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The circadian rhythm as a temporal frame to detect phase differences in physiological and psychological functions

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To my beloved father

His name is Xingming Wang (王兴明), and he forgets his name.

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Zusammenfassung

Die physiologischen und psychologischen Funktionen des Menschen stehen unter der Kontrolle der zirkadianen Uhr. Ziel dieser Studie war es, die potenziellen Auswirkungen der zirkadianen Modulation auf kognitive Leistungen zu analysieren, und die Phasenbeziehungen zwischen physiologischen und psychologischen Funktionen zu quantifizieren. Für das Experiment wurden 18 chinesische Teilnehmerinnen mittleren Alters rekrutiert, die in München studieren, um in einem isolierten Raum mit konstanter Beleuchtung den tageszeitlichen Verlauf von Funktionen zwischen 7:00 und 23:00 Uhr zu messen. Die Teilnehmerinnen gaben unter anderem subjektive Bewertungen zu Schläfrigkeit, Sättigung und Stimmung ab. Außerdem wurden Körpertemperatur, Griffstärke, Herzfrequenz, Blutdruck und das Speichelcortisol gemessen. Des Weiteren wurde eine kognitive Batterie eingesetzt mit Aufgaben zur Prüfung der zeitlichen Fusion, der psychomotorischen Vigilanz, der zentralen Hemmung mit einer Go/No-Go-Aufgabe, des persönlichen Tempos und der zeitlichen Reproduktion. Im Hinblick auf die zeitliche Wahrnehmung wurden Zeitfenster von zehn bis tausend Millisekunden eingeteilt; dieser Bereich der Studie zeigte den signifikanten Einfluss des zirkadianen Rhythmus auf die zeitliche Wahrnehmung in allen diesen Zeitbereichen. Diese unterschiedlichen Muster deuten darauf hin, dass die zeitliche Wahrnehmung am Morgen und am Nachmittag unterschiedlich ist. Die Tagesrhythmen der Biomarker sowie der subjektiven und objektiven Funktionen zeigen die regulierende Rolle der endogenen circadianen Uhr. Die verschiedenen Phasenbeziehungen der Funktionen erlauben Hinweise auf zu Grunde liegende neuronale Prozesse.

Abstract

Human physiological and psychological functions are under control of the circadian clock. The purpose of this study was to analyze the potential effects of circadian modulation on cognitive performances, and to quantify the phase relationships between physiological and psychological functions. For the experiment, 18 Chinese female participants were recruited who were studying in Munich. In an isolated room with constant light conditions the subjects participated in the experiment from 7:00 to 23:00. They gave their subjective evaluations on sleepiness, satiety, and mood; their body temperature, grip strength, hear rate, blood pressure, and salivary cortisol were measured. A cognitive battery was used for objective testing, including a two-flash fusion task, psychomotor vigilance task, a Go/No-go task, a finger tapping task, and a temporal reproduction task. Within the concept of temporal perception, the tested domains were classified into a tens-millisecond to a thousands-millisecond time window. This study showed the significant influence of circadian rhythm on temporal perceptions for all tasks. Clustering different functions suggested that temporal perception is different in the morning and in the afternoon. The diurnal rhythms of biomarkers and subjective and objective functions indicated the regulatory role of the endogenous circadian clock. The different phase relationships of functions provide hints for underlying neural processes.

List of abbreviations

Abbreviation	*Definition*
BFI-2	Big Five Inventory-2
CSS	composite satiety score
DBP	diastolic blood pressure
DTW	Dynamic Time Warping
ELISA	Enzyme-linked Immunosorbent Assay
ET	ear temperature
FDR	False Discovery Rate
FTT	finger tapping task
GNG	Go/no-go task
GS	grip strength
HR	heart rate
IE	interaction effect
ISI	inter stimulus interval
ITI	inter trial interval
KSS	Karolinska Sleepiness Scale
LGS	left-hand grip strength
LVF	left visual field
ME	main effect
MEQ	Morningness-Eveningness Questionnaire
MESOR	Midline Statistic of Rhythm
MTCQ	Munich Chronotype Questionnaire
NAS	negative affect score
PANAS	Positive and Negative Affect Schedule
PAS	positive affect score
PSE	point of subjective equality
PVT	Psychomotor Vigilance Task
RGS	right-hand grip strength
RT	reaction time
RVF	right visual field
SAS	Self-rating Anxiety Scale
SBD	shape-based distance
SBP	systolic blood pressure
SCN	suprachiasmatic nucleus
SDS	Self-rating Depression Scale
SE	simple effect
SMT	spontaneous motor tempo
TFT	two-flash fusion task
TMB	tetramethylbenzidine
TRT	temporal reproduction task
VAS	Visual Analogue Scale

1. Introduction

1.1 Circadian rhythm

Circadian rhythms are behavioral and physiological oscillations of approximately 24 hours that are internally generated and synchronized to environmental changes related to the solar day. The circadian clock is a complex mechanism that governs a large number of cyclical physiological and behavioral processes by manipulating different metabolic and gene expression pathways (Masri and Sassone-Corsi, 2018). Mammalian circadian rhythms display both top-down and bottom-up processes (Roenneberg and Merrow, 2016). The top-down process in mammals is regulated by the pacemaker-suprachiasmatic nucleus (SCN) located in the anterior hypothalamus (Reppert and Weaver, 2001). The SCN receives photic and non-photic input from photosensitive ganglion cells in the retina via the optic tract, synchronizes its own neuron cells, and transduces endogenous rhythms to the peripheral clock network (Yamazaki et al., 2000). The bottom-up generation of daily rhythms is the result of a network formed by a number of cellular clocks that establish circadian rhythms in tissues, organs and the whole organism (Gekakis et al., 1998; Hogenesch et al., 1998; Kume et al., 1999; Okamura et al., 1999).

1.1.1 The circadian clock in modern life

The invention of electric light and the application of the working regime have changed the primal biological rhythms of human beings (Wright et al., 2013). Light is considered to be the predominant time giver (also called as Zeitgeber) that entrains the circadian clock into 24 hours. In addition to light, food timing, temperature, and exercise time are important exogenous factors affecting endogenous rhythms (Haupt et al., 2021; Lewis et al., 2020; Zheng et al., 2019). Disruption of circadian rhythms not only affects work efficiency even increase the risk of disease.

Epidemiological studies suggest that sleep deprivation is associated with circadian rhythm disturbances (Bunney and Bunney, 2013; Goel et al., 2013; Möller-Levet et al., 2013). Sleep deprivation and circadian rhythm disorders are almost simultaneously present in shift workers, accompanied by a high risk of metabolic disorders, gastrointestinal disorders, cardiovascular diseases (Deng et al., 2018; Ha and Park, 2005; Papantoniou et al., 2018; Thosar et al., 2018). A growing number of studies have proven that artificial lighting at night has a negative impact on health and even leads to increased risk of cancers in breast, prostate, colon, and lung (Bauer et al., 2013; Chepesiuk, 2009; Kloog et al., 2009). Patients with neurodegenerative diseases, specifically Parkinson's disease, Alzheimer's disease, and Huntington’s disease have also shown the abnormal circadian rhythms (Coogan et al., 2013; Hastings and Goedert, 2013; Kondratova and Kondratov, 2012). Seasonal affect disorders (SAD) prevalent at high geographical latitudes have been shown to be associated with circadian dysregulation induced by the absence of sunlight exposure (Magnusson and Boivin, 2003; Rosen et al., 1990).

1.1.2 Markers of circadian rhythm

Melatonin and cortisol are well known as traditional biomarkers of circadian rhythms. Melatonin is a pineal hormone that is secreted at its peak during the night and lower to minimal during the day (Koch et al., 2017). The rhythm of melatonin is believed to be less masked by changes in the behavioural cycling. Melatonin has been proven to be suppressed by light, with low concentrations during the day or under bright light conditions (Lewy et al., 1980; McLntyre et al., 1989; Wood et al., 2013; Zeitzer et al., 2000). Cortisol or corticosterone is a steroid hormone that peaks in the morning and gradually decreases throughout the day. Plasma, saliva and urine samples are commonly used to measure these two biomarkers, with cortisol at higher concentrations than melatonin (Kirschbaum and Hellhammer, 1994; Meng et al., 2020; Selmaoui and Touitou, 2003b). A recent study found that β- Arrestin 1 works as a candidate biomarker of the peripheral circadian rhythm at molecular level (Tomita et al., 2019).

Core body temperature serves as another peripheral marker of the circadian phase of the SCN, as well as melatonin and cortisol (Aschoff and Wever, 1981; Kenneth P. Wright et al., 2002). Rectal temperature is considered to be an approximation of core temperature and is usually measured by an inserted sensor or swallowed pill. The circadian rhythm of rectal temperature peaks in the afternoon and decreases in the early morning hours during sleep (Aschoff and Wever, 1981). Due to the practical and hygiene reasons for core temperature, skin temperatures from oral, ear and extremities, are also extensively employed in researches (Bracci et al., 2016; Cuesta et al., 2017; Reinberg et al., 1980;

Simões and De Martino, 2007). The temperature of the eardrum reflects the temperature of the nearby carotid artery and has been supported by studies to measure core body temperature (Childs et al., 1999; Yeoh et al., 2017).

1.2 Rhythms of performance

1.2.1 Human chronobiology

Humans show great inter-individual variation in the performance of their behavior over a 24-hour period, as evidenced by their chronotypes (Roenneberg et al., 2007). By the Munich Chronotype Questionnaire (MCTQ) or Morningness-Eveningness Questionnaire (MEQ) individuals can be categorized as morning type, intermediate type, or evening type (Horne and Ostberg, 1976; Roenneberg et al., 2003). Chronotype has been shown to be dependent on genotype (Toh et al., 2001; Vink et al., 2001), environmental factors (Roenneberg et al., 2003), and habitual diet (Zuraikat et al., 2021). It has been found that the variation in human sleep behavior may be traced to a mutation in a gene, hPER2, which alters the cycle of circadian rhythms (Toh et al., 2001). Genotyping results of subjects with different chronotypes and patients with delayed sleep phase syndromes have revealed that the length of the circadian clock gene Per3 is associated with extreme circadian preference (Archer et al., 2003). The duration of exposure to daylight outdoors significantly affects sleep duration among all chronotypes (Roenneberg et al., 2003). Surveys in American women aged from young to old have shown that evening chronotypes compared to morning/intermediate chronotypes are more associated with poorer diet quality and unhealthy eating patterns (Zuraikat et al., 2021).

Epidemiological findings based on the large MCTQ database indicate that chronotype is also correlated with age and sex (Roenneberg et al., 2007; Roenneberg et al., 2004). Children are morning larks. On reaching adolescence, the ability to stay up late and sleep in is increased. The first biomarker of the end of adolescence is the sudden change in sleep duration by about age 20, when the chronotype changes to the night owl type. However, as individuals age into older, the chronotype shifts back to the morning type again. Girls reach their latest chronotype at 19.5 years, while boys can maintain this late chronotype until 21 years. Men on average have a later clock pattern than women, and this gender difference disappears when they reach about 50 years, which is the age when menstruation stops. Older adults over the age of 65 become morning types due to decreased outdoor activities accompanied by reduced sunlight reception and the advanced melatonin rhythm with lower secretion level (Kim et al., 2014; Van Someren, 2000; Weinert, 2000; Zeitzer et al., 2007).

1.2.2 Protocols to explore cognitive functions

One of the commonly accepted methods in human circadian rhythm studies is the constant routine protocol. In this method, participants are kept awake for at least 24 hours under constant light and temperature, they are provided with a continuous small amount of food and are required to maintain a semi-recumbent bed posture (Dijk et al., 2012; Duffy and Dijk, 2002). Endogenous circadian rhythms, such as core body temperature and melatonin, are studied to be independent of exogenous influences following the constant routine protocol (Dijk et al., 2012). Nevertheless, ongoing wakefulness is paralleled with increasing sleep pressure (Borbély, 1982). The constant routine protocol has failed to separate adequately the two processes of sleep cycle and circadian cycle.

In another protocol, the forced desynchronization protocol, participants are isolated from zeitgebers and exposed to an artificial sleep/wake cycle for days or weeks with "days" of shorter or longer duration than a typical 24-hour day. The endogenous circadian clock cannot be synchronized with the imposed sleep-wake cycle, but runs freely according to its own rhythm (Dijk and Lockley, 2002; Santhi et al., 2016). This greatly mitigates the effects of homeostatic sleep pressure on circadian rhythms compared to a constant routine protocol. However, it comes at an expensive time expense and experimental cost. Moreover, the circadian rhythms of the experimental tasks are potentially masked by practice effects (Schmidt et al., 2007).

A protocol based on chronotype has been used to perform group-based biorhythm differences as well. This protocol tends to follow a normal work regime where participants are able to engage in activities at their own pace (Randler et al., 2017; Schmidt et al., 2009), while more factors such as age and personality have also been integrated into the design(Adan et al., 2012; Duarte et al., 2014). Chronotype-based protocols do not separate the two processes of sleep and circadian in their interactions, though it has the advantages of specifying the interindividual differences in chronotype and the ease of manipulation.

1.2.3 Circadian fluctuations in subjective evaluations

The subjective evaluation in the 24-hour or diurnal time course essentially includes self-ratings of sleepiness, mood, hunger level, fatigue, pain, etc., and is generally assessed by the Visual Analog Scale (VAS) or Likert scale (Clark et al., 1989; Daguet et al., 2022; Dongen and Dinges, 2000; O'Donnell et al., 2009; Scheer et al., 2013b).

Subjective rating of sleepiness is a conveniently applied, sensitive and valid indicator, as is the objective alertness measures (Horne and Burley, 2010; Santhi et al., 2016). Higher sleepiness ratings have been shown to be associated with sleep disturbance in EEG studies (Akerstedt et al., 2014; Akerstedt and Gillberg, 1990). The diurnal rhythm of subjective sleepiness presents higher self-rating in the morning and evening (Akerstedt et al., 2013; Söderström et al., 2004). Sleep deprivation or increased sleep stress has been implicated as the one of the causes to fatigue (Mills and Young, 2008). And dysregulation of circadian rhythms can also lead to increased fatigue and pain sensitivity, which subsequently impairs the performance of diurnal activities (Hagenauer et al., 2017; Walker et al., 2020).

The VAS self-rating has revealed that the periodicity of mood shifts is close to 24 hours, with the happiest affects occurring during the day and the saddest affects occurring at night (Boivin et al., 1997). Furthermore, with the use of the Positive and Negative Affect Schedule (PANAS), where positive and negative affect were scored separately, only positive affect is found to have significant diurnal variation (Clark et al., 1989; Murray et al., 2009), whereas the rhythmic variation in negative affect is inconsistently concluded (Emens et al., 2020; Porto et al., 2006; Stone et al., 2006).

In the forced desynchronized protocol, hunger and satiety have been shown to exhibit significant intrinsic circadian rhythms, with hunger being highest and satiety being lowest in the evening (Sargent et al., 2016). It has been suggested that this intrinsic rhythmicity in appetite is a potential contributor to the high dietary demand at dinner (Scheer et al., 2013a). However, these studies are currently based on data collected in Europe or the US, in which dietary and cultural differences are not addressed. Asian regions, where the dietary structure differs significantly from that of Europe and the US, are undoubtedly worthy of investigation.

1.2.4 Circadian fluctuations in objective performances

The cognitive battery is a set of tasks in the cognitive domain that is widely used in health care, sleep and circadian rhythm studies (Abasaeed et al., 2018; Lo et al., 2012b; Rahman et al., 2022). The optimal time of day for performance on a cognitive test depends on the specific characteristics of the task, including the cognitive domain to which it belongs, its complexity, the observed indicators, the total duration of the task, the paradigm applied, and the employed experimental protocol (Schmidt et al., 2007).

Psychomotor Vigilance Task (PVT) has been considered as the gold standard for measuring the behavior effected by sleep loss and circadian rhythm disruption due to its remarkable reliability, sensitivity to prolonged wakefulness and circadian rhythm effects, and its low learning effect (Basner and Dinges, 2011; Dinges et al., 1997). PVT has also been commonly embedded in cognitive batteries as a measure of objective alertness and sleepiness (Arsintescu et al., 2019; Rahman et al., 2022; Santhi et al., 2016). The rhythmicity of alertness has been linked to core body temperature in studies with either constant routine or forced desynchrony or ultrashort sleep/wake protocols of PVT, for which higher body temperature is positively correlated to higher alertness (Cajochen et al., 1999; Kline et al., 2010; Wright et al., 2002).

At a higher cognitive level, working memory, spatial orientation, emotion recognition, and executive function have been applied to sleep deprivation and circadian rhythm studies in preclinical experiments and space missions (Basner et al., 2015; Nasrini et al., 2020). Researches investigating the relationships between the circadian rhythm and cognitive functions have shown that individuals have better performances at their optimal time in a diurnal day (Adan, 1991; Buela Casal et al., 1990; Hahn et al., 2012; Paradee et al., 2005). The n-back task is one of the most popular working memory paradigms. The circadian rhythm of n-back performance has been found in both verbal and visuospatial tasks (Ramírez et al., 2006). Females have lower discriminability on the verbal 2-back task compared to males in a circadian period (Santhi et al., 2016). The diurnal rhythm of visual spatial reactions assessed by mental rotation performance displays chronotype difference. Morning chronotype and evening chronotype participants perform the fastest response time at their preferred time respectively. In comparison, the speed and accuracy of the mental rotation performance among the evening chronotype participants are higher (Nishida et al., 2022). Inferior sleep quality and sleep deprivation can impair facial emotion recognition in the teen and adult population (Kyle et al., 2014; Soffer-Dudek et al., 2011). Circadian variation in emotion recognition has been found in adolescents, with higher sensitivity to anger in the morning among morning chronotype and intermediate chronotype participants, but lower sensitivity in those of evening chronotype (Lunn and Chen, 2022). However, no time of day effect is shown in a study with young adults (Yaremenko et al., 2021). In addition to age differences, the inconsistent findings may also be related to sample size and racial differences.

Besides the above, the short-term temporal perception in seconds has rarely been systematically studied in a circadian time course, even though temporal production has been suggested to be modulated by the circadian clock (Aschoff, 1998). Our perception and reaction processes to events have been shown to take place over time, and this might attribute to the timing mechanisms that structure the perception and motor processes in the brain (Akerstedt et al., 2014; Wittmann, 1999). Short-term duration perception has been studied on different time windows from 100-150 ms to 2 s with auditory stimuli (Itoh et al., 2019; Repp, 2004). The integration time window for auditory perception has been found to be approximately 100-150 ms (Repp, 2004). In a temporal order, two events are only discriminated within at least 20 to 40 ms apart in human studies (Hirsh, 1959; Pastore and Farrington, 1996). In the visual studies, a stronger inhibition of return magnitude has been found in the peripheral compared to the perifoveal visual field (Bao, Lei, et al., 2013). Whether there is circadian rhythmicity in the above described temporal resolution and eccentricity effects has not been well addressed.

A two-process model of time perception proposes that the perception and estimation of duration is anchored on a time window of 2-3 s (Fraisse, 1984). Below this time window is the process of time perception, while beyond this time window is the estimation obtained from memory. This model has been identified by studies varied from different research interests, especially in the temporal structure of poems (Turner and Pöppel, 1988), language production (Kien and Kemp, 1994; Yu and Bao, 2020), music perception (Wittmann and Pöppel, 1999), duration perception in a continuous competition (Gómez et al., 1995). The 2-3 second time window becomes one of our research interests when examining short-term temporal perception in the temporal frame under a circadian period.

There is no doubt that when placing cognitive functions in a circadian framework, the main Zeitgeber- light - must be accounted. The light-dark cycle, light intensity, and the spectrum are moderators influencing cognitive functions (Aschoff, 1985; Chen et al., 2021; Grant, Kent, et al., 2021; Rahman et al., 2021; Rahman et al., 2022). Meanwhile, other factors such as meal timing and meal size have impacts on human cognitive function while affecting blood glucose and lipid levels (Grant, Czeisler, et al., 2021). Therefore, the design of the cognitive battery deserves to be explored in detail not only by examining the performance of each task, but also by exploring the independence between tasks, the impacts of physiological factors and subjective evaluations on these tasks.

1.3 Methods of rhythmometry

1.3.1 Phase and phase relationship

Phase in chronology is defined as any point of an oscillation (Roenneberg and Merrow, 2016). Clocks that are entrained to each other or entrained to a common third oscillator have a specific phase relationship between them. The inter-phase relationship can be advancing and delaying or synchronous and opposing based on a comparison of the peaks or troughs of the rhythms. Entrainment is the process of establishing stable phase relationships between circadian biomarkers, such as peak cortisol concentrations (Molteni et al., 1979; Pina et al., 2010), the onset of melatonin secretion (Lewy et al., 1999; Lewy and Sack, 1989), and core body temperature nadir (Mina, 2021), and cyclic environmental cues, such as the onset and offset of the light-dark cycle (Skeldon et al., 2017; Stothard et al., 2017), the timing of feeding (Schibler and Sassone-Corsi, 2002), and so on . When entrainment is excluded, circadian clocks go to free-run with their endogenous period under the constant conditions (Czeisler et al., 1999). Such as blind people, they have difficulty maintaining a 24-hour time routine because they lack the photic pathway to synchronize with 24 hours and consequently present a free-running rhythm (Sack et al., 2007). The absence of environmental time cues is key to quantifying the circadian cycle, as it allows the endogenous nature of the body clock to be discovered without external influences and enables the circadian rhythms of multiple physiological and behavioral variables and their interactions to be assessed (McHill et al., 2017).

The application of chronology in biology and medicine depends on whether time influences the data. The process of quantification of time series is undoubtedly an important topic in chronobiology.

1.3.2 Rhythmometry

In general, the analysis of temporal effects on individual time series, such as daily rhythms of a particular physiological function or cognitive behavior, can be achieved by repeated measures ANOVA (Refinetti et al., 2007). It is worth noting that repeated ANOVAs need to be designed to obviate the order effects. Randomization of sequences is one way to counterbalance temporal effects by addressing, for example, randomizing the execution sequence of laboratory tasks in psychological experiments (Brooks, 2012). ANOVA applied in circadian rhythms merely assesses whether main effects or interactions are significant by comparing whether one or more means are significantly different from other means. A drawback is that it does not estimate patterns of rhythmicity.

Cosinor-based analysis is another traditional method established by Halberg F., Tong Y.L., and Johnson E.A. (Halberg et al., 1967) to use a cosinor regression model to quantify the circadian rhythmicity and parameters, such as period, amplitude, MESOR (Midline Estimating Statistic of Rhythm, a rhythm- adjusted mean), and acrophase, for time series. The method has been further developed by Cornelissen (Cornelissen, 2014) for the analysis of long time series, specializing in rhythmicity detection and parameter estimation. It is applicable both to non-equidistant and sequence-independent data. Fortunately, open sources for cosinor-based rhythmometry has been available on several popular platforms, such as MATLAB (Cheart, 2022), R (Augustin, 2018), Python (Moškon, 2020), and so on. Moreover, Fourier transform-based spectral analysis, wavelet transform and other methods have been developed for circadian rhythm fragmentations, such as daytime naps and nighttime activities that interrupt sleep (Ruben et al., 2018).

For the comparison of multiple time series, apart from identifying the characteristics of a single time series, the similarity among the patterns of various rhythms across the time course is also worthwhile to explore further. For decades, clustering has been one of the most common methods used in data mining (Berkhin, 2006). In the field of machine learning, the clustering process is considered to be an unsupervised process because there are no predefined categories and no empirical indication of what the ideal relationship between data should be (Linoff and Berry, 2011). The process of clustering can be summarized as: feature selection, algorithm selection, validity of the results, and interpretation of the results (Fayyad et al., 1996). In the step of algorithm selection, it is necessary to define the criteria for clustering, such as the minimum distance and or minimum variance between the members in a cluster (Halkidi et al., 2001). In a word, clustering is the method of separating data with similar summarized features and interesting correlations and then assigning them to clusters (Guha et al., 2001; Halkidi et al., 2001).

Clustering of time series has received a great deal of interest, as a powerful independent data mining method and an important preliminary processing step (Bagnall and Janacek, 2005; Gavrilov et al., 2000; Petitjean et al., 2011; Rakthanmanon et al., 2011). The methods of time-series clustering, such as *k*-Means, *k*-Medians, *k*-Shape, have been well used in identifying patterns of time-series data (Jain et al., 1988; Paparrizos and Gravano, 2016; Petitjean et al., 2011). *K*-Means as a partitional clustering, is one of the most widely used clustering methods. It aims to cluster multiple inputs into *k* clusters, where each data point has the closest mean (cluster centroid) (Hartigan and Wong, 1979). *K*-means is a point-based clustering method. It starts with the cluster centers initially arranged at random locations and iteratively moves the cluster centers to obtain the minimum clustering error. The main drawback of this method is its dependency on the initial location of the cluster centers (Likas et al., 2003). Therefore, the clustering centers must be arranged multiple times to obtain the optimal solution. *K*-Shape is a novel algorithm that relies on a scalable iterative refinement procedure that uses a normalized cross-correlation measure (Paparrizos and Gravano, 2016). This method preserves well the shape of the time series during the comparison. The distance metric based on a method for computing cluster centroids, which are used to update the distribution of the time series within the cluster at each iteration. Either diurnal or circadian rhythms can be considered as time series, and the exploration of patterns between multiple rhythms by clustering methods will provide an improved explanation of phase relationships.

Over all, circadian rhythms have been increasingly emphasized as a key factor to be considered in the treatment of sleep disorders, mood disorders (depression, bipolar disorder, crankiness, etc.), pharmacological design (Gaspar et al., 2019), and space missions (Luo et al., 2022). Scientific quantitative analysis of the circadian relationship between physiological and psychological changes will not only reveal the neural mechanisms behind circadian rhythms, but will also benefit more successful preclinical and clinical studies and contribute to more individualized treatment, ultimately benefiting patients.

1.4 Aims of this study

In order to design our experiment in which we combined physiological measures and subjective evaluations and behavioral performances across a range of cognitive domains in temporal resolution, alertness, inhibitory motor control, spontaneous motor tempo, and temporal reproduction. In accordance with the duration of the perceived temporal perception, we divide the task into three time-windows of tens-milliseconds, hundreds-milliseconds, and thousands-milliseconds. Here we use a modified constant routine protocol to establish and quantify circadian regulation in subjective and objective performances with physiological changes in healthy young Chinese females who are studying in Munich.

The aim of this work is to determine whether there are phase differences in the circadian modulation of the examined cognitive domains and how the phase relationships differ between the studied physiological and psychological functions.

2. Material and Methods

2.1 Participants

Eighteen young female participants provided the written informed consent prior to entering the study. They were paid for their participation. The protocol, screening questionnaires, and consent were approved by the Ethical Committee of Ludwig Maximilian University Munich, Munich, Germany. Exclusionary criteria were psychiatric and sleep disorders, medication or drug consumption, shift work within the three past months, transmeridian travel or disturbances in the sleep-wake cycle within one month before the experiment, obesity (BMI ≥30 kg/m^2), >10 pack-year of smoking, alcohol abuse, excessive caffeine (>500 mg caffeine per day) consumption, excessive physical activity, skin perfusion and tattoos on arms, pregnancy or menstruation during the experiment.

Table 1 Demographic and circadian characteristics (Mean ± SD)

Items	***Mean ± SD***
Age (years)	27.17 ± 2.07
BMI (kg/m2)	20.24 ± 1.89
Study time (years)	20.16 ± 2.01
BFI-2 Extraversion	3.72 ± 1.67
BFI-2 Agreeableness	9.22 ± 1.64
BFI-2 Conscientiousness	6.50 ± 1.73
BFI-2 Negative emotionality	-5.89 ± 2.07
BFI-2 Open-mindedness	9.44 ± 1.05
SAS score	35.39 ± 2.95
SDS score	44.22 ± 3.67
MEQ score	51± 4.19
MSFsc (hh:mm)	04:21± 00:42
Workday sleep duration (hh:mm)	23:23 ± 00:36 to 07:34 ± 00:36
Freeday sleep duration (hh:mm)	23:53 ± 00:37 to 08:46 ± 00:58

BMI, Body-Mass-Index; BFI-2, Big Five Inventory-2; SAS, Self-rating Anxiety Scale; SDS, Self-rating Depression Scale; MEQ, Morningness-Eveningness Questionnaire; MSFsc, mid-sleep on free days corrected for sleep dept on work days.

Participants represented a homogeneous group with respect to age, personality based on The Big Five Inventory-2 (BFI-2) (Soto and John, 2017a; Soto and John, 2017b; Zhang et al., 2021), bedtime and wake times on workdays and free days based on MTCQ (Roenneberg et al., 2003) and MEQ (Horne and Ostberg, 1976), and good mental health based on the Self-rating Depression

Scale (SDS) (Zung, 1965) and Self-rating Anxiety Scale (SAS) (Zung, 1971) (Table 1).

2.2 Procedure

Assessment of habitual sleep-wake timing

Participants were required to keep a strict sleep schedule from 23:30 to 6:30 and complete a sleep diary (see Appendix 1) daily for the duration of one week before the formal experiment (Fig.1). The screened participants came to the sleep laboratory for a habituation night. After this night, they followed the experimental schedule for 24 hours free from any social constraints.

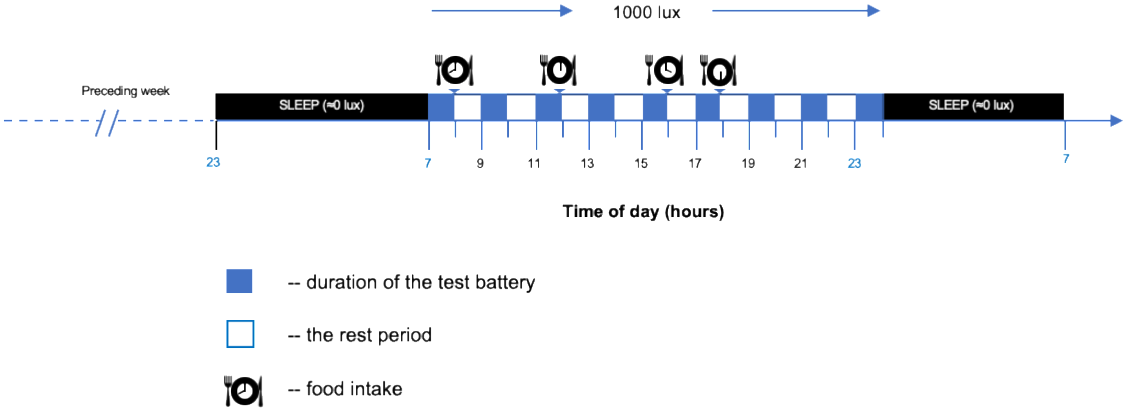

Fig. 1 Schematic representation of the experimental protocol. Participants came to the laboratory 5 hours before the adaptation sleeping time and stayed for two consecutive nights. The environmental light conditions were controlled as 1,000 lux for wake periods and around 0 lux for sleep periods. The physiological measurements were collected at hourly intervals and the psychological tests were conducted every two hours. Several meals were served at fixed time points.

Laboratory study

During the experimental day, participants completed all task operations independently. Participants underwent a 24-hour laboratory protocol. The experimental light duration was 17 hours (7:00- 24:00). The laboratory protocol started at 7:00 in the morning with 2 hours interval, 7:00, 9:00, 11:00, 13:00, 15:00, 17:00, 19:00, 21:00, 23:00 respectively.

The experimental days were arranged in weekdays in July to September in Munich (48° 8' N 11° 34'E), and the average day length was about 14 hours. During the adaptation and experimental days, participants stayed indoors and no visitors were allowed. Apart from the time when data were collected, participants spent the majority of their waking hours in the room where they can study, read, write or listen to soft music. They were exposed to normal indoor light during waking time, the illumination to the face was around 1,000 lux. Three main meals (at 8:00, 12:00, and 18:00) and a 200 to 300 g supply of watermelon (at 16:00) were served each day, and participants were free to have water. Napping and vigorous physical exercise were not allowed.

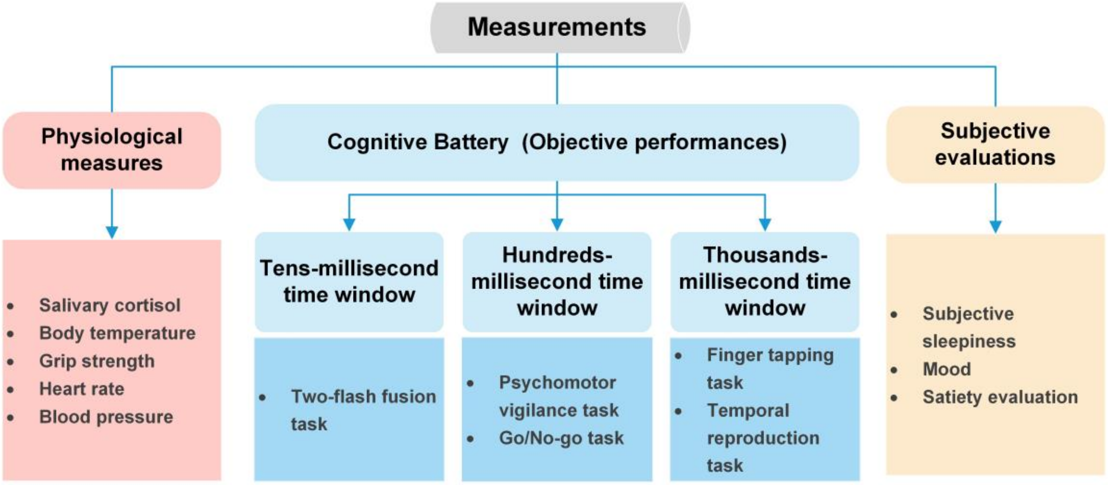

Fig. 2 General view of all measurements in our study.

As is shown in Fig.2, several physiological measures were designed in our study including salivary cortisol, body temperature, grip strength, heart rate, and blood pressure. Except for salivary cortisol, which was collected every two hours, other physiological indicators were measured hourly.

An up to 40 min cognitive battery was administered several times before the formal experiment to familiarize participants with the cognitive tasks and to minimize any effect of practice and learning. On the experimental day, the cognition battery was administered 9 times every 2 h on the scheduled wake time. The test battery was presented on an iMac with screen resolution of 4096×2304 pixels, refresh rates of 60 Hz, and running Psychtoolbox of Matlab 2020b (Mathworks, Sherborn, MA). Each test lasted for up to one hour, including the two-flash fusion task (TFT), the Psychomotor Vigilance Task (PVT), the Go/no-go task (GNG), the finger tapping task (FTT), and the temporal reproduction task (TRT).

In addition to this, a number of questionnaires were administered, subjective sleep and mood were required to be self-rated at two-hour intervals, and self-rated hunger levels were logged hourly.

2.3 Physiological measures

2.3.1 Salivary cortisol

The cortisol level was determined from the saliva samples collected before cognitive battery measurement at two-hour interval during waking time. For saliva collection, the Salivette (SARSTEDT AG & Co, Nuembrecht, Germany) was used and centrifuged for 5 minutes at 1,000 x g at 4 °C. The clear samples were frozen at -20 °C until quantification, which were done with ELISA (IBL International GmbH, Hamburg, Germany) following the instruction procedure. Briefly, add enzyme conjugate and incubate for 1 h at room temperature, wash 3 times, then add the TMB (3,3´,5,5´-tetramethylbenzidine) chromagen substrate and incubate for 15 min at room temperature. Lastly, add the TMB stop solution to terminated the substrate reaction. The optical density was measured with the microplate photometer (Thermo Fisher Scientific, USA) at 450 nm within 3 min after the terminating step. Each sample was measured with three technical replicates.

2.3.2 Body temperature

In this protocol, the bilateral ear temperature was used as a body temperature measurement. The ear thermometer (accuracy: ± 0.2 °C) detected infrared light emitted from the tympanic membrane by its sensor inserted into the ear canal. The measurement was repeated three times hourly during waking time.

2.3.3 Grip strength

This is a test that measures how strong a person's hand grip is, estimating muscle strength in the upper body (Reuben et al., 2013). This was measured by a digital hand dynamometer (tolerance: ± 0.5 kg/lb). The dynamometer was reset before every test. Each of the dominant and non-dominant hands had a practice trial. The grip strength test was measured three times with each hand alternately, at hourly intervals.

2.3.4 Heart rate and blood pressure

Blood pressure and heart rate (HR) were measured three times per hour while awake using an electronic upper arm sphygmomanometer (Omron M400, Omron electronics GmbH, Japan).

During the measurements, each participant sat in a comfortable chair, placed her feet flat on the floor, and kept her legs uncrossed. Each participant was instructed to place the measuring arm with the cuff on the table at chest level. The systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart beats per minute were recorded.

2.4 Subjective evaluations

2.4.1 Subjective sleepiness

The Karolinska Sleepiness Scale (KSS) was used to assess subjective sleepiness hourly (Akerstedt and Gillberg, 1990). Participants were required to rate how sleepy they were at the beginning and the end of the test on a 9-point Likert scale (1: very alert; 9: very sleepy.). The average of the two measurements was used to assess the level of subjective sleepiness during the cognitive test session.

2.4.2 Mood measurement

The PANAS was used to assess self-reported mood at two-hour intervals (Watson et al., 1988). Participants were required to rate their positive (interested, excited, strong, enthusiastic, proud, alert, inspired, determined, attentive, active) or negative (distressed, upset, guilty, scared, hostile, irritable, ashamed, nervous, jittery, afraid) affect over the past 2 hours on a 5-point Likert scale (1: very slightly or not at all; 5: extremely). The positive affect score (PAS) and negative affect score (NAS) were collected separately by summing the scores of positive or negative items, with higher positive/negative scores representing higher levels of positive/negative affect.

2.4.3 Satiety evaluation

Satiety was evaluated by the composite satiety score (CSS) (Flint et al., 2000; Gilbert et al., 2012; Laurila et al., 2021) with the equation:

$$CSS = \mathrm{satiety} + \mathrm{fullness} + (100 - \mathrm{hunger}) + (100 - \mathrm{prospective\ consumption}) \tag{1}$$

The items of hunger, fullness, satisfaction, and prospective consumption (pc) were self-rated by four VAS questions (described in Fig. 3). Participants were instructed to mark a cross on the 100 mm line corresponding to their satiety in the moment. Quantification proceeded by measuring the distance from the left terminal on the 100 mm line to the mark they had made. The satiety measure was administrated every hour, preceding the mealtime when the meal was served.

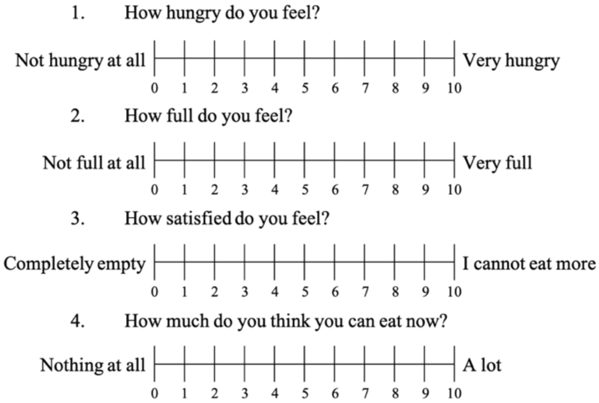

Fig. 3 The satiety visual analogue scale (VAS). VAS was applied to indicate hunger (question 1), fullness (question 2), satisfaction (question 3), and prospective consumption (question 4).

2.5 Objective measures- cognitive battery

This cognitive battery consists of five objective tests classified from temporal perception domain into tens-millisecond time window (including TFT), hundreds-millisecond time window (including PVT and GNG) and thousands-millisecond time window (including TFF and TRT), concerning temporal resolution, vigilance, inhibitory motor control, spontaneous motor tempo and duration perception. The order of the tasks was counterbalanced across participants but was fixed for each participant in the experimental period, which was aiming to reduce the practice effect (Lo et al., 2012a; Santhi et al., 2016). The objective measures totally lasted around 40 min and were conducted at a two-hour interval.

2.5.1 Two-flash fusion task (TFT)

In the two-flash fusion task (Fig. 4), participants were required to sit approximately 48 cm in front of the monitor with their heads fixed to a head rest and maintain their fixation at the central fixation without shifting their gaze during each trial. All trials started with a central fixation cross displayed for 1,000 ms, after which a peripheral cue (1.5°×5°) was randomly presented for 83.5 ms (five times the screen flip interval) in the left or right hemifield at 7° or 21° of eccentricity, aligned to the horizontal axis. The two target flashes each displayed for 16.7 ms (time interval for one flip of the computer screen), will be displayed after the cue stimulus disappears. The two target stimuli (1.5°×1.5°) are separated by four different inter stimulus interval (ISI) between the first and the second flash (0 ms,16.7 ms, 33.4 ms, and 50.1 ms). Participants were asked to indicate whether they perceived one or two flashes by pressing the corresponding “C” or “M” keys using both the left and right hand. The inter trial interval was set of

1,000 ms. Each condition was presented 15 times, leading to a total of 240 trials. The total task was divided into 6 sessions. A short break of 30 s between each session was inserted. The entire task lasted for approximately 11 minutes.

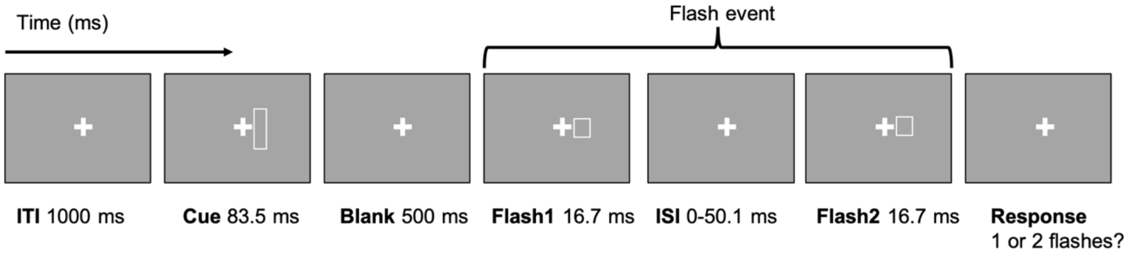

Fig. 4 The diagram of two-flash fusion task (TFF) procedure. ITI, inter trial interval; Flash1, the first flash (the first target); Flash2, the second flash (the second target); ISI, inter stimulus interval, varying from 0 to 50.1 ms in 16.7-ms steps.

The accuracy of the response in each condition was computed as the number of correct keystrokes divided by the number of events in that case. A 4 (ISI: 0 ms, 16.7 ms, 33.4 ms, 50.1 ms) by 2 (visual field: left visual field and right visual filed) by 2 (eccentricity: 7° and 21°) by 9 (clock: 7:00, 9:00, 11:00, 13:00, 15:00, 17:00, 19:00, 21:00, 23:00) within-subject repeated ANOVA was performed to analyze the rhythmic variation in TFT accuracy.

The two-flash fusion threshold is defined as the time resolution at which two sequentially presented, spatially overlapping flashes can be distinguished from one another within a certain ISI (Reeves, 1996). In psychophysics, the point of subject equality (PSE) is the point at which a comparable stimulus is judged by the observer to be equivalent to the standard stimulus (Meese, 1995). In our study, the stimulus length corresponding to the 0.5 probability point was considered the temporal fusion threshold. We employed a probability distribution with the Weibull function to fit the proportion of correct response at four flash events. The thresholds were estimated for each participant. The cumulative distribution functions for the applied Weibull distribution is:

$$F(x;k,\lambda) = 1 - e^{-(\frac{x}{\lambda})^k} \tag{2}$$

where, the parameters k represents the shape and λ represents the scale of the distribution.

For the repeated ANOVA, two visual fields, two eccentricities and nine clocks were taken as the independents to analyze the PSE.

2.5.2 Psychomotor vigilance task (PVT)

The PVT is regarded as the gold standard to assess sustained attention and vigilance (Basner and Dinges, 2011; Dinges and Powell, 1985; Lim and Dinges, 2008), which is proved to be insensitive to learning effect of neurobehavioral functions (Graw et al., 2004). A running time counter in the middle of the computer screen started counting (Fig. 5), and participants were asked to respond with striking the space bar as quickly as possible. After each key press, the screen scrolling numbers will stay for 1 s and then disappear, which refers the response time that has been taken before. The next counter will run at a certain time interval, which occurs randomly from 1-9 s. This requires that the participants must focus their attention on each event, and maintain their fixation at the central screen without shifting their gaze during each trial. The total task lasted for 5 min. The average reaction time (RT) of the responses and the number of lapses (reaction time > 500 ms) were used to indicate level of sustained attention (Basner and Dinges, 2011, 2012; Basner et al., 2011).

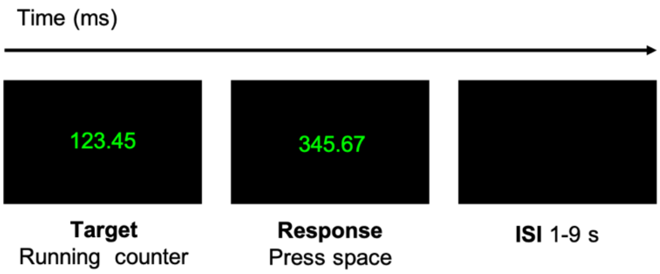

Fig. 5 The diagram of the psychomotor vigilance task (PVT) procedure. ISI, inter stimulus interval, varying from 1 to 9 s.

2.5.3 Go/No-go task (GNG)

The Go/no-go task is a common measurement to assess inhibitory cognitive control. Participants have to respond as quickly and accurately as possible to “Go” stimuli, and withhold responding to “No-go” stimuli. The Go/ no-go task had three blocks, each consisting of six different patterns of stimuli, with 30 s of rest during each break. Each block consisted of 18 no-go trials and 42 go trials. The six patterns of stimuli were designed with arrows to left or right, with triangle or rectangle or diamond above or below them (Fig. 6). Participants were asked to respond with their right index finger quickly to the stimuli (Go trials), but withheld their responding of the repeated stimuli (No-go trials) (Harms et al., 2017; Liu et al., 2019; Yin et al., 2016). The stimulus disappears once the key is pressed, while the response time is recorded. The stimulus lasts for a maximum of 500 ms, and the ISI is 500 ms. A short break of 30 s between each session was inserted. The entire task lasted for approximately 5 minutes.

Fig. 6 The diagram of the Go/no-go task (GNG) procedure.

Note that if no key is pressed for a "Go" stimulus, it is a "Miss"; if the key is pressed for a "No-go" stimulus, it is a "False", and the sum of these two cases are the GNG errors.

2.5.4 Finger tapping task

A finger tapping task was applied to measure spontaneous motor tempo (SMT) in correspondence with the preferred and natural pace. Participants were asked to tap the table at their “most comfortable and natural pace at this moment” for 30 s and to maintain the pace as steady as possible (Fraisse, 1982).

The experimenter counted the number of taps by a stopwatch, and subjects were not informed of the chosen tapping rhythm as the primary measure in this study. Any miscount and apparent tempo mismatch were requested to start over with a break of at least one minute in between.

2.5.5 Temporal reproduction task (TRT)

Based on the symmetry of the anatomical structure of visual pathway, only the left monocular visual field was employed in the temporal reproduction task. We employed a 2 (eccentricity: 7° and 21°) x 2 (durations: 1.5 s and 4.5 s) within-subjects design (Fig. 7). Each trial started with a duration of 1,000 ms of a white fixation cross (1°) centered on the black screen. Participants were required to wear an eye pad to mask their right eye, and seated approximately 48 cm in front of the monitor with their heads fixed to a head rest. They were instructed that they would see a white frame lasting for a certain amount of time. Afterwards they would see a white square at the same position lasting until they pressed a button on the computer keyboard. They were told to press the button when they thought the same amount of time had elapsed as for the first stimulus. The stimuli and targets only appeared in the left screen. Participants were instructed not to count and to maintain their fixation at the central cross without shifting their gaze during each trial. An inter trial interval of 1,000 ms with a blank screen were presented after their responds. Each condition was presented 15 times, leading to a total of 60 trials. The total task was divided into 6 sessions. A short break of 30 s between each session was inserted. The entire task lasted for approximately 10 minutes.

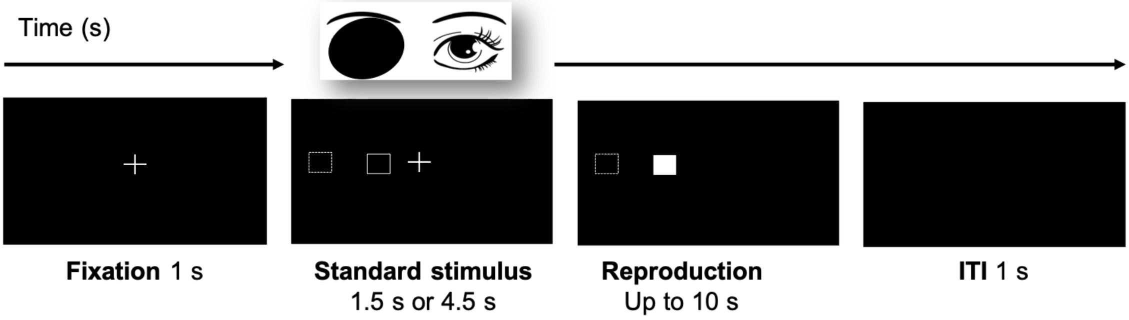

Fig. 7 The diagram of the temporal reproduction task (TRT) procedure. ITI, inter trial interval. The stimuli and targets only appeared in the left screen, and participants' right eyes were masked.

2.6 Data analysis methods

All statistical analyses were performed using SPSS 28.0 (SPSS Inc., Chicago, IL, USA), R version 4.1.3 (R Core Team, Vienna, Austria) and Python 3.10.0 (Rossum et al., 2009). Data was visualized using GraphPad Prism 8.0.0 (GraphPad Software, San Diego, CA, USA) and OriginLab 2022b (OriginLab Corporation, Northampton, MA, USA).

2.6.1 Repeated ANOVA

Data in 24- hour time course were analyzed with a repeated ANOVA with *Bonferroni* post-hoc tests. In repeated ANOVA, the independent variables contained clock time and the within-group factors for each measurement. These measurements were repeated over a daily period, which was specified as dependents. For the repeated ANOVA, interaction effect was always given first priority. If the interaction effect was significant, simple effects analysis and *post hoc* tests with *Bonferroni* correction would be performed. Otherwise, the main effect would be considered for the main explanation. *P*-values less than 0.05 were considered significant.

Repeated ANOVA was performed by SPSS 28.0 (SPSS Inc., Chicago, IL, USA), and the results were visualized by GraphPad Prism 8.0.0 (GraphPad Software, San Diego, CA, USA) or OriginLab 2022b (OriginLab Corporation, Northampton, MA, USA).

2.6.2 Cosinor regression model

In our study, the cosinor analysis of the diurnal rhythms was conducted by the *cosinor2* package in R (Cornelissen, 2014). The data was fitted to the cosinor function (Bingham et al., 1982; Cornelissen, 2014; Halberg et al., 1967):

$$\mathrm{f(t)} = \mathrm{M} + \mathrm{A} * \cos(\frac{2\pi \mathrm{t}}{\tau} + \emptyset) + \epsilon_t \tag{3}$$

where M is the MESOR, A is the amplitude, ∅ is the acrophase (time of peak), τ is the period (duration of the cycle), and ϵ_t is the error term. The parameters (MESOR, amplitude and acrophase) of cosinor models were compared by the F statistics (Bingham, 1970). The fit of the model was assessed by rhythm detection test (Cornelissen, 2014) and its significance and percentage of rhythmicity were determined. The iterative cosine procedure was used for the determination of the best-fit period (Klemfuss and Clopton, 1993). The iterative cosinor procedure increased the period τ by 1 at each iteration. The percent of rhythm was calculated at each iteration so that the maximum value corresponded to the best-fit period.

A zero-amplitude test was applied to detect the rhythmic significance of the cosinor model. The test is based on the F-ratio as follows (Cornelissen, 2014) :

$$F = \frac{\frac{\sum(\hat{Y}_i - \bar{Y})^2}{df_1}}{\frac{\sum(Y_i - \bar{Y})^2}{df_2}} \tag{4}$$

where $df_1 = 2$, $df_2 = N - 3$, N is the number of clocks, $\hat{Y}_i$ is the fitted data, Y_i is the observed data, and $\bar{Y}$ is the arithmetic mean value of observed data.

Data visualization of cosinor analysis was conducted by OriginLab 2022b (OriginLab Corporation, Northampton, MA, USA).

2.6.3 Correlation network visualization

The correlations among physiological measures, subjective evaluations, and cognitive functions were analyzed by *Spearman's* correlation tests with the *corrr* package in R. The *p*-values were adjusted for multiple inference using *False Discovery Rate (FDR)* method. The visualized network was conducted by the *igraph* package in R. *P* values less than 0.05 were considered statistically significant for all analysis.

2.6.4 Time series clustering

We applied the *tslearn* machine learning framework in python 3.10.0 to process time series clustering (Tavenard et al., 2020). A combination of Elbow method and Silhouette coefficient/score was employed for clustering validation. In the Elbow plot, the sum of the squared distances from each point in a cluster to its centroid was calculated as the distortion score. The best *k*-value was selected when the distortion score drops sharply and the addition of more data samples could not significantly alter the clustering membership. In this case, the elbow diagram showed a sharp drop followed by a plateau. The *k* at the transition point was referred to as the "elbow", which represented the optimal solution(Bholowalia and Kumar, 2014).

The Silhouette method was as well used to find the best clustering solution and to validate the coherence within the clusters of data (Rousseeuw, 1987). The Silhouette method first calculated the Silhouette coefficient of each object, which measured how similar objects in one cluster are to other objects and to objects in neighboring clusters. Then, the Silhouette coefficients of all objects in a cluster were averaged to obtain a Silhouette score. The Silhouette plot ranged from -1 to 1, where a high value indicated that an object has a good match with its own cluster and a poor match with the neighboring clusters. The score was bounded by -1 for improper clustering and 1 for highly densified clustering. Scores at about zero indicated agglomerative clusters.

Nevertheless, the evaluation of the clustering effect of these above two methods depends on applied algorithms. Two clustering algorithms, DTW *k*-Means and *k*-Shape (Paparrizos and Gravano, 2016; Petitjean et al., 2011), were compared in our study.

Both of these two clustering methods are based on the iterative and refinement procedures to preserve the shapes of time series. The centroids of the two algorithms depend on their distance measures. The DTW distance is combined in DTW *k*-Means algorithm (Keogh and Ratanamahatana, 2005):

$$DTW(\vec{x},\vec{y}) = \min\sqrt{\sum\nolimits_{i=1}^{k}\omega_i} \tag{5}$$

$\vec{x}=(x_1,\dots,x_m)$ and $\vec{y}=(y_1,\dots,y_m)$ are two time series with a length of m, $W=\{\omega_1,\omega_2,\dots,\omega_k\}, with\ k\geq m,$ is the warping path between $\vec{x}$ and $\vec{y}$. The shape-based distance (SBD) is used in k-Shape algorithm (Paparrizos and Gravano, 2016):

$$SBD(\vec{x},\vec{y}) = 1 - \max_{\omega}\left(\frac{CC_{\omega}(\vec{x},\vec{y})}{\sqrt{R_0(\vec{x},\vec{x}) \cdot R_0(\vec{y},\vec{y})}}\right) \tag{6}$$

$CC_{\omega}(\vec{x},\vec{y})$ is the cross-correlation sequence, where $R_{\omega-m}(\vec{x},\vec{y})$ is calculated based on the cross-correlation thought (Paparrizos and Gravano, 2016):

$$R_k(\vec{x},\vec{y}) = \begin{cases} \sum_{n=1}^{m-k} x_{n+k} \cdot y_n\,, & k \geq 0 \\ R_{-k}(\vec{y},\vec{x}), & k < 0 \end{cases} \tag{7}$$

The z-normalized data was treated as time series with a mean of 0 and a standard deviation of 1 for the clustering analysis. The data visualization was performed with OriginLab 2022b (OriginLab Corporation, Northampton, MA, USA).

3. Results

3.1 Physiological measures

We measured salivary cortisol and ear temperature (ET) as biomarkers to evaluate the internal circadian rhythm in the wake period. A significant clock effect was observed in both of the salivary cortisol secretion and ET (Fig. 8A-B, main effect of clock, $F_{(3.11,\ 52.89)} = 8.51$, $p < 0.001$, η_p^2=0.334; $F_{(17,\ 289)} = 8.71$, $p < 0.001$, η_p^2=0.339, respectively). The cosinor fitting model showed significant rhythmicity (Table 2, $p < 0.001$ respectively), with the estimated acrophases in cortisol secretion at 8:36 (95% CI: 07:06 to 10:00) and in ET at 18:50 (95% CI: 17:41 to 20:26).

A 2 (handness) by 18 (clock) general linear model repeated ANOVA for grip strength revealed no two-way interaction ($F_{(5.86,\ 175.82)} = 0.192$, $p = 0.097$, η_p^2= 0.006) of clock*handness (Fig.8C). The result showed significant main effect of clock ($F_{(5.86,\ 175.82)} = 9.84$, $p < 0.001$, η_p^2= 0.247) and handness ($F_{(1,\ 30)} = 9.84$, $p = 0.031$, η_p^2= 0.146). The MESOR of the average grip strength (Table 2) during a diurnal day was estimated as 23.16 (95% CI: 22.12 to 24.20) kg. And the acrophase appeared in the morning at 11:32 (95% CI: 10:05 to 13:31).

The heart rate and blood pressure showed significant circadian effect (HR: $F_{(17,\ 272)} = 6.95$, $p < 0.001$, η_p^2= 0.303; SBP: $F_{(17,\ 289)} = 3.29$, $p < 0.001$, η_p^2= 0.162; DBP: $F_{(6.51,\ 110.59)} = 3.03$, $p = 0.007$, η_p^2= 0.151, respectively) with multiple waves (Fig.8 D-E) in the experimental time course. Determined by cosine analysis, the periods of HR, SBP and DBP were identified respectively as 5 hours, 7 hours and 5 hours. The first acrophases estimated were all in the morning, appearing at 09:42 (95%CI: 09:30 to 09:53), 11:23 (95%CI: 10:51 to 11:52), 07:33 (95% CI: 07:14 to 07:56), respectively. The F-test did not show significant difference of the acrophases between SBP and DBP, $F_{(1,34)} = 3.36$, $p = 0.076$.

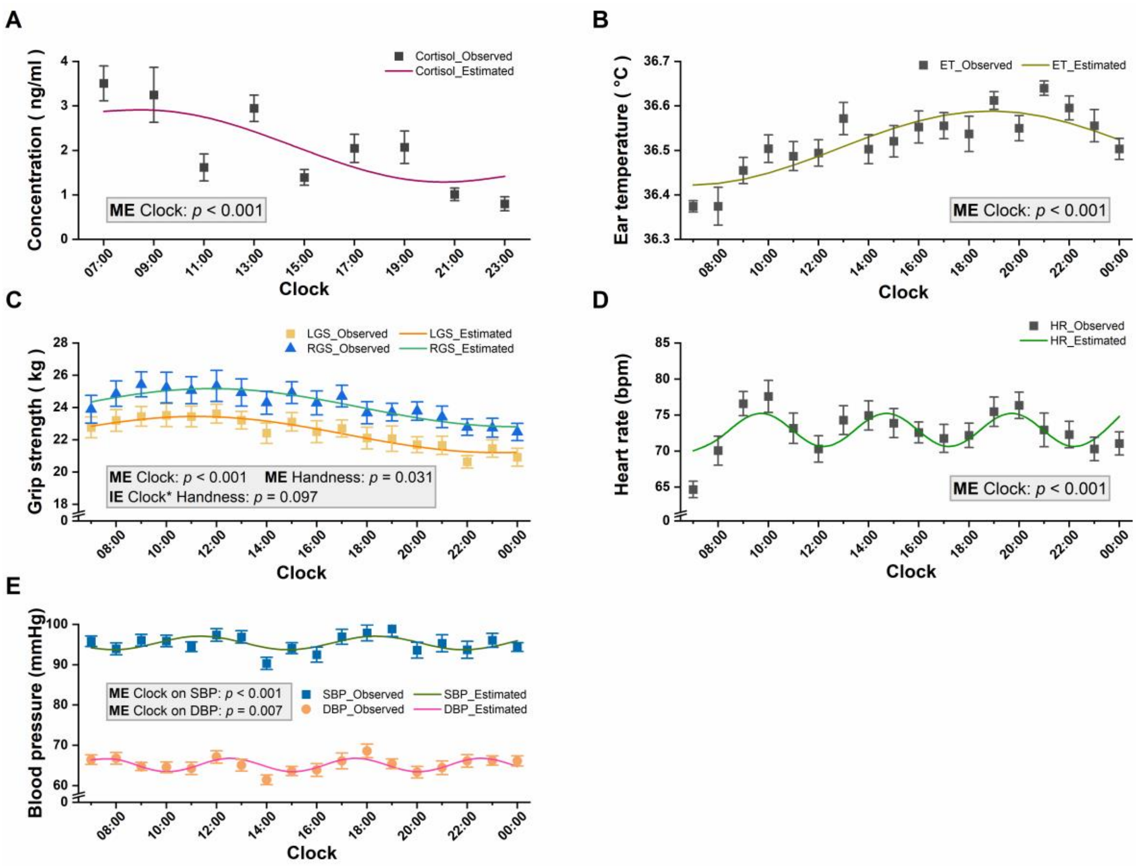

Fig. 8 The diurnal changes of physiological measures. (A) the concentration of salivary cortisol at two-hour intervals, (B) the average bilateral ear temperature at one-hour intervals, (C) the grip strength of both hands at one-hour intervals, (D) the heart rate at one-hour intervals, (E) the overlaid plotting of systolic and diastolic blood pressures at one-hour intervals. The solid line depicts the fitted values by cosinor analysis of indicators. The scattered points represent the mean value (mean ± SEM) at respective clocks. ME, main effect; IE, interaction effect; ET, ear temperature; LGS, left-hand grip strength; RGS, right-hand grip strength; HR, heart rate; SBP, systolic blood pressure; DBT, diastolic blood pressure.

3.2 Subjective evaluations

Subjective sleepiness showed significant diurnal rhythm (Fig.9A, $F_{(8, 136)} = 7.29$, $p < 0.001$, $\eta_p^2 = 0.300$) with lower score in the afternoon and higher score in the evening. The highest level of alertness occurred at 12:34 (95% CI: 10:59 to 14:18).

The positive and negative affect showed significant clock main effect in the awake period (Fig.9B, ME of clock, $F_{(3.76, 63.96)} = 3.99$, $p = 0.007$, $\eta_p^2 = 0.190$; $F_{(3.12, 53.10)} = 4.99$, $p = 0.004$, $\eta_p^2 = 0.227$, respectively). The PAS and NAS were reported of higher level in the morning, with the acrophases estimated at 08:40 (95%CI: 06:30 to 11:07) and 07:41 (95%CI: 05:37 to 10:37) (Table 2). The difference was significant for the MESORs comparison, $F_{(1,34)} = 56.26$, $p < 0.001$.

Howerver, no statistically considerable difference was for the two amplitudes and two acrophases ($F_{(1,34)} = 0.15$, $p = 0.704$; $F_{(1,34)} = 1.09$, $p = 0.305$, respectively).

A significant circadian rhythm was found in satiety self-report, $F_{(5.44,\ 92.54)} = 22.77$, $p < 0.001$, $\eta_p^2 = 0.572$. The CSS approached a peak value at the mealtime point (Fig.9C) with an estimated period of 5 hours by the cosinor analysis (Table 2). The first spike of satiety on the experimental day occurred at 07:04 am (95%CI: 06:58 to 07:10), and the second to fourth spikes occurred on the following 5 hours, 10 hours and 15 hours around at 12:04, 17:04, and 22:04 (Fig.9C, Table 2).

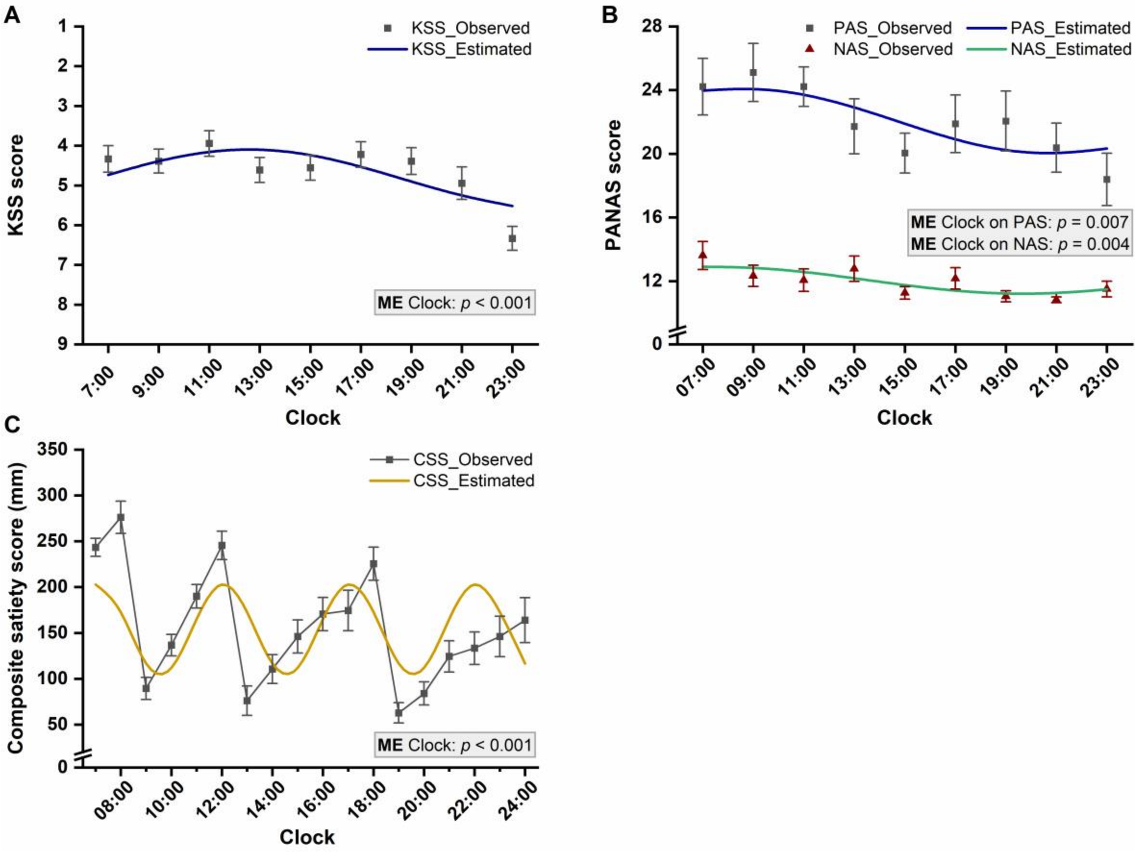

Fig. 9 The subjective evaluations in the diurnal time course. (A) subjective sleepiness evaluated by the Karolinska Sleepiness Scale (KSS) plotted in reversed y-axis, (B) the overlaid plotting of positive and negative affect measured by the Positive and Negative Affect Schedule (PANAS), (C) satiety evaluated by the composite satiety score (CSS). The solid line depicts the fitted values by cosinor analysis of indicators. The observations of CSS were also connected by a straight line to better demonstrate the circadian rhythm of satiety. The scattered points represent the mean value (mean ± SEM) at respective clocks. ME, main effect; PAS, positive affect score; NAS, negative affect score.

Table 2 Clock effect of ANOVA analysis and cosinor parameters on physiological and subjective measures.

Measures	**ANOVA**		**COSINOR analysis**					
	F	***p***	**Period (h)**	***p***	**Rhythmicity (%)**	**MESOR (95% CI)**	**Amplitude (95% CI)**	**Acrophase (95% CI)**
Cortisol (ng/ml)	8.51^a	< 0.001^a	24	< 0.001	51.65	2.10 (1.76 to 2.44)	0.85 (0.60 to 1.10)	08:36 (07:06 to 10:00)
ET (°C)	8.71	< 0.001	24	< 0.001	70.47	36.51 (36.47 to 36.54)	0.08 (0.06 to 0.11)	18:50 (17:41 to 20:26)
GS (kg)	9.84^a	< 0.001^a	24	< 0.001	89.31	23.16 (22.12 to 24.20)	1.16 (0.67 to 1.64)	11:32 (10:05 to 13:31)
HR (bpm)	6.95	< 0.001	5	< 0.001	52.34	72.95 (69.73 to 76.17)	3.00 (2.38 to 3.62)	09:42 (09:30 to 09:53) ^{b}
SBP (mmHg)	3.29	< 0.001	7	< 0.001	33.61	95.42 (92.79 to 98.04)	1.69 (1.04 to 2.33)	11:23 (10:51 to 11:52) ^{b}
DBP (mmHg)	3.03^a	0.007^a	5	< 0.001	52.69	65.11 (62.80 to 67.42)	1.68 (0.97 to 2.38)	07:33 (07:14 to 07:56) ^{b}
KSS	7.29	< 0.001	24	0.003	54.78	4.82 (4.38 to 5.27)	0.76 (0.36 to 1.16)	12:34 (10:59 to 14:18) ^{c}
PAS	3.99^a	0.007^a	24	0.032	62.41	22.06 (19.42 to 24.70)	2.11 (0.63 to 3.59)	08:40 (06:30 to 11:07)
NAS	4.99^a	0.004^a	24	0.031	61.57	12.04 (11.06 to 13.03)	0.87 (0.25 to 1.50)	07:41 (05:37 to 10:37)
Hunger (mm)	17.95^a	< 0.001^a	5	< 0.001	36.53	27.62 (21.86 to 33.40)	14.27 (11.22 to 17.32)	07:07 (06:58 to 07:14) ^{b}
Fullness (mm)	12.39^a	< 0.001^a	5	< 0.001	27.55	51.62 (42.15 to 61.09)	11.91 (8.17 to 1.57)	09:35 (09:25 to 09:45) ^{b}
Satisfaction (mm)	11.47^a	< 0.001^a	5	< 0.001	32.39	57.30 (51.31 to 63.28)	11.54 (8.89 to 1.42)	09:33 (09:23 to 09:44) ^{b}
Prospective consumption (mm)	18.53^a	< 0.001^a	5	< 0.001	34.15	35.09 (29.56 to 40.61)	11.41 (9.30 to 1.35)	06:60 (06:53 to 07:08) ^{b}
CSS (mm)	22.77^a	< 0.001^a	5	< 0.001	33.77	153.80 (130.63 to 176.97)	49.05 (39.14 to 58.96)	07:04 (06:58 to 07:10) ^{b}

^{a} represents the adjusted F value and *p* value with the Greenhouse-Geyser correction. ^{b} represents the first peak value during wake period. ^{c} represents the trough value of the fit. ET, ear temperature; GS, grip strength; HR, heart rate; SBP, systolic blood pressure; DBT, diastolic blood pressure; KSS, Karolinska Sleepiness Scale; PAS, positive affect score; NAS, negative affect score; CSS, composite satiety score; MESOR, Midline Estimating Statistic of Rhythm.

3.3 Cognition battery

3.3.1 Two-flash fusion task (TFT)

A 4 (ISI) by 2 (visual field) by 2 (eccentricity) by 9 (clock) general linear model repeated ANOVA for the accuracy of TFT revealed no significant four-way interaction nor any three-way interactions (*p* > 0.05, respectively). The two-way interactions were not significant other than the clock*ISI (Fig.10, $F_{(24,\ 408)} = 2.124$, $p = 0.002$, $\eta_p^2 = 0.111$). The simple effect analysis of clock on the accuracy of ISI of 16.7 ms and 33.4 ms were significant ($F_{(8,\ 136)} = 3.422$, $p = 0.001$, $\eta_p^2 = 0.168$; $F_{(3.60,\ 61.10)} = 2.828$, $p = 0.037$, $\eta_p^2 = 0.143$, respectively), however, no significant clock effects on the accuracy of the shortest ISI (0 ms) and longest ISI (50.1 ms) were found (Fig.10, *p* > 0.05 respectively). The cosinor fitting only showed significant rhythmicity of ISI of 16.7 ms (Table 3, *p* = 0.042), indicating the lowest accuracy of TFT at the ISI of 16.7 ms occurred at 10:41 (95% CI: 08:08 to 13:31).

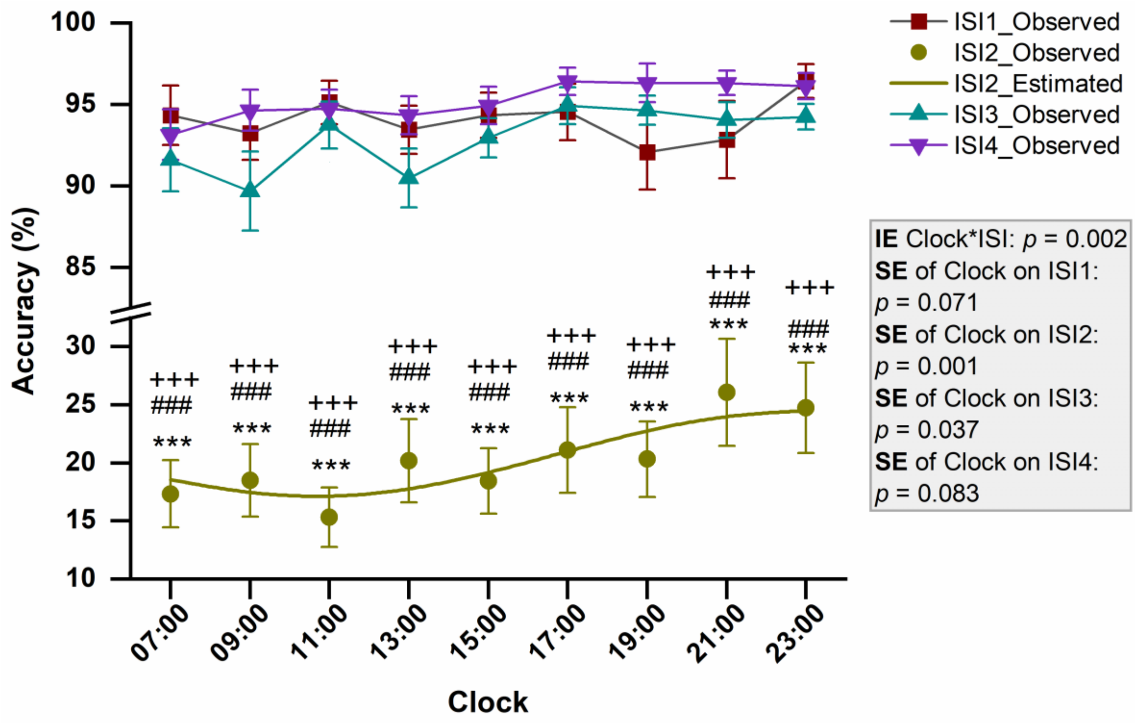

Fig. 10 The response accuracy of two-flash fusion task in the diurnal time course. The respective inter stimulus intervals (ISIs) were 0 ms, 16.7 ms, 33.4 ms, 50.1 ms. The solid line in green depict the fitted values by cosinor analysis within ISI of 16.7 ms. The scattered points represent the mean value (mean ± SEM) at respective clocks. IE, interaction effect; SE, simple effect; ISI1, ISI of 0 ms; ISI2, ISI of 16.7 ms; ISI3, ISI of 33.4 ms; ISI4, ISI of 50.1 ms. ***, ###, +++ symbols indicate differences of ISI2 vs. ISI1, ISI2 vs. ISI3, ISI2 vs. ISI4 respectively with *p* < 0.001.

The main effect of visual field showed significant difference (Fig. 11A, $F_{(1, 17)}$ = 5.791, $p = 0.028$, $\eta_p^2 = 0.254$), indicating a higher accuracy was found in the right visual field (left vs right, -0.89% (95% CI: -1.66% to -0.11%)). And the significant eccentricity effect (Fig. 11B, $F_{(1, 17)}$ = 11.38, $p = 0.004$, $\eta_p^2 = 0.401$) showed that the perifoveal visual field performed a higher accuracy than the peripheral visual field (7° vs 21°, 2.42% (95% CI: 0.91% to 3.94%)).

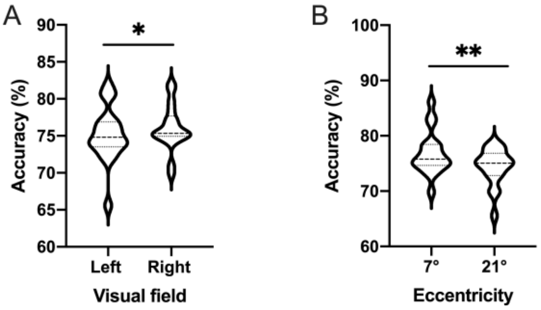

Fig. 11 The main effect of visual field (A) and eccentricity (B) in two-flash fusion task (TFT). Data are presented as mean ± SEM. Significant differences are shown as *$p < 0.05$, **$p < 0.01$

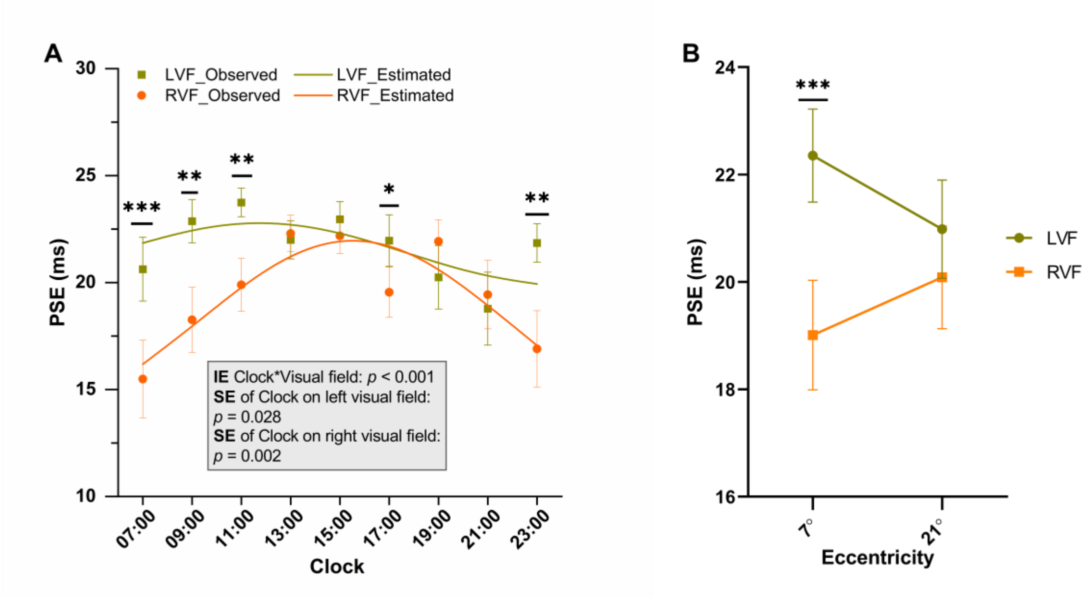

Fig. 12 The interaction effects of clock * visual field (A) and of the eccentricity * visual field (B) on the PSEs of two-flash fusion task. IE, interaction effect; SE, simple effect; PSE, point of subjective equality; LVF, left visual field; RVF, right visual field. Data are presented as mean ± SEM. Significant differences are shown as *$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$.

PSEs (PSE, point of subjective equality) were analyzed with a 2 (visual field) × 2 (eccentricity) × 9 (clock) general linear model repeated ANOVA. The main effect of clock on PSEs was significant, $F_{(3.335,\ 56.703)}$ = 3.540, $p = 0.017$, η_p^2 = 0.172. The main effect of visual field was also significant, $F_{(1, 17)}$ = 17.724, p <

0.001, η_p^2 = 0.510. These main effects were qualified by the significant interactions of clock* visual field and eccentricity * visual field (Fig.12A, $F_{(4.511,\ 76.694)}$ = 4.960, p < 0.001, η_p^2 = 0.226; $F_{(1,\ 17)}$ = 6.463, p = 0.021, η_p^2 = 0.275 respectively). The simple effect analysis showed that, circadian clock effect on the PSEs of both left and right visual field were significant (F $_{(4.130,\ 70.212)}$ = 2.874, p = 0.028, η_p^2 = 0.145; F $_{(3.724,\ 63.302)}$ = 4.879, p = 0.002, η_p^2 = 0.223, respectively). Bonferroni-adjusted comparisons indicated that, the PSEs in left visual field were significantly higher than in right visual field at 7:00 [5.133 (95% CI: 2.721 to 7.545) ms, p < 0.001], 9:00 [4.612 (95% CI: 1.311 to 7.912) ms, p = 0.009], 11:00 [3.848 (95% CI: 1.771 to 5.924) ms, p = 0.001], 17:00 [2.410 (95% CI: 0.421 to 4.400) ms, p = 0.020] and 23:00 [4.948 (95% CI: 2.081 to 7.816) ms, p = 0.002]. The F-test showed a higher MESOR of PSE in the left visual field than the right visual field (Table 3, $F_{(1,34)}$ = 4.860, p = 0.034), and no significant difference were found in amplitude or acrophase (Table 3, p > 0.05 respectively).

Moreover, at the visual eccentricity of 7°, the simple visual field effect was significant, $F_{(1,\ 17)}$ = 36.825, p < 0.001, η_p^2 = 0.684 (Fig. 12B). Bonferroni-adjusted comparisons showed higher PSEs [3.346 (95% CI: 2.183 to 4.510) ms, p < 0.001] estimated in left visual field than in right visual field at the visual eccentricity of 7°.

3.3.2 Psychomotor vigilance task (PVT)

The PVT RT showed significant clock effect (Fig.13A, $F_{(8,\ 136)}$ = 2.08, p = 0.042, η_p^2= 0.109) by repeated ANOVA. The rhythm detection test found significant rhythmicity of the cosinor regression model on PVT RT (Table 3, p = 0.026). The percent rhythm of 68.91% reflected a strong diurnal oscillation (Table 3). The cosinor analysis (Table 3) showed the shortest reaction time appeared at 13:45 (95% CI: 12:07 to 16:37), indicating the highest reaction time and the highest vigilance in the afternoon. The rhythm adjusted mean PVT RT was estimated of 354.01 (95% CI: 337.38 to 370.64) ms. The fitted cosinor model showed an amplitude of 9.73 (95% CI: 2.89 to 16.58) ms during a diurnal time course. No significant clock effect by ANOVA (Fig.13B, F $_{(3.73,\ 59.80)}$ = 1.04, p =0.391, η_p^2=0.061) nor notable rhythmicity (p = 0.160) by cosinor fitting was found on PVT lapses (Table 3).

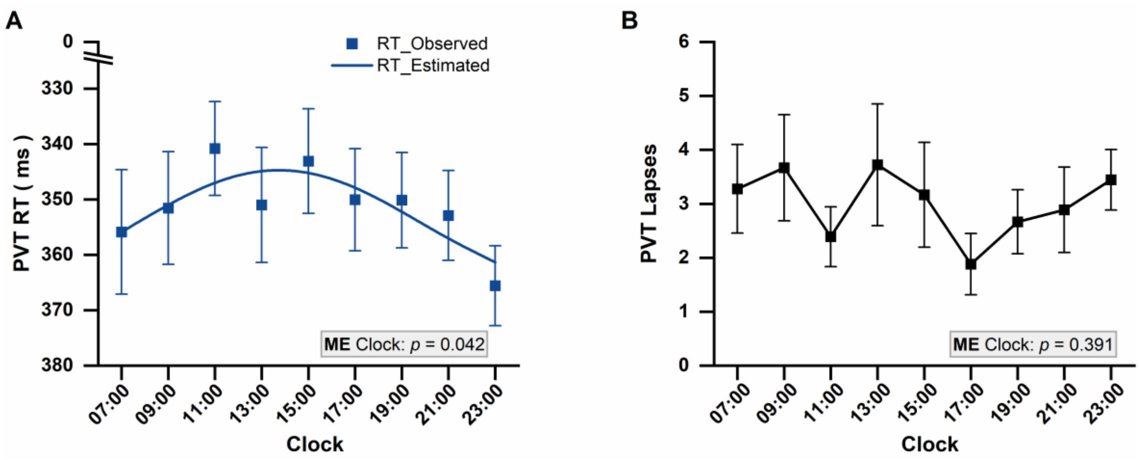

Fig. 13 The diurnal rhythm of psychomotor vigilance task (PVT). (A) the PVT mean reaction time plotted in reversed y-axis, (B) the PVT lapses (reaction time > 500 ms). The solid line depicts the fitted RTs (A) by cosinor analysis and the observed lapses (B) which cannot be fitted by cosinor model. The scattered points represent the mean value (mean ± SEM) at respective clocks. RT, reaction time; ME, main effect.

3.3.3 Go/No-go task (GNG)

Two independences, the reaction time to “GO” trials (GNG RT) and the errors which referred to the missed “Go” trials and false reaction to “No-go” trials, were analyzed in GNG task. The repeated ANOVA showed significant clock effect (Fig.14A, $F_{(8,\ 136)} = 4.434$, $p < 0.001$, $\eta_p^2 = 0.207$) in GNG RT. The cosinor model showed a significant diurnal rhythm ($p < 0.001$) of GNG RT with 66.66% percent rhythm (Table 3). The fastest reaction to go signals appearing at 18:07 (95%CI: 15:51 to 20:29), indicating the good inhibitory control performed in the afternoon. The MESOR and amplitude of the fitted curve were estimated as 455.24 (95% CI: 433.99 to 476.50) ms and 12.79 (95% CI: 7.26 to 18.31) ms respectively. No variation in the number of error occurrences was found in the GNG task during the diurnal time course. (Fig. 14B and Table 3).

Within the hundreds-millisecond time window, we compared the cosinor parameters of PVT and GNG tasks. The results showed a significant faster RT of 101.23 ms (MESOR, $F_{(1,\ 34)} = 62.606$, $p < 0.001$) in PVT than in GNG. No significant differences were found in amplitude ($F_{(1,\ 34)} = 0.031$, $p = 0.862$) and acrophase comparisons ($F_{(1,\ 34)} = 1.128$, $p = 0.296$).

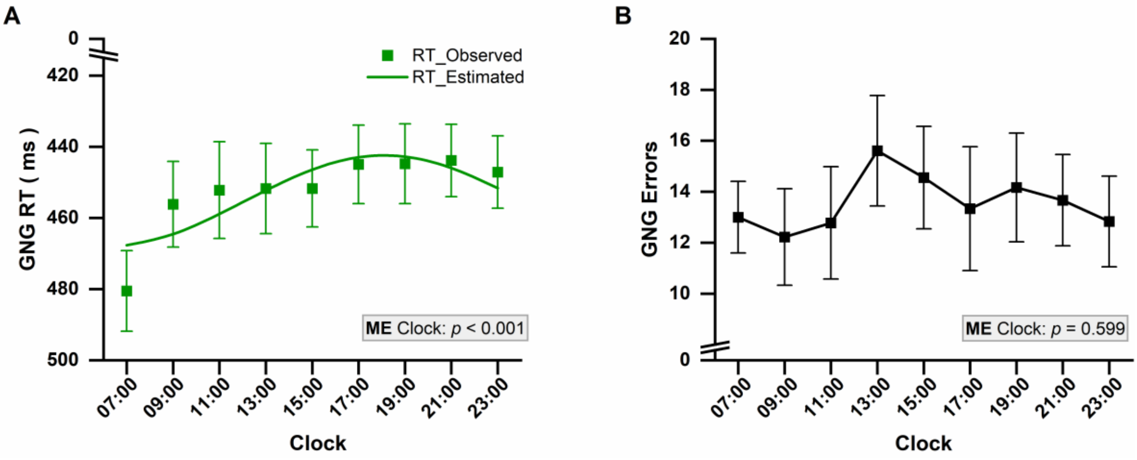

Fig. 14 The diurnal rhythm of Go/No-go task. (A) the mean reaction time of the "Go" trails plotted in reversed y-axis, (B) the GNG errors, which referred to the missed "Go" trials and false reaction to "No-go" trials. The solid line depicts the fitted RTs (A) by cosinor analysis and the observed errors (B) which cannot be fitted by cosinor model. The scattered points represent the mean value (mean ± SEM) at respective clocks. RT, reaction time; ME, main effect.

3.3.4 Finger tapping task (FTT)

The spontaneous motor tempo in 30 s showed significant circadian rhythm (Fig. 15, ME of clock: $F_{(3.65,\ 61.97)} = 3.14$, $p < 0.024$, $\eta_p^2 = 0.156$), with the acrophase occurring at 15:21 (95% CI: 13:20 to 17:27). The result suggested a rhythm adjusted mean of 43.80 (95% CI: 34.78 to 52.83) of SMT in 30 seconds.

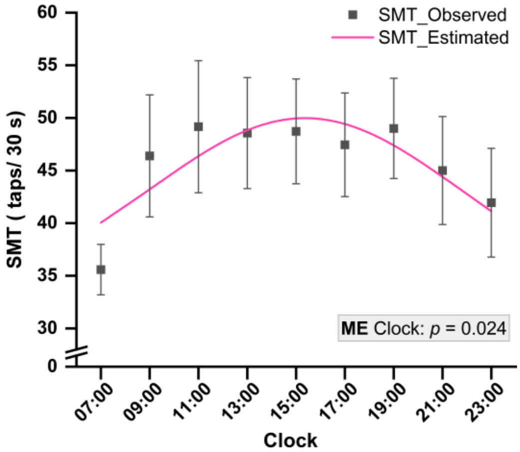

Fig. 15 The diurnal rhythm of spontaneous motor tempo (SMT) in finger tapping task. The solid line depicts the fitted data by cosinor analysis. The scattered points represent the observed mean value (mean ± SEM) at respective clocks. ME, main effect.

3.3.5 Temporal reproduction task (TRT)

A 2 (duration) by 2 (stimulus eccentricity) by 9 (clock) general linear model repeated ANOVA for reproduced durations revealed no significant three-way interaction ($F_{(8,\ 136)} = 1.741$, $p = 0.094$, $\eta_p^2 = 0.093$). No significant two-way interaction effect of eccentricity*duration ($F_{(1, 17)}$ =1.288, p = 0.272, η_p^2= 0.070) and eccentricity*clock ($F_{(8, 136)}$ =1.462, p =0.177, η_p^2=0.079) were found. The results showed significant clock*duration interaction ($F_{(8, 136)}$ = 2.057, p =0.044, η_p^2= 0.108), main effects of duration and clock, $F_{(1, 17)}$ = 223.034, p < 0.001, η_p^2= 0.929, $F_{(8, 136)}$ = 2.160, p =0.034, η_p^2=0.113, respectively. The simple effect analysis of clock on the reproduction of 1.5 s was significant ($F_{(8, 136)}$ = 3.229, p = 0.002, η_p^2= 0.160), however, no significant clock effect ($F_{(8, 136)}$ = 1.692, p = 0.106, η_p^2= 0.091) on the reproduction of 4.5 s was found (Fig.16A).

Both the reproductions were characterized by significant circadian rhythms (p < 0.05, Table3). The Cosinor analysis showed that the MESOR of the reproduction of 4.5 s (M = 3735.41 ms) was significant higher than of 1.5 s (M = 1902.62 ms), $F_{(1, 34)}$ = 176.31, p < 0.001. Although the zero-amplitude-test showed that the reproduction of 4.5 s had a higher amplitude than of 1.5 s, the comparison was not significant (Table 3, $F_{(1, 34)}$ = 0.069, p = 0.794). The overlap of 95% confidence intervals indicated no statistically significant difference was found between the circadian acrophases in the two reproductions (Table 3, $F_{(1, 34)}$ = 1.232, p = 0.275).

The ratio of the absolute deviation to standard duration ($Ratio = \frac{|Reproduction-Standard|}{Standard}$) indicated significant circadian rhythms of these two reproductions by both ANOVA and cosinor analysis (Fig.16B and Table 3). The three-way interaction of eccentricity*duration*clock was not significant, $F_{(8, 136)}$ =1.194, p = 0.307, η_p^2= 0.066. The significant duration*clock interaction was shown ($F_{(8, 136)}$ = 2.070, p = 0.043, η_p^2= 0.109), with the significant simple effect analysis of clock on the reproduction ratio of 1.5 s ($F_{(8, 136)}$ = 2.240, p = 0.028, η_p^2= 0.116), however, but no significant clock effect ($F_{(8, 136)}$ = 1.486, p = 0.168, η_p^2= 0.080) on the reproduction ratio of 4.5 s.

The cosinor analysis of the ratio showed no significant differences of MESOR, amplitude or acrophase between these two conditions (Table 3, MESOR: $F_{(1, 34)}$ = 3.887, p = 0.057; Amplitude: $F_{(1, 34)}$ = 0.077, p = 0.783; Acrophase: $F_{(1, 34)}$ = 0.867, p = 0.358).

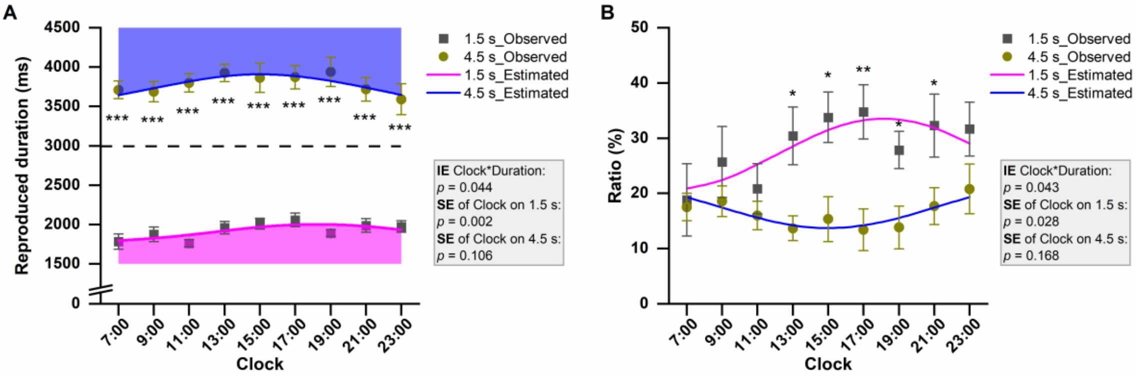

Fig. 16 The diurnal rhythm of temporal reproduction (mean ± SEM). (A) the reproduced duration of 1500 ms and 4500 ms, (B) the ratio of two reproductions (the absolute deviation of the reproduction from the standard duration divided by the standard duration). The solid line depicts the fitted values by cosinor analysis of indicators. The scattered points represent the mean value (mean ± SEM) at respective clocks. IE, interaction effect; SE, simple effect. Significant differences are shown as *$p<0.05$, **$p<0.01$, and ***$p<0.001$.

Table 3 Cosinor analysis of cognitive battery.

Cognitive battery		COSINOR analysis					
Tasks	**Dependent variables**	**Period (h)**	***p***	**Rhythmicity (%)**	**MESOR (95% CI)**	**Amplitude (95% CI)**	**Acrophase (95% CI)**
TFT	Accuracy of ISI_0 ms (%)	24	0.648	7.44	94.22 (90.99 to 97.46)	0.60 (-0.72 to 1.92)	03:51 (NA)
	Accuracy of ISI_16.7 ms (%)	24	0.042	75.55	20.72 (14.37 to 27.06)	3.77 (0.10 to 6.54)	10:41 (08:08 to 13:31) ^{c}
	Accuracy of ISI_33.4 ms (%)	24	0.115	59.73	92.82 (90.51 to 95.14)	1.79 (0.11 to 3.47)	20:15 (16:48 to 01:13)
	Accuracy of ISI_50.1 ms (%)	24	0.052	80.66	95.13 (93.32 to 96.94)	1.26 (0.26 to 2.26)	19:59 (16:60 to 24:08)
	PSE of left visual field (ms)	24	0.031	48.22	21.38 (19.62 to 23.14)	1.47 (0.43 to 2.50)	11:44 (08:01 to 14:49)
	PSE of right visual field (ms)	24	0.001	81.17	18.44 (16.25 to 20.63)	3.68 (1.95 to 5.40)	15:30 (13:50 to 16:53)
PVT	RT (ms)	24	0.026	68.91	354.01 (337.38 to 370.64)	9.73 (2.89 to 16.58)	13:45 (12:07 to 16:37) ^{c}
	Lapses	24	0.160	23.86	3.13 (2.02 to 4.24)	0.46 (-0.03 to 0.95)	05:05 (NA)
GNG	RT (ms)	24	< 0.001	66.66	455.24 (433.99 to 476.50)	12.79 (7.26 to 18.31)	18:07(15:51 to 20:29) ^{c}
	Errors	24	0.450	44.19	13.22 (10.09 to 16.35)	1.18 (-0.99 to 3.35)	15:49 (NA)
FTT	SMT (taps/ 30 s)	24	0.001	70.06	43.80 (34.78 to 52.83)	6.46 (3.51 to 9.41)	15:21 (13:20 to 17:27)
TRT	Reproduction of 1.5 s (ms)	24	< 0.001	57.10	1902.62 (1777.65 to 2027.60)	105.37 (51.37 to 159.37)	18:15 (16:09 to 21:33)
	Reproduction of 4.5 s (ms)	24	0.010	75.74	3735.41 (3472.37 to 3998.45)	179.61 (71.75 to 287.46)	15:05 (12:02 to 17:20)
	Ratio of 1.5 s (%)	24	0.006	67.56	27.14 (18.55 to 35.74)	6.40 (2.39 to 10.42)	18:09 (15:53 to 21:53)
	Ratio of 4.5 s (%)	24	0.012	73.38	17.45 (11.66 to 23.25)	3.74 (1.47 to 6.01)	15:01 (12:11 to 17:39) ^{c}

NA represents that amplitude confidence interval contains zero and acrophase confidence interval cannot be calculated. ^{c} represents the trough value of the fit. TFT, two-flash fusion task; ISI, inter stimulus interval; PSE, point of subjective equality; PVT, Psychomotor Vigilance Task; RT, reaction time; GNG, Go/no-go task; FTT, finger tapping task; TRT, temporal reproduction task; Ratio is represented as the absolute deviation of the reproduction from the standard duration divided by the standard duration; MESOR, Midline Estimating Statistic of Rhythm.

3.4 Phase relationships

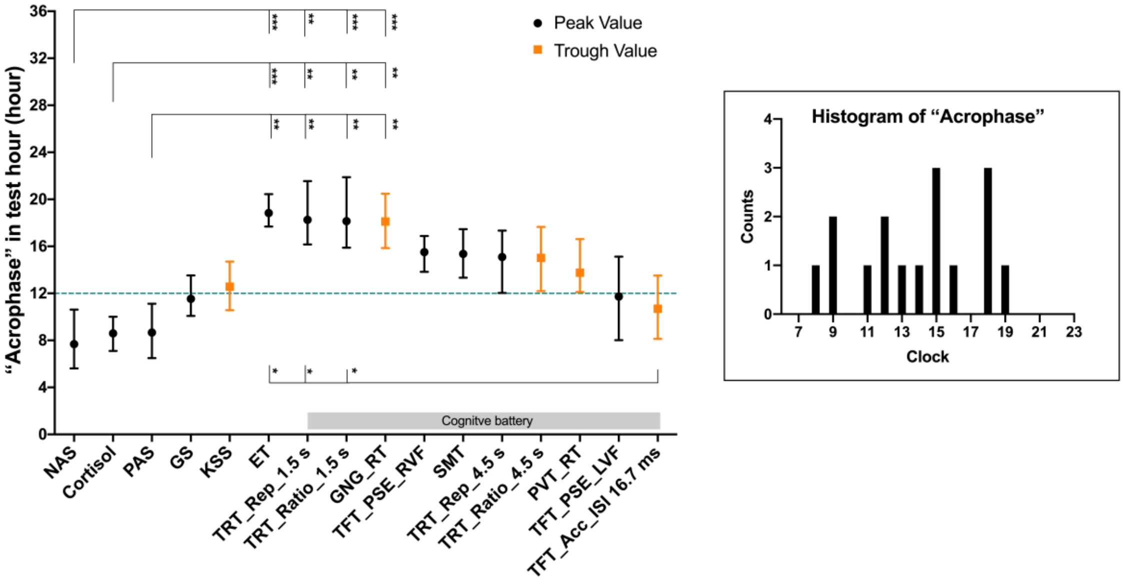

Fig. 17 "Acrophases" of the cosinor analysis for the circadian rhythms of the test variables. The "Acrophase" refers to the peak values or the actual trough values showed in reverse. "Acrophases" are converted into hours. Values in the left pane are shown as means, and error bars represent 95% confidence intervals. Significant differences are shown as *p<0.05, **p<0.01, and ***p<0.001. The right pane showed the histogram of the "Acrophase" distribution in the diurnal time course. The abbreviations of the x-axis titles from left to right are: NAS, negative affect score; PAS, positive affect score; GS, grip strength; KSS, Karolinska Sleepiness Scale; ET, ear temperature; TRT_Rep_1.5 s, the reproduced duration of 1.5 s in the temporal reproduction task (TRT); TRT_Ratio_1.5 s, the ratio of absolute deviation to standard duration of 1.5 s in the temporal reproduction task (TRT); GNG_RT, the mean reaction time (RT) of "Go" trails in Go/no-go task (GNG); TFT_PSE_RVF, the point of subjective equality (PSE) in right visual field (RVF) of two-flash fusion task (TFT); SMT, spontaneous motor tempo; TRT_Rep_4.5 s, the reproduced duration of 4.5 s in the temporal reproduction task (TRT); TRT_Ratio_4.5 s, the ratio of absolute deviation to standard duration of 4.5 s in the temporal reproduction task (TRT); PVT_RT, the mean reaction time (RT) in Psychomotor Vigilance Task (PVT); TFT_PSE_LVF, the point of subjective equality (PSE) in left visual field (LVF) of two-flash fusion task (TFT); TFT_Acc_ISI_16.7 ms , accuracy of inter trail interval (ISI) of 16.7 ms in two-flash fusion task(TFT).

The F statistics were applied to analyze the differences between acrophases. We selected the indicators showing significant clock effects in repeated ANOVA analysis. The acrophase or trough phase of the cosine analysis was used for comparison. To keep all fitted peak phases in the experimental time course, the fitted acrophases appearing at or near the sleep period were replaced with trough phases. The trough phase denoted a drastic change in the metric and has great significance for our study as well.

The results in Fig. 17 showed that the NAS, Cortisol, PAS, and the error rate (as was the trough of accuracy) with an ISI of 16.7 ms in TFF were the four indicators with the earliest acrophases. While they were significantly advanced with body temperature and 1.5 s reproduction /ratio in TRT, in which showing the latest acrophases (Fig. 17, $p < 0.01$). The reversed GNG RT also showed a later phase compared to the first three earlier metrics (Fig. 17, $p < 0.01$).

Moreover, the histogram of “Acrophase” showed that the peak phase or trough phase of most of the indicators occurred in the afternoon (Fig.17). This gives the insight that the performances of time related tasks may be significantly affected by the circadian rhythm in the afternoon.

3.5 Spearman correlation between the measurements

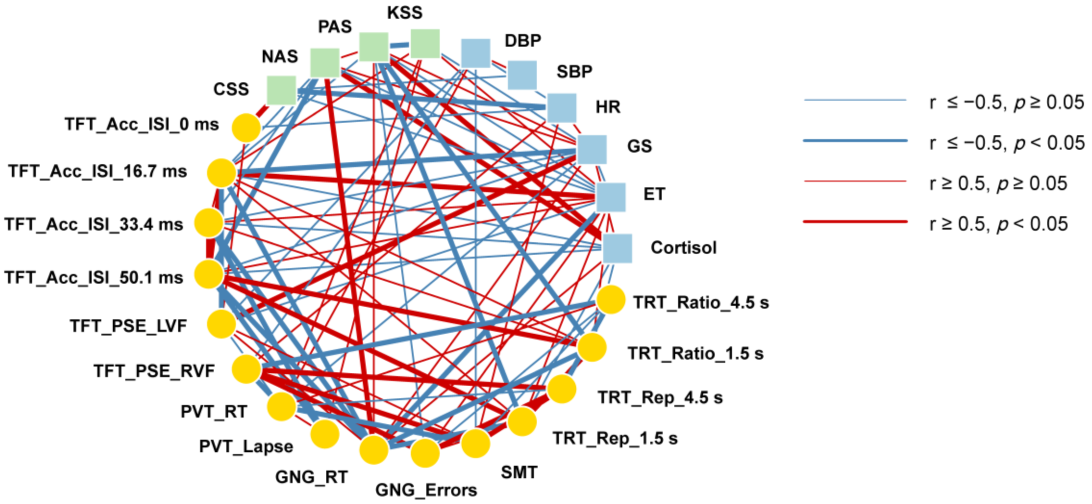

Fig. 18 Spearman’s correlation network visualizing pairwise correlations among physiological measures (blue colored squares), subjective evaluations (green colored squares), and cognitive functions (yellow colored circles). Each node represents a test variable. The link between each paired nodes indicates Spearman’s correlation ($|r| \geq 0.5$). The red and blue lines represent positive and negative correlations, respectively. Particularly, the bolded lines signify significant correlations ($p < 0.05$). The abbreviations of the nodes in a clockwise direction are: CSS, composite satiety score; NAS, negative affect score; PAS, positive affect score; KSS, Karolinska Sleepiness Scale; DBP, diastolic blood pressure; SBP, systolic blood pressure; HR, heart rate; GS, grip strength; ET, ear temperature; TRT_Ratio_4.5 s, ratio of the absolute deviation to standard duration of 4.5 s in the temporal reproduction task (TRT); TRT_Ratio_1.5 s, ratio of the absolute deviation to standard duration of 1.5 s in the temporal reproduction task (TRT); TRT_Rep_4.5 s, the reproduced duration of 4.5 s in the temporal reproduction task (TRT); TRT_Rep_1.5 s, the reproduced duration of 1.5 s in the temporal reproduction task (TRT); SMT,

spontaneous motor tempo; GNG_Errors, the missed “Go” trials and false reaction to “No-go” trials in Go/no-go task (GNG); GNG_RT, the mean reaction time (RT) of “Go” trials in Go/no-go task (GNG); PVT_Lapse, the lapses (reaction time > 500 ms) in Psychomotor Vigilance Task (PVT); PVT_RT, the mean reaction time (RT) in Psychomotor Vigilance Task (PVT); TFT_PSE_RVF, the point of subjective equality (PSE) in right visual field (RVF) of two-flash fusion task (TFT); TFT_PSE_LVF, the point of subjective equality (PSE) in left visual field (LVF) of two-flash fusion task (TFT); TFT_Acc_ISI_50.1 ms , accuracy of inter stimulus interval (ISI) of 50.1 ms in two-flash fusion task(TFT); TFT_Acc_ISI_33.4 ms , accuracy of inter stimulus interval (ISI) of 33.4 ms in two-flash fusion task(TFT); TFT_Acc_ISI_16.7 ms , accuracy of inter stimulus interval (ISI) of 16.7 ms in two-flash fusion task(TFT); TFT_Acc_ISI_0 ms , accuracy of inter stimulus interval (ISI) of 0 ms in two-flash fusion task(TFT).

All the variable we measured showed strong interactions with other tests (Fig. 18, $|r| \geq 0.5$). Cortisol, which we chose as a biomarker of circadian rhythms, showed strong correlations ($|r| \geq 0.5$) with subjective evaluations and multiple cognitive tasks, and specifically correlated significantly with positive and negative emotions (cortisol with PAS: r = 0.78, *p* = 0.014, cortisol with NAS: r = 0.75, *p* = 0.020). Ear temperature was also strongly correlated with up to 13 other test indicators ($|r| \geq 0.5$), with a significant positive correlation (r = 0.78, *p* = 0.014) with ISI of 16.7 ms for accuracy in the two-flash fusion task and a significant negative correlation (r = -0.90, *p* = 0.001) with the response time of the Go signal in the GNG task. In addition, grip strength in the physiological test task was negatively correlated with the accuracy of the response to two-flash at the ISI of 16.7 ms (r = -0.68, *p* = 0.042), but was significantly positively correlated with the point of subjective equality (PSE) in the left visual field (r = 0.82, *p* = 0.007). Blood pressure and heart rate did not show more significant correlations with other indicators, except for a significant negative correlation between heart rate and composite satiety score (r = -0.77, *p* = 0.015).

In the subjective evaluation tasks, in addition to the above, positive affect was also significantly and negatively correlated with the 1.5 s reproduction task (PAS with TR_Rep_1.5 s: r = -0.73, *p* = 0.026, PAS with TR_Ratio_1.5 s: r = -0.73, *p* = 0.026). Interestingly, subjective sleepiness did not show a direct significant correlation with other more tests, but was directly and negatively correlated with positive emotion (r = -0.75, *p* = 0.020). Besides that, negative affect was found to be significantly and positively correlated with the number of errors in the GNG task (r = 0.82, *p* = 0.007), and CSS was significantly and positively correlated with correct responses with an ISI of 0 ms in TFT (r = 0.69, *p* = 0.038).

There were also strong correlations between the performances in the cognitive battery (Fig.18). The accuracy of the responses to two-flash at ISI of 16.7 ms, 33.4 ms and 50.1 ms were significantly and negatively correlated with the RT of the GNG go signal (r = -0.82, *p* = 0.007; r = -0.77, *p* = 0.016; r = -0.90, *p* < 0.001, respectively). In addition, GNG RT was also negatively correlated with reproduction of 1.5 s (GNG RT with TR_Rep_1.5 s: r = -0.67, *p* = 0.049; GNG RT with TR_Ratio_1.5 s: r = -0.70, *p* = 0.036). However, 4.5 s temporal reproduction was positively correlated with PSE in the right field (r = 0.83, *p* = 0.005), the number of GNG errors (r = 0.73, *p* = 0.025), and SMT (r = 0.70, *p* = 0.036). In contrast, the ratio of deviations in 4.5 s reproduction was significantly and negatively correlated with PSE in the right field on a daily basis (r = -0.72, *p* = 0.030). Moreover, 1.5 s temporal reproduction was positively correlated with the ratio of deviations (r = 0.98, *p* < 0.001), and vice versa for 4.5 s (r = -0.91, *p* < 0.001).

Furthermore, the PVT RT was found to be significantly and negatively correlated with PSE in the right visual field (r = -0.72, *p* = 0.030) and also significantly and negatively correlated with SMT (r = -0.90, *p* < 0.001) on a daily rhythm basis, while the latter two were significantly positively correlated (r = 0.82, *p* = 0.007).

The correlation analysis suggests some ideas about the complex relationships of circadian rhythms between physiological variables, subjective evaluations, and objective cognitive performances. In turn, in what patterns do these relationships change throughout the day? Further exploration of these distinct patterns was undertaken by time series clustering in the next section.

3.6 Time series clustering of physiological and psychological function

3.6.1 The validation of the clustering method

We compared the distortion score and Silhouette score of two broadly adopted algorithms of Dynamic Time Warping (DTW) *k*-Means and *k*-Shape.

The distortion score of Elbow plots were shown in Fig.19A-B, which suggested an optimal number of 4 for clustering. It was not obvious to see the transition with DTW *k*-means in the diagram of the Elbow plot, but presenting a clear "elbow" with k-shape. This implied that based on the elbow method, the optimal clustering solution with DTW *k*-means could not be decided independently.

The Silhouette score provided more validation information in Fig. 19C. The Silhouette score at each clustering solution of the metric of *k*-Shape was higher than DTW *k*-means, suggesting the *k*-Shape showing better performance than DTW *k*-means for the Silhouette method. The highest Silhouette score also appeared at the numbers of 4 referring to the optimal number of clusters. Combining the data from the Elbow plot (Fig. 19B) illustrated that clustering into 4 clusters enabled all time-series to be well separated, and the data within each cluster was densely packed.

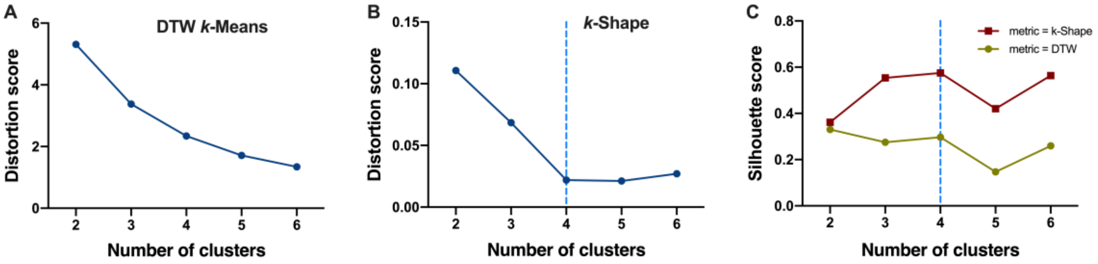

Fig. 19 The optimal number of clusters for the DTW *k*-means and *k*-shape algorithms compared by Elbow plots and Silhouette analysis. (A) the Elbow plot of DTW *k*-means algorithm, (B) the Elbow plot of *k*-shape algorithm, (C) the Silhouette scores with both metrics of DTW and *k*-Shape. The dash line points the optimal number of clusters. DTW, dynamic time warping.

3.6.2 The clustering results by k-Shape algorithm

We finally employed *k*-Shape clustering for time series to discover patterns from multiple measurements in the diurnal period. Based on the shape-based distance measurement, the centroids of each cluster were calculated which preserved the shapes of time series. Each normalized daily performance for observations was considered as a time series. The result showed that cluster 1 was characterized by a gentle rise from morning to 15:00 in the afternoon, followed by a plateau to 19:00, which was then succeeded by a steeper period of decline but not to morning levels (Fig. 20A). Whereas, cluster 2 was characterized by a short peak plateau in the early morning from 7:00 to 9:00, a subsequent slow decline to the afternoon between 17:00 and 19:00, then a steeper rise but not reaching the early morning level (Fig. 20B).

These two clusters contain most of the cognitive and physiological indicators, but present different patterns, suggesting the presence of different rhythmic variations in our experimental tasks. In Cluster1, the temporal fusion task showed similar circadian rhythmicity with temporal reproduction, spontaneous motor tempo and ear temperature. While the PSE of temporal fusion in the right visual field and the accuracy of intervals of 0 ms were subsorted to Cluster2, suggesting that the circadian variation of PSE in both visual fields was not highly similar and that the mechanisms of circadian rhythmic variation of visual fusion thresholds for intervals of 0 ms and tens of milliseconds might be different.

On the other hand, another variable for the temporal replication task, the ratio of the reproduced difference to the standard 4.5 s, showed dissimilarity to the other three variables (TRT_Rep_1.5 s, TRT_Ratio_1.5 s, and TRT_Rep_4.5 s). This suggested that the mechanisms of circadian rhythmogenesis may differ between a perceived error in a longer reproduction task and a shorter duration reproduction as well as the reproduced length itself.

However, the similar rhythmic changes were presented of grip strength, cortisol, mood, and GNG_RT in cluster 2. It has been shown that positive affect is associated with lower cortisol, and negative affect is associated with higher cortisol (Smyth et al., 1998). However, our study showed a synchronous decrease in cortisol levels, positive and negative moods from morning to evening. This change may be related to psychological changes influenced by the isolated environment. On the other hand, rhythmic changes in cortisol and mood, as well as in physiological grip strength, may be key factors underlying the distinct rhythms of tasks in the cluster 2 versus other tasks in the neighboring clusters.

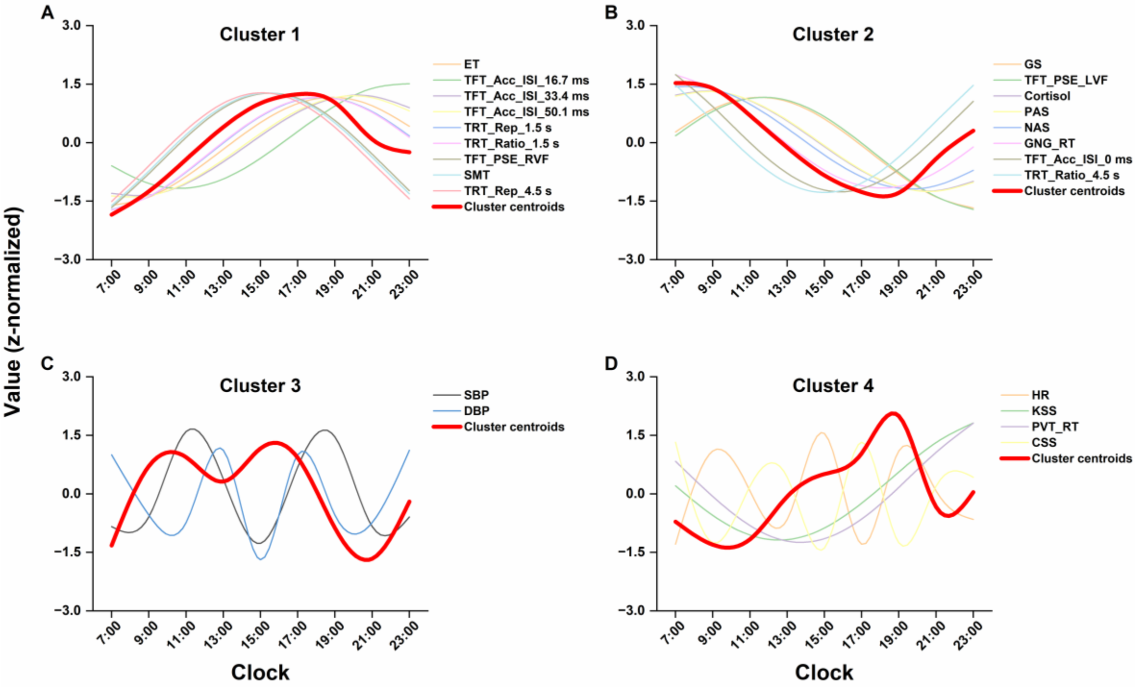

Fig. 20 Clustering result of diurnal physiological and psychological functions with two-hour intervals by k-Shape. The highlighted lines in red represent the centroids of each cluster. The abbreviations are: ET, ear temperature; TFT_Acc_ISI_16.7 ms , accuracy of inter stimulus interval (ISI) of 16.7 ms in two-flash fusion task(TFT); TFT_Acc_ISI_33.4 ms , accuracy of inter stimulus interval (ISI) of 33.4 ms in two-flash fusion task(TFT); TFT_Acc_ISI_50.1 ms , accuracy of inter stimulus interval (ISI) of 50.1 ms in two-flash fusion task(TFT); TRT_Rep_1.5 s, the reproduced duration of 1.5 s in the temporal reproduction task (TRT); TRT_Ratio_1.5 s, ratio of the absolute deviation to standard duration of 1.5 s in the temporal reproduction task (TRT); TFT_PSE_RVF, the point of subjective equality (PSE) in right visual field (RVF) of two-flash fusion task (TFT); SMT, spontaneous motor tempo; TRT_Rep_4.5 s, the reproduced duration of 4.5 s in the temporal reproduction task (TRT); GS, grip strength; TFT_PSE_LVF, the point of subjective equality (PSE) in left visual field (LVF) of two-flash fusion task (TFT); PAS, positive affect score; NAS, negative affect score; GNG_RT, the mean reaction time (RT) of “Go” trials in Go/no-go task (GNG); TFT_Acc_ISI_0 ms , accuracy of inter stimulus interval (ISI) of 0 ms in two-flash fusion task(TFT); TRT_Ratio_4.5 s, ratio of the absolute deviation to standard duration of 4.5 s in the temporal reproduction task (TRT); SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; KSS, Karolinska Sleepiness Scale; PVT_RT, the mean reaction time (RT) in Psychomotor Vigilance Task (PVT); CSS, composite satiety score.

The centroid curves of the other two clusters showed multiple fluctuations (Fig.20C-D). Cluster3 separated the blood pressure variable from the other variables, suggesting that blood pressure may not be well associated with other designed variables (Fig.20C). Cluster4 grouped the two multi-peak variables HR and CSS together with KSS and PVT RT. On one hand, this validates the similarity of the two gold standards of circadian rhythm, KSS and PVT RT (Santhi et al., 2016; Schmidt et al., 2009). On the other hand, it provides more information that changes in heart rate and hunger level may influence subjective sleepiness and vigilance. Therefore, food supply and food size have also been considered as important zeitgeber in diverse time course protocols (Grant, Czeisler, et al., 2021; Stephan, 2002).

In conclusion, our study identified four different patterns. The widely used reference indicators of circadian rhythm, such as blood pressure, heart rate, and subjective sleepiness, PVT RT did not closely correspond to the performance of the temporal domain. While in the tens - milliseconds time window the accuracy of the response and the subjective equilibrium point of the right visual field were more similar to the rhythmic variation of the common indicator of body temperature.

Moreover, body temperature also exhibited a similar pattern of performance to the task performance in the thousand millisecond time window.

Positive emotion, negative emotion, and cortisol were more similar to GS, TFT_PSE_LVF, GNG RT, TFT_Acc_ISI_0 ms, and TRT_Ratio_4.5 s. This potentially illustrates that the accuracy of the TFT with ISI of 0 ms and the error of 4.5 s reproduction could be interpreted as an inhibitory feedback. Such feedback may, however, be correlated with the inhibitory response in the GNG task. The subjective balance point of the left visual field and grip strength may also be influenced by this inhibitory effect or by factors such as decreased mood and increased stress.

4. Discussion

4.1 Rhythmical sensitivity of different tasks

A modified constant routine protocol was applied in our study. We provided a constant bright artificial light of approximate 1000 lux, offered three low-calorie meals and once snack, and controlled the timing of food serving. However, participants were free to control their body posture, as opposed to a strict semi-recumbent posture (Duffy and Dijk, 2002). We expect to explore diurnal changes in physiological and psychological functions under low workload without strenuous physical activities and without strong timing cues intervention. Previous studies preferred dim light in constant routine and forced desynchrony protocols (Dijk et al., 2012; Duffy et al., 1999; Kenneth P. Wright et al., 2002; Santhi et al., 2016). One of the most important considerations is the sensitivity of melatonin to light (Zeitzer et al., 2000). On this basis, we employed cortisol rather than melatonin at the hormone level. While bright light facilitates increased levels of alertness, which acted as another basis regarding our experimental design (Phipps-Nelson et al., 2003; Smolders and De Kort, 2013).

Robust endogenous rhythms of cortisol and ear temperature: In our study, salivary cortisol and ear temperature, showed very large effect size of clock time (η_p^2=0.334, η_p^2=0.339, respectively). The acrophase of salivary cortisol appeared in the early morning, which is consistent with the previous results in serum cortisol, plasma cortisol, and urine cortisol within different light intensities (Meng et al., 2020; Raff and Trivedi, 2013; Selmaoui and Touitou, 2003a). In the results presented here, salivary cortisol concentrations showed a transient peak at the nearest time point after each meal, but were not higher than the maxima just after wakefulness. This phenomenon has also been presented in previous studies, which potentially proves that diet has an effect on the cortisol secretion (Follenius et al., 1982; Quigley and Yen, 1979; Raff and Trivedi, 2013). On the other hand, as an indicator of stress (Kirschbaum and Hellhammer, 1994), the lower level of cortisol during the daytime demonstrated that the participants felt not stressful over the whole diurnal time course. Ear temperature was detected lower in the morning and peaked at early evening, which reaffirmed its robustness as a biomarker as core body temperature either in the previous studied dim lighting protocol (Kräuchi and Wirz-Justice, 1994) or the present bright lighting constant routine.

__Shortly cycled heart rate and blood pressure:__ Heart rate and blood pressure have been widely demonstrated to exhibit rhythmicity as two of the most basic physiological indicators of the human body. In the constant routine, the endogenous circadian rhythm of heart rate has been found at higher levels during the day than at night (Vandewalle et al., 2007). However, these variations vary throughout the day in accordance with mental and physical activities (Kawano, 2011). It has been proven that food intake can result in an increase of cardiac output as well as a rise of heart rate for a while post meal (Waaler et al., 1991). In our study, the heart rate was lowest at waking time in the early morning and reached to a peak two hours after each meal, with an average period predicted to be 5 hours. The food size we offered may have influenced the heart rate cycle and allowed it to fluctuate at a certain level.

The circadian rhythm of blood pressure has been widely accepted that it rises rapidly in the morning after waking and falls at night during sleep (Mancia et al., 1983; Millar-Craig et al., 1978). However, one study employed protocols of constant routine and forced desynchrony and found that almost identical rhythm patterns in SBP and DBP, with acrophases appearing at around 9:00 pm (Shea et al., 2011), which is inconsistent with the former conclusion. This study also found that the circadian rhythm of blood pressure appears to be independent of cortisol and heart rate, and this is compatible with our correlation as well as the clustering results. Recent studies have tended to directly apply 24 hours as the endogenous period for blood pressure, but ignore the implications of the experimental protocol on the de facto period. In our protocol, where we performed a cosinor fit for SBP and DBP respectively, the optimal cycles were obtained as 7 and 5 hours rather than 24 hours. Neither the correlation analysis nor the clustering results showed related physiological or psychological indicators, potentially suggesting an independent rhythmicity of blood pressure distinct from other functions. Alternatively, it is possible indicating that the blood pressure in healthy participants is inappropriate to be considered as a proxy for physiological levels when exploring the phase relationship between circadian rhythms and cognitive function.

High correlation and similarity between grip strength and the temporal resolution in the left visual field: The effect of dominant hand (Incel et al., 2002) was found among the 18 right-handed participants, and the grip strength was averagely stronger with right hand than with left hand during a day. But no interactions between clock effect and handness were found, which suggests the simultaneous circadian rhythms of both hands. GS showed a significant positive correlation with the temporal resolution in the left visual field (TFT_PSE_LVF), r = 0.82, *p* = 0.01, and the normalized diurnal variation curves almost coincided. It has been suggested that muscle movements is predicted by the activities of ipsilateral or contralateral hemisphere (Ames and Churchland, 2019). As the left visual field is represented in the right hemisphere, the correlation between the averaged GS and TFT_PSE_LVF may indicate that the right hemisphere is more involved in grip strength control.

The independence of the cognitive battery from the subjective sleepiness: In the correlation analysis, only PAS presented a significant negative correlation with KSS, indicating a negative association between positive mood and subjective sleepiness. The relevant test metrics of the cognitive battery did not show any significant correlation with the KSS, which proves that the test tasks are insensitive to the subjective sleepiness. On the other hand, the KSS and heart rate, PVT_RT, and CSS were clustered together, confirming again the consistency of the circadian rhythm of KSS and objective alertness (Horne and Burley, 2010; Santhi et al., 2016). Based on the similarity of the cluster, our study gives more clues to the correlation between subjective sleepiness and food intake.

Positive correlation between positive/negative affect and cortisol: Previous studies have shown that only positive affect displays a significant circadian rhythm (Clark et al., 1989; Murray et al., 2009), while findings on the rhythmicity of negative affect are inconsistent (Emens et al., 2020; Murray et al., 2002; Stone et al., 2006). In spite of this, the diurnal variability of PAS and NAS has been shown with opposite patterns (Emens et al., 2020). Our results presented a strong positive correlation (r = 0.50, Fig. Appendix 2.A) between PAS and NAS, although statistically insignificant (*p* = 0.17, Fig. Appendix 2.B). There are also studies demonstrating that higher cortisol levels are associated with lower PAS and higher NAS in minutes of reaction or averaged in a day (Het et al., 2012; Steptoe et al., 2008), which is not consistent with our study within a diurnal time course. In our results, there were significant positive correlations between diurnal changes in both PAS and NAS and cortisol. PAS and NAS displayed higher scores in the morning than in the afternoon during a day, which gives us a hint that the circadian rhythm of human emotions may change from enriched to flat in an isolated environment especially under constant bright illumination.

Sawtooth-like oscillation of composite satiety correlated with heart rate, subjective sleepiness and simple reaction time (objective vigilance): As was shown in Fig.9, the original data showed that the diurnal variation of satiety displayed sawtooth-like oscillations. The results of the cosinor analysis predicted a 5-hour diurnal period for composite satiety, and it is clear that the fitted results produced a large shift after lunch. It has been discussed by Pöppel (Pöppel, 1975) that the cosinor fitting may not favorable in such sawtooth-like oscillations. Three meals were served at 8:00, 12:00, and 18:00, and a small amount of fruit was served at 16:00 in order to balance the varying hunger levels between the three meals. The composite satiety score tends to be hungrier as time passes after each meal. The maximum and minimum values of satiety occurred before and after each meal. Interestingly, the satiety ratings before and after the three meals remained almost equal, whether the timing of the meal or the size of the food or changes in physiological signals influenced this phenomenon is worth investigating in more detail. Furthermore, correlation analysis showed significant positive correlations between CSS and TFF_ISI_0 ms, while clustering results showed closer similarities between CSS and HR, KSS, and PVT_RT. The above results suggest that composite satiety is associated not only with subjective sleepiness, but also with heart rate and objective alertness. However, in the TFF, we used flashes with an interval of 0 ms, which was actually a continuous dwell of the signal, which essentially served to test whether the subject's attention was focused and whether the judgment was at a high level of accuracy. Thus, the relationship between composite satiety and such response to an ISI of 0 ms is difficult to interpret from a higher cognitive level, as in integration or segregation.

The discrimination with the inter-stimulus-interval less than the temporal integration unit showed circadian variation: In the TFT, the estimated time resolution either in left visual field (Table 3, MESOR = 21.38 ms) or in right visual field (Table 3, MESOR = 18.44 ms) predicted a low fusion threshold around 20 ms. Circadian variations were shown in the discriminating accuracy with an ISI of 16.7 ms by repeated ANOVA or by cosinor regression. Though the repeated ANOVA showed significant circadian effect on the discrimination accuracy with ISI of 33.4 ms, the cosinor analysis did not. The accuracy of ISIs over the estimated time resolutions appeared to show a ceiling effect while failing to present diurnal variation. It has been suggested that the endogenous property of the temporal integration unit may be triggered by some biological clock, and it was not influenced by the stimulus (Reeves, 1996). Our study further demonstrates that there is a significant circadian rhythm in discrimination accuracy for temporal lengths slightly shorter than the integration unit (not to 0 ms), while the circadian rhythm disappears for longer than it. If we set the time integration unit to a time interval of 18-22 ms, 16.7 ms is undoubtedly closer to approximately 20 ms than 0 ms, 33.4 ms and 50.1 ms. Then, there is two ways to understand it. One is to believe that there is a circadian rhythm for the discrimination with a flashing interval slightly shorter than the temporal integration. The other way is to consider this flashing interval close to the temporal integration unit as the unit itself, and conclude that there is a circadian rhythm in the discriminating accuracy of the temporal integration unit.

<u>Different diurnal patterns of temporal resolution in two visual fields:</u> The PSE results in TFF showed significant clock effects both in left visual field and right visual field (Fig. 12A). Larger differences between two visual fields were shown in the morning than in the evening. No significant correlations were found between TFT_PSE_LVF and TFT_PSE_RVF, and the clustering results separated these two indicators into two clusters as well. Although the phase difference was not significant, the MESOR of TFT_PSE_LVF was 2.94 ms longer than of TFT_PSE_RVF. Both the left and right cerebral hemispheres have their own visual cortex that receives information from the contralateral visual field (Huff et al., 2022; Wandell et al., 2007). The present results potentially indicate an asymmetry in the temporal resolution processing in the left and right hemispheres. The presented results showed a higher accuracy of response in the perifoveal visual field at an eccentricity of 7° than in the peripheral visual field at 21°. This difference may due to the fewer stimulated ganglion receptive areas and fewer active cortical areas according to the constant size of the stimuli at the peripheral visual field (Poggel and Strasburger, 2004). Furthermore, there was a shorter temporal discrimination in the right visual field compared to the left visual field at the visual eccentricity of 7°, while there was no difference at 21° in the peripheral visual field. Even though, there were few studies taking the effect of visual field on temporal resolution into account. Our study for the first time found the different diurnal patterns of the temporal resolution and the variability of information integration processed in the two visual fields.

Signal discrimination and inhibitory motor control may lead to a different diurnal pattern as compared to the simple reaction time: Within the hundreds-millisecond time window, we measured the fast reaction time and the lapses/errors to PVT and GNG. The simple reaction time for both tasks showed circadian rhythmicity, accompanied by small amount of lapses/errors, and these lapses/errors showed no diurnal variation. This suggests that participants' alertness and motor control do not produce efficiency changes throughout the day. In addition, our results showed a significantly slower GNG reaction time compared to the simple reaction time of PVT. A classic hypothesis has been proposed by Donders (Donders, 1969) demonstrating that reaction time obtained in simple, Go/no-go and choice tasks present different lengths depending on the existence or non-existence of certain mental stages. Donders suggested a subtraction method to estimate the differentiating phases. The Go/no-go task was considered to contain three processes of signal detection, signal discrimination, and motor execution, while the simple reaction task was considered to require only two phases, detection and execution. Our results confirmed that the response time to the “Go” signal in GNG contained a much longer mental processing than in the PVT. Alternatively, inhibitory control in the executive phase involves more mental engagement, including the control of emotion, attention, and behavior (Diamond, 2013; Donders, 1969). Signal discrimination and inhibitory control not only affect response speed may also potentially lead to different circadian rhythmic patterns.

Different temporal processing mechanisms above and below 2-3 s time window: In TRT, we set two durations for reproduction, in the range of 4.5 s above 2-3 s and 1.5 s below. The earlier findings have shown veridical or slightly longer reproduction for shorter durations from 1s up to 2-3 s, and underestimation patterns for durations longer than 2-3 s (Kagerer et al., 2002; Szelag et al., 2002; Ulbrich et al., 2007). Our results are in accordance with the above findings and provide further evidence of diurnal rhythmic variation in temporal reproduction of 2-3 s time window. Reproduction of 1.5 s was averagely overestimated, while of 4.5 s was averagely underestimated, and reproduction reached its highest point in the afternoon. A typical two-process model has been proposed by Fraisse (Fraisse, 1984) and verified in auditory and visual modalities (Ulbrich et al., 2007). According to this model, the temporal process of intervals up to 2-3 s is categorized as duration perception, and for intervals exceeding 2-3 s is categorized as duration estimation. It has been identified that intervals that are exceeding 2-3 s can no longer be perceived as a temporal integration unit (Wittmann, 1999), because of more mental load and attentional demand (Pöppel, 1997). Our results provided further evidence to the two temporal mechanisms present for the duration reproduction in the 2-3 s time window with the circadian variations. In addition, no temporally generated eccentricity effects were detected, which indicated the temporal processing of reproduction is homogenously shared in the perifoveal and peripheral visual field. This is consistent with the previous findings where the two attentional systems in the visual field share the same time window (Bao, Wang, et al., 2013). Our results found that circadian rhythms played an important role for the temporal perception in visual studies, which contributes a plausible explanation to the mechanisms of the two-process model of the 2-3 s time window (Fraisse, 1984). Our study also found a close clustering similarity between the observed diurnal variations in metrics of temporal reproduction and temporal resolution. These variations are also similar to those of spontaneous tempo. As in the hierarchical model proposed by Pöppel (Pöppel, 1997), a 30 ms system state and a 3 s integration interval, processing with memory storage, have provided an explanatory neurocognitive mechanism for the differential subjective timing.

<u>High correlation and similarity among spontaneous motor tempo, the temporal resolution in the right visual filed, and the temporal reproduction of 4.5 s:</u> Interestingly, the normalized diurnal curves of SMT, TFT_PSE_RVF, and TRT_Rep_4.5 s nearly overlapped as shown in cluster1. The participants were asked to present their spontaneous tempo with their dominant hand, and all of them are right-handed. The perceived temporal resolution in the right visual field had a similar diurnal change as the spontaneous right-handed tempo, which demonstrates the ipsilateral neurological regulation of temporal perception and spontaneous motor control. A recent study has revealed a link between rhythmic modulation of visual discrimination and SMT (Snapiri et al., 2022), with greater rhythmic modulation associated slower SMT. As was discussed that the reproduction of 4.5 s had a different mechanism as the short duration of 1.5 s, and the dependent factors such as spontaneous motor tempo could be taken into accounts.

4.2 Phase difference between different tasks

Overall, with the exception of ear temperature, the transition point for diurnal variation in physiological measures and subjective evaluations occurred from morning to noon, whereas for most of the cognitive tests the transition point occurred from afternoon to evening. There was a statistically significant difference between the peak/trough phases in the morning and evening, while the difference from the midday to afternoon was not significant for each measurement. Although the acrophases distributed from afternoon to evening, no significant phase differences were found among the time windows from tens-millisecond to thousands-milliseconds.

Four patterns estimated by the clustering method displayed different diurnal changes of each cluster, particularly the big phase difference about to 12 hours between cluster 1 and cluster2. As the phase differences between body temperature and cortisol (Bailey and Heitkemper, 2001), the related cognitive functions to each two biomarkers had a varied phase pattern in a diurnal rhythm. The circadian rhythm of cortisol is considered to be driven by the SCN in the same way as the circadian mechanism of body temperature (Moore-Ede et al., 1984). This potentially suggests that the circadian mechanisms of these associated cognitive functions are regulated by the central pacemaker SCN.

4.3 Limitation of this study

Although the effect of food intake on the cognitive battery is almost non-existent, it is still one of the most significant points for improvements. Multiple methods including repeated ANOVA, cosinor analysis, correlation comparisons and cluster analysis were applied to quantify circadian rhythms, the results were not completely consistent in every indicator as discussed above. Circadian rhythm studies require a combination of methods for interpretation. Due to time constraints, the diversity of tasks related to time perception is too small. Although the study initially controlled for the effect of gender on cognition, employing only female subjects also missed important comparative results with males. Likewise, we employed only 18 healthy young Chinese, a group disproportionately singular in age, geography, and knowledge differences.

4.4 Conclusions and recommendations

This study showed the significant influence of circadian rhythm in temporal perceptions within tens-millisecond to thousands-millisecond time window. The clustering different patterns suggested that temporal perception was supposed to be different in the morning and afternoon. The similarities of diurnal rhythms between biomarkers and subjective and objective functions indicated the regulatory role of endogenous clock. The varying properties of similarity gave hints of differential mechanisms underlying the phase relationships.

This study systematically examined the phase relationships between physiological functions, subjective evaluations and objective cognitive performances in a diurnal time course. The diversity of phase maps in a diurnal shift was found, suggesting that perceptual performance at different time windows does not follow the same pattern. This provides some clues for the variation of human temporal perception in millisecond or second time windows throughout the day, contributing a temporal scheme for improving productivity.

However, only correlations rather than causality were obtained in this experiment. Therefore, further biological and neural mechanism studies need to be implemented in combination with molecular or brain imaging techniques. Based on the findings obtained from this experiment, further experiments on sex, age and geographical differences can be used to refine the systematic effects of circadian rhythms on different time windows.

On the other hand, the effect on the phase shift and phase response in short time windows can be explored by synchronizing or desynchronizing the endogenous clocks with different lighting settings. What is the effect of nocturnal hours on time perception? How to divorce the fatigue of time perception at night from the nocturnal rhythm? These above questions in investigating the nocturnal cycle of short-term time perception in shift workers are worth to be further addressed.

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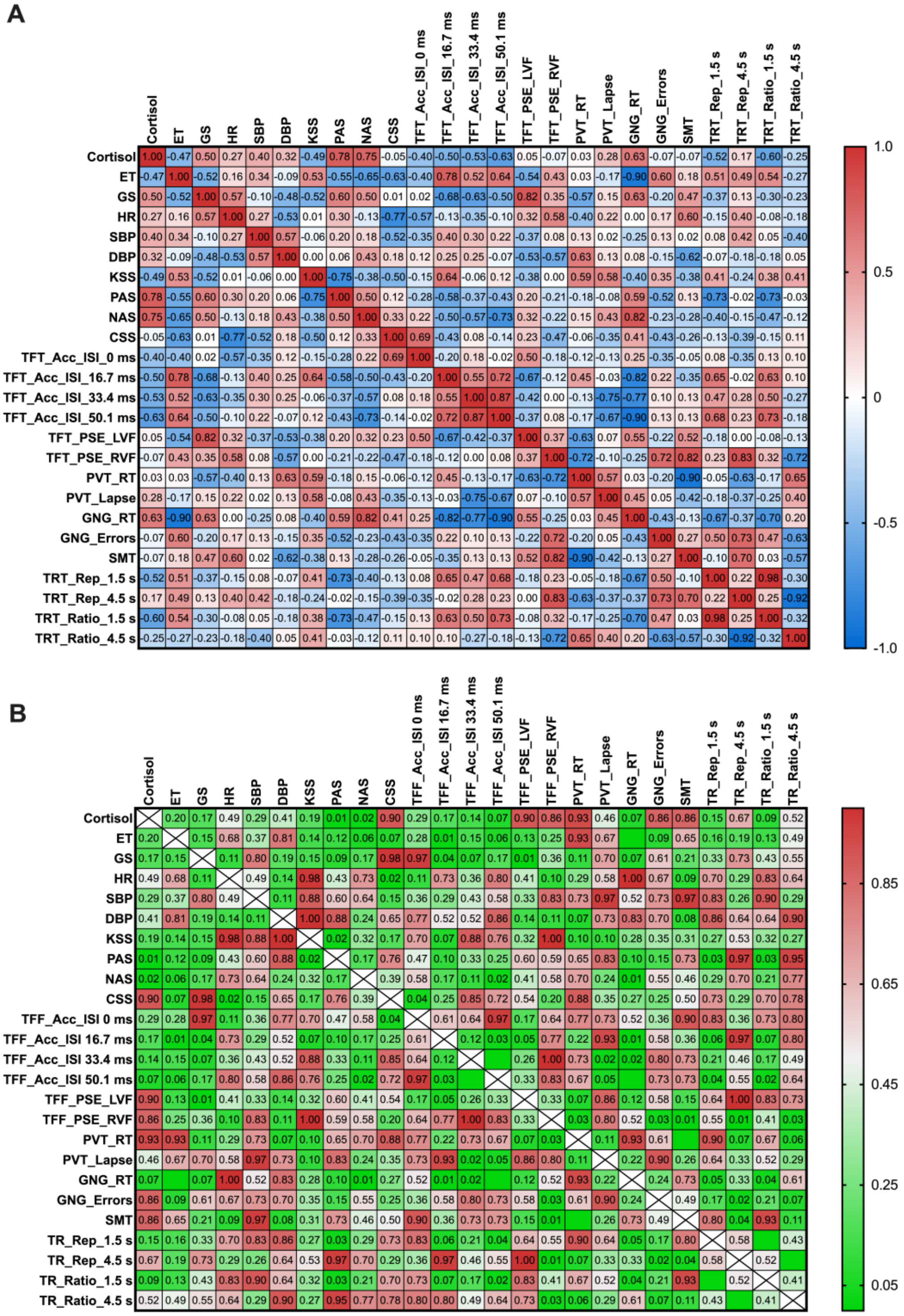
Appendix 1: Sleep diary sheet

Participate ID : **Start date:**

	Exampel Day **30.11.2020**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
When did you go to bed last night?	**22:30**							
When did you turn off the lights last night?	**23:00**							
How fast do you fell asleep (in minute)	**15 min**							
How many times did you wake during the night and how long did these awakening last in total?	**3** **30 min**							
How would you rate your sleep? 1 poor, 2 satisfactory, 3 average, 4 good, 5 excellent	**2**							
Did you take any naps during the day? if so, for how long?	**1 nap** **(15:00-15:30)**							
When did you wake up this morning?	**06:15**							
When did you leave your bed this morning?	**06:30**							

Appendix 2: Correlation matrix



A

	Cortisol	ET	GS	HR	SBP	DBP	KSS	PAS	NAS	CSS	TFT_Acc_ISI_0 ms	TFT_Acc_ISI_16.7 ms	TFT_Acc_ISI_33.4 ms	TFT_Acc_ISI_50.1 ms	TFT_PSE_LVF	TFT_PSE_RVF	PVT_RT	PVT_Lapse	GNG_RT	GNG_Errors	SMT	TRT_Rep_1.5 s	TRT_Rep_4.5 s	TRT_Ratio_1.5 s	TRT_Ratio_4.5 s
Cortisol	1.00	-0.47	0.50	0.27	0.40	0.32	-0.49	0.78	0.75	-0.05	-0.40	-0.50	-0.53	-0.63	0.05	-0.07	0.03	0.28	0.63	-0.07	-0.07	-0.52	0.17	-0.60	-0.25
ET	-0.47	1.00	-0.52	0.16	0.34	-0.09	0.53	-0.55	-0.65	-0.63	-0.40	0.78	0.52	0.64	-0.54	0.43	0.03	-0.17	-0.90	0.60	0.18	0.51	0.49	0.54	-0.27
GS	0.50	-0.52	1.00	0.57	-0.10	-0.48	-0.52	0.60	0.50	0.01	0.02	-0.68	-0.63	-0.50	0.82	0.35	-0.57	0.15	0.63	-0.20	0.47	-0.37	0.13	-0.30	-0.23
HR	0.27	0.16	0.57	1.00	0.27	-0.53	0.01	0.30	-0.13	-0.77	-0.57	-0.13	-0.35	-0.10	0.32	0.58	-0.40	0.22	0.00	0.17	0.60	-0.15	0.40	-0.08	-0.18
SBP	0.40	0.34	-0.10	0.27	1.00	0.57	-0.06	0.20	0.18	-0.52	-0.35	0.40	0.30	0.22	-0.37	0.08	0.13	0.02	-0.25	0.13	0.02	0.08	0.42	0.05	-0.40
DBP	0.32	-0.09	-0.48	-0.53	0.57	1.00	0.00	0.06	0.43	0.18	0.12	0.25	0.25	-0.07	-0.53	-0.57	0.63	0.13	0.08	-0.15	-0.62	-0.07	-0.18	-0.18	0.05
KSS	-0.49	0.53	-0.52	0.01	-0.06	0.00	1.00	-0.75	-0.38	-0.50	-0.15	0.64	-0.06	0.12	-0.38	0.00	0.59	0.58	-0.40	0.35	-0.38	0.41	-0.24	0.38	0.41
PAS	0.78	-0.55	0.60	0.30	0.20	0.06	-0.75	1.00	0.50	0.12	-0.28	-0.58	-0.37	-0.43	0.20	-0.21	-0.18	-0.08	0.59	-0.52	0.13	-0.73	-0.02	-0.73	-0.03
NAS	0.75	-0.65	0.50	-0.13	0.18	0.43	-0.38	0.50	1.00	0.33	0.22	-0.50	-0.57	-0.73	0.32	-0.22	0.15	0.43	0.82	-0.23	-0.28	-0.40	-0.15	-0.47	-0.12
CSS	-0.05	-0.63	0.01	-0.77	-0.52	0.18	-0.50	0.12	0.33	1.00	0.69	-0.43	0.08	-0.14	0.23	-0.47	-0.06	-0.35	0.41	-0.43	-0.26	-0.13	-0.39	-0.15	0.11
TFT_Acc_ISI_0 ms	-0.40	-0.40	0.02	-0.57	-0.35	0.12	-0.15	-0.28	0.22	0.69	1.00	-0.20	0.18	-0.02	0.50	-0.18	-0.12	-0.13	0.25	-0.35	-0.05	0.08	-0.35	0.13	0.10
TFT_Acc_ISI_16.7 ms	-0.50	0.78	-0.68	-0.13	0.40	0.25	0.64	-0.58	-0.50	-0.43	-0.20	1.00	0.55	0.72	-0.67	-0.12	0.45	-0.03	-0.82	0.22	-0.35	0.65	-0.02	0.63	0.10
TFT_Acc_ISI_33.4 ms	-0.53	0.52	-0.63	-0.35	0.30	0.25	-0.06	-0.37	-0.57	0.08	0.18	0.55	1.00	0.87	-0.42	0.00	-0.13	-0.75	-0.77	0.10	0.13	0.47	0.28	0.50	-0.27
TFT_Acc_ISI_50.1 ms	-0.63	0.64	-0.50	-0.10	0.22	-0.07	0.12	-0.43	-0.73	-0.14	-0.02	0.72	0.87	1.00	-0.37	0.08	-0.17	-0.67	-0.90	0.13	0.13	0.68	0.23	0.73	-0.18
TFT_PSE_LVF	0.05	-0.54	0.82	0.32	-0.37	-0.53	-0.38	0.20	0.32	0.23	0.50	-0.67	-0.42	-0.37	1.00	0.37	-0.63	0.07	0.55	-0.22	0.52	-0.18	0.00	-0.08	-0.13
TFT_PSE_RVF	-0.07	0.43	0.35	0.58	0.08	-0.57	0.00	-0.21	-0.22	-0.47	-0.18	-0.12	0.00	0.08	0.37	1.00	-0.72	-0.10	-0.25	0.72	0.82	0.23	0.83	0.32	-0.72
PVT_RT	0.03	0.03	-0.57	-0.40	0.13	0.63	0.59	-0.18	0.15	-0.06	-0.12	0.45	-0.13	-0.17	-0.63	-0.72	1.00	0.57	0.03	-0.20	-0.90	-0.05	-0.63	-0.17	0.65
PVT_Lapse	0.28	-0.17	0.15	0.22	0.02	0.13	0.58	-0.08	0.43	-0.35	-0.13	-0.03	-0.75	-0.67	0.07	-0.10	0.57	1.00	0.45	0.05	-0.42	-0.18	-0.37	-0.25	0.40
GNG_RT	0.63	-0.90	0.63	0.00	-0.25	0.08	-0.40	0.59	0.82	0.41	0.25	-0.82	-0.77	-0.90	0.55	-0.25	0.03	0.45	1.00	-0.43	-0.13	-0.67	-0.37	-0.70	0.20
GNG_Errors	-0.07	0.60	-0.20	0.17	0.13	-0.15	0.35	-0.52	-0.23	-0.43	-0.35	0.22	0.10	0.13	-0.22	0.72	-0.20	0.05	-0.43	1.00	0.27	0.50	0.73	0.47	-0.63
SMT	-0.07	0.18	0.47	0.60	0.02	-0.62	-0.38	0.13	-0.28	-0.26	-0.05	-0.35	0.13	0.13	0.52	0.82	-0.90	-0.42	-0.13	0.27	1.00	-0.10	0.70	0.03	-0.57
TRT_Rep_1.5 s	-0.52	0.51	-0.37	-0.15	0.08	-0.07	0.41	-0.73	-0.40	-0.13	0.08	0.65	0.47	0.68	-0.18	0.23	-0.05	-0.18	-0.67	0.50	-0.10	1.00	0.22	0.98	-0.30
TRT_Rep_4.5 s	0.17	0.49	0.13	0.40	0.42	-0.18	-0.24	-0.02	-0.15	-0.39	-0.35	-0.02	0.28	0.23	0.00	0.83	-0.63	-0.37	-0.37	0.73	0.70	0.22	1.00	0.25	-0.92
TRT_Ratio_1.5 s	-0.60	0.54	-0.30	-0.08	0.05	-0.18	0.38	-0.73	-0.47	-0.15	0.13	0.63	0.50	0.73	-0.08	0.32	-0.17	-0.25	-0.70	0.47	0.03	0.98	0.25	1.00	-0.32
TRT_Ratio_4.5 s	-0.25	-0.27	-0.23	-0.18	-0.40	0.05	0.41	-0.03	-0.12	0.11	0.10	0.10	-0.27	-0.18	-0.13	-0.72	0.65	0.40	0.20	-0.63	-0.57	-0.30	-0.92	-0.32	1.00

B

	Cortisol	ET	GS	HR	SBP	DBP	KSS	PAS	NAS	CSS	TFF_Acc_ISI 0 ms	TFF_Acc_ISI 16.7 ms	TFF_Acc_ISI 33.4 ms	TFF_Acc_ISI 50.1 ms	TFF_PSE_LVF	TFF_PSE_RVF	PVT_RT	PVT_Lapse	GNG_RT	GNG_Errors	SMT	TR_Rep_1.5 s	TR_Rep_4.5 s	TR_Ratio_1.5 s	TR_Ratio_4.5 s
Cortisol	☒	0.20	0.17	0.49	0.29	0.41	0.19	0.01	0.02	0.90	0.29	0.17	0.14	0.07	0.90	0.86	0.93	0.46	0.07	0.86	0.86	0.15	0.67	0.09	0.52
ET	0.20	☒	0.15	0.68	0.37	0.81	0.14	0.12	0.06	0.07	0.28	0.01	0.15	0.06	0.13	0.25	0.93	0.67		0.09	0.65	0.16	0.19	0.13	0.49
GS	0.17	0.15	☒	0.11	0.80	0.19	0.15	0.09	0.17	0.98	0.97	0.04	0.07	0.17	0.01	0.36	0.11	0.70	0.07	0.61	0.21	0.33	0.73	0.43	0.55
HR	0.49	0.68	0.11	☒	0.49	0.14	0.98	0.43	0.73	0.02	0.11	0.73	0.36	0.80	0.41	0.10	0.29	0.58	1.00	0.67	0.09	0.70	0.29	0.83	0.64
SBP	0.29	0.37	0.80	0.49	☒	0.11	0.88	0.60	0.64	0.15	0.36	0.29	0.43	0.58	0.33	0.83	0.73	0.97	0.52	0.73	0.97	0.83	0.26	0.90	0.29
DBP	0.41	0.81	0.19	0.14	0.11	☒	1.00	0.88	0.24	0.65	0.77	0.52	0.52	0.86	0.14	0.11	0.07	0.73	0.83	0.70	0.08	0.86	0.64	0.64	0.90
KSS	0.19	0.14	0.15	0.98	0.88	1.00	☒	0.02	0.32	0.17	0.70	0.07	0.88	0.76	0.32	1.00	0.10	0.10	0.28	0.35	0.31	0.27	0.53	0.32	0.27
PAS	0.01	0.12	0.09	0.43	0.60	0.88	0.02	☒	0.17	0.76	0.47	0.10	0.33	0.25	0.60	0.59	0.65	0.83	0.10	0.15	0.73	0.03	0.97	0.03	0.95
NAS	0.02	0.06	0.17	0.73	0.64	0.24	0.32	0.17	☒	0.39	0.58	0.17	0.11	0.02	0.41	0.58	0.70	0.24	0.01	0.55	0.46	0.29	0.70	0.21	0.77
CSS	0.90	0.07	0.98	0.02	0.15	0.65	0.17	0.76	0.39	☒	0.04	0.25	0.85	0.72	0.54	0.20	0.88	0.35	0.27	0.25	0.50	0.73	0.29	0.70	0.78
TFF_Acc_ISI 0 ms	0.29	0.28	0.97	0.11	0.36	0.77	0.70	0.47	0.58	0.04	☒	0.61	0.64	0.97	0.17	0.64	0.77	0.73	0.52	0.36	0.90	0.83	0.36	0.73	0.80
TFF_Acc_ISI 16.7 ms	0.17	0.01	0.04	0.73	0.29	0.52	0.07	0.10	0.17	0.25	0.61	☒	0.12	0.03	0.05	0.77	0.22	0.93	0.01	0.58	0.36	0.06	0.97	0.07	0.80
TFF_Acc_ISI 33.4 ms	0.14	0.15	0.07	0.36	0.43	0.52	0.88	0.33	0.11	0.85	0.64	0.12	☒		0.26	1.00	0.73	0.02	0.02	0.80	0.73	0.21	0.46	0.17	0.49
TFF_Acc_ISI 50.1 ms	0.07	0.06	0.17	0.80	0.58	0.86	0.76	0.25	0.02	0.72	0.97	0.03		☒	0.33	0.83	0.67	0.05		0.73	0.73	0.04	0.55	0.02	0.64
TFF_PSE_LVF	0.90	0.13	0.01	0.41	0.33	0.14	0.32	0.60	0.41	0.54	0.17	0.05	0.26	0.33	☒	0.33	0.07	0.86	0.12	0.58	0.15	0.64	1.00	0.83	0.73
TFF_PSE_RVF	0.86	0.25	0.36	0.10	0.83	0.11	1.00	0.59	0.58	0.20	0.64	0.77	1.00	0.83	0.33	☒	0.03	0.80	0.52	0.03	0.01	0.55	0.01	0.41	0.03
PVT_RT	0.93	0.93	0.11	0.29	0.73	0.07	0.10	0.65	0.70	0.88	0.77	0.22	0.73	0.67	0.07	0.03	☒	0.11	0.93	0.61		0.90	0.07	0.67	0.06
PVT_Lapse	0.46	0.67	0.70	0.58	0.97	0.73	0.10	0.83	0.24	0.35	0.73	0.93	0.02	0.05	0.86	0.80	0.11	☒	0.22	0.90	0.26	0.64	0.33	0.52	0.29
GNG_RT	0.07		0.07	1.00	0.52	0.83	0.28	0.10	0.01	0.27	0.52	0.01	0.02		0.12	0.52	0.93	0.22	☒	0.24	0.73	0.05	0.33	0.04	0.61
GNG_Errors	0.86	0.09	0.61	0.67	0.73	0.70	0.35	0.15	0.55	0.25	0.36	0.58	0.80	0.73	0.58	0.03	0.61	0.90	0.24	☒	0.49	0.17	0.02	0.21	0.07
SMT	0.86	0.65	0.21	0.09	0.97	0.08	0.31	0.73	0.46	0.50	0.90	0.36	0.73	0.73	0.15	0.01		0.26	0.73	0.49	☒	0.80	0.04	0.93	0.11
TR_Rep_1.5 s	0.15	0.16	0.33	0.70	0.83	0.86	0.27	0.03	0.29	0.73	0.83	0.06	0.21	0.04	0.64	0.55	0.90	0.64	0.05	0.17	0.80	☒	0.58		0.43
TR_Rep_4.5 s	0.67	0.19	0.73	0.29	0.26	0.64	0.53	0.97	0.70	0.29	0.36	0.97	0.46	0.55	1.00	0.01	0.07	0.33	0.33	0.02	0.04	0.58	☒	0.52	
TR_Ratio_1.5 s	0.09	0.13	0.43	0.83	0.90	0.64	0.32	0.03	0.21	0.70	0.73	0.07	0.17	0.02	0.83	0.41	0.67	0.52	0.04	0.21	0.93		0.52	☒	0.41
TR_Ratio_4.5 s	0.52	0.49	0.55	0.64	0.29	0.90	0.27	0.95	0.77	0.78	0.80	0.80	0.49	0.64	0.73	0.03	0.06	0.29	0.61	0.07	0.11	0.43		0.41	☒

Fig. Appendix 2 Spearman' correlation matrix. (A) the heatmap of Spearman' r and (B) the heatmap of *p* values in the correlation matrix. Significant differences are shown as $p < 0.05$. For abbreviations of measurements, see Material and Methods.

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Affidavit

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I hereby declare, that the submitted thesis entitled:

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I further declare that the submitted thesis or parts thereof have not been presented as part of an examination degree to any other university.

Munich, June 29, 2023 Wei Wang

place, date Signature doctoral candidate

List of publications

Research Investigations

1. Hao Zikai, **Wang Wei**, Guo Rong, Liu Hong (2019) *Faecalibacterium prausnitzii* (ATCC 27766) has preventive and therapeutic effects on chronic unpredictable mild stress-induced depression-like and anxiety-like behavior in rats. Psychoneuroendocrinology, 104, 132-142. https://doi.org/10.1016/j.psyneuen.2019.02.025
2. Meng Chen*, **Wang Wei***, Hao Zikai, Liu Hong (2020) Investigation on the influence of isolated environment on human psychological and physiological health. Sci Total Environ, 716, 136972. https://doi.org/10.1016/j.scitotenv.2020.136972

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3. Chen Haishan, Meng Xiaoping, Liu Dianlei, **Wang Wei**, Xing Xiaodong, Zhang Zhiyong, Dong Chen (2022) Closed-loop microbial fuel cell control system designed for online monitoring of TOC dynamic characteristics in public swimming pool. Int J Environ Res Publ Health, 19, 13024. https://doi.org/10.3390/ijerph192013024
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