regarding stroke, Bassetti and Valko (2006) defined post stroke hypersomnia, as “exaggerated sleep propensity with excessive daytime sleepiness, increase daytime napping, or prolonged nighttime sleep following cerebrovascular event” (p.1).

16 Mixed stroke and TBI sample.
5.1.2 Measuring Sleepiness

Measuring Sleepiness

Sleepiness research typically involves studying waking behaviour under experimental conditions where sleepiness is monitored or even induced using sleep deprivation paradigms. Habitual sleepiness levels in the natural environment have also been studied. There are four main methods used to quantify sleepiness: 1) subjective ratings, 2) performance decrements, 3) sleep propensity measures and 4) arousal decrease measures.

Subjective assessments of sleepiness are useful as they address feelings of sleepiness from the participant’s perspective. This is typically measured using questionnaires. Many studies employ validated and highly reliable questionnaires such as the Epworth Sleepiness Scale (ESS; Johns, 1991) and Karolinska Sleepiness Scale (KSS; Akerstedt & Gillberg, 1990). The ESS is a general measure of habitual sleepiness, sometimes referred to as ‘trait sleepiness’. The KSS is an immediate rating of current sleepiness, referred to as ‘state sleepiness’, and is particularly useful in addressing sleepiness over close time points. The KSS is highly sensitive to EEG and behavioural variables (Gillberg et al., 1994; Kaida et al., 2006).

Performance decrements on psychometric tests are also used as an objective measure of increasing sleepiness such as psychomotor vigilance, motor performance, memory, mental addition, logical reasoning and visual search tasks (Pilcher & Huffcutt, 1996; Samkoff & Jacques, 1991). Performance is usually measured in terms of reaction time, correct responses and lapses. It is also important to consider that length and type of task have deferential affects upon performance (Pilcher and Huffcutt, 1996).

Sleep propensity tests have been devised to objectively examine sleepiness in laboratory conditions. The two most commonly used tests are the Multiple Sleep
Latency Test (MSLT; Carskadon, p962-96, 1994) and the Maintenance of Wakefulness Test (MWT; Mitler et al., 1982). The MSLT measures how long it takes a person to fall asleep within 20 minutes whereas the MWT examines how long a person can stay awake for 20 minutes. Both tests are conducted in a dark sleep laboratory and use polysomnographic (PSG; See Section 1.2.3, Chapter 1) signals to determine when stage one sleep has commenced. The shorter the sleep latency, the more sleepy a person is considered to be.

Physiological arousal are used to measure sleepiness. The most commonly used method is electroencephalography (EEG). EEG records brain activity which is used to determine whether a person is awake or asleep (for further clarification of EEG recording please refer to Section 1.2.3, Chapter 1). Moreover, quantitative EEG (QEEG) analysis enables additional information regarding brain activity characteristics to be obtained, i.e. the frequency composition. EEG patterns in the normal waking adult consist primarily of beta and alpha rhythms (>12 Hz), however when arousal decreases, the rhythm becomes dominated by alpha. The transition to increased sleepiness is associated with the presence of theta (4-7 Hz) (Finelli, Baumann, Borbely, & Achermann, 2000; Harris, 2005) pertaining to the onset of stage one sleep. Sleep deprivation studies have shown that in increase in power within the alpha and theta range (Cajochen, Brunner, Krauchi, Graw, & Wirz-Justice, 1995; De Gennaro et al., 2007). In healthy participants, a significant increase alpha and theta in the EEG normally coincides with an increase in subjective sleepiness ratings (Akerstedt & Gillberg, 1990; Marzano et al., 2007; Torsvall & Akerstedt, 1988). Although some delta, otherwise known as slow wave activity, is present in severely sleepy yet healthy individuals (Chapotot, Pigeau, Canini, Bourdon, & Buguet, 2003), increased power is considered in the absence of sleep deprivation is considered abnormal and is usually present after brain damage (Finnigan et al., 2004; Finnigan et al., 2007; Lukashevich et al., 1999; Murri et al., 1998; Sainio et al., 1983). Other methods used to determine physiological arousal levels include heart rate variability, pupillary unrest index and slow eye movement detection (Franzen et al., 2008; Kaida et al., 2007).
According to Curcio, Casagrande, & Bertini (2001), the varying measures used to address sleepiness as discussed above, are differentially associated with sleepiness. Subjective rating should not be solely relied upon when examining clinical populations (Roth & Roehrs, 1996). Furthermore, performance measures are associated with lower motivation and boredom which is sometimes misinterpreted as sleepiness (Akerstedt et al., 2008). A combination of objective and subjective measures provides useful information when addressing sleepiness.

5.1.3 Sleepiness in Chronic Stroke

Excessive sleepiness is commonly reported after stroke in the acute phase (Bliwise et al., 2002; Davies et al., 2003; Good et al., 1996). For some patients, this evolves into a chronic problem (Bassetti et al., 1996; Campos et al., 2005; Masel et al., 2001; Schuiling et al., 2005; Vock et al., 2002; Worthington & Melia, 2006). Brain damage may directly cause decreases in wake promoting neurotransmitters such as dopamine and serotonin, and excitatory neurons such as hypocretin (Bassetti and Valko, 2006). Overall, post stroke sleepiness has been attributed to a myriad of causes, in addition to the brain damage per se (Happe, 2003) such as depression (Bassetti and Valko, 2006), low social interaction (Campos et al., 2005), medication use (Bourne & Mills, 2004; Lowson & Sawh, 1999; Novak & Shapiro, 1997; Obermeyer & Benca, 1996), poor sleep at night (Bassetti et al., 1996) and general poor health (Schuiling et al., 2005). The results of Chapter 3 have shown that psychological factors are an important contributor to subjective sleepiness. Strokes of varying topographies have been associated with sleepiness which has been attributed to the widespread arousal system in the brain (Bassetti and Valko, 2006).

17 Mixed stroke and TBI.
The majority of studies examining sleepiness after stroke use subjective measures however several authors have speculated that patients may underestimate their sleepiness levels (Bassetti et al., 1996; Bassetti & Valko, 2006; Castriotta & Lai, 2001; Makley et al., 2008; Masel et al., 2001). Patients may either be influenced by experimental biases by modifying their responses due to demand characteristics (Lied & Kazandjian, 1998) or they have an inability to accurately perceive how they are feeling (Trudel, Tryon, & Purdum, 1998). Using the MSLT, Masel et al. (2001) compared objective sleep propensity with subjective reports on the Epworth Sleepiness Scale. It was concluded that patients did not appear aware of their sleepiness. However this study used a mixed TBI and stroke sample which may differentially present differences in the manifestation of daytime sleepiness. Furthermore, a subjective measure of habitual sleepiness was used rather than current state sleepiness. Another potential issue within this study is that MSLTs require patients to try to fall asleep in unnatural laboratory conditions which may impact the sleep onset latency during the day. For example, patients may find it more natural to fall asleep in front on the television at home, but less likely to fall asleep in a purpose built sleep laboratory wearing electrodes and awareness of others monitoring them.

Another option to measure objective sleepiness in stroke patients is to record the EEG during wakefulness. This method would not require patients to unnaturally force themselves to fall asleep or stay awake therefore enabling the capture of brain arousal in a normal waking state. Furthermore, patients can rate their current sleepiness levels subjectively whilst the recording is taking place, similarly to the studies of Akerstedt & Gillberg (1990), Marzano et al. (2007) and Torsvall & Akerstedt (1988), however without the use sleep deprivation.

At present, waking EEGs in stroke patients are usually used it as a clinical tool to detect abnormality in brain function after stroke (Nuwer, 1988b). Increased delta activity has been associated with a poorer prognosis in acute stroke (Finnigan et al., 2004; Lukashevich et al., 1999; Murri et al., 1998; Sainio et al., 1983). Furthermore, EEG abnormalities persist for months stroke (Giaquinto, Cobianchi, Macera, &
Nolfé, 1994; Mattia, Spanedda, Babiloni, Romigi, & Marciani, 2003; Nagata, 1989a; Nagata, Tagawa, Hiroi, Shishido, & Uemura, 1989b; Yokoyama et al., 1996; Yuasa, Maeda, Higuchi, & Motohashi, 2001) and are associated with the current levels of functional recovery (Yuasa et al., 2001). EEG mapping techniques (see section 2.5.1, chapter 2) have also shown that increased slow waves are typically most prominent on the same side as the lesion (ipsilateral), however some studies have shown abnormalities within the less affected hemisphere (contralateral), opposite to the lesion (Giaquinto et al., 1994; Hachinski et al., 1987; Juhasz, Kamondi, & Szirmai, 1997; Mattia et al., 2003; Nagata, 1989a; Nagata et al., 1989b). Furthermore, greater symmetry between hemispheres was associated with better functional outcome (Giaquinto et al., 1994).

One study acknowledges sleepiness in post stroke waking EEG however it was considered a confounder within the EEG rather than an effect that requires measuring (Finnigan, Rose, & Chalk, 2008; Finnigan et al., 2007). Another study incorporated a 'biosocial' rhythm parameter when examining the EEG of chronic stroke patients, however this measure contained items relating to nocturnal sleep, social activity, napping behaviour and fatigue, not an independent measure of sleepiness. A relationship between increased alpha and better biosocial rhythms was observed (Yuasa et al., 2001). Critically, no study has used EEG in the context of post stroke sleepiness in chronic patients.

5.1.4 The Rationale For Study 3

More research on post stroke sleepiness is essential. It is important for the medical profession to identify and treat sleepiness in long term chronic illness (El-Ad & Korczyn, 1998). Increased sleepiness poses serious risks to a patient's safety (Michael, Allen & Macko, 2006) and others around them (K. Kaida et al., 2007). Stroke patients are more likely to have car accidents, attributed to sleepiness and fatigue (Lundqvist et al., 2008; Sagberg, 2006). If patients are unaware of their...
sleepiness, as speculated by some authors (Bassetti et al., 1996; Bassetti & Valko, 2006; Masel et al., 2001; Trudel et al., 1998), their lifestyle may not accommodate the possible deficits in daytime functioning and not involve precautions to minimise risk.

Living with excessive sleepiness contributes to a poorer quality of life after stroke (Schuiling et al., 2005). Excessive sleepiness in patients prevents social activities (Campos et al., 2005) and severely impacts the ability to return to work (Murray et al., 2003). The cognitive problems associated with stroke have been partly attributed to sleepiness (Van Zandvoort et al., 1998). This may explain why rehabilitation sessions are also problematic for sleepier patients (Morley et al., 2005; Muller et al., 2006; Worthington & Melia, 2006).

5.1.5 The Current Study

The aim of the current study was to use EEG as an objective measure of sleepiness. This method will not only contribute to the understanding of the level of sleepiness experienced by chronic stroke patients but it will also help determine if stroke patients are aware of arousal decrements in an experimental situation. Furthermore, the EEG set up employed in this study allowed the topography of frequency composition to be examined.

The CIT protocol provided an opportunity for waking EEGs to be recorded in relation to a motor priming task. Prior to this study, laboratory observations indicated an increase in subjective sleepiness after the motor priming task. Therefore the recording of waking EEGs were subsequently introduced pre and post of the motor task as well as asking patients for a subjective sleepiness rating. This paradigm was also carried out in healthy matched controls for comparison with stroke patients.

Research Aims
The aim of this part of the study within the larger framework of the thesis was to provide a physiological biomarker of sleepiness in chronic stroke patients. Based on the literature, the following research questions were formulated:

1. What are the differences of the EEG frequency composition (<30 Hz) between chronic stroke patients and matched controls?

2. To what degree is subjective sleepiness and the EEG altered after the motor priming task in stroke patients and controls?

3. Is subjective sleepiness related to the EEG in stroke patients and controls?

4. Is a larger increase in sleepiness after the task related to performance decrements on the motor task?

5.2 Methods

5.2.1 Design

The waking EEG paradigm for this study was carried out during the pre-CIT test point (T2; Figure 5.1). The EEG paradigm comprised a repeated measures design whereby clean EEGs (no task) were recorded before and after a motor priming task (Figure 5.2). Four groups completed this paradigm: 1) left stroke patients, 2) matched controls for left stroke patients, 3) right stroke patients, and 4) matched controls for right stroke patients. Pre task data was examined in order to analyse differences in the EEG between stroke patients and matched controls. The degree of symmetry between hemispheres was also addressed. Pre and post task changes in the EEG and subjective
sleepiness ratings were examined per group. Furthermore, the relationships between subjective and objective sleepiness within each group was examined.

**Figure 5.1.** Design of CIT trial. The highlighted section indicates time point from which data for this study was collected.

**Figure 5.2.**

### 5.2.2 Participants

<table>
<thead>
<tr>
<th>Electrode Application</th>
<th>Motor Priming Task</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Task</td>
<td>2 mins</td>
</tr>
<tr>
<td>EEG Recording</td>
<td>45 mins</td>
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<td>No Task</td>
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Thirty-two community dwelling chronic stroke patients attended pre-CIT testing (T2) prior to the CIT phase of the trial which formed an opportunity sample for data collection analysis for the current result chapter\textsuperscript{18}. All participants fulfilled the inclusion/exclusion criteria as described in Section 2.2.1 (Chapter 2).

In addition, 32 age and gender matched non-brain injured control participants drawn from the general population were recruited. People with clinically significant sleep disorders were excluded to avoid the confounds of sleep related treatment during the study, however the sample is likely to contain what would be classified as poor sleepers (a sampling method used by Lichenstien et al. 2004, p.73).

5.2.3 Materials

Waking EEGs were recorded using a 64 channel set up (Brain Products GmbH ©). Electrodes were applied using a cap with pre-defined sites based on the internationally standardised 10-10 system\textsuperscript{19}. Electrode impedances were kept below 5kOhm and were recorded against an average reference calculated by the amplifier hardware. EEG and EOG signals were continuously recorded in DC mode. Raw EEG data was analysed offline for frequency analysis (QEEG). The KSS was used as a subjective measure of state sleepiness (see Section 2.3.4, Chapter 2). The KSS requires patients to rate their current level of sleepiness ranging from 1 (very alert) to 7 (very sleepy).

\textsuperscript{18} A total of 52 patients attended T2 (pre-CIT test point; section 2.2.1, chapter 2). Twenty patients were not included in the analysis for this study. Two patients were excluded from this study as they presented of bilateral strokes. One patient could not complete then EEG due to having braided hair which affected electrode application. Six could not complete the full protocol due to tiredness and being uncomfortable. The data of nine patients was not used as the EEG contained too much artefact to yield at least one minute of artefact free recording. The EEGs of two patients could not be used due to loss of C3 or C4 channels during the experiment.

\textsuperscript{19} Please refer to section 2.3.5 (Chapter 2) for a detailed description of EEG equipment used for EEG data acquisition in this chapter.
This study used a motor priming paradigm (Section 2.3.5, Chapter 2) which was designed to elicit preparation and execution of movement. The task involved the presentation of one of four pre-cues (left <<, right >>, uninformative <> or no-response >>). Immediately following the prime, participants were presented with one of three response cues (left half, right half, or bottom half circle filled in white). Pre-cues were 100% predictive of response cue. Each pre-cue was randomised. Pre-cues and corresponding response cue were presented 12 times which equated to 60 trials in a approximately 4 minute block. The response window was 1830 to 3500 milliseconds.

5.2.4 Procedure

Both patients and controls followed the same procedure for this study. After electrode application, waking EEGs were recorded for two minutes pre and post of the motor priming task with eyes open. During the waking EEG, participants were instructed to focus on a black dot on the centre of the screen. Immediately preceding the waking EEGs, participants were asked to complete the KSS. The full EEG procedure is described in Section 2.4.2 (Chapter 2).

5.2.5 Analysis

For data acquisition, filtering and storage information, please refer to section 2.3.5 (Chapter 2). Left and right stroke groups were analysed separately.

**QEEG Analysis**

---

20 Response window was extended for those patients who have difficulty using their affected within the set time of 4000 milliseconds.
EEG signals were analysed offline. The raw EEG recording from the experiment was approximately 45 minutes long. Pre and post clean EEG (no task) was segmented from the raw data for each participant. Each pre and post section was subjected to manual artefact inspection for the removal of eye blinks and muscle noise which contaminate the recording. Artefact free epochs were used for analysis. The pre and post segment of two minutes each were further subdivided into equally divided two second epochs for frequency analysis. The frequency composition was analysed using the Fast Fourier Transform (FFT) method (see Section 2.5.1, Chapter 2). FFT criteria was set to full spectrum, resolution 0.5 Hz, power density output (µV²/Hz) and the hanning window (10%) was applied. The FFT produced power density spectra values (µV²/Hz) per two second epoch. These two second power spectra values were then averaged together. Averaged values were exported as text files which contained the power density spectra in 0.5 Hz bins ranging from 1 to 30 Hz (at a resolution of 0.5). From this data, continuous frequency information per 0.5 Hz was transformed into 1 Hz bins for analysis. In addition, the values within these 1 Hz bins were further subdivided into discrete, non-overlapping frequency bands: delta (1-3 Hz), theta (4-7 Hz), alpha (8-12 Hz) and beta (13-30 Hz). Due to the high variability in the EEG between patients, power density values were log transformed using Lg10 to normalise the distribution. This technique has been used in previous studies (Lockley et al., 1999; Viola et al., 2008).

**Motor Paradigm Performance Measures**

In addition to the EEG, behavioural parameters including reaction time (ms) and percent of correct responses on the motor preparation task were recorded a measure that is sensitive to sleepiness. Reaction time (ms) was defined as time between response cue onset and button press. Correct response mapped on the instruction given by the response cue. Reaction time and percent correct as determined by the non affected hand was used for stroke patient responses. Reaction time and correct responses were averaged across blocks.

**Statistical Analysis**
Transformed EEG data and other variables were entered into SPSS for statistical analysis. Statistical analyses were performed using C3 and C4. All 64 electrodes sites were used for topographical mapping. The p values obtained from the test of difference as calculated in SPSS were reimported back into Brain Vision Analyser. This enabled the p values to be mapped onto brain masks to demonstrate areas of significant changes, a technique known as probability mapping, used in previous studies (Bódizs, Lazar, & Rigo, 2008; Hassainia, Petit, & Montplaisir, 1994). Data for left and right affected patients and the corresponding matched controls were analysed and presented separately. For all stroke patients, the more affected hemisphere is referred to as the ipsilateral (same side as lesion) and the less affected hemisphere is termed the contralateral (opposite to the lesion).

In order to clearly indicate differences between different conditions for EEG data in graphical format, it was useful to express the power density values of the stroke patients as a percentage of the control group, a method previously been used by others (James, 2008; Lockley et al., 2006; Viola et al., 2008). This was achieved by calculating geometric means through the following steps: 1) transforming power density values by log base 10 (Lg10), 2) averaging across participants, 3) subtracting one condition from another, e.g. stroke patients minus controls, 4) antilogging these values and 5) multiplying by 100. Therefore the control condition becomes 100% and any increase or decrease of this baseline represents a change in the stroke patient group. Geometric means were calculated for visual representation of the data only. Geomeans calculations were also utilised for between hemisphere differences. In this instance, the ratios of power density between hemispheres were calculated per frequency bin (1-30Hz), i.e. the ipsilateral hemisphere was divided by the contralateral hemisphere.

Between tests of difference for the logged power density values were calculated using t-tests, whereas the Mann Whitney U Test was used for between group demographic data which was non-normal. To analyse between hemisphere differences within groups, t-tests against 1 were conducted using the ratio data. Therefore the closer the
ratio value is to 1, the less difference there is between hemispheres. Correlation analyses was applied to address the relationship between the EEG and the KSS. Analyses models were applied to the whole sample to examine group and task related differences. A two-way analysis of variance (ANOVA) was conducted to assess differences in KSS scores. A two-way between groups multivariate analysis of variance (MANOVA) was performed to assess if there are any differences or interactions between group, brain hemisphere and task on the EEG. For AVONA analyses, the Wilk's Lambda statistic was reported.

For EEG data, statistical tests were conducted on the power density values calculated for each 1 Hz bin between 1 and 30 Hz or for each frequency band. All EEG statistical analyses were performed on logged data only. Statistical tests were carried out using a one tailed analyses and the alpha level was set to \( p \leq 0.05 \). The Bonferroni multiple comparisons correction was used for ANOVA and MANOVA results.

5.3 Results

5.3.1 Demographics

Fourteen patients experienced left hemispheric stroke and 18 experienced right hemispheric stroke. The demographics of left and right stroke patients and the corresponding matched control groups are presented in Tables 5.1 and 5.2 respectively. The majority of patients had a primary caregiver, usually a family member, and those who lived alone required assisted living from local services. Left and right patient groups were generally comparable. There were no significant differences between groups for age, BMI, Mini Mental State Exam, chronicity, or nicotine consumption between stroke patients and controls. Left stroke patients consumed significantly more caffeine (\( U = 43, p = 0.0106 \)) and drank more alcohol.
(U=56, p=0.0556) compared to controls. Right stroke patients also consumed significantly more alcohol than controls (U=75, p=0.0301).
Table 5.1. The ‘Left Group’. Data presented as mean, +/- 1 SD and range or percent valid where appropriate. The remaining 57.14% of stroke patients unlisted for employment status were classified as not working. Sleep medication was taken by one control participant (Zipiclone taken irregularly). For individual case information for all participants, see Appendix C.

<table>
<thead>
<tr>
<th>Demographical Variables</th>
<th>Left Stroke Patients</th>
<th>Matched Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=14)</td>
<td>(n=14)</td>
</tr>
<tr>
<td>Gender (M:F)</td>
<td>8:6</td>
<td>8:6</td>
</tr>
<tr>
<td>Age (Years)</td>
<td>56.57 ± 11.11 (32-73)</td>
<td>56.30 ± 12.46 (33-72)</td>
</tr>
<tr>
<td>BMI</td>
<td>23.48 ± 3.02 (18.20-27.30)</td>
<td>24.12 ± 3.28 (19.20-30.40)</td>
</tr>
<tr>
<td>NART (IQ)</td>
<td>113.52 ± 8.03 (96-125)</td>
<td>-</td>
</tr>
<tr>
<td>Mini Mental State Exam*</td>
<td>28.63 ± 11.12 (23-30)</td>
<td>-</td>
</tr>
<tr>
<td>Education Level:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>School Leavers Certificate</td>
<td>42.87%</td>
<td>28.57%</td>
</tr>
<tr>
<td>Further Study</td>
<td>28.57%</td>
<td>14.29%</td>
</tr>
<tr>
<td>Higher Education</td>
<td>28.57%</td>
<td>57.14%</td>
</tr>
<tr>
<td>Employment Status:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full Time</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Part Time</td>
<td>14.29%</td>
<td></td>
</tr>
<tr>
<td>Retired</td>
<td>28.57%</td>
<td></td>
</tr>
<tr>
<td>Studying</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Living Support:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Living Alone</td>
<td>78.57%</td>
<td></td>
</tr>
<tr>
<td>Living With Family</td>
<td>21.43%</td>
<td></td>
</tr>
<tr>
<td>Chronicity (Months)</td>
<td>59.74 ± 50.41 (11-252)</td>
<td>n/a</td>
</tr>
<tr>
<td>Type of Stroke:†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>14.29%</td>
<td>n/a</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>21.43%</td>
<td>n/a</td>
</tr>
<tr>
<td>Both</td>
<td>71.43%</td>
<td>n/a</td>
</tr>
<tr>
<td>Lesion Hemisphere</td>
<td>30 Left, 31 Right</td>
<td>n/a</td>
</tr>
<tr>
<td>Co-morbid Conditions:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychological</td>
<td>21.43%</td>
<td>None</td>
</tr>
<tr>
<td>Muscular</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Neurological$</td>
<td>71.43%</td>
<td>None</td>
</tr>
<tr>
<td>Cardiac</td>
<td>50%</td>
<td>None</td>
</tr>
<tr>
<td>Cancer</td>
<td>71.43%</td>
<td>None</td>
</tr>
<tr>
<td>Diabetes</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Pain</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Dysphasia</td>
<td>55.56%</td>
<td>None</td>
</tr>
<tr>
<td>Medication:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti depressant</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Pain Relief</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Cardiac Control</td>
<td>71.43%</td>
<td>None</td>
</tr>
<tr>
<td>Anti epileptic</td>
<td>71.43%</td>
<td>None</td>
</tr>
<tr>
<td>Sleep Hypnotics</td>
<td>None</td>
<td>1.64%</td>
</tr>
<tr>
<td>Alcohol (Units per week)</td>
<td>8.07 ± 9.25 (0.28)</td>
<td>1.90 ± 3.31 (0.10)</td>
</tr>
<tr>
<td>Caffeine (Cups per day)</td>
<td>5.43 ± 3.16 (0.12)</td>
<td>2.24 ± 2.35 (0.7)</td>
</tr>
<tr>
<td>Nicotine (Cigarettes Per Day)</td>
<td>0.07 ± 0.27 (0.13)</td>
<td>0.21 ± 0.87 (0.19)</td>
</tr>
</tbody>
</table>

(-) not required or recorded as part of this study.
* 55.56% of the patients experienced expressive aphasia and only completed the 3-step command on the MSE only therefore were not included in the total mean score. These patients also did not complete the NART.
† The remainder of these values were classified as unknown.
$ Neurological conditions other than stroke.
Table 5.2. The ‘Right Group’. Data presented as mean, +/- 1 SD and range or as percent valid where appropriate. The remaining 38.89% of stroke patients unlisted for employment status were classified as not working. Sleep medication was taken by one control participant (Zipiclone taken irregularly). For individual case information for all participants, see Appendix C.

<table>
<thead>
<tr>
<th>Demographical Variables</th>
<th>Right Stroke Patients (n=18)</th>
<th>Matched Controls (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M:F)</td>
<td>10:8</td>
<td>10:8</td>
</tr>
<tr>
<td>Age (Years)</td>
<td>51.89 ± 12.83 (28-69)</td>
<td>56.44 ± 13.71 (33-72)</td>
</tr>
<tr>
<td>BMI</td>
<td>24.58 ± 3.94 (21.40-28.90)</td>
<td>24.79 ± 3.71 (18.00-30.80)</td>
</tr>
<tr>
<td>NART (IQ)</td>
<td>115.88 ± 6.87 (100-126)</td>
<td>-</td>
</tr>
<tr>
<td>Mini Mental State Exam</td>
<td>29.28 ± 1.02 (26-30)</td>
<td>-</td>
</tr>
<tr>
<td>Education Level:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>School Leavers Certificate</td>
<td>35.89%</td>
<td>26.57%</td>
</tr>
<tr>
<td>Further Study</td>
<td>33.33%</td>
<td>15.29%</td>
</tr>
<tr>
<td>Higher Education</td>
<td>27.78%</td>
<td>57.14%</td>
</tr>
<tr>
<td>Employment Status:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full Time</td>
<td>11.11%</td>
<td>-</td>
</tr>
<tr>
<td>Part Time</td>
<td>21.76%</td>
<td>-</td>
</tr>
<tr>
<td>Retired</td>
<td>22.22%</td>
<td>-</td>
</tr>
<tr>
<td>Studying</td>
<td>None</td>
<td>-</td>
</tr>
<tr>
<td>Living Support:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Living Alone</td>
<td>83.33%</td>
<td>-</td>
</tr>
<tr>
<td>Living With Family</td>
<td>16.67%</td>
<td>-</td>
</tr>
<tr>
<td>Chronicity (Months)</td>
<td>65.81 ± 40.40 (13-210)</td>
<td>n/a</td>
</tr>
<tr>
<td>Type of Stroke:*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischaemic</td>
<td>50.00%</td>
<td>n/a</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>11.11%</td>
<td>n/a</td>
</tr>
<tr>
<td>Both</td>
<td>5.95%</td>
<td>n/a</td>
</tr>
<tr>
<td>Co-morbid Conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychological</td>
<td>44.44%</td>
<td>None</td>
</tr>
<tr>
<td>Muscular</td>
<td>5.56%</td>
<td>None</td>
</tr>
<tr>
<td>Neurological†</td>
<td>33.33%</td>
<td>None</td>
</tr>
<tr>
<td>Cardiac</td>
<td>55.56%</td>
<td>None</td>
</tr>
<tr>
<td>Cancer</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Diabetes</td>
<td>5.56%</td>
<td>None</td>
</tr>
<tr>
<td>Pain</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Dysphasia</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Medication:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-depressant</td>
<td>11.11%</td>
<td>None</td>
</tr>
<tr>
<td>Pain Relif</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Cardiac Control</td>
<td>5.56%</td>
<td>None</td>
</tr>
<tr>
<td>Anti-epileptic</td>
<td>22.22%</td>
<td>None</td>
</tr>
<tr>
<td>Sleep Hypnotics</td>
<td>None</td>
<td>1.64%</td>
</tr>
<tr>
<td>Alcohol (Units per week)</td>
<td>9.69 ± 12.00 (1.45)</td>
<td>4.06 ± 8.48 (0.35)</td>
</tr>
<tr>
<td>Caffeine (Cups per day)</td>
<td>3.54 ± 2.07 (0.7)</td>
<td>3.34 ± 2.71 (0.10)</td>
</tr>
<tr>
<td>Nicotine (Cigarettes Per Day)</td>
<td>1.67 ± 5.15 (0.20)</td>
<td>0.58 ± 2.36 (0.10)</td>
</tr>
</tbody>
</table>

(-) not required or recorded as part of this study.
* The remainder of these values were classified as unknown.
† Neurological conditions other than stroke.

5.3.2 The Effects of Stroke On The EEG (Pre Task Data Only)

*Between Groups Power Density of Central Electrodes Across 1-30 Hz*
Figures 5.3a and 5.4a present the logged $\mu V^2/Hz$ values of the ipsilateral and contralateral hemisphere (either C3 or C4 channels) for the stroke patients as a percentage of control values (geometric mean) per 1 Hz bin. The corresponding $t$ values are presented below for between group differences.

Figures 5.3a and 5.4a show significantly increased power between 2 and 7 Hz within the ipsilateral hemisphere compared to controls. There is also a significant increase in power between 2 and 5 Hz within the contralateral hemisphere. More specifically, power increases observed in right affected stroke extended to 8 Hz and 9 Hz in the contralateral and ipsilateral hemispheres respectively (Figure 5.3).

After summing 1 Hz bins into corresponding frequency bands, it was revealed that patients had increased delta (left stroke patients: $t(26)=2.11$, $p=0.0449$; right patients: $t(34)=4.12$, $p=0.0002$) and theta (left stroke patients: $t(26)=2.90$, $p=0.0090$; right stroke patients: $t(34)=4.55$, $p=0.0000$) in the ipsilateral hemisphere compared to controls. Increased ipsilateral alpha was found in the right stroke group ($t(34)=2.43$, $p=0.0206$; Figure 5.4). Furthermore, contralateral increases were observed for delta ($t(34)=3.28$, $p=0.0033$) and theta ($t(34)=3.86$, $p=0.0006$) in the right stroke group. The increases in power observed in the lower frequencies (>8 Hz) of patients are suggestive of high levels of sleepiness.
Figure 5.3. a) logged power density (µV²/Hz) per 1 Hz bin, pink line=ipsilateral hemisphere (left, C3), blue line=contralateral hemisphere (right, C4), dashed black line (100%)=controls and left stroke EEG expressed as a percentage of controls. Figure 5.1 b) t values (df26) and corresponding one tailed p values of left stroke vs control. See Appendix E1 for the corresponding data tables.
Power Density Per 1 Hz Frequency Bin For Right Stroke Patients (Pre Motor Task)

Figure 5.4. a) logged power density ($\mu V^2$/Hz) per 1 Hz bin, pink line=ipsilateral hemisphere (right, C4), blue line=contralateral hemisphere (left, C3), dashed black line (100%)=controls and right stroke EEG expressed as a percentage of controls. Figure 5.1 b) $t$ values ($df34$) and corresponding one tailed p values of right stroke vs control. See Appendix E2 for the corresponding data tables.

Topographical Maps of Difference Between Groups

To further examine the $\mu V^2$/Hz distribution across the brain, topographical maps of the p values calculated for tests of difference between groups, per electrode, within each frequency band were computed. Figure 5.5 shows significant increases in global theta and alpha in the left stroke patients compared to controls. This effect is
particularly prominent within central and occipital areas for delta. Less affected occipital areas produced the least significant effects. Significant increases in beta was observed across the contralateral hemisphere, particularly within the frontal and right centro-parietal region.

These maps show that frequencies <8 and >4 Hz are occur globally across the brain (Figure 5.5). The small increase in power in comparison to controls within frontal and right centro-parietal regions for the delta band may have occurred due to patients trying to remain alert whilst focusing on the dot on the screen despite feeling sleepy.

![Figure 5.5. Topographical map of p values of one tailed t test for power density (µV²/Hz) across all electrodes (df26) per frequency band left stroke vs controls. See Appendix E3 for values for each value per electrode within the map. Values between electrodes were interpolated using spherical splines.](image)

Global increases in theta and delta were observed for the right stroke patients. These effects were particularly prominent within the ipsilateral hemisphere (Figure 5.6). No significant differences across the brain were observed for the beta frequency range. The maps for right stroke patients suggest a different pattern to that observed in left patients. Right stroke patients present greater presence of slow wave activity, <4 Hz, during wakefulness.
Figure 5.6. Topographical maps of the p values calculated for tests of difference between µV^2/Hz of right stroke vs controls across all electrodes (df34) per frequency band right stroke vs controls. See Appendix E4 for values for each value per electrode. Values between electrodes were interpolated using spherical splines.

**Hemispheric Difference**

Figures 5.7 and 5.8 present the geometric means of one hemisphere as a percentage of the other for both patients and controls. For stroke patients, the ipsilateral hemisphere is expressed relative to the contralateral hemisphere. The closer the values are to 100%, the less difference between hemispheres. T-tests against the baseline value of 1 (100%) per group revealed that stroke patients showed the greatest level of hemispheric asymmetry. Left stroke patients showed significant increase in power within the affected hemisphere between 5 to 13 Hz. Right stroke patients revealed a significant increased in power for all frequencies <12 Hz decreased power in the higher frequencies for 17, 18 and 24Hz. Controls did not show a systematic pattern of between hemispheric differences.
Figure 5.7. a) logged power density (µV²/Hz) per 1 Hz bin, pink line=left hemisphere or contralateral to stroke (C3), solid black line= control left hemisphere (C3), dashed black line (100%)=ipsilateral hemisphere for left stroke or right hemisphere for controls (C4). Figure 5.5 b) t values (df/13) and corresponding one tailed p values. See Appendix E5 for corresponding data table.
Figure 5.8. a) logged power density (µV²/Hz) per 1 Hz bin, pink line=right hemisphere or contralateral to stroke (C4), solid black line= control right hemisphere (C4), dashed black line (100%)=ispilateral hemisphere for left stroke or right hemisphere for controls (C3). Figure 5.6 b) t values (df/17) and corresponding one tailed p values. See Appendix E5 for corresponding data table.

5.3.3 Motor Priming Task Effects

Performance Measures
Mean reaction time for the non-affected arm was 546 ms (SD 107, range 362-740) and 612 ms (SD 306, range 291-1664) for left and right stroke patients respectively. Both control groups were faster than the stroke patients. The left control group mean reaction time was 447 ms (SD 71.81, range 333-601) and the right group mean reaction time was 428 ms (SD 68.51, range 326-601). Group differences in performance measures was statistically confirmed for right stroke patients versus controls (z=-2.5, p=0.0117) and left stroke patients versus controls (z=-2.62, p=0.0079). Percent correct responses were 99.43% (SD 0.73, range 97.9-100) for left and 97.2 (SD 7.34, range 68-100) for right stroke groups. The left controls were 99.29% correct (SD 0.83, range 97.4 to 100) and the right controls were 99.34% correct (SD 0.75, range 96.4 to 100). These differences were not significantly different. Both patients and controls were similar in their level of correct responses.

**Subjective Alertness**

A two-way between groups ANOVA was performed to investigate group (stroke patients and controls) and task (pre and post) interactions on KSS ratings. Left and right stroke groups were analysed separately using the same ANOVA model. There were no significant effects for the group factor as patients and controls did not differ in subjective sleepiness ratings. A significant interaction of task was observed for task for the left, \( F(1, 52)=8.33, p=0.0056, \eta^2_\text{p}=0.14 \), and right group, \( F(1, 68)=10.74, p=0.0017, \eta^2_\text{p}=0.14 \). KSS rating significantly increased by at least 1 point after the task for all groups (Table 5.3).
Table 5.3. KSS ratings pre and post motor task. Data reported as mean, +/- 1 SD. $t$ and $p$ values for left stroke and control ($df/13$), and right stroke and control ($df/17$).

<table>
<thead>
<tr>
<th></th>
<th>Pre Task KSS</th>
<th>Post Task KSS</th>
<th>Mean Difference</th>
<th>$t$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right Stroke</td>
<td>3.72 ± 2.32</td>
<td>5.28 ± 2.02</td>
<td>1.56</td>
<td>-3.50</td>
<td>0.0027</td>
</tr>
<tr>
<td>Right Controls</td>
<td>3.05 ± 1.69</td>
<td>4.69 ± 2.21</td>
<td>1.67</td>
<td>-5.51</td>
<td>0.0000</td>
</tr>
<tr>
<td>Left Stroke</td>
<td>3.43 ± 2.06</td>
<td>4.57 ± 2.03</td>
<td>1.14</td>
<td>-3.04</td>
<td>0.0095</td>
</tr>
<tr>
<td>Left Controls</td>
<td>2.79 ± 1.42</td>
<td>4.71 ± 2.33</td>
<td>1.93</td>
<td>-5.21</td>
<td>0.0000</td>
</tr>
</tbody>
</table>

**EEG**

Post task effects were observed for the higher frequencies (>8 Hz) in left affected stroke, demonstrated by significant increases in bilateral alpha and beta (Figure 5.9, Table 5.4). A similar effect was found for controls. Post task increases were found within the contralateral hemisphere of the right stroke patients for delta and theta activity. However, this effect was not observed for controls (Figure 5.10, Table 5.5).
Figure 5.9. Left stroke pre and post task mean log power density values (±1 SE) for ipsilateral (C3), contralateral (C4) hemispheres and right hemisphere (C4) for control. * in corresponding colour denotes a significant difference pre and post task (p<0.05).

Table 5.4. Left group pre and post task mean raw power density values (±1 SE) and t values (df/13) for ipsilateral (C3), contralateral (C4) hemispheres and right hemisphere (C4) for control. One tailed t-test completed on logged values of raw data.

<table>
<thead>
<tr>
<th>Left Stroke</th>
<th>Ipsilateral Raw Power Density (μV²/Hz)</th>
<th>t-test</th>
<th>Contralateral Raw Power Density (μV²/Hz)</th>
<th>t-test</th>
<th>Control Raw Power Density (μV²/Hz)</th>
<th>t-test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>t</td>
<td>p</td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td>Beta</td>
<td>10.04 ± 2.20</td>
<td>15.24 ± 4.74</td>
<td>-2.90</td>
<td>0.0126</td>
<td>12.85 ± 17.58</td>
<td>13.99 ± 3.29</td>
</tr>
<tr>
<td>Alpha</td>
<td>6.70 ± 1.00</td>
<td>8.41 ± 1.39</td>
<td>-2.74</td>
<td>0.0168</td>
<td>14.32 ± 16.01</td>
<td>17.26 ± 4.44</td>
</tr>
<tr>
<td>Theta</td>
<td>7.86 ± 2.50</td>
<td>6.91 ± 3.16</td>
<td>-0.11</td>
<td>0.91</td>
<td>9.16 ± 7.89</td>
<td>10.64 ± 2.48</td>
</tr>
<tr>
<td>Delta</td>
<td>9.91 ± 2.45</td>
<td>9.45 ± 1.93</td>
<td>0.03</td>
<td>0.98</td>
<td>14.36 ± 17.58</td>
<td>15.29 ± 4.17</td>
</tr>
</tbody>
</table>
Figure 5.10. Right stroke pre and post task mean log power density values (±1 SE) for ipsilateral (C4), contralateral (C3) hemispheres and left hemisphere (C3) for control. * in corresponding colour denotes a significant difference pre and post task (p≤0.05).

Table 5.5. Right group pre and post task mean raw power density values (±1 SE) and t values (df/17) for ipsilateral (C4), contralateral (C3) hemispheres and right hemisphere (C3) for control. One tailed t-test completed on logged values of raw data.
Three-way between groups MANOVA was applied to investigate differences between \( \mu V^2/Hz \) of frequency bands (delta, theta, alpha and beta, and a combined variable of all frequency bands) using three independent variables, including group (stroke patients and controls), hemisphere (ipsilateral and contralateral) and task (pre and post motor task). Left and right stroke groups were analysed separately using the same MANOVA model. Bonferroni adjustment was incorporated into the analyses by dividing the set alpha value (\( p < 0.05 \)) by the amount of tests performed (3 IVs x 4 DVs) therefore the new alpha value is 0.0042.

A significant effect of group was observed for delta; \( F(1, 104)=28.22, p=0.0000, \eta^2_p=0.21 \), and theta; \( F(1, 104)=19.02, p=0.0000, \eta^2_p=0.16 \), for left group. This indicated that patients had increased power in delta and theta bands before and after task compared to controls. This effect was also observed for the right group (delta; \( F(1, 136)=40.58, p=0.0000, \eta^2_p=0.23 \), and theta; \( F(1, 136)=36.42, p=0.0000, \eta^2_p=0.21 \)). There was a noteworthy trend for an interaction of hemisphere x task for the right group for the combined variable of all frequency bands; \( F(4, 133)=2.89, p=0.0246; \) Wilk's Lambda=0.92, \( \eta^2_p=0.08 \). More specifically, near significant interactions of hemisphere x task were found for delta; \( F(1, 136)=5.18, p=0.0245, \eta^2_p=0.04 \) and theta \( F(1, 136)=5.68, p=0.0185, \eta^2_p=0.04 \).

**Relationship Between Objective and Subjective Sleepiness**

Correlation analyses revealed that patient KSS ratings were not related to the EEG for pre and post task data (Table 5.6, Figure 5.11 and 5.12). This suggests that patients were not informative of their current sleepiness state. For the right control group, increased pre task KSS correlated with pre task alpha \((r=0.48, p=0.0106)\) and theta \((r=0.56, p=0.0039)\). Also for controls, increased KSS correlated with post task alpha \((r=0.58, p=0.0026)\). From visual inspection of the scatter plots (Figures 5.8 to 5.9), it was observed that increased KSS scores were mildly related to increased alpha, pre and post task, however this did not reach significance. These results indicate that controls could accurately perceive their level of sleepiness during the experiment.
Table 5.6. Spearman’s Rho correlation coefficient for logged $\mu V^2/\text{Hz}$ per frequency band pre and post task and KSS score. Significance indicated (*$p<0.01$).

<table>
<thead>
<tr>
<th>Correlation with KSS</th>
<th>Right Stroke Ipsilateral</th>
<th>Right Stroke Contralateral</th>
<th>Left Stroke Ipsilateral</th>
<th>Left Stroke Contralateral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre Task EEG:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta</td>
<td>0.32</td>
<td>0.29</td>
<td>0.31</td>
<td>0.33</td>
</tr>
<tr>
<td>Alpha</td>
<td>0.15</td>
<td>0.18</td>
<td>0.48*</td>
<td>0.10</td>
</tr>
<tr>
<td>Theta</td>
<td>0.14</td>
<td>0.20</td>
<td>0.56*</td>
<td>-0.29</td>
</tr>
<tr>
<td>Delta</td>
<td>0.16</td>
<td>0.04</td>
<td>0.30</td>
<td>-0.08</td>
</tr>
<tr>
<td>Post Task EEG:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta</td>
<td>0.40</td>
<td>0.30</td>
<td>0.35</td>
<td>0.02</td>
</tr>
<tr>
<td>Alpha</td>
<td>0.38</td>
<td>0.28</td>
<td>0.58*</td>
<td>-0.11</td>
</tr>
<tr>
<td>Theta</td>
<td>0.27</td>
<td>0.21</td>
<td>0.37</td>
<td>-0.42</td>
</tr>
<tr>
<td>Delta</td>
<td>0.22</td>
<td>0.23</td>
<td>0.11</td>
<td>-0.18</td>
</tr>
</tbody>
</table>
Figure 5.11. Scatter plots for left stroke KSS and μV²/Hz per frequency band. 1a) C3=ipsilateral/left hemisphere and 1b) C4=contralateral/right hemisphere. 2a and 2b display C3 and C4 sites as described for 1a and b however present post task data. Linear regression fit lines as indicated per group.
Scatter plots displaying KSS and Power Density per frequency band for right affected stroke and controls.

Figure 5.12. Scatter plots for right stroke KSS and μV^2/Hz per frequency band.  
1a) C4 = ipsilateral/left hemisphere for control  
1b) C3 = contralateral/right hemisphere for control.  
2a and 2b display C4 and C3 sites as described for 1a and b however present post task data. Linear regression fit lines as indicated per group.
As performance decrements are associated with increased sleepiness in previous studies (Pilcher and Huffcutt, 1996; Samkoff and Jacques, 1991), the association between motor task behavioural outcomes (reaction time and percent correct) and change in KSS was assessed. Mean change in KSS (post minus pre) was not related to mean reaction time or percent correct on the motor task for the stroke patients or controls (Figure 5.13). Therefore, the observed increase in KSS, even though this was >1 point for both patients and controls, did not affect performance on the motor task (Figure 5.13). One major outlier within the right stroke patient group was removed for visual clarity of graphs 2a and 2c. This outlier was not removed for analysis. For scatter plots including outlier case in right stroke group, please refer to Appendix C10.
Figure 5.13. Mean change in KSS (post minus pre) and performance measures on the motor task; reaction time (RT) and percent correct (%). Linear regression fit lines as indicated per group.

5.4 Discussion

This study aimed to measure objective and subjective daytime sleepiness in stroke patients within the context of a motor priming paradigm. Furthermore, it was intended to
compare stroke patient data with a group of healthy non-brain injured matched controls. This was achieved by using EEG and subjective ratings on a state sleepiness questionnaire (KSS). According to the EEG, stroke patients appeared significantly more sleepy compared to controls. Engaging in the motor task increased subjective sleepiness of both patients and controls. The task did affect the EEG, however left stroke patients demonstrated increases in the higher frequencies whereas right stroke patients had increased lower frequencies after task. Subjective sleepiness was not related to EEG parameters in patients however was related in controls. This indicated that patients did not perceive their own sleepiness levels.

5.4.1 Overall Findings

*Increased Objective Sleepiness In Patients*

The results of the waking EEG in the stroke patients clearly showed high levels of sleepiness, characterised by greater slow wave activity compared to controls, particularly within the ipsilateral hemisphere. A striking finding from results of the frequency analysis is that the high levels of power density observed (<10 Hz) in patients during wakefulness resembled the frequency composition of the EEG in sleep deprived non-brain injured participants (Cajochen et al., 1995; De Gennaro et al., 2007; Dumont, Macchi, Piche, & Herbert, 1997). Other studies have also found increased slow waves within the waking EEG in chronic stroke (Leon-Carrion, Martin-Rodriguez, Damas-Lopez, Barroso y Martin, & Dominguez-Morales, 2008; Yuasa et al., 2001) however this effect is interpreted as an indicator of brain abnormality rather than sleepiness in these studies (Simon P. Finnigan et al., 2007; Lukashevich et al., 1999; Nagata, 1989a; Sainio et al., 1983). The higher frequencies were only affected in the right stroke patients where a decrease in activity between 18 and 21Hz was recorded in the affected hemisphere compared to controls. This result is consistent with other findings in acute stroke (Murri et al., 1998).

*Slow Wave Activity Distribution*
The slowing of the EEG occurred globally across the brain. This was demonstrated for delta and theta bands in all patients as shown in the topographic maps. Furthermore, between hemispheric differences was greatest for frequencies <11 Hz. This effect has also been demonstrated in other studies (Giaquinto et al., 1994; Hachinski et al., 1987; Juhasz et al., 1997; Mattia et al., 2003; Nagata, 1989a; Nagata et al., 1989b). Increased slow wave activity during wakefulness and sleep over the unaffected hemisphere reflects global disruption of the cortex after stroke (Müller et al., 2002; Nagata, 1989a). The current study, in addition to others, shows that EEG alterations in both hemispheres during wake remain even years after insult (Seitz, Knorr, Azari, Herzog, & Freund, 1999).

Perception of Sleepiness
The motor task elicited increases in sleepiness by >1 point on the KSS, average post task sleepiness levels reached a maximum of 5 (neither alert nor sleepy). Changes the EEG for both patients and controls. The EEG of the left stroke patients and controls both revealed increased post task alpha. In contrast, the right stroke patients experienced increases of slow wave activity in the contralateral hemisphere only. Right stroke patients presented a greater presence of slow waves (<4 Hz) pre-task which appeared to be little affected by task, unlike left stroke patients. In other studies, post task increases within the alpha range are indicative of mild subjective sleepiness whereas increased slow wave activity in suggestive of more severe sleepiness (Finelli et al., 2000; Harris, 2005).

Despite task effects on the EEG, patient sleepiness ratings did not correlate with greater presence of slower waves or increased alpha whereas a relationship was observed for controls. Therefore, in contrast to controls, patients did not seem to perceive the extent of their own sleepiness, a similar phenomenon observed in sleep deprived healthy participants (Belenky et al., 2003; Van Dongen et al., 2003) and sleep disordered patients (Greene et al., 2008; Sforza, Grandin, Jouny, Rochat, & Ibanez, 2002). It has been suggested that participants cannot reliably introspect their level of arousal when sleep deprived (Van Dongen et al., 2003). A crucial finding of the current study is that stroke

249
patients not only have similar EEGs to sleep deprived participants, they behave in a similar manner as they also cannot perceive sleepiness.

Patients revealed an increase in beta after the task in the affected hemisphere. This effect was also observed in controls. This increase may be a result of the increased effort required to complete the task when experiencing sleepiness, known as 'neurophysiological compensation' (Portas et al., 1998; Van Zandvoort et al., 1998). This can take the form of increased activity in brain regions important to the task and recruitment of other areas to aid the task when sleepy (Drummond & Brown, 2001; Portas et al., 1998; Szelenberger, Piotrowski, & Dabrowska, 2005). Neurophysiological compensation as a result of sleepiness has not yet been investigated in stroke patients however it has been suggested that as attentional capacity is limited, attentional effort reflects the allocation of cognitive and behavioural resources (Van Zandvoort et al., 1998).

In addition, the present study examined performance measures as a possible indicator of sleepiness. It was found that reaction time and percent correct were not related to KSS scores. This may be because sleepiness experienced by participants was not strong enough to generate show measureable performance decrements. Previous studies which have found performance decrements are usually under extreme sleepiness conditions, i.e. sleep deprivation paradigms (Akerstedt & Gillberg, 1990; Cajochen et al., 1995; De Gennaro et al., 2007; Marzano et al., 2007; Torsvall & Akerstedt, 1988).

5.4.2 Mechanisms Behind Objective Sleepiness In Stroke Patients

Objective Sleepiness

The EEG in stroke patients is altered during wakefulness, as demonstrated in the current study and others (Finnigan et al., 2004; Finnigan et al., 2007; Lukashevich et al., 1999; Murri et al., 1998; Sainio et al., 1983). Disruption in the EEG also extends to nocturnal sleep (Hachinski et al., 1990; Korner et al., 1986; Yokoyama et al., 1996). The greater
presence of slow waves after stroke can be attributed to impact of the neural damage caused by stroke. This is most likely due to alterations in sleep/wake mechanisms implicated in control of arousal (Evans, 2002).

Left and right stroke also presented different patterns in their EEG. More specifically, right stroke had greater presence of global slow wave activity which did not increase as a result of the task as observed in left stroke. One possible explanation for these differences is that left and right stroke follow different pathologies as there is evidence to suggest this at a behavioural and neural level (Hermann et al., 2008; Sisson, 1995, 1998). Mattia et al., (2003) also found waking EEG differences between left and right stroke two months after injury. In comparison to controls, the right stroke group presented greater presence of delta over the affected hemisphere whereas left stroke did not. Another study has shown that increased delta activity occurs to a greater degree within the affected side of right strokes compared to left strokes (Korner et al., 1986). Therefore the sequelae of left and right stroke may follow independent paths.

Subjective Sleepiness
Poor perception of sleepiness within brain injured (including TBI) populations has been reported in other studies (Bassetti et al., 1996; Bassetti & Valko, 2006; Masel et al., 2001). Other authors investigating other brain injured samples have reported similar findings. This disassociation may have occurred for several reasons: 1) those with severe injuries may underreport their symptoms due to poor introspection as a result of lack of awareness or cognitive deficit, 2) stroke patents have an altered threshold as to what they consider sleepiness or, 3) the changes in brain arousal attenuate the cognitive processes underlying sleepiness perception, i.e. arousal of the cortex, as evident by EEG frequency composition, is the cause of poor sleepiness perception.

Some authors have suggested that lack of awareness of post brain injury symptoms are a result of disturbed cognitive function (Trudel et al., 1998). This may explain why patients did not report feeling sleepy, however those recruited for the current study did not present
any difficulties in all cognitive domains including memory\textsuperscript{21}. Masel et al. (2001) objectively measured sleepiness using the MSLT technique did not correlate with ESS suggesting that brain injured patients did not perceive their own sleepiness. In the current study, laboratory observations did confirm that some patients were extremely sleepy, even falling asleep during the experiment, however this was not reflected in the KSS rating. Patients further seemed unaware of their sleepiness. Based on the evidence provided by the current study, it may also be that the threshold for what is considered a ‘problem’ changes as what is sleepy for someone who has had a brain injury may be different to a non-brain injured person. If a stroke patient is sleepy all the time, they may interpret that as normal for them, not for a healthy person. Bassetti and Valko (2006) found that those with hypersomnia interpreted did not report increased sleepiness in comparison to those without hypersomnia. In other non-brain injured samples with clinical sleep disorders, even though the EEG was suggested of sleepiness, the patients underestimated their sleepiness levels (Greeneche et al., 2008; Sforza et al., 2002). Balkin, Rupp, Picchioni, Wesensten (2008) found chronically sleep deprived persons in the general population habituate to their level of daytime functioning. This results in an underestimation of sleepiness compared to those with adequate sleep. This evidence suggests that the disassociation between sleepiness and the EEG may be common to clinical patients, however healthy persons are able to accurately estimate their sleepiness levels.

5.4.2 Implications of Findings

Patients underestimation of sleepiness levels suggests that they do not view it as a significant problem. This may explain why sleepiness is not typically addressed in post stroke treatment as reported in Study One of this thesis and as commented in other reports (Bassetti & Valko, 2006; Castriotta & Lai, 2001; Castriotta et al., 2007; Makley et al., 2008; Parcell et al., 2006; Wessendorf et al., 2000). Early recognition and treatment of chronic sleepiness is critical due to severe safety risks if patients continue to go about

\textsuperscript{21} As measured by the MMS.
their daily activities without awareness that they are vulnerable to sleepiness. This is particularly relevant for those patients who drive or operate other machinery at work (Lukashevich et al., 1999; Sagberg, 2006). Another study showed that patients with disrupted daytime alertness were more susceptible to falls (Michael et al., 2006). Importantly, presence of subjective sleepiness, as part of a combined variable with sleep disturbance, is associated with poorer quality of life in this population (Schuiling et al., 2005). Moreover, if patients do underestimate the degree to which they experience sleepiness, the relationship with lower quality of life may be even stronger. Sleepiness may be a forgotten mediator of quality of life after stroke.

Furthermore, more research should focus on treatment options for sleepiness. As well as managing sleepiness as part of their lifestyle, such as taking rest and naps, pharmacological options may also be of benefit to sleepy patients (Schneerson, 2005; Thaxdon & Myers, 2002; Zafonte, Mann, & Fichtenberg, 1996). CNS active drugs which act upon those neurotransmitters involved in the arousal system, such as amphetamines and dopaminergic agents, have been used to promote wakefulness (Al-Adawi, Burke, & Dorvlo, 2006; Autret et al., 2001; Bassetti, 2005a; Bassetti & Valko, 2006; Roth & Roehrs, 1996; Schneerson, 2005).

It is also important to highlight to clinicians and researchers the potentially differential pathologies between left and right stroke. As these groups responded differently to the motor task in terms of their EEG in this study, this suggests that it may not appropriate to group left and right stroke together in the same EEG analysis, a common procedure for smaller samples (Giaquinto et al., 1994; Yokoyama et al., 1996).

5.4.3 Limitations of This Study

Limitations of this study arise from the low ecological validity of the laboratory conditions which may not be representative of sleepiness circumstances in the real world. The lengthy process of electrode application followed by the motor priming task may be
more conducive to sleepiness due to the monotony of residing in the same seat for that length of time. Unfortunately, this cannot be avoided when using an EEG paradigm. However KSS ratings taken before the task did not suggest that patients or controls were highly sleepy prior to engaging in the motor priming task.

Another limitation within this study is the potential experimental bias upon participant responses on the KSS. Researcher presence may momentarily alter KSS scoring, merely by their presence which stops feelings of sleepiness for a brief time. (Akerstedt et al., 2008; Kosuke Kaida et al., 2007). Although there is a possibility that patients may monitor their response to fit what they believe the experimenter wants, patients were asked to answer as honestly as possible.

5.4.4 Future Studies

Future studies to investigate post stroke objective sleepiness could involve modifications of the current protocol as this particular study was limited within the constraints of the CIT protocol. Rather than using the motor priming task, perhaps use of validated and reliable psychometric tests of vigilance would provide an additional behavioural measure of sleepiness. Such tests could include the Psychomotor Vigilance Test (PVT) which primarily relies on high levels of alertness to quickly respond to stimuli (Dinges & Powell, 1985). In the PVT, longer reaction times are indicative of increased sleepiness. With regard to the potential risk of driving when sleepy, experiments could utilise driving simulators to examine if poor perception of sleepiness is more likely to be associated with dangerous driving (Groeger, 2006; Groeger & Banks, 2007).

Other methods of measuring sleepiness such as eye movements, heart rate variability and pupillary unrest index (as described in (Franzen, Siegle et al., 2008; Kaida et al., 2007) could be introduced to support arousal levels as provided by the EEG. Furthermore, examining objective sleepiness in other contexts would also be useful, particularly in situations where patients predictable become tired such as when engaging in challenging
rehabilitation sessions (Barker-Collo et al., 2007; Morley et al., 2005; Muller et al., 2006; Worthington & Melia, 2006).

**Conclusion to Chapter 5**

It is evident that there is a physiological alteration in the EEG in chronic patients with may have a role in the increased sleepiness experienced in stroke patients. Critically, stroke patients do not perceive high levels of sleepiness which are likened to that of a sleep deprived person.

The main conclusions of this study are:

- Chronic stroke patients have a greater presence of slow waves in their waking EEG which indicated increased sleepiness to the level that is experienced by a sleep deprived person.
- The motor priming task increased subjective sleepiness, however scores only increased to a mild state of sleepiness (neither alert nor sleepy), and elicited changes in the EEG.
- Changes in the EEG reflected more power in the lower frequencies of right stroke and increased in the higher frequencies for left stroke.
- Stroke patients did not reliability perceive their own sleepiness.
- The increase in higher frequencies may reflect the greater effort used by these patients to complete the task.

Now that it understood there are post stroke disruptions to sleep on a behavioural level as well as physiological daytime functioning disturbance, the impact sleep these dimensions have on neurorehabilitation needs to be investigated. The following Chapter presents the fourth and final study of this thesis which aims to examine the extent to which poor sleep
and day functioning deficits, as observed in the previous three studies, affect motor
neurorehabilitation in these patients.
Chapter 4 Overview

Studies 1, 2 and 3 aimed to characterise sleep and daytime functioning in chronic stroke patients with residual motor deficits. Sleep disturbance and poor daytime functioning was clearly evident in patients. These disturbances were sever in some patients. Furthermore, the waking EEG of patients was abnormal, revealing similarities with the EEG of sleep deprived non-brain injured persons. Crucially, poorer quality sleep was associated with poorer motor ability. Also, those with better motor ability experienced greater fatigue. These findings, in addition to evidence within the literature that shows sleep may be a modulator for motor learning, provide strong theoretical reason to address sleep behaviour in a motor neurorehabilitation context. The final study for this thesis therefore aimed to explore sleep and daytime functioning during an upper limb motor neurorehabilitation programme and the potential association of sleep and rehabilitation outcome. No known study has systematically monitored sleep in a sample of chronic stroke patients with hemiparesis during CIT. The most critical aspect of this study is the utilisation of a homogenous group of stroke patients (n=32) who were in a chronic state with regard to their physical and psychological functioning. Furthermore, these patients were selected based on a narrow window of motor ability. The findings of this study will have important implications for patients undergoing neurorehabilitation treatment after stroke but also will inform further research of this kind.
6.1 Introduction

The findings from previous studies, as well as the this thesis so far, suggest that sleep has a beneficial function for the following aspects of stroke recovery: 1) health and well being, 2) daytime functioning, 3) motor learning, and 4) neuroplasticity. Therefore there is strong theoretical reason to predict a relationship between sleep and post stroke neurorehabilitation. Previous studies have shown a relationship between healthy sleep and improved recovery outcome, however no known study has examined the role of sleep specifically in a neurorehabilitation context for chronic upper limb hemiparesis.

6.1.1 Theoretical Underpinnings: Somatic, Behavioural, Cognitive, and Neural Evidence

**Somatic Evidence: Sleep and Health**

It is now undoubted that sleep is essential for maintaining health and wellbeing in the general population (Groeger et al., 2004; Steptoe et al., 2008; Zeithofer et al., 2000). The nature of this relationship may also be reciprocal as symptoms of poorer health such as pain, muscular discomfort and psychological stress, affects quality of sleep (Kamaleri, Natvig, Ihlebaek, Benth, & Bruusgaard, 2008). Chronically ill populations suffer high levels of sleep disturbance including those with primary physical, mental and neurological conditions (Foley et al., 2004; Katz & McHorney, 1998; Manocchia et al., 2001; Ohayon, 2005; Parish, 2009) including stroke (Cadihae et al., 2005; Campos et al., 2005; Masel et al., 2001; Muller et al., 2006; Schuiling et al., 2005; Worthington & Melia, 2006). In particular, chronic stroke patients with sleep disturbance experience a poorer quality of life compared to those with healthy sleep (Schuiling et al., 2005). Furthermore, Study 1 of this thesis showed that those who reported disturbance had poorer perceived health compared to those without sleep problems. This evidence highlights the critical role of sleep in general health and that it may be a crucial modulator physical and psychological wellbeing of stroke patients. Alarmingly, post

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Mixed stroke and TBI sample.
Behavourial and Cognitive Evidence: Sleep and the Maintenance of Daytime Functioning

Adequate sleep is essential for minimising levels of sleepiness and fatigue as demonstrated in laboratory based sleep deprivation studies (Akerstedt & Gillberg, 1990; Franzen, Siegel, & Buysse, 2008; Ikegami et al., 2009; Marzano et al., 2007) and sleep disturbance experienced in the natural environment (Martikainen et al., 1992; Philip et al., 2005; Pilcher & Huffcutt, 1996; Torsvall & Akerstedt, 1987; Wilhelm et al., 2009). Sleep disordered patients frequently complain of increased daytime sleepiness (Moul et al., 2002; Ulfberg et al., 2007; Ulfberg, Carter, Talback, & Edling, 1996) and fatigue (Chervin, 2000; Hossain et al., 2005; Lichstein et al., 1997). Sleep difficulties may, in part, contribute to increased sleepiness and fatigue in stroke patient populations (Bassetti and Valko, 2006). However poorer daytime functioning may also occur despite normal nocturnal sleep due to damaged neural arousal mechanisms (Bassetti and Valko, 2006), depressed mood (Choi-Kwon et al., 2005; Ingles et al., 1999; Naess et al., 2005; Staub & Julien Bogousslavsky, 2001), and diminished reserves for physical (Macko et al., 2001; Muller et al., 2006) and mental effort (Van Zandzoort et al., 1998). Increased sleepiness adversely affects cognitive performance in non-brain injured participants (Dinges et al., 1997; Durmer & Dinges, 2005; Pilcher & Huffcutt, 1996; van den Berg et al., 2005; Van Dongen et al., 2003) and is known to affect attention capacity of stroke patients (Hermann et al., 2008; Van Zandvoort et al., 1998). Moreover, cognitive deficits negatively impact rehabilitation participation and outcome (Galski et al., 1993; Mokler et al., 2000; Zinn et al., 2004). Based on this evidence, it is reasonable to assume that minimising sleepiness and fatigue in patients may facilitate optimum conditions when engaging in rehabilitation.

Cognitive Evidence: Sleep and Learning

There is ample evidence that demonstrates the explicit role of sleep for motor learning in healthy non-brain injured participants (Cohen et al., 2005; Fischer et al., 2002; Gaab et
al., 2004; Karni et al., 1994; Kuriyama et al., 2004; Robertson et al., 2004; Wagner et al., 2004; Walker et al., 2002a; Walker et al., 2003b). Furthermore, daytime napping also enhances motor learning (Backhaus & Junghanns, 2006; Milner et al., 2006; Nishida & Walker, 2007). This amounting evidence has led several authors to conclude that sleep may have be a crucial function for post stroke motor neurorehabilitation (Gomez-Beldarrain et al., 2008; Kuriyama et al., 2004; Robertson & Cohen, 2006; Siengsukon & Boyd, 2009b; Walker et al., 2003b) however this notion has not been explored in stroke patients undergoing a motor neurorehabilitation programme. Firstly, it is important to establish if the enhancement of motor learning through sleep and napping also applies to patients.

Siengsukon and Boyd are the first known research group to exclusively investigate sleep dependent motor learning in a group of chronic stroke patients. Their experiments utilised a continuous tracking task designed to generate implicit and explicit motor learning in a group of older (>60 years old) chronic stroke patients and non-brain injured matched controls (Siengsukon & Boyd, 2008a, 2009a; Siengsukon & Boyd, 2008b). Participants were trained and then retested for retention of motor skill learning. Patients and controls were assigned to one of two conditions to include a sleep period between learning and retesting, or a period of wakefulness. It is important to note that, unlike previous studies examining sleep dependent learning, this study did not incorporate a sleep deprivation paradigm. Participants practiced the task either in the evening (sleep group) or in the morning (wake group) and were retested 12 hours later.

The overall findings of these experiments revealed that patients who slept between practice and retention testing demonstrated enhanced implicit and explicit learning compared to patients who did not sleep and the controls. This suggests that stroke patients do have the capacity for sleep dependent motor learning which holds clinical relevance for post stroke motor neurorehabilitation (Siengsukon & Boyd, 2008a, 2009a). In addition, a study by Gomez et al. (2008) examined sleep dependent learning in sample of chronic brain injured patients, four of which, had a stroke. Enhanced learning on the
serial reaction time task was enhanced by sleep to a greater degree in patients compared to controls.

It is important to note that the above studies all examined motor learning whilst using the non-affected hand. It is not yet known if motor learning in the affected hand may also respond to sleep dependent learning in the same manner. Further investigation is required to establish if sleep benefits motor learning within the affected hemisphere.

**Neural Correlates of Sleep and Plasticity**

Practice induced plasticity is believed to be facilitated by processes during sleep which enhance motor learning (Walker & Stickgold, 2006). These processes behind sleep dependent plasticity may occur during stage 2 sleep as spindles are possible triggers for long term synaptic plasticity (Contreras, Destexhe, & Steriade, 1997; Sejnowski & Destexhe, 2000). Neural mechanisms within slow wave (Huber & Ghilardi, 2004) and REM (Maquet et al., 2000; Peigneux et al., 2003) sleep have also been implicated in sleep dependent plasticity. It was concluded that sleep may create a conductive environment for promoting neuroplasticity which serve the function of consolidating motor skills (Datta, 2000; Datta, Mavanji, Ulloor, & Patterson, 2004; Sejnowski & Destexhe, 2000; Mircea Steriade, 1999; Mircea Steriade & Timofeev, 2003; Tononi & Cirelli, 2003; Tononi & Cirelli, 2006).

Neuroplasticity is an essential part of recovery after stroke. This process enables some functions which were lost as a result of stroke, to be restored or at least partly recovered (Matthews et al., 2004; Mulder & Hochstenbach, 2001; Platz, 2004). This largely involves regaining motor function as a result of hemiparesis. Through spontaneous recovery and motor neurorehabilitation, neuroplasticity mechanisms are driven in response to injury. Based on the evidence presented above, several authors have suggested that sleep may have a critical role for post stroke rehabilitation (Robertson and Cohen, 2006), more specifically, sleep may facilitate re-learning of lost motor skills as a result of hemiparesis (Gomez-Beldarrain et al., 2008; Kuriyama et al., 2004; Siengsukon & Boyd, 2009b; Walker et al., 2002a). This may be due to the supportive environment it
provides for neuroplasticity (Datta, 2000; Datta et al., 2004; Sejnowski & Destexhe, 2000; Mircea Steriade, 1999; Mircea Steriade & Timofeev, 2003; Tononi & Cirelli, 2003; Tononi & Cirelli, 2006).

**Sleep and Post Stroke Recovery Outcome**

Several studies have shown a relationship between increased sleep disturbance and poorer recovery in both acute (Bassetti & Aldrich, 1999; Bassetti & Aldrich, 2001; Good et al., 1996; Hachinski et al., 1987; Kaneko et al., 2003a; Leppävuori et al., 2002; Sandberg et al., 2001; Siccoli & Bassetti, 2008; Takekawa et al., 2007) and chronic stroke samples (Bassetti & Aldrich, 2001; Giubilei et al., 1992; Hermann et al., 2008; Vock et al., 2002). Furthermore, the results of Study 2 of this thesis indicated that sleep and levels of fatigue are related to levels of residual motor recovery in the chronic stage of stroke. Furthermore, initial evidence shows that improvement or normalisation of the sleep EEG is associated with better recovery in stroke patients (Gottselig et al., 2002; Vock et al., 2002).

6.1.2 Sleep and Rehabilitation Outcome

Healthy sleep may be of benefit for offline improvements as well as increasing cognitive capacities for rehabilitation participation. Several studies have examined the impact of sleep and daytime functioning in a range of rehabilitation settings within various brain injured cohorts, however no known studies have examined this idea with regard to motor learning during a neurorehabilitation paradigm in patients with chronic hemiparesis.

Worthington and Melia (2006) acquired sleep data from nurses and carers of a mixed group of chronic stroke and TBI patients admitted to a rehabilitation facility. They found that observable sleepiness, attributed to brain injury or sleep disturbance, which affected daily functional performance generally and during rehabilitation sessions. The authors highlighted that healthy sleep management is critical to rehabilitation success. Other studies have also attributed poor daytime functioning to poorer rehabilitation.
participation and a lack of motivation in stroke patients (Barker-Collo et al., 2007; Morley et al., 2005; Muller et al., 2006). A study involving a large sample of older patients (≥65 years) with a range of conditions (10% of which experienced stroke) admitted to a post acute rehabilitation facility reported that increased napping was associated with worse rehabilitation outcome (Alessi et al., 2008). This relationship was believed to be the result of attenuated functional gains within rehabilitation sessions due to decreased motivation and need to sleep. In contrast to this finding, previous studies have suggested that napping is beneficial for motor learning in healthy non-brain injured samples (Backhaus & Junghanns, 2006; Milner et al., 2006; Nishida & Walker, 2007). Seingsukon and Boyd (2009b) postulated that sleep could be used as a tool to capitalise on motor learning in between rehabilitation during the day. It may be that there is an optimum nap length for patients undergoing rehabilitation, however this idea has not yet been examined in stroke patients.

The presented evidence suggests that sleep and daytime functioning may be modulating factors for motor neurorehabilitation participation and ultimately outcome. Therefore it is postulated that interventions to improve abnormal sleep/wake patterns during rehabilitation may result in better functional recovery (Alessi et al., 2008; Bassetti & Aldrich, 1999; Masel et al., 2001; Fabienne Staub & Julien Bogousslavsky, 2001) and should be considered an integral part of the rehabilitation process (Cohen et al., 1992; Hyvppä & Kronholm, 1995; Parcell et al., 2006; Terzoudi et al., 2009; Uomoto, 2008). However this idea has not been directly investigated. There a clinical demand for further studies regarding the role of sleep for neurorehabilitation outcome. According to Terzoudi et al. (2009), future studies should utilise a highly controlled rehabilitation setting and include homogenous samples to reduce the effects of inter patient variability.

6.1.3 The Rationale For Study 4: Clinically Application of Sleep Research Within CIT
It is the aim of this thesis to make the transition from postulations of other authors (Alessi et al., 2008; Bassetti & Aldrich, 1999; Masel et al., 2001; Staub & Julien Bogousslavsky, 2001) to clinically applied research in order to ultimately investigate the role of sleep and daytime functioning in a highly controlled motor neurorehabilitation context. Research of this nature was made possible by the opportunity to research patients undergoing a form of neurorehabilitation known as Constraint Induced Movement Therapy (CIT).

CIT: The Testable Model To Explore Sleep Aims Motor Neurorehabilitation

The CIT protocol under investigation for this thesis has provided the ideal model situation to explore the potential link between sleep and neurorehabilitation. More specifically, it is the central aim of CIT to facilitate upper limb motor ability, which holds particular relevance for the sleep dependent motor learning theory. Motor ability is increased via CIT by creating the optimum environment to drive neuroplasticity mechanisms (Cramer & Bastings, 2000; Hamzei, Liepert, Dettmers, Weiller, & Rijntjes, 2006). CIT creates these conditions by facilitating motor learning based the following principles: 1) non-use of the affected limb is partly learned, therefore may be reversed, 2) introducing mass practice of the affected limb and 3) incorporating a strong learning component to shape motor movements in correct manner.

The ‘learned non-use’ principle behind CIT refers to repeated failure of affected arm use as well as greater success with non-affected upper limb (Taub, 1980). This learning pattern results in reduced usage of the affected limb and reliance on the non-affected limb which may inhibit recovery (Kunkel et al., 1999; Morris et al., 1997; Sterr, Freivogel, & Schmalohr, 2002a; Taub et al., 1994; Taub et al., 1993; Taub & Wolf, 1997). Therefore, CIT incorporates a ‘forced use’ aspect within the protocol involving constraint (using an arm splint or sling) of the non-affected limb to increase use and reverse association between the affected limb and failure to achieve goals. The CIT technique also employs an upper limb motor learning component (Taub et al., 1994) involving mass practice of everyday tasks under the guidance of a CIT therapist for a set amount of hours per day for two weeks. The therapist selects tasks that to address the motor deficits encountered
by individual. The therapist’s role involves modelling motor movement, prompting, providing feedback and systematically increasing the difficulty level of tasks (Taub, 2006, p.1046).

The other important principle behind CIT is the recognition of recovery potential. Most recovery occurs during the acute phase post stroke, with retainable function within a few weeks (Duncan et al., 1992; Jorgensen et al., 1995) which begin to plateau within 6 months (Kwakkel, Kollen, van der Grond, & Prevo, 2003; Sullivan, 2007; Tilling et al., 2001). Recent research has shown that the brain’s ability to reorganise towards optimum levels has previously been underestimated (Taub, 1976; Taub, Uswatte, & Elbert, 2002) as neuroplastic changes may occur even years after insult (Page, Gater, & Bach, 2004).

CIT has demonstrated high efficacy for the treatment of upper limb hemiparesis in matched control trials (Taub, 1999; Taub et al., 1993; Taub et al., 2004; Taub & Uswatte, 2003; Van der Lee et al., 1999; Wolf et al., 2006) as well as within groups designs (Bonifer et al., 2005; Kunkel et al., 1999; Sterr et al., 2002b). The research has shown that CIT helps to improve the ability to use the affected arm on structured movement tests as well as real world arm use. Furthermore, studies using Magnetic Resonance Imaging (MRI) have shown new activation in motor areas as a result of CIT (Kim et al., 2004; Liepert, Bauder, Wolfgang et al., 2000). Follow-up investigations revealed that the functional gains with the affected arm are maintained beyond one year (Taub et al., 1993; Taub et al., 2006; Wolf et al., 2006). Moreover, the functional improvements obtained through the intervention enhance confidence in using the affected limb in everyday situations and contribute to a greater quality of life (Dettmers et al., 2005; Lin, Chang, Wu, & Chen, 2009).

6.1.4 The Current Study

The initial evidence presented above shows that sleep has implications for motor neurorehabilitation. However, no known study has prospectively addressed sleep in a
tightly controlled motor rehabilitation setting with particular reference to motor functioning in stroke patients suffering from hemiparesis. The current study was developed to explore under researched avenues of post stroke recovery and to ultimately to promote a paradigm shift in rehabilitation protocols for a 24 hour approach to rehabilitation.

**Research Aims**

The study aimed to investigate the relationship between sleep and motor neurorehabilitation outcome in a group of chronic stroke patients, based on a narrow range of motor ability and who are in a stable state with regard to their physical and psychological recovery. This will be investigated in patients undergoing CIT. The standard CIT protocol consists of 6 hours of training per day for two weeks, excluding weekends (Taub et al., 1993). The CIT trial used for this study utilises a modified CIT protocol whereby session length was reduced to 1.5 or 3 hours per day for two weeks. Modified CIT protocols have also shown high efficacy in comparison to longer treatment lengths (Sterr et al., 2002b). CIT was administered to patients in a highly controlled setting therefore all patients had similar schedules.

Based on the literature described above, the following research questions were formulated:

1) Does enduring CIT influence normal sleep or daytime functioning behaviour?

2) Is sleep and daytime functioning related to CIT outcome as measured by a battery of motor ability tests?

**6.2 Methods**

266
6.2.1 Design

Longitudinal sleep assessments were carried out throughout the CIT trial for a total of six weeks. This period was split into three phases: baseline (BL), CIT and post equating to two weeks each (Figure 6.2.1). A repeated measures design was employed to compare results of the sleep diary and actigraphy per phase. CIT induced motor ability outcome was subject to a repeated measures design, comparing of motor ability scores recorded at pre-CIT (T2) with that of post-CIT (T3).

![The CIT Trial Framework](image)

Figure 6.1. Design of CIT trial, The highlighted section indicates time point from which data for this study was collected.

6.2.2 Participants

An opportunity sample of 32 community dwelling chronic stroke patients were recruited directly from the CIT trial. All patients fulfilled the inclusion/exclusion criteria, as

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23 Similarly with Study 4, baseline motor testing (T1) was not used for analysis due to unfamiliarity of the testing situation. Therefore it is recommended that a second testing opportunity produces more reliable results (Whitall et al. 2006).

24 A total of 38 patients received 1.5 or 3 hours of CIT (section 2.2.1, chapter 2). Six patients were not included in the analysis for this study. Two patients were non-compliant regarding sleep diary completion. Two patients data was not included due to actigraphy fault. Two patients did not complete the full protocol.
described in Section 2.2.1, Chapter 2, forming a highly selective homogenous group of low motor functioning patients.

For the purposes of the CIT trial, all patients were randomly assigned to one of four groups: a) 1.5 hours of CIT with constraint (n=10), b) 1.5 hours of CIT without constraint (n=9), c) 3 hours with constraint (n=4) and d) 3 hours without constraint (n=9). For the purposes of the current study, groups a) and b) were combined to form the 1.5 hour group (n=19). Groups c) and d) were combined to form the 3 hour group (n=13). Overall compliance rates were poor for constraint use and home. In addition two patients changed from 3 hour groups to 1.5 hours of CIT per day. Furthermore, 3 hour sessions were terminated early on several occasions for patients who were too tired to continue with CIT. For these reasons, it was deemed appropriate to combine patient groups for analyses for this study. However where necessary, 1.5 and 3 hour groups were examined separately.

6.2.3 Materials

Sleep and daytime functioning was assessed via sleep diaries and 24 hour actigraphy throughout the baseline, CIT and post phase. The pen and paper based sleep diary requested patient perception of nocturnal sleep parameters. Furthermore, the sleep diaries also contained twice daily Karolinska Sleepiness Scale (KSS; Akerstedt & Gillberg, 1990) and Daily Fatigue Scales (D-FIS; Fisk & Doble, 2002) to assess sleepiness and fatigue during the morning and evening. Actigraphy recordings were conducted using the ‘Actiwatch Mini ®’ (CamNtech Ltd., © 2009), worn on the non-affected wrist. Sleep diaries and actigraphy materials are described in more detail within Section 2.3.4, Chapter 2. CIT induced upper limb motor ability was assessed using a battery of motor assessments including the Wolf Motor Function Test (WMFT; Wolf et al., 1989) and Motor Activity Log (MAL; Taub et al., 1993), described in Section 2.3.3, Chapter 2.
6.2.4 Procedure

All patients attended the baseline test point (T1) which comprised the first administration of the motor test battery (Figure 6.1). Additionally during T1, patients were fitted with the actiwatches, given the sleep diary and provided with instructions. Participants were asked to complete the sleep diaries as accurately as possible and to report any instances when the actiwatches were removed to avoid miscoding of a daytime sleep period. The sleep diaries and actigraphy recordings were continued for a total of six weeks (baseline, CIT and post). The motor test battery was conducted at baseline (T1), pre-CIT (T2) and post-CIT (T3).

6.2.5 Analysis

Data drawn from the sleep diary and actiwatch were aggregated across the days recorded for each of the three phases. Due to differences in weekday sleep schedules to that of weekends as observed in Study 2, only weekday measures were used for analysis.

**Sleep Diary**

The following nocturnal sleep parameters were drawn from the sleep diary: time in bed (minutes), sleep duration (minutes), sleep onset latency (minutes), sleep efficiency (%) and night awakenings (frequency and duration). Daytime functioning parameters were represented by morning and evening KSS and D-FIS ratings as well as daytime nap reports (frequency and duration minutes).

**Actigraphy**

Actigraphy recordings were analysed using Actiwatch Sleep Analysis Software (Version 7.22, CamNtech Ltd, © 2009) in order to calculate the following sleep parameters: time in bed (minutes), sleep duration (minutes), sleep onset latency (minutes), sleep efficiency (%) and night awakenings (frequency and duration in minutes). Bed time and get up time were entered manually (using the sleep diary for guidance) whereas the remaining
parameters were calculated using the sleep scoring function within the Actiwatch Sleep Analysis Software. Similarly to Study 2, sleep scoring analysis was set using a medium sensitivity of $\leq 40$ activity counts per minute to define wake. A napping period was defined as any daytime sleep which occurred between get up time and bed time for a minimum of 15 minutes. The sensitivity was set to $\leq 10$ activity counts per minute to define an epoch of daytime sleep.

**CIT Outcome**

The WMFT provided two measures of motor ability, median reaction time (mins) and mean functional ability (score out of 7) across all items. The MAL provided two measures of subjectively rated arm use outside of the laboratory including amount of use (AOU) and quality of use (QOU). See Section 2.3.4, Chapter 2, for more details.

**Statistical Analysis**

As the distribution of the data was non-normal, non-parametric alternatives were used for all statistical analyses. CIT outcome was calculated by subtracting post motor test scores (T3) from pre scores (T2). Mean CIT outcome was compared between the 1.5 and 3 hour using the Mann Whitney U Test. Mean sleep and daytime functioning analyses for BL, CIT and post phases were statistically compared using the Friedman Test. Further analysis between two phases (e.g. BL and CIT) utilised the Wilcoxon signed ranks test. Relationships between sleep, daytime functioning with CIT outcome were determined using Spearman’s Rank Correlation Coefficient.

### 6.3 Results

#### 6.3.1 Demographics

The demographics for all patients is presented in Table 6.1.
Table 6.1. Data presented as mean (+/- 1 SD and range) or percent valid where appropriate. The remaining 28.12% of stroke patients unlisted for employment status were classified as not working. For individual case information for all participants, see Appendix C.

<table>
<thead>
<tr>
<th>Demographical Variables</th>
<th>n=32</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M:F)</td>
<td>17:15</td>
</tr>
<tr>
<td>Age (Years)</td>
<td>50.26 ± 10.57 (28.73)</td>
</tr>
<tr>
<td>BMI</td>
<td>23.84 ± 2.39 (18.2-28.9)</td>
</tr>
<tr>
<td>NART (IQ)</td>
<td>115.98 ± 7.03 (96-125)</td>
</tr>
<tr>
<td>Mini Mental State Exam</td>
<td>29.56 ± 0.97 (26-30)</td>
</tr>
<tr>
<td>Education Level:</td>
<td></td>
</tr>
<tr>
<td>School Leavers Certificate</td>
<td>28.13%</td>
</tr>
<tr>
<td>Further Study</td>
<td>50%</td>
</tr>
<tr>
<td>Higher Education</td>
<td>21.88%</td>
</tr>
<tr>
<td>Employment Status:</td>
<td></td>
</tr>
<tr>
<td>Full Time</td>
<td>12.5%</td>
</tr>
<tr>
<td>Part Time</td>
<td>18.75%</td>
</tr>
<tr>
<td>Retired</td>
<td>40.63%</td>
</tr>
<tr>
<td>Studying</td>
<td>None</td>
</tr>
<tr>
<td>Living Support:</td>
<td></td>
</tr>
<tr>
<td>Living Alone</td>
<td>15.59%</td>
</tr>
<tr>
<td>Living With Family</td>
<td>84.42%</td>
</tr>
<tr>
<td>Chronicity (Months)</td>
<td>38.43 ± 38.43 (11-140)</td>
</tr>
<tr>
<td>Type of Stroke:†</td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>50%</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>15.63%</td>
</tr>
<tr>
<td>Both</td>
<td>3.13%</td>
</tr>
<tr>
<td>Lesion Hemisphere</td>
<td>13 Left, 19 Right</td>
</tr>
<tr>
<td>Co-morbid Conditions:</td>
<td></td>
</tr>
<tr>
<td>Psychological</td>
<td>28.13%</td>
</tr>
<tr>
<td>Muscular</td>
<td>3.13%</td>
</tr>
<tr>
<td>Neurological‡</td>
<td>18.75%</td>
</tr>
<tr>
<td>Cardiac</td>
<td>43.75%</td>
</tr>
<tr>
<td>Cancer</td>
<td>3.13%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3.13%</td>
</tr>
<tr>
<td>Pain</td>
<td>3.13%</td>
</tr>
<tr>
<td>Dysphasia (From Mild to Severe)‡</td>
<td>18.75%</td>
</tr>
<tr>
<td>Medication:</td>
<td></td>
</tr>
<tr>
<td>Anti-depressant</td>
<td>9.38%</td>
</tr>
<tr>
<td>Pain Relief</td>
<td>None</td>
</tr>
<tr>
<td>Cardiac Control</td>
<td>3.13%</td>
</tr>
<tr>
<td>Anti-epileptic</td>
<td>15.65%</td>
</tr>
<tr>
<td>Sleep Hypnotics</td>
<td>None</td>
</tr>
<tr>
<td>Alcohol (Units per week)</td>
<td>7.76 ± 8.41 (0-32)</td>
</tr>
<tr>
<td>Caffeine (Cups per day)</td>
<td>5.23 ± 2.88 (0-12)</td>
</tr>
<tr>
<td>Nicotine (Cigarettes Per Day)</td>
<td>0.99 ± 3.09 (0-20)</td>
</tr>
</tbody>
</table>

(-) not required or not recorded as part of this study.
* 38.87% of the patients experienced expressive aphasia and only completed the 3-step command on the MSE only therefore were not included in the total mean score. These patients also did not complete the NART.
† The remainder of these values were classified as unknown.
‡ Neurological conditions other than stroke.
6.3.2 CIT Outcome

Figure 6.2 presents results of the motor test battery recorded pre (T2) and post (T3) CIT for individual treatment groups; 1.5 and 3 hours. A larger mean difference (post minus pre), indicates better CIT effect. Negative scores indicate faster reaction time for WMFT RT whereas positive scores represent greater improvement for WMFT FA and MAL. There were no significant differences in CIT outcome between the 1.5 and 3 hour groups. This suggests that 3 hours of therapy does not appear to facilitate an overall greater outcome compared to 1.5 hours. This further demonstrates that it was appropriate to combine all patients into one group for analysis.

Figure 6.2. Pre and post CIT mean scores (+/-1 SD and range) for all motor. Pre and post significant differences are indicated (*p≤0.05).

6.3.3 Sleep and Daytime Functioning Per Phase

Sleep and daytime functioning were examined for the BL, CIT and post phase. Mean change (Δ) from BL to CIT, CIT to post and BL to post were also examined.
Nocturnal Sleep

Figure 6.3 and 6.4 present the nocturnal parameters extracted from the sleep diary and actigraphy recordings per phase. A significant effect of phase was observed for subjective sleep duration ($\chi^2=4.98; p=0.0414$). Further Wilcoxon signed-ranks test showed that this difference was greatest between BL and post phases where patients slept less during the post phase ($Z=-1.70; p=0.0448$). An effect was also found for actigraphy determined sleep duration, however this showed that patients slept less during CIT compared to BL ($Z=-1.84; p=0.0327$). This may reflect the impact of the CIT trial on sleep schedules where patients had less opportunity to sleep longer in order to attend morning CIT sessions. Actigraphy revealed lower time in bed during CIT which was significantly different from that of baseline ($Z=-1.70; p=0.0444$). This further shows that attending CIT affected normal sleep schedules.

Although a difference was not observed across all phases, a closer inspection of the subjective reports of night awakenings revealed a significant difference between BL and CIT ($Z=-1.70; p=0.0448$). This is an indication that patients felt they slept better during CIT due to less night awakenings. This was also reflected in a more reliable estimate of night awakenings from the actigraphy recordings for night awakening frequency between BL and CIT ($Z=-2.47; p=0.0068$). In addition, a difference was observed between CIT and post ($Z=-1.69; p=0.0462$). Unlike sleep diary results, actigraphy did not reveal any differences for night awakening duration.
Using actigraphy as a more accurate estimation of sleep, the results showed that despite the sleep changes incurred during CIT, the patient group demonstrated low sleep efficiency throughout all phases (Figure 6.4; >85%). This is partly due to the longer time in bed endured by patients. However, patients also slept less than 8 hours per night, even during CIT. Case analysis showed that 28.13% of patients demonstrated extremely poor sleep during CIT (>7 hours), as low as 5.81 hours on average per night.
Figure 6.4. Mean (+/-1 SD and range) nocturnal sleep data drawn from actigraphy recordings per phase. Friedman test statistic ($X^2$) and significance value ($p$) is presented ($df/2$). Significant values are indicated ($*p \leq 0.05$).

**Daytime Functioning**

Figure 6.5 presents KSS and D-FIS scores, during the morning and evening, per phase. Figure 6.6 displays both sleep diary and actigraphy reports of napping per phase. Both sleepiness and fatigue significantly increased during the evening for all phases (Figure 6.5). There were no differences between BL, CIT and post for both sleepiness and fatigue. Upon closer inspection of the data, a near significant trend was revealed where evening KSS scores were mildly increased during CIT compared to BL ($r=-1.31$; $p=0.0945$).
Figure 6.5. Mean (+/-1 SD and range) KSS and D-FIS scores. Friedman test statistic ($X^2$) and significance value ($p$) is presented. Significant values indicated (*$p$≤0.05).

Figure 6.6 shows that napping behaviour was reduced during the CIT phase. Statistical analyses revealed a significant difference for subjective napping between CIT and post ($Z=-1.29; p=0.0986$) and a near significant trend between BL and CIT ($Z=-1.69; p=0.0454$). This effect was not observed for actigraphy results. A possible explanation for this discrepancy may be due to patients’ perception. The structure that the CIT imposes on the patients’ day may be associated with a sense of napping less even though actigraphy suggests otherwise.
Figure 6.6. Mean (+/-1 SD and range) daytime functioning data drawn from actigraphy recordings per phase. Friedman test statistic ($\chi^2$) and significance value (p) is presented. Significant values indicated (*p<0.05).

6.3.4 Sleep, Daytime Functioning and CIT Outcome

Correlations were carried out to determine the level of associations between sleep, daytime functioning during the CIT phase and CIT outcome. Sleep parameters were based on actigraphy results only.

Sleep

The scatter plots for significant and near significant results are presented in Figure 6.7. Longer time in bed correlated with better MAL QOU ($r=0.39; p=0.0129$) and by near significant trend with improvement on the WMFT FA ($r=0.28; p=0.0578$). Longer sleep duration was associated with increased MAL QOL ($r=0.30; p=0.0459$). A small
A relationship was also observed for increased MAL QOU and shorter duration of night awakenings ($r=-0.25; p=0.0857$). These results present suggestive evidence in the initial assumption that good sleep promotes treatment outcome.

**Figure 6.7.** Significant correlations of CIT outcome and sleep as recorded by actigraphy recorded during the CIT phase.

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**Sleepiness and Fatigue**

KSS and D-FIS ratings did not correlate with any CIT outcome measure whereas a relationship was observed for actigraphy calculated napping (Figure 6.8). The scatter plots of significant and near significant trends are presented in Figure 6.8. Increased
MAL AOU correlated with lower napping frequency ($r=-0.28$; $p=0.0603$) and duration ($r=-0.27$; $p=0.0711$). Increased MAL QOU also correlated less napping frequency ($r=-0.38$; $p=0.0195$) and length of naps ($r=-0.35$; $p=0.0236$). These associations may be due to greater time spend practicing tasks and using the affected arm as much as possible at home. Those that nap more, may be more sleepy and therefore do not have as much capacity to complete motor activities outside of CIT.

Figure 6.8. Significant correlations of CIT outcome and napping as recorded by actigraphy during the CIT phase.

6.3.5 Laboratory Observations
The author of this thesis and colleagues have made several observations from spending long periods of time with the patients involved in the current study. The most commonly reported observation was that poorer daytime functioning interfered with CIT sessions. Furthermore, sleepy or fatigued patients required more breaks within therapy sessions as progress could not be made without ample rest. It was common for patients to report a greater drive to nap, and would typically nap during their lunch break in the laboratory. Surprisingly, these observed naps were not always reported in the sleep diary. Caregivers of patients also commented on the greater drive to nap and feelings of exhaustion in patients as a result of CIT sessions. Several carers commented that patients would fall asleep in the car on the return home after treatment. In several cases, three hours of CIT had to be aborted early due to patients reporting being too tired to continue till the end of the session. For patients who drove themselves to the laboratory, it was of the opinion the therapists involved and the patients themselves, that naps and/or rest should be taken before attempting to drive home as their high sleepiness levels were considered detrimental to their safety.

6.4 Discussion

There is good theoretical reason to predict a relationship between sleep, daytime functioning and CIT outcome, Therefore it was the aim of the current study to investigate this potential link. This was achieved by monitoring sleep and daytime functioning via sleep diaries and actigraphy throughout a highly controlled neurorehabilitation setting whereby patients received two weeks of CIT. CIT outcome was determined by change in reaction time and ability scores on a battery of motor tests. This is the first known study to monitor sleep in a homogenous group of chronic stroke patients, selected based on their upper limb motor ability who received neurorehabilitation in a carefully controlled environment,
6.4.1 Overall Findings

Phase Changes
Several changes in sleep between each of the three phases of the CIT protocol were observed. Patients reported sleeping less during post compared to BL. Actigraphy determined sleep duration showed that patients slept less and spent less time in bed during CIT compared to BL. Patients may spend less time in bed as attending CIT added more structure to their day. A reduction in both perceived and actigraphy determined night awakenings were observed during CIT when compared to BL and post phases. Even though patients slept less during this time, which was also reflected in lower sleep efficiency, their sleep may have been more restful and less fragmented during CIT. In order to truly determine the extent to which CIT affected normal sleep patterns, PSG recordings would be required. Furthermore, such data would enable the analysis of changes in sleep architecture.

Twenty-eight percent of patients slept less that seven hours per night. Sleeping less than seven hours per night is associated with decrements in cognitive performance (Banks & Dinges, 2007; Van Dongen et al., 2003). Furthermore, it has been suggested that poor sleep during the night may account for poorer functioning and participation in rehabilitation (Worthington & Melia, 2006). Post hoc analyses revealed that patients who slept less that seven hours per night had lower scores on the MAL QOL and AOU (z=-2.04; p=0.0427 and z=-2.37; p=0.0169 respectively). This suggests that in future, efforts should be made to manage sleep in those patients who are vulnerable to getting less sleep.

Self reported sleepiness and fatigue increased during the evening for BL, CIT and post phases. Although it was expected that patients would be sleepier and more fatigued when engaging in daily CIT sessions, only a near significant trend was observed for increased evening sleepiness. Given that patient perception of daytime functioning levels is unreliable, according to Study 3 and other studies (Bassetti & Aldrich, 1999; Bassetti & Valko, 2006; Masel et al., 2001), it may be that sleep diaries were not sensitive enough to detect such changes. Furthermore, laboratory observations confirmed that several patients
were virtually falling asleep during CIT sessions, and as a result, sessions were terminated early. Family and caregiver reports also supported this observation. Despite these anecdotal reports, patients did not accurately report their behaviour in the diaries. Interestingly, patients reported napping less during CIT even though observations would suggest they napped during the lunch break in the laboratory and again when they were at home. One explanation may be the structure that CIT added to their day may be perceived as an environment not conductive to napping therefore this would occur less. According to actigraphy, general napping behaviour did not change as a result of CIT. Therefore, it may be that patients who consistently napped, still did so during the CIT phase.

**CIT Outcome**

Longer time in bed and sleep duration was mildly associated with better CIT outcome. Furthermore, a small effect was observed for less night awakenings and better CIT outcome. This suggests that good sleep patterns are beneficial to CIT outcome. Perceived sleepiness and fatigue was not related to CIT outcome however patient daytime functioning reports are likely to be inaccurate. Alternative measures of daytime functioning would need to be employed to determine if there is a relationship between sleepiness and fatigue. Other studies using nursing reports have found that poorer daytime functioning affected rehabilitation participation (Worthington & Melia, 2006) and outcome (Alessi et al., 2008).

Less napping was also associated with better CIT outcome. This may have occurred as extremely sleepy patients, who needed to nap more, could not attend to tasks during CIT. Furthermore, such patients received less CIT in instances when sessions were terminated earlier. It was also concluded by Alessi et al. (2008) that increased napping, as a result of severe sleepiness, adversely impacted rehabilitation success. However other studies have suggested that napping supports motor learning (Backhaus & Junghanns, 2006; Milner et al., 2006; Nishida & Walker, 2007), but these findings were in non-brain injured samples. Although this idea has not been directly tested in stroke patients, Siengsukon & Boyd (2009b) suggested that napping between rehabilitation sessions may have some benefit.
There may be an optimum nap duration for stroke patients which may be conductive for motor learning and allow adequate rest.

6.4.2 Further Theoretical Considerations

Possible Confounds
The small effects observed for the relationship between sleep and CIT suggest that other factors may also contribute to the success of CIT in patients. Response to rehabilitation is a multi factorial process which is influenced by other long term consequences of stroke beyond control for this study. Such factors may include stroke pathogenesis, genetics, quality of medical care and as well as the patients own motivation, personality traits and family support (Herholz & Heiss, 2000).

Psychological Benefits of CIT and Perception of Sleepiness
Many patients commented on the fact that they enjoyed having an activity which enabled them to leave the house everyday. This fits in with the findings of Campos et al. (2005) who showed that increased social occupation, as well as rehabilitation, has positive effects on the patient’s sleep and mood. Improved mental health as a result of increasing social networks and purpose is reflected in reduced self reporting of fatigue (Glass, Matchar, Belyea, & Feussner, 1993). This may also explain why napping behaviour was perceived as occurring less during CIT as patients affect was considerable improved as result of achieving increased motor function during CIT. CIT has known beneficial effects for psychological functioning (Dettmers et al., 2005).

6.4.3 Implications of Findings
The effects of motor neurorehabilitation and sleep are complex. Although factors other than sleep may also contribute to the success of CIT treatment, the results of this study hold important implications for rehabilitative interventions after stroke.
**Practical Implications For Rehabilitation**

Firstly, ensuring optimum sleep is achieved by patients may be critical to better CIT success. This is particularly important for patients who slept below seven hours per night during treatment. Better sleep has known effects for daytime functioning, general health and learning in stroke patients (Bassetti & Valko, 2006; Schuiling et al., 2005; Siengsukon & Boyd, 2009b), therefore applying sleep management may not only benefit CIT, but also general quality of life. Less napping was associated with better CIT outcome. However the literature suggests that encouraging rest and even a moderate nap in between rehabilitation sessions may benefit the latter session (Borgaro, Baker, Wethe, Prigatano, & Kwasnica, 2005). Siengsukon and Boyd (2008b) proposed that sleep should be encouraged between therapy sessions to promote offline learning. It may be that excessively napping during the day reflects excessive sleepiness which is associated with poorer participation in rehabilitation and outcome success (Barker-Collo et al., 2007; Morley et al., 2005; Muller et al., 2006). Napping in moderation may have benefits for CIT however further investigation is required to establish this idea. Furthermore, sessions needed to be terminated early as patients were too tired to continue, therefore adequate rest is crucially advised.

**Value of Clinical Observations and Case Studies**

Laboratory observations and caregiver reports proved to be a vital source of information to help explain results of this study. These important insights into patient behaviour however were not documented therefore could not be statistically examined. It would be advantageous for future studies to systematically record researchers and caregiver observations of sleep and daytime functioning in stroke patients.

**6.4.4 Limitations of the Study**

**Practical Limitations**
In order to attend CIT, patients had to alter their normal sleep schedule. Several patients also stayed in local accommodation, often without a carer, for the CIT phase which may have affected sleep. However this was beyond the control of the current study as patients were recruited from a various locations in the UK.

Reliability of Patient Reports

Results from Studies 1, 2 and 3 of this thesis, in addition to other published work (Bassetti & Valko, 2006; Castriotta et al., 2007; Makley et al., 2008; Masel et al., 2001; Parcell et al., 2006), have suggested that perception of sleepiness, fatigue and napping are less reliable in brain injured patients. Therefore, the self reports in the current study may also be vulnerable to the same issue. Critically, laboratory observations and caregiver reports however suggested that daytime functioning was underestimated.

Sleep and Daytime Functioning Assessment

This study showed that sleep diaries and actigraphy only showed a mild relationship between sleep, daytime functioning and CIT outcome, as well as changes in sleep as a result of attending CIT. Despite the strong theoretical underpinnings that strongly point towards a link between a relationship sleep and neurorehabilitation, the results of this study are mixed and inconclusive at this stage. It may be that sleep diaries and actigraphy are not sensitive enough to pick up changes in patients sleep and daytime functioning whilst undergoing CIT. More sensitive measures, i.e. PSG, may not only reveal changes as a result of CIT, this method may also enable a closer examination of the relationship between sleep and CIT. Analysis of the frequency composition of the sleep EEG may help determine if CIT induces changes at this level and if this is associated with CIT outcome. This idea is postulated by several authors (Gottselig et al., 2002; Hachinski et al., 1990) but has not yet been investigated.

6.4.5 Further Studies
More studies are clearly required to fully assess if there is a pattern between healthy sleep and increased rehabilitation outcome in a larger group of patients. It may be additionally useful to employ PSG recordings in order to examine sleep architecture as this may contribute important information regarding changes in the EEG as a direct result of motor learning during neurorehabilitation. The next avenue to explore requires protocols which test sleep related inventions to examine if this improves sleep and ultimately leads to clinically relevant gains (Alessi et al., 2008). Sleep related adaptations to rehabilitation protocols may also benefit outcome. For example, Seingsukon and Boyd (2008b) suggested that therapy may need to be conducted in the evening or late in the day in order to be in closer proximity with a sleeping period. The results of this study have suggested that optimising nap opportunities may even have some benefit for rehabilitation sessions. Further research is required to investigate this notion.

Conclusion of Study 4

This study has shown that there is a mild relationship between sleep and CIT outcome which fits in with the theoretical underpinnings of the research question.

- Normal sleep schedules were altered during CIT as compared to BL and post. These alterations consisted of increased time in bed, shorter sleep duration and less night awakenings.
- The sleep of patients may have improved during CIT as night awakenings were reduced in this phase.
- Overall, the results suggested that better sleep was mildly related to greater improvements for CIT outcome however further research is necessary. It may be that sleep management is essential in order for patients to gain maximum benefit of CIT.
Anecdotal reports of this study were consistent with reports of other therapists who highlight that sleepiness and fatigue impacts participation in therapy sessions.

Some of the effects observed in this study fit in with the theoretical perspective which hold clinical implications for neurorehabilitation treatment provisions. Sleep management programmes that are specifically designed for stroke patients are required to facilitate healthy sleep and further minimise sleepiness and fatigue. Furthermore, this study has provided important information for future study design. It is clear that more research is required to fully address the relationship between sleep and CIT outcome. This idea may also be applied to other modes of motor neurorehabilitation as well as the CIT method.
CHAPTER 7: General Discussion

7.1 Summary of The Findings

This thesis was developed in response to a surprising lack knowledge on sleep in chronic stroke patients with residual motor deficits and lack of research on the role of sleep in recovery and neurorehabilitation outcome. Four studies were carried out using a range of methods to explore the idea that sleep may be a modulating factor for healthy wellbeing, motor recovery and neurorehabilitation success after stroke. This involved employing retrospective questionnaires, prospective long term sleep monitoring, electroencephalography (EEG) and motor ability tests within the context of a Constraint Induced Movement Therapy (CIT) trial. These methods captured data on nocturnal and diurnal sleep, daytime functioning, psychological adjustment, health related quality of life, residual motor functioning and neurorehabilitation outcome. The studies revealed that sleep is associated with the quality of life of patients as well as having implications for motor recovery and CIT. In addition, the results of daytime functioning assessments showed potential safety risks in this population. The results confirmed a proportion of previous literature as well as revealing several contrasts which will be discussed in this chapter. By and large, the results of this thesis have clinically relevant implications for both medical practitioners and patients. Furthermore, the main findings can be applied to post stroke treatment provisions thus driving forward a 24 hour approach to rehabilitation.

7.1.1 Thesis Objectives

Gap In The Literature

The literature suggests a potentially crucial link between sleep, recovery, neurorehabilitation outcome and ultimately, the quality of life of stroke patients (Cadilhac
et al., 2005; Schuiling et al., 2005; Siensukon & Boyd, 2009b; Worthington & Melia, 2006). In addition to the lack of studies contributing to this link, the sparse research conducted poses several limitations stresses a necessity for further investigation. Sleep is largely ignored as part of post stroke treatment and long term care in clinical settings (Castriotta & Lai, 2001; Parcell et al., 2006; Wessendorf et al., 2000). The poor support provisions for patients may unnecessarily prolong suffering and hinder recovery potential.

This thesis was developed based on five main research questions of which has not yet fully addressed in the literature and in clinical practice: 1) how does a chronic stroke population sleep and function during the day from a subjective point of view? 2) how do chronic stroke patients sleep as determined by objective methods? 3) can chronic stroke patients accurately perceive their own sleep behaviour and daytime functioning levels? 4) is sleep and daytime functioning related to level of residual motor recovery after stroke? and 5) does sleep and daytime functioning have a role in motor neurorehabilitation?

7.1.2 The Findings

Overall Results of Studies 1 to 4

- Study 1

The findings of Study 1 showed that 41% of patients felt their sleep was disturbed during the first month after stroke which evolved into a chronic problem in 39% at one year. The majority of patients (81%) experienced deficits in their daytime functioning which remained chronic in 25%. When using the cut off criterion as provided by the PSQI, ESS and FSS to indicate a significant difficulty, 32% of patients reported disturbed sleep, 28% were excessively sleepy, half of patients regularly napped and 25% were highly fatigued in the chronic phase of recovery. The PSQI further revealed that patient sleep schedules were different to that of the general

25 Mixed stroke and TBI sample.
population as they reported longer time in bed and sleep duration. A crucial finding of Study 1 was that patient sleep needs were not addressed as part of their medical care.

Furthermore, this study highlighted that the nature of the control group was decidedly important for determining if the sleep behaviour manifested in stroke patients was different to non-brain injured persons. Sleep behaviour in patients was significantly different to that of healthy controls with no sleep disorders whereas in comparison to the general population, sleep was similar. With regard to daytime functioning, patients did not report greater sleepiness in comparison to a range of control groups.

This study also showed that psychological adjustment was highly associated with sleep disturbance, in both stroke patients and controls. A particularly interesting finding of the regression analyses was that anxiety and depression was more predictive of sleep and daytime functioning than a stroke event per se. Fatigue and psychological disturbance were also more related to perceived post stroke health than sleep disturbance.

- **Study 2**

This study built upon the findings of study one and further confirmed that sleep was severely disturbed in stroke patients using actigraphy. Most notably, these disturbances were increased night awakenings. It was demonstrated that stroke patients napped longer than the general population.

Patients' perceptions of nocturnal sleep indices, apart from night awakening estimations, were in good concordance with actigraphy. However, patients were not as accurate for daytime functioning reports. This was indicated by the observation that increased napping and lower levels of activity, were not related to subjective reports of sleepiness and fatigue.

Study 2 also found that residual motor ability levels were poorer in those patients who spent longer in bed and had more night awakenings. This is inline with the
assumption that poorer sleep is associated with poorer recovery. However those with increased fatigue, had better motor ability. This might be explained by the increased effort executed by a group of highly motivated patients to perform motor activities.

- **Study 3**

  This study revealed crucially important findings with regard to patient perception of sleepiness. Not only was the frequency composition of the waking EEG in patients significantly different from matched controls, the EEG of patients was similar to that of sleep deprived non-brain injured patients. This indicated that patients demonstrated high levels of objective sleepiness. High levels of patient sleepiness was also confirmed by laboratory observations. It was particularly alarming that patients did not appear to recognise the high presence of sleepiness. This behavioural observation has also been observed in sleep deprived non-brain injured persons. It appears that stoke patients manifest the behavioural and objective characteristics of a healthy sleep deprived person, despite the majority of patients slept at least 7 hours per night. This indicated a severe underestimation in a potentially debilitating deficit in daytime functioning.

- **Study 4**

  This study showed that participating in a highly demanding motor neurorehabilitation trial was reflected in self reported sleep and actigraphy. Normal time in bed and sleep duration was reduced when engaging in daily CIT sessions. Furthermore, patients appeared to sleep better during CIT as night time awakenings were reduced. As suggested in the literature, better sleep was associated with greater improvement in motor ability induced by CIT.

The findings on napping behaviour contrasted to the literature which suggests that napping is beneficial for motor learning. In fact, patients that napped more frequently and for longer, had a poorer CIT outcome. With regard to the findings of Alessi et al. (2008), this result may have occurred as those who are more sleepy, do not have the cognitive capacity to engage well in CIT. Consistent sleepiness, and perhaps fatigue,
reflected in greater napping, may be associated with poorer CIT outcome. The results of this study highlighted a need for a better understanding of napping behaviour in a rehabilitation context.

7.1.3 Findings In Comparison To Previous Literature

The lack of existing studies that explore sleep in chronic stroke add complexity to the interpretation of data the current study in light of published findings. Of the sparse literature, varying recruitment criteria and methods employed between studies further contribute to the difficulty in direct comparisons. Therefore when comparing data from the current study with previous studies, it is important to take into account: 1) the sample chronicity, 2) the in/exclusion criteria and 3) the measures used, i.e. subjective or objective.

General sleep disturbance prevalence rates in patients reported in Study 1 and 2 are comparable with that of other studies using chronic stroke samples without motor ability as part of the exclusion criteria, ranging from 31-67% (Campos et al., 2005; Masel et al., 2001; Schuiling et al., 2005; Worthington & Melia, 2006). The prevalence rates of clinically relevant sleep disorders reported in this thesis are considerably lower than reported rates in the literature regarding insomnia (48%; Palomaki) and sleep disordered breathing (81%; Cadilhac et al., 2005). However the assessment of sleep disorders reported in thesis was based on subjective perception whereas those reported in Palomaki et al. (2003) and Cadilhac et al. (2005) were based on detailed clinical assessments. With regard to subjective sleepiness, the results were not overly different from reports in other studies (Bassetti & Valko, 2006; Campos et al., 2005; Masel et al., 2001; Schuiling et al., 2005; Worthington & Melia, 2006). The waking EEG results of Study 3 suggested that subjective sleepiness is underestimated. The only other known study to use objective measures in this cohort was a study by Masel et al. (2001). They found a dissociation

26 Mixed stroke and TBI sample.
between objective, based on sleep propensity determined by EEG, and perceived sleepiness (Masel et al., 2001). Perceived prevalence of fatigue was reported as 5% lower in this study compared to rates in other chronic samples (Choi-Kwon et al., 2005; Ingles et al., 1999; Park et al., 2009; Valko et al., 2008; van der Werf et al., 2001; Visser-Meily et al., 2005). This may reflect the highly motivated nature of the particular cohort addressed in this thesis.

With regard to motor recovery and neurorehabilitation, the results of this thesis present some complexity when comparing to previous work as no known study has specifically assessed upper limb motor ability only. Therefore comparisons have been made with studies that measure general functional outcome. In this respect, the present findings were in line with acute (Bassetti & Aldrich, 1999; Bassetti & Aldrich, 2001; Hachinski et al., 1987; Leppävuori et al., 2002; Siccoli & Bassetti, 2008; Takekawa et al., 2007), chronic (Cadilhac et al., 2005; Worthington & Melia, 2006) and prospective (Bassetti & Aldrich, 2001; Giubilei et al., 1992; Hermann et al., 2008; Spriggs et al., 1992a; Vock et al., 2002) data which suggested that poorer sleep was associated with poorer outcome. Poorer sleep mildly affected motor neurorehabilitation outcome which fits in with the postulations of Walker and Stickgold 2002a, Kuriyama et al., (2004), Siengsukon & Boyd (2009b), (Gomez-Beldarrain et al., 2008) and Robertson and Cohen (2006). Other studies examining rehabilitation patients have reported adverse effects of poorer daytime functioning on treatment outcome rather than sleep per se (Alessi et al., 2008; Barker-Collo et al., 2007; Morley et al., 2005; Worthington & Melia, 2006). The results of study 4 showed that increased napping was associated with poorer CIT outcome. This observation is consistent with the findings of Alessi et al. (2008) which showed that greater napping behaviour was associated poorer rehabilitation participation.

7.2 Proposed Explanations For The Findings
7.2.1 Disturbed Sleep and Daytime Functioning In Chronic Stroke

The origin of sleep behaviour traits in patients recruited for the current study is yet to be fully determined. Several important factors for post stroke sleep have been noted in the literature and may explain the observations in Studies 1 to 4. Possible mechanisms behind sleep and daytime functioning alterations in patients may be neurological, somatic, psychological or as a result of other external attributes such as medications and lifestyle.

Neural Mechanisms Behind Sleep Problems

Lesion location may, in part, determine specific changes in sleep and daytime functioning. As populations of neurons implicated in sleep-wake cycles are widespread across the neural axis (Evans, 2002; Jones, 2005), various lesion locations may contribute to sleep problems. Lesions within the cortices (Bassetti & Aldrich, 2001; Beebe & Gozal, 2002; Gottselig et al., 2002; Mohsenin & Valor, 1995; Müller et al., 2002; Siccoli & Bassetti, 2008; Vock et al., 2002) and subcortical regions including the midbrain (Bassetti et al., 1997; Evans, 2002) and brain stem (Blanco, Espinosa, Arpa, Barreiro, & Rodriguez-Albarino, 1999; Good et al., 1996; Markand & Dyken, 1976) are associated with sleep disturbance. Sleepiness after stroke may arise from an interruption of the arousal system, in particular the reticular formation (Autret et al., 2001). Subcortical stroke, usually involving the thalamus, is largely accompanied by poor alertness and hypersomnia (Bassetti et al., 1996; Catsman-Berrevoets & Harskamp, 1988; Christian Guilleminault et al., 1993; Hermann et al., 2008). Fatigue has also been attributed to neurological origins as a result of subcortical and brain stem lesions (Naess et al., 2005; Staub & Julien Bogoousslavsky, 2001). However, the commonly observed overlap between post stroke fatigue and depression makes it difficult to determine the degree to which fatigue originates from the psychological stresses endured after stroke or as a result of the brain injury per se (Bassetti & Valko, 2006). After controlling for psychological disturbance, fatigue may occur in chronic stroke, independent of depression (Choi-Kwon et al., 2005; Ingles et al., 1999; Naess et al., 2005). Moreover, Cantor et al. (2008) found fatigue exists independent of other post stroke comorbidities. The authors therefore argued that fatigue can be attributed to brain damage. This
evidence demonstrates that fatigue has a multifactorial nature which may be caused and maintained by both the physiological consequences as well as part of psychological changes associated with stroke.

**Somatic Origins of Poor Sleep**
The physical consequences of stroke, described in Section 1.1.2 (Chapter 1), further compromise sleep (Bassetti & Aldrich, 2001; Gamble et al., 2000; Kong et al., 2004; Krachman et al., 1995; Widar et al., 2004). Mobility restrictions experienced by patients with hemiparesis may affect manoeuvring for sleep position and ease of returning to bed after toileting. Several patients from the current research commonly acknowledged this difficulty. Pain endured after brain injury has also been attributed to increased sleep disturbance (Fictenberg et al., 2001; Widar et al., 2004). Furthermore, this relationship may be reciprocal as the presence of sleep disturbances may modulate the acute and chronic pain (Lautenbacher et al., 2006).

Premorbid sleep characteristics may partly explain the prevalence of post stroke sleep disturbance. Risk of stroke was greater for those who slept more than eight hours a night and those with increased daytime sleepiness (Qureshi et al., 1997). These findings were independent of age, race, gender, education, smoking, BMI, serum cholesterol, systolic blood pressure and diabetes (Qureshi et al., 1997). A history of sleep disordered breathing, snoring and circadian variation in blood pressure during the night is also associated with increased stroke risk (Martinez-Garcia et al., 2004; Plante, 2006; Wolf, Lewicka, & Narkiewicz, 2007). These sleep problems may remain after a stroke event.

**Psychological Correlates of Post Stroke Sleep**
According to the results, the psychological consequences of stroke are clearly associated with poorer sleep and daytime functioning, which further impact perceived health. The direction of this relationship, however, remains unclear. Based on previous research, the cause and effect nature between sleep and psychological adjustment are likely to be reciprocal (Ellis et al., 2007; Jansson & Linton, 2006; Steptoe, O'Donnell, Marmot, & Wardle, 2008). Therefore psychological disturbance may not only be related to the
development but also the maintenance of sleep related disorders in the chronic phase of stroke. Fichtenberg et al. (2001) suggested that neurological factors have a primary role in sleep disturbance during acute TBI whereas psychological factors were greater contributors during the chronic phase. The results of this thesis indicate that this idea can be translated into stroke populations.

The daytime functioning of patients observed for this thesis was also related to psychological well being. These results are in line with previous literature in chronic stroke samples which show that depression in particular, is associated with increased sleepiness and fatigue (Astrom, Adolfsen, & Asplund, 1993b; Choi-Kwon et al., 2005; Ingles et al., 1999; Naess et al., 2005; Staub & Bogousslavsky, 2001). Fewer studies have paid attention to anxiety in these patients, however Study 1 and the findings of McCoy (2006) and Sterr et al. (2008) have highlighted that post stroke anxiety contributes to poorer sleep.

**External Factors Affecting Sleep**

Medication use may have a role in sleep alterations after stroke as patients are often prescribed drugs with sedentary side effects which impact daytime functioning and also affect brain activity (Bourne & Mills, 2004; Lowson & Sawh, 1999; Novak & Shapiro, 1997; Obermeyer & Benca, 1996). Approximately seven percent of patients in this study were on antidepressants, which is slightly lower than in the general population (Petty, House, Knapp, Raynor, & Zermansky, 2006). This may be due to the positive selection criteria employed in the current research. In the stroke population, antidepressants are commonly prescribed (Paolucci et al., 2001) and have well documented effects on sleep. Tricyclic antidepressants may improve sleep whereas others, e.g. serotonin reuptake inhibitors, may worsen sleep (Holshoe, 2009). More specifically, some antidepressants are known to alter sleep architecture and reduce sleep efficiency (Holshoe, 2009; Mayers & Baldwin, 2005).

The majority of patients in the studies carried out for this thesis regularly consumed caffeine and a smaller proportion drank alcohol. Some patients consumed excessive
amounts of caffeine, up to 12 cups a per day. Alcohol reached excess, i.e. over 14 units for women and 21 for men (The Department of Health, UK), in only 8.06% of patients. Increased amounts of caffeine have known affects upon sleep including delayed sleep onset latency, reduced sleep length, increasing proportion of stage 1 and reducing REM sleep (Roehrs & Roth, 2008). Furthermore, increased alcohol consumption shortens sleep latency, and has profound effects upon sleep continuity and architecture (Rogers et al., 2001). Nicotine also affects sleep (Zhang, Samet, Caffo, Bankman, & Punjabi, 2008; Zhang, Samet, Caffo, & Punjabi, 2006) however only 9.68% of patients smoked. Within Studies 1 to 4, no relationships were found between any of the above lifestyle drugs and subjective sleep. This indicates that caffeine and alcohol use in patients were not affecting sleep in patients recruited for this study.

External life style factors, including environmental, societal and occupational, may contribute to poorer sleep after stroke. Non-sleep promoting cues in the home environment may be counteractive to sleep. Bedroom conditions negatively influence sleep such as light curtains, uncomfortable bed, stimulation from various electronics (Ellis, Hampson, & Cropley, 2002; Gellis & Lichstein, 2009). Although these behaviours were not measured in patients, evidence suggests that poor sleep hygiene routines is common in the general population and is highly associated with the existence of sleep disturbance (Gellis & Lichstein, 2009). Improving sleep hygiene is starting point for non-pharmacological sleep disorder treatments (Zafonte et al., 1996). It is difficult to isolate to what extent social and occupational activities contribute to sleep behaviour in a chronically ill population, the majority of which, does not work. Although it is evident that chronically ill populations, including stroke, that have a greater percentage of sleep per day as a result of poor health (Bassetti & Valko, 2006; Kapur et al., 2002; Parish, 2009), low levels of social and occupational activities are possible contributors to the development of a weak circadian cycle and ultimately problematic sleep (Campos et al., 2005). This may partly explain why patients’ sleep schedules were different to that of the general population. It may be that chronically ill, non-working, populations have greater opportunity, as well as a need, to sleep longer and nap during the day. Interestingly in study 6, during CIT treatment, patients sleep schedules became more regulated. This
suggests that daytime activities might be beneficial to patient sleep wake-cycles as concluded by Campos et al. (2005).

7.2.2 Self Perceived Sleep and Daytime Functioning

Patient reports of sleep schedules were in agreement with objective measures whereas variables involving night time awakenings were least accurate. This observation is common in sleep research in both healthy and sleep disordered samples (Fontaine, 1989; Kushida et al., 2001; Lockley, Skene, & Arendt, 1999; Means et al., 2003; Vanable et al., 2000). It is generally accepted that human perception of night awakenings are not as accurate as a minute to minute analysis by actigraphy or PSG, particularly detection of arousals during deeper stages of sleep (Kushida et al., 2001).

The observed dissociation between sleep and daytime functioning showed that patients' behaviour did not follow the normal model of sleep, i.e. poorer sleep leads to decrements in daytime functioning (Drake et al., 2004; Franzen, et al., 2008; Gold et al., 1992; Harma et al., 2002; Papp et al., 2004; Pilcher & Huffcutt, 1996; Torsvall & Akerstedt, 1987). Some patients exhibited severely disturbed sleep however reported normal daytime functioning whereas others manifested sleepiness and fatigue despite sleeping well at night. The lack of correlation between sleep, sleepiness and fatigue suggests that patients did not accurately report their sleep or this sample does not follow the normal model of sleep. Study 3 strongly indicated that poor perception was a plausible explanation with regard to sleepiness. This was also considered in another study (Masel et al., 2001). Although further research is necessary, these results suggest that patients may find it easier to report factual information about sleep, e.g. bed time and sleep duration, however struggle with gauging levels of daytime functioning.

Patients tended to underestimate the extent of sleepiness, this has been observed in other studies, either by observation or clinician or patient reports (Bassetti et al., 1996; Bassetti & Valko, 2006; Masel et al., 2001). It was speculated that daytime functioning data was
subjected to biases. Possible biases may have arisen from underreporting as a result of social desirability or experimenter bias (Bardwell, Ancoli-Israel, & Dimsdale, 2001; Mahmood et al., 2004). It is also possible that patients are generally unaware of daytime deficits due cognitive deficits, as a result of stroke, that may impair introspection and ability to rate themselves accurately (Bassetti et al., 1996; Masel et al., 2001; Trudel et al., 1998). According to Clinchot, Bogher, Mysiw, Fugate, & Corrigan (1998) and Beetar, Guilmette, & Sparadeo, (1996), those with mild brain injuries are more likely to report sleep disturbances compared to those with more severe injuries due to a better aptitude of self perception as their injury was less severe than stroke/TBI. Another possibility is that patients may develop a higher threshold of what they consider sleepiness after stroke. This idea was indicated in the results published by Bassetti and Valko (2006) who found that those diagnosed with hypersomnia did not rate their sleepiness levels any differently to those who were not diagnosed. The results of this thesis showed that even in a homogenous sample of stroke patients of relatively good health, difficulties in self perception of daytime functioning is clearly evident. As an objective measure of fatigue was not used for this thesis, is not yet known if patients poorly perceive this aspect of daytime functioning.

7.2.3 Sleep, Daytime Functioning and Motor Ability

Sleep
The evidence which shows that sleep is important for maintaining health, daytime functioning and motor learning provided the theoretical foundation for the development of this thesis. Examination of the literature enabled the development of a hypothesis that predicted poor sleep will be associated with worse residual motor recovery after stroke. It was also hypothesised that poorer sleep would be associated with CIT outcome. However, only a mild relationship between better sleep and better motor ability was observed, and a relationship with therapy outcome was not observed. This result does not necessarily indicate that sleep is not an important factor in stroke recovery and neurorehabilitation success, it could be seen as part of a broad range of factors which
collectively contribute to motor outcome influences motor outcome. For example, the sample of highly motivated patients involved in Study 4 were more likely to achieve good therapy outcomes whether they slept well or not. Furthermore, the sample contained a small number of severely poor sleepers who fit the criteria for a clinical sleep disorder. Should the sample have involved a greater proportion of those with sleep disorders, the hypothesised detrimental effects of poor sleep for motor ability and CIT outcome may become increasingly observable.

Although excessive napping was associated with poorer CIT outcome, the literature suggests that optimum level of napping may be of benefit for stroke patient (Muller et al., 2006; Siengsukon & Boyd, 2009b). Napping may assist in alleviating sleepiness and fatigue acquired during the day. In addition, several studies have shown that napping also has a role in motor memory consolidation (Backhaus & Junghanns, 2006; Milner et al., 2006; Nishida & Walker, 2007). It may be that napping helps patients cope with the demands of neurorehabilitation as well as being a process to optimise motor learning. Further studies are necessary to particularly address the latter.

**Fatigue: Not Necessarily A Marker of Poor Sleep**

In contrast to previous literature in healthy participants (Franzen et al., 2008; Ikegami et al., 2009) and stroke patients (Park et al., 2009), which showed that increased fatigue is related to poor sleep, this study revealed that increased subjective fatigue is not necessarily a marker of poor sleep. Fatigue may develop as part of the multifactorial consequences of stroke and may not be resolved by improving sleep-wake cycles. Presence of fatigue is not necessarily detrimental to motor functioning or neurorehabilitation outcome. In fact, patients in the current study who performed better in the motor ability tasks reported greater fatigue. Patients with high levels of functioning have also shown greater fatigue in other studies (Staub & Julien Bogousslavsky, 2001; Van Zandvoort et al., 1998). Furthermore, the high levels of motivation within the patient cohort used in this thesis are likely to comprise those who capitalise on residual motor ability by putting in a great amount of effort. However it is important to bear in mind that
fatigue measurements in this thesis, and other studies in the literature, rely on subjective reports.

It is unlikely that the development or maintenance of sleep difficulties after stroke stem from one single factor. The findings of this thesis and that of other authors show that multifactorial nature of sleep problems after stroke consist of a complex interaction of neurological, somatic and environmental stressors (Bassetti, 2005a; Bassetti & Aldrich, 2001; Gamble et al., 2000; Glader et al., 2002; Kong et al., 2004; Krachman et al., 1995; Leegaard, 1983; Sisson, 1998; Widar et al., 2004). These factors are necessary to consider when treating and researching these patients.

7.3 Further Theoretical Considerations

There are several issues that need to be considered when interpreting results derived from the current study. Firstly, the current standpoint of sleep dependent learning theory within the literature presents some concerns. As this theory is one of the main theoretical perspectives from which the current research evolved, these concerns are addressed in this section. Furthermore, there are particular aspects regarding patient characteristics which are essential when interpreting data from this thesis and when considering the findings in a wider context. These theoretical considerations are also important for future studies following on from this work.

7.3.1 Sleep Dependent Learning Theory

Criticisms of The Sleep Dependent Learning Theory

The sleep dependent motor learning theory has been subject to criticism by some researches (Vertes, 2004). There are three main arguments that are used to support the idea that sleep does not have a critical role for learning: 1) experimental methodology is
limited, 2) consolidation occurs over time rather than sleep per se, and 3) REM suppression does not affect learning in psychiatric patients.

The experimental evidence behind the sleep dependent learning theory presents several methodological limitations. The majority of studies within the evidence base do not control for stress (including animal studies) or circadian effects which may influence cognitive performance on the learning tasks (Vandewalle et al., 2009). The studies also have low ecological validity, particularly regarding laboratory based learning tasks, which may not be representative of learning that occurs in real life.

It is also argued, particularly for procedural memory, that sleep merely coincides with memory consolidation over time, and does not facilitate learning any more so than wake. Walker et al. (2002a) investigated the time dependent verses sleep dependent learning issue. The results showed that new motor skills are considerably improved (20.5%) after a night’s sleep compared to the same amount of time awake (3.9%). It was concluded that consolidation may be partly time dependent in that research suggests stabilization occurs during wake (Brashers-Krug et al., 1996; Muellbacher et al., 2002; Matthew P Walker et al., 2003b) whereas enhancement and improvement without practice occurs during sleep (Fischer et al., 2002; Gais & Born, 2004; Karni et al., 1994; Korman, Raz, Flash, & Karni, 2003; Stickgold, James, & Hobson, 2000; Walker et al., 2003a; Walker et al., 2003b).

Another argument against sleep dependent learning stems from research in psychiatric patients. Patients who take antidepressants show a reduction in REM and in some cases, no REM for several years (Vertes & Eastman, 2000). It appeared that lack of REM had little effect on memory and learning (Thompson, 1991). It is important to note that these studies focused on simple declarative memory tasks, rather than more complex procedural learning which is more likely to be affected by lack of REM sleep (Stickgold, Whidbee, Schirmer, Patel, & Hobson, 2000). Other studies have shown that there is a sudden increase in REM when the medication is ceased which may indicate a surplus
demand for REM after prolonged periods of REM deprivation (Landolt et al., 2001; Minot, Luthringer, & Macher, 1993).

**Applicability of Sleep Dependent Learning Theory To Stroke Patients**

Sleep dependent learning paradigms include the motor reaching adaptation task (Huber & Ghilardi, 2004), continuous tracking (Siensukon & Boyd, 2008a, 2009a; Siensukon & Boyd, 2008b), serial reaction time task (Gomez-Beldarrain et al., 2008) and sequential finger tapping task (Walker et al., 2002a). Not only do these tasks lack ecological validity, it may not be appropriate to translate the findings of these experiments to stroke patients.

The work of Siensukon and Boyd (2008a, 2008b and 2009a) are the first studies to address sleep dependent motor learning in chronic stroke patients. The results of these studies showed that patients demonstrated improvements in learning which were associated with a period of sleep, rather than the same amount of time awake. These findings provided theoretical evidence for investigating the role of sleep in motor neurorehabilitation as investigated Study 4. However results of Siensukon and Boyd (2008a; 2008b; 2009a) presented some limitations. It is important to note that patients' level of learning in the non-sleep groups was tested in the evenings after the learning session in the morning. Patients in the sleep group were tested for learning after a nights sleep. It is not yet clear if patient activities between learning and testing were controlled in the non-sleep group. This may be an important factor as Walker et al. (2002a) found that participant activities between learning and testing may affect results. Furthermore, only habitual subjective sleep behaviour was reported, an assessment which cannot reliably detect if patients slept well the night before learning or testing level of learning.

**Translating Sleep Dependent Motor Learning To Motor Neurorehabilitation**

Previous research using healthy and stroke patient cohorts have related their findings to motor learning after brain injury (Gomez-Beldarrain et al., 2008; Kuriyama et al., 2004; Robertson & Cohen, 2006; Siensukon & Boyd, 2009b; Walker et al., 2002a). With regard to CIT, the therapy sessions are based on real life tasks and it may not be
appropriate to translate findings from standardised task based motor learning in the laboratory to CIT. Furthermore, motor skills facilitated by CIT comprise implicit and explicit learning and is strongly goal orientated. This may be influenced by the motivation of the patient as well as the possibility of new motor skills being enhanced by sleep. In addition learning occurred over a two week period rather than a one off testing session as employed in the studies mentioned above. Further research is required to determine the degree to which these factors have affected motor learning after stroke.

7.3.2 Patient Characteristics

Patient Selection
The positive selection of patients for the current research is an important factor for result interpretation. With regard to findings relating to prevalence of sleep disturbance, it is important to consider that the results may be underestimated. Severely sleepy or fatigued patients may be less likely to volunteer to participate in research. Therefore the results of studies reported in this thesis should be interpreted with relation to the specific patient sample that is researched and used with caution if translated to patients in a wider context.

It is also postulated that recruitment of a fully homogenous group is not entirely possible amongst chronically brain injured participants (Terzoudi et al., 2009). From a neural perspective, the various anatomical location where strokes occur makes it difficult to generalize across individuals. Although patients in this study were psychologically stable, the dramatic impact of stroke on the individual is unlikely not to have at least some effect on psychological health from time to time (Langhorne et al., 2000). However some authors argue that despite the significant ongoing physical disability, stroke survivors appear to adjust well psychologically to the disease (Hackett, Duncan, Anderson, Broad, & Bonita, 2000). Overall, the recruitment procedures for this thesis have enabled a greater level of homogeneity compared to other studies in the post stroke sleep literature.
Age

Although age did not appear to be a contributing factor to the results of this thesis, age related changes in sleep, daytime functioning and memory consolidation may be important to consider as 16% of patients in the sample were over 65 years old. Moreover, in the wider context of stroke, the incidence increases with age (Hollander et al., 2003). Age related changes include a reduction in sleep duration, frequency night awakenings, early morning awakenings and alterations in circadian rhythm (Dijk, Duffy, & Czeisler, 2000; Dijk, Duffy, Riel, Shanahan, & Czeisler, 1999; Kramer, Kerkhof, & Hofman, 1999). Actigraphy did not reveal any age differences in patients however this may not be sensitive enough. Neurological alterations in sleep architecture have also been documented in older populations, such as reduced proportion of slow wave and REM sleep (Crowley, Trinder, Kim, Carrington, & Colrain, 2002; Danker-Hopfe et al., 2005; Dijk et al., 1999). Additional research is necessary to find out if this is also the case in stroke patients.

With regard to daytime functioning, older adults report increased sleepiness, fatigue and napping compared to younger persons (Ancoli-Israel, Poceta, Stepnowsky, Martin, & Gehrman, 1997b). Furthermore, aging differences have been observed in the waking EEG, most notably, a reduction in theta waves (Cummings & Finnigan, 2007; Dijk et al., 2000). Given that sleepiness and fatigue may not be accurately described by the patients in the current study, it cannot be determined at present if age has a role in increased daytime functioning problems after stroke. Some authors have suggested that illnesses and medication associated with increasing age better explains observed effects of age on sleep (Foley et al., 2004). Crowley and Colrain (2000) reported a comparison between healthy young and healthy older adults on sleep parameters finding no significant differences between the groups using subjective sleep diaries. Kramer et al., 1999 also found no difference in subjective ratings between young and older adults however objectively the older persons had a weakened circadian rhythmicity and increased night awakenings. Increased nocturia with age (Ali & Snape, 2004) which has an effect upon sleep quality and daytime functioning (Jennnum, 2002). Results of the present study showed no effects of age upon subjective sleep or daytime functioning which has
previously been shown in other brain injured populations (Fictenberg et al., 2001). This may be because the sample within the current study is considered relatively young for a stroke cohort.

**Gender Differences**

It is important to recognise gender differences in sleep as the study samples were relatively small and contained a greater proportion of men (ranging from 47-61% across all studies). Although the results did not reveal any gender effects, studies have gender specific differences regarding sleep (Armitage & Baker, 2005; Collop, Adkins, & Phillips, 2004) and post stroke recovery (Saini & Shuaib, 2008). Gender differences may be necessary when considering sleep after stroke in a wider context than that of the cohort addressed in this thesis.

The prevalence of insomnia and general sleep disturbance such as increased night awakenings and poor sleep quality is greater amongst women (Groeger et al., 2004; Reyner, Horne, & Reyner, 1995; Valipour et al., 2007). Women are known to experience greater levels of anxiety (Bekker & van Mens-Verhulst, 2007) compared to men which is attributed to the existence of increased sleep disturbance (Roth, 2007). Men are particularly associated with sleep related breathing disorders (Valipour et al., 2007). Gender differences in sleep also arise from differences in life style and health (Roth, 2007), as well as sleep architecture (Carrier, Land, Buysse, Kupfer, & Monk, 2001; Dijk, Beersma, & Bloem, 1989; Goel, Kim, & Lao, 2005). It is not yet known if gender specific differences in sleep architecture differentially affect sleep dependent learning (Vassalli & Dijk, 2009).

Gender differences are also apparent in the context of post stroke recovery. Studies show that women have poorer functioning, greater levels of comorbidity after stroke compared to men (Gargano & Reeves, 2007; Herrmann et al., 1998; Lai, Duncan, Dew, & Keighley, 2005; Tilling et al., 2001). This may in part be due to increased survival rates for women (Gresham et al., 1998) and increased levels of depression affecting their ability to cope with the disease (Chong, Lee, Boden-Albala, Paik, & Sacco, 2006;
Herrmann et al., 1998). However, several studies have found that gender was not a factor for rehabilitation outcome (Heinemann, Roth, Cichowski, & Betts, 1987; Henrik Stig Jorgensen et al., 2000) and quality of life (Kwa et al., 1996; Naess, Waje-Andreassen, Thomassen, Nyland, & Myhr, 2006a).

7.4 Limitations of Thesis Research

The research carried out for this thesis was subjected to several methodological limitations that are necessary to acknowledge for data interpretation and to highlight aspects for improvement when planning future studies. The main limitations have arisen from apparent constraints of the CIT trial framework and issues with the chosen assessments.

7.4.1 Constraints of The CIT Trial Protocol

As an opportunity sample was utilised for the current thesis research, the planning of the studies was restricted in some respects. Attending the CIT trial imposed several psychological, cognitive and practical demands on patients that may have affected their sleep which could not be controlled.

Enduring CIT has great emotional connotations for several reasons. Firstly, patients are often apprehensive prior to visiting the laboratory due to the unfamiliarity of the research situation. Anecdotally, several patients commented on their sleep being affected prior to attending screening and the first CIT session as a result of increased anxiety. This demonstrates that stroke patients’ psychological state highly impacts sleep, which was reflected in the results of Study 1. Conversely, observable improvement in motor ability over the course of CIT was usually paired with a great sense of achievement and
improved mood in patients. It remains unknown if short term alterations in mood affected sleep in these patients. Other studies have shown that after two weeks of CIT, many patients report improvements in their quality of life and mood (Demetters, 2005). This may have a beneficial effect on sleep and daytime functioning in those who experience psychological difficulties. This may in part explain why there was less self reported napping in patients during CIT.

The CIT project also inflicted cognitive demand on patients in addition to the motor learning required in therapy sessions. The trial involved several appointments of which patients and families needed to organize themselves to attend. Patients were also required to read several study documents and remember to bring certain items to sessions, such as home CIT or sleep diaries. Completion of sleep diaries also required an additional task for patients on a daily basis for a total of six weeks of which some patients found tiresome.

For some patients, the CIT trial imposed practical demands which almost certainly affected their sleep. Attending sessions involved traveling great distances everyday, of which contributed to patient sleepiness and fatigue. Furthermore, some patients stayed in alternative accommodation therefore had to adjust to a new sleeping environment. Therefore the observed changes during the CIT trial are vulnerable to the practicalities of enabling the patient to attend sessions. However it is important to note that sleep did become more regulated as a result of adding structure to the day.

7.4.2 Subjective Assessments

Sleep and Daytime Functioning Scales
The sleep and daytime functioning scales employed in this thesis have provided useful information regarding post stroke sleep. However, as with any scale that measures constructs of behaviour, issues regarding validity and reliability should be considered when interpreting the data collected in the current studies.
The PSQI and ESS are two of the most widely used assessments of sleep quality and daytime sleepiness respectively. Tachibana & Taniguchi (2007) pointed out that there is a tendency to rely on measures due to popularity rather than reliability and validity. Buysse et al. (2008) carried out a study to examine the validity of the PSQI and ESS with PSG in 187 participants. It was found that neither of these measures were related to the objective assessment. It was concluded that the PSQI and ESS measure different aspects of sleep to that of PSG, therefore it is expected they would not correlate. With regard to patients involved in the current research, it may be that these assessments are not sensitive to pick up subtle sleep abnormalities of clinical significance and should be reported as self perceived sleep, rather than assuming a correlations with objective measures. The Buysse et al. (2008) study suggested that sleep problems may not be detected subjectively which may explain why prevalence 31-44% of sleep problems in patients of this study was less than those reported in other studies using other forms of assessment. Furthermore, the ESS is less sensitive to those with sleep disorders due to their inability to detect their own sleepiness (Fong, Ho, & Wing, 2005).

The FSS is another widely used measure to assess fatigue however there have been several criticisms of this scale which are relevant to the current research. The FSS asks participants to rate how much they agree with a list of statements that assumes they already have fatigue, e.g. “My motivation is lower when I have fatigue”. Patients who felt they did not have fatigue felt that this questionnaire was not applicable to them and rated their response as zero for each item. A similar process occurred when completing the D-FIS. However, it was suspected that they may be more fatigued than a healthy person. Therefore, it might have been more appropriate to ask them to rate what their fatigue levels are like compared to premorbid levels.

Stone et al. (2002) reported that participants may become less motivated to complete sleep diaries over long periods of time. This can result in participants completing several days’ worth of the diary at the end of a study before returning them to the researcher. Non-compliance with regard to sleep diaries meant exclusion of two patents in Study 4
and 6. In addition, the content of the diary presented some limitations. Firstly, the sleep diaries did not track daily caffeine and alcohol use. Only a habitual measure was obtained during screening. This information may have been useful as whilst the majority of patients continued to drink their usual amount of caffeine per day, some patients commented on a greater need for more caffeine during CIT. Furthermore, some patients who attended social events and drank alcohol commented that this affected their sleep. As this was not systematically documented, it was not possible to include this in the analyses. However for future studies, it would be useful to include these measures.

Another issue which arose from the sleep diaries was the apparent overlap between the first item on the D-FIS, "I feel less alert", and KSS which asked participants to rate alertness. This highlights the similarity in sleepiness and fatigue in the view of the scale developers. Furthermore, sleepiness and fatigue share conceptually share some overlap (Hossain et al., 2005; Mahowald & Mahowald, 2000). It may just be that the first item on the D-FIS represents the aspect of fatigue that extends to sleepiness. Therefore patients were given clarification in order to complete the sleep diaries accurately.

Assessment of QOL

There are some validity issues with use of the SF-36 and HADS. The SF-36 is vulnerable to response bias as those who score highly on this measure also score highly on Marlowe-Crowne Social Desirability Scale27 in a group of sleep disordered patients (Bardwell et al., 2001). Therefore the SF-36 may not be representative of their true behaviour (Bardwell et al., 2001). Moreover, the SF-36 is considered less valid when assessing health outcome in stroke patients due the variable ways it is administered and scored across studies (Hobart, Williams, Moran, & Thompson, 2002; O'Mahony, Rodgers, Thomson, Dobson, & James, 1998). Other authors have concluded that the SF-36 is a valuable measure of perceived health in stroke patients and is less susceptible to ceiling effects compared to other questionnaires therefore can be applied to a broad range of patients (Anderson et al., 1996).

27 This scale statistically determines the degree to which a person is likely to adjust their answers in a socially desirable manner.
**Subjective Upper Limb Use**

The upper limb motor test battery incorporated the MAL as a subjective assessment of real world arm use beyond the laboratory. Particular caution should be applied to patient reports of their affected arm usage. Dettmers et al. (2005) found that greatest improvement of arm/hand usage was reported on the MAL compared to other commonly used forms of assessment. It is difficult to judge whether eliciting movements due to the nature of an assessment would worsen performance compared to completing activities of daily living within the person’s home. In contrast, other studies have reported that pessimistic patients underestimate their ability when completing the MAL (Heller et al., 1987). The semi-structured nature of the MAL may lead to variability in the way it is administered and also how authors present the findings (Liepert et al., 1998; Taub et al., 1993; Van der Lee et al., 1999). It was highlighted by Van der Lee et al. (2004) that the MAL has good uses within a research project, however the generalisability of the results are assessment not likely to extent beyond the context of which the test was used. However it is important to drawn on strengths of this form of assessment. In particular, the subjective nature of this test supplements other tests in this field which have lower ecological validity. Furthermore improvements on the MAL as a result of CIT have been shown to correlate with objective measures (Kopp et al., 1999; Levy, Nichols, Schmalbrock, Keller, & Chakeres, 2001; Liepert et al., 1998).

### 7.4.3 Objective Assessment

In addition to subjective scales, some limitations arose with regard to actigraphy, EEG and a non-subjective motor ability test (WMFT).

**Actigraphy**

Although the issue of using actigraphy in those with motor deficits was addressed in Chapter 4, it is necessary to further discuss this issue in more detail. The motor movement difficulties associated with brain damage, i.e. hemiparesis, may inflict artefact
within actigraphy recordings (Sadeh, & Acebo, 2002). More specifically, lower activity may be interpreted as sleepiness or even a period of sleep however may actually be related to physical limitations. The possibility of such artefact may have occurred in actigraphy recordings within patients used in this current research as the sensitivity algorithm was developed for normally moving persons. At present there is no algorithm specifically developed for stroke patients with upper limb hemiparesis. Therefore further research to develop an algorithm for this population.

The Actiwatch ® equipment and software used in the present studies (CamNtech Ltd., © 2009) could be adjusted to one of three levels of threshold sensitivity to define wake; low (≥80 activity counts), medium (≥40 activity counts) and high (≥20 activity counts). Nap sensitivity could be set to 10 activity counts to define sleep at a medium sensitivity and up to 0 for high sensitivity. After careful consideration of the available literature and the prospective sample being studies, a medium sensitivity was chosen for both nocturnal and daytime sleep. This sensitivity was chosen for several reasons: 1) patients were selected based on a narrow range of motor criteria, 2) patients physical ability allowed them to attend the CIT trial, 3) approximately 70% of patients were retired or currently able to work, 4) actiwatches were worn on the non-affected wrist which resembled normal movement, 5) varying sensitivities of actiwatches within a group of motor handicapped persons did not significantly impact results (Laakso et al., 2004), 6) the chosen sensitivities were recommended by the manufacturer, and 7) sensitivities set too high or too low tend to over/underestimate night time awakenings (Littner et al., 2003).

In addition, further measures were taken to correct for artefact. Sleep schedules were inputted manually with the guidance of the sleep diary and visual inspection of the actigram. For napping analyses, automatic nap detection was adjusted if the watch was removed for any reason. Watch removal was reported in the sleep dairies and could be detected visually as the actigram remained at zero for longer periods of time, as it is expected that some movement would occur a sleep period (Carskadon & Rechtschaffen, 2005). These suspected periods of watch removal were also checked using the highest sensitivity of the nap analysis (>0 defined wake) to determine if this period was a nap.
Waking EEG

Some limitations arose from the waking EEG protocol described in Chapter 5. One particular limitation within the protocol is the length of time between the beginning of the experimental paradigm and the first waking EEG recordings which was up to an hour. Patients remained sat in the chair during this time and often commented on the laboriousness of this part of the experiment which made them more tired that usual. Therefore subjective and objective sleepiness ratings in this study may not represent how the patient felt in natural conditions. With regard to EEG capture, some authors argue that recording with eyes closed is a better indication of sleepiness (Marzano et al., 2007). However other authors have found little difference between eyes open and eyes closed (Akerstedt & Gillberg, 1990).

Wolf Moto Function Test (WMFT)

The WMFT is a laboratory based test of upper limb motor ability, although tightly controlled in this study, is subject to limitations. The most prominent limitation is the low ecological validity a test of this nature as the scores may not represent what the patient can or can not do outside the clinic or research facility. However there are no known studies which have reported problems with this test regarding reliability or validity. However to supplement this test, the MAL was employed in order to broaden the assessment of upper limb motor ability from that of a structured laboratory based assessments to real world arm usage.

7.5 Implications and Practical Applications of The Findings

The results presented in this thesis have great implications the healthcare profession and patients by build on clinical knowledge of the post stroke sequelae. The findings are informative for treatment protocols, including medical, psychological and sleep. The results also have ramifications for neurorehabilitation programmes, including CIT, and can be translated into other rehabilitation protocols. From the current findings and those
provided in the literature, the development of practical solutions for promoting healthy sleep as well as treating sleep related difficulties in stroke patients can be established. In addition, these results have implications for further research.

7.5.1 Informing The Medical Profession

**Understanding Post Stroke Sleep Behaviour**

This thesis has shown that post stroke sleep and daytime functioning are part of the complex and multifactorial consequences of stroke. Not only does stroke influence sleep, any disturbances present in patients impact quality of life, recovery and rehabilitation participation. It is therefore important for clinicians to have knowledge of sleep and how to recognise a difficulty in this respect. However, at present there is a surprising lack of attention paid to sleep in medical training (Wessendorf et al., 2000). Furthermore there is a lack of consideration of sleep when treating conditions of which sleep disturbance may be a secondary consequence (Chesson et al., 2000). This thesis has also shown that there are dimensions of daytime functioning, i.e. sleepiness and fatigue, which differentially affect the patient. It is known that sleepiness and fatigue are not necessarily considered as distinct entities in the medical profession (Hossain et al., 2005; Mahowald & Mahowald, 2000), therefore this common misconception should be addressed as this may impact patient treatment (Pigeon et al., 2003). In addition to diagnosis and recognition of maladaptive sleep behaviour, it is also important for clinicians to understand the modulating properties of sleep in somatic, behavioural, cognitive and psychological contexts of stroke.

**Underestimation of a Chronic Problem**

This thesis particularly highlights that sleep and daytime functioning difficulties, initially believed to have resolved within the acute phase of injury, by both patients and their clinicians, may remain beyond a year after injury. It is for that reason, especially important to increased awareness of these continuing problems which may evolve with the disease. The apparent lack of medical attention paid to sleep as part of post stroke
care is alarming and requires addressing in medical education as well as raising patient awareness. One of the reasons that sleep is not largely addressed as part of treatment may be due to lack of awareness from the patient themselves of which they do not express to their clinician. It was postulated that patients threshold of what they consider poor levels of sleep quality or daytime functioning may be higher than a non-brain injured person. This may be due to long term adjustment to their illness. This suggests that it will be beneficial for patients to be educated early on during stroke treatment in recognising and available treatments for these problems throughout their recovery. Increased awareness and appropriate treatment throughout the course of stroke may hold beneficial implications for patient quality of life and adjustment to stroke (Ingles et al., 1999; La Chapelle & Finlayson, 1998; Naess et al., 2006b; Schuiling et al., 2005; Siengsukon & Boyd, 2009b; Van Zandvoort et al., 1998). Moreover, ensuring healthy daytime functioning levels have critical implications for patient safety (Hyndman & Ashburn, 2003; Lundqvist et al., 2008; Michael et al., 2006).

Clinical Implications For Post Stroke Treatment and Rehabilitation Protocols

The results of Chapter 3 showed that patients felt their sleep was disrupted by the hospital environment within the acute phase, a common finding in clinical cohorts other than stroke (Dogan et al., 2005; Freedman, Gazendam, Levan, Pack, & Schwab, 2001; Gabor et al., 2003; Southwell & Wistow, 1995). In order to treat post stroke sleep disturbance and facilitate healthy sleep in acute stroke, Henmann et al. (2008) advises private rooms at night, with adequate noise and light reduction and also the use of sleep hyponotics during the night. Turkington, Bamford, Wanklyn, & Elliott, (2002) pointed out that acute stroke patients who were nursed in the supine position had significantly higher respiratory disturbance. Due to the high presence of sleep disordered breathing after stroke, this suggests that nursing staff should be educated with regards to optimum sleeping positions in hospital. The authors also advise exposure to light and increased mobility during the day to improve daytime functioning levels in these patients.

The results of this thesis, in addition to findings in the literature, show that predominately focusing on wakefulness and ignoring sleep, may be detrimental to quality of life and
rehabilitation outcome to some extent, and ultimately, overall recovery after stroke. Therefore a ‘24 Hour Approach’ to stroke care is a critical direction for treatment and rehabilitation protocols. This applies to rehabilitation within hospital stay as well continuation of rehabilitation sessions after the patient has been discharged. Maintenance of good sleep over the course of stroke should be addressed by clinicians and reiterated to the patients themselves.

7.5.2 Treatment Options For Post Brain Injury Sleep Disturbance

Several pharmacological and non-pharmacological treatments have been developed. More specifically, such treatment are aimed to treat insomnia, however can also be applied to those with only mild sleep disturbance as a way of facilitating healthy sleep management in brain injured populations. Syndromes such as sleep disordered breathing and parasomnias are more complex and require specialist treatment (Bassetti, 2005a, 2005b).

Several authors have outlined treatment strategies for post brain injury sleep disturbance (Rao & Rollings, 2002; Thaxton & Myers, 2002; Zafonte et al., 1996). Thaxton and Myers (2002) described potential strategies for managing sleep disturbance after brain injury, including non-pharmacological options. In light of the present study, these options may prove beneficial to not only managing sleep after stroke, but as part of maintaining a healthy life style and contributing to better prognosis and rehabilitation success. By applying sleep management to stroke patients, improvements in sleepiness and fatigue may also be observed (Annoni et al., 2008; Ingles et al., 1999; Zwarts, Bleijenberg, & van Engelen, 2008). There are behavioural and pharmacological treatment options for excessive daytime sleepiness including napping, improving nocturnal sleep and use of stimulants (Roth & Roehrs, 1996). There are few therapy studies available for post stroke treatment of fatigue. The authors of one study suggest low-intensity training, cognitive therapy, treatment of psychological problems, use of wakefulness promoting drugs,
correction of risk factors and adaptation of activities may alleviate fatigue (Annoni et al., 2008).

Zafonte et al. (1996) introduced an outline hierarchy of approaches to addressing sleep disturbance for those with TBI (Figure 7.1). The hierarchy presents a stepped care model for addressing post brain injury sleep problems. The model will be discussed as well as incorporating more recent findings, including clinical trials and other therapeutic approaches and how this can be applied to stroke patients.

Figure 7.1. Reproduced from Zafonte, Mann and Fichtenberg (1996) Neurorehabilitation, p.192.

**Structured Evaluation**

As part of sleep treatment it is important to incorporate a comprehensive evaluation of sleep disturbance. Criteria of sleep disorders should be applied to the symptoms described by patients. The results of this thesis particularly show that patient perception may be different to what is reported via objective measures. Therefore the type of assessment is critical to determining the nature of a sleep problem in stroke patients.
Sleep Hygiene Techniques

Sleep hygiene is the term used to describe the implementation or adjustment of those behaviours that are conductive to healthy sleep such as a regular sleep schedule, avoiding caffeine 4 to 6 hours before bed, scheduling exercise at least 2 hours or more before bed and eliminating a bedside clock (Hauri, 1992 cited in Stepanski and Wyatt, 2003; Thaxdon & Myers, 2002). One of the simplest strategies to apply as an early form of treatment for a sleep problem is to address the sleep hygiene behaviour of the patient. Even minor adjustments to sleep habits may facilitate a healthy sleep schedule (Stepanski & Wyatt, 2003). Sleep hygiene approaches overlap with other non-pharmacological treatments for insomnia, including environmental modification and stimulus control (Stepanski & Wyatt, 2003).

Environmental Modification/ Stimulus Control

Should improving sleep hygiene be insufficient, the next stage of the model is to introduce modifications to the sleeping environment to further encourage healthy sleep. People with sleep problems typically associate the bedroom as a stressful place where they cannot sleep. The aim of environmental modification, sometimes referred to as stimulus control, is to remove stimuli that are counteractive of sleep in the bedroom. This includes work related stimuli, electronic devices such as computers, visible clock and only using the bedroom for sleep. Removal of this stimuli aims to facilitate a stronger association between the bedroom and sleep. Therefore the bedroom becomes a more conductive environment for sleep (Ellis et al., 2002; Stepanski & Wyatt, 2003; Thaxdon & Myers, 2002).

Napping behaviour requires some degree of control when managing sleep disturbance. Ill timed or excessive napping may lead to poorer quality nocturnal sleep as well as affecting regularity of the sleep schedule (Werth, Dijk, Achermann, & Borbely, 1996). However in extreme conditions, such as illness or sleep deprivation, an optimal nap holds beneficial properties (Takahashi, 2003). Naps help alleviate sleepiness (Rosekind et al., 1995; Vgontzas et al., 2007) and can be part of a health active lifestyle if structured well (Ceolim & Menna-Barreto, 2000).
Furthermore, alterations to the amount and type of light in the waking environment can improve daytime functioning and subsequent sleep. Approaches expose patients to natural light such as Chronotherapy and Bright Light Therapy (Rao & Rollings, 2002). The aim of this treatment is to strengthen circadian rhythm (Czeisler et al., 1989) which ultimately facilitates a healthy sleep-wake cycle. Bright light therapy has been useful for treating sleep disorders due to regulation of circadian rhythm (Czeisler et al., 1989; Lockley et al., 2006) as well as treating excessive daytime sleepiness (Black et al., 2007) and improving mood (Goel & Etwaroo, 2006).

Cognitive and Behavioural Intervention

A challenging yet effective behavioural intervention is sleep restriction therapy (Glovinsky & Speilman, 1991). This involves reducing the time that the patient is allowed to spend in bed to four hours for the first night and gradually increasing time in bed by 15 minutes per subsequent night. As patients with insomnia may find it takes them over an hour to fall asleep, the prescribed time in bed may only allow them a further three hours of sleep until they need to get up as part of the restriction therapy. This process, although exhausting for the patient, facilitates partial sleep deprivation thereby shortening sleep onset and increasing sleep maintenance after several days. The 15 minute increases per night gradually introduces the patient to a regular, and more efficient sleep pattern. This intervention has shown great success for those with insomnia (Morin et al., 2006).

Cognitive strategies have also been applied to the treatment of insomnia and addresses dysfunctional beliefs about sleep which may hinder healthy sleep practice (Belanger, Savard, & Morin, 2006). Psychoeducation is beneficial patients to gain a better understanding of their sleep problem, what may have caused it and likely modulators that maintain it (Morin & Espie, 2003). In addition to promoting sleep awareness, cognitive techniques include thought stopping (Morin & Espie, 2003), changing maladaptive thinking whilst trying to fall asleep (Wicklow & Espie, 2000a), and more recently,


‘mindfulness’ (Ong, Shapiro, & Manber, 2008). Cognitive treatments for insomnia have benefits for improving sleep as well as having psychological benefits (Morin et al., 2003).

Behavioural and cognitive treatments, are most successful when combined together. A well researched form of this combined approach is termed Cognitive Behavioural Therapy for Insomnia (CBTi; Morin & Espie, 2003). This is an intervention specifically designed to target insomnia however, can be applied to guide healthy sleep. CBTi systematically introduces a new skill, in the form of psychoeducation, sleep hygiene, relaxation, stimulus control and cognitive techniques to encourage patients to ‘switch off’, into the patient’s routine. CBTi has shown high efficacy (Espie, Inglis, & Harvey, 2001). Moreover, the treatment has better long term outcome in comparison to pharmacological treatment and is often preferred by patients (Morin & Wooten, 1996). However these studies examined non-brain injured patients with insomnia. As clinical insomnia was not largely evident in patients of the current study, it is not yet known if CBTi type treatment, or elements within it, is effective in stroke cohorts. Although it may not be appropriate to apply some aspects of CBTi to brain injured patients, sleep restriction in particular, non-pharmacological treatment for sleep disturbance may be beneficial for stroke patients, even as part of a healthy sleep routine in those without a diagnosable sleep disorder.

**Pharmacologic and Medical Intervention**

Pharmacological treatments are commonly prescribed to those suffering from insomnia. The aim of the prescribed medications, categorised as benzodiazepines or non-benzodiazepine hypnotics, is to decrease sleep onset latency and maintain continuous sleep (Morin and Espie, 2003, p.101-103). These medications act on the sleep receptor agonists in order to drive the neural mechanisms that initiate sleep (see Section 1.2.2, Chapter 1). However sleep medications are largely associated with a ‘hangover’ effect whereby patients experience daytime sedation (Charles, Kirkham, Guyatt, & Parker, 1987; Morin & Espie, 2003, p.105). These effects are particularly less preferable with

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28 Mindfulness is a meditation technique used to treat anxiety and depressive disorders where a person may ruminate for long periods of time. It aims to teach a person to focus on the present and to gain control over ruminating thoughts and regulate emotion (Chambers, Gillen and Allen, 2009).
those with brain injury who may experience excessive daytime sleepiness (Zafonte et al., 1996) regardless of good sleep at night. Non-benzodiazepine hypnotics are newer drugs that produce less side effects than traditional benzodiazepines (Ramsey & McGlohn, 1997). Therefore this approach may be appropriate for short term alleviation of sleep disturbance in patients however non-pharmacological options are worthwhile for long term sleep management (Hajak & Rodenbeck, 1996; Morin & Wooten, 1996).

There are also pharmacological treatments for treating excessive daytime sleepiness (Billiard et al., 1994) and to some extent these drugs may alleviate fatigue (Caldwell, 2001). Brain injured patients who suffer from hypersomnia despite having healthy sleep, may benefit from pharmacological intervention for sleepiness and fatigue (Mitler, Erman, & Hajdukovic, 1993; Shneerson, 2005). Some improvements using drugs to increase wakefulness, such as amphetamines, modafinil, methylphenidate and dopaminergic agents, have shown an improvement in brain injured patients (Al-Adawi et al., 2006; Autret et al., 2001; Bassetti & Valko, 2006; Roth & Roehrs, 1996; Shneerson, 2005). Fluoxetine, a selective serotonin reuptake inhibitor used to treat depression, has been implemented in the treatment of post stroke fatigue (Choi-Kwon et al., 2005). It was found that although psychological symptoms improved, the presence of fatigue did not.

Sleep disordered breathing is normally treated using Continuous Positive Airway Pressure (CPAP). CPAP acts as a pneumatic splint by preventing the upper airway collapsing to reduce the occurrence of apnoeas. As sleep apnoea is both a pre and co-morbid sleep disordered associated with stroke. Studies have shown that sleep apnoea is related to recovery (Bassetti, 2005b), early detection and treatment must be implicated as it may affect recovery and rehabilitation if left untreated (C. Bassetti & Aldrich, 1999; Neau, Paquereau, Meurice, Chavagnat, & Gil, 2002). CPAP treatment is well tolerated (Broadley et al., 2007) and has helped treat 70% of stroke patients (Wessendorf et al., 2000). Furthermore surgery and medication are alternative treatments for post stroke sleep related breathing disorders (Hermann & Bassetti, 2003) however further clinical trials are necessary to investigate the efficacy of these methods in stroke patient. It may
also be critical to implement such treatment into stroke care to avoid a second stroke in patients with sleep disordered breathing (Bassetti, 2005b).

Additional Treatments Applicable To Those With Sleep Disturbance

In addition to the above treatment for sleep disturbance, further strategies regarding patients’ lifestyle, health and psychological adjustment may also be beneficial for sleep and daytime functioning. Maintaining a healthy lifestyle by encouraging regular exercise, balanced diet and cutting down on alcohol has great benefit for sleep in brain injured patients (Hermann et al., 2008). It was particularly obvious in the current thesis, and in the literature (Rao & Rollings, 2002; Schuiling et al., 2005), that sleep problems after stroke are associated with psychological disturbance. Therefore attending to psychological needs as treating or neglecting one may impact the other (Bassetti & Valko, 2006; Rao & Rollings, 2002). Therefore the treatment of psychological disorders may help alleviate sleep and daytime functioning problems (de Groot et al., 2003). Treating depression using antidepressants or Cognitive Behavioural Therapy for anxiety or depression may also enhance daytime functioning by improving mood and alertness (Scheidtmann, Fries, Muller, & Koenig, 2001).

7.5.3 Implications For Further Research

The results and experienced gained from carrying out the research for this thesis has crucial implications for future research. Most notably, the findings highlight three main aspects of study protocols that should be taken into account when planning and conducting experiments within the field of post stoke sleep: sampling, operationalisation of behaviour and the dissociation between objective and subjective measures.

Sampling

Scrutiny of the literature as well as the present findings indicated that varying recruitment strategies of stroke patients may reveal inter group differences. For example, patients recruited for the current study were selected based on their chronicity and level of
physical and psychological health. Furthermore, the patients fit a narrow range of motor ability as part of the inclusion criteria. Few studies in the sleep field have recruited patients in this manner which indicates that patients in other studies are more heterogeneous than those in this study. Therefore the results of studies on stroke patients should be interpreted with caution if generalised to samples outside of the recruitment boundaries.

In addition to patient sampling, the results of Chapter 3 of this thesis strongly suggested that choice of control group has great impact on the interpretation of the data. Control groups selected from the general population may not appear any different from stroke patients in terms of subjective sleep and daytime functioning levels. Differences only appear when control groups are positive selected based on their health and presence of sleep problems.

Operationalisation of Behaviour Capture

This research has also shown clear operationalisation of behavioural dimensions measured as part of the study is critical. Other studies poorly define sleepiness and fatigue which suggests that their results are subject to overlap between both dimensions. Moreover, the definition of these concepts is not communicated to the patient which may contaminate their responses. It was therefore imperative that patients involved in the current research received clear instructions to clarify the differences between sleepiness and fatigue to ensure their complete the subjective indices more accurately.

Materials

It should also be strongly conveyed to other researchers that the combination of subjective and objective measures is more advantageous than such measures alone when exploring post stroke sleep. This allows sleep to be characterised in two different ways: 1) how they actually behave as determined by objective measures and 2) how the patient perceives their sleep. Moreover, brain injured cohorts are particularly more susceptible to inaccurate self reports, therefore measures other than subjective may be critical to applying sleep disorder criteria and monitoring daytime functioning.
There is a lack of literature that addressed treatment and management for post stroke mild to severe sleep disturbance. Due to this under researched area, inferences from research in other cohorts such as primary insomnia and sleep disordered breathing may not be applicable in stroke patients. Pharmacological options are effective but only for short term, therefore combined approaches of medication and behavioural intervention are more favourable than drug therapy alone (Morin & Wooten, 1996). Moreover, non-pharmacological interventions are as good as, or better, than pharmacological treatments and has preference for insomnia patients (Edinger & Wohlgemuth, 1999). Combination approaches are particularly useful for preventing relapse (Morin, Belanger, Bastien, & Vallieres, 2005). Furthermore, the side effects of sedatives, including daytime drowsiness, may compromise the safety of patients therefore non-pharmacological options should perhaps be implemented first when devising sleep treatment (Zafonte et al., 1996).

7.6 Future Studies

The findings from the present study have achieved a critical knowledge base which is informative for practical reasons including medical and rehabilitative interventions after stroke. Moreover, the findings and experience of carrying out this research has provided a foundation from which further research can continue and stimulate new avenues of stroke related sleep research.

7.6.1 Methodological Improvements To The Current Research
Given that there are few studies in the literature that are similar to the studies carried out for the current thesis, it would be advantageous to replicate these studies, include a greater number of participants and incorporate additional measures.

In particular, it would be useful to employ an objective measure of fatigue. Some researchers have used computer test batteries to measure fatigue (Dirnberger, Duregger, Trettler, Lindinger, & Lang, 2004; Philip et al., 2005). As sleepiness was underestimated in this Study 3, it is currently unknown if a similar effect may be observed with fatigue. However psychometric tests batteries design to measure fatigue may also be subject to overlap with sleepiness as observed with subjective measures (Bailes et al., 2006; Hossain et al., 2005; Mahowald & Mahowald, 2000).

Sleep diaries used for the current study could also be improved by including daily mood measures to examine if fluctuations in psychological functioning affected sleep or vice versa. It may further be useful to monitor daily alcohol and caffeine use throughout the experiments. It is important to keep sleep diaries brief however as compliance may be affected by lengthy questionnaires per day.

Based on the findings in the present studies and those within the literature, a measure to detect possible bias may highlight those patients more susceptible to underreporting of post traumatic symptoms (Mahmood et al., 2004). For example, the Marlowe-Crowne Social Desirability Scale, has been used to detect for possible bias in patients with sleep apnoea (Bardwell et al., 2001). Those who score higher on the scale are more susceptible to inaccurate responses on subjective questionnaires to due an increased desire to socially acceptable.

7.6.2 Exploring Other Stroke Cohorts

This study specifically investigated chronic patients with chronic upper limb hemiparesis. Further research could study sleep and daytime functioning other stroke samples
including acute (within 1 month), sub-acute (within 6 months) and involving those with greater co-morbid complications who were excluded for the research for this thesis.

Anecdotal reports from families of the patients for the current research raised several issues for discussion however their responses were not systematically documented. Therefore, recruiting family members and primary caregivers of stroke patients would also be an imperative sample for future research. Other studies have used caregiver reports for sleep research which provided an useful perspective in addition to stroke patients (Alessi et al., 2008; Worthington & Melia, 2006). Moreover, a stroke suffer within the family has been shown to affect sleep of the primary carer within the family (Rittman, Hinojosa, & Findley, 2009). Consequently, it may be imperative to consider stroke and sleep in the wider context of the family network for the benefit of both patients and their families.

7.6.3 Future Paradigms For Applied Clinical Research

Home PSG

While behavioural measures of sleep such as questionnaires and actigraphy give some insight, by far the most informative method is polysomnography. This method constitutes the gold standard in sleep research. Few studies have used PSG to measure sleep architecture chronic stroke. Furthermore, no known study has incorporated PSG in CIT to monitor possible affects on sleep architecture.

PSG is typically applied in the highly controlled sleep laboratory conditions, a situation that is very different from the natural sleep environment and is not necessarily practical for studying persons with physical disabilities. Furthermore, sleep laboratory protocols are extremely cost intensive, applicable to a highly selective group of volunteers only, and available to limited number of institutions across the UK. Critically, the laboratory setting is rarely wheelchair adapted. Patients may further rely on mobility aids in the bed and bathroom in their home environment that are not available in the standardised
laboratory setting and hence reduce their independence in this situation. This makes sleep studies in stroke patients much more difficult and stressful for participating individuals. As a result there is limited knowledge on the effects of stroke on sleep physiology and sleep architecture. For these reasons, the development of a PSG study protocol for the home environment is a suitable way forward for this line of research.

**Neurorehabilitation Protocol Adaptations**

Further consideration towards sleep could be incorporated into rehabilitation protocols, applicable to acute and chronic care as well as research trials. Firstly, more studies are needed to test if inventions to improve sleep and daytime functioning lead to clinically relevant gains, including increased dependence and less care giving needs (Alessi et al., 2008). This could be addressed as part of a randomised controlled trial, one of the treatment groups could participate in sleep management programme in addition to rehabilitation and compared to those who patients who did not have sleep management. The feasibility of sleep management for patients as well as rehabilitation outcome could be assessed to determine the subjective and objective benefits of sleep in this context. In addition, it was postulated by Seingsukon and Boyd (2008b) that napping between therapy sessions may have beneficial properties for motor memory consolidation. Therefore rehabilitations paradigms could incorporate a group who nap after therapy session and a group who does not. Comparisons of treatment outcome as well as the effect regular napping has on the patient who further explore this idea of Siengsukon & Boyd.

The findings and experience of carrying out all four studies for this thesis have not only contributed to the existing literature on sleep and stroke but opened up several directions for future research. In particular, substantial funding opportunities would be of great benefit to use home PSG technology in these patients. This data would help answer the questions that this thesis can only speculate at present.
Final Conclusion

Each study contributed its own unique findings with regard to the particular research questions addressed. Collectively, the findings of these studies have revealed several prominent patterns. The major findings of this thesis can be summarised as follows:

- Disturbed sleep is a chronic problem in approximately one third of patients. These disturbances were largely associated with psychological disturbance after stroke and poor quality of life.

- Daytime functioning deficits are highly prominent in patients, based on objective, family and observer observations, however remains unrecognised and it is suspected that this has not been alerted to their health practitioner. The exact cause of the sustaining sleep and daytime functioning difficulties remains unknown, however the results did suggest that psychological adjustment had a large impact on behaviour. It is also possible that this relationship is reciprocal although further research is necessary to establish the cause and effect nature of this association.

- It was concluded that fatigue is highly associated with motor functioning, in terms of residual ability as well as neurorehabilitation outcome. It was concluded that the resounding fatigue was a result of increased effort employed by patients who tried hard to increase capacity of affected limb use.

- As the association between sleep and CIT outcome were only mild, it cannot yet be concluded that better sleep results in better neurorehabilitation outcome. However, the results suggested that those who nap less, therefore are less sleepy, had a better CIT outcome.

Overall, the results mean that sleep should not be ignored as part of stroke care and rehabilitation protocols throughout acute and chronic stages of recovery. To further build on this work, studies should utilise more sensitive measures of sleep. This will enable
researchers to identify if sleep changes physiologically as a result of engaging in motor neurorehabilitation and if there correlates associated with better outcome.

The main clinical message of this thesis is that maintaining healthy sleep and tackling daytime functioning problems with prescribed medication or naps may be essential to maximise rehabilitation success. Furthermore, healthy sleep in the long term has benefits for health and wellbeing, therefore better quality of life for patients.
References


Ellis, J., Hampson, S. E., & Cropley, M. (2002). Sleep hygiene or compensatory sleep practices: an examination of behaviours affecting sleep in older adults

Sleep hygiene or compensatory sleep practices: an examination of behaviours affecting sleep in older adults. *Psychology, Health & Medicine, 7*(2), 156.


Sullivan, K. J. (2007). Acute, subacute, and chronic phases of stroke recovery. Rapid response to: Modified Constraint-Induced Movement Therapy in patients with
chronic stroke exhibiting minimal ability in the affected arm. *Physical Therapy*, 87(7), 872-878.


APPENDICES

Appendix A: Study Consent Documents
Appendix B: Materials Supplement for Chapter 2
Appendix C: Case Tables For All Participants
Appendix D: Supplement For Study 2
Appendix E: Supplement For Study 3
Appendix F: List of Abbreviations
APPENDIX A: Study Consent Documents

Patient Information Sheet

Control Information Sheet

Patients Consent Form

Control Consent Form
Information for Participation in Research

Study Title: Assessment of sleeping habits during Constrained Induced Movement Therapy (CIT): Does sleep have a role in motor rehabilitation after stroke?

Invitation Paragraph
You are being invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. Thank you for reading this.

What is the purpose of the study?
This purpose of this study is to monitor your sleeping habits before, during and after your participation in the Constraint Induced Movement Therapy trial. Recent research suggests that your sleeping behaviour is just as important as your waking behaviour. Your participation in Constraint-Induced Movement Therapy will involve learning new skills involved in your affected arm. Such learning must be processed in some way in order for it to be stored and retained in your brain. What scientists didn’t know until recently is that many of these learning processes occur when you are sleeping.

Why have I been chosen?
You have been selected as you have been accepted onto the Constraint-Induced Movement Therapy trial.

Do I have to take part?
It is up to you to decide whether or not to take part. If you decide to take part you are still free to withdraw at any time and without giving a reason.

What will happen to me if I take part?
You will be asked to complete the Pittsburgh Sleep Quality Index (PSQI), the Epworth Sleepiness Scale (ESS) and the Sleep-50 (S-50), the Fatigue Severity Scale (FSS) and the Ford Insomnia Response To Stress Test (FIRST) as a measure of your general sleep behaviour. These assessments will be made during your first visit to our laboratory and will be administered by the chief investigator of the sleep study. You will also be asked to complete a daily sleep diary, consisting of the Sleep Questionnaire (SQ), the Karolinska Sleepiness Scale (KSS) and the Daily Fatigue Scale (D-FIS) so we can monitor your sleep before, during and after CIT. Detailed instructions and contact details of the chief investigator are provided, should you have any problems. The daily sleep diary only takes a short moment to complete and should pose no additional cognitive load on those who have suffered a traumatic brain injury.

You will also be asked to wear an ‘Actiwatch®’ on each of your wrists. The Actiwatch® is a small, watch-like device which measures your activity levels during wake and sleep. The reason that we ask you to wear the watch on both wrists is so we can assess activity levels based on your affected arm as well as your unaffected arm. The Actiwatch® is completely waterproof and does not need to be removed for showering or taking baths. The Actiwatch® can be removed just like a wrist watch, however, should you wish to remove the Actiwatch® during the study, please contact the chief investigator first.

You will be asked to complete the sleep diary and wear the Actiwatches® for a total of 6 weeks. This will include a 2 week baseline period prior to CIT, 2 weeks during CIT and 2 weeks after CIT. You will be provided with a prepaid envelope to post the Actiwatch® back to our laboratory after the 6 weeks.

**What is the procedure that is being tested?**
We are testing whether sleep plays an important role during Constraint-Induced Movement Therapy. We intend to do this by assessment of sleeping habits during Constraint-Induced Movement Therapy. More specifically, we will also be able to look at different aspects of sleep, such as napping during the day.

**What are the possible disadvantages and risks of taking part?**
There is no known risk of completing the questionnaires. The questions are not of a sensitive nature and do not require detailed responses.

**What are the possible benefits of taking part?**
There is no known study which has investigated the role of sleep in Constraint-Induced Movement Therapy. Therefore this study is pioneering work as it aims to examine how we can improve current treatment schemes. This study will pave the way for future experiments that will investigate sleep and Constraint-Induced Movement Therapy in more detail, such as involving brain wave recordings overnight. We hope that with the knowledge we gain from investigative sleep, we will be able to properly advice positive sleep behaviour programmes to those who undergo Constraint-Induced Movement Therapy.

**Will my taking part in this study be kept confidential?**
All information that is collected about you during the course of the research will be kept strictly confidential. Any papers that contain your personal details can only be accessed by the research group and will not leave the laboratory.

Who is doing the research?
Katherine Herron, a PhD student will be heading the project. She has been working with the Clinical Neuroscience Research Team (headed by Professor Annette Sterr) at the University of Surrey for the past 2 years.

What will happen to the results of the research trial?
The results will be used for a PhD thesis for a degree taken at the University of Surrey. It is also hoped that the results will be published in a journal. You will not be identified in any of these publications.

Who has reviewed the study?
The University of Surrey Ethics Committee
The Surrey Research Ethics Committee

Contact for Further Information

Katherine Herron, Chief Investigator
Phone: 01483 686935; e-mail: kh00002@surrey.ac.uk

Professor Annette Sterr, Principle Supervisor
Phone: 01483 682883, e-mail: a.sterr@surrey.ac.uk

Jenny Sanders, Project Manager
Phone: 01483 682877; e-mail: CIT@surrey.ac.uk

Any complaint or concerns about any aspects of the way you have been dealt with during the course of the study will be addressed; please contact Katherine Herron, Chief Investigator on (01483) 686935.

This copy is for you to keep. If you decide to participate, you will also be given a copy of the signed consent form and treatment contract to keep.

😊 Thank you for considering participation in this study! 😊
Information for Participation in Research

Study Title: Assessment of sleeping habits during Constrained Induced Movement Therapy (CIT): Does sleep have a role in motor rehabilitation after stroke?

Invitation Paragraph
You are being invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. Thank you for reading this.

What is the purpose of the study?
This purpose of this study is to collect sleep behaviour data from a non-brain injured population for comparison with a brain injured population. The literature suggests that those with brain injury experienced increased sleep disturbances compared to those who have not experienced brain injury. In addition, scientists have recently discovered that sleep may play an important role in for our learning processes. This is particularly important during brain injury recovery as many patients undergo intense re-learning of skills lost through injury. Therefore healthy sleep is important during neurorehabilitation, however if sleep is likely to be disturbed in those with brain injury, we predict that this may affect how well they recover. We are currently assessing sleep behaviour in those undergoing Constraint-Induced Movement Therapy, a neurorehabilitation process facilitating new skills in motor movement. Your participation in this study will enable us to compare the prevalence of sleep disturbances in a non-brain injured population.

Why have I been chosen?
You have been selected as your demographic details, including age, gender and handedness, match another participant on the Constraint-Induced Movement Therapy trial.
Do I have to take part?
It is up to you to decide whether or not to take part. If you decide to take part you are still free to withdraw at any time and without giving a reason.

What will happen to me if I take part?
You will be asked to complete the Pittsburgh Sleep Quality Index (PSQI), the Epworth Sleepiness Scale (ESS), the Sleep-50 (S-50), the Fatigue Severity Scale (FS) and the Ford Insomnia Response To Stress Test (FORD) as a measure of your general sleep behaviour.

What is the procedure that is being tested?
General sleep behaviour questionnaires and the consent form will be posted out to suitable non-brain injured participants. A stamped addressed envelope will be provided so you can post them back to us free of charge.

What are the possible disadvantages and risks of taking part?
There is no known risk of completing the questionnaires. The questions are not of a sensitive nature and do not require detailed responses.

What are the possible benefits of taking part?
There is no known study which has investigated the role of sleep in Constraint-Induced Movement Therapy. Therefore this study is pioneering work as it aims to examine how we can improve current treatment schemes. This study will pave the way for future experiments that will investigate sleep and Constraint-Induced Movement Therapy in more detail, such as involving brain wave recordings overnight. We hope that with the knowledge we gain from investigative sleep, we will be able to properly advice positive sleep behaviour programmes to those who undergo Constraint-Induced Movement Therapy.

Will my taking part in this study be kept confidential?
All information that is collected about you during the course of the research will be kept strictly confidential. Any papers that contain your personal details can only be accessed by the research group and will not leave the laboratory.

Who is doing the research?
Katherine Herron, an PhD student will be heading the project. She has been working with the Clinical Neuroscience Research Team (headed by Professor Annette Sterr) at the University of Surrey for the past 2 years.

What will happen to the results of the research trial?
The results will be used for a PhD thesis for a degree taken at the University of Surrey. It is also hoped that the results will be published in a journal. You will not be identified in any of these publications.

Who has reviewed the study?
The University of Surrey Ethics Committee
The South West Surrey Local Research Ethics Committee

Contact for Further Information
Katherine Herron, Chief Investigator
Phone: 01483 686935; e-mail: kh00002@surrey.ac.uk

Professor Annette Sterr, Principle Supervisor
Phone: 01483 682883, e-mail: a.sterr@surrey.ac.uk

Caroline Khurana, Project Manager
Phone: 01483 682877; e-mail: CIT@surrey.ac.uk

Any complaint or concerns about any aspects of the way you have been dealt with during the course of the study will be addressed; please contact Katherine Herron, Chief Investigator on (01483) 686935.

This copy is for you to keep. If you decide to participate, you will also be given a copy of the signed consent form and treatment contract to keep.

😊 Thank you for considering participation in this study! 😊
CONSENT FORM

Researcher who holds scientific responsibility:
Katherine Anne Herron

Study Title: Assessment of sleeping habits during Constrained Induced Movement Therapy (CIT): Does sleep have a role in motor rehabilitation after stroke?

Please initial box

1. I confirm that I have read and understand the information sheet dated ....... (version .......) for the above study and have had the opportunity to ask questions.

2. I understand and agree to complete the questionnaires and sleep diary.

3. I agree to wear an actiwatch on each wrist for the scheduled 6 weeks.

4. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason and without my medical care or legal rights being affected.

5. I agree to take part in the above study.

Name of Participant ___________________________ Date __________________ Signature __________________
CONSENT FORM

Researcher who holds scientific responsibility:
Katherine Anne Herron

Study Title: Assessment of sleeping habits during Constrained Induced Movement Therapy (CIT): Does sleep have a role in motor rehabilitation after stroke?

Please initial box

1. I confirm that I have read and understand the information sheet dated ......
   (version ....) for the above study and have had the opportunity to ask questions. □

2. I understand and agree to complete the questionnaires. □

3. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason and without my medical care or legal rights being affected. □

4. I agree to take part in the above study. □
APPENDIX B: Materials Supplement for Chapter 2

Sleep, Daytime Functioning, Quality of Life and Psychological Adjustment Questionnaires

1. General Screening Form (use one from CIT trial)
2. Mini-Mental State Exam (MMSE)
3. In House Sleep Questionnaire Version 1a (Stroke Patients Only)
4. In House Sleep Questionnaire Version 1b (Control Participants Only)
5. Pittsburgh Sleep Quality Index
6. Sleep 50
7. FIRST
8. ESS
9. FSS
10. SF-36
11. HADS

Upper Limb Motor Movement Assessments

12. Wolf Motor Function Test (WMFT) Standardised Instructions
13. Wolf Motor Function Test (WMFT) Score Sheet
14. Motor Activity Log (MAL) Standardised Instructions
15. Motor Activity Log (MAL) Score Sheet

Longitudinal Sleep Assessments

16. Subjective Sleep Diary (One Day Example)
## Screening Evaluation Form

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### GP Details

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<td>Elbow:</td>
</tr>
<tr>
<td>Shoulder:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Level Overall?</th>
<th>High</th>
<th>Medium</th>
<th>Low</th>
<th>Low low</th>
</tr>
</thead>
</table>
Spasm (Ashworth grade): ________________________________________________

Non-use: __________________________________________________________

Walking aids/ balance: ______________________________________________

Secondary Conditions

Cardiovascular:
Hypertonia (medication): _____________________________________________
Diabetes: ___________________________________________________________
Kidney disease: _____________________________________________________
Neurological (e.g. MS): _____________________________________________
Epilepsy: __________________________________________________________
Arthritis: __________________________________________________________
Osteoporosis: _______________________________________________________
Depression or other emotional problems: ______________________________
Other head injuries: _________________________________________________
Surgery: ___________________________________________________________
Bladder control: ____________________________________________________
Other: _____________________________________________________________

Any metal in body (e.g. clip, pace maker)? ______________________________

General health

Pain: ______________________________________________________________

Medication: _________________________________________________________

Psychosocial status:
• Living (alone/w.partner):___________________________________________
• Current employment: _____________________________________________
• Previous employment: _____________________________________________
• Education: _______________________________________________________

394
Expectancies and major goals of treatment:

________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
________________________________________________________________________

Travel needs: ____________________________________________________________
________________________________________________________________________
________________________________________________________________________

395
APPENDIX B2

Mini-Mental State Examination Test (MMSE)

**Orientation**

<table>
<thead>
<tr>
<th>Day of week</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year</td>
<td></td>
</tr>
<tr>
<td>Month</td>
<td></td>
</tr>
<tr>
<td>Date</td>
<td></td>
</tr>
<tr>
<td>Time</td>
<td></td>
</tr>
<tr>
<td>Country</td>
<td></td>
</tr>
<tr>
<td>Town/City</td>
<td></td>
</tr>
<tr>
<td>County</td>
<td></td>
</tr>
<tr>
<td>Exact Location (University of Surrey) (2 points)</td>
<td></td>
</tr>
</tbody>
</table>

**Registration**

Examiner names 3 objects (apple, table, penny)

Patient repeats the names (score one for each correct) __/3

Then Patient learns 3 objects (repeat until correct)

**Attention and Calculation**

"Subtract 7 from 100, then repeat subtracting 7 from the result…"

100, 93, 86, 79, 72, 65. (stop after 5)

Or

spell ‘world’ backwards D, L, R, O, W __/5

**Recall**

Ask for 3 objects learnt earlier __/3

**Language**

Name a pencil and a watch __/2

Repeat (no ifs, ands, or buts) __/1

Give a three-stage command. (Score one for each stage) __/3

("Place the index finger of your right hand on your nose, and then on your left ear")

Ask patient to read and obey a written command on a piece of paper stating: __/1

"Close your eyes."

Ask patient to write a sentence. (Score if it is sensible and has a subject + verb) __/1

**Copying**

Ask patient to copy a pair of intersecting pentagons. __/1

**Total score:** ____/30

396
APPENDIX B3

In House Sleep Questionnaire (Version 1a; Stroke Patients)

Participant Code........................ Date................................

1. Are you currently taking any medication to help you sleep? (medication name, dosage, timing, how long it has been taken)

...................................................................................................

2. Have you previously taken any medication to help you sleep?

...................................................................................................

3. Are you currently taking any medication that has side effects which may affect your sleep? (medication name, dosage, timing, how long it has been taken)

...................................................................................................

4. Do you drink caffeinated drinks? If so, how many cups/glasses on average per day?

...................................................................................................

5. Do you drink alcohol? If so, how many units on average per day and per week if you only drink at weekends? (1 unit = 1/2 pint beer, small glass of wine, a single spirit)

...................................................................................................

6. Do you smoke? If so, how many cigarettes do you smoke per day?

...................................................................................................

7. Are you often disturbed during the night for reasons other than your own sleeping habits? For example, young children at home, partner, busy road, loud family members? If so how often per night?

...................................................................................................

8. Do you get up during the night? For example, to use the bathroom, or to have a drink? If so how often per night?

...................................................................................................
9. Any sleep disturbances prior to brain injury?
...................................................................................................

10. Did you nap before brain injury?
...................................................................................................

11. What was your sleep like during the first month of your stroke in hospital?
...................................................................................................

12. What was your daytime functioning like during the first month of your stroke?
...................................................................................................

11. Have you noticed any major changes in your sleep behaviour since your brain injury? If so, can you describe these changes?
...................................................................................................

12. What is your sleep like now?
...................................................................................................

13. What is your daytime functioning like now?
...................................................................................................

14. Do you nap regularly?
...................................................................................................
APPENDIX B4

In House Sleep Questionnaire (Version 1b; Control Participants)

Participant Code.......................... Date.......................... Age.........
Gender...................

Education (e.g. Degree, School Leavers Certificate).................................

Weight.......................... Height.................................

1. Are you currently taking any medication to help you sleep? (medication name, dosage, timing, how long it has been taken)

...................................................................................................

2. Have you previously taken any medication to help you sleep?

...................................................................................................

3. Are you currently taking any medication that has side effects which may affect your sleep? (medication name, dosage, timing, how long it has been taken)

...................................................................................................

4. Do you drink caffeinated drinks? If so, how many cups/glasses on average per day?

...................................................................................................

5. Do you drink alcohol? If so, how many units on average per day and per week if you only drink at weekends? (1 unit = ½ pint beer, small glass of wine, a single spirit)

...................................................................................................

6. Do you smoke? If so, how many cigarettes do you smoke per day?

...................................................................................................

7. Are you often disturbed during the night for reasons other than your own sleeping habits? For example, young children at home, partner, busy road, loud family members? If so how often per night?

...................................................................................................
8. Do you get up during the night? For example, to use the bathroom, or to have a drink? If so how often per night?
APPENDIX B5

PITTSBURG SLEEP QUALITY INDEX (PSQI) QUESTIONNAIRE

Volunteer code: ___________________________ Date: ___________________________

Instructions: The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all the questions.

1) During the past month, when have you usually gone to bed at night?

Usual bed time ___________________________

2) During the past month, how long (in minutes) has it usually take you to fall asleep each night?

Number of minutes ___________________________

3) During the past month, when have you usually got up in the morning?

Usual getting up time ___________________________

4) During the past month, how many hours of actual sleep did you get at night? (This may be different from the number of hours spent in bed.)

Hours of sleep per night ___________________________

For each of the remaining questions, check the one best response. Please answer all questions.

5) During the past month, how often have you had trouble sleeping because you.....

a) Cannot get to sleep within 30 minutes

Not during the past month _____  Less than once a week _____ Once or twice a week _____ Three or more times a week _____

b) Wake up in the middle of the night or early morning

Not during the past month _____  Less than once a week _____ Once or twice a week _____ Three or more times a week _____

c) Have to get up to use the bathroom

Not during the past month _____  Less than once a week _____ Once or twice a week _____ Three or more times a week _____

d) Cannot breathe comfortably

Not during the past month _____  Less than once a week _____ Once or twice a week _____ Three or more times a week _____

e) Cough or snore loudly

Not during the past month _____  Less than once a week _____ Once or twice a week _____ Three or more times a week _____
### Health Concerns

**f) Feel too cold**
- Not during the past month
- Less than once a week
- Once or twice a week
- Three or more times a week

**g) Feel too hot**
- Not during the past month
- Less than once a week
- Once or twice a week
- Three or more times a week

**h) Had bad dreams**
- Not during the past month
- Less than once a week
- Once or twice a week
- Three or more times a week

**i) Have pain**
- Not during the past month
- Less than once a week
- Once or twice a week
- Three or more times a week

### Other Reason(s)

<table>
<thead>
<tr>
<th>Reason(s) please describe</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

How often during the past month have you had trouble sleeping because of this?

<table>
<thead>
<tr>
<th>Not during the past month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than once a week</td>
</tr>
<tr>
<td>Once or twice a week</td>
</tr>
<tr>
<td>Three or more times a week</td>
</tr>
</tbody>
</table>

6) **During the past month, how would you rate your sleep quality overall?**

- Very good
- Fairly good
- Fairly bad
- Very bad

7) **During the past month, how often have you taken medicine (prescribed or “over the counter”) to help you sleep?**

<table>
<thead>
<tr>
<th>Not during the past month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than once a week</td>
</tr>
<tr>
<td>Once or twice a week</td>
</tr>
<tr>
<td>Three or more times a week</td>
</tr>
</tbody>
</table>

8) **During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?**

<table>
<thead>
<tr>
<th>Not during the past month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than once a week</td>
</tr>
<tr>
<td>Once or twice a week</td>
</tr>
<tr>
<td>Three or more times a week</td>
</tr>
</tbody>
</table>

9) **During the past month, how much of a problem has it been for you to show enthusiasm to get things done?**

- No problem at all
Only a very slight problem

Somewhat of a problem

A very big problem
Please respond to what extent a statement (item) has been applicable to you during the past 4 weeks. Please circle your answer accordingly: 1 = not at all, 2 = somewhat, 3 = rather much and 4 = very much.

### Sleep Apnea
1. I am told that I snore.  
2. I sweat during the night.  
3. I am told that I hold my breath when sleeping.  
4. I am told that I wake up gasping for air.  
5. I wake up with a dry mouth.  
6. I wake up during the night while coughing or being short of breath.  
7. I wake up with a sour taste in my mouth.  
8. I wake up with a headache.  

<table>
<thead>
<tr>
<th>Item</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
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<td>8. I wake up with a headache.</td>
<td></td>
<td></td>
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</tbody>
</table>

### Insomnia
9. I have difficulty in falling asleep.  
10. Thoughts go through my head and keep me awake.  
11. I worry and find it hard to relax.  
12. I wake up during the night.  
13. After waking up during the night, I fall asleep slowly.  
14. I wake up early and cannot get back to sleep.  
15. I sleep lightly.  
16. I sleep too little.  

<table>
<thead>
<tr>
<th>Item</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
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<tr>
<td>16. I sleep too little.</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

### Narcolepsy
17. I see dreamlike images when falling asleep or waking up.  
18. I sometimes fall asleep on a social occasion.  
19. I have sleep attacks during the day.  
20. With intense emotions, my muscles sometimes collapse during the day.  
21. I sometimes cannot move when falling asleep or waking up.  

<table>
<thead>
<tr>
<th>Item</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
<td></td>
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<td></td>
</tr>
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<td></td>
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<tr>
<td>20. With intense emotions, my muscles sometimes collapse during the day.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21. I sometimes cannot move when falling asleep or waking up.</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

### Restless Legs/PLMD
22. I am told that I kick my legs when I sleep.  
23. I have cramps or pain in my legs during the night.  
24. I feel little shocks in my legs during the night.  
25. I cannot keep my legs at rest when falling asleep.  

<table>
<thead>
<tr>
<th>Item</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
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<tr>
<td>25. I cannot keep my legs at rest when falling asleep.</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

### Circadian Rhythm Sleep Disorder
26. I would rather go to bed at a different time.  
27. I go to bed at very different times (more than 2 hr difference).  
28. I do shift work.  

<table>
<thead>
<tr>
<th>Item</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>26. I would rather go to bed at a different time.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>27. I go to bed at very different times (more than 2 hr difference).</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28. I do shift work.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Sleepwalking
29. I sometimes walk when I am sleeping.  
30. I sometimes wake up in a different place than where I fell asleep.  
31. I sometimes find evidence of having performed an action during the

<table>
<thead>
<tr>
<th>Item</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30. I sometimes wake up in a different place than where I fell asleep.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>31. I sometimes find evidence of having performed an action during the</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Nightmares
32. I have frightening dreams (if not, go to Item 37). 1 2 3 4
33. I wake up from these dreams. 1 2 3 4
34. I remember the content of these dreams. 1 2 3 4
35. I can orientate quickly after these dreams. 1 2 3 4
36. I have physical symptoms during or after these dreams (e.g., movements, sweating, heart palpitations, shortness of breath). 1 2 3 4

Factors Influencing Sleep
37. It is too light in my bedroom during the night. 1 2 3 4
38. It is too noisy in my bedroom during the night. 1 2 3 4
39. I drink alcoholic beverages during the evening. 1 2 3 4
40. I smoke during the evening. 1 2 3 4
41. I use other substances during the evening (e.g., sleep or other medication). 1 2 3 4
42. I feel sad. 1 2 3 4
43. I have no pleasure or interest in daily occupations. 1 2 3 4

Impact of Sleep Complaints on Daily Functioning
44. I feel tired at getting up. 1 2 3 4
45. I feel sleepy during the day and struggle to remain alert. 1 2 3 4
46. I would like to have more energy during the day. 1 2 3 4
47. I am told that I am easily irritated. 1 2 3 4
48. I have difficulty in concentrating at work or school. 1 2 3 4
49. I worry whether I sleep enough. 1 2 3 4
50. Generally, I sleep badly. 1 2 3 4
When you experience the following situations, how likely has it been for you to have difficulty sleeping during the past month? Circle an answer even if you have not experienced these situations recently.

★ Before an important meeting the next day
Not likely  Somewhat likely  Moderately likely  Very Likely

★ After a stressful experience during the day
Not likely  Somewhat likely  Moderately likely  Very Likely

★ After a stressful experience in the evening
Not likely  Somewhat likely  Moderately likely  Very Likely

★ After getting bad news during the day
Not likely  Somewhat likely  Moderately likely  Very Likely

★ After watching a frightening movie or TV show
Not likely  Somewhat likely  Moderately likely  Very Likely

★ After having a bad day at work
Not likely  Somewhat likely  Moderately likely  Very Likely

★ After an argument
Not likely  Somewhat likely  Moderately likely  Very Likely

★ Before having to speak in public
Not likely  Somewhat likely  Moderately likely  Very Likely

★ Before going on vacation the next day
Not likely  Somewhat likely  Moderately likely  Very Likely
The Epworth Sleepiness Scale (ESS)

Instructions: How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life during the past month. Even if you have not done some of these things recently try to work out how they would have affected you. Use the following scale to choose the most appropriate number for each situation:

0 = no chance of dozing

1 = slight chance of dozing

2 = moderate chance of dozing

3 = high chance of dozing

<table>
<thead>
<tr>
<th>SITUATION</th>
<th>CHANCE DOZING OF</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitting quietly after a lunch without alcohol</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>In a car, while stopped for a few minutes in traffic</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Sitting and reading</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Watching TV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sitting inactive in a public place (e.g. a theatre or a meeting)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>As a passenger in a car for an hour without a break</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lying down to rest in the afternoon when circumstances permit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sitting and talking to someone</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The Fatigue Severity Scale

Participant code ........................................ Date ................................

We would like to know if you are affected by fatigue during the past month. Please note, fatigue is defined as **physical or mental weariness resulting from exertion NOT sleepiness** (how likely you are to fall asleep).

Please circle which response is most applicable to you to indicate whether you disagree or agree with the following statements about yourself. 1 indicates strong disagreement and 7 indicates strong agreement. If your response is neutral, please circle 4.

<table>
<thead>
<tr>
<th>Statement</th>
<th>Disagree</th>
<th>Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>During the past week, I have found that:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>My motivation is lower when I am fatigued</td>
<td>0 1 2 3 4 5 6 7</td>
<td></td>
</tr>
<tr>
<td>Exercise brings on my fatigue</td>
<td>0 1 2 3 4 5 6 7</td>
<td></td>
</tr>
<tr>
<td>I am easily fatigued</td>
<td>0 1 2 3 4 5 6 7</td>
<td></td>
</tr>
<tr>
<td>Fatigue interferes with my physical functioning</td>
<td>0 1 2 3 4 5 6 7</td>
<td></td>
</tr>
<tr>
<td>Fatigue causes frequent problems for me</td>
<td>0 1 2 3 4 5 6 7</td>
<td></td>
</tr>
<tr>
<td>My fatigue prevents sustained physical Functioning</td>
<td>0 1 2 3 4 5 6 7</td>
<td></td>
</tr>
<tr>
<td>Fatigue interferes with carrying out certain duties and responsibilities</td>
<td>0 1 2 3 4 5 6 7</td>
<td></td>
</tr>
<tr>
<td>Fatigue is among my three most disabling symptoms</td>
<td>0 1 2 3 4 5 6 7</td>
<td></td>
</tr>
<tr>
<td>Fatigue interferes with my work, family or</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
SF-36 Health Survey

INSTRUCTIONS: This survey asks your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.
Please answer every question by marking the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

When complete, please return the questionnaire in the envelope provided.

1. In general, would you say your health is:

(circle one)

Excelle .......................................................... 1
nt ........................................
Very .......................................................... 2
good .................................................. 3
Good .................................................. 3
Fair .......................................................... 4
Poor .......................................................... 5

2. Compared to one year ago, how would you rate your health in general now?

(circle one)

Much better now than one year ago .......................................................... 1
Somewhat better than one year ago .......................................................... 2
About the same as one year ago .............................................................. 3
Somewhat worse than one year ago .......................................................... 4
Much worse now than one year ago .......................................................... 5

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

(circle one number on each line)

<table>
<thead>
<tr>
<th>Activities</th>
<th>Yes, limited a lot</th>
<th>Yes, limited a little</th>
<th>No, not limited at all</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports.</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling or playing golf</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Activity</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Lifting or carrying groceries</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Climbing several flights of stairs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Climbing one flight of stairs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bending, kneeling or stooping</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walking more than a mile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walking half a mile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walking one hundred yards</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bathing or dressing yourself</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health? (circle one number on each line)

<table>
<thead>
<tr>
<th>Problem</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cut down on the amount of time you spent on work or other activities</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Accomplished less than you would like</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Were limited in the kind of work or other activities</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Had difficulty performing the work or other activities (for example, it took extra effort)</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)? (circle one number on each line)

<table>
<thead>
<tr>
<th>Problem</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cut down on the amount of time you spent on work or other activities</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Accomplished less than you would like</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Didn’t do work or other activities as carefully as usual</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours or groups? (circle one)

<table>
<thead>
<tr>
<th>Extent</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not at all</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slightly</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderately</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quite a</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

411
7. How much bodily pain have you had during the past 4 weeks? (circle one)

None ................................................................. 1

Very ................................................................. 2

Mild ................................................................. 3

Moderate .......................................................... 4

Severe ............................................................. 5

Very severe ...................................................... 6

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)? (circle one)

Not at all ............................................................. 1

A little bit .......................................................... 2

Moderate ......................................................... 3

Quite a bit ........................................................ 4

Extreme .......................................................... 5

Extremely .......................................................
9. These questions are about how you feel and how things have been with you during the past 4 weeks.
For each question please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks...

<table>
<thead>
<tr>
<th>All of the time</th>
<th>Most of the time</th>
<th>A good bit of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did you feel full of life?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Have you been a very nervous person?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Have you felt so down in the dumps that nothing could cheer you up?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Have you felt calm and peaceful?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Did you have a lot of energy?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Have you felt downhearted and low?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Did you feel worn out?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Have you been a happy person?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Did you feel tired?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?
(circle one)

<table>
<thead>
<tr>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>........................</td>
<td>........................</td>
<td>........................</td>
<td>........................</td>
<td>1</td>
</tr>
<tr>
<td>Most of the time</td>
<td>........................</td>
<td>........................</td>
<td>........................</td>
<td>2</td>
</tr>
<tr>
<td>Some of the time</td>
<td>........................</td>
<td>........................</td>
<td>........................</td>
<td>3</td>
</tr>
<tr>
<td>A little of the time</td>
<td>........................</td>
<td>........................</td>
<td>........................</td>
<td>4</td>
</tr>
<tr>
<td>None of the time</td>
<td>........................</td>
<td>........................</td>
<td>........................</td>
<td>5</td>
</tr>
</tbody>
</table>

11. How TRUE or FALSE is each of the following statements to you?
(circle one number on each line)

<table>
<thead>
<tr>
<th>Definitely true</th>
<th>Mostly true</th>
<th>Don’t know</th>
<th>Mostly false</th>
<th>Definitely false</th>
</tr>
</thead>
</table>

413
<table>
<thead>
<tr>
<th>Statement</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>I seem to get ill more easily than other people</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>I am as healthy as anybody I know</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>I expect my health to get worse</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>My health is excellent</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>
Hospital Anxiety and Depression Scale (HADS)

Patients are asked to choose one response from the four given for each interview. They should give an immediate response and be dissuaded from thinking too long about their answers. The questions relating to anxiety are marked "A", and to depression "D". The score for each answer is given in the right column. Instruct the patient to answer how it currently describes their feelings.

<table>
<thead>
<tr>
<th>A</th>
<th>I feel tense or 'wound up':</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most of the time</td>
<td>3</td>
</tr>
<tr>
<td>A lot of the time</td>
<td>2</td>
</tr>
<tr>
<td>From time to time, occasionally</td>
<td>1</td>
</tr>
<tr>
<td>Not at all</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>D</th>
<th>I still enjoy the things I used to enjoy:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definitely as much</td>
<td>0</td>
</tr>
<tr>
<td>Not quite so much</td>
<td>1</td>
</tr>
<tr>
<td>Only a little</td>
<td>2</td>
</tr>
<tr>
<td>Hardly at all</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>A</th>
<th>I get a sort of frightened feeling as if something awful is about to happen:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very definitely and quite badly</td>
<td>3</td>
</tr>
<tr>
<td>Yes, but not too badly</td>
<td>2</td>
</tr>
<tr>
<td>A little, but it doesn't worry me</td>
<td>1</td>
</tr>
<tr>
<td>D</td>
<td>I can laugh and see the funny side of things:</td>
</tr>
<tr>
<td>---</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>As much as I always could</td>
<td>0</td>
</tr>
<tr>
<td>Not quite so much now</td>
<td>1</td>
</tr>
<tr>
<td>Definitely not so much now</td>
<td>2</td>
</tr>
<tr>
<td>Not at all</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>A</th>
<th>Worrying thoughts go through my mind:</th>
</tr>
</thead>
<tbody>
<tr>
<td>A great deal of the time</td>
<td>3</td>
</tr>
<tr>
<td>A lot of the time</td>
<td>2</td>
</tr>
<tr>
<td>From time to time, but not too often</td>
<td>1</td>
</tr>
<tr>
<td>Only occasionally</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>D</th>
<th>I feel cheerful:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not at all</td>
<td>3</td>
</tr>
<tr>
<td>Not often</td>
<td>2</td>
</tr>
<tr>
<td>Sometimes</td>
<td>1</td>
</tr>
<tr>
<td>Most of the time</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>A</th>
<th>I can sit at ease and feel relaxed:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definitely</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>-------</td>
<td>---</td>
</tr>
<tr>
<td>Usually</td>
<td></td>
</tr>
<tr>
<td>Not Often</td>
<td></td>
</tr>
<tr>
<td>Not at all</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>I feel as if I am slowed down:</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Nearly all the time</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very often</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sometimes</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not at all</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>I get a sort of frightened feeling like 'butterflies' in the stomach:</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Not at all</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occasionally</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quite Often</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very Often</td>
<td>3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>I have lost interest in my appearance:</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Definitely</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I don’t take as much care as I should</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I may not take quite as much care</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I take just as much care as ever</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**A** I feel restless as I have to be on the move:
- Very much indeed: 3
- Quite a lot: 2
- Not very much: 1
- Not at all: 0

**D** I look forward with enjoyment to things:
- As much as I ever did: 0
- Rather less than I used to: 1
- Definitely less than I used to: 2
- Hardly at all: 3

**A** I get sudden feelings of panic:
- Very often indeed: 3
- Quite often: 2
- Not very often: 1
- Not at all: 0

**D** I can enjoy a good book or radio or TV program:
- Often: 0
- Sometimes: 1
- Not often: 2
- Very seldom: 3
Scoring (add the As = Anxiety. Add the Ds = Depression). The norms below will give you an idea of the level of Anxiety and Depression.

<table>
<thead>
<tr>
<th>Score Range</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-7</td>
<td>Normal</td>
</tr>
<tr>
<td>8-10</td>
<td>Borderline abnormal</td>
</tr>
<tr>
<td>11-21</td>
<td>Abnormal</td>
</tr>
</tbody>
</table>
APPENDIX B12
Graded WFMT Instructions

Today we are going to take a look at how you are able to use your arm. Let me tell you how we are going to go about this. First, I will give you instructions on how to do the task, and then I will show you how to do it. I will describe and demonstrate each task two times. Do not practice the task while I’m describing and demonstrating it. However, I will be happy to clarify any confusing points. Then I will say “ready, set, go” and you will do the task. It is important that you do not start until I say “go” otherwise we will need to repeat the entire task. Each of the activities you will be asked to do should be carried out as rapidly as possible. You can work on each task for up to 30 seconds. We ask that you attempt each part of the test even if you do not think that you can do it. If you are unable to carry out a task then we will go onto the next one. Again, try to do each task as rapidly as possible. Do you have any questions?
**APPENDIX B13**

**Graded Wolf Motor Function Test**

<table>
<thead>
<tr>
<th>Tasks</th>
<th>Time</th>
<th>Functional Ability</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Forearm to table (side)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) chair normal</td>
<td>0 1 2 3 4 5 6 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>b) chair raised</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Forearm to box (side)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) full height box</td>
<td>0 1 2 3 4 5 6 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>b) ½ height box and chair raised</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 Extend elbow (to side)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) 40 cm line</td>
<td>0 1 2 3 4 5 6 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>b) 28 cm line</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 Extend elbow with weight (to side)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) 40 cm line</td>
<td>0 1 2 3 4 5 6 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>b) 28 cm line</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 Hand to table</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) chair normal</td>
<td>0 1 2 3 4 5 6 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>b) chair raised</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 Hand to box</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) full height box</td>
<td>0 1 2 3 4 5 6 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>b) half height box</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 Reach and retrieve</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) 40 cm line</td>
<td>0 1 2 3 4 5 6 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>b) 28 cm line</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 Moving foam stick</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) supination then pronation</td>
<td>0 1 2 3 4 5 6 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>b) pronation only</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tasks</td>
<td>Time</td>
<td>Functional Ability</td>
<td>Comments</td>
</tr>
<tr>
<td>--------------------</td>
<td>------</td>
<td>--------------------</td>
<td>----------</td>
</tr>
<tr>
<td>Lift washcloth</td>
<td></td>
<td>0 1 2 3 4 5 6 7</td>
<td></td>
</tr>
<tr>
<td>a) appropriate grasp</td>
<td></td>
<td>0 1 2 3 4 5 6 7</td>
<td></td>
</tr>
<tr>
<td>b) inappropriate grasp</td>
<td></td>
<td>0 1 2 3 4 5 6 7</td>
<td></td>
</tr>
<tr>
<td>Flip light switch</td>
<td></td>
<td>0 1 2 3 4 5 6 7</td>
<td></td>
</tr>
<tr>
<td>a) appropriate grasp</td>
<td></td>
<td>0 1 2 3 4 5 6 7</td>
<td></td>
</tr>
<tr>
<td>b) inappropriate grasp</td>
<td></td>
<td>0 1 2 3 4 5 6 7</td>
<td></td>
</tr>
<tr>
<td>Lift pen</td>
<td></td>
<td>0 1 2 3 4 5 6 7</td>
<td></td>
</tr>
<tr>
<td>a) appropriate grasp</td>
<td></td>
<td>0 1 2 3 4 5 6 7</td>
<td></td>
</tr>
<tr>
<td>b) inappropriate grasp</td>
<td></td>
<td>0 1 2 3 4 5 6 7</td>
<td></td>
</tr>
<tr>
<td>Lift cotton balls</td>
<td></td>
<td>0 1 2 3 4 5 6 7</td>
<td></td>
</tr>
<tr>
<td>a) appropriate grasp</td>
<td></td>
<td>0 1 2 3 4 5 6 7</td>
<td></td>
</tr>
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<td>b) inappropriate grasp</td>
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<td>Lift basket</td>
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<tr>
<td>b) table level height</td>
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APPENDIX B14
MAL instructions

The purpose of this test is to examine how much and how well you use your more affected arm when you are not in our laboratory. You will use two separate rating scales to describe how much and how well you use your weaker arm while you are doing specific activities. Please note that you can give half ratings if that best describes your performance of the activity in question. If for some reason you do not perform these tasks, we will try to determine why. We will first discuss how much you do each of the tasks with your weaker arm and then we will discuss how well you do them using your weaker arm. It is important that you realise that these questions are about what you actually do outside the laboratory and not what you think you may be able to do with your weaker arm. There are no right or wrong answers; simply select the ratings you believe best describe what you do. Do you have any questions?
APPENDIX B15
Motor Activity Log V2—Score sheet

Code: .............................................................................. Date: ...
Visit (e.g. BL/pre/post etc): ..........................................................
Period of time referred to: .........................................................
Examiner: ..............................................................................

<table>
<thead>
<tr>
<th>Task</th>
<th>Amount Scale</th>
<th>How well scale</th>
<th>No Code</th>
<th>Comments</th>
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<tr>
<td>1) Pull back chair</td>
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</tr>
<tr>
<td>2) Take off socks or stockings</td>
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<tr>
<td>3) Pick up a telephone receiver</td>
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<tr>
<td>4) Carry an object in your hand</td>
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<tr>
<td>5) Open a door</td>
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<tr>
<td>6) Use a fork, knife or spoon to eat</td>
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<tr>
<td>7) Close a Zipper</td>
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<tr>
<td>8) Fasten belt or brassiere</td>
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<td></td>
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<tr>
<td>9) Button a shirt or blouse</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>10) Pulling on trousers or underwear with both hands</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11) Put on socks</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>12) Dry back or hair</td>
<td></td>
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</table>

Codes for recording No responses
   1. I used unaffected arm entirely
2. Someone else did it for me
3. I never do that activity because it is impossible (e.g. never wear shirt/blouse)
4. I did not have the opportunity to do that activity since I last answered the questions
APPENDIX B16
Sleep diary, version 1, October 2006

Baseline Day 1 PART 1 (30mins-1 Hour after waking):

Today's Date ....................... Current Time ....................... 

★ How refreshed did you feel upon waking up?
Not at all refreshed .......................... Very refreshed

★ How was the quality of your sleep last night?
Very Bad .................................. Very good

★ When did you go to bed last night (lights out)? ................. hours (24 hours clock)

★ How long did it take you to fall asleep? ............... hours............... mins

★ If you woke in the night, please list the times you awoke and duration (if you woke more than 4 times, please add the extra details on the reverse of this page):

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<th>Time</th>
<th>Duration Awake</th>
<th>Reason</th>
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<td>2</td>
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<td>(24 hr clock)</td>
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<tr>
<td>4</td>
<td>(24 hr clock)</td>
<td></td>
</tr>
</tbody>
</table>

★ When did you finally wake up this morning (not including night awakenings mentioned above)? ........................ hours (24 hours clock)

★ When did you finally get up this morning? ........................ hours (24 hours clock)

★ How long did you sleep last night (time from falling asleep to waking in the morning, excluding all waking periods)? .............. hours............... mins

★ Using the scale below, please circle the number which corresponds to how sleepy you currently feel.

1 2 3 4 5 6 7 8 9
Very Alert Alert-normal level Neither alert nor sleepy sleepy but no effort to keep awake Very sleepy, great effort to keep awake
Because of my fatigue........ (although this assumes you have fatigue, if yes problem please circle '0' for each response.

- reduce my workload or responsibilities
- motivated to do anything that requires physical effort
- able to maintain physical effort for long periods
- difficult to make decisions
- able to finish tasks that require thinking
- wed down in my thinking
- limit my physical activities

Baseline Day 1 PART 2 (1-2 Hours before bed):

Current Time......................

* Did you take any naps today? No □ Yes □ If yes: how many naps in total...........and for how long in total? ...............hours.............mins

* Using the scale below, please circle the number which corresponds to how sleepy you currently feel.

1 2 3 4 5 6 7 8 9
Very Alert Alert-normal level Neither alert nor sleepy sleepy but no effort to keep awake Very sleepy, great effort to keep awake

* Please read each statement carefully with the prefix 'Because of my fatigue' and circle your response.
of my fatigue. (although this assumes you have fatigue, if you do not, please circle '0' for each response.)

- s alert
- reduce my workload or responsibilities
- s motivated to do anything that requires physical effort
- double maintaining physical effort for long periods
- difficult to make decisions
- s able to finish tasks that require thinking
- wed down in my thinking
- limit my physical activities

Additional Information (please report any additional information regarding your sleep last night and/or how you felt today):
APPENDIX C: Case Tables For All Participants

Case Tables

1. Stroke Patients
2. Control Participants
APPENDIX C.1

**Stroke Patient Case Table**

Case table for all stroke patients (n=61) involved in the study. Missing data is indicated by a dash (-). Listed medications are those other anti-coagulants such as Warfarin and Aspirin.

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<th>BMI</th>
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<th>Chronicity (years)</th>
<th>MMSE</th>
<th>Dysphasia</th>
<th>NART</th>
<th>Education Level</th>
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APPENDIX C2: Control Case Table

Control Participants Case Table

Case table for all control participants (n=61) involved in the study. Missing data is indicated by a dash (-).

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* Zipiclon taken irregularly
APPENDIX D: Supplement For Study 2

Additional Data

1. Scatter plots for weekday and weekend matching parameters from the sleep diary and actigraphy recordings.
2. Scatter plots for weekday and weekend matching parameters from the sleep diary and actigraphy recordings.
3. Scatterplots for significant correlations between sleep parameters, daytime functioning and residual upper limb motor ability tests.
APPENDIX D1

Scatterplots for Sleep and Motor Ability

Significant correlations between sleep parameters (drawn from actigraphy recordings), daytime functioning (drawn from the sleep diaries) and residual upper limb motor ability tests.
Appendix E: Supplement For Study 3

1. Data table for left stroke EEG expressed as a percentage of controls.
2. Data table for right stroke EEG expressed as a percentage of controls.
3. Brain map values for left stroke vs controls.
4. Brain map values for right stroke vs controls.
5. Hemisphere ratio values for left stroke group and controls.
6. Hemisphere ratio values for right stroke group and controls.
# APPENDIX E1

## Data Table for Left Stroke EEG Expressed as a Percentage of Controls

Pre motor task raw data for left stroke group and matched controls. Data presented as mean raw power density values (±1 SE) and t values (d/26) for ipsilateral (C3), contralateral (C4) hemispheres and right hemisphere (C4) for control. One tailed t-test completed on logged values of raw data. Values in bold are p<0.05, * p<0.01, ** p<0.005, *** p<0.001.

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<thead>
<tr>
<th>Frequency Bin (Hz)</th>
<th>Ipsilateral Hemisphere vs. Controls</th>
<th>Contralateral Hemisphere vs. Controls</th>
<th>Ipsilateral Hemisphere vs. Contralateral Hemisphere</th>
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<td>3.57±1.17</td>
<td>0.46 ±0.65</td>
</tr>
<tr>
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<td>3.76 ±0.52</td>
</tr>
<tr>
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</tr>
<tr>
<td>6</td>
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<td>0.60±0.09</td>
<td>2.42 ±0.52</td>
</tr>
<tr>
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<td>1.46±0.37</td>
<td>0.94 ±0.36</td>
</tr>
<tr>
<td>9</td>
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<td>1.82±0.46</td>
<td>0.45 ±0.66</td>
</tr>
<tr>
<td>10</td>
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<td>2.64±0.94</td>
<td>-0.38 ±0.71</td>
</tr>
<tr>
<td>11</td>
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<td>1.27±0.23</td>
<td>-0.20 ±0.84</td>
</tr>
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<td>0.91±0.21</td>
<td>0.69 ±0.49</td>
</tr>
<tr>
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<td>0.96±0.13</td>
<td>0.96±0.26</td>
<td>0.76 ±0.64</td>
</tr>
<tr>
<td>14</td>
<td>0.91±0.21</td>
<td>0.99±0.33</td>
<td>0.66 ±0.95</td>
</tr>
<tr>
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<td>0.91±0.24</td>
<td>1.11±0.35</td>
<td>-0.66 ±0.51</td>
</tr>
<tr>
<td>16</td>
<td>0.75±0.16</td>
<td>1.17±0.36</td>
<td>-1.02 ±0.32</td>
</tr>
<tr>
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<td>18</td>
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<tr>
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<td>-1.23 ±0.23</td>
</tr>
<tr>
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<td>0.21±0.04</td>
<td>0.55 ±0.59</td>
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<td>0.69 ±0.49</td>
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APPENDIX E2

Data Table For Right Stroke EEG Expressed as a Percentage of Controls

Pre motor task raw data for right stroke group and matched controls. Data presented as mean raw power density values (±I SE) and t values (df34) for ipsilateral (C4), contralateral (C3) hemispheres and left hemisphere (C3) for control. One tailed t-test completed on logged values of raw data. Values in bold are p<0.05, * p<0.01, ** p<0.005, *** p<0.001.

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<th>Raw Power Density (μV²/Hz)</th>
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<td>Ipsilateral vs. Controls t p</td>
<td>Contralateral Control t p</td>
<td>Contralateral vs. Controls t p</td>
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<td>20</td>
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<tr>
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<tr>
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<tr>
<td>29</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>30</td>
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</tr>
<tr>
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<tr>
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<tr>
<td>Theta</td>
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</tr>
<tr>
<td>Delta</td>
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### APPENDIX E3

#### Brain Map Values For Left Stroke vs Controls

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<td>1.15</td>
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</tr>
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</tr>
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</tr>
<tr>
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<td>-2.13</td>
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### Thera

<table>
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<th>Control</th>
<th>t Test</th>
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<td>0.46</td>
<td>1.00</td>
</tr>
<tr>
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<td>0.87</td>
<td>0.41</td>
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### Notes

- The mean and standard error (SE) are calculated for each data point.
- The t test values indicate the significance level for each comparison.
- Positive t test values indicate a significant difference favoring the Left Stroke group.
- Negative t test values indicate a significant difference favoring the Control group.
- The symbol * indicates statistical significance at the 0.05 level.

---

446
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Note: The table includes mean and standard error values for each condition, along with t-tests and p-values.
### Brain Map Values For Right Stroke vs Controls

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APPENDIX E5

Hemisphere ratio values for left stroke group and controls

One tailed t test against 1 for between hemisphere ratios (C3/C4) of left stroke group and controls. Values in bold are p≤0.05, * p≤0.01, ** p≤0.005, *** p≤0.001

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Hemisphere Ratio Values for Right Stroke Group and Controls

One tailed t test against I for between hemisphere ratios (C4/C3) of right stroke group and controls. Values in bold are p<0.05, * p<0.01, ** p<0.005, *** p<0.001.

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Appendix F: List of Abbreviations

Fatigue Impact Scale (FIS)
Oxford Handicap Scale (OHS)
Tinetti Test (TT)
Basic Activities of Daily Living (BADL)
Modified Rankin Scale (MRS)
Motricity Index (MI)
Scandinavian Stroke Scale (SSS)
Stroke Severity Scale (SSVS)
Multidimensional Health Locus of Control Scale (MHLC)
Geriatric Depression Scale (GDS)
Beck Depression Inventory (BDI)
Activities of Daily Living (ADLs)
Apathy Evaluation Scale (AES)