Invited Chapter to **PROGRESS IN BRAIN RESEARCH**

Title: Noisy and individual, but doable: Shift-work research in humans

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Short running title: Shift-work research in humans

ABSTRACT

Working around the clock is common for many occupations, as diverse as nurses, truck drivers, physicians, steel workers, and pilots. Each shift-work profession is individual in more aspects than just work hours and individual work scenarios, each posing a different impact on the health of workers. Related health problems in shift-workers, therefore, are also diverse and encompass sleep problems, metabolic and cardiovascular system disturbances, as well as cancer. Little is known about how all these individual factors influence a shift-worker's health status, partly because many shift-work studies show inconsistent results. In addition, these individual factors create many methodological difficulties for researchers who investigate such work scenarios. This chapter presents examples from our laboratory and field studies of shift-workers, which emphasise the importance of taking individual circumstances into account. Both study approaches, laboratory and field based, are needed to fully account for the difficulties that shift-work studies pose on both workers and researchers. Finally, understanding the mechanisms that underpin inter-individual differences in response to shift-work will advance our understanding of how to design better and healthier shift-work schedules in the future.

Key words: Chronotype, Social jetlag, Stress, Sleep, Health, Shift-work, Cardiovascular system

Introduction

Studying shift-workers means studying individuals at a variety of workplaces employed in different and often flexible working time arrangements. Studying the effects of shift-work on health is thus complex and poses challenges to researchers to control the many individual factors – economic, social and biological – that characterise modern shift-work settings. Each of these individual factors by themselves and in combination may negatively affect health (Kantermann et al., 2010, Knutsson, 2004, Saksvik et al., 2011). Therefore, the effects of shift-work on health are very diverse (Costa, 2003b, Sookoian et al., 2007, Kantermann, 2008, Wang et al., 2011) and studies on shift-work and health are often inconsistent in their findings. Related health problems in shift-workers broadly fall into four categories: (i) sleep problems (Åkerstedt et al., 2007, Åkerstedt and Wright, 2009, Folkard et al., 2005, Lemos et al., 2009, Moreno et al., 2004), (ii) metabolic problems (Esquirol et al., 2009, Sookoian et al., 2007, Wang et al., 2011), (iii) cardiovascular system disturbances (Boggild and Knutsson, 1999, Hublin et al., 2010, Puttonen et al., 2010), and (iv) cancer (Erren et al., 2008, Stevens, 2009). Notably, none of the reported health problems constitute an occupational disease unique to shift-workers. By contrast, all of these health problems belong to a group of "normal" epidemiological and age-related health problems. Interestingly, many of these epidemiological health problems occur more frequently and at an earlier age in shift-workers than in the normal non-shift working population. To date, however, no study has tested the hypothesis that exposure to shift-work is associated with advanced ageing. Obviously, such a broad range of health problems affects a worker's quality-of-life and life expectancy, which makes shift-work studies highly relevant not only for the health care system but for society as a whole. Little is known about how these individual factors interact at an economic, social and biological level and how these interacting factors then affect health (Kantermann et al., 2010, Kantermann and Roenneberg, 2009, Knutsson, 2004, Wang et al., 2011). Therefore, there is a need to understand the mechanisms underlying shift-work associated health deteriorations to design better shift-work conditions.

The complexity of the issue extends to understanding disruptions to the internal circadian timing system by shift-work. Human daily behaviour and physiology, including our mental and physical performance, shows a clear time-of-day variation, which is governed by an endogenous circadian timing system. In temporal isolation, such internal clocks produce *internal* days, which in humans are usually longer than 24 hours (Aschoff, 1965, Brown et al., 2008). Under normal conditions, circadian clocks are synchronised to the 24-h day by zeitgebers (Roenneberg et al., 2003). The light-dark cycle is the most important zeitgeber for the human circadian timing system (Freedman et al., 1999, Kantermann et al., 2007, Panda et al., 2002, Roenneberg et al., 2007b). Synchronisation of circadian clocks to a zeitgeber cycle, called *entrainment*, is an active process that works via response characteristics which, in turn, depend on *internal* time of day (Roenneberg et al., 2003, Roenneberg et al., 2010): during the late *internal* night or early morning, light shortens the *internal* day, and lengthens it during *internal* afternoon or evening, whereas there is little or no response to light around *internal* midday. These *principles of entrainment* are important for understanding the disruption of the body clock in rotating shift-workers when they are exposed to light at unusual and continually changing times. The relationship between *external* and *internal* time is called *phase of entrainment*, which shows large inter-individual differences, often referred to as *chronotype* (Roenneberg et al., 2007a). In non-shift work populations, for example, late chronotypes have been shown to be at higher risk of suffering from bipolar disorders (Wood et al., 2009), headaches (Bruni et al., 2008), seasonal depression (Natale et al., 2005), depression (Levandovski et al., 2011), and fibromyalgia syndrome (Kantermann et al., 2012).

To date, only a few shift-work studies have implemented the concept of *internal time* into their analyses. Complete adjustment of the circadian clock to shift-work is rare, even in permanent night workers in conventional shift-work settings (Folkard, 2008). Circadian adjustment supporting work environments have been identified only in highly specialised settings such as offshore oilrigs (Barnes et al., 1998, Gibbs et al., 2002) or workstations in Antarctica (Lund et al., 2001, Midwinter and Arendt, 1991, Ross et al., 1995). As an alternative, recent shift-work simulation studies have demonstrated that establishing a compromise circadian phase position facilitated adjustment in people switching between night shifts and day work (Lee et al., 2006, Smith et al., 2008, Smith and Eastman, 2008, Smith et al., 2009). These observations may be of interest in the future design of shift schedules. In addition, the few studies that have implemented the concept of *internal time* into their study design show evidence of chronotype-specific differences in shift-work adjustment: later chronotypes exhibited higher shift-work tolerance and less rigid sleep-wake behaviour compared to earlier chronotypes (Duffy et al., 1999, Härmä, 1993, Östberg, 1973, Vidacek et al., 1988). Furthermore, later chronotypes appeared to accumulate less sleep deficit during a shift-work cycle (Folkard and Monk, 1981). These findings were also supported by reports of better sleep quality in later chronotypes trying to sleep during the daytime (Khaleque, 1999). Later chronotypes are therefore assumed to suffer less from night shifts (Burgess et al., 2002, Folkard and Monk, 1981, Hildebrandt and Stratmann, 1979). By contrast, later chronotypes appear to be more challenged by early morning shifts (Åkerstedt and Torsvall, 1981, Griefahn et al., 2002). This latter result has also been confirmed in our study discussed in more detail below (Kantermann et al., unpublished-a). Another important factor in this context is the effect of age, since younger people have later chronotypes and chronotype, in turn, advances with age (Roenneberg et al., 2007a). These findings have been used to explain why older, earlier chronotypes, on average, withdraw sooner from shift-work than younger, later chronotypes (Bohle and Tilley, 1989, Costa et al., 1989, Hauke et al., 1979). In addition, a study (Moreno et al., in press) involving 514 nursing professionals, found among the day workers that the higher the morningness, the more satisfied the workers were with their job. By contrast, among night workers, job satisfaction was associated with sleep quality and hospital seniority rather than diurnal preference. Although this study has been conducted with night workers, these findings reinforce the idea that individual preferences for evening activities cannot be seen as the sole factor leading to shift-work adaptation. Currently, however, there are no conclusive data showing that later chronotypes would develop less (chronic) health problems than earlier chronotypes when working in alternating shifts.

There are a number of comprehensive review articles on shift-work and health (Costa, 2003b, Kantermann et al., 2010, Knutsson, 2004, Wang et al., 2011). Aiming to add to this existing pool of knowledge, in this chapter we present results from both our field and laboratory studies on shift-workers. These studies emphasise the importance of taking individual factors – especially *internal time* – into account. Clearly, the insights gained when we study people under controlled laboratory conditions (e.g., by strictly controlling circadian phase, posture, diet, light exposure, etc.) helps to design better field studies and interpret findings gathered in noisy and less controllable real-life settings. Therefore, we have structured this chapter into two sections: (1) studies performed in the field, and (2) studies performed under controlled conditions in the laboratory.

1. Studying shift-workers in real-life settings

Stress and adverse effects on health in shift-workers has been related to adverse working conditions, poor adaptation of work and social life, sleep deprivation and interference in the synchronisation of the internal circadian clock by the light-dark cycle (Costa, 2003a, Kantermann et al., 2010, Knutsson, 2003, Thompson, 2009, Wang et al., 2011). Therefore, we have performed a number of shift-work field studies, to investigate acute stress (measured via levels of morning and evening cortisol), as well as chronic stress (measured via arterial stiffness as a surrogate for atherosclerotic risk), and consequences of shift-work demand as estimated by the incidence rate at work.

1.1. Cortisol awakening response and stress in shift-working truck drivers

In a cross-sectional study (Ulhôa et al., 2011), we investigated the individual cortisol awakening response (CAR) (Dahlgren et al., 2009) in truck drivers working day shifts (n=21) or 'irregular shifts' including night work (n=21). In addition, we investigated subjective and objective sleep and cardiovascular blood parameters in these workers. All participants worked for the same transportation company in Brazil. Objective sleep was obtained from actigraphy measurements. Salivary cortisol samples for the CAR analysis were obtained at two time points: at waking time and at 30 minutes after waking time. In addition, cortisol at bedtime was also measured. These three cortisol samples were collected both during a workday and on a day off work. The 'irregular' shift-workers showed a significantly higher waist-hip ratio and elevated VLDL-cholesterol. In addition, the 'irregular' shift-workers reported more tiredness after work, more disturbances due to truck vibration, and less job demand compared to day workers. In addition, the 'irregular' shift-workers were employed as truck drivers for longer than the day workers. Cortisol collected both in the morning and at bedtime in the 'irregular' shift-workers was positively correlated to short sleep duration, low job satisfaction, total cholesterol, HDL, LDL, VLDL, and triglycerides. Day workers showed higher cortisol at 30 minutes after waking and a higher CAR on their workdays compared to their days off. The 'irregular' shift-workers had higher cortisol levels on their days off compared to the day workers. These results suggest that the 'irregular' shift-workers might have had a prolonged stress response on their days off, since they had higher cortisol levels on these days compared to their workdays (Figure 1). An earlier study of 470 truck drivers reported extended working hours as a stressor at work, and this was associated with minor psychiatric disorders (Ulhôa et al., 2010). Regulation of working hours and avoidance of extended work hours may thus be an important way to reduce stress in truck drivers. Future studies of shift-workers with irregular work hours are warranted for a more detailed investigation of stress responses.

INSERT FIGURE 1 about here

1.2. Individual "shift-work load" in rotating shift-workers

Regarding the effects of shift-work on the individual, the different shift types has become subject to investigation. For example, clockwise rotating schedules (e.g. rotating from the morning shift to the late shift to the night shift) compared to counter-clockwise rotation (e.g. rotating from nights to mornings to late shifts) is considered the shift direction of choice as it is assumed that clockwise rotation causes less sleep and circadian rhythm disruption (Costa, 2003a, Härmä, 1993, Knauth, 1993). Conclusive evidence, however, in particular on chronic health parameters, is limited. For the first time in a field study of rotating shift-workers, we have measured pulse wave velocity (PWV) in fast clockwise (CW) and slow counter-clockwise (CC) shift-workers compared to day workers (DW) (Kantermann et al., unpublished-a). The aim of this study was to assess cardiovascular risk using arterial stiffness in workers undertaking different shift rotations. Male workers (n = 77, mean (± SD) age 42 ± 7.6 yrs) in a Belgian steel factory with at least 5 years experience in their current work schedule participated. All participants completed questionnaires covering demographics, details about their shift-work schedule, health, and stimulant consumption. All shift- and day workers also completed the Munich Chronotype Questionnaire for shift-workers ($MCTQ_{shift}$) (Juda, 2010). Data obtained from the $MCTQ_{shift}$ were used to calculate each worker's chronotype (time of mid-sleep on free days (MSF_{sc}), corrected for the sleep deficit on workdays) and the amount of their social jetlag (difference between the time of mid-sleep on workdays (MSW) and free days (MSF)) (Wittmann et al., 2006) in each work shift (early-, late-, night-, and day shift). Shift-workers also self-rated how sleep, social and work life were affected due to working shifts. In 63 workers we measured PWV, in addition to blood pressure (BP) and heart rate (HR) on one morning shift between 08:00 and 12:30 h (no caffeine/smoking/exercise). There were no differences in chronotype, age, body mass index (BMI), waist-hip-ratio (WHR), BP, HR, smoking, and coffee consumption between shift-workers and day workers. By contrast to day workers, however, shift-workers (CW and CC combined) reported more stomach and digestion problems, and more weight fluctuations. In addition, as expected, shift-workers had more social jetlag. In previous investigations, social jetlag has been found to vary with chronotype and work shift (Juda, 2010, Vetter, 2010). This finding was also corroborated in our study. The highest level of social jetlag was found for early chronotypes while doing night shifts, with only a small amount of social jetlag observed for early chronotypes during morning and late shifts. Late chronotypes, however, showed the highest amount of social jetlag on the morning shift, although this was less than observed in the early chronotypes on night shifts. The two shift-work groups (CW, CC) did not differ in the ratings of how shift-work affected their sleep, social and work life. In all workers combined (CW, CC, and DW), HR and average social jetlag were significantly positively associated (r = 0.309, p = 0.021 adjusted for age). This association also was significant for DW alone (r = 0.679, p = 0.015 adjusted for age). There was no statistically significant difference in PWV between fast CW, slow CC and day workers (DW).

In a subsequent step, and to introduce a new and simple concept to shift-work research, we calculated the "individual shift-work load" (ISL), to measure the impact of a worker's schedule, using the following two formulae:

(i) For shift-workers: $ISL_{shift} = (SJL / \#WD) * \#SW_{years}$

(ii) For day workers: $ISL_{day} = (SJL / \#WD) * \#W_{years}$

The individual shift-work load (ISL) is composed of a worker's individual social jetlag (SJL, difference between time of mid-sleep on workdays (MSW) and free days (MSF), Wittmann et al., 2006) divided by the total number of days per shift cycle (#WD; representing speed of rotation) and multiplied by the individual's total number of years of exposure to shift-work ($\#SW_{years;}$). As the day workers were not exposed to shift-work, the respective number of years of employment at the current company ($\#W_{years}$) was used instead. There was a significant positive correlation (r = 0.493, p = 0.005) between "individual shift-work load" and pulse wave velocity (PWV_{aBP}, which is PWV adjusted for age and BP). This finding provides first evidence that arterial stiffness assessed by PWV and the chronic strain of shift-work (estimated from measures of social jetlag) may be inter-related. The group differences in both speed and direction of shift rotation, the small number of subjects, and its cross-sectional design are limitations of this study. We hope, however, that the findings from this pilot study will initiate future studies of this kind. Indeed, more studies in workers employed in shift schedules with different speeds and directions of rotation but working in the same work setting are needed.

1.3. Effect of shift type on incidence rate in rotating shift-workers

Previous studies have shown that the night shift in rotating shift schedules is characterised by the lowest levels of alertness and vigilance and the highest amount of sleep deprivation and hence has been suggested to lead to an elevated incidence risk in night workers (Costa, 2003b, Folkard, 1997, Mitler et al., 1988). Studies have shown influences of, *inter alia*, work duration (length of time of being at work), start time of a work shift, number of consecutive work shifts, type of occupation, and prior sleep duration (Folkard et al., 2005), even when the work tasks were comparable across shifts (Folkard, 1997). Such findings are supported by controlled circadian laboratory studies on alertness, vigilance, sleepiness and fatigue, which show a clear 24-hour variation in these parameters (Åkerstedt, 2007, Aschoff, 1965, Cajochen et al., 1999, Dijk et al., 1992, Graw et al., 2004) and deterioration in these parameters after sleep deprivation (Axelsson et al., 2008, Dinges et al., 1997, Doran et al., 2001, Franzen et al., 2008, Sallinen et al., 2008, Van Dongen et al., 2003). We investigated the incidence rate in rotating shift-workers (undertaking morning, late, and night shifts) employed in two different shift-work rotations (Kantermann et al., unpublished-b). A retrospective analysis of the incidence data from 730 male shift-workers employed in either a clockwise (e.g. rotating from the morning shift to the late shift to the night shift) or counter-clockwise rotation (e.g. rotating from the night to the morning to the late shift) with comparable work conditions at the same steel factory over a 5-year period has been performed. Morning shifts exhibited a significantly higher incidence rate compared to night shifts, independent of shift-work rotation. The incidence rate across the 24-h day did not differ between clockwise and counter-clockwise rotation. The elevated incidence rate in the morning shift at this steel factory could be related to the morning shift being the most labour-intensive one of the three work shifts in both the clockwise and counter-clockwise rotation. In addition, there could be an effect of sleep deprivation due to the early start of the morning shift at 06:00 h, which means an even earlier get up time for the workers. These findings suggest that, in addition to, or even irrespective of, work shift and direction of shift rotation, the impact of work time and work demand may have a strong modulating effect on the incidence rate.

2. Studying shift-workers in controlled laboratory settings

2.1. Advantages of laboratory studies

What is the benefit of performing studies in shift-workers under strictly controlled laboratory conditions? To answer that question, one needs to consider all the confounding factors in real life, which are very difficult to control in field studies. Such confounders encompass, *inter alia* inter-individual and intra-individual differences in shift-work history (e.g. work schedule, work tasks, number of work hours, etc.), the lighting environment both at and away from work, stress both mental and physical (which is often dependent upon job type and work load), diet, sleep duration and sleep deprivation prior and after a shift, and individual *internal time* (chronotype). Epidemiological studies, for example, often fail to take account of the exact time (especially relative to *internal* time) samples of biomarkers have been collected in relation to a shift-worker's actual work hours (Boggild and Knutsson, 1999, Sookoian et al., 2007), whereas other studies have such a control (Esquirol et al., 2009). The lack of control of confounders is not merely a matter of the number of study subjects, since there are also smaller field studies with fewer subjects that have failed to address one or more of these important points mentioned above (Adams et al., 1998, Amir et al., 2004, Rauchenzauner et al., 2009). Such confounding differences must be taken into account else substantial information that could explain group differences may be missed, for example, when studying groups employed in different shift-work rotations or when comparing shift-workers with non-shift workers. To disentangle the different causes that may contribute to the effects of shift-work on health and wellbeing, laboratory studies are able to control many factors and hence are able to manipulate single, specific variables at pre-defined time points. Shift-work simulation studies (Hampton et al., 1996, Ribeiro et al., 1998), for example, were able to demonstrate that glucose, insulin and lipid levels following food intake were dependent on a person's *internal time*. In addition, so-called 'forced desynchrony' experiments showed that circadian misalignment negatively affects metabolism (Scheer et al., 2009). To our knowledge there is only one study that has investigated real shift-workers under laboratory conditions (Simon et al., 2000), more commonly laboratory studies investigate shift-work naïve subjects that are mostly healthy and young.

Therefore, we have compared experienced shift-workers (n=11, with at least five years of shift-work experience) to matched (for age, BMI and cholesterol) non-shift workers (n=14) in their response to one night of total sleep deprivation (TSD) (as a proxy for the first night of shift-work) and recovery sleep under controlled laboratory conditions (Wehrens et al., 2010, Wehrens et al., 2011). The effect of sleep deprivation on the participants' metabolic and cardiovascular function as well as alertness, mood and performance was assessed. Both groups followed a 7-day regular sleep-wake cycle prior to the laboratory session. This was done to ensure that shift-workers were either on day shifts or days off to avoid sleep deprivation and circadian misalignment in the study subjects. The in-laboratory study protocol consisted of one night of adaptation sleep, followed by one night of baseline sleep, and one night of total sleep deprivation (30.5 h wakefulness). A subsequent daytime nap opportunity of four hours and a full recovery sleep period were provided. All measurements were performed relative to wake up time and controlled for body posture, diet and light exposure. *Post hoc* measurement of dim light salivary melatonin onset (DLMO) prior to the baseline night confirmed that there were no significant differences in circadian phase between shift-workers and non-shift workers. Compared to the non-shift workers, however, shift-workers showed a lower heart rate variability (HRV) variance and higher sympathetic activity, as well as a trend towards lower endothelial function (assessed by flow-mediated dilatation of the brachial artery) throughout the study. In addition, after the recovery sleep period, the postprandial insulin response was significantly increased and the non-esterified fatty acid (NEFA) response reduced compared to after sleep deprivation and/or baseline sleep in the non-shift workers only. In this study, the shift-workers also felt more alert, more cheerful, more elated and were calmer throughout the protocol compared to the non-shift workers (Wehrens et al., 2012). In addition, shift-workers showed a faster median reaction time (RT) compared to non-shift workers although five other psychovigilance test (PVT) parameters did not differ significantly between the two groups. These findings suggest that experienced shift-workers cope better with laboratory sleep deprivation than non-shift workers. These group differences could be explained *inter alia* by a selection bias into and out of shift-work, the absence of actual shift-work that was inherent to the laboratory study and regular scheduled sleep prior to the laboratory study. The data on HRV and endothelial function, however, suggest increased cardiovascular risk in the shift-workers, although this was not significantly affected by sleep deprivation. The observed effects of recovery sleep on metabolism in the non-shift-workers suggest a tendency towards a state of insulin resistance in non-shift workers compared to the shift-workers. This may either be a direct effect of recovery sleep or a delayed response to sleep deprivation. Such responses after recovery sleep are similar to the findings of the delayed stress response on days off in our study on truck drivers in Brazil (Ulhôa et al., 2011). The results from both these laboratory and field studies emphasise that shift-work schedules should be designed to allow for optimal physiological recovery. From a neurobehavioural point of view shift-workers may underestimate how much recovery time they actually need. A similar mismatch between the subjective perception of increased sleep deprivation and objective measures in performance has been shown previously (Franzen et al., 2008, Galliaud et al., 2008, Van Dongen et al., 2004, Van Dongen et al., 2003) and remains an intriguing aspect for future shift-work studies.

2.1. Disadvantages of laboratory studies

Despite all the advantages listed in the previous section, there is one major limitation to laboratory shift-work studies: only a small number of subjects can be studied under strictly controlled conditions. Often due to costs for research staff, consumables and laboratory space, time constraints or recruitment issues (*i.e.*, the more strict the inclusion criteria the more difficult recruitment becomes), these studies can be statistically underpowered. This latter aspect prevents detecting small differences in study parameters, especially as many biological parameters show large intra- and inter-individual variation. In addition, as laboratory studies are obviously not performed under ‘real life’ conditions, information on many aspects of shift-work is not recorded, for example, the social and economic reasons for choosing a shift-work job. In addition, shift-work simulation studies often use shift-work naïve subjects instead of experienced shift-workers. Although simulation studies on non-shift workers can show the acute effects of a shift-work schedule, they cannot assess the chronic effects shift-work poses on employees. By contrast, field studies can achieve this by studying the same subjects repeatedly and prospectively at regular intervals (presuming no worker leaves the company). However, from controlled laboratory investigations we can determine which parameters to control when performing field studies and *vice versa* – clearly a win-win collaboration.

CONCLUSION

With this overview of our laboratory and field studies on shift-workers and non-shift workers we aimed to illustrate the importance of the following aspects:

- Studying shift-workers and non-shift workers in the same work environment is imperative to best control for inter-individual variation and worksite-related effects (e.g., as we have done in a Belgian steel factory study and in the study of Brazilian truck drivers).
- Strictly controlled laboratory studies (as we have presented) on real shift-workers and non-shift workers are fundamental to understand the immediate and acute effects that shift-work and total sleep deprivation pose on health, as these studies allow for adequate matching of subjects.
- Findings from strictly controlled laboratory studies must be translated into field investigations, firstly to validate these findings and secondly to discover new aspects, which in turn can be translated back into laboratory studies – a clear win-win circulation of scientific knowledge.
- The introduction of new, non-invasive (bio-) markers into shift-work research has the potential to elucidate the underlying mechanisms of the pathophysiological pathways involved in shift-work. These new (bio-) markers, for example, are: chronotype (phase of entrainment), social jetlag (SJL), "individual shift-work load" (ISL), pulse wave velocity (PWV), heart rate (HR), heart rate variability (HRV), and flow mediated dilation (FMD).

Only by combining laboratory and field studies and by comparing these data, will it be possible to identify the individual predictors that constitute important set-points in the interaction between shift-work and health status. Furthermore, although not explicitly discussed in this chapter, these data can then be subjected to shift-work models. Such models will help, not only to rapidly generate new hypotheses for future studies (both in the laboratory and in the field), but also to develop better and healthier shift-work schedules that take individual factors into account (Figure 2). Although there remain some profound gaps in our knowledge, for example how shift-work puts one individual but not another at risk, the existence of good research tools and our current knowledge makes this noisy and individual shift-work research doable.

INSERT FIGURE 2 about here

ACKNOWLEDGEMENTS

TK is supported by the DFG (German Research Foundation), SMTW is supported by the BBSRC (BB/I008470/1), MU and CM are supported by Santander, USP, FAPESP and Surrey (2011/50169-6), and DJS is a Royal Society Wolfson Research Merit Award holder. The research was supported by an EU Marie Curie Research Training Network grant (CT-2004-512362), 6th Framework project EUCLOCK (018741) and Stockgrand Ltd., University of Surrey, Guildford, UK.

We especially thank our participants at ArcelorMittal Industeel Belgium in Charleroi, the truck drivers in São Paulo, Brazil, and the participants in our laboratory shift-work study. We also thank Shelagh Hampton, Françoise Duboutay, Myriam Kerkhofs, Damien Haubruge, and Arno Schmidt-Trucksäss for their valuable help with the studies. Without their contribution these studies would not have been made possible.

CONFLICTS

None to declare

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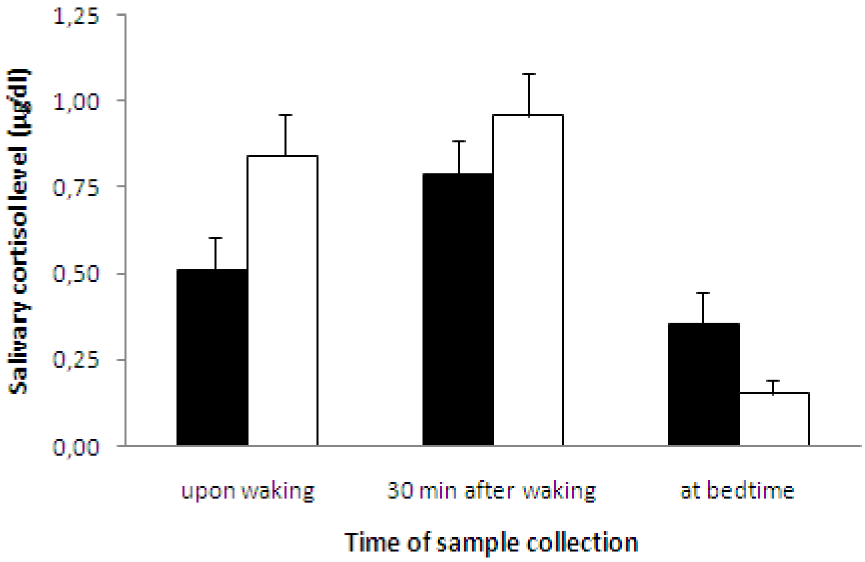
Figure Legends

Figure 1 Salivary cortisol levels (mean ± SEM) according to the time of sample collection in irregular shift workers. Samples were collected upon awaking, 30 minutes after waking and at bedtime during a work day (■) and during a day off (□).

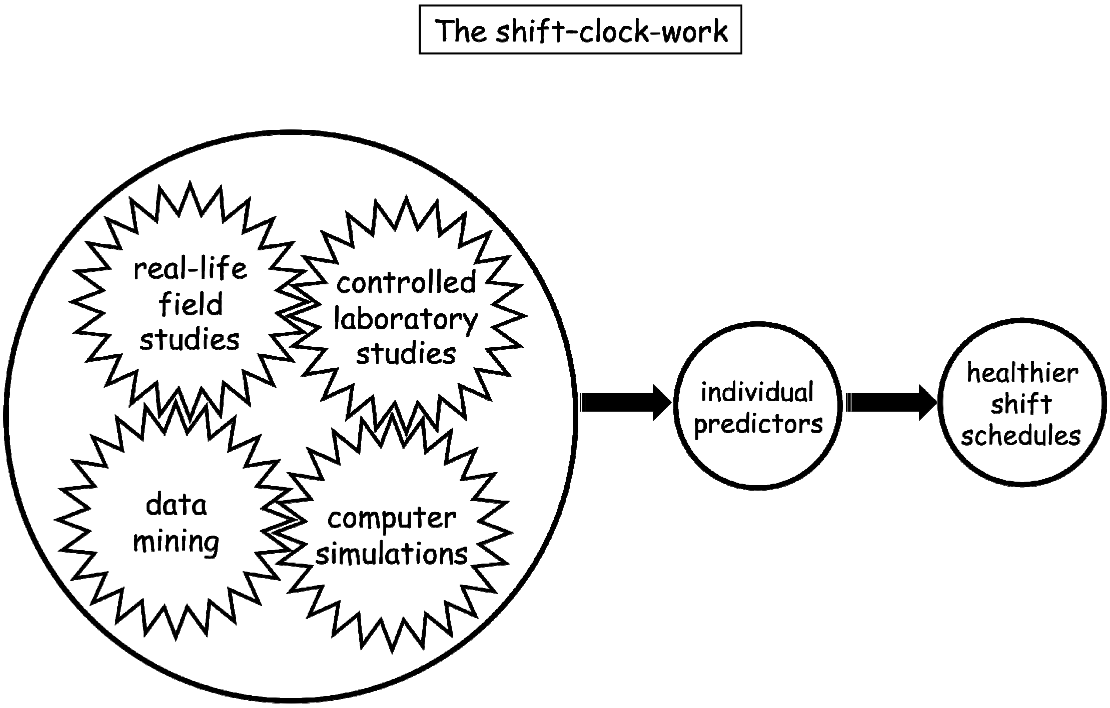
Figure 2 The "shift-clock-work" illustrates the inter-connectivity between field studies performed in real life and controlled laboratory investigations helping to cross-validate data, which in turn drives databases for data mining and computer simulations. The outcome is "individual predictors" helping to design better and healthier shift-work schedules. (Figure modified from Kantermann et al., 2010).

Figure 1



Salivary cortisol level (µg/dl)
1,25
1,00
0,75
0,50
0,25
0,00
upon waking
30 min after waking
at bedtime
Time of sample collection

Figure 2


The shift-clock-work
real-life field studies
controlled laboratory studies
data mining
computer simulations
individual predictors
healthier shift schedules