Human Temporal Perception and the Circadian System: Effects of Age, Sleep Pressure and Light

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Summary

Temporal control is essential to adaptive behavior but not all aspects of this faculty are well understood. The intention of this work was to examine cognitive aspects of temporal regulation in humans, to identify the mechanisms sub-tending them and to delineate their connections to a well-characterized instance of organismic temporal control, the circadian and homeostatic modulation of many bodily functions.

The first experiment described in this work addressed what may be understood as the direct cognitive complement to circadian timing i.e., cognitive temporal orientation on the twenty-four hours scale. This capacity was operationalized here as the conscious awareness about time of day in absence of external time cues.

Using the technique of simple verbal report in two age groups studied under conditions of high vs. low sleep pressure, we observed a remarkable pattern. Both age groups tended to overestimate actual time-of-day under both conditions, sleep satiation and prolonged wakefulness, but overestimation of actual time-of-day was more pronounced in *older* participants and significantly so under conditions of *s*ustained wakefulness. Interestingly, under both sleep pressure conditions, both age groups displayed a circadian oscillation in estimation errors which ran parallel to the endogenously generated oscillation in core body temperature. In the *younger* participants, under conditions of *s*ustained wakefulness, this pattern was combined with an overall increase in the magnitude of estimation errors, such that the degree of error observed in this group of participants approached the one observed in the *older* participants during the last part of the protocol (i.e., under high sleep pressure

conditions). Our results gave evidence that interval timing may provide a basis for cognitive temporal orientation via a temporal integration mechanism,

In two further studies, we aimed at characterizing circadian and sleep-wake homeostatic modulations in interval timing, with the secondary aim of corroborating our hypothesis about the relationship between this faculty and cognitive temporal orientation.

We assessed interval timing in young healthy male participants for several stimulus magnitudes (3.75–15 sec) using the methods of temporal production and temporal reproduction concurrently under conditions of sustained wakefulness and controlled multiple 75 min sleep episodes (i.e., nap protocol, low sleep pressure).

During the *production* task conducted under *c*ontrolled napping conditions (i.e., low sleep pressure), all durations were over-produced (i.e., produced intervals were longer than the actual target intervals) and a slight linear increase in this behavior across the 64 h protocol was observed. During the *reproduction* task carried out under the same (napping) conditions, smaller durations (3.75, 5, 7.5 sec) were over-reproduced but larger durations were under-reproduced, particularly during the biological night.

During temporal *production* conducted under conditions of *s*ustained wakefulness however, all durations were under-produced (i.e., produced intervals were shorter than the actual target intervals). During the *reproduction* paradigm conducted under these (sustained wakefulness) conditions, smaller durations were over-reproduced, as was the case under napping conditions, especially so during the second half of the protocol, after 20 h of sustained wakefulness (high sleep pressure conditions). As observed in the data collected under controlled napping conditions, larger durations (10, 15 sec) were under-reproduced under conditions of sustained wakefulness. Remarkably, absolute levels and time courses of responses in both studies varied greatly not only across different methods and stimulus magnitudes employed, but especially so across different participants.

Our findings contrast with those reported in earlier studies in that they suggest a rather weak effect of circadian phase on interval timing and a slightly stronger effect of elevated sleep pressure. The results also indicate that circadian phase and sleep pressure probably interact with attentional or working memory-related processes, rather than with the rate at which a hypothesized pacemaker of the standard model of interval timing emits pulses, as it is often assumed.

Due to the large degree of inter-individual variability observed for many aspects of interval timing in both studies, inferences with respect to the underlying mechanisms made on the basis of these data have to be taken with caution; the complex pattern observed probably also accounts for part of the disagreement and conflicting or inconclusive results with respect to circadian and homeostatic modulation of interval timing currently present in the literature. The large degree of inter-individual variability in interval timing behavior probably reflects the influence of other variables that are not accounted for adequately in most comparable studies and the most important of these variables may be the strategy adopted by the participants in executing the timing tasks.

Finally, we present an investigation into the effects of differential computer screen illumination technologies on temporal perception during human-machine interaction. Recent observations on the impact of exposure to light emitting diode (LED) LCD-screen illumination on physiology and cognition are complemented by our finding that this technology also differentially affects interval timing in that responses are typically lowered under LED-screen illumination conditions when compared to exposure to a NON-LED illuminated computer screen. This result is in good accordance with recent findings on the impact of specific illumination technology on arousal and availability of attentional resources and can be explained by assuming that the increased availability of these resources under LED-screen illumination translate into an elevation in pacemaker rate and increased permeability of the attentional switch of the standard interval timing model, thus leading to the observed changes in interval timing. Our results demonstrate that computer screen background illumination represents a possible pathway for the control and manipulation of interval timing during human-machine interaction, and may thus be employed to improve usability and reliability in the use of information technology.

Taken together, we have demonstrated in this work, that data collected using the seemingly primitive tasks of interval timing may help elucidate more complex and abstract aspects of temporal adaptation such as temporal orientation by proposing the straightforward and testable hypothesis that interval timing may act as a critical measure and basis to a temporal path integration mechanism.

On the other hand, we were able to show, that interval timing needs to be tested under more strictly controlled conditions within a sophisticated design that takes into account the effects of different methods and stimulus durations as well as those of subject-specific characteristics. Data collected in this manner may then be analysed by using a random coefficient modeling approach. This statistical method does not treat inter-individual variability as noise, as it essentially happens in analysis of variance; instead, it is especially powerful at meaningfully integrating inter-individual differences in analysis and interpretation.

Our results regarding the effects of differential screen illumination technologies on interval timing should be of great interest to the development of biologically and ergonomically optimized user interfaces in information technology.

To summarize, the findings with respect to the influences of light, circadian phase and homeostatic sleep pressure suggest that interval timing seems to be rather robust with respect to *circadian* challenges. The influence of *homeostatic sleep pressure* on interval timing can be considered to be slightly stronger, but interval timing clearly is affected by the external influence of *illumination conditions*. We show that interval timing behavior is relatively robust with respect to modulations by the circadian system and may be more strongly determined by other subjects-specific or external variables.

The challenge will be to expand upon these findings in further studies that include a concurrent assessment of cognitive temporal orientation and interval timing during various interventions. In combination with the use of a random coefficient modeling approach to data analysis, this strategy will certainly help attain a clearer and more coherent view on the functional relationships delineated in the current work, at the same time accommodating inter-individual differences in their exact form and emphasis.

Contents

1 Introduction[1]

The capacity to reliably sense, process, and react to relevant features of the physical environment is a hallmark of life and when this faculty is compromised, inadequate and possibly debilitating performance ensues. During the course of evolution, increasingly sophisticated and robust receptive and processing structures have formed that provide the organism with dependable and multi-modal representations of its surroundings.

While the physical stimulus as well as the corresponding receptors seem to be plainly and transparently given for some modalities, characterization of these entities is much more elusive in others. Thus, while we have a relatively good understanding of the stimuli and receptors for the visual, auditory or tactile modalities, the structures and processes mediating perception of e.g., space or time seem to involve much less well understood mechanisms, which probably operate at a greater level of abstraction. With respect to the appreciation of time for example, the classical terminological framework of sensation and perception provides a valuable basis on which to understand its psychophysics but simply seems to fail to accommodate many physiological and anatomical facts in an adequate manner. It is not clear in any way, in which sense time is to constitute a physical stimulus and what form the corresponding receptors and downstream mechanisms should take.

And yet, as Fraisse [Fraisse, 1957] illustrates, most organisms seem to be highly competent in appreciating and navigating the temporal architecture of their environment: Birds migrate in spring and in autumn [Bartell and Gwinner, 2005]; water lilies close before

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ebb in order to prevent their drying out [Pieron, 1910]; bees learn to return to a food source at a particular time of day [Wahl, 1933]; hummingbirds time the interval between successive visits to flowers that replenish at different rates [Crystal, 2006]. Precise timing is ubiquitous and of great importance to human behavior as well, be it in social interactions, traffic or many other activities. Time forms an important axis that spans the space in which life takes place and every organism has to find its way along the viable paths within this complex structure.

One possible way to approach this vast and intricate structure may be to indicate the different scales at which time is appreciated (cf. figure 1.1). A spatial metaphor also helps in better understanding this complex. In these terms, a basic prerequisite to dealing successfully with the contingencies of the environment seems being able to appreciate 'locations', 'distances' and 'trajectories' within this structure on the basis of which more complex features of the temporal scenery can then be apprehended.

But how does an organism gain awareness of these features?— In the following paragraphs, we want to take a closer view at two defined domains in which awareness of time plays a central role and try to shed some light on how this awareness is achieved. We then look at a point of contact between these two domains with the aim of attaining greater insight into possible links between basic timing capacities and the more sophisticated and less researched feature of cognitive temporal orientation.

1.1 Biological Time

Nearly all organisms have developed systems and structures which facilitate an internal representation of geophysical cycles and thus endow them with a form of anticipatory homeostasis. In mammals, the core of these systems is formed by the circadian master clock, which is located within the suprachiasmatic nuclei of the anterior hypothalamus (cf. figure 1.2). Drawing upon transcrip-

Time [ms]		Scale	Mechanisms
0.001			
0.01			
		Microsecond Processing	
0.1		Sound Localization	Axonal Conduction Delays
1		Echolocation	Variable Inhibition
		Millisecond Processing	
10		Motion Detection	?
100		Motor Coordination	
1000	← 1 sec	**Second Processing**	
		Interval Timing	?
10^4			
	← 1 min		
10^5			
10^6			
	←1 hour		
10^7			
	← 1 day	**Circadian Rhythms**	
10^8		Sleep/Wake	Transcription/Translation
10^9		Appetite	Suprachiasmatic Nuclei

Figure 1.1: Scales of temporal processing. Temporal information is processed across at least twelve orders of magnitude, from the circadian rhythms of cognition and physiology to the microsecond processing sub-tending sound localization. Redrawn from [Mauk and Buonomano, 2004].

tional feedback-loops within individual neurons, these nuclei modulate many aspects of physiology and behavior either directly, or by synchronizing peripheral oscillators, via neural and endocrine signals. This system interacts with homeostatic processes in providing an adaptive framework, within which all live takes place. In particular, the homeostatic component in sleep regulation—whose physical substrate has not been clearly established yet—interacts with the circadian system in determining the characteristic modulation in arousal levels and many other variables across a day [Borbely, 1982].

Using chronobiological methods, it is possible to dissociate the effects on physiology and cognition of these two systems as well as of many of the confounding variables present in everyday life such as physical activity, posture or food intake. The so-called constant-routine protocol [Mills et al., 1978; Czeisler et al., 1985; Refinetti, 2005] involves constant bed rest under constant illumination with frequent, equally spaced meals. In combination with an imposed ultra-short or ultra-long day (forced desynchrony) as it is implemented e.g. in the NAP protocol [Cajochen et al., 2001], this setup is adequate to unmask the endogenous rhythmicity determined by the circadian system; if conducted under sustained wakefulness, the dependent variables are under the combined influence of circadian and homeostatic regulation.

1.2 Psychological Time

While the circadian system endows the organism with a means to adapt to predictable, cyclically changing conditions in the environment, this system does not constitute a suitable basis for interaction with spontaneously occurring events of variable duration—organisms are in need here of more flexible timing mechanisms. Research on humans and non-human animals, including invertebrates such as the bumblebee, has shown that mechanisms do indeed exist which allow not only for an appreciation of simultaneity, succession

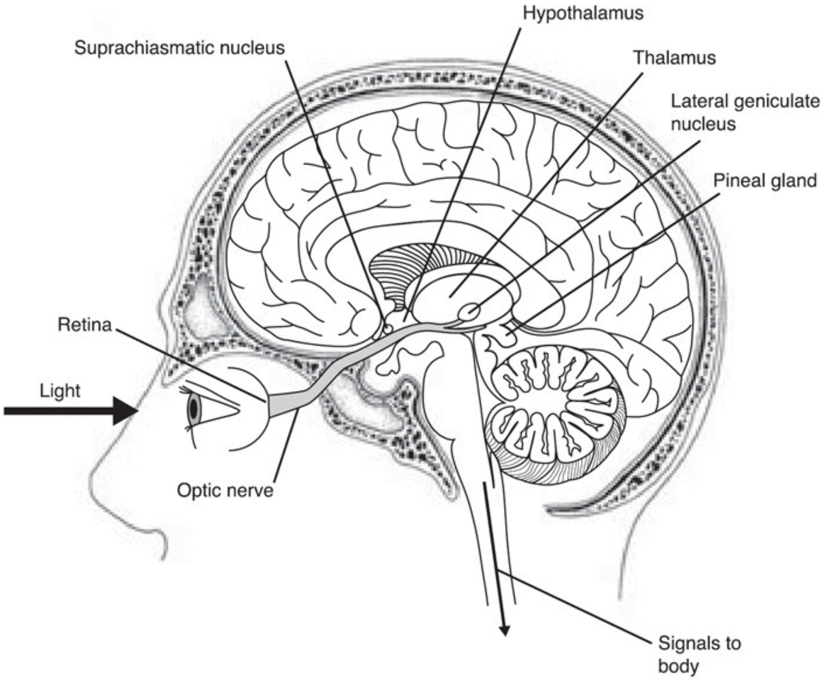

Figure 1.2: The suprachiasmatic nuclei of the anterior hypothalamus form the master clock of the circadian system and drive oscillations in a large number of biological and physiological variables [Moore, 1997]

and temporal order but also for the timing of arbitrary durations—a faculty commonly referred to as interval timing—and thus predict irregularly occurring events, without the need to refer to geophysical markers or internal representations thereof [Hills, 2003; Skorupski and Chittka, 2006; Boisvert and Sherry, 2006].

A major focus in human timing research has been on the characteristics, influencing factors and sub-tending mechanism of duration perception [Eagleman et al., 2005; Grondin, 2010]. In this research, subjective duration is defined as the temporal interval estimated or produced by a participant and is different from objective duration which corresponds to the physical duration of an event or process [Bindra and Waksberg, 1956; Grondin, 2010].

In research on interval timing subjective duration is compared to objective duration and in prospective studies on interval timing i.e., studies in which the participant knows beforehand what his or her task will be, the most commonly used methods are the following [Clausen, 1950; Bindra and Waksberg, 1956; Wallace and Rabin, 1960]:

Production — The participant is presented a symbolic (e.g., numerical) representation of a given target duration in conventional units (e.g., seconds). Upon request, the participant produces the target interval via a motor act e.g., by holding down a push-button for the required duration or by pressing a response key after the required duration has subjectively elapsed. If the duration produced by the participant is smaller than the target duration, we speak of under-production; if it is larger, we speak of over-production.

Estimation — The participant gives an (e.g., verbal) estimate in conventional units on the duration of a 'carrier' stimulus (e.g., tone) presentation. If the duration estimate is larger than the target stimulus, we speak of over-estimation. Conversely, if the duration estimate is smaller than the target duration, we speak of under-estimation.

Reproduction — The participant reproduces the duration of a 'carrier' stimulus (e.g., tone) presentation via a motor action, e.g., by holding down a push-button for the required duration or by pressing a response key after the target duration has subjectively elapsed. We speak of over-reproduction, if the participant's response was greater than the stimulus and of under-production in the opposite case.

Comparison — The participant compares the lengths of two target intervals presented by means of 'carrier' stimuli (e.g., tones). Upon request, the participant makes a judgement as to which duration was greater, e.g., verbally or by selectively pressing one of two response keys.

As a common feature to interval timing, typically, timing performance shows scalar properties, that is, the coefficient of variation (standard deviation/mean) in responses gathered during an experiment is constant across different ranges of stimulus durations. The shape of the distributions is approximately Gaussian [Hinton and Meck, 1997]; the distributions of responses to different stimulus magnitudes thus superimpose, when scaled by relative time (cf. figure 1.3).

On the other hand, as has been emphasized by a number of authors [Fraisse, 1984; Bindra and Waksberg, 1956], the experimental results on interval timing do not always allow for an easy comparison, a fact that certainly contributed to the somewhat unordered state of affairs in the literature on interval timing. It is thus conceivable that the different methodologies and even the different durations applied in research on interval timing measure different processes. Whereas behavior collected during e.g., time production experiments typically shows a linear trend in that the participants systematically over- or under-produce target durations, irrespective of stimulus magnitude, in time reproduction behavior, a progressive relative shortening of reproduced durations with respect to stimulus durations is often observed [Poeppel and Giedke, 1970; Wackermann and Ehm, 2006; Wackermann, 2007].

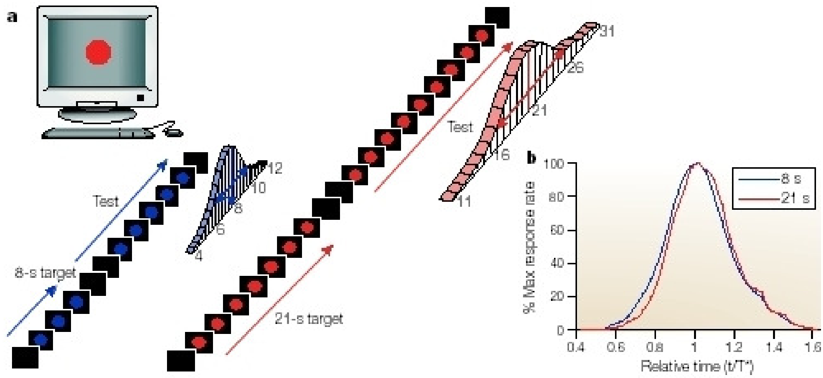

Figure 1.3: Scalar timing; (a) In a specific reproduction paradigm, participants are first trained on particular target durations (e.g., 8 s and 21 s). Participants are then asked to reproduce the target interval during test trials; the responses typically distribute normally around the target interval with a width proportional to the target duration. (b) When the response distributions are scaled and superimposed, they demonstrate scalarity at the behavioral level. [Buhusi and Meck, 2005]

In spite of these caveats, many of the results yielded by research on interval timing can be accommodated within a framework developed during the last fifty years or so. The seminal studies on the relationship between body temperature and the perception of short durations carried out by M. François [Francois, 1927] and H. Hoagland [Hoagland, 1933] around 1930, were among the first to establish a link between interval timing and the general kinetic properties of physiological processes; these authors demonstrated that manipulation of body temperature produces modifications in interval timing: When body temperature is elevated artificially or naturally, a given interval is subjectively perceived or estimated to be extended; in contrast, produced durations are depressed under these conditions. On the other hand, a decrease in body temperature entails a compression in subjectively perceived intervals and extended productions.

Upon these foundations, twenty years later, M. Treisman [Treisman, 1963] grounded his formulation of an internal-clock model of interval timing which is able to explain these seemingly contradictory findings in a natural manner. The clock mechanism consists of three main parts (cf.figure 1.4): a pacemaker, an accumulator and a comparator. The pacemaker emits periodic or stochastic pulses at a mean constant rate, probably with a period much less then a second [Hinton and Meck, 1997]. The pulses emitted by the pacemaker are gated—via a switch controlled by attentional processes—into the accumulator. The number of accumulated pulses increases monotonically with elapsed time and it thus constitutes an internal representation of the perceived duration that can be stored transiently in a working memory system for comparison with the content of a reference memory, which contains a long-term memory representation of the approximate number of pulses accumulated on past trials. The comparator continuously compares the value in the accumulator with the value stored in reference and thus allows the organism to decide on an adequate temporal response.

In the case of elevated body temperature, the hypothesized pacemaker emits pulses at higher rate which leads to the accumulation

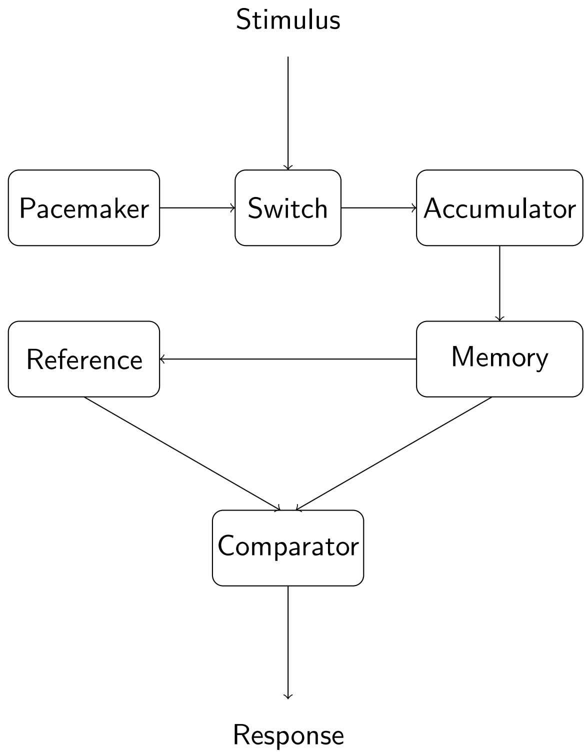

Figure 1.4: Outline of the pacemaker-accumulator model of interval timing. The pacemaker emits pulses which are gated into the accumulator and working memory components via an attention-controlled switch. The comparison of the working memory contents with a reference memory forms the basis for overt behavior. Redrawn from [Wearden, 2004].

of a given number of pulses within a briefer period of time and production is thus shortened. When a given interval is evaluated using the estimation task however, the increased number of pulses accumulated during that defined period leads to an overestimation. An analogous explanation can be given for the case of depressed body temperature and many other (e.g., pharmacological—via stimulants or depressants that act via dopaminergic and norepinephrinergic pathways [Wittmann et al., 2007; Cheng et al., 2006; Tinklenberg et al., 1976; Arzy et al., 2008]) manipulations can be explained along these lines.

While the model described here continues to represent the dominating theoretical framework within which interval timing is commonly explained, it should not be left un-noted that a broad spectrum of alternative theoretical approaches exists [Wackermann and Ehm, 2006; Staddon and Higa, 1999; Ivry and Schlerf, 2008; Spencer et al., 2009], including models that avoid the postulate of a central, dedicated timing mechanism but instead hypothesize timing to be a distributed intrinsic property of neural networks. In our discussion of interval timing however, we mostly stay within the dominant framework of the pacemaker-accumulator model.

Another factor of interest to this work which possibly affects the pacemaker speed of the internal clock is exposure to light of different intensities and spectral compositions. A number of studies have examined the impact on interval timing in the seconds to hours range of intensity [Geer et al., 1964; Delay and Richardson, 1981; Hancock et al., 1994; Aschoff and Daan, 1997; Morita et al., 2007] and spectral composition [Katsuura et al., 2007; Huang et al., 2009] of lighting conditions, including, in some cases, the interaction of these parameters with time-of-day [Morita et al., 2007; Katsuura et al., 2007; Huang et al., 2009] and the effects reported have been mostly been explained in terms of the effects of these factors on pacemaker speed due to changes in arousal levels but also via the increased availability of attentional resources.

Clearly, the pacemaker is not the only component sensitive to interventions: The switch that gates the pulses emitted by the pacemaker into the accumulator is thought to be controlled by attentional mechanisms which might explain attentional influences on interval timing (cf. 'A watched pot never boils' vs. 'Time flies when you are having fun'). If attention is directed to the passage of time, the switch is predominantly closed, allowing pulses emitted by the pacemaker to reach the accumulator. The total number of pulses accumulated during a certain period of time under these conditions is thus larger than under conditions in which attention is distracted from temporal information, and this leads to larger duration estimates. Other stages of the pacemaker-accumulator model such as working- and reference memory systems constitute further candidate targets to experimental manipulation of interval timing.

The concept of a clock-like mechanism constituting the basis for the organismic representation of short durations continues to dominate theorizing and research, but the precise anatomical and physiological correlates of its functional components remain subject to debate (figure 1.5). The pattern however emerges, that sub-cortical structures such as the basal ganglia or cerebellum may play the role of the pacemaker with prefrontal and parietal cortices sub-tending duration accumulation as well as the attentional and executive aspects involved [Correa et al., 2006]:

Specifically, Ivry and colleagues [Hazeltine et al., 1997; Ivry, 1996; Ivry and Spencer, 2004] hypothesized that the cerebellum might act as the pacemaker that generates the pulses which serve as the basis for temporal judgments. According to the authors, the pulses are accumulated in the prefrontal cortex which they identify with the working memory component of the pacemaker-accumulator model; working memory is continuously updated by the action of the basal ganglia. A different mapping between cortical and sub-cortical structures and the components of the pacemaker-accumulator model is proposed by Meck and colleagues, who attribute the role of the pacemaker to the substantia nigra [Meck, 1996, 2005]. The pulses emitted by this structure reach the globus pallidus, which acts as the accumulator, via the striatum (switch). From here it reaches the prefrontal cortex, which is the seat of the reference memory and

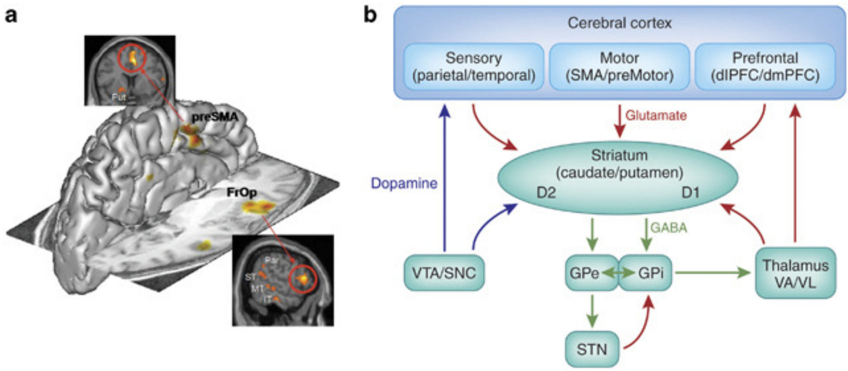

Figure 1.5: Corticostriatal circuits involved in interval timing (a) human functional imaging data recorded during an interval timing paradigm reveal participation of the preSMA and the frontal operculum in temporal processing (b) some of the anatomical structures that probably participate in interval timing; blue lines: dopaminergic input; green lines: gabaergic input; red lines: glutamatergic input. [Coull et al., 2011]

of the comparison mechanism. In contrast, Harrington et al. identify the basal ganglia as the pacemaker [Harrington and Haaland, 1999; Rao et al., 2001] which interacts with attentional processes via the right parietal cortex. The pulses are accumulated in the premotor area and compared to the standard duration via the dorsolateral prefrontal cortex. Lewis and Miall [Lewis and Miall, 2003, 2006] make a clear distinction between circuits supporting automatic timing and circuits sub-tending more controlled aspects of timing, respectively.

A much less thoroughly researched aspect of temporal control is that of cognitive temporal orientation. While it seems clear now, that physiology is informed about the current time of day by a biological clock, the mechanisms by which humans and other animals keep track of their position within the geophysical cycle of night and day on a cognitive level is not clear. Naturally, under normal conditions, the necessary information is directly given by environmental cues such as fluctuations in light and temperature levels as well as social interaction. There is evidence however, that animal and human subjects are able to keep track of time during temporal isolation as well and while a large amount of behavioral data on this problem, especially in animals, can be explained by recurrence to the circadian pacemaker directly influencing behavior, research on human participants raises doubts about a direct link between the output of the circadian system and cognitive temporal orientation [Macleod and Roff, 1936; Vernon and McGill, 1963; Thor and Crawford, 1964]. A clarification of this mechanism is especially desirable in light of the many neurological and psychiatric conditions in which orientation in time can be disturbed of absent (such as may occur e.g., in dementia or as a consequence of ischemic strokes) as well as with respect to the increasing number of working environments in which natural time cues are not reliably given [Aziz and Warner, 2005; Giannakopoulos et al., 2000; Berrios, 1983; O'Keeffe et al., 2001].

1.3 Aims of this work

In the present work, we assessed the impact of circadian and sleep-homeostatic challenges on interval timing, as well as the effects of light on this faculty. These factors are assumed to provide reliable and systematic probes into the mechanisms sub-tending temporal perception and may also disclose the connections between these mechanisms and physiological state or the effects of external stimuli. The influence of these factors on interval timing has been studied before but previous studies revealed contradictory results, probably due to incompatibilies in methods and stimulus magnitudes between the different experimental paradigms. In the present work, we thus aimed at employing a range of conditions which allow for comparison with literature and hopefully identify sensitive and stable features of interval timing and allow for inferences about the underlying mechanisms and their relationship to lighting conditions and the circadian and sleep-homeostatic systems. Specifically, if the main variable affected by differential illumination or circadian and homeostatic challenges is indeed the rate at which the pacemaker of the pacemaker-accumulator model emits pulses as has been proposed before, we would expect a relatively uniform modulation by these factors across several stimulus magnitudes within one task, but not necessarily so across different tasks. As an example, modulations in temporal reproduction cannot be explained in a straightforward manner in this way, as the duration reproduced in this task is the result of a comparison process with the encoded duration in relative terms. It is independent of the absolute rate at which the pacemaker emits pulses. Another aim of this work was to characterize cognitive temporal orientation and possibly trace back the observed behavior to findings obtained in interval timing research. Due to their possible relevance to psychiatric and neurologic considerations, we were also interested in the effects of age on cognitive temporal orientation in this experiment. It is not clear how temporal orientation arises and traditional attempts at explaining this phenomenon are not satisfactory. We intended to establish a link and test a promising and possibly widely applicable hypothesis in this context, namely that temporal orientation, at least under some circumstances, could be closely tied to interval timing mechanisms.

2 Impact of Age, Sleep Pressure and Circadian Phase on Time-of-Day Estimates[1]

[1]Published as: Späti, J., Münch, M., Blatter, K., Knoblauch, V., Jones, L.A. and Cajochen, C. Impact of age, sleep pressure and circadian phase on time-of-day estimates. *Behavioural Brain Research*, **2009**, Vol. 201, pp. 48–52

Abstract

Orientation and self-location within the temporal fabric of the environment involves multiple organismic systems. While temporal self-location on the physiological level has been known for some time to be based on a 'biological clock' located within the hypothalamus, the mechanisms that participate in temporal position finding on the cognitive level are not yet fully understood.

In order to probe the mechanisms that underlie this faculty, verbal estimates on time-of-day were collected at 3.75 h-intervals from 16 young (7 m, 8 f; 20–31 years) and 16 older (8 m, 8 f; 57–74 years) subjects in a balanced crossover design during 40-h epochs of prolonged wakefulness and 40-h epochs of sleep satiation spent under constant routine conditions.

An overestimation of clock time during prolonged wakefulness was found in both age groups, with significantly larger errors for the older group (young: 0.5 ± 0.2 h; older: 1.5 ± 0.2 h, $p < 0.05$). In both age groups, estimation errors ran roughly parallel to the time course of core body temperature. However a significant interaction between time of day and age-group was observed (rANOVA, $p < 0.05$): younger subjects exhibited similar estimation errors as the older subjects after 16 hours of prior wakefulness, whereas the latter did not manifest decrements under high sleep pressure.

Data collected under conditions of sleep satiation also displayed a diurnal oscillation in estimation errors and a general overestimation (young: 0.8 ± 0.2 h; older: 1.3 ± 0.3 h, $p < 0.05$). Here however, the age-groups did not differ significantly nor was there an interactive effect between time of day and age-group.

The effects of age, duration of wake time and circadian phase on temporal position finding are in line with predictions based on the idea that awareness about current position in time is derived from interval timing processes.

2.1 Introduction

Orientation and self-location within the temporal environment plays a critical role in any organism's adaptive behavior. A well characterized system serving this purpose on the *physiological* level is the circadian master oscillator situated within the suprachiasmatic nuclei of the hypothalamus. Drawing upon transcriptional and translational feedback loops, this structure provides the organism with information about its current position within the environmental daily light-dark cycle. Sensory inputs act as 'zeitgebers' i.e., as signals controlling the synchronized run of internal and external time (circadian entrainment) [Moore, 1997] and, via its neural and hormonal output signals, the master oscillator allows the organism to anticipate and prepare for changes in the physical environment that are associated with day and night. It thereby ensures that the organism will 'do the right thing' at the right time of day, and it provides internal temporal organization so internal changes take place in coordination with one another [Vitaterna et al., 2001]. Dislocations between external time and its physiological correlate as well as alterations in the phase relationships between different physiological parameters can have detrimental health-related consequences [Rajaratnam and Arendt, 2001]; Among the many conditions that have been linked to circadian misalignment are cardiovascular, respiratory, endocrine, rheumatological, psychiatric and neurological diseases (for references see [Rajaratnam and Arendt, 2001]).

The mechanisms that underlie temporal self-location and orientation on the *cognitive* level and their potential connections to the circadian system are still poorly understood [Macleod and Roff, 1936; Thor and Crawford, 1964; Vernon and McGill, 1963]. Whereas some species employ information about time of day to anticipate food availability [Pizzo and Crystal, 2002] and others use time compensated sun compass orientation to navigate long distances [Reppert, 2007], the competence of temporal self-location on the diurnal scale has seemingly become dispensable in humans with the advent and proliferation of precise time-telling devices. Its undiminished relevance can however be sensed from situations in which its function is compromised. Blatant dislocations between external time and its mental representation may occur e.g., in association with organic and functional mental disorders (such as schizophrenia or strokes) [Joslyn and Hutzell, 1979] and are a hallmark of dementia [Berrios, 1983; Giannakopoulos et al., 2000], but milder and transient distortions in orientation for time and temporal self-location are part of everyday life: The bewilderment we may experience upon emerging from the fictional world of an absorbing film or the fleeting moments of perplexity we may undergo upon awakening from an unscheduled nap may serve as examples. Additional relevance for the topic arises from the proliferation of working environments in which the most important of natural time cues, illumination levels, no longer ensure reliable orientation. A better understanding of the mechanisms involved in temporal self-location may also help elucidate the basis of mental time travel (imagined projection of one's temporal position to the past or the future) and, more broadly speaking, the processes that interact to produce the distinct percept of having a stable and continuous 'self' located in—and moving across—time and space.

In spite of the diversity in approaches that address the issue of cognitive temporal orientation and self-location and that range from research on time-place learning in animals [Carr and Wilkie, 1997] to anthropological psychiatry [Lehmann, 1967], models of this faculty are coarse and little is known about the mechanisms and substrates that mediate it. The establishment of quantitative theories of temporal orientation/self-location in a diurnal context (judgments about time of day) is complicated by the fact, that a relationship between this capacity and interval timing i.e., the appreciation of durations in the seconds-to-hours range is often implicitly presupposed in the human literature [Campbell et al., 2001]. The assumption that humans and non-human animals in some way make use of duration judgments to infer their current location in time seems plausible. However, research on time-place learning in animals [Carr and Wilkie, 1997; Van der Zee et al., 2008] and on timed awakening in humans [Aritake et al., 2004] point to a critical involvement of entirely different processes in temporal self-location.

Here, we thus aimed at investigating the role of interval timing in temporal self-location. Specifically, we hypothesized that judgments about *durations experienced* serve a function for self-location within time which is reminiscent to the role estimates on *distances travelled* play for self-location within space: While navigating through space, humans and non-human animals continuously integrate cues from proprioception, inertial sensors and optical flow to infer distances covered and thus arrive at an estimate on their position relative to a starting point (spatial path integration). In moving through *time*, knowledge about one's current temporal location could be informed by judgments about stretches of time (i.e., durations) travelled with respect to a (temporal) starting point (temporal path integration). If this really were the case, then the inferences about temporal position drawn from duration judgments should be susceptible to factors known to modulate the latter.

Therefore, we chose to manipulate factors that are known to have a systematic impact on duration judgments and to test temporal self-location (operationalized as time-of-day judgments during temporal isolation) performed under the influence of these factors against the predictions that would ensue from the assumption of interval timing acting as sketched above (temporal path integration) in temporal position finding:

Circadian phase Based on the compression in subjectively perceived duration that reportedly accompanies decreased core body temperature [Wearden and Penton-Voak, 1995], we expected subjects to underestimate the time spent in temporal isolation (and thus clock time) w.r.t. the average, during the lower part of the core body temperature cycle. Conversely, elevated core body temperature dilates a given interval's perceived duration, presumably leading to relatively positive deviations from actual clock time in time-of-day judgments.

Duration of wake time Increasing sleep pressure, which leads to a shortening in subjectively perceived duration [Miro et al., 2003], is expected to be reflected in a decreasing component in clock time estimates across an epoch of extended wakefulness.

Age As a result of the expansion of subjectively perceived durations with age [Block et al., 1998], we expect older subjects to display relatively more (w.r.t. the average) positive deviations in their clock-time estimates than younger subjects.

2.2 Methods

2.2.1 Participants

Sixteen healthy young (8 m, 8 f, mean age 25 $\pm$ 3.5 y, age range 20–31 y) and 16 healthy older volunteers (8 m, 8 f , mean age 65 $\pm$ 5.5 y, age range 57–74 y) successfully completed the study. All participants were non-smokers, free from medical, psychiatric, neurologic and sleep disorders (Pittsburgh Sleep Quality Index [Buysse et al., 1989] score $\leq$ 5) and average chronotypes (Horne-Ostberg Morningness-Eveningness [Horne and Ostberg, 1976] score between 12 and 23) as assessed by screening questionnaires, a physical examination and a polysomnographically recorded screening night. An additional neuropsychological assessment ensured that none of the older volunteers suffered motor, attentional or memory impairments. Other exclusion criteria were: shift work within three months and transmeridian flights within one month prior to the study, excessive caffeine and alcohol consumption, drug use and excessive physical activity. Young female participants started the study on days 1–5 after menses onset in order to complete the entire study block within the follicular phase. All study participants gave signed informed consent; the local Ethics Committee approved the study protocol, screening questionnaires and consent form and all procedures conformed to the Declaration of Helsinki.

2.2.2 Protocol

The entire study consisted of two study legs of 5 days each with two weeks in between. During the week prior to each study leg (baseline week) participants were instructed to maintain a regular sleep-wake-cycle (bed- and wake times within ± 30 min of a self-selected target time), which was verified via wrist activity monitors (Cambridge Neurotechnologies, UK) and sleep logs. The two study legs comprised two conditions: high sleep pressure (SD protocol) and low sleep pressure (NAP protocol), which were conducted in a balanced crossover design. Each study leg consisted of an adaptation night and a baseline night, followed by 40 h of either sleep deprivation or sleep satiation, and a recovery night. The sleep-wake schedules were calculated by centering the 8 h sleep episodes on the midpoint of each individual's habitual sleep time as assessed by actigraphy and sleep logs during the baseline week. Low sleep pressure was attained using 10 alternating cycles of 75 min of scheduled sleep (naps) and 150 min of scheduled wakefulness. In both the SD and the NAP protocol, wake episodes were spent under constant routine conditions (constant dim light levels, < 8 lux, semi-recumbent posture in bed, food and liquid intake at regular intervals, no cues on time of day. During scheduled sleep episodes, a minor shift to supine posture was allowed and lights were turned off (0 lux, for more information see [Cajochen et al., 2001].

2.2.3 Measures

Temporal orientation Cognitive temporal orientation was assessed across the 40 h constant routine episode by prompting a verbal estimate about time of day every 3.75 h (centered within the phases of wakefulness during NAP and at equivalent positions during SD). A lab technician prompted the estimate via an inter-phone by asking the subject the standard question: "What time is it now according to your opinion?". Subjects were instructed to respond spontaneously and to avoid calculations or comparable cognitive strategies to infer actual clock time. We used a set interval as opposed to randomized intervals to sample time-of-day judgments in order to keep possible masking effects constant.

Core body temperature (CBT) CBT was recorded at 20-s intervals using an in-dwelling rectal probe (Interstar, Cham, Switzerland; Therm, type 5500-3, Ahlborn, Holzkirchen, Germany). The temperature was displayed on a personal computer screen and continuously monitored by a lab technician. After the study, the recordings were visually inspected and artifacts resulting from removal or malfunction of the probe were excluded from further analysis.

2.2.4 Statistical analyses

Mean temporal orientation errors were calculated based on individual differences between clock time estimate and actual clock time; One participant from the younger group (m, 28 y) had to be excluded from further analyses because he did not comply with the test procedure. Statistical analyses of the time course in temporal orientation errors and core body temperature respectively, were carried out using ANOVA for repeated measures (rANOVA) with Huynh-Feldt's statistics and Curran Everett's alpha-corrected t-test for post-hoc tests. Correlations between temporal orientation errors and core body temperature were calculated on an individual basis and separately for the CR and the NAP protocols.

The alpha-criterion was set at $p = 0.05$. The statistical packages R (The R Foundation for Statistical Computing, Vienna, Austria; Version 2.7.0), SAS (SAS Institute, Inc., Cary, NC; Version 6.12), and STATISTICA (StatSoft Inc., Tulsa, OK; Version 6.1) were used.

2.3 Results

2.3.1 Core body temperature

A three-way rANOVA on the CBT data using the factors “sleep pressure”, “age-group” and “time of day” yielded significance for the factor “time of day” ($F(10,290) = 57.73$, $p < 0.001$), but no further significant effects or interactions.

2.3.2 Temporal orientation

A five-way rANOVA using the factors “age-group”, “gender”, “order of protocols” and the repeated factors “time of day” and “sleep pressure” (SD/NAP) on mean estimation errors revealed significant effects for the factors “time of day” ($F(10,230) = 3.5$, $p < 0.001$) and “age-group” ($F(1,23) = 4.5$, $p < 0.05$) and a significant interaction of the factors “time of day” and “sleep pressure” ($F(10,230) = 5.0$, $p < 0.001$). Other factors, including the effect of protocol order and gender did not yield significance. Separate four-way rANOVAs for the young and the older age-group respectively, yielded no significant effect for the factors “gender”, “sleep pressure” and “order of protocols” on mean estimation errors.

Sleep satiation (NAP) Under conditions of sleep satiation (NAP), young and older subjects generally overestimated time of day (young: 0.8 ± 0.2 h; older: 1.3 ± 0.3 h). This overestimation of clock time did not differ significantly between age groups, but indicated a strong temporal correlation with the time course of CBT for both age groups (Figure 1, top right panel, factor “time of day”: $F(10,290) = 3.5$, $p < 0.000$) with low (close to zero) values during the CBT minimum and high values (up to 3 h) during the plateau of the CBT maximum.

Prolonged wakefulness (SD) During SD we found an average overestimation of clock time in both age groups, with significantly higher values for older subjects (Figure 1, top left panel,

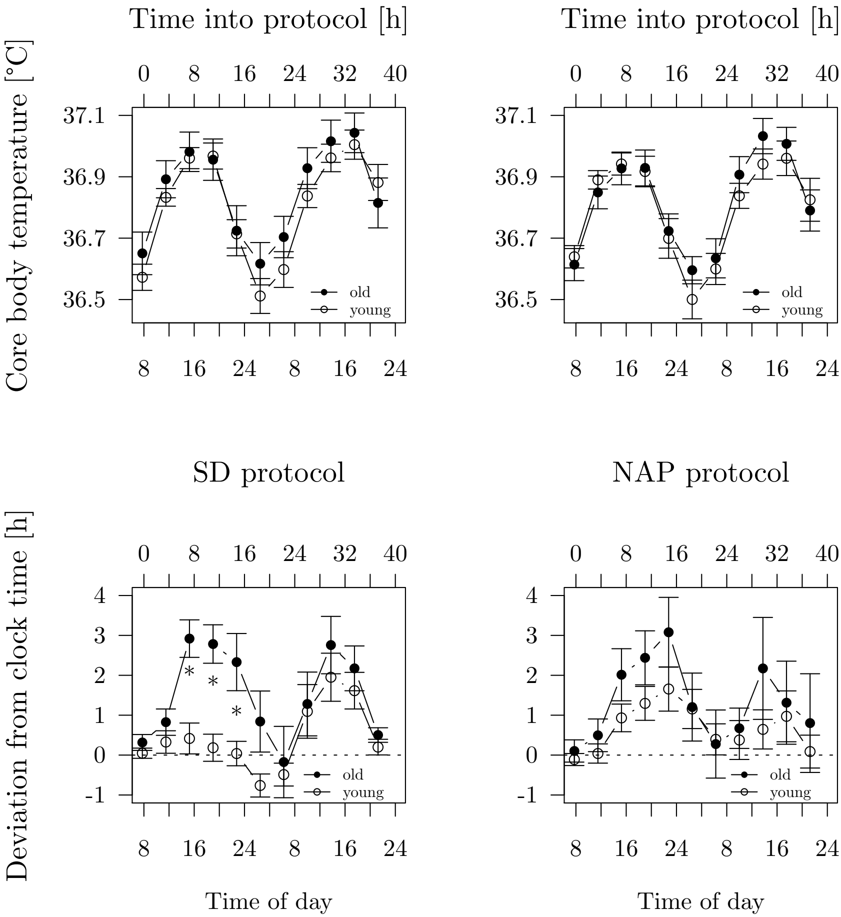

Figure 2.1: Core body temperature (upper panels) and temporal self-location (estimated clock time − actual clock time, lower panels) during CR (left) and during NAP (right) for older (filled circles) and younger (open circles) subjects. Data were binned in 3.75 h-intervals, mean ± S.E.M., n = 15 for young and n = 16 for older subjects.

young: 0.5 ± 0.2 h; older: 1.5 ± 0.2 h, factor “age-group”: $F(1,29) = 5.6$, $p = 0.025$). Estimation errors varied in a diurnal fashion in both age-groups ($F10,290 = 8.3$, $p < 0.001$), the oscillation running roughly parallel to the time course of CBT (Figure 1, bottom left panel). Furthermore, a significant interaction of the factors “time of day” and “age-group” was found ($F10,290 = 2.7$, $p = 0.04$). Post-hoc analysis on the SD data revealed significantly larger estimation errors for older subjects after 8.6 h of prior wakefulness (corresponding time of day 16.6 h), after 12.4 h (corresponding time of day 20.4 h) and after 16.1 h (corresponding time of day 24.1 h); Beyond 16.1 h of elapsed time into protocol, the mean estimation error found in the younger group increased up to the level present in the older group.

Analysis of the correlation between temporal orientation errors and core body temperature on average yielded a higher correlation for the CR condition (mean: 0.60; range: -0.39–0.81) than for the NAP condition (mean: 0.22; range: -0.67–0.09).

2.4 Discussion

During 40 hours of constant posture, ambient light and temperature conditions and without information about time of day, awareness about temporal position is clearly affected by circadian phase and duration of wake time (i.e., sleep pressure) and it is generally impaired in older participants. These findings militate in favor of the idea of interval timing processes participating prominently in temporal self-location, because critical features of the data are in line with predictions that ensue from this hypothesis:

Circadian phase The diurnal modulation in estimation errors and its striking synchronicity with the daily core body temperature cycle (particularly under CR conditions) provide strong support for an interval timing basis of self-location: A given interval is known to subjectively appear compressed or dilated as a function of lowered or elevated core body temperature, respectively [Hoagland, 1933; Bell, 1975; Wearden and Penton-Voak, 1995], and the intrinsic diurnal oscillation in core body temperature—which is ultimately driven by the circadian master clock [Krauchi, 2002]—thus entails a synchronous oscillation in the appreciation of temporal intervals [Aschoff, 1998; Poeppel and Giedke, 1970]. We argue that this diurnal oscillation in duration judgments in turn plays a pivotal role in the observed under- and overestimations of actual clock time, as it may cause a distortion in perceived 'temporal distance' travelled from the last 'temporal landmark' i.e., the last indexed (i.e., cognitively appreciated) point in time.

Duration of wake time The wake-time dependency in estimation errors observed in younger subjects are more difficult to conciliate with this idea. Previous studies on the effect of sleep deprivation on interval timing yielded inconclusive results, but they suggest a compression of perceived durations with prolonged wakefulness [Miro et al., 2003], which would entail increasingly negative (w.r.t. to the baseline) errors in temporal self-location across the SD protocol, rather than the increase observed in our data. Why this effect is seen in the younger subjects solely is a complex question. Interestingly, psychomotor vigilance task (PVT) data collected within the same study, displayed a number of similar features for reaction times assessed under low and high sleep pressure conditions [Blatter et al., 2006]: Older subjects displayed slower reaction times during the biological day in the NAP protocol, and during the first 16 h in the SD protocol. An observed PVT performance decline after SD 'was significantly less pronounced in the older than in the young subjects, so that both age groups exhibited similar performance decrements after 16 h into the SD protocol.' [Blatter et al., 2006], a feature that is in support of previous findings on the differential impact of sleep deprivation on reaction time measures in different age groups [Bonnet, 1989; Philip et al., 1999, 2004]. The significance for temporal orientation of this strikingly similar response of PVT measures in the face of sleep deprivation remains to be elucidated but could indicate an overlap in functional components of the mechanisms sub-serving these outputs and could relate to 'the reduced effect of sleep loss in the elderly due to a loss in profound build-up of homeostatic sleep pressure as indexed by a reduced relative increase of frontal EEG delta activity in the elderly during recovery sleep.' [Blatter et al., 2006; Munch et al., 2004]. Another point worth considering is the possibility that the differences found between SD and NAP are due to an interfering effect of the interspersed sleep episodes in NAP vs. the lack thereof in SD *per se*, rather than the resulting difference in sleep pressure. It is conceivable, that the regular spacing of sleep episodes during NAP provided time cues absent in SD or that a state of sleep inertia impacted duration judgments made after naps. We tried to avoid the latter problem by centering the sampling points within the wake phases during NAP and, while a possible 'pacemaker effect' of the naps during NAP cannot be excluded, a timing signal was in principle given equally for both NAP and SD conditions by the prompts on time-of-day judgments themselves.

Age The age-related differences in average estimation errors present in our data again back the notion of temporal path integration. Several studies have reported an expansion of subjectively perceived durations in older subjects, which is consistent with the larger overestimation of clock time found in this age group.

The circadian and age-related effects observed in our data are similar to those described in a study by Campbell et al. [Campbell et al., 2001]. In this study, 69 subjects living in temporal isolation for 72 h with freely chosen sleep episodes gave estimates on time at irregular intervals (mean interval = 3.1 h; s.d. = 0.85 h), from which the authors derived the measure of a mean subjective hour within a given interval. Although the overall average subjective hour for the entire group in this study lasted for 67.8 min (i.e., for each elapsed hour, subjects experienced the passage of only 53.1 min) which—in contrast with our findings—reflects an overall underestimation of clock time, the data revealed a significant effect of age with shorter subjective hours for older subjects and a diurnal modulation of the subjective hour with a relatively longer duration within the lower portion of the temperature cycle (which translates into the perception that physical time is passing at a relatively faster rate and shorter estimates) and and a relative compression of the subjective hour (which translates into the perception that physical time is passing at a relatively slower rate and longer estimates) at the upper part of the temperature cycle, two features that are consistent with our data. On the other hand, Aschoff [Aschoff, 1998] found a close temporal relationship between the estimation of time intervals in the seconds range with the circadian time course of core body temperature but no effect of the duration of wake time (but see [Miro et al., 2003]; paragraph about duration of wake time effects above). In contrast, perception of intervals in the hours range correlated positively with the duration of wake time but not with body temperature in the findings reported by Aschoff. These discrepancies are most likely due to the fact that in Aschoff's study, subjects were asked to produce time intervals whereas in Campbell's and ours studies interval timing measures were derived from time of day judgments which may fall into a completely different class of phenomena. The overall underestimation of clock time described by Campbell has been reported in number of other studies on temporal orientation and is in contrast with what we found for our sample; we believe however, that the general overestimation present in our data can be explained in terms of the experimental setting: It is a well-known feature of duration judgements that a duration appears to be dilated in retrospect, if the interval to be judged is filled with a rapid succession of novel events. In our study, and contrasting with earlier work on temporal orientation, subjects experienced frequent contextual change due to the fast-paced sequence of events (snacks, saliva samples, neurocognitive testing, etc.) imposed by the protocol which, via exaggerated retrospective duration judgments, could have led to the observed overestimations.

In spite of the aforementioned caveats, we are thus confident that our hypothesis can be fruitfully applied to the study of temporal orientation and that alternative explanations of temporal self-location under constant routine conditions (i.e., inferences from beard growth, information on the state of the circadian clock pushing into cognition) either yield predictions inconsistent with the empirical data or would require a number of additional assumptions in order to achieve the same predictive power as the concept of temporal path integration. As we followed a purely correlative approach here to back our hypothesis, we suggest further investigation of this topic using experimental interventions, e.g., active manipulation of core body temperature and even more careful control for possibly confounding variables (spacing of prompts, sleep episodes, etc). Experiments of this kind could eventually provide us with a much clearer view on cognitive temporal orientation than is currently available.

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3 Impact of Circadian Phase on Temporal Production and Temporal Reproduction in the Seconds Range[1]

[1]In preparation for submission

Abstract

Several studies have reported the finding of diurnal fluctuations in short-term interval timing i.e., in the ability to appreciate durations in the seconds range. The precise waveform of this fluctuation as well as its origin however remain subject to debate and seem to be a function of both methods and stimulus magnitudes employed. This could reflect the respective involvement of distinct mechanisms. A clear characterization of interval timing with respect to circadian challenges using various methods and stimulus magnitudes in parallel may thus provide a valuable probe into the inner workings of this aspect of our 'time sense'.

In order to arrive at a differentiated view on the temporal dynamics on the 24 hours-scale of short-term interval timing, we concurrently probed temporal production of 5 s, 10 s and 15 s and temporal reproduction of 3.75 s, 5 s, 7.5 s, 10 s and 15 s at intervals of 3.75 h in 10 healthy young male participants during 63.3 h spent in a short sleep-wake cycle protocol under constant conditions.

Analysis of variance conducted on paired durations using factors *session* (session number), *task* (production vs. reproduction) and *stimulus* (stimulus duration) revealed significant effects for *stimulus* as well as for $stimulus \times task$ but no effect of *session* or any interaction therewith. We observed a general over-reproduction for shorter intervals and a general under-reproduction for the 15 s interval. The 10 s interval, on average, was reproduced accurately across the protocol.

On the other hand, all durations were consistently over-produced and displayed a linearly increasing component across the protocol but no indication of a circadian modulation.

We observed a large degree of inter-individual variability in absolute levels, variability and progression across the protocol of responses during both interval timing tasks, temporal production and temporal reproduction.

Our findings are in line with the idea that a variety of mechanisms participate in interval timing under different conditions and raise doubts about changes in pacemaker rate being primarily responsible for the patterns observed. We believe that a better characterization of interval timing responses to circadian challenges might reveal valuable cues with respect to these mechanisms. The almost complete absence of a clear circadian rhythmicity and the large degree of inter-individual variability encountered is interpreted with respect to possible methodological problems. In light of the evident circadian modulation in sleepiness ratings and salivary melatonin levels, it is taken as an indication of only limited susceptibility of interval timing to circadian challenges.

3.1 Introduction

During the course of evolution, several systems have formed that allow organismic functions to occur in adjustment with the temporal structures imposed by the internal and external environments: developmental processes unfold in a precisely harmonized choreography, endogenously generated physiological fluctuations help anticipate changes in the physical environment, and exactly timed behavior interacts with and anticipates the forces and flows of a dynamical world. Accordingly, the discovery and detailed characterization of a biological clock that modulates nearly all organismic functions has spectacularly complemented the established principle of homeostasis and provided a novel framework within which to understand and interpret a multitude of physiological and behavioral processes.

On the other hand, behavioral timing has been a topic of interest to psychology since its establishment as an independent scientific discipline in the second half of the 19th century, and the most intensely pursued questions within this realm relate to the perception of durations in the seconds range i.e., to short-term interval timing [Debru, 2006].

An interesting phenomenon situated at the intersection of these two domains of biological timing consists in the fact that short-term interval timing itself may be modulated by the biological clock responsible for the circadian rhythmicity in many physiological and cognitive variables; several reports note a time-of-day dependent modulation in the perception of durations in the seconds range [Poeppel and Giedke, 1970; Nakajima et al., 1998; Kuriyama et al., 2003]. The specific waveform of this modulation as well as its exact cause however have not been unequivocally determined to this date [Refinetti, 2005] and, as among others [Grondin, 2010; Wiener et al., 2010; Pande and Pati, 2010] have pointed out, the relevant literature is in a somewhat unordered state. The authors attribute this problem primarily to incompatibilities in methods, stimuli and terminologies employed in research on interval timing. Specifically, the relationship between perceived and actual duration depends not only on the experimental methods and stimulus magnitudes employed but these relationship itself is differentially influenced by a multitude of other factors. An assessment of interval timing using different methods and stimulus magnitudes within one single experiment should thus help to separate many of the confounding variables from factors of interest and expose the underlying mechanisms to defined manipulations.

Short term interval timing is typically assumed to rely on a pacemaker and accumulator mechanism in which modulations in pacemaker rate are among the critical variables that affect the perception of durations. If the modulation of interval timing within this context is ultimately driven by circadian changes in the rate at which the pacemaker emits pulses as has been proposed by several authors [Poeppel and Giedke, 1970; Kuriyama et al., 2003], we expect a relatively uniform modulation of interval timing across several stimulus magnitudes but not necessarily so across tasks. Whereas modulations in produced durations can be readily explained in terms of altered pacemaker speed and the ensuing alterations in the absolute number of pulses accumulated during the task, concurrently assessed duration reproduction will most probably show different characteristics as temporal judgments made during this task must be based on a comparison of the relative number of pulses accumulated during the 'encoding' phase of the task and the 'playback' phase of the task and are thus not vulnerable to physiologically determined, global changes in pacemaker speed.

As a consequence and contrasting with production, in the case of the temporal reproduction task, circadian changes in pacemaker rate should not directly affect the behavioral response and any systematic changes observed here need to be attributed to modulations in subsystems of the pacemaker-accumulator model other than the pacemaker itself.

In the present study, we aimed at testing this assumption and building upon what is known about the perception of short durations and its putative modulation by the chronobiological system in order to arrive at a much more detailed view of the complex. This in turn may help elucidate the processes involved and their interactions and thus resolve some of the contradiction currently present in the literature. From this experiment, we also expect insights as to the possible basis of higher-order faculties of temporal processing, specifically temporal orientation. To accomplish our aim, we decided to expose the study volunteers to an array of stimulus durations, concurrently using the methods of temporal production and temporal reproduction during repeated sessions at various circadian phase angles in the context of a short sleep-wake cycle protocol.

3.2 Methods

3.2.1 Participants

Ten healthy young male volunteers (mean age: 23.8 years; age range: 20–28 years) successfully completed the study. All participants were non-smokers, free from medical, psychiatric, neurologic and sleep disorders (Pittsburgh Sleep Quality Index [Buysse et al., 1989], PSQI score $\leq$ 5) and of average chronotype (diurnal type scale score [Torsvall and Akerstedt, 1980] between 14 and 21) as assessed by screening questionnaires, a medical examination and a polysomnographically recorded screening night. Exclusion criteria comprised: shift work within three months and transmeridian flights within one month prior to the study, excessive caffeine and alcohol consumption, drug use and excessive physical activity. All study participants gave signed informed consent; the local Ethics Committee approved the study protocol, screening questionnaires and consent form and all procedures conformed to the Declaration of Helsinki.

3.2.2 Protocol

The week prior to the in-lab part of the study (baseline week) participants were instructed to maintain a regular sleep-wake-cycle (bed- and wake times within $\pm$ 30 min of a self-selected target time), which was verified via wrist activity monitors (Cambridge Neurotechnologies, UK) and sleep logs.

The laboratory part of the study consisted of a 3.5 days short sleep-wake cycle protocol (NAP protocol) spent under constant routine conditions. The protocol consisted of one adaptation night followed by 63.3 h of alternating cycles of 75 min of scheduled sleep (naps) and 150 min of scheduled wakefulness, beginning 15.25 hours after habitual wake-up time, as determined via actigraphy and sleep logs during the baseline week (cf. figure 3.1). Wake episodes were spent under constant dim light levels, < 8 lux, semi-recumbent posture in bed, food and liquid intake at regular intervals and no cues about time of day. During scheduled sleep, a minor shift to supine posture was allowed and lights were turned off (0 lux, for more information about the protocol see [Cajochen et al., 2001]).

3.2.3 Measures

Interval timing was sampled via the concurrent use of two standard methods of timing research, temporal production and temporal reproduction, which were administered sequentially during epochs of scheduled wakefulness.

Production Target durations were displayed in conventional units (number of seconds to be produced), centrally on a liquid crystal computer display using black Arabic digits on grey background. The participant's task was to identify the target duration and immediately begin holding down the space bar on the computer keyboard, stopping to depress the space bar after a duration that subjectively matched the target duration had elapsed. Thereafter, the machine displayed the next

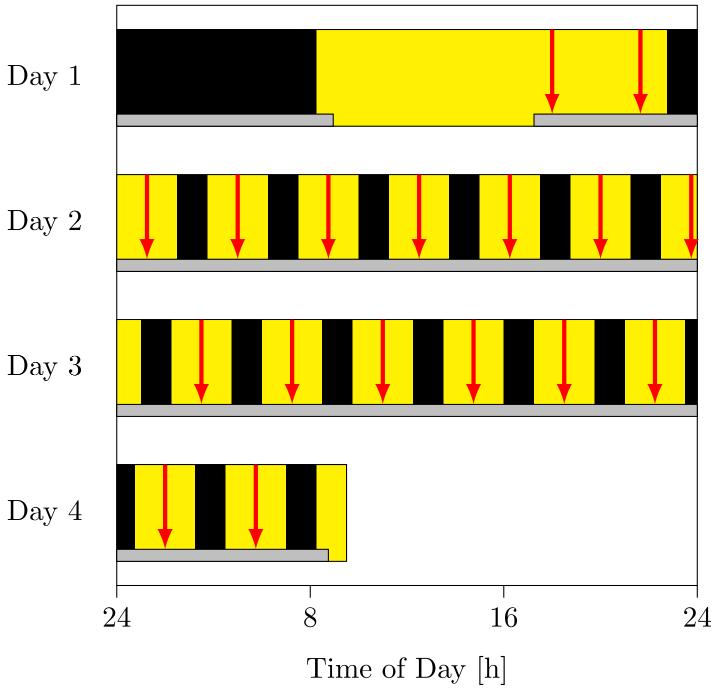

Figure 3.1: Schematic representation of the protocol design. Sleep (0 lux); Constant Supine Posture; Interval Timing Session (Production and Reproduction Tasks); Wakefulness (< 8 lux)

target duration until all stimuli for the current condition were exhausted.

Reproduction Target durations were given via a 'carrier stimulus' i.e., via a temporally delimited display of a black square on grey background, centrally on a liquid crystal computer display. Participants were instructed to hold down the space bar on the computer keyboard as soon as possible upon the extinction of the target stimulus, and to release the space bar after a duration subjectively corresponding to the target duration had elapsed. Thereafter, the machine displayed the next target duration until all stimuli for the current condition were exhausted.

Interval timing sessions consisted of either 15 (production; 3 target durations, each presented 5 times in random order) or 25 (reproduction; 5 target durations, each presented 5 times in random order) sweeps respectively of the above structure. Production and reproduction sessions were conducted centered within each wake phase, the first task occurring 45 min after lights on, followed by the second task 50 min later (95 min after lights on). Task order alternated across volunteers and participants were instructed to refrain from counting, tapping or similar sequencing strategies.

Among a number of other physiological and cognitive variables, salivary melatonin concentration was assessed concurrently with subjective sleepiness ratings (Karolinska Sleepiness Scale, KSS). Saliva collection and subjective sleepiness ratings occurred at half-hourly intervals during each wake phase, beginning immediately upon lights on.

3.2.4 Statistical Analyses

Sessions 1–3 of the interval timing tasks were considered adaption sessions and excluded from further analyses. Following outlier removal, the 5 sweeps per condition were collapsed onto their median. Subsequently, a three-way repeated measures analysis of variance using factors *session* (elapsed time into protocol), *task* (production vs. reproduction) and *stimulus* (stimulus duration) was calculated on median values of those durations that were present in both tasks, followed by a one-way repeated measures analysis of variance on each stimulus/task combination, using factor *session*.

Melatonin assays were conducted using direct double-antibody radioimmunoassay (RIA; validated by gas chromatography-mass spectroscopy with an analytical least detectable dose of 65 pg/ml). To obtain the average melatonin time course, values were averaged on a per-measurement basis. The same procedure was applied to the KSS ratings in order to obtain the average time course of subjective sleepiness.

The alpha-criterion was set at $p = 0.05$. The statistical packages R (The R Foundation for Statistical Computing, Vienna, Austria; Version 2.7.0) and STATISTICA (StatSoft Inc., Tulsa, OK; Version 6.1) as well as the CLEAVE (T. J. Herron, UC Davis and VANCHCS, 2003) and pyANOVA (R. Lew, University of Idaho, 2011) utilities were used in data analysis.

3.3 Results

Time perception data displayed the typical feature of scalarity i.e., the average standard deviation of responses across participants increased with stimulus duration for both tasks (cf. figure 3.2). The standard deviations were significantly lower during the production task ($F(1,9) = 6.3$, $p < 0.05$).

Repeated measures analysis of variance on paired durations i.e., durations present in both tasks using factors *session* (session number), *task* (production vs. reproduction) and *stimulus* (stimulus duration) revealed significant effects of *stimulus* ($F(2, 18) = 207.6$, $p < 0.001$) as well as of $\textit{stimulus} \times \textit{task}$ ($F(2, 18) = 10.8$, $p < 0.01$) (cf. figure 3.9) but no effect of *session* and no interaction therewith. Separately conducted repeated measures analyses of variance on the time courses of individual stimulus durations in both tasks

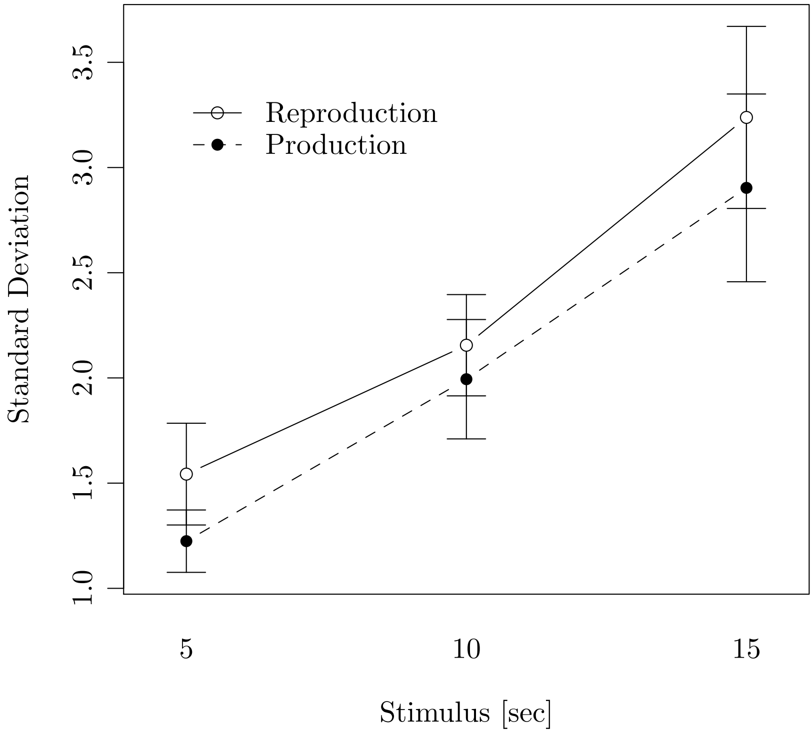

Figure 3.2: Relationship between stimulus magnitude and response variability (standard deviation); mean standard deviation across participants ± s.e.m.

confirmed the absence of session-related effects or interactions. Another repeated measures analysis, conducted on the 3.75 sec and 7.5 sec intervals of the reproduction task equally failed to yield a main or interactive effect of session.

Visual inspection of the time course in produced durations revealed a consistent overestimation which was proportional to the stimulus magnitude as well as a slight linearly increasing component across the protocol (cf. figure 3.3). Against the backdrop of the time courses of melatonin and sleepiness ratings, there was no indication of a circadian modulation in any of the produced durations. Reproduction curves showed a general overestimation for shorter intervals the extent of which was roughly indirectly proportional to stimulus magnitude and a putative circadian modulation combined with general underestimation for the 15 s interval. A similar pattern was also present in reproduction of the 3.75 s interval. The 10 s interval, on average, was reproduced accurately across the protocol. The linear trend found in production was absent in reproduction (cf. figure 3.3).

Moving away from averaged values, a look at the individual trajectories reveals a high degree of inter-individual variability; absolute levels in production and reproduction of all durations were subject-specific, the extent of inter-individual differences scaling with stimulus magnitude in production but not as clearly so in reproduction. Variance was subject-specific as well, larger in reproduction and scaling with stimulus magnitude. The great degree of individuality also applied to progression of production and reproduction across the protocol. In some participants and under some conditions, there was a linear trend and a circadian course was putatively observed in some of the reproductions of longer durations (cf. figures 3.4 and 3.5).

Overall correlations between interval timing and subjective sleepiness ratings were low (range: -0.11–0.14) and did not reach significance for any stimulus/task combination (cf. figures 3.6). Correlations between individual responses in each interval timing task, stimulus magnitude (on a per-subject basis) and the subjective

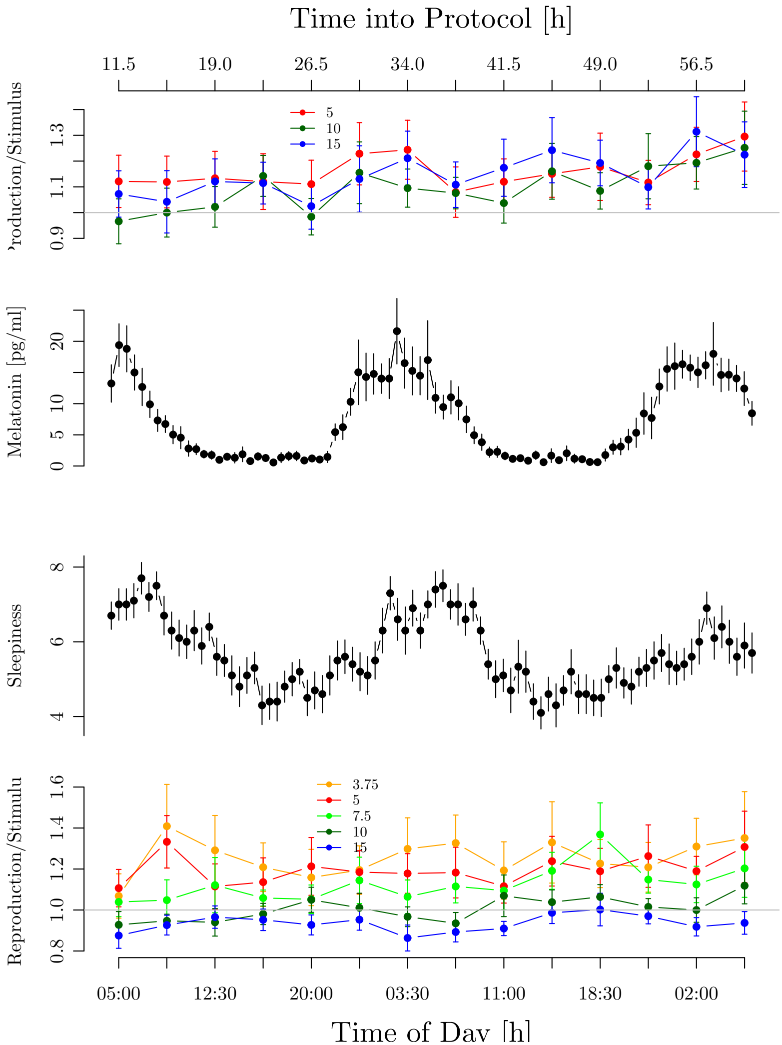

Figure 3.3: Progression of production (top) and reproduction (bottom) during the short sleep-wake cycle protocol. The middle panels show the average time courses of salivary melatonin (above) and sleepiness (below); mean ± s.e.m.

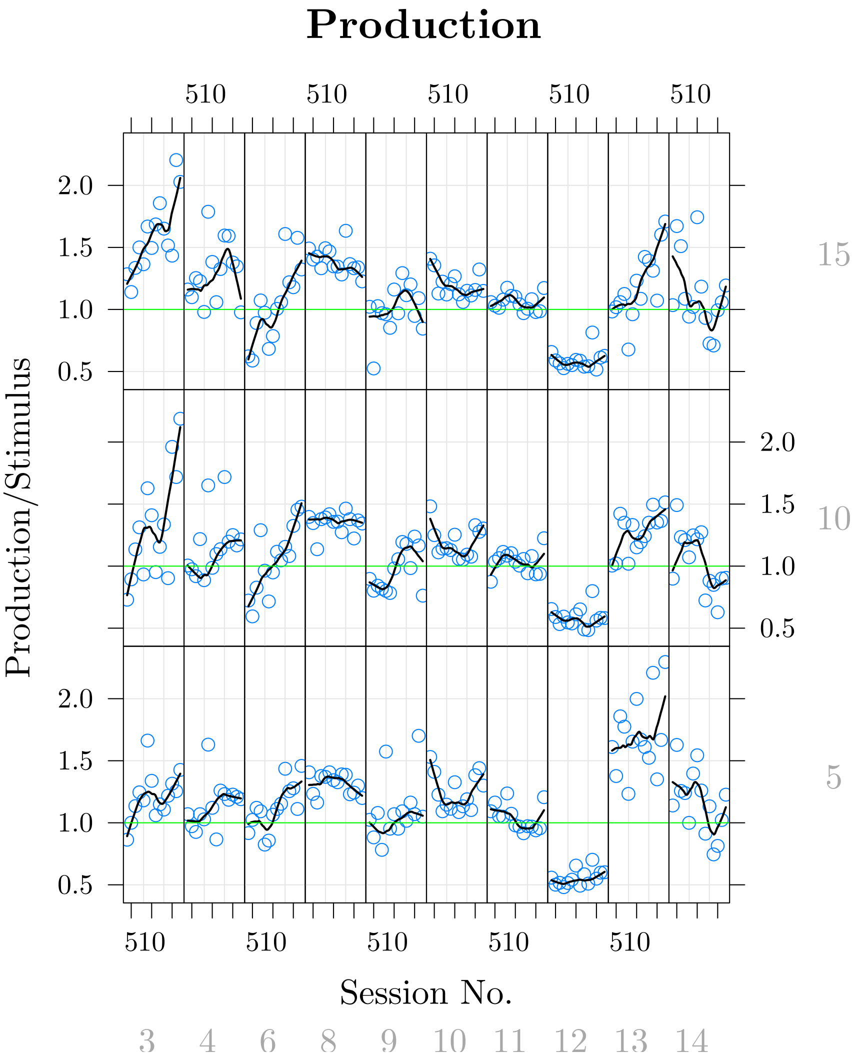

Figure 3.4: Individual profiles (IDs 3–14) across the protocol—Production, Stimuli (5–15 sec; row-wise) × Subjects (column-wise), Median values (blue), added loess smoother (black), and target duration (green)

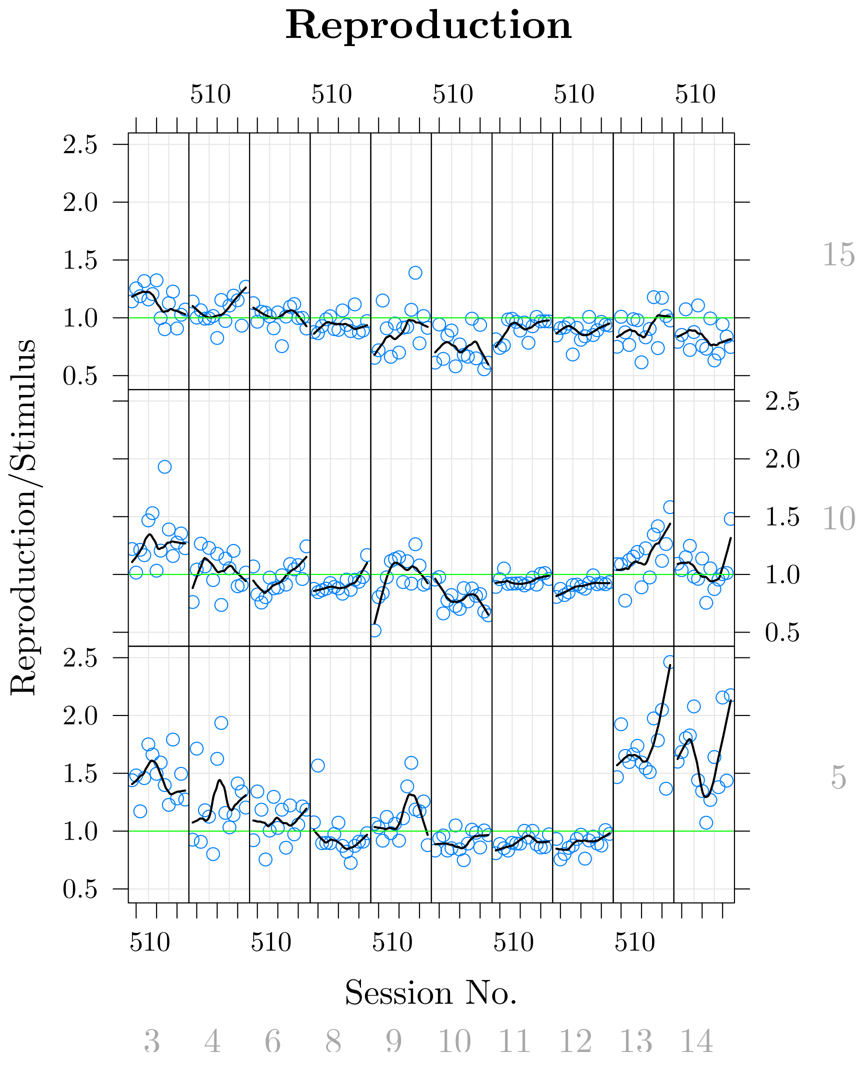

Figure 3.5: Individual profiles (ID3–ID14) across the protocol—Reproduction, Stimuli (5–15 sec; row-wise) × Subjects (column-wise), Median values (blue), added loess smoother (black), and target duration (green)

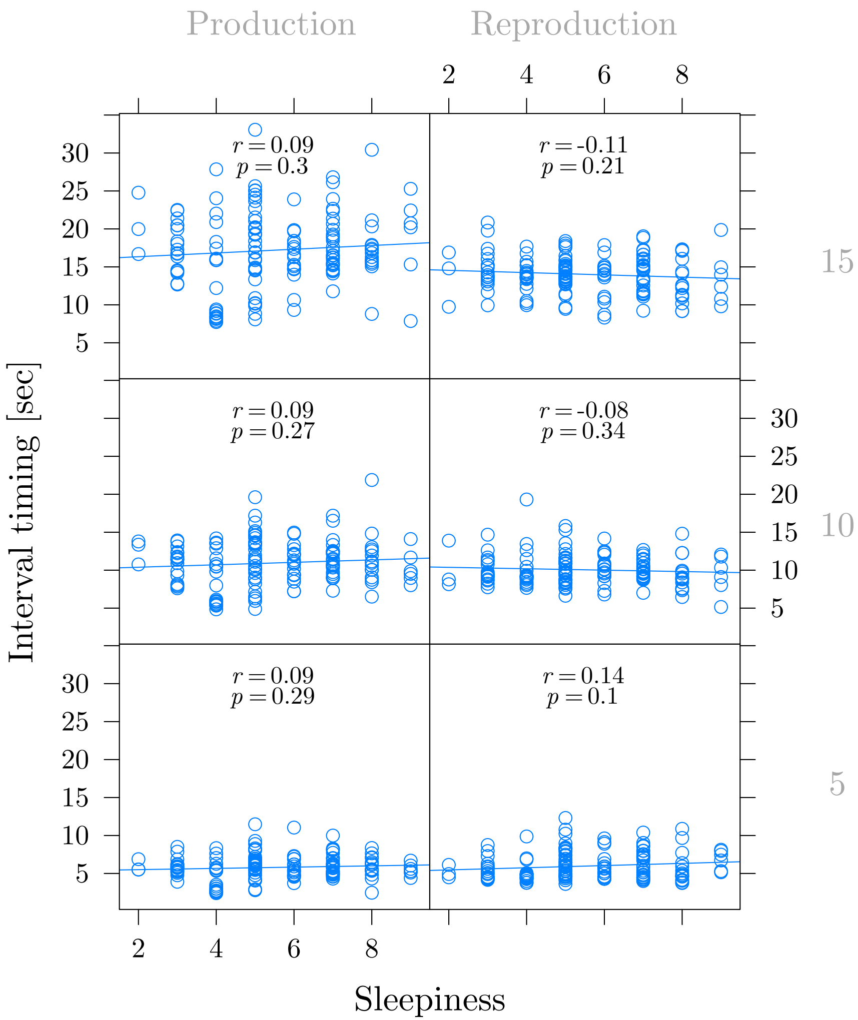

Figure 3.6: Correlation between interval timing and subjective sleepiness by stimulus (5–15 sec; row-wise) and task type (P, R; column-wise) across all participants; embedded numbers: correlation coefficients (above); p-values (below)

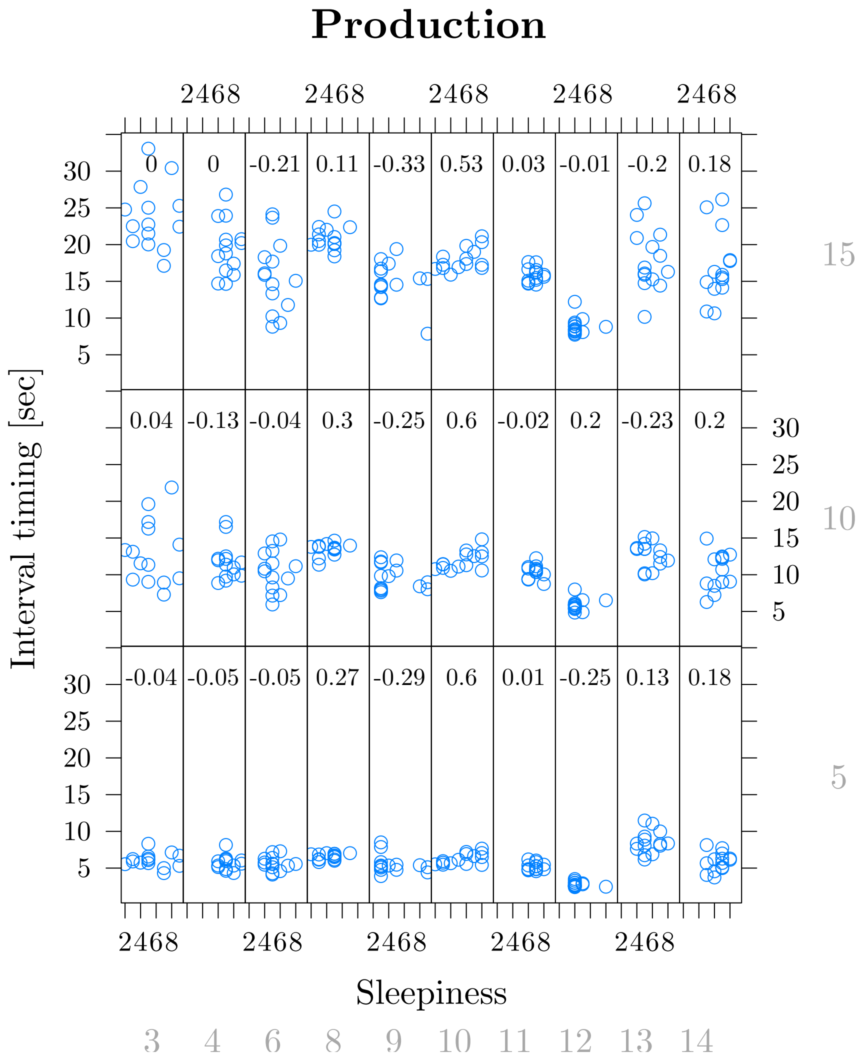

Figure 3.7: Correlation between produced duration and subjective sleepiness by stimulus (5–15 sec; row-wise) and participant (ID3–ID14; column-wise); embedded numbers: correlation coefficients

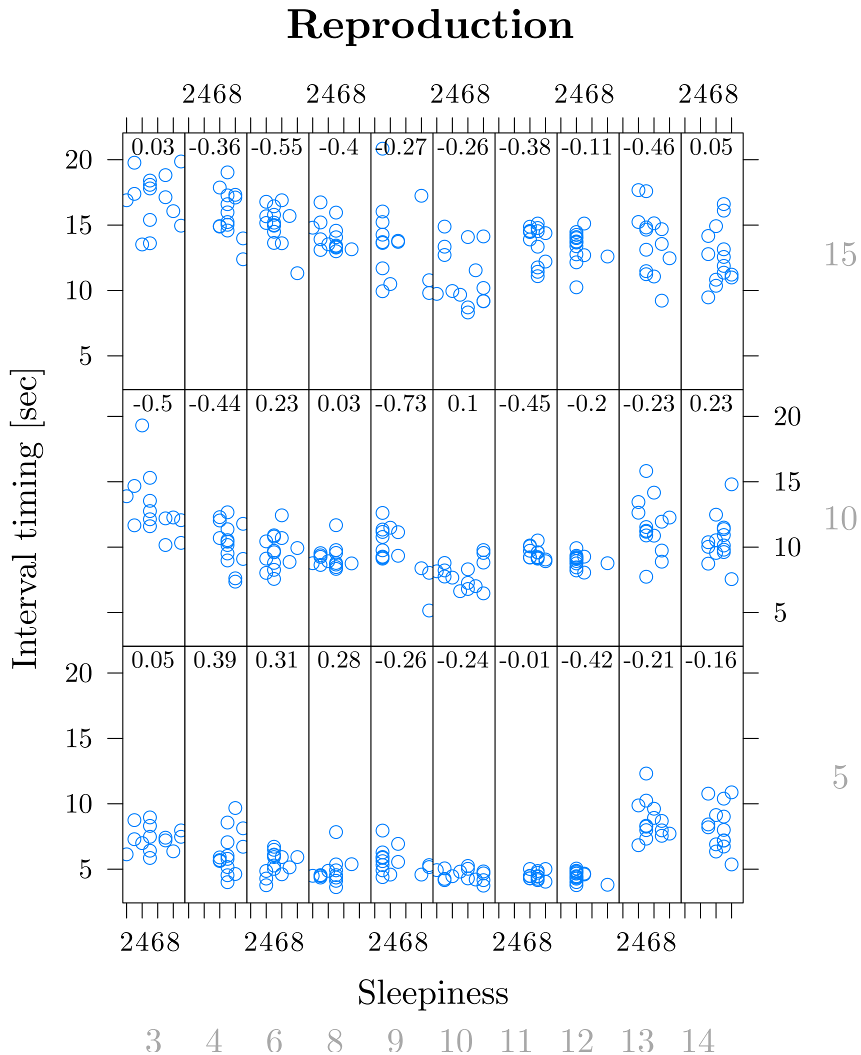

Figure 3.8: Correlation between reproduced duration and subjective sleepiness by stimulus (5–15 sec; row-wise) and participant (ID3–ID14; column-wise); embedded numbers: correlation coefficients

sleepiness ratings (cf. figures 3.7 and 3.8) were equally low and confirmed the absence of a straightforward systematic relationship between these two variables.

3.4 Discussion

Our data reveal an over-production of all durations during the *production* task and an over-reproduction of shorter durations during the *reproduction task*; longer durations were under-reproduced. The circadian features implied by some of the literature could not be clearly confirmed for this cohort which instead displays a high degree of inter-individual variability in time courses and other aspects of interval timing.

Most comparable studies have used single durations or tasks and their design thus corresponds to a relatively small subset of the one employed in our study. An exception to the typical use of a single method to study interval timing in a chronobiological context is the study by Pöppel and Giedke [Poeppel and Giedke, 1970], in which a single volunteer was required to produce a duration of 10 s and to reproduce a duration of 6 s during the course of a day. This study revealed a negative correlation between produced and reproduced duration on one side and core body temperature on the other side with peak production and peak reproduction occurring during the morning. Unfortunately however, this finding can be attributed only limited relevance due to the inclusion of only one single participant. The general pattern observed by Pöppel and Giedke could however be confirmed for temporal production in a number of later studies: in four healthy young male volunteers, Nakajima et al. found afternoon troughs and morning peaks in a 10 s time production task [Nakajima et al., 1998] and in a study on eight volunteers involving sustained wakefulness conditions, Kuriyama et al. found a maximum in a 10 s time production task during the morning and a minimum during the early evening [Kuriyama et al., 2005]. On the other side, using a time production task during a free-run ex-

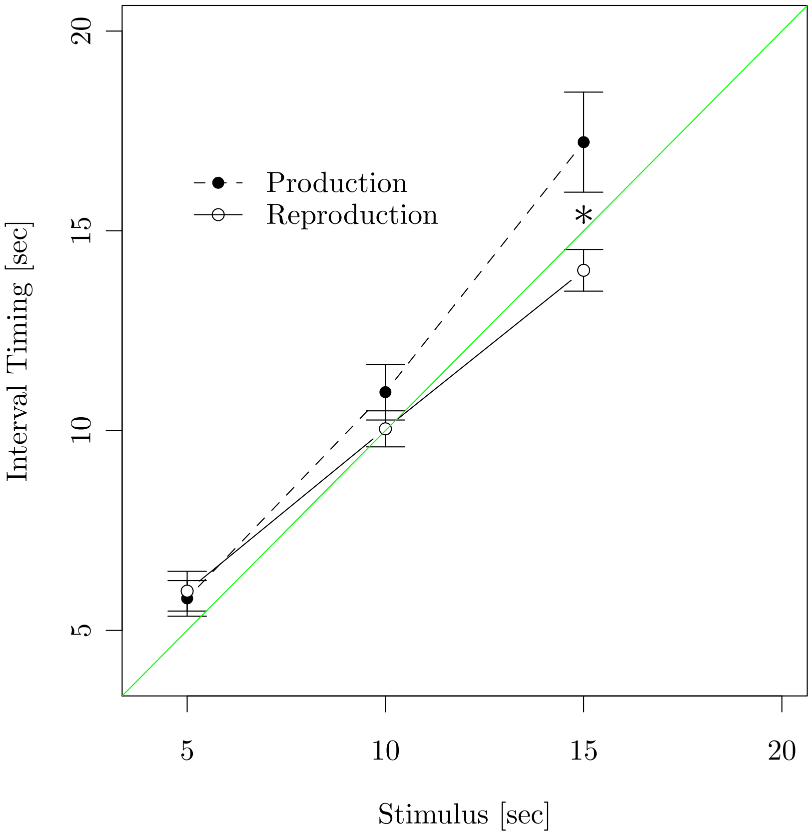

Figure 3.9: Production and Reproduction vs. target duration; mean ± s.e.m.; green: line of identitiy (veridical interval timing performance); produced durations were significantly larger than reproduced durations for the 15 sec interval, as indicated by the asterisk

periment, Aschoff found no circadian rhythmicity [Aschoff, 1984] and Pati and Gupta found no consistent peak time across participants [Pati and Gupta, 1994]. Taken together, a circadian pattern in time production of 10 s with morning peaks and evening troughs has mixed support in the literature; it should also be noted that some authors [Campbell, 1990] have expressed more general doubts as to the presence of a circadian modulation in time perception.

In our study, we see a tendency for the under-reproduction of longer durations to be more pronounced during subjective night; we find no support however for similar patterns in reproduction of intermediate and short durations or for production of any duration. The greater degree of under-reproduction observed during the night cannot be attributed to modulations in pacemaker speed and is more plausibly interpreted in terms of attentional changes. Due to attentional lability during the night, the switch allowing pulses generated by the pacemaker to flow into the accumulator may be more susceptible to interruptions than during the day, thus leading to a relative decrease in the number of accumulated pulses. A surprising finding consists in the appearance of a linearly increasing trend in production. This result could reflect both a decrease in pacemaker rate across the protocol (cf. Soshi et al.) or an increase in the amount of attentional resources allocated to the timing task (cf. Miro et al.). Neither hypothesis is however easily reconciled with our findings on temporal reproduction within the pacemaker-accumulator framework. A promising alternative model of interval timing has been developed by Wackermann and Ehm [Wackermann and Ehm, 2006]. This model avoids the assumption of an oscillatory base to interval timing and instead heavily relies on activation- and memory related processes, thus circumventing the problem that is introduced by the assumption of a locally constant pacemaker rate.

We conclude with the observation that there seems to be an endogenous circadian modulation in some aspects of interval timing, but this influence is probably much weaker and more isolated in terms of conditions and generally more fragile and subject-specific then suggested by previous reports. Our observations also militate against modulations in pacemaker speed as the dominating factor that influences interval timing in this context. These inferences should however taken with some caution: an explanation for these rather inconclusive findings as well as for the great inter-individual variability in our data which hints at a more fundamental problem with our study as well as with those conducted by other groups may be the lack of control on the strategies effectively adopted by individual participants, a factor of obviously great importance [Doob, 1971; Miro et al., 2003; Wearden, 1991; Grondin, 2001; Hinton et al., 2004; Clement and Droit-Volet, 2006]. In fact, many of the aforementioned studies encouraged counting/sequencing strategies, while others give no information about the exact instructions given and/or compliance with these instructions.

In our study, counting or sequencing were explicitly discouraged but compliance is difficult to control and maybe even difficult to expect, especially so during the production task, where stimuli are actually presented in the form of numerical values. A possible solution to this problem may be the introduction of post-hoc questionnaires after each timing session which would provide the subject with a means to self-evaluate his or her performance with respect to the strategies adopted; this measure could subsequently be introduced as a predictor in a random coefficient modelling analysis which is a very promising approach to analyzing this type of data [Albert and Hunsberger, 2005; Barnett and Dobson, 2010; Cudeck and Harring, 2007; Olofsen et al., 2004; Durban et al., 2005; Schneider et al., 2004; Holden et al., 2008; Pinheiro and Bates, 2009; Young et al., 2009]. This method takes into account individual differences instead of simply pooling across participants as it happens in analysis of variance and related techniques. The approximate logic, briefly, is to fit a function describing the time course of responses to the data on a per-subject basis. The functional form fitted to the data is the same for each subject but its parameters are allowed to vary across participants. Some of the variance in these parameters may then be attributed to subject-specific traits or individually distinctive modulations in time-varying covariates. This logic contrasts with the analysis of variance approach, in that inferences are not based on aggregated values, but, by allowing inferences to be made directly on the basis of the full data set, this technique is able to provide more detailed information and more accurate estimates on the data.

To alleviate the problem of the contradictory results pervading the literature on interval timing in the chronobiological context it is furthermore crucial to use an unequivocal terminology (cf. Pande and Pati [Pande and Pati, 2010]). It is a common observation e.g. that the term 'time estimation task' is employed both as a generic term denoting almost any kind of cognitive task that assesses temporal perception and, more properly, as a term describing a very specific method (i.e., the estimation task as opposed to the methods of e.g. production, reproduction and comparison) used in research on interval timing. Another source of possible confusion and mis-interpretation is the use of relatively vague statements in the literature with respect to the behavior observed or the underlying states in interval timing tasks, such as that of 'time subjectively speeding up' or 'time subjectively slowing down'. Instead, along the critique expressed by [Pande and Pati, 2010], we see a strong need here for greater precision and clarity in the terminology used.

Another necessity are clear and controllable instructions in interval timing tasks, in order to minimize the role of or to control for the different strategies employed by individuals. Additionally, to separate possible confounding variables from real differences in the mechanism sub-tending production and reproduction of durations of various stimulus magnitudes, data might possibly be examined using a random coefficient modeling approach, a technique suitable for explaining inter-individual differences which may mask circadian features in the population average in terms of individual characteristics in covariates and traits. Accounting for the caveats and pitfalls identified here should permit future experiments to corroborate our finding on the limited effect of circadian phase on interval timing and allow for an identification of the factors responsible for the large degree of inter-individual variability.

Acknowledgements

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4 Circadian Phase, Sleep Pressure and Interval Timing[1]

[1]In preparation for submission

Abstract

Due to its practical relevance, sustained wakefulness, along with circadian phase, deserves special attention among the factors reported to have an impact on interval timing. In modern society, an increasing number of people suffer from chronic sleep deprivation and the crucial role of interval timing to interaction with the physical environment makes this faculty, along with the modulation in other parameters, a putative key link in human errors occurring due to sleep deprivation. Its assessment is thus of great practical relevance. As with research on the circadian modulation of interval timing, a major shortcoming with nearly all of the studies conducted on the relationship between sustained wakefulness and interval timing so far is the limited range of stimuli and methods employed as this is known to have an effect on the results and is necessary in order to be able to identify the participating mechanisms. Here, in an attempt to extend similar research on the circadian modulation of interval timing, we aimed at investigating the *combined* effects of sustained wakefulness and circadian phase on duration production and duration reproduction of several time intervals in the seconds range. Since there is evidence that different processes and mechanisms are involved in the two tasks, we hypothesized that the tasks would respond unequally to homeostatic and circadian challenges.

Aiming to arrive at a differentiated view on the impact of temporal dynamics in physiology on short-term interval timing, we probed production of 5 s, 10 s and 15 s intervals and reproduction of 3.75 s, 5 s, 7.5 s, 10 s and 15 s intervals in parallel at 3-hourly intervals in twelve healthy young male participants during 40 hours of sustained wakefulness under near constant routine conditions.

Repeated measures analysis of variance using factors *session* (session), *task* (production vs. reproduction) and *stimulus* (stimulus

duration) yielded no significant effect for factor *session*, but significant effects for factor *task* and *stimulus* and significant interactions of factors *stimulus* x *task*, *stimulus* x *session* and *stimulus* x *task* x *session*. Reproduction displayed a wake-dependent increase combined with a general overestimation for shorter and possible circadian modulation combined with a general underestimation for longer intervals; intermediate intervals were reproduced accurately during the entire protocol. In contrast, during the production task, durations were consistently under-produced. Produced durations did not exhibit clear wake-dependent dynamics but did display possible circadian dynamics for the 10 sec and 15 sec stimulus durations. As was the case in a previous experiment carried out by our group, that studied the isolated effects of circadian phase on interval timing, we found a large degree of inter-individual variability in both tasks, production and reproduction. The considerable degree of inter-individual variability encountered is interpreted as a possible indicator of methodological problems present in our study as well as in the majority of published research on interval timing.

Our findings reveal a complex interaction between task type, interval length, circadian phase and state of the homeostat, which needs to be incorporated into current models of interval timing. Specifically our data indicate, that interval timing may be more susceptible to the effects of elevated sleep pressure than to those of circadian phase. Our results also suggest a more important role of changes induced by sustained wakefulness to attentional and memory components of the standard model of interval timing, contrasting with relatively limited effects of this intervention on pacemaker rate per se.

4.1 Introduction

Among the multitude of factors reported to modulate the perception of durations in the seconds range, sustained wakefulness is of particular interest due to its practical relevance. In today's 24/7 h society, an increasingly large proportion of the population suffers from chronic sleep deprivation and the crucial role of interval timing in interacting with the physical environment suggests that its disruption may be a key factor to human errors that occur due to sleep deprivation.

A number of reports have assessed the interaction between circadian and wake dependent modulations of short-term interval timing with mixed results. As with research on the circadian modulation of interval timing, a big shortcoming with the majority of the previous studies is the limited range of stimuli and methods employed, as choice of method and stimulus magnitude is known to influence results differentially. Instead, a wide array of stimulus durations and methods tested within one experiment would be necessary to identify the possible mechanisms involved. Here, in an attempt to extend similar research on the circadian modulation of interval timing and our own research on the topic, we aimed at investigating the *combined* effects of sustained wakefulness and circadian phase on duration production and duration reproduction of multiple time intervals in the range of several seconds.

The effect of sustained wakefulness on interval timing has been the focus of several research articles [Nakajima et al., 1998; Kuriyama et al., 2005; Soshi et al., 2010; Miro et al., 2003] but results are unclear. The most robust finding seems to be an attenuation of circadian rhythmicity in production that occurs with increasing sleep pressure. This feature has been attributed to a slowing of the pacemaker in response to sleep deprivation. There is, an urgent need to study several durations using different methods in order to test this hypothesis and characterize interval timing behavior during the reproduction task, as performance in this task will probably not change due to modulations in pacemaker speed. We thus expected to be able to confirm the changes in production with sustained wakefulness that have been described in previous reports. This assumption was complemented by the hypothesis that behavior during temporal reproduction would respond differently, due to the limited significance of global changes in pacemaker speed to this task.

4.2 Methods

4.2.1 Participants

Ten healthy young male participants (mean age: 24.9 ± 2.96 years; age range: 21–29 years) successfully completed the study. All participants were non-smokers, free from medical, psychiatric, neurologic and sleep disorders and of average chronotype as assessed by screening questionnaires and a medical examination. Exclusion criteria comprised: shift work within three months and transmeridian flights within one month prior to the study, excessive caffeine and alcohol consumption, drug use and excessive physical activity. All study participants gave signed informed consent; the local Ethics Committee approved the study protocol, screening questionnaires and consent form and all procedures conformed to the Declaration of Helsinki.

4.2.2 Protocol

During the week prior to admission, participants were required to maintain a regular sleep-wake cycle, compliance to which was verified via the use of wrist activity monitors (Cambridge Neurotechnologies, UK) and sleep logs. Participants reported to the lab in the evening and attended a practice session for the purpose of familiarization with the task. Following an in-lab baseline night, participants were studied during 40 h of sustained wakefulness, beginning at 08:00 h and spent under near constant routine (CR) conditions [Mills et al., 1978; Czeisler et al., 1985] (constant dim light levels, < 8 lux, semi-recumbent posture in bed, food and liquid intake at regular intervals, no cues on time of day). The epoch of sustained wakefulness was followed by a recovery night.

4.2.3 Measures

During the sustained wakefulness epoch, interval timing performance was sampled via the concurrent use of two standard methods used in this field i.e., temporal production and temporal reproduction. Testing began at 09:00 h.

Production Target durations were displayed centered on screen using black Arabic digits on grey background. The participant's task was to identify the target duration and immediately begin holding down the space bar on the computer keyboard, stopping to depress the space bar after a duration that subjectively matched the target duration had elapsed. Thereafter, the next target duration was displayed on the computer screen, until all stimuli for the given condition (defined by task type, subject id and session number) were exhausted.

Reproduction Target durations were indicated via a temporally delimited display of a black square on grey background, appearing centered on the computer screen. Participants were instructed to hold down the space bar on the computer keyboard as soon as possible upon the extinction of the target stimulus, and release the space bar after a duration that subjectively corresponded to the target duration had elapsed. Thereafter, the machine displayed the next target duration until all stimuli for the current condition were exhausted.

Each interval timing session consisted of 15 (production; 3 target durations, each presented 5 times in random order) and 25 (reproduction; 5 target durations, each presented 5 times in pseudorandom order) sweeps of the above structure, respectively. Both stimulus types were of approximately equal width and height. Production and reproduction sessions were conducted in sequence and immediately following each other, at intervals of 3.75 h. Task order alternated across participants and participants were instructed to refrain from counting, tapping or any similar sequencing strategy. Among a number of other physiological and cognitive variables, salivary melatonin concentration was assessed concurrently with sleepiness ratings and performance during PVT sessions. Saliva collection occurred at hourly intervals, beginning 08:00 h.

4.2.4 Statistical Analyses

Following outlier removal, the 5 sweeps per condition were collapsed onto their median value. Results obtained during the first (adaptation) session were excluded from further analyses. Subsequently, repeated measures analysis of variance using factors *session* (session), *task* (production vs. reproduction) and *stimulus* (stimulus duration) was applied to the median values of paired durations, followed by one-way repeated measures analyses of variance, conducted separately for each stimulus/task combination, using the factor *session*. The melatonin assay was conducted using a direct double antibody radioimmunoassay (RIA, validated by gas chromatography mass spectroscopy with an analytical least detectable dose of 65 pg/ml). To obtain the average melatonin time course, values were averaged on a per-measurement basis. The same procedure was applied to the KSS and PVT values, in order to arrive at averaged time courses for these variables.

The alpha-criterion was set at $p = 0.05$. The statistical packages R (The R Foundation for Statistical Computing, Vienna, Austria; Version 2.7.0) and STATISTICA (StatSoft Inc., Tulsa, OK; Version 6.1) as well as the specialized CLEAVE (T. J. Herron, UC Davis and VANCHCS, 2003) and pyANOVA (R. Lew, University of Idaho, 2011) analysis of variance utilities were used.

4.3 Results

Time perception data in both tasks displayed the typical feature of scalarity i.e., the standard deviation of responses was roughly proportional to stimulus duration (cf. figure 4.1); standard deviations were significantly lower during the production task than during the reproduction task ($F(1,9) = 11.36$, $p < 0.01$).

Repeated measures ANOVA on paired durations using factors *session* (session), *task* (production vs. reproduction) and *stimulus* (stimulus duration) yielded no significant effect for factor *session*, but significant effects for factor *task* ($F(1,9) = 6.4$, $p < 0.05$) and *stimulus* ($F(2,18) = 33.9$, $p < 0.001$) and significant interactions of factors *stimulus* x *task* ($F(2,18) = 31.0$, $p < 0.001$; cf. figure 4.11), *stimulus* x *session* ($F(24,216) = 1.7$, $p < 0.05$) and *stimulus* x *task* x *session* ($F(24,216) = 2.0$, $p < 0.01$; cf. figure 4.2). Separately conducted repeated measures analyses of variance on the time courses of individual stimulus durations in both tasks, followed by post-hoc testing allowed for identification of time-points at which response/stimulus ratios differed significantly from one (cf. figure 4.2).

Visual inspection of reproduction data suggested a wake-dependent increase in responses, combined with a general over-reproduction for shorter and putative circadian modulation combined with a general under-reproduction for longer intervals; intermediate intervals were reproduced accurately during the entire sustained wakefulness epoch (cf. figures 4.2 and 4.11). In contrast, produced durations were consistently under-produced, did not exhibit clear wake-dependent changes but putative circadian dynamics in responses to the 10 sec and 15 sec stimulus durations (cf. figures 4.2 and 4.11).

A look on a per subjects-basis at the individual trajectories reveals a high degree of inter-individual variability; absolute levels in production and reproduction of all durations were subject-specific, the extent of inter-individual differences scaling with stimulus magnitude in production as well as in reproduction. Variance was subject-specific especially in shorter durations, larger in production

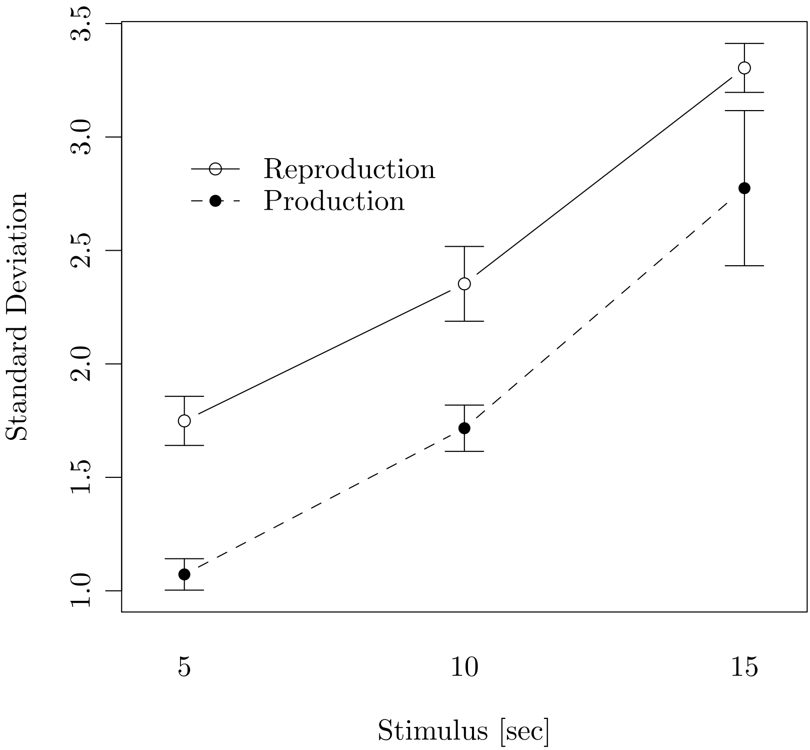

Figure 4.1: Relationship between stimulus magnitude and response variability (standard deviation); mean standard deviation across volunteers ± s.e.m.

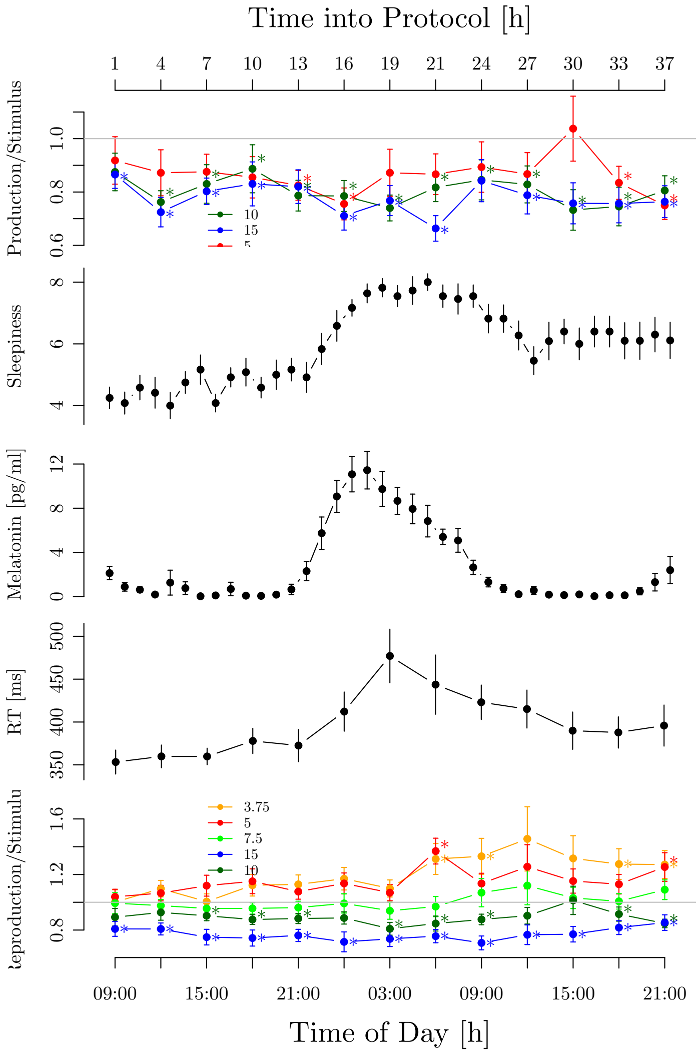

Figure 4.2: Progression of production (top) and reproduction (bottom) during sustained wakefulness. Asterisks indicate sign. differences from one in response/stimulus ratios. The middle panels show the average time courses of sleepiness, salivary melatonin and PVT performance; mean ± s.e.m.

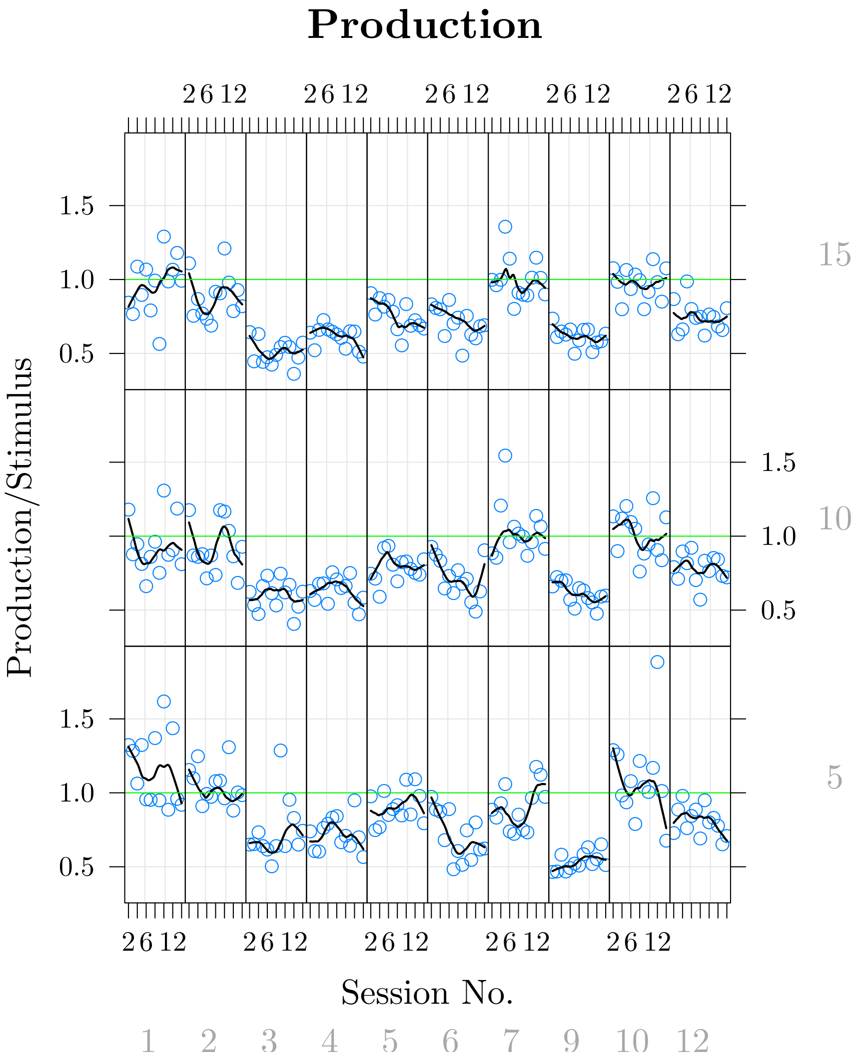

Figure 4.3: Individual profiles (IDs 1–12) across the protocol—Production, Stimuli (5–15 sec; row-wise) × Subjects (column-wise), Median values (blue), added loess smoother (black), and target duration (green)

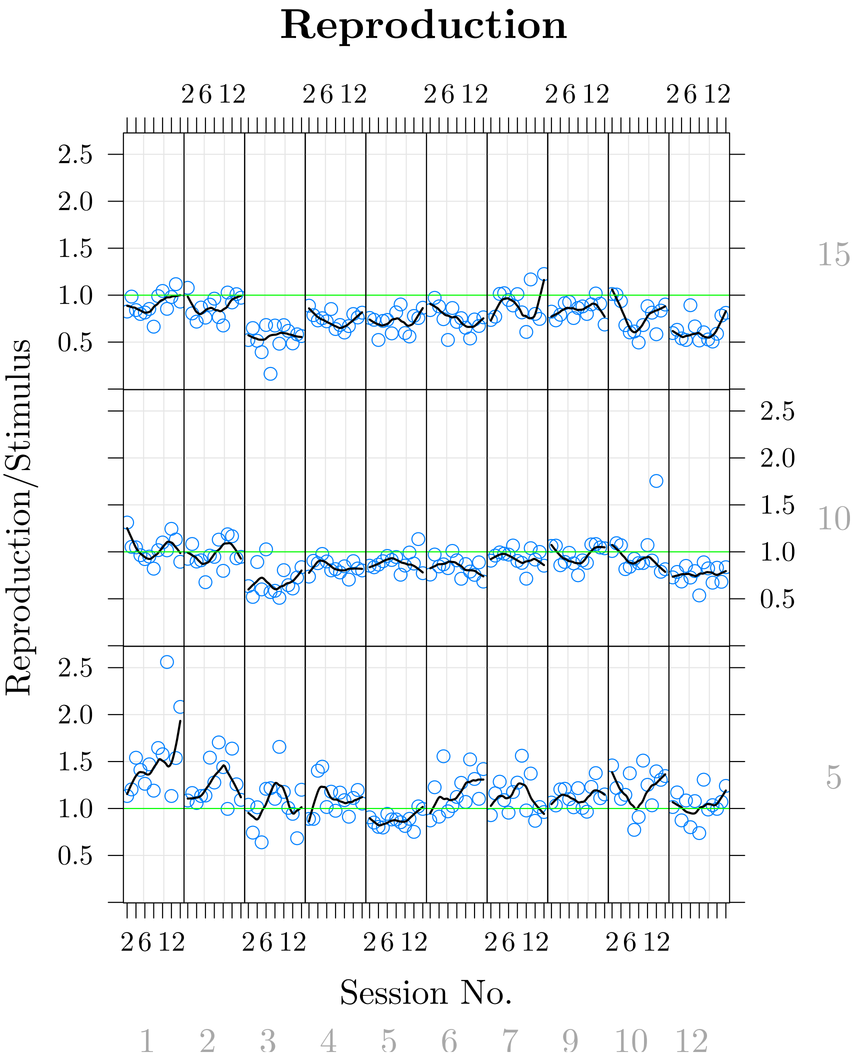

Figure 4.4: Individual profiles (IDs 1–12) across the protocol—Reproduction, Stimuli (5–15 sec; row-wise) × Subjects (column-wise), Median values (blue), added loess smoother (black), and target duration (green)

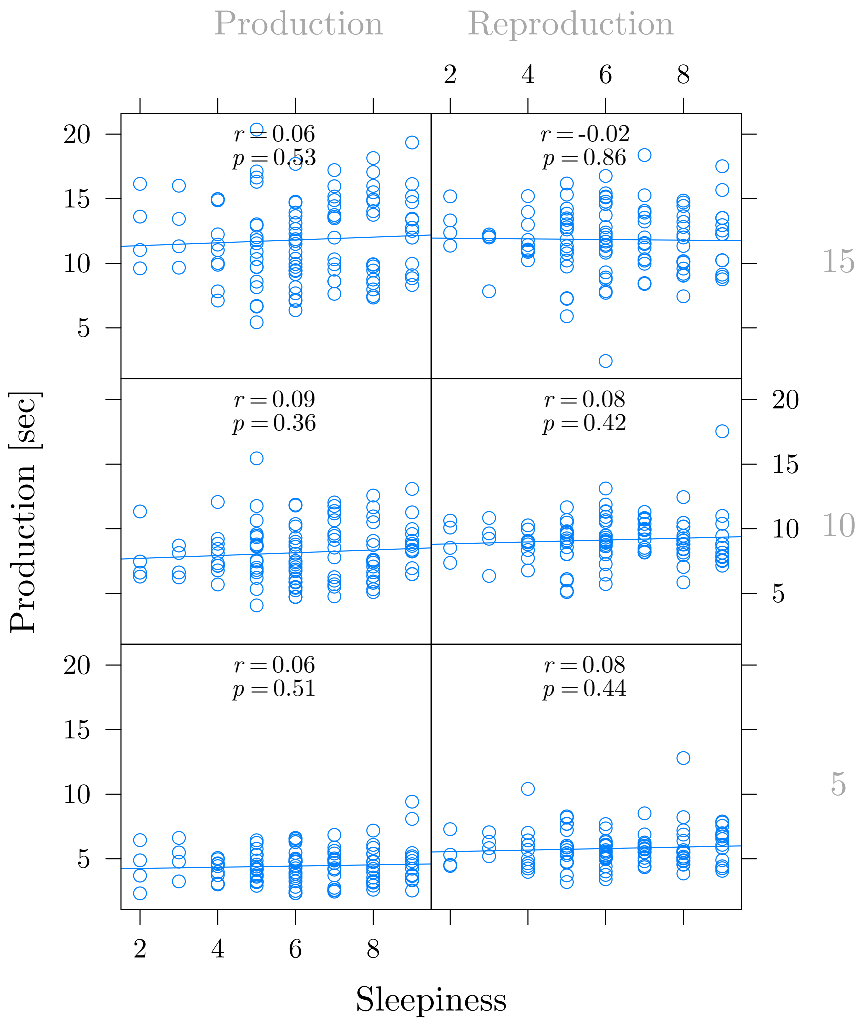

Figure 4.5: Correlation between interval timing and subjective sleepiness by stimulus (5–15 sec; row-wise) and task type (P, R; column-wise) across all participants; embedded numbers: correlation coefficients (above); p-values (below)

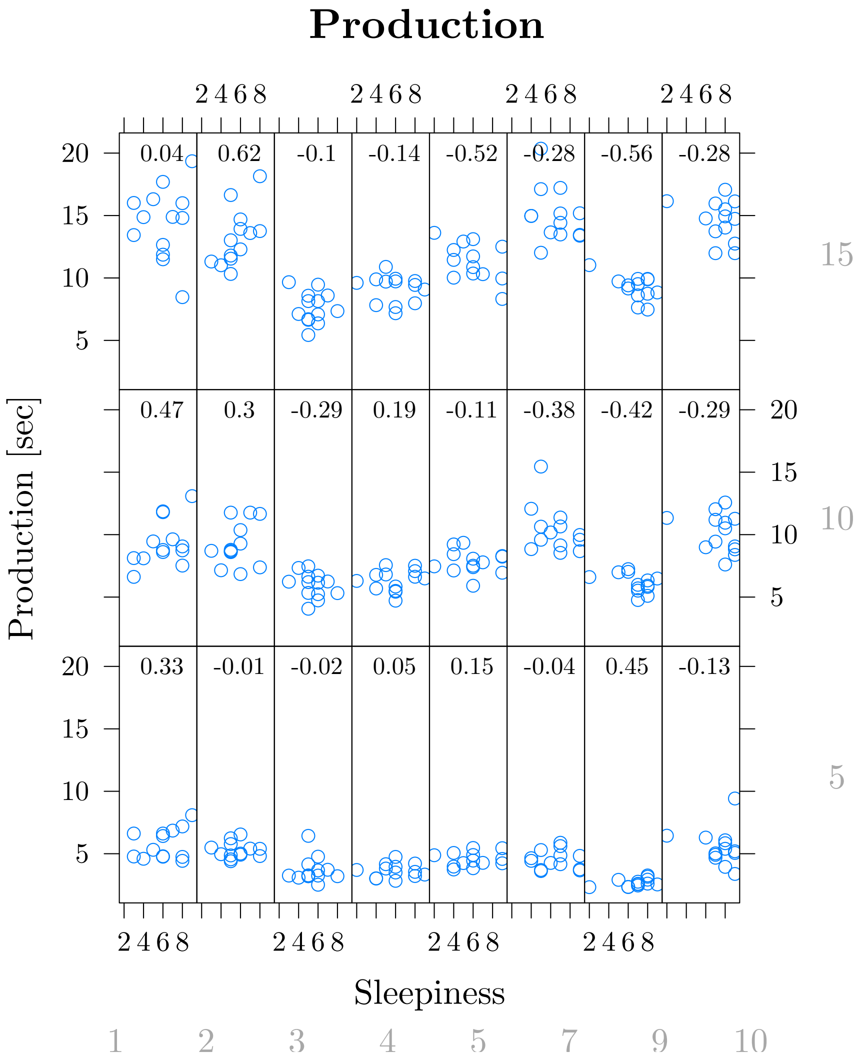

Figure 4.6: Correlation between produced duration and subjective sleepiness by stimulus (5–15 sec; row-wise) and participant (ID1–ID12; column-wise); embedded numbers: correlation coefficients

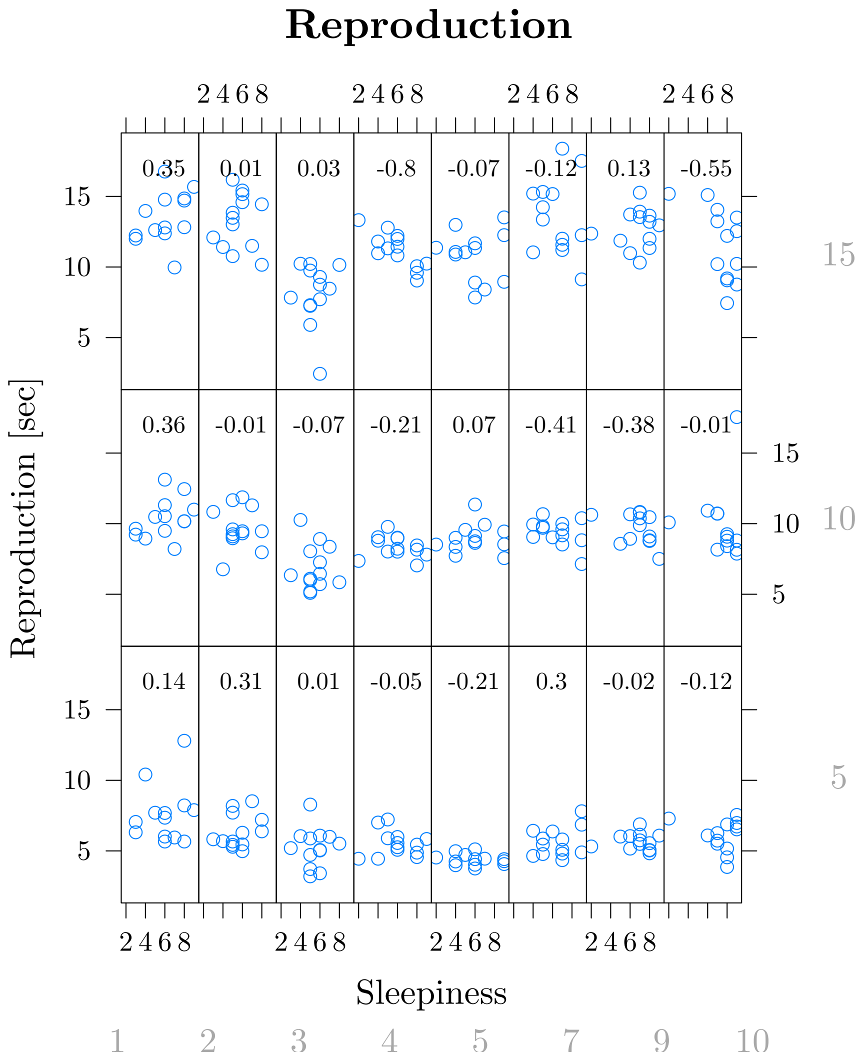

Figure 4.7: Correlation between reproduced duration and subjective sleepiness by stimulus (5–15 sec; row-wise) and participant (ID1–ID12; column-wise); embedded numbers: correlation coefficients

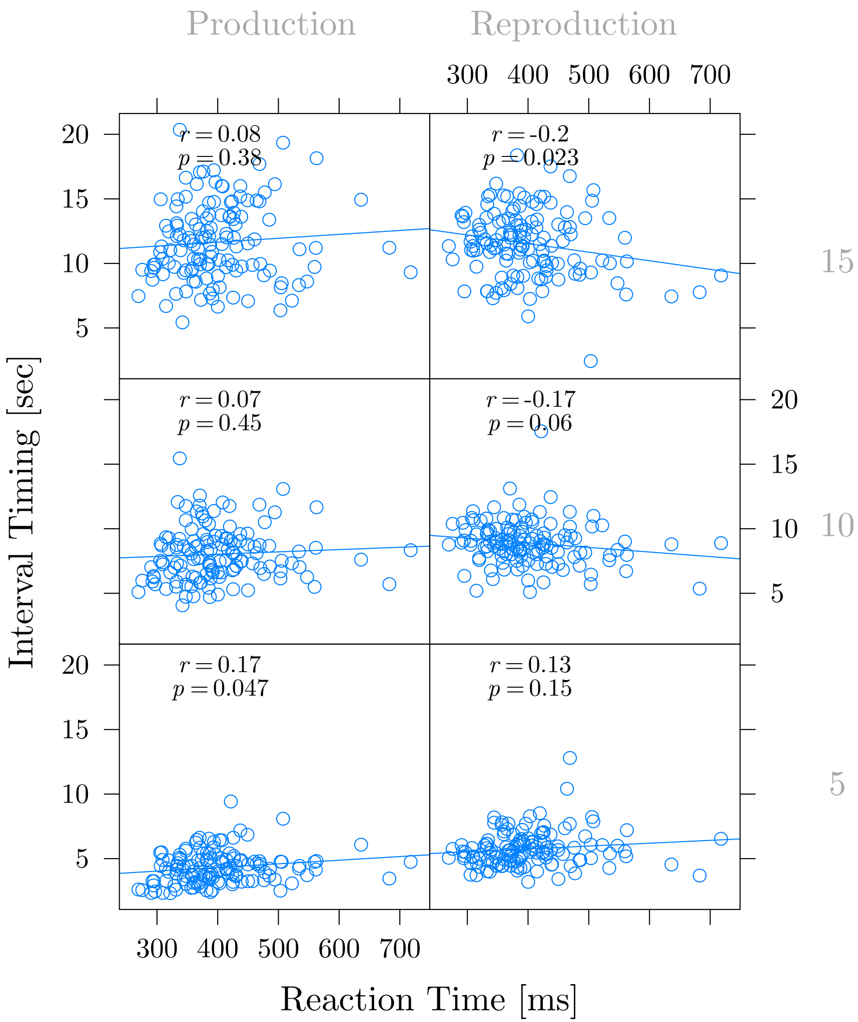

Figure 4.8: Correlation between interval timing and simple reaction time by stimulus (5–15 sec; row-wise) and task type (P, R; column-wise) across all participants; embedded numbers: correlation coefficients (above); p-values (below)

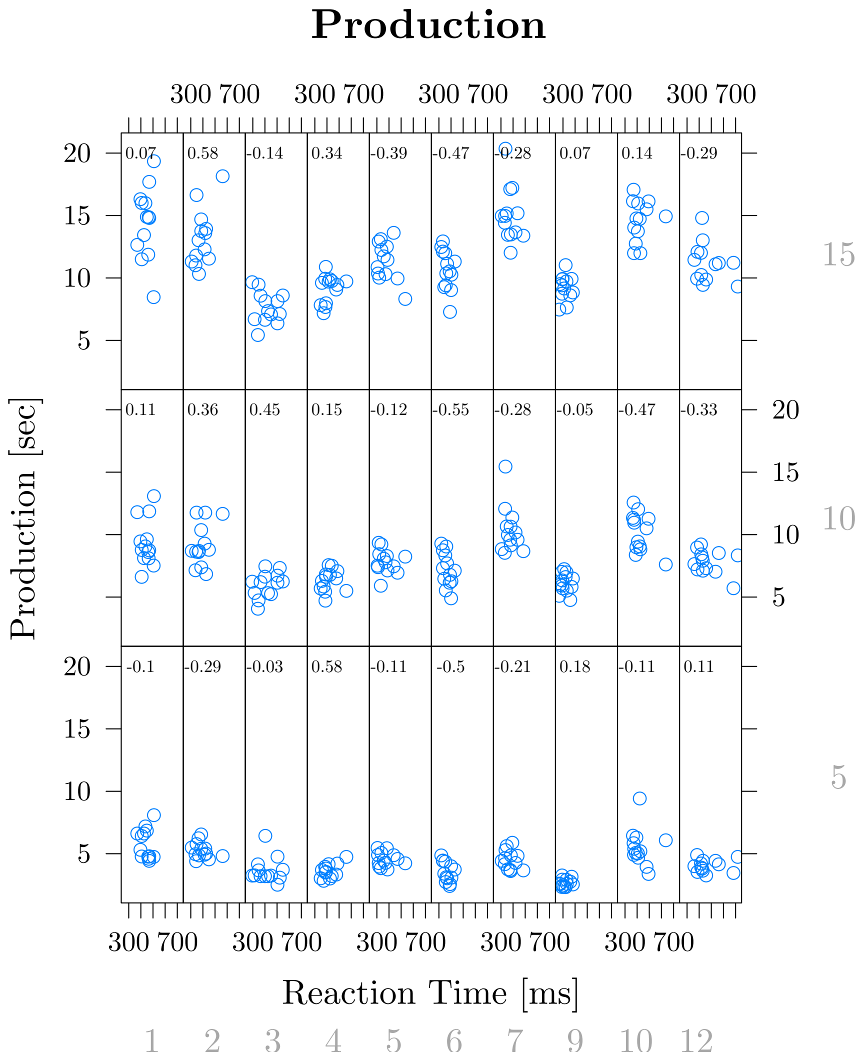

Figure 4.9: Correlation between produced duration and simple reaction time by stimulus (5–15 sec; row-wise) and participant (ID1–ID12; column-wise); embedded numbers: correlation coefficients

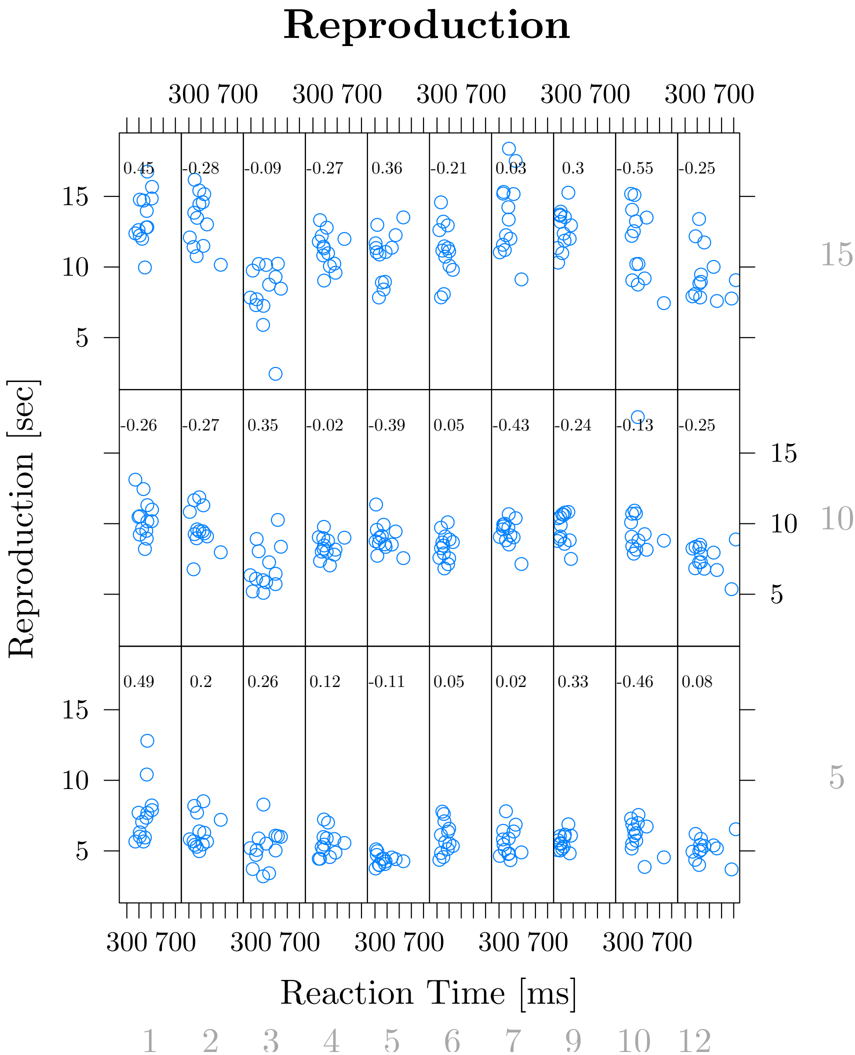

Figure 4.10: Correlation between reproduced duration and simple reaction time by stimulus (5–15 sec; row-wise) and participant (ID1–ID12; column-wise); embedded numbers: correlation coefficients

and scaling with stimulus magnitude but did not change substantially with progression of the protocol. The great degree of inter-individual variability also applied to progression of both production and reproduction across the protocol which revealed very different waveforms. In some participants and under some conditions, there seemed to be a linear trend which was combined with a putative circadian course in most conditions, the precise waveform of which was however highly subject-specific (cf. figures 4.3 and 4.4).

Overall correlations between interval timing and subjective sleepiness ratings were low (range: -0.02–0.09) and did not reach significance for any stimulus/task combination (cf. figure 4.5).

Correlations between individual responses in each interval timing task, stimulus magnitude (on a per-subject basis) and the subjective sleepiness ratings during the sustained wakefulness epoch (cf. figures 4.7 and 4.6) were low but indicated a weak positive relationship between these two variables for reproduction of shorter durations in some subjects.

Overall correlations between interval timing and performance during PVT sessions were relatively low (range: -0.2–0.17) but reached statistical significance for reproduction of the 15 sec interval as well as for production of the 5 sec interval (cf. figure 4.8). Correlations between individual responses during each interval timing task, stimulus magnitude (on a per-subject basis) and performance during PVT sessions (cf. figures 4.9 and 4.10) were relatively low in all participants.

4.4 Discussion

Using the methods of temporal production and temporal reproduction on several stimulus magnitudes in parallel, we collected interval timing data from ten healthy young male participants during 40 h of sustained wakefulness.

All durations were consistently under-produced and larger duration were also under-reproduced. Smaller durations were over-

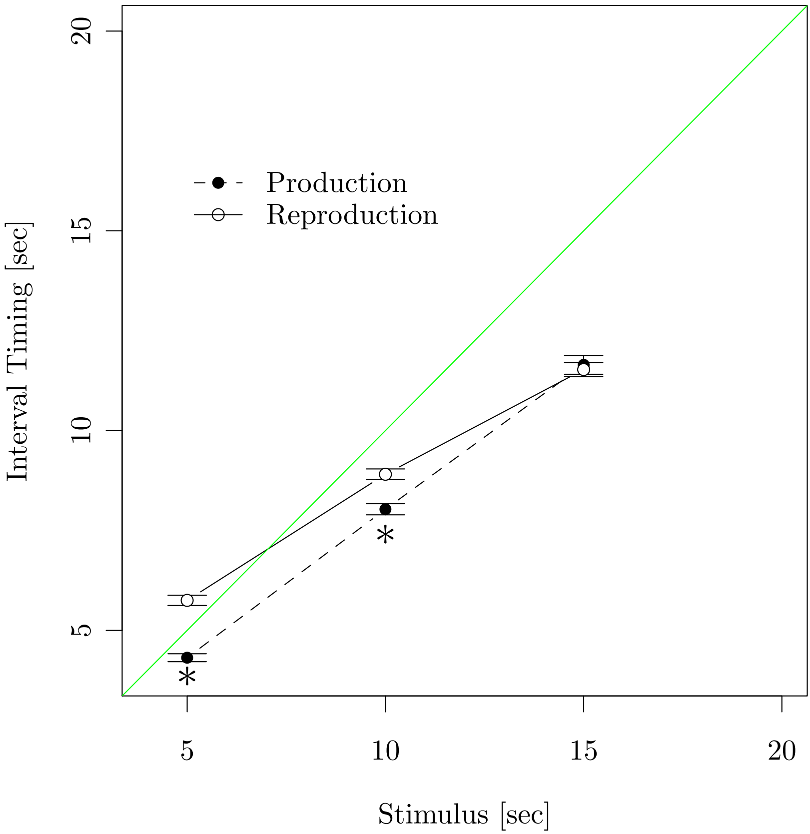

Figure 4.11: Production and reproduction vs. target duration; mean ± s.e.m.; green: line of identity (veridical interval timing performance). Produced durations were significantly lower than reproduced durations for the 5 sec and for the 10 sec intervals, as indicated by the asterisks

reproduced, especially during the second half of the protocol. The circadian features implied by some of the literature could not be clearly confirmed for our cohort, but we did observe moderate homeostatic changes during sustained wakefulness. We found a considerable degree of inter-individual variability in absolute levels, time courses and other aspects of interval timing which interacted with the stimulus magnitudes and experimental methods employed in a complex manner. This speaks against a central role of modulations in pacemaker speed.

On the other hand, the literature is not free of contradictory results, which might partly be due to the employment of unique and incompatible stimulus durations and methods in each particular study; also, most published designs comprise only a relatively limited subset of the conditions tested here.

One feature a number of studies agrees upon is an elevation of produced durations in the morning combined with a depression of produced durations during the night. Beyond this *circadian* pattern however, many studies fail to find a *homeostatic* modulation in interval timing. In production of 10 s and 60 s during 36 h of sustained wakefulness, Nakajima et al. observed a circadian pattern with afternoon troughs and morning peaks, but no changes related to sustained wakefulness [Nakajima et al., 1998]. Esposito et al. found neither circadian nor homeostatic changes in a 15 s production task across one night with sustained wakefulness.

According to Soshi et al. the pattern found for the time course of duration production by Nakajima et al. and other groups with morning peaks and evening troughs is attenuated by sleep deprivation for a 10 s stimulus. This finding is in contrast however to the data collected by Miro et al. on a 10 s production task which, during 60 h epoch of sustained wakefulness displayed a linearly *increasing* component adding to the circadian modulation. This group also describes an overall under-production, which was most pronounced during the night, a finding that is in line with our data. Similarly to the characteristics of our data, Miro et al. found consistent subject-specific differences in interval timing behavior. In contrast to the data presented here however, variability of produced durations increased with the duration of wake time in the data reported by Miro et al..

It should be pointed out that, in contrast to our study, Miro et al. explicitly instructed volunteers to adopt a counting strategy, whereas no information on enforced strategies is given in the works by Soshi et al., Nakajima et al. and a number of other groups. Our own data seem to confirm the presence of a circadian modulation reported in a number of studies. However, we do not find any wake-dependent changes in production which could be interpreted along the argumentation of Soshi et al., namely that sustained wakefulness dampens the increase in production that would have been observed under conditions of sleep satiation (cf. chapter two of this work), an observation seemingly coupled to a compensatory increase in activity of the prefrontal cortex (PFC). This may possibly also be related to the observed increase in reproduction of shorter durations if we assume that the accumulated temporal memory relaxes more slowly under compensatorily elevated PFC activity. In any case, this finding can not easily be interpreted in terms of the pacemaker rate of the hypothetical oscillator, as changes in the rate at which pulses are emitted cannot influence reproduction in a straightforward manner. A promising formulation of activation and working memory related modulation has besides been proposed by Wackermann and Ehm [Wackermann and Ehm, 2006] which may lend itself to a possibly fruitful interpretation of follow-up experiments.

Another explanation, namely that, despite the increasingly labile attention that accompanies sustained wakefulness, participants allocate more attentional resources to the task, due to boredom, was originally put forward in the context of temporal production by Miro et al.. This, via greater permeability of the hypothesized attentional switch, would lead to a greater number of pulses reaching the accumulator and thus to an elevated reproduction. On the other hand, the necessary differential action of the switch during the encoding and 'playback' phases is not very plausible and we have to conclude that the stage most likely to be involved in the observed phenomenon is the working memory of the prefrontal cortex with the memory trace for the encoded duration not attenuating as quickly as under conditions of sleep satiation.

In conclusion, we want to point out that the great degree of inter-individual variability present in our data may reflect in part the contradictory results in literature and on this basis, solid conclusions are difficult to make. A fundamental problem with our study as well as with those carried out by other groups seems to be the lack of control on the strategies adopted by individual participants. In fact, some of the aforementioned studies encouraged counting/sequencing strategies, while others give no information about the exact instructions given and/or compliance with these instructions.

In our study, counting or sequencing were explicitly discouraged but compliance is difficult to control and maybe even difficult to expect, especially in the production task, where the durations to produce are actually given as numerical values. A possible solution to this problem, as has been suggested before (cf. our own research on the circadian modulation of interval timing) may be the introduction of post-hoc questionnaires after each timing session which provides the participant with a means to self-evaluate his or her performance (with respect to the strategies employed) in the task. This could then be included as a predictor in a random coefficient modeling approach to data analysis which takes into account individual differences instead of simply pooling across participants as it happens in analysis of variance [Albert and Hunsberger, 2005; Barnett and Dobson, 2010; Cudeck and Harring, 2007; Olofsen et al., 2004; Durban et al., 2005; Schneider et al., 2004; Holden et al., 2008; Pinheiro and Bates, 2009; Young et al., 2009].

As indicated by the contrasting findings in the literature as well as our own data, interval timing seems to be a complex involving possibly several mechanisms operating in different tasks and stimulus magnitudes and possibly under great influence of individual characteristics in other variables. There are homeostatic and possibly circadian modulations in some aspects of interval timing, but especially the influence of circadian phase seems to be much weaker, fragile and isolated in terms of conditions then suggested by previous reports. To confirm these observations and attain a fine-grained and reliable view on the problem, an extension of usual research on interval timing in the circadian context is indicated, which needs to test several stimuli and methods in parallel and account for individual variability by taking into account possible predictors in a random coefficient modeling approach to data analysis.

Acknowledgements

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5 Time perception is sensitive to computer screen background illumination[1]

[1]In preparation for submission

Abstract

Advances in computer software engineering combined with research on human error and ergonomical and usability considerations have brought about an increased awareness in recent years, of the necessity to control and manipulate the way in which time is perceived in the context of human-machine interaction. Concurrently, the modern proliferation of information technology into almost all areas of everyday life, along with the technological transition in display technology towards light emitting diodes (LED) back-lit computer monitors and TV screens exposes an increasing number of people to light of biologically very potent wavelengths at nearly all times of day.

The recent finding, that exposure to LED-illuminated display technology in the evening differentially affects a broad range of physiological and psychological parameters, including arousal level, availability of attentional resources and different memory systems constitutes an interesting fact that links the developments mentioned above. As many of the cognitive subsystems that are differentially affected by LED-illuminated display technology—arousal, attention, memory systems—have been known for some time to play critical roles in the mechanisms sub-tending the perception and evaluation of durations in the seconds range, our intention in the current study was to assess the specific impact of exposition to different screen illumination technologies on interval timing.

We found a decrease in responses during exposure to a LED-illuminated screen, compared to exposure to a NON-LED-illuminated screen for both temporal production and temporal reproduction of varying durations in the seconds range. This finding is interpreted in terms of increased arousal as well as increased availability of attentional resources during exposition to a LED-illuminated display. Increased arousal and attentional resources availability entail changes in the operation of the pacemaker and attentional gating

components of the pacemaker-accumulator model of interval timing thus leading to the observed behavior.

In combination with recent findings that relate screen illumination technology to changes in a number of cognitive and physiological variables, our data is of considerable value to the design and implementation of equipment in the information industry that is optimized with respect to its bioactive and ergonomical characteristics and—more broadly—to architecture and lighting technology.

5.1 Introduction

With the dramatic advances made during the last number of decades in the field of micro-electronics and in associated areas, information technology has now become ubiquitous, readily accessible at all times of day and is of continuously increasing importance to both our working environments and our leasurly activities.

The most important modes of interacting with this kind of technology currently include the use of mechanical controllers (keyboard, mouse, joystick, nunchuck) for input as well as of various kinds of visual and, to a lesser degree, auditory displays (computer or TV screen, loudspeakers) for output. While traditionally, visual displays have been based on CRT or cold cathode fluorescent lamp (CCFL) illuminated LCD-technology, an increasing number of modern computer and TV screens now make use of light emitting diodes (LEDs) for illumination and display purposes. This transition in technology may have wide-spread biological and psychological implications since LED-lit displays, in contrast to more traditional technologies, typically show a peak in spectral composition of the emitted light in the high frequency region of the visual band, at a wavelength of around 460 nm.

This domain of the electromagnetic spectrum coincides with the region of highest sensitivity of photosensitive retinal ganglion cells, and these cells have been demonstrated to centrally participate in a master pathway by which light exerts a multitude of non-visual effects on physiology and cognition [Brainard et al., 2001; Cajochen et al., 2005; Chellappa et al., 2011]. An investigation into the differential effects of exposition to a LED-lit display vs. exposition to a NON-LED-lit display within a biologically particularly sensitive time window on various physiological and cognitive parameters has been recently discussed in a report published by Cajochen and colleagues [Cajochen et al., 2011]. The authors observed that a 5 h exposure to a white LED-back-lit screen screen during the evening elicited a significant suppression in the evening rise in endogenous melatonin as well as of subjective and objective measures of sleepiness, when compared to a 5 h evening exposure to a white NON-LED back-lit screen. Additionally, neurocognitive testing revealed overall greater arousal that was accompanied by enhancements in sustained attention, working memory and declarative memory systems during LED-back-lit screen exposure when compared to NON-LED-back-lit screen exposure.

Control and manipulation of the way temporal intervals are perceived and evaluated have been recognized to play an important role and to be accessible to interventions, including manipulation of lighting conditions in problems as diverse as the optimization of human-machine interaction [Seow, 2008] and architecture [Ando, 2004; Huang et al., 2009; Kacar, 2005]. In the present report, we intend to focus on a subset of the data collected in the study by Cajochen et al. with the aim of assessing the specific impact of exposure to LED-lit vs. NON-LED-lit screens on duration estimates in the seconds range. A number of studies have examined the impact on interval timing in the seconds to hours range of intensity [Geer et al., 1964; Delay and Richardson, 1981; Hancock et al., 1994; Aschoff and Daan, 1997; Morita et al., 2007] and spectral composition [Katsuura et al., 2007; Huang et al., 2009] of lighting conditions, including, in some cases, the interaction of these parameters with time-of-day [Morita et al., 2007; Katsuura et al., 2007; Huang et al., 2009] and the effects reported have been mostly linked to changes in arousal levels and the availability of attentional resources. The changes reported in the study recently published by Cajochen and colleagues [Cajochen et al., 2011] in these parameters under differential screen exposure may thus also entail corresponding changes in interval timing. A clarification of this issue would be of considerable significance to engineering biologically and ergonomically optimized user interfaces.

5.2 Methods

5.2.1 Participants

Thirteen healthy young male participants (mean age: 23.8 ± 0.5 years successfully completed the study. All participants were non-smokers, free from medical, psychiatric, neurologic, and sleep disorders (Pittsburgh Sleep Quality Index [Buysse et al., 1989], PSQI score ≤ 5) and of average chronotype (Munich Chronotype Questionnaire [Zavada et al., 2005], MCTQ score between 3 and 6) as assessed by screening questionnaires, and by a medical examination carried out by the physician in charge.

An additional opthalmologic examination was carried out by a certified optometrist, in order to exclude volunteers from the study that suffered from visual impairments, such as color blindness, diminished pupil reaction to light or reduced visual field. Wearing glasses or contact lenses did not belong to the exclusion criteria. Exclusion criteria comprised shift work or transmeridian flights within three months prior to the study and excessive caffeine and alcohol consumption, or drug use. All study participants gave signed informed consent; the local Ethics Committee approved the study protocol, screening questionnaires and consent form and all procedures conformed to the Declaration of Helsinki.

5.2.2 Protocol

The entire study protocol comprised two weeks; during this interval, participants kept a regular sleep-wake schedule (bed- and wake-times within ± 30 min of self-selected target time), compliance to which was verified via the use of sleep logs and ambulatory activity measurements (Cambridge Neurotechnologies, UK).

The laboratory phase of the study consisted of two separately conducted in-lab episodes of 5 h each, which were conducted on different days and separated by an interval of one week. During each of these in-lab sessions, participants were seated individually at a distance of approximately 60 cm from one of two computer screens (see below, section 5.2.3) inside a completely light-shielded cubicle. The order of exposition to each computer screen was balanced and crossed over to avoid potential sequence effects.

For each in-lab session, participants reported 6 hours prior to their usual bedtime, and were subsequently equipped with several physiological recording devices and trained on the tasks. Four and a half hours prior to usual bedtime, volunteers were dark adapted for 30 minutes, and then seated in front of the computer screen, thus starting the 5 h exposure episode, which ended one hour after their usual bedtime (for a detailed description of the protocol see [Cajochen et al., 2011]).

Cognitive testing was interrupted by a number of short breaks: every 50 min starting with the beginning of the protocol, volunteers were asked to relax for 10 min under dim red light conditions. Additionally, two hours after the beginning of the protocol, a relaxing film containing scenes in a snowy environment (i.e. white light) was displayed on the computer screen for 20 min, which the participants were instructed to watch at a distance of approximately one meter. The tasks carried out by the participants fit between these interruptions as follows: Salivary melatonin, sleepiness ratings (Karolinska Sleepiness Scale; KSS) at half-hourly intervals, starting with the beginning of the protocol, Karolinska Drowsiness Test (KDT) in hourly intervals, starting 30 min after the beginning of the protocol.

One hour before and one hour after the relaxing movie presentation, cognitive testing was carried out (time estimation, GO/NOGO-task, word-learning paradigm; for a detailed description of the tasks employed see [Cajochen et al., 2011]). Time estimation was sampled four times, beginning 30 min after protocol onset, at hourly intervals. The sampling session that would naturally have been the third was omitted such that the temporal distance between the second and the actual third sampling session was two hours rather than one.

5.2.3 Apparatus

The two computer screens employed were a LED-illuminated LCD-screen (HP LP2480zx) and a CCFL-illuminated LCD-screen (HP LP2475w). Both devices had a screen diagonal of 24 inches and a screen resolution of 1920×1200 pixels adjusted to identical luminance (250 nits). Both computer screens were set to a white background with a color temperature of 6953 K for the LED-illuminated screen and of 4775 K for the CCFL-illuminated screen. The amount of blue light in the LED-illuminated screen was approximately one third of the CCFL-illuminated screen. Spectral measurements were carried out using a Konica Minolta CS-1000 spectroradiometer. The difference in color temperature was visible, but the participants did not notice the difference after one week, when they changed to the other computer screen.

5.2.4 Measures

Interval timing was sampled via the concurrent use of two standard methods i.e., temporal production and temporal reproduction.

Production Target durations were displayed centered on screen using black Arabic digits on grey background. The participant's task was to identify the target duration and immediately begin holding down the space bar on the computer keyboard, stopping to depress the space bar after a duration that subjectively matched the target duration had elapsed. Thereafter, the machine displayed the next target duration until all stimuli for the current condition were exhausted.

Reproduction Target durations were indicated via the temporally delimited display of a black square on grey background, centered on the computer screen. Participants were instructed to hold down the space bar on the computer keyboard as soon as possible upon the extinction of the target stimulus, releasing the space bar after a duration subjectively corresponding to the target duration had elapsed. Thereafter, the machine displayed the next target duration until all stimuli for the current condition were exhausted.

Each interval timing session consisted of 15 (production; 3 target durations, each presented 5 times in pseudo-random order) or 25 (reproduction; 5 target durations, each presented 5 times in pseudo-random order) sweeps of the above structure. Both stimulus types were of approximately equal width and height. Production and reproduction sessions were conducted in sequence and immediately following each other. Task order alternated across participants and screen conditions and participants were instructed to refrain from counting, tapping or related sequencing strategies. Among other physiological and cognitive variables, salivary melatonin concentration was assessed concurrently with subjective sleepiness ratings at half-hourly intervals.

5.2.5 Statistical Analyses

Following outlier removal, the 5 sweeps per condition were collapsed onto their median value. Subsequently, a repeated measures analysis of variance using factors *session* (session), *task* (production vs. reproduction) and *stimulus* (stimulus duration) was calculated on the median values of paired durations, followed by separate one-way repeated measures analyses of variance using factor *session* on each stimulus duration.

The melatonin assay was conducted using a direct double-antibody radioimmunoassay (RIA, validated by gas chromatography-mass spectroscopy with an analytical least detectable dose of 65 pg/ml). To obtain average melatonin and KSS time courses, the corresponding values were averaged on a per-measurement basis.

The alpha-criterion was set at $p = 0.05$. The statistical packages R (The R Foundation for Statistical Computing, Vienna, Austria; Version 2.7.0), STATISTICA (StatSoft Inc., Tulsa, OK; Version 6.1) and SAS (SAS Institute Inc., Cary, NC, USA; Version 6.12) as well as the specialized CLEAVE (T. J. Herron, UC Davis and VANCHCS, 2003) and pyANOVA (R. Lew, University of Idaho, 2011) utilities for analysis of variance were used.

5.3 Results

Analysis of subjective sleepiness ratings yielded a significant effect for the factor 'session' ($F12,132 = 25.9$, $p < 0.0001$) but no significant effects for 'display' and 'display' × 'session'. A separate analysis on subjective sleepiness ratings confined to the period when the volunteers watched a relaxing film however revealed significantly lower sleepiness during the LED-screen condition vs. the NON-LED-screen condition ($p < 0.04$).

Analysis of salivary melatonin yielded a significant effect for factors 'display' ($F(1,11) = 5.9$, $p < 0.05$) 'session' ($F(12,132) = 137.5$, $p < 0.0001$) and for the interaction 'display' × 'session' ($F(12,132) = 3.0$, $p < 0.05$). Melatonin levels were suppressed during exposure to LED-screen vs. NON-LED-screen conditions and significantly so at 21:15 h, 22:15 h, 22:45 h, and 23:15 h.

Time perception data displayed the typical feature of scalarity i.e., the standard deviation of responses on average increased with stimulus duration for both tasks (cf. figure 5.1). Standard deviation was lower during temporal production than during temporal reproduction ($F(1,12) = 24.55$, $p < 0.0005$). Repeated measures analysis of variance on paired durations (i.e., durations employed in both tasks, production and reproduction; 5, 10, 15 sec) using factors 'display', 'task', 'session' and 'stimulus duration' revealed significant effects of factors 'session' ($F(3,36) = 4.3$, $p < 0.05$), 'task' ($F(1,12) = 5.2$, $p < 0.05$) and 'stimulus duration' ($F(2,24) = 153.3$, $p < 0.001$) as well as significant interactions 'session' × 'display' ($F(3,36) = 3.5$, $p < 0.05$) and 'session' × 'stimulus duration' ($F(6,72) = 3.7$, $p < 0.01$). Overall, production yielded smaller responses than did reproduction (cf. figure 5.5). Post-hoc testing revealed that responses were overall significantly lower during the

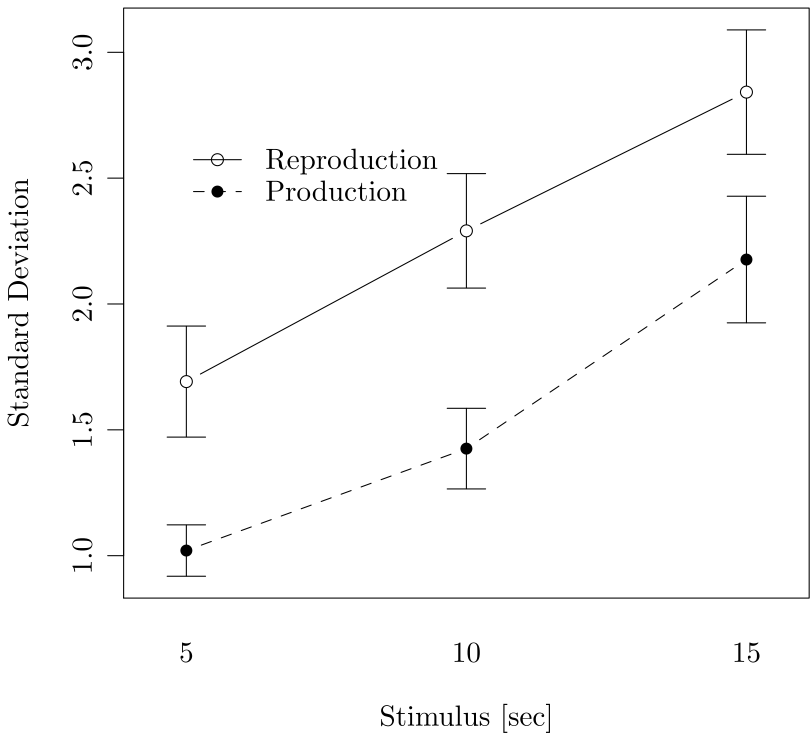

Figure 5.1: Relationship between stimulus magnitude and response variability (standard deviation); mean standard deviation across volunteers ± s.e.m.

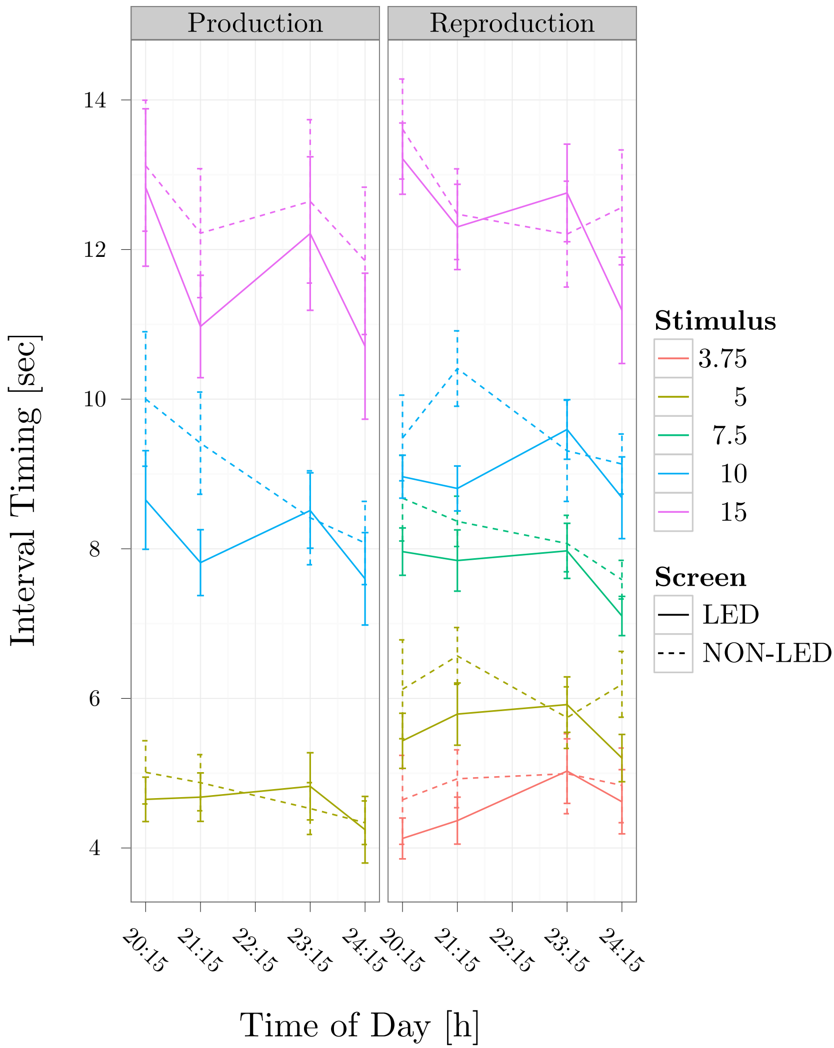

Figure 5.2: Temporal production (left panel) and temporal reproduction (right panel) under LED- (continuous lines) and NON-LED (dashed lines) screen conditions; mean $\pm$ s.e.m.

last session, when compared to the first session which subsequently conducted analyses of variance on individual stimulus durations attributed to changes in timing of the 10 s and 15 s stimulus durations (cf. figure 5.3). We observed almost continuously reduced responses under the LED-illuminated screen condition (except for the third measurement i.e., at 23:15 h) and post-hoc testing on the interaction between 'session' and 'display' revealed a significantly reduced response under the LED-illuminated screen condition during the second measurement, at 21:15 h (cf. figure 5.4).

5.4 Discussion

In our experiment, we found significantly smaller responses during the production task in comparison to the reproduction task as well as significantly reduced responses during the last session with respect to the first session which we could attribute primarily to changes in the timing of the larger stimulus durations. Both, produced and reproduced durations were almost continuously lower under LED-screen conditions than under NON-LED-screen conditions; the effect was significant during the second measurement session, around 21:15 h and turned over punctually during the third measurement session, at around 23:15 h.

We believe that the differences across the two tasks and the four sessions observed in the responses should be regarded with some caution in the light of our previous results gathered under even more strictly controlled conditions and the findings reported in literature. While a decrease in the response across sessions during the evening is in principle not contradicted by previous research, our own findings on the circadian and homeostatic influences on interval timing suggest a relatively large degree of inter-individual variability with respect to reactions to circadian and homeostatic challenges. The effects of circadian phase and, to a lesser degree, the state of the sleep homeostat on interval timing seem to be rather complex and highly variable across participants; furthermore, these effects are

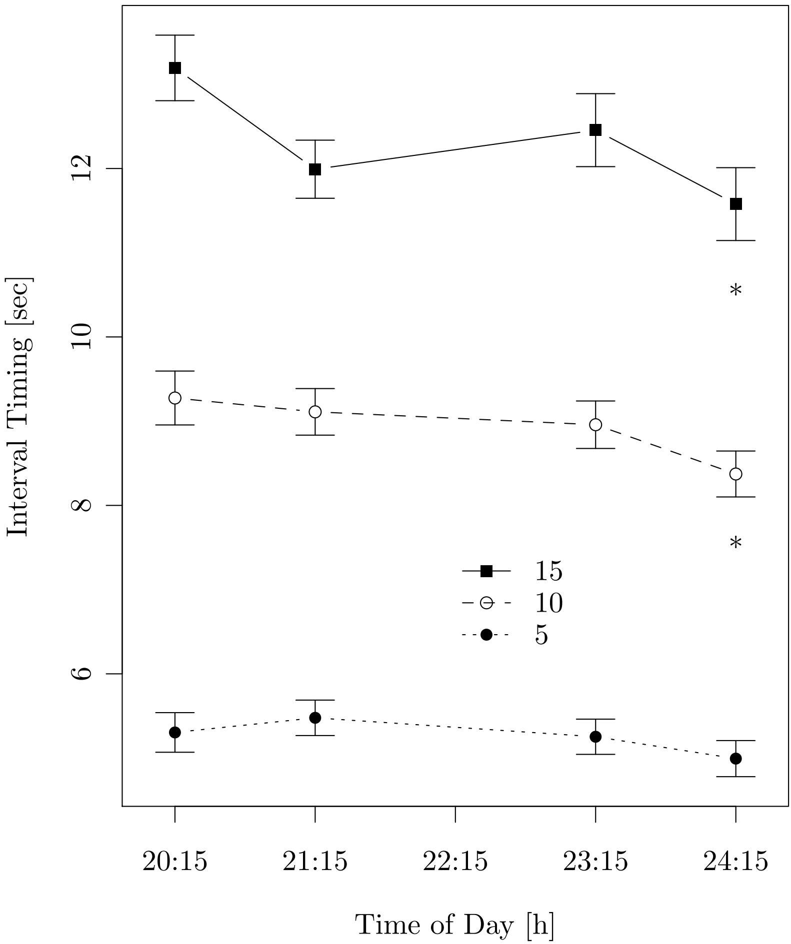

Figure 5.3: Progression in interval timing of different durations across the protocol. Asterisks denote significant differences from the first session; mean ± s.e.m.

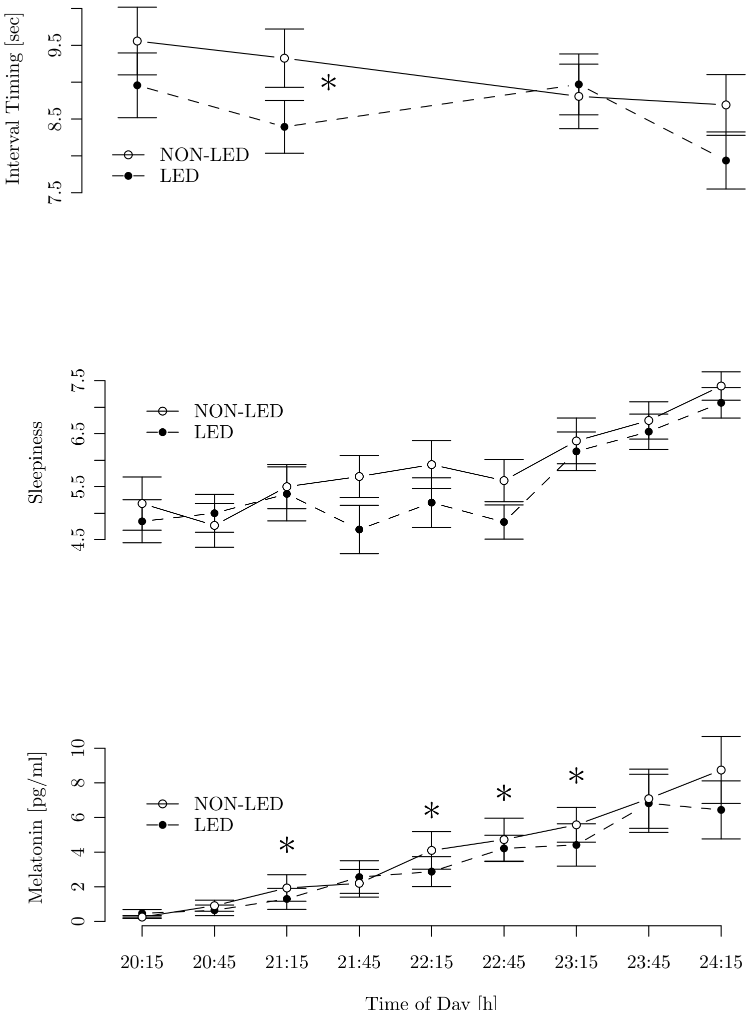

Figure 5.4: Interval timing (top panel), Sleepiness (middle panel) and salivary melatonin concentration (bottom panel) across the protocol under LED- (dashed lines) and NON-LED (continuous lines) screen conditions; mean $\pm$ s.e.m.

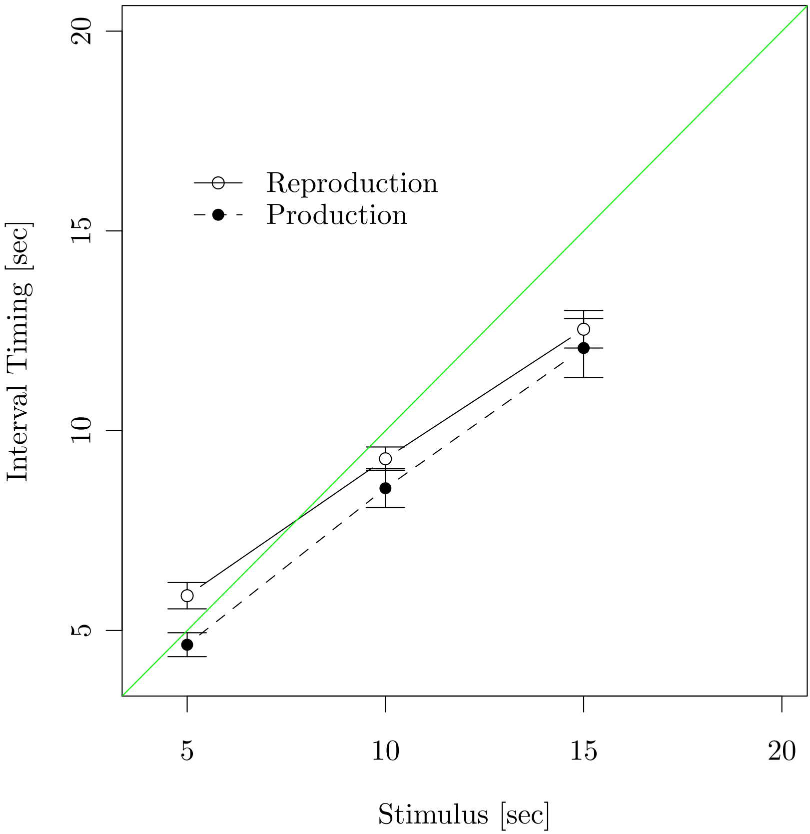

Figure 5.5: Production and Reproduction vs. target duration; mean $\pm$ s.e.m

probably relatively weak and seem to evolve over a considerably longer time-span than the five hours period observed here.

Also, the effect of task type has been repeatedly demonstrated to interact with that of stimulus duration in the sense that the production task usually yields roughly linear stimulus-response curves of varying slopes, whereas the reproduction task shows more curvilinear characteristics with the degree of curvature varying [Wackermann, 2007; Wackermann et al., 2008]; there is no support for stimulus-independent differences in absolute levels across these tasks however.

On the other hand, we find remarkable interest in the effects related to screen illumination. All stimulus magnitudes in both tasks, production and reproduction, yielded diminished responses under the LED-screen condition during all but one measurement sessions (in which a local reversal occurred in some task/stimulus combinations) and this effect was significant during the second measurement session at around 21:15 h. This result is complemented by several concurrently assessed physiological and psychological effects of exposition to LED-screen illumination: a generally increased arousal, a significant suppression in the evening rise of melatonin and sleepiness, an enhancement of sustained attention as well as working memory and declarative memory systems were reported by Cajochen and colleagues [Cajochen et al., 2011].

The literature on the effects of light of different illumination intensities and spectral compositions on interval timing is not free of inconsistent findings but this problem is more serious with respect to the effects of different illumination intensities than with respect to those of spectral composition, the latter being of primary interest here. To briefly touch on the literature discussing the assessment of different illumination intensities on interval timing, it can be summarized that Geer and colleagues [Geer et al., 1964] found no clear association between illumination intensity and interval timing behavior during a 5 min estimation task. Delay and colleagues [Delay and Richardson, 1981], using the method of temporal reproduction for a 15 sec interval reported significant effects of three illumination levels in that increased light levels typically entailed reduced durations during temporal reproduction; these authors also reported an interactive effect of illumination with sex. Hancock and colleagues [Hancock et al., 1994], using the method of temporal production during daytime testing reported explicitly instructing their participants to adopt a counting strategy. The authors could not find a significant effect of illumination intensity on mean response during the task. Aschoff and Daan [Aschoff and Daan, 1997] found that higher illumination levels entailed an elevated production for relatively short intervals (10 to 120 seconds) but not for durations of one hour. Finally, Morita and colleagues [Morita et al., 2007] reported that, after a 6 h morning exposure to bright light vs. dim light, a time estimation task around noon was characterized by increased estimates.

While the findings on illumination levels are thus not free of conflicting results they are of only limited relevance to our study in which the primary interest was on the effects related to spectral composition of illumination.

Our findings of reduced interval timing responses, increased arousal and availability of attentional resources during exposure to a LED-back-lit computer screen are in good accordance with results obtained by Huang and colleagues who, in twelve healthy young male participants of average chronotype, studied the time-of-day dependent effects of two different wavelengths of monochromatic light on the time course in a number of physiological and psychological parameters [Huang et al., 2009].

In order to assess the specific time-of-day dependent effects of short wavelength monochromatic light on physiology and cognition, the authors tested the differential effect of a 458 nm light source vs. a 550 nm light source. The experiment was carried out twice, on two separate days, once during the day and once in the late evening.

The nighttime session was scheduled to occur approximately 9.25 h before the respective individual participant's habitual wake time and the daytime session was scheduled to occur 12 h earlier. Unfortunately, the exact time-points are not reported in absolute terms, but given the chronobiological typology of the participating volunteers (average chronotypes), we may infer that the time of nighttime testing did not deviate substantially from the time of testing in the study reported here and probably coincided with the period between our third and fourth measurement sessions and that daytime testing probably occurred in the late morning or around noon.

The authors report that exposure to monochromatic light of 458 nm vs. monochromatic light of 550 nm at equal levels of irradiance density entailed a decreased response during a 180 s time production task along with a larger P300 amplitude during an oddball paradigm task as well as lower fatigue and that these effects were more pronounced during nighttime testing than during daytime testing [Huang et al., 2009]. This observation is in line with our own results, i.e. the finding of reduced interval timing response and reduced sleepiness under exposure to LED-screen illumination compared with exposure to NON-LED-screen illumination during the evening. Huang and colleagues interpreted the increase in P300 amplitude as indicative of an increase in availability of attentional resources under the LED-screen condition during nighttime testing [Gaillard, 1988; Huang et al., 2009]. This very effect, along with a generally increased arousal could also account for the decrease in interval timing responses observed in our study: increased arousal entails an increase in the rate at which the pacemaker of the pacemaker-accumulator model emits pulses, thus leading to reduced duration productions. Additionally, the enhancement in availability of attentional resources will allow the attentional switch that gates the pulses emitted by the pacemaker into the accumulator, to remain predominantly in the closed position, thus allowing the majority of the pulses to reach the accumulator stage. This would plausibly account for the observation of diminished production under LED-screen conditions in the evening but cannot readily explain the concomitant reduction in responses during the reproduction task. The effects of increased attentional resources may play a role here if we assume that attention is generally more effectively sustained during the encoding phase and more labile during the proper reproduction phase of the task. An increase in attentional resources would thus be of benefit primarily during the 'playback phase' of the reproduction task rather than during the 'encoding phase' and, as a consequence, lead to a decreased response. The enhancements observed in working memory and declarative memory systems observed in the present study [Cajochen et al., 2011] may also play a role here, but a better understanding of the mechanisms sub-tending the reproduction of temporal intervals is required, in order to make robust inferences in this regard.

The observations reported by Huang and colleagues as well as our own findings are also profitably related to results obtained in a study conducted by Katsuura and colleagues, in which nine healthy young participants (7 m, 2 f) were required to produce intervals of both 90 s and 180 s under red light (peak emission at 612 nm) and blue light (peak emission at 436 nm), both at 310 lx at the participant's eye level. According to these authors, production of 90 s did not differ significantly across lighting conditions but production of 180 s was significantly depressed under red light with respect to blue light. Whereas P300 amplitudes during an auditory oddball paradigm were of equal magnitude under both lighting conditions, P300 latency was reduced under red light. These researchers attributed the observed differences in time production and P300 characteristics to an overall greater degree of cerebral activity under red light [Katsuura et al., 2007].

The seeming inconsistency of these results with the data described in the study conducted by Huang and colleagues and our own data with respect to the effects of short vs. longer wavelength light on arousal and activation levels could be explained by the time-of-day specificity of the lighting effects: a number of findings indicate that, specifically during daytime, cortical activity may be enhanced by red-light exposure [Ali, 1972; Ueda et al., 2004] rather then blue light exposure which may be more effective during the night [Cajochen et al., 2005; Lockley et al., 2006]. In the study by Katsuura et al. which was conducted during the day, the P300 latency, a measure known to depend on the activity level of the cortex [Koshino et al., 1993] was significantly shorter in the red light condition than in the blue light condition. This finding is in line with results obtained by Ali and colleagues [Ali, 1972], who studied the effects of daytime exposure of red and blue light on the EEG alpha band amplitude. The authors reported that the alpha band amplitude had decreased more from its pre-stimulus value during red light illumination than during blue light illumination. In a similar line, Ueda and colleagues [Ueda et al., 2004] found that the priority of excitement intensity to colors presented on a computer screen was red>white>blue in Brodmann's area 17 and that the EEG beta wave intensity in the occipital lobe was red>white>blue. Taken together, these findings could indicate that the activity level of the cortex during the day may be higher under red light exposure than under blue light exposure. Conversely, during the night, the effects of light of different wavelengths may be different as suggested by research conducted by [Cajochen et al., 2005; Lockley et al., 2006; Revell et al., 2006]. Lockley and colleagues found that, during a night-time exposition of 6.5 h to light of different wavelengths, the delta-theta band power density was lower in blue light than in green light while the reverse was the case for the alpha band power density and that subjective sleepiness was lower during blue light exposition, when compared to green light exposition. Cajochen and colleagues found that blue light exposure during the night inhibited subjective sleepiness more strongly than green light exposure. Also, Revell et al. report that subjective alertness during nighttime testing was highest under 420 nm light compared to 470 nm light and lowest under 600 nm light. Finally, the increase in the effects of blue light during nighttime testing as compared to daytime testing reported by Huang and colleagues can be seen as support for the general idea of an interaction between wavelength and time of day.

In conclusion, the good accordance between the data obtained by Huang and colleagues, Katsuura and colleagues and our own research indicate that there is indeed a wavelength-dependent effect of light on interval timing which may be more robust than the effects of circadian phase or homeostat as endogenous variables and which is probably mediated by the actions of elevated arousal and increased attentional resources. Further research into this question is expected to lead to improvement of human-computer interaction which is critical to ergonomic and human-error considerations and should also impact a wide range of other domains, in which artificial illumination plays a role, such as in e.g., architecture or lighting technology.

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6 Concluding Remarks

Our aims with this work were to investigate the effects of circadian, homeostatic, and sensory challenges on several aspects of temporal control and, in consequence, delineate possible functional relationships among them.

In the first study described here, we investigated the relatively high-level feature of cognitive temporal orientation, which we operationalized as awareness about time of day, in two age groups consisting of sixteen volunteers each using a balanced crossover design that involved 40 h of sustained wakefulness and sleep satiation, respectively. During prolonged wakefulness, time of day was overestimated in both age groups and estimation errors varied in parallel with core body temperature. Overestimation was constantly high in older volunteers but increased with sustained wakefulness in young volunteers.

Data collected under sleep satiation equally revealed a diurnal oscillation in estimation errors as well as a general overestimation but showed no difference in magnitude of error between age groups and no interactive effects with progression of the protocol.

The behavior observed in this study led us to hypothesize a link between temporal orientation and the ability to time durations in the seconds range, a faculty generally referred to as interval timing. Specifically, based on what had been reported in previous research on the impact of age, circadian phase and sleep pressure on duration judgments, our results suggested the participation of a 'temporal path integration' mechanism in which an assessment of actual temporal position may ultimately be based on duration judgements.

In two further studies (chapters three and four of this work), we aimed at characterizing the circadian and homeostatic modulations of interval timing in more detail than had been done before with the intention to isolate the underlying mechanisms. We assessed interval timing in young healthy male volunteers for several stimulus magnitudes using the methods of temporal production and temporal reproduction in parallel under conditions of sustained wakefulness and controlled sleep, respectively.

Under controlled sleep conditions (NAP protocol; chapter three), all durations were over-produced with a slight linear increase in this behavior across the protocol. Smaller durations were equally over-reproduced but larger durations were under-reproduced, and more strongly so during the night

Under conditions of sustained wakefulness however, (chapter four) all durations were under-produced. Smaller durations were still over-reproduced, especially so during the second half of the protocol (high sleep pressure). Larger durations were under-reproduced, as it was the case for the data obtained under sleep-controlled conditions (cf. figure 6.1).

Absolute levels and time courses of the responses in both studies however varied greatly not only across different methods and stimulus magnitudes employed, but especially so across different volunteers.

We have to point out, as a consequence, that our inferences regarding the underlying mechanisms have to be taken with caution. Our findings do suggest however, that the effects of circadian phase and sleep pressure probably interact with attentional or working memory-related processes, rather than with the rate at which a hypothesized pacemaker emits pulses. The complex pattern observed in our data probably accounts for part of the disagreement and conflicting or inconclusive results with respect to the circadian and homeostatic modulation of interval timing that presently exist in the literature and may reflect the influence of other variables that are not accounted for in a proper way in most comparable studies, the most important of which may be the strategies adopted by the volunteers while executing the timing tasks. It is thus necessary to control for these variables and/or account for their effects, ideally in combination with a random coefficient modeling approach to data analysis.

In the last study described here, we investigated the effects of evening exposition to a LED-illuminated computer screen vs. a NON-LED-illuminated computer screen on temporal perception.

We found that durations were generally under-produced and that reproduced durations were generally higher than produced duration. Interval timing responses in both tasks were clearly lowered under LED-illuminated screen conditions when compared to exposure to the NON-LED illuminated screen. This result is in good accordance with the recently discovered differential effects of LED-screen illumination on general arousal, working and declarative memory systems and availability of attentional resources (cf. figure 6.2).

Taken together, our studies demonstrate the relative robustness of interval timing to circadian and, to a lesser degree, sleep-homeostatic challenges and a greater susceptibility to external stimulation. There is however a strong need for further strictly controlled experiments employing a range of stimulus magnitudes and methods in parallel as well as of recording of subject-specific co-variates that might be able to account for the great degree of inter-individual variability observed in this kind of experiments.

Bearing this caveat in mind, studies involving an assessment of cognitive temporal orientation and possibly a number of other measures of temporal control in parallel with interval timing may be suitable to delineate new terrain and interconnect previously isolated areas in our understanding of temporal control, which clearly is a key factor to human and animal behavior.

The findings reported here on the impact on interval timing of exposition to a LED-illuminated computer screen in the evening is of utility to the development of ergonomically and biologically optimized display technology and a better understanding of circadian and homeostatic influences on interval timing will certainly be beneficial to research on human error. Finally, linking the basic faculties of interval timing to higher-order features of our temporal perception may provide a better understanding of conditions in which these faculties are challenged and compromised and benefit areas as diverse as psychiatry and research into human performance and orientation in temporally isolated environments.

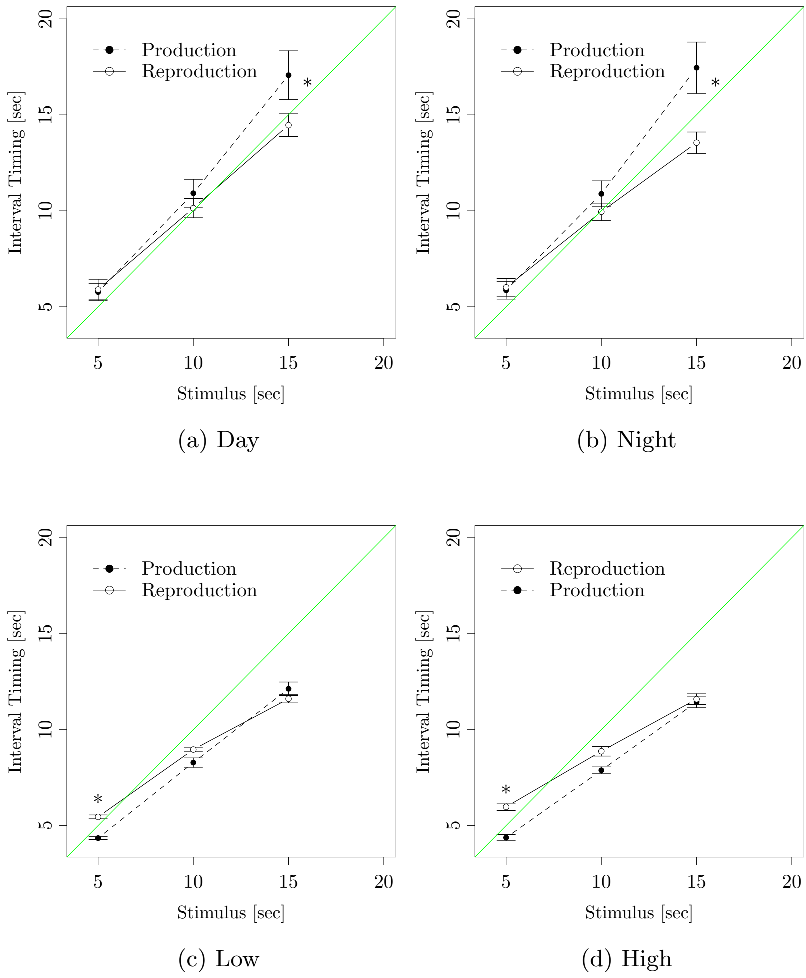
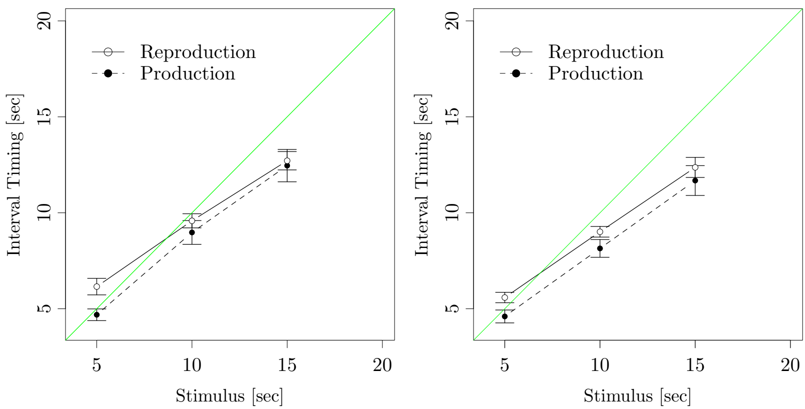


Figure 6.1: Production and reproduction vs. target duration in the NAP protocol (above) during the day (a) and during the night (b) and in the SD protocol (below) under low (c) and high (d) sleep pressure; mean ± s.e.m.; green: line of identity (veridical interval timing performance); asterisks denote significant differences between task types



(a) NON-LED

(b) LED

Figure 6.2: Production and Reproduction vs. target duration during exposure to differently back-lit computer screens; mean ± s.e.m.; green: line of identity (veridical interval timing performance)

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