Aus der Klinik für Psychiatrie und Psychotherapie
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DISSERTATION

The association of sleep and stress with psychological well-being and neuronal functional connectivity

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1 Abstract

Sufficient sleep and an adequate stress response are two important components when it comes to coping with adverse events. Previous studies have shown that both are related to the occurrence of psychological and physical disorders, emphasizing the necessity to explore both concepts within the scope of this PhD thesis individually as well as their association among each other.

In Study 1, we investigated the association of sleep-related variables with psychological well-being based on an online survey. We found evidence that the association of psychological well-being towards chronotype follows a U-shaped function, which means that being an early or late chronotype is related to impaired well-being. Additionally, reduced sleep durations, especially when occurring on work days, was associated with depressive symptomatology and sleep quality.

For Study 2 and 3 we deployed neuroimaging data, as both sleep deprivation and psychosocial stress have been proven to change neuronal activity and connectivity patterns in the aftermath of stress. Study 2 focused on replicating results concerning the previously reported increased connectivity of the amygdala with regions involved in the down-regulation of the physiological stress response, in emotion regulation, and in memory consolidation. Analyzing resting state connectivity after stress compared to the pre-stress condition, we found an increase in bilateral amygdala resting-state functional connectivity (RSFC) with the posterior cingulate cortex (PCC) and the adjacent precuneus only in male cortisol non-responders, but not in responders. We did not detect changes in amygdala RSFC between female cortisol responders and non-responders. This finding shows the influence of sex and cortisol reactivity, when exploring neural signatures of stress reactivity and recovery.

In Study 3 we focused on male participants only, now expanding the results from Study 2 by exploring the impact of sleep loss on neural signatures of stress recovery. We found a negative association of sleep loss, as reported in a seven-day sleep diary, with the stress-induced change of left amygdala RSFC to several cortical brain regions, including the medial prefrontal cortex, dorsolateral prefrontal cortex, dorsal anterior cingulate cortex, anterior insula, and PCC. That is, the higher the sleep loss, the more decrease in left amygdala RSFC was found with these regions after stress.

Taken together, the results of this PhD thesis contribute to a better understanding of associations between sleep, stress, and psychological well-being on a behavioral as well as neuronal level.

1.1 Zusammenfassung

Ausreichend Schlaf und eine angemessene Stressantwort stellen zwei wichtige Faktoren im Umgang mit belastenden Ereignissen dar. Frühere Studien berichteten von einem Zusammenhang mit dem Auftreten von psychologischen und physischen Erkrankungen. Dies belegt die Notwendigkeit, deren Wirkung im Rahmen der vorliegenden Doktorarbeit sowohl als einzelne Konstrukte als auch in Verbindung zueinander zu explorieren.

Im Rahmen der ersten Studie untersuchten wir den Zusammenhang von schlafbezogenen Variablen zu psychologischem Wohlbefinden mithilfe einer Online-Umfrage. Die Ergebnisse zeigten, dass der Zusammenhang zwischen psychologischem Wohlbefinden und Chronotyp einer u-förmigen Funktion folgt. Damit haben vor allem sehr frühe und späte Chronotypen ein erhöhtes Risiko für vermindertes Wohlbefinden. Zusätzlich fanden wir, dass eine reduzierte Schlafdauer, vor allem an Arbeitstagen, mit vermehrten depressiven Symptomen und geringerer Schlafqualität assoziiert war.

Für die anderen beiden Studien setzten wir bildgebende Verfahren (funktionelle Magnetresonanztomografie) ein, da sowohl Schlafmangel als auch psychosozialer Stress nachweislich einen Einfluss auf die neuronale Aktivität und funktionelle Konnektivität während der Erholung von Stress haben. In Studie 2 konzentrierten wir uns auf die Replikation von früheren Studienergebnissen, die eine stressbedingte Steigerung der Konnektivität zwischen der Amygdala und Gehirnregionen fanden, die in die Herabregulation der physiologischen Stressantwort, in die emotionale Antwort, und die Gedächtniskonsolidierung involviert sind. In der Phase nach einem Stressor fanden wir im Vergleich zu vor dem Stressor eine gesteigerte bilaterale Konnektivität der Amygdala zum posterioren cingulären Cortex (PCC) und dem angrenzenden Precuneus nur in männlichen Teilnehmern ohne Cortisolreaktion im Vergleich zu männlichen Teilnehmern mit einer Cortisolreaktion. Bei weiblichen Teilnehmerinnen fanden sich keine Unterschiede in funktioneller Konnektivität. Die Ergebnisse unterstreichen die Relevanz von Geschlecht und Cortisolraktion beim Betrachten der Erholungsphase nach Stress.

Studie 3 erweitert die Ergebnisse aus Studie 2, indem nur bei männlichen Teilnehmern zusätzlich den Einfluss von Schlafmangel auf die neuronale Erholung von Stress untersuchten. Die Auswertung zeigte eine negative Assoziation zwischen Schlafmangel, der in einem siebentägigen Tagebuch festgehalten wurde, und der stressbedingten funktionelle Konnektivtät der linke Amygdala zu mehreren Gehirnregionen, u.a. dem medialen Präfrontalcortex, dem dorsolateralen Präfrontalcortex, dem dorsalen anterioren cingulären Cortex, der anterioren Insula, und dem PCC. Das bedeutet, je mehr Schlafmangel berichtet wurde, desto schwächer war die funktionelle Konnektivität der linken Amygdala zu den genannten Regionen.

Zusammengefasst tragen die Ergebnisse der Doktorarbeit zu einem besseren Verständnis des Zusammenhangs von Schlaf, Stress und psychologischem Wohlbefinden auf sowohl Verhaltens. als auch neuronaler Ebene bei.

1.2 Introduction

The superior aim of an organism is to maintain *homeostasis*, i.e., "the stability of physiological systems (…) that are truly essential for life and are therefore maintained within a range optimal for the current life history stage" (McEwen & Wingfield, 2003; p. 3). In case of environmental challenges, i.e. stressors, those physiological systems have to adapt. This process is called *allostasis* and describes the biological responses that are necessary in order to promote adaptation. It comprises several systemic mediators, e.g. sympathetic and parasympathetic activity, hormones of the hypothalamic-pituitary-adrenal (HPA) axis and cytokines. However, in case of insufficient adaptation, the stressor induces allostatic overload, which can result in disorders on a physiological as well as psychological level (McEwen, 1998). One contributor to allostatic overload are interruptions in the sleep-wake-cycle, as many mediators follow a circadian rhythm (Karatsoreos & McEwen, 2011). Therefore, it is no surprise that a well-established relationship has been reported between sleep (disorders) and stress responsivity (Lo Martire, Caruso, Palagini, Zoccoli, & Bastianini, 2019; van Dalfsen & Markus, 2018).

1.2.1 On the importance of sleep

During sleep, our brain temporarily disconnects from environmental input in order to enable memory consolidation, integration, and synaptic plasticity (Tononi & Cirelli, 2014). Sleep itself can be characterized by several dimensions, i.e., duration, efficiency, timing, sleepiness, and quality (Daniel J. Buysse, 2014), which have been shown to vary considerably between individuals (Goel, Basner, Rao, & Dinges, 2013; Roenneberg et al., 2007). Sleep timing is regulated by so called *Zeitgebers*, namely the solar clock (light – dark), the biological clock (e.g., genes) and the social clock (e.g., work schedule), together determining an individual's circadian rhythm (Roenneberg, Wirz-Justice, & Merrow, 2003). This process is termed entrainment. A group of people who share the same phase of entrainment have a certain chronotype (Roenneberg, 2015). The later one's chronotype is, the more misalignment there will often be between the biological (inner) and social (outer) clock, a phenomenon referred to as social jetlag (Wittmann, Dinich, Merrow, & Roenneberg, 2006). Multiple tools exist to assess chronotype (Adan et al., 2012), whereas social jetlag is a more recent concept and can be assessed with the Munich Chronotype Questionnaire (MCTQ; Roenneberg et al., 2003).

Numerous studies have been conducted exploring the association of sleep-related variables with physiological and psychological health outcomes, like hypertension (Fiorentini, Valente, Perciaccante, & Tubani, 2007; Gangwisch, 2014), obesity and metabolic syndrome (Grandner, Jackson, Pak, & Gehrman, 2012; Jennings, Muldoon, Hall, Buysse, & Manuck,

2007; Koren & Taveras, 2018), or anxiety and mood disorders (Goldstein & Walker, 2014; Krystal, 2012; Tsuno, Besset, & Ritchie, 2005). Concerning chronotype, previous studies have reported an association with depressive symptomatology (Antypa, Vogelzangs, Meesters, Schoevers, & Penninx, 2015; Hidalgo et al., 2009; Kitamura et al., 2010; Levandovski et al., 2011) and impaired sleep quality (Sun et al., 2019; Vardar, Vardar, Molla, Kaynak, & Ersoz, 2008) for later chronotypes mainly. Furthermore, preliminary evidence suggests an association of chronotype with subjectively reported stress (Kantermann, Theadom, Roenneberg, & Cropley, 2012). The evidence is not so conclusive for co-occurrence of social jetlag with a late chronotype (Wittmann et al., 2006). Whereas some studies reported significant associations of both late chronotype and social jetlag with impaired well-being (Levandovski et al., 2011; Önder, Beşoluk, İskender, Masal, & Demirhan, 2014), others reported non-significant findings for social jetlag (Polugrudov et al., 2016; Rutters et al., 2014; Sheaves et al., 2016). In sum, there is currently no conclusive evidence that clarifies the associations between sleep-related MCTQ variables and psychological well-being.

1.2.2 On the importance of adequate stress reactivity

Coping with stressors and regulating one's emotions properly is a dynamic process, which gives every individual a chance to adapt to adverse events in his or her own range of capabilities in the time they need (Bonanno & Burton, 2013). A circuit important for allostasis is the secretion of glucocorticoids, commonly known as stress hormones. The hypothalamic-pituitary-adrenal (HPA) axis belongs to the neuroendocrine system, releasing corticotropin-releasing hormone (CRH) from the hypothalamus in order to induce the secretion of adrenocorticotropic hormone (ACTH) from the anterior pituitary. After endocrine transport, ACTH leads to the secretion of glucocorticoids, mainly cortisol, from the adrenal cortex (Stephens, Mahon, McCaul, & Wand, 2016). The release of cortisol follows a diurnal rhythm, with an increase after awakening, followed by a continuous decrease during the day. Additionally, it can be triggered by various stimuli, e.g., stress, pain, hypotension (Fries, Dettenborn, & Kirschbaum, 2009). Deviations from HPA axis reactivity have been reported for psychiatric disorders, e.g., depression, anxiety disorders and schizophrenia (Zorn et al., 2017).

Most studies apply a laboratory paradigm to induce psychosocial stress in participants in order to assess HPA axis reactivity. There is consensus that especially social-evaluative threat and uncontrollability affect the magnitude of HPA axis response (Dickerson & Kemeny, 2004). Typically, the paradigm entails a cognitively challenging task (e.g., public speaking, mathematical subtraction) while the participant is being observed by an expert panel and receives negative feedback for his or her performance (Kirschbaum, Pirke, & Hellhammer,

1993; Noack, Nolte, Nieratschker, Habel, & Derntl, 2019). Several factors influence the magnitude of the cortisol response. One major component is sex: Men have repeatedly shown larger cortisol increases after stress exposure compared to women (Juster et al., 2016; Kudielka & Kirschbaum, 2005; Liu et al., 2017). In addition, women's hormonal level depend on which phase of the menstrual cycle they are in and if they take oral contraceptives, which seems to blunt salivary cortisol responses (Kudielka, Hellhammer, & Wüst, 2009). Another important fact is that not all participants show an increase or only a minimal increase of cortisol concentrations after stressor exposure (so called non-responders), which gives rise to the question if those non-responders actually are not stressed by the paradigm and should be handled separately in analyses (Miller, Plessow, Kirschbaum, & Stalder, 2013).

1.2.3 Association of sleep and stress with neuronal functional connectivity

Both sleep and stress may affect an individual not only on a behavioral, but also on a neuronal level, which has been shown in several functional magnetic resonance imaging (fMRI) studies that explored either task-based activity or resting-state functional connectivity (RSFC) between brain regions.

A key brain region, affected by sleep deprivation and stress exposure likewise, is the amygdala (Arnsten, 2015; Krause et al., 2017), which belongs to a larger neural network known as the Salience Network (SN). Other regions that belong to the SN are the anterior insula (AI), the dorsal anterior cingulate cortex (dACC), and the temporal poles (van Oort et al., 2017). Together they play a role in detecting salient stimuli and focus attention towards a potential threat (Hermans, Henckens, Joëls, & Fernández, 2014). Sleep deprivation has been reported to enhance activity in the amygdala while being confronted with negative emotional stimuli (Ben Simon, Maron-Katz, Lahav, Shamir, & Hendler, 2017; Motomura et al., 2013; Yoo, Gujar, Hu, Jolesz, & Walker, 2007). Likewise, acute stress can be perceived as a threatening experience which increases activity, amongst other regions, in the amygdala (Dahm et al., 2017; Dedovic, D'Aguiar, & Pruessner, 2009; Lederbogen et al., 2011; Streit et al., 2014).

Whereas the SN mediates emotional responses, the Default Mode Network (DMN) is hypothesized to be involved in the down-regulation of amygdala activity via enhanced functional connectivity with the medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC), and precuneus during stress recovery (Veer et al., 2011) and, additionally, with the hippocampus (van Oort et al., 2017). However, previous research reported divergent findings with respect to neuronal recovery after acute stress, which may be explained by differences in the type of stress induction, the experimental design, gender distribution of the study sample, and choice of seed regions. A consistent finding is an increased RSFC of the

amygdala with the hippocampus (van Oort et al., 2017), whereas connectivity with other regions, like the ACC, the anterior insula (AI), medial PFC, and PCC, still have to be explored more in depth (Quaedflieg et al., 2015; Vaisvaser et al., 2013; van Marle, Hermans, Qin, & Fernández, 2010; Veer et al., 2011). As opposed to this, sleep deprivation has been shown to reduce functional connectivity within several brain networks and the segregation of networks (Ben Simon et al., 2017; Kaufmann et al., 2015; Killgore, 2013; Yeo, Tandi, & Chee, 2015), leading, amongst others, to a diminished prefrontal control on limbic regions during emotional processing (Lei et al., 2015; Shao et al., 2014; Yoo et al., 2007).

Taken together, previous research has focused on functional connectivity changes in the aftermath of acute stress without considering the effect of sleep loss, in spite of the impact this might have on our everyday emotional well-being.

1.2.4 Aims and hypotheses

The aim of this PhD thesis is to explore the relationship between sleep-related variables, stress reactivity, and psychological well-being on a behavioral and neuronal level. In the first study, we conducted an online survey, enquiring about sleep-wake-rhythms and psychological well-being in terms of depressive symptomatology, sleep quality, and perceived stress. Previous research suggests an association between having a later chronotype and impaired psychological well-being, whereas so far findings are inconclusive with regard to social jetlag, though higher social jetlag occurs more likely in later chronotypes.

Hypothesis Study 1: We expected higher values in depressive symptomatology, sleep disruptions, and perceived stress in later chronotypes and with increasing social jetlag.

Further, we conducted two separate neuroimaging studies. First, we focused on the effects of psychosocial stress on amygdala resting state functional connectivity (RSFC) in order to replicate and extend previous findings.

Hypothesis Study 2: We expected that the amygdala would demonstrate increased RSFC after stress exposure with regions involved in the down-regulation of the physiological stress response, in emotion regulation, and in memory consolidation. Moreover, as cortisol plays a key role in reaching homeostasis, we expected that these connections would be engaged differentially in people who demonstrate a cortisol increase in response to stress compared to those who do not.

In the second neuroimaging study, we expanded those results by exploring the impact of sleep loss on neuronal stress recovery. So far, sleep loss has not been linked to amygdala RSFC after stress exposure, in spite of the impact this might have on our everyday emotional well-being.

Hypothesis Study 3: We expected that the strength of amygdala RSFC after stress exposure would be associated with the amount of sleep loss accumulated during one week.

1.3 Methods

1.3.1 Study 1: Sleep and psychological well-being

Participants: The online study was conducted in two successive steps. A first survey enquired about sleep-wake-habits via the Munich Chronotype Questionnaire (Roenneberg et al., 2003), obtaining complete information from 1111 participants (806 females; mean age = 37.45 ± 13.16). In case the participant provided his or her email address, he or she was invited for a second survey on sociodemographic data and psychological well-being. 588 participants (450 females; mean age = 38.45 ± 13.20) completed questions concerning depressive mood (Patient Health Questionnaire 9, Löwe, Spitzer, Zipfel, and Herzog (2002)), sleep quality (Pittsburgh Sleep Quality Index, D. J. Buysse, Reynolds, Monk, Berman, and Kupfer (1989)) and perceived stress (Perceived Stress Scale, Cohen and Williamson (1988)). The only relevant exclusion criterion for this study was performing shift work. The study was approved by the Medical Ethics Committee of the Charité - Universitätsmedizin Berlin. Informed consent was obtained from all participants.

Questionnaires: The Munich Chronotype Questionnaire (MCTQ) was developed to assess an individual's chronotype and the amount of social jetlag, i.e. misalignment of social and biological time (Wittmann et al., 2006), by asking the participant to estimate their sleep onset and wake-up time for work and free days separately. This allows the calculation of sleep duration (SDw = work days; SDf = free days) and midpoint of sleep (MSW = midpoint of sleep on work days, MSF = midpoint of sleep on free days). An individual's chronotype is reflected by the estimation of MSF. Because sleep during work days is often shortened by social obligations, such as having to get up early for work, people accumulate a sleep debt that is mostly compensated for on free days by sleeping in for a longer time. As this delays the MSF, it must be accounted for in calculating an individual's chronotype by correcting the MSF for sleep debt (MSFsc: MSF sleep corrected). Social jetlag (SJL) is reflected by the mismatch of MSW and MSF. And lastly, as sleep loss often accompanies social jetlag, we evaluated its relationship with psychological well-being as well. (For exact calculations of MCTQ variables, see Table 2 in Dimitrov et al. (2020)).

In order to assess psychological well-being, we chose three questionnaires that reflect different areas. Firstly, we applied the Patient Health Questionnaire (PHQ9) to assess the nine criteria of Major Depression in the *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association, 2013) on a score range for each item from 0 to 3. A maximum of 21 points can be obtained, with higher scores indicating higher depressive symptom severity. Secondly, the Pittsburgh Sleep Quality Index (PSQI) was used to assess sleep patterns, quality of sleep, and sleep disturbances over a period of 4 weeks. Seven components are deducted, equally scoring between 0 and 3, thus allowing a general PSQI

score with a maximum of 21 points, with higher scores indicating worse sleep quality. And thirdly, a 10-item-version of the Perceived Stress Scale (PSS) was applied, assessing subjectively perceived stress over the past 4 weeks with 0 to 4 points for each item. A maximum of 40 points can be scored, with higher scores indicating higher levels of perceived stress.

Statistical Analysis: To compare our sample to previous samples employing the MCTQ, we first examined the 1111 participants from the first survey and compared the MCTQ scores to the epidemiological results from Roenneberg et al. (2007). Due to our cross-sectional design, we calculated correlations between MCTQ variables (SDw, SDf, MSF, MSFsc, SJL, and sleep loss) and age. Sex differences were tested by means of a two-sample t-test.

To assess associations with psychological well-being, partial correlations were calculated, controlling for age and sex. In total 588 participants were included for the analysis of PHQ9 and PSS, but only 570 participants for the analysis of PSQI, due to missing data. Additionally, we divided the sample into equal thirds according to the MSFsc scores (early, intermediate, and late chronotype) and repeated nonparametric partial correlation analysis within each chronotype group as exploratory follow-up analyses.

All statistical analyses were performed with IBM SPSS Statistics for Windows, Version 22 (IBM Corp., Armonk, NY, USA). The significance threshold for all tests was set at $p < .05$. Multiple comparison correction was applied by controlling the false discovery rate (FDR) at $q = .05$, that is, we accepted a maximum of 5 percent false positives among the total number of tests (Benjamini & Hochberg, 1995).

1.3.2 Study 2: Functional connectivity changes after acute stress

Participants: The final sample consisted of 86 participants (mean age 28.38 ± 7.25, range 20–58, 50 females). Twenty-three females in our sample used contraceptives (19 oral contraceptive pill, 4 NuvaRing). Excluded were individuals who reported a history of psychiatric diseases, a first-degree relative with psychiatric diseases, contraindications for MRI scanning (e.g., metallic implants), acute or chronic neurological or physical diseases, a history of alcoholism and/or drug abuse, current intake of prescription medication, color blindness, irregular sleep-wake rhythm, uncorrectable vision, regular smoking (>5 cigarettes per day) and studying or having studied psychology, medicine, or neuroscience to avoid a potential previous knowledge of stress paradigms.

Stress Induction and Assessment: To induce social stress in a neuroimaging environment, we employed the ScanSTRESS task (Streit et al., 2014). It combines social evaluative threat components (verbal and non-verbal feedback by the experimenters), as well as

uncontrollable components (task difficulty, time constraints, and mock feedback of poor performance), which have been reported to induce the strongest physiological stress responses (Dickerson & Kemeny, 2004). During control blocks, participants had to match one of three presented figures or one of four presented numbers to a target figure or four-digit-number. During stress blocks, participants had to match a rotated figure to the target figure or consecutively subtract a two-digit-number from the target number (see Figure 1).

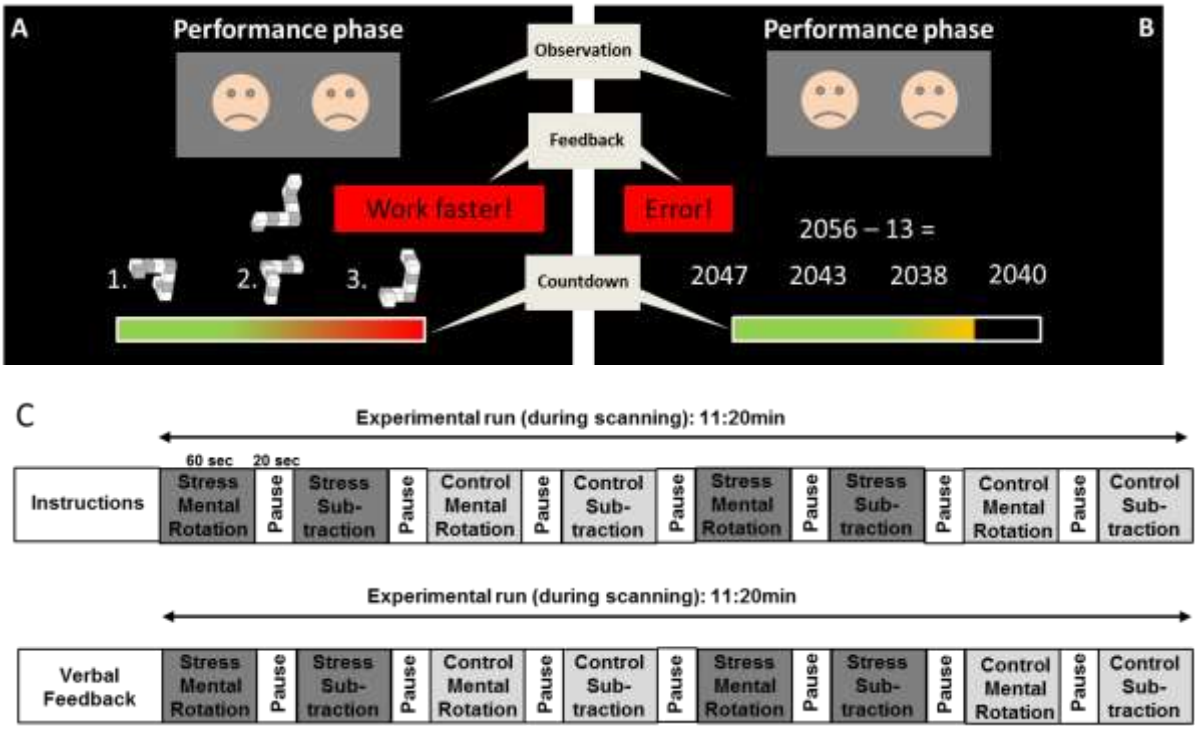

Figure 1. Illustration of stress block ("Performance phase"), including observation by a panel (real video feedback of a male and female observer, here only shown symbolically), visual feedback of performance and an adapted time limit based on previous performance. (A) Rotation: One of three rotated figures had to be matched to a target figure. (B) Subtraction: A two-digit number had to be consecutively subtracted from a four-digit target number. (C) The ScanSTRESS paradigm consisted of two experimental runs inside the MRI scanner (each 11:20min).

Nine saliva samples were collected throughout the protocol (see Figure 1 in Dimitrov et al. (2018)) in order to assess absolute changes in salivary cortisol concentrations (in nmol/l) and the area under the curve with respect to increase (AUCi) (Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003). Heart rate was continuously monitored by an infrared pulse oximeter placed on the left ring finger with a sampling rate of 50 Hz, allowing us to determine heart rate frequency (HRF) and heart rate variability (HRV) as a proxy for parasympathetic activity (Tarvainen, Niskanen, Lipponen, Ranta-Aho, &

Karjalainen, 2014). Subjective stress experience was assessed after the last saliva sample by asking about negative affect during the task. Six items were rated on a four-point scale ranging from “fully agree” to “fully disagree”, leading to a sum score afterwards.

fMRI Data Acquisition: Two resting-state (RS) fMRI scans, one before and one directly after the stress task, were acquired on a Siemens MAGNETOM TIM Trio 3.0 Tesla MRI scanner equipped with a 12-channel head coil (Siemens, Erlangen, Germany). For each RS scan, a total of 154 images was acquired using T_2* weighted gradient-echo echo-planar imaging with the following scan parameters: 37 slices using an interleaved slice-acquisition in a descending order; repetition time (TR) = 2.020ms, echo time (TE) = 25ms, flip angle = 80°, field of view (FOV) = 192 x 192mm, 64 x 64 matrix, 3mm isotropic voxels with a 0.6mm slice gap. Participants were instructed to lie still with their eyes closed in the darkened scanner room, not to think of anything in particular, and to stay awake during the entire scan.

For registration to standard space, a high-resolution anatomical image of the whole brain (voxel size 1 mm^3) was obtained using a T_1 weighted magnetization-prepared rapid gradient-echo (MP-RAGE) sequence with the following scan parameters: 192 sagittal slices, TR = 1.900ms, TE = 2.52ms, flip angle = 9°, FOV = 256 x 256mm, 256 x 256 matrix, slice gap = 0.5mm, parallel imaging technique GRAPPA acceleration factor 2. The scan took 4min and 26 s.

Note that fMRI data were acquired during the stress task as well, but the results were not part of this thesis.

fMRI Preprocessing: The following preprocessing was carried out using FSL (Smith et al., 2004): motion correction, brain extraction, and spatial smoothing with a FWHM of 6mm. Linear registration parameters were obtained for the functional-to-structural transformation, using FLIRT with the Boundary Based Registration (BBR) algorithm. Non-linear normalization parameters for the structural-to-standard-space (2mm MNI) transformation were obtained with FNIRT, using the standard warp resolution setting of 10mm. Next, functional data were further cleaned from artifacts using ICA-AROMA (Pruim et al., 2015), which regresses out latent signal sources (independent components) that it classifies as noise. Lastly, a high-pass temporal filter of 125 s was applied to the cleaned 4D images, which were then normalized to standard space using the previously derived registration parameters.

fMRI Time-Course Extraction: After creating standard-space binary masks of left and right amygdala as defined by the Harvard Oxford Subcortical Probability Atlas within FSL (voxels ≥ 80% probability of belonging to the amygdala), they were registered to each participant’s RS data set. The first eigenvariate time series was extracted for each amygdala mask and for

each RS scan separately. The same was done for deep white matter (WM) and cerebrospinal fluid (CSF) in order to be used as covariates. Single subject general linear models (GLMs) were tested, including the seed's time-course as regressor of interest, together with the WM- and CSF-signal as covariate regressors. Four subject-level functional connectivity maps (left/right amygdala and pre/post stress) were thus obtained, representing voxels of which the time series were correlated with the time of series of the seed. The functional connectivity maps were then fed into a second-level fixed effects analysis to calculate a difference (z-statistic) map between pre- and post-stress amygdala connectivity.

Statistical Analysis: HRF, HF-HRV, and cortisol were analyzed using three-way repeated measures ANCOVAs (mixed design) in IBM SPSS Statistics for Windows, Version 22.0 (Armonk, NY: IBM Corp), with Group and Sex as between-subject factors, and Age as covariate, followed-up by relevant Post hoc t-tests. When the assumption of sphericity was violated, the degrees of freedom were corrected using the Greenhouse-Geisser adjustment. Post-hoc t-tests were conducted using Bonferroni adjusted alpha levels. To achieve a normal distribution, the HF-HRV values were log-transformed.

Before the statistical analysis of amygdala RSFC, participants were categorized as cortisol responder or non-responder based on a baseline-to-peak cortisol increase >2.5 nmol/l in response to the stress task (Miller et al., 2013). To test for existing baseline-differences, the groups were compared on all baseline physiological and psychometric measures with non-parametric Mann–Whitney U-tests.

The difference maps between pre- and post-stress were assessed for each amygdala in an ANCOVA, with Group (responder and non-responder), Sex (males and females), and the interaction between those factors as between-subject variables, adding Age as covariate. The resulting t-statistical maps then underwent Threshold-Free Cluster Enhancement (TFCE) (Smith & Nichols, 2009), using the default parameter settings ($H = 2$, $E = 0.5$, $C = 6$), and significance testing was carried out with permutation testing (4,000 iterations) using the in-house developed TFCE_mediation software (Lett et al., 2017). In the latter step, a null distribution of random results was generated against which the empirical findings were tested, which resulted in statistical images that are family-wise error corrected for multiple comparisons at $p < 0.05$. Follow-up test between responders and non-responders were conducted for males and females separately, using the same settings mentioned above. The test was repeated using a small volume correction for regions that were expected to change their connectivity with the amygdala in response to stress a priori. For this purpose, a mask containing the mPFC, the hippocampus, as well as the PCC and precuneus was created without a probability threshold, to be as unbiased as possible. The same multiple comparison correction as before was then applied, but this time only for voxels falling inside the mask.

1.3.3 Study 3: Sleep loss and the decrease of functional connectivity after acute stress

Participants: Due to differences in stress reactivity between sexes, the sample of Study 3 comprised 45 male participants (mean age = 29.271 ± 4.84, range 20–48 years). Included were participants (1) with a regular Monday-to-Friday work week of 30–50 hours with weekend days off, (2) with no shift-work, (3) with a late chronotype conflicting with early start of work, (4) with no current or past psychiatric disorders, (5) who were non-smokers. Scanning took place either on Wednesday (n = 25) or Thursday evenings (n = 21) between 5 pm and 10 pm.

Sleeping Parameters: In analogy to Study 1, the MCTQ was applied during a telephone screening in order to assess the chronotype and habitual sleep loss (SLoss [MCTQ]). Additionally, participants were asked to complete a sleep diary during the week before the scanning session to estimate the amount of sleep loss during seven nights preceding scanning (SLoss [diary]). Both measures of sleep loss were assessed to test whether effects would be more pronounced for trait-like (MCTQ) or state-like (diary) sleep loss.

Stress Induction and Assessment: In analogy to Study 2, social stress was applied using the ScanSTRESS task with a minor change for the first half of the task, which was shortened and used as a practice run (see Figure 2). Salivary cortisol concentrations were measured at seven time points (see Fig. 1A in Nowak et al. (2020)). At the same time the current stress level was enquired on a 10-point Likert scale (1 = very low stress to 10 = very high stress). Heart rate was assessed, and HRF and HRV calculated, as described in Study 2.

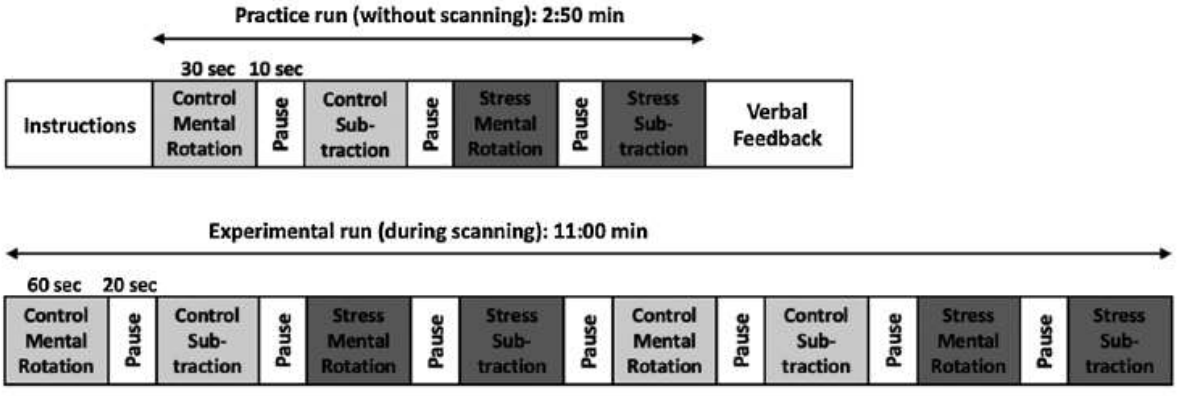

Figure 2. The ScanSTRESS paradigm consisted of two runs inside the MRI scanner: a practice run without scanning (duration: 2:50 min) and an experimental run during scanning (duration: 11:00 min).

fMRI Data Acquisition: Two resting-state fMRI scans, one before and one directly after the stress task, were acquired on a Siemens 3 T Magnetom Trio system with a 32-channel head coil (Siemens, Erlangen, Germany) with the following parameters: T_2*-weighted gradient-echo echo-planar imaging (EPI) sequence, echo time (TE): 25 ms, repetition time (TR): 1560 ms, flip angle: 64°, number of volumes: 308, field of view: 192 mm × 192 mm, number of axial slices: 28 (descending slice order), in-plane matrix size: 64 × 64, 3 mm isotropic voxels, inter-slice gap: .75 mm, scan duration: 8 min 4 s. During resting-state scans, participants were required to lie still, keep their eyes open, and focus on a fixation cross on the monitor. For registration to standard space, a high-resolution structural image of the whole brain was acquired with the parameters as in Study 2.

Note that fMRI data were acquired during the stress task as well, but the results were not part of this thesis.

fMRI Preprocessing and Time-Course Extraction: fMRI preprocessing was conducted similarly to Study 2. Additionally, preprocessing included slice-timing correction for the descending slice order and registration to T1 space included a fieldmap to take into account distortions due to local field inhomogeneity. Non-linear normalization parameters for the structural-to-standard-space was done using Advanced Normalization Tools (Avants et al., 2011). A quality check was performed to exclude participants with a mean framewise displacement >.5, and with clearly visible acquisition artifacts on temporal signal-to-noise-ratio and temporal standard deviation images, which were calculated across all volumes of each resting-state scan. The time-course extraction was done in analogy to Study 2.

Statistical Analysis: Salivary cortisol concentrations, subjective stress ratings, and heart rate (variability) were tested with a repeated-measures ANCOVA with Time as within-subjects factor, followed by post-hoc paired t-tests using IBM SPSS Statistics for Windows, Version 25.0 (Armonk, NY: IBM Corp) to confirm success of stress induction. We repeated these tests including SLoss [MCTQ/diary] as continuous between-subjects factor to test for effects of sleep loss on the physiological and psychological variables.

The difference maps between pre- and post-stress were entered into a higher-level analysis, entering either SLoss [MCTQ] or SLoss [diary] as predictor and Age as covariate. The resulting t-statistical maps then underwent Threshold-Free Cluster Enhancement and significance testing as in Study 2. Furthermore, a region of interest (ROI) analysis was performed for brain regions of the Default Mode Network (DMN), based on previous results from our group on amygdala functional connectivity after psychosocial stress (Veer et al., 2011), selecting the medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC), and precuneus as main DMN regions, but also the anterior insular cortex (AI) and dorsal ACC as

main Salience Network (SN) regions, and additionally the dorsolateral prefrontal cortex (dlPFC) and the hippocampus (no probability threshold).

1.4 Results

1.4.1 Study 1: Sleep and psychological well-being

After replicating normal distributions for SDw, SDf, MFSsc and SJL in analogy to epidemiological findings of Roenneberg et al. (2007), we also found negative correlation of those values with age (the older, the lower sleep durations and earlier chronotype), a sex difference in relation to MSFsc (women had an earlier chronotype than men) and a positive association between MSFsc and SJL (the later the chronotype, the higher the social jetlag), indicating that our sample, though smaller than Roenneberg's, was representative (see Table 3, Figures S-1 to S-6, and Table S-1 in Dimitrov et al. (2020)). Sleep loss was positively associated with SJL, illustrating a close connection between the two variables.

As our sample mainly included participants experiencing higher levels of psychological well-being, PHQ9 and PSQI were right-skewed, whereas PSS values resembled a normal distribution (see Table 4 in Dimitrov et al. (2020)). All three scales were strongly correlated amongst each other. Women scored higher than men on both PHQ9 and PSS. Also, PHQ9 and PSS showed small negative associations with age. Correlations of the three psychological scales with the MCTQ variables resulted in negative associations, on the one hand, between PHQ9 and SDw, and on the other hand, between PSQI and SDw as well as SDf and sleep loss. After adjusting PSQI for its own subscale of sleep duration, only the association towards SDw remained significant (see Table 5 in Dimitrov et al. (2020)).

Lastly, we divided the sample into three equal groups depending on MSFsc, to explore possible associations for only specific subgroups of chronotype (i.e., early, intermediate, late). Results showed opposing associations for PHQ9 as well as the adjusted PSQI within early and late chronotype groups: In the early chronotype group, depression scores and sleep impairment tended to be higher when MSFsc values were lower. In contrast, in late chronotypes, higher average depression scores and sleep impairment were associated with higher MSFsc values, suggesting that psychological well-being is lower in more extreme chronotypes on both ends of the spectrum. Additionally, negative correlations were found within the early chronotype group between SDw and PHQ9, adjusted PSQI and PSS. Within the intermediate chronotype group, SDw was negatively associated with PHQ9 and the adjusted PSQI, but not PSS (see Table 6 in Dimitrov et al. (2020)).

1.4.2 Study 2: Functional connectivity changes after acute stress

Firstly, participants were classified as 47 cortisol responders and 38 cortisol non-responders. Importantly, males were more likely to show a cortisol increase to the stress task than females. There was no significant difference between responders and non-responders for baseline cortisol concentrations, as well as for HRF and HRV before stress induction. Responder had higher cortisol levels at all time-points after the stress induction compared to

non-responders (see Figure 2 in Dimitrov et al. (2018)), reported more negative affect during the stress task, as did females compared to males. Higher subjective stress ratings were related to higher cortisol AUCi responses in responders irrespective of sex, and in females irrespective of being a responder or not. Heart rate data for both RS scans were available for 57 participants (35 of them responders). There was a trend of increased HRF after stress in both responders and non-responders. Furthermore HF-HRV decreased in responders in response to stress, whereas non-responders depicted no change. Women displayed higher HF-HRV than men. Lastly, stronger increases in HRF from pre- to post-stress were associated with higher cortisol in responders irrespective of sex, in females irrespective of being a responder or non-responder, and in male non-responders. Stronger decreases in HF-HRV from pre- to post-stress were associated with higher cortisol in females irrespective of being a responder or non-responder (see Table 2 in Dimitrov et al. (2018)).

For both hemispheres, the seed-based correlation analysis across all participants and both RS scans revealed a pattern of amygdala functional connectivity that was highly comparable to patterns previously reported in literature, including the medial prefrontal cortex, lateral orbitofrontal cortex, temporal poles, hippocampus, and brainstem (see Figure 3).

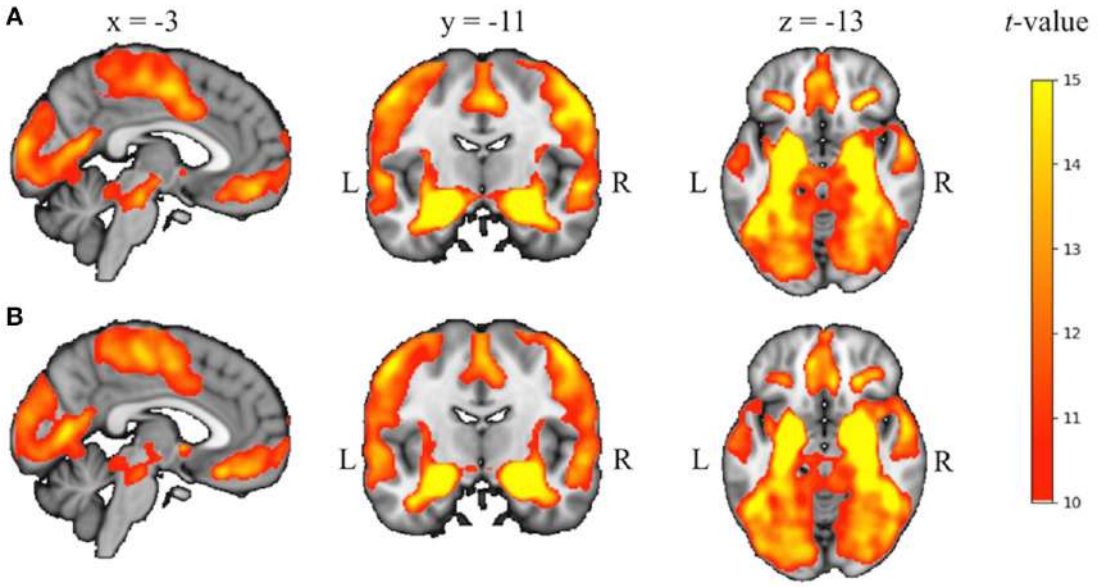

Figure 3. Seed-based correlation results across all participants and both RS scans for left (A) and right (B) amygdala, overlaid on the 2mm isotropic 152-MNI standard space brain ($p < 0.05$, TFCE and FWE-corrected for multiple corrections). R, right, L, left.

Due to an unequal distribution of cortisol responders and non-responders between males and females as well as a significant Responder-by-Time-by-Sex-Interaction for both left and right amygdala, follow-up group level comparisons between responders and non-

responders were carried out in males and females separately. In male participants, we found an increase for RSFC between left and right amygdala and PCC/precuneus in non-responders from pre- to post-stress and stronger RSFC in non-responders than responders post-stress. A trend was found for stronger RSFC pre-stress in responders than non-responders (see Figure 4). The between-group analysis in female participants did not reveal RSFC of the left or right amygdala with any other brain region. Follow-up analysis, that included baseline cortisol concentrations as a covariate, did not change the outcome of the analysis.

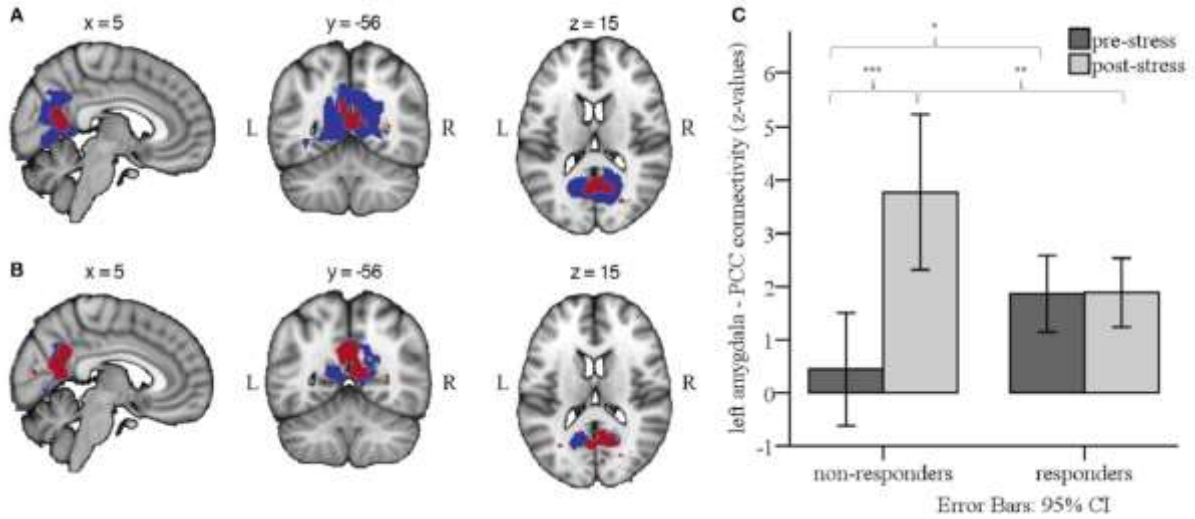

Figure 4. (A) Group-by-Sex-by-Time interaction effects for left (blue) and right (red) amygdala RSFC ($p < 0.05$, whole brain TFCE and FWE-corrected for multiple corrections). (B) Group-by-Time interaction effects for left (blue) and right (red) amygdala RSFC in males only, indicating enhanced RSFC from pre- to post-stress for non-responders compared to responders ($p < 0.05$, whole brain TFCE and FWE-corrected for multiple corrections). Results are overlaid on the 2mm isotropic 152-MNI standard space brain. R, right; L, left. (C) Bar graph illustrating the Group × Time interaction effect for left amygdala RSFC, depicting mean z-values from each of the RS scans in male responders and non-responders. ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$.

1.4.3 Study 3: Sleep loss and the decrease of functional connectivity after acute stress

Cortisol concentrations (n = 40) depicted an increase from 35min before stress exposure (t_1) to 20min after stress exposure (t_3), and a following decrease (t_4 to t_6, t_4 to t_7) (see Figure 2A and Table 2 for descriptive statistics in Nowak et al. (2020)). Subjective stress ratings increased from t_2 (pre-stress) to t_3 (post-stress) and decreased again to t_4 (after RS), though still remaining above ratings from t_2 (see Figure 2B in Nowak et al. (2020)). HRF (n = 41)

increased from resting-state 1 to stress induction and decreased again from stress induction to resting-state 2.

For both hemispheres, the seed-based correlation analysis across all participants and both RS scans revealed a pattern of amygdala functional connectivity similar to the one reported in Study 2 (see Figure 5).

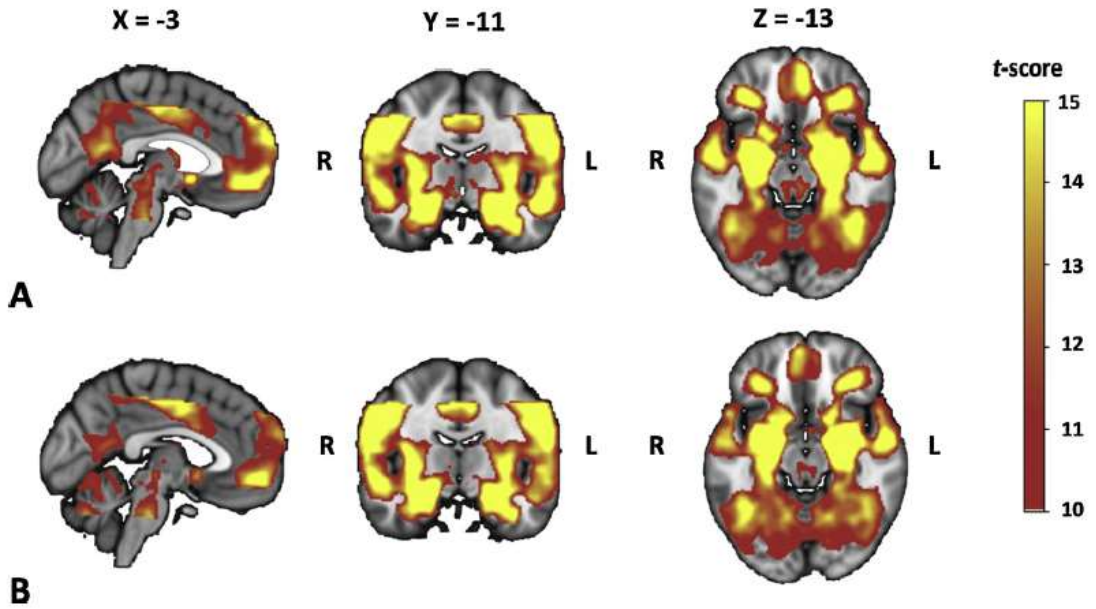

Figure 5. Main effects of seed-based correlation across all participants and both resting-state scans for left (A) and right (B) amygdala (t-values, thresholded between 10 and 15, p<.05, TFCE-corrected for multiple comparisons). R, right; L, left.

No main effect of time (pre- vs. post-stress) was found. However, a negative correlation between SLoss [diary] and the temporal difference in left amygdala RSFC was found for several cortical regions (post-stress>pre-stress; p<.05, whole-brain TFCE-corrected for multiple comparisons), comprising the right OFC, right inferior frontal gyrus (IFG), right anterior insular cortex (AI), right frontal pole, and right paracingulate gyrus (see Table 1 for peak voxels and corresponding t-values in Nowak et al. (2020)). That is, participants with higher amounts of SLoss [diary] showed a decrease in amygdala functional connectivity with these brain regions after stress. Masking for regions of the DMN as a priori regions of interest, additional SLoss [diary]-related decreased connectivity was found with the right superior frontal gyrus, right and left PCC, right middle frontal gyrus, and left dorsal anterior cingulate cortex (dACC) (see Figure 6). No association was found between SLoss [MCTQ] and amygdala RSFC, neither whole-brain nor when masking for our ROIs.

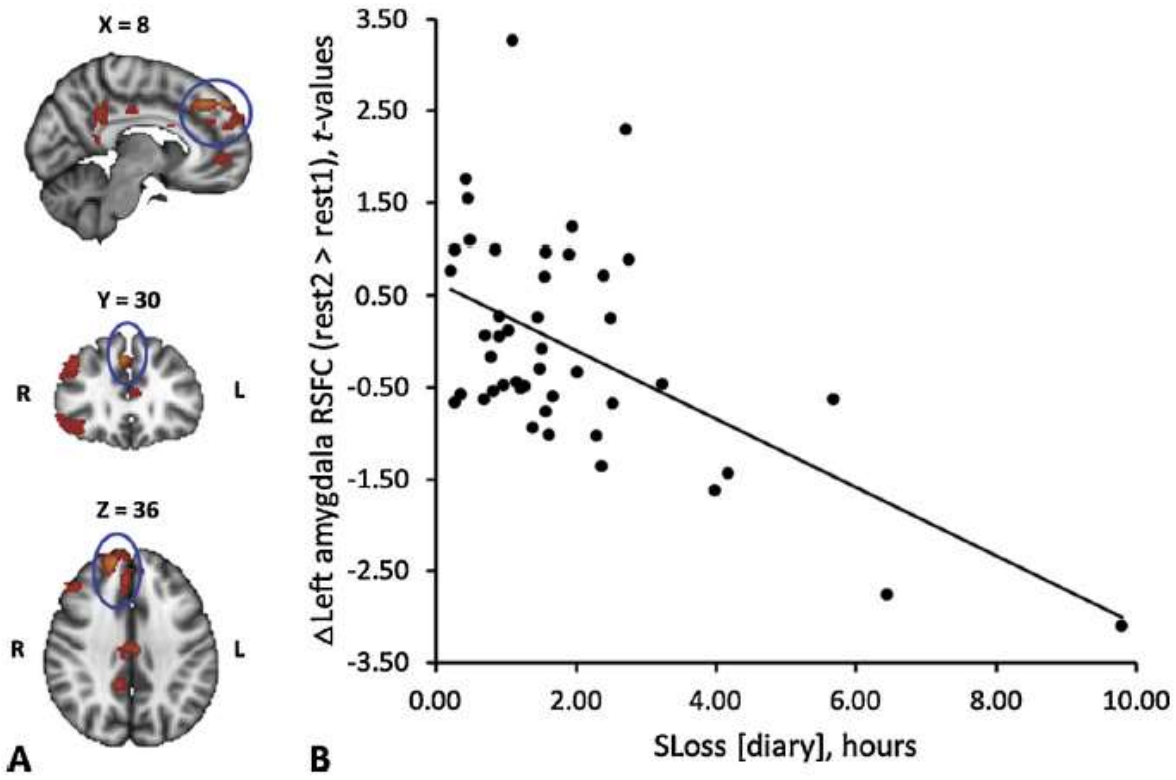

Figure 6. (A) Negative association between SLoss [diary] and temporal difference in left amygdala resting-state functional connectivity (RSFC; resting-state 2>resting-state 1, t-values) with cortical midline structures ($p<.05$, TFCE-corrected for multiple comparisons inside the ROI mask). R = right; L = left. (B) Scatter plot illustrating the association between SLoss [diary] and temporal difference in mean left amygdala RSFC with the prefrontal activation patterns marked blue in (A), representing the largest cluster in the ROI analysis.

1.5 Discussion

1.5.1 Study 1: Sleep and psychological well-being

In contrast to previous studies, we were able to demonstrate that in terms of sleep timings, our sample corresponded well to an epidemiological study that applied the MCTQ (Roenneberg et al., 2007). When we analyzed the total sample with regard to psychological well-being, we did not detect any association of chronotype or social jetlag with depressive symptoms, sleep quality, or perceived stress. This coincides with several studies on the association between chronotype, social jetlag, and health- or performance-related variables (Haraszti, Ella, Gyöngyösi, Roenneberg, & Káldi, 2014; Polugrudov et al., 2016; Rutters et al., 2014; Sheaves et al., 2016; Wittmann et al., 2006; Yong et al., 2016)

However, after dividing the sample into an early, intermediate, and late chronotype group, we found that MSFc had opposing associations with the PHQ9 and adjusted PSQI scores within the early and late chronotype groups: In the early chronotype group, depression scores and sleep impairment tended to be higher when MSFsc values were lower. In contrast, in late chronotypes, higher average depression scores and sleep impairment were associated with higher MSFsc values, suggesting that psychological well-being is lower in more extreme chronotypes on both ends of the spectrum. Keeping this in mind, the composition of samples should be closely monitored when interpreting results. A previous study reported positive correlations between depressive symptoms and both chronotype and social jetlag (Levandovski et al., 2011). It should be mentioned, though, that this particular sample had a mean chronotype earlier than 3 a.m., which would have qualified as early chronotype in other studies. Another study reported positive correlations between PSQI scores and both chronotype and social jetlag (Önder et al., 2014), although this sample had a mean chronotype of 6 a.m., which would have qualified as late chronotype in other studies.

This leads us to two conclusions: (1) depending on the composition of the total sample (i.e., with respect to their MSFsc) and on how accurately the sample represents chronotype distributions of the general population, associations with mental-health-related outcomes might vary, and (2) associations between psychological wellbeing and chronotype might follow a u-shaped function and therefore cannot be detected when examined across the entire sample.

Besides chronotype and social jetlag, we included sleep duration and sleep loss in our analyses, as sleep disturbances are strongly related to almost all psychiatric disorders (Gruber & Cassoff, 2014). Our respondents reported higher depressive symptoms and a stronger reduction of sleep quality when sleep durations during work days were shorter, confirming previously reported results of a negative correlation between the global score of PSQI and total sleep time reported in a sleep diary (Grandner, Kripke, Yoon, & Youngstedt,

2006). Two points should be considered when analyzing sleep loss, though. Firstly, sleep loss and social jetlag are strongly intertwined, which has recently been addressed by introducing a sleep-corrected formula to calculate social jetlag (Jankowski, 2017). However, even when implementing the sleep-corrected social jetlag scores, this did not change our results with respect to psychological well-being. Secondly, it is unclear to what extent people can temporarily adjust their sleeping behavior without any physical or psychological consequences. It has been proposed that humans can adapt to shorter or longer sleep durations within a range of approximately 6–9 hours without increased daytime sleepiness or negative health consequences (Horne, 2011).

1.5.2 Study 2: Functional connectivity changes after acute stress

Using a seed-based correlation approach, we examined the effects of psychosocial stress on amygdala RSFC in healthy volunteers, as a function of the acute cortisol response. Participants were classified as either cortisol responders or non-responders based on their change in cortisol after stress induction. There was no difference in baseline salivary cortisol concentrations between the two groups. Responders reported higher negative affect during the stress task and demonstrated a decrease in HF-HRV, which likely reflects a sustained autonomic arousal (Thayer, Ahs, Fredrikson, Sollers, & Wager, 2012), whereas non-responder showed no change in HF-HRV. Taken together, the physiological and behavioral measures confirmed successful stress induction in the cortisol responders as compared to non-responders. We found an increase in bilateral amygdala RSFC with the PCC and the adjacent precuneus from pre- to post-stress in male non-responders, but not in responders. Additionally, we did not detect changes in amygdala RSFC between female responders and non-responders.

The coupling of amygdala and PCC/precuneus is consistent with a previous finding (Veer et al., 2011), though it should be noted that the previous study reported increased RSFC an hour after the stress task in a stressed compared to a non-stressed group, irrespective of being a responder or not. The connectivity pattern might indicate an increased engagement of the amygdala within the Default Mode Network (DMN) directly after stress in non-responders. The DMN is known to be implicated in several functions related to the self, including mind wandering (Mason et al., 2007), self-referential thought (Gusnard, Akbudak, Shulman, & Raichle, 2001; Northoff & Bermpohl, 2004; Northoff et al., 2006), autobiographical memory, as well as integrating past, present, and future experiences (Buckner & Carroll, 2007). Several assumptions could explain the group-dependent connectivity changes. First, the stress paradigm we used may have been unable to induce stress in our non-responding participants. This could, for example, stem from earlier experiences with similar stressful situations, which then have led to a higher threshold of stress reactivity for this particular class of stressors (Brosschot, Verkuil, & Thayer, 2016).

Second, non-responders might be able to activate this specific pattern more rapidly than responders, which could facilitate immediate updating of memory schemata by integrating recent experiences. Comparing this to the previous finding of increased RSFC between amygdala and PCC/precuneus across all stressed participants (Veer et al., 2011), it could mean that responders might have shown a similar pattern an hour after stress. Lastly, not responding to the stress task with an increase in cortisol might relate to maladaptive stress processing (Elzinga et al., 2008).

Considering that our connectivity analysis across participants and RS scans demonstrated strong RSFC between the amygdala and hippocampus, the RSFC between the amygdala and PCC/precuneus found here could in fact be driven or mediated by the hippocampus, a key region for storage and retrieval of episodic information (Squire, 1992). As the amygdala and hippocampus are bordering each other, and as the fMRI resolution is not high enough to completely disentangle signal from the amygdala and the anterior part of the hippocampus, the amygdala signal could be contaminated by signal from this area. This could also explain why we did not find any interaction effect for amygdala RSFC with the hippocampus.

1.5.3 Study 3: Sleep loss and the decrease of functional connectivity after acute stress

In order to explore the association of sleep loss with functional connectivity changes after induction of psychosocial stress, we used a seed-based correlation approach. Stress was successfully induced as confirmed by an increase in subjective stress ratings, higher heart rates during stress induction and a slight cortisol increase from baseline to post-stress time points.

We found a negative association of SLoss [diary] with the stress-induced change of left amygdala RSFC to several cortical brain regions, including the right medial prefrontal cortex (mPFC), right dorsolateral prefrontal cortex (dlPFC), left dorsal anterior cingulate cortex (dACC), right anterior insula (AI), and bilateral posterior cingulate cortex (PCC). That is, the more sleep loss, as reported in the diary, the more decrease in left amygdala RSFC was found after stress. Those connectivity patterns are in line with previously reported findings from RSFC studies where participants underwent total sleep deprivation in a range between 24 and 36 hours (Goldstein-Piekarski, Greer, Saletin, & Walker, 2015; Lei et al., 2015; Shao et al., 2014; Yoo et al., 2007). It gives the impression that naturally occurring sleep loss might modulate neuronal stress recovery by attenuating the otherwise reported increased amygdala RSFC to the mPFC, PCC and precuneus in the aftermath of stress (Maron-Katz, Vaisvaser, Lin, Hendler, & Shamir, 2016; Veer et al., 2011).

1.5.4 Limitations

Several limitations have to be considered when interpreting and discussing findings. Both in Study 1 and 3, sleep-related measurement was based on self-report. Future studies could benefit from including more objective measures, such as actimetry, or dim light melatonin onset (Jungquist, Pender, Klingman, & Mund, 2015; Roenneberg, 2015) to validate sleep variables. Moreover, the study designs of Study 2 and 3 did not include a non-stress control group, which would allow to distinguish between effects of general diurnal patterns of cortisol decline and those of the actual stress recovery. For this, one challenge would be to find an equivalent task in terms of cognitive load for the control group, which does not induce any stress, but still is comparable to the stress task (Woody, Hooker, Zoccola, & Dickerson, 2018).

As for Study 1, only few participants among our respondents reported severely reduced psychological well-being, while associations may only emerge in samples with more pronounced symptoms (Antypa et al., 2015). Furthermore, using a cross-sectional design, it is impossible to draw conclusions about causal mechanisms. As Kantermann et al. (2012) have pointed out, it is important to disentangle whether a specific chronotype is more vulnerable to psychological impairment, or whether sleep disturbances that co-occur with psychiatric disorders artificially induce late chronotypes. Additionally, the time period between filling out the MCTQ and the other questionnaires varied considerably between participants. Therefore, the change of seasons may have had an impact on our results (Allebrandt et al., 2014). Although 52.3 percent responded within 7 days and 90.4 percent within 30 days, the longest response period took as much as 161 days. However, when taking differences in response time into account, this did not change our results. In addition, when comparing respondents who filled out the MCTQ during summer to those who did so in autumn, a delay in chronotype and an increase in SJL were found for individuals participating in autumn, but still no significant differences in their associations with the PHQ9, PSQI, or PSS.

As for Study 2, it should be noted that our results are limited to amygdala-based circuits only, given the seed-based approach used. Surely, stress affects many other brain regions, so there is a fair chance that we have missed changes in functional connectivity that emerged independent of the amygdala. Nonetheless, as the amygdala plays a pivotal role in most central stress-related processes, the selection of the amygdala as a seed is reasonable, and has provided a good insight in the role of stress-related brain circuits during recovery from stress. Furthermore, the difference in stress response between women and men found in the current study are in line with previous reports. In general, men tend to show larger salivary cortisol increases in response to a psychological stress task than women (Kudielka et al., 2009). Studies suggest that age (Kudielka, Buske-Kirschbaum, Hellhammer,

& Kirschbaum, 2004), the use of contraceptives and phase of menstrual cycle (Kudielka & Kirschbaum, 2005; Liu et al., 2017; Stephens et al., 2016), as well as sex hormones (Juster et al., 2016) contribute to differences in cortisol response. In our sample, 23 female participants took contraceptives. However, this could not account for the differences in any of our dependent variables. The number of days between the onset of the last menstrual cycle until the MRI assessment was enquired, but not individual cycle durations. As such, we could not estimate the exact menstrual phase of our female participants and test for its effects in our connectivity analyses.

As for Study 3, generalizability to the general population is limited by having included male participants only. As mentioned above, women on average demonstrate weaker cortisol responses to psychosocial stress than men. However, due to the moderate sample size, it was decided to create an as homogeneous sample as possible. Furthermore, we obtained significant results when using the SLoss [diary] values, but not when using the values from SLoss [MCTQ]. This difference, together with the rather weak association between our two measures of sleep loss, suggests there may exist more state- and trait-like effects of sleep loss. Data from sleep diaries might represent a rather state-like variable, since these were estimated during the seven days prior to our scanning session. The MCTQ, in contrast, asks for habitual sleep and waking times, which could mean that sleep timings during the week preceding scanning might be more influential than estimates of general sleeping patterns.

1.5.5 Conclusions

In order to deal with stressors, the organism needs to adapt several systemic mediators (McEwen & Wingfield, 2003). Two important factors are a well-balanced sleep-wake-pattern and an HPA axis reactivity that puts the organism into an aroused state to prepare for the challenges to come (Lo Martire et al., 2019).

Our results show that the analysis of sleep-wake patterns is a delicate topic as the composition of the sample likely will influence the association with psychological well-being. Therefore, future studies should investigate the representativeness of a sample before examining specific hypotheses. When it comes to exploring stress responsivity, it is important to analyze the progress of cortisol concentrations as non-responders seem to recover differently from stress than responders do. Moreover, our results showed that sleep loss was associated with functional connectivity changes in the aftermath of stress, which could reflect attenuated cortical down-regulation of the amygdala linked to reaching a homeostatic state.

Sleep, which tends to get less in our all-around-the-clock society, impacts psychological well-being and influences the way how the brain recovers from a stressful event. As both sleep and stress responsivity play a role in the development of mental disorders (Krystal, 2012; Zorn et al., 2017), it is important to replicate and extend our findings

so that in the future, individuals with a high risk for impairment in either one of those two factors can be identified and provided with coping strategies to prevent the manifestation of a mental disorder.

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2 Eidesstattliche Versicherung

„Ich, Annika Dimitrov, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: „The association of sleep and stress with psychological well-being and neuronal functional connectivity“ („Der Zusammenhang zwischen Schlaf und Stress mit psychologischem Wohlbefinden und neuronaler funktioneller Konnektivität“) selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe. Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren/innen beruhen, sind als solche in korrekter Zitierung kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) werden von mir verantwortet.

Ich versichere ferner, dass ich die in Zusammenarbeit mit anderen Personen generierten Daten, Datenauswertungen und Schlussfolgerungen korrekt gekennzeichnet und meinen eigenen Beitrag sowie die Beiträge anderer Personen korrekt kenntlich gemacht habe (siehe Anteilserklärung). Texte oder Textteile, die gemeinsam mit anderen erstellt oder verwendet wurden, habe ich korrekt kenntlich gemacht.

Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem/der Erstbetreuer/in, angegeben sind. Für sämtliche im Rahmen der Dissertation entstandenen Publikationen wurden die Richtlinien des ICMJE (International Committee of Medical Journal Editors; www.icmje.og) zur Autorenschaft eingehalten. Ich erkläre ferner, dass ich mich zur Einhaltung der Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis verpflichte.

Weiterhin versichere ich, dass ich diese Dissertation weder in gleicher noch in ähnlicher Form bereits an einer anderen Fakultät eingereicht habe.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§§156, 161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

_____ _____

Datum Unterschrift

3 Anteilserklärung an den erfolgten Publikationen

Annika Dimitrov hatte folgenden Anteil an den folgenden Publikationen:

Publikation 1

Dimitrov, A., Veer, I. M., Kleeblatt, J., Seyfarth, F., Roenneberg, T., Ising, M., Uhr, M., Keck, M. E., Kramer, A., Berger, M., von Koch, L., Walter, H., & Adli, M., Chronotype is associated with psychological well-being depending on the composition of the study sample, Journal of Health Psychology, 2020

Beitrag im Einzelnen:

- Organisation der Datenerhebung (in Zusammenarbeit mit I. M. Veer, H. Walter und M. Adli)
    - Auswahl der Fragestellungen und Hypothesen, Planung der psychologischen Fragebögen, Erstellung des Zeitplans
- Rekrutierung der Studienteilnehmenden, Durchführung der Online-Befragung, Dateneingabe & -pflege (in Zusammenarbeit mit J. Kleeblatt, F. Seyfarth und I. M. Veer)
    - Organisation der Online- und Flyer-Werbung für Studienteilnahme
    - Programmierung und Betreuung der Online-Umfrage mit LimeSurvey
- Datenanalyse (unter Supervision von I. M. Veer)
    - Durchführung der Auswertung mit SPSS
    - Erstellen von Tabellen (1 bis 6) und der Abbildung (1) für das Manuskript
    - Erstellen der Tabelle (S-1) und Abbildungen (S-1 bis S-9) für das Supplementary Material
- Erstellung des Manuskripts
    - Verfassen folgender Abschnitte: Abstract, Introduction, Methods, Results, Discussion, References, Supplementary Material
- Einarbeitung der Kommentare der Koautoren
- Einreichung und Bearbeitung der Revision im Peer Review-Prozess

Publikation 2

Dimitrov, A., Demin, K., Fehlner, P., Walter, H., Erk, S., & Veer, I. M., Differences in Neural Recovery From Acute Stress Between Cortisol Responders and Non-responders, Frontiers in Psychiatry, 2018

Beitrag im Einzelnen:

- Datenpflege
    - Aktualisierung der SPSS-Datei, Berechnung neuer Variablen
- Datenanalyse (unter Supervision von I. M. Veer)
    - Durchführung der Auswertung mit SPSS: Berechnung von Gruppenunterschieden zwischen Männern und Frauen für Cortisolkonzentrationen
    - MRT-Analyse: Second-level Fixed Effects Analyse, separate Follow-up Tests für Männer und Frauen
- Erstellung des Manuskripts
    - Das Manuskript basiert auf der Masterarbeit der Koautorin K. Demin. Folgende Abschnitte wurden für das Manuskript neu verfasst bzw. überarbeitet: Einleitung, fMRT statistische Analyse, Ergebnisse RSFC, Diskussion
    - Tab. 1, Tab. 2, Fig. 1 wurden aus der Masterarbeit übernommen & überarbeitet
    - Fig. 2, Fig. 3, Fig. 4 wurden von mir basierend auf den neuen Analysen erstellt
    - Abbildungen 1A – C meiner Dissertationsschrift wurden in Anlehnung an die Original-Publikation zur ScanSTRESS (Streit et al., 2014) von mir erstellt
- Einarbeitung der Kommentare der Koautoren
- Einreichung und Bearbeitung der Revision im Peer Review-Prozess

Publikation 3

Nowak, J., Dimitrov, A., Oei, N. Y. L., Walter, H., Adli, M., & Veer, I. M., Association of naturally occurring sleep loss with reduced amygdala resting-state functional connectivity following psychosocial stress, Psychoneuroendocrinology, 2020

Beitrag im Einzelnen:

- Organisation der Datenerhebung (in Zusammenarbeit mit I. M. Veer)
    - Auswahl der Fragestellungen und Hypothesen, Planung der psychologischen Fragebögen und MRT-Aufgaben, Erstellung des Zeitplans
- Rekrutierung der Studienteilnehmenden, Durchführung der psychologischen und MRT-Untersuchungen, Dateneingabe & -pflege (in Zusammenarbeit mit J. Nowak, A. Ligdorf und I. M. Veer)
    - Organisation der Online- und Flyer-Werbung für Studienteilnahme
    - Durchführung Telefonscreenings
    - Durchführung der MRT-Messungen als Advanced User
- Datenanalyse
    - Vorverarbeitung der MRT-Daten (in Zusammenarbeit mit I. M. Veer)
- Überarbeitung des Manuskripts im Peer Review-Prozess, welches von J. Nowak erstellt wurde
    - Abbildungen 2, 5 und 6 meiner Dissertationsschrift wurden vom Erstautor J. Nowak erstellt

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Unterschrift, Datum und Stempel des erstbetreuenden Hochschullehrers

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Unterschrift der Doktorandin

4 Druckexemplare der ausgewählten Publikationen

Publikation 1

Dimitrov, A., Veer, I. M., Kleeblatt, J., Seyfarth, F., Roenneberg, T., Ising, M., Uhr, M., Keck, M. E., Kramer, A., Berger, M., von Koch, L., Walter, H., & Adli, M. (2020). Chronotype is associated with psychological well-being depending on the composition of the study sample. *Journal of Health Psychology*, *25*(9), 1236–1247.

doi: 10.1177/1359105317751618
https://doi.org/10.1177/1359105317751618

Publikation 2

Dimitrov, A., Demin, K., Fehlner, P., Walter, H., Erk, S., & Veer, I. M. (2018). Differences in Neural Recovery From Acute Stress Between Cortisol Responders and Non-responders. *Frontiers in Psychiatry, 9*(631).

doi: 10.3389/fpsyt.2018.00631
https://doi.org/10.3389/fpsyt.2018.00631

Publikation 3

Nowak, J., Dimitrov, A., Oei, N. Y. L., Walter, H., Adli, M., & Veer, I. M. (2020). Association of naturally occurring sleep loss with reduced amygdala resting-state functional connectivity following psychosocial stress. Psychoneuroendocrinology, 114, 104585.

doi: 10.1016/j.psyneuen.2020.104585
https://doi.org/10.1016/j.psyneuen.2020.104585

5 Lebenslauf

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

6 Publikationsliste

Dimitrov, A., Veer, I. M., Kleeblatt, J., Seyfarth, F., Roenneberg, T., Ising, M., Uhr, M., Keck, M. E., Kramer, A., Berger, M., von Koch, L., Walter, H., & Adli, M. (2020). Chronotype is associated with psychological well-being depending on the composition of the study sample. *Journal of Health Psychology*, *25*(9), 1236–1247. doi: 10.1177/1359105317751618

Dimitrov, A., Demin, K., Fehlner, P., Walter, H., Erk, S., & Veer, I. M. (2018). Differences in Neural Recovery From Acute Stress Between Cortisol Responders and Non-responders. *Frontiers in Psychiatry, 9*(631). doi:10.3389/fpsyt.2018.00631

Nowak, J., Dimitrov, A., Oei, N. Y. L., Walter, H., Adli, M., & Veer, I. M. (2020). Association of naturally occurring sleep loss with reduced amygdala resting-state functional connectivity following psychosocial stress. Psychoneuroendocrinology, 114, 104585. doi: 10.1016/j.psyneuen.2020.104585

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