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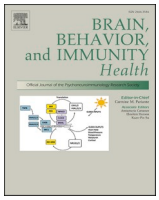

Understanding the combined effects of sleep deprivation and acute social stress on cognitive performance using a comprehensive approach

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ABSTRACT

Background: Sleep deprivation (SD) and acute social stress are common, often unavoidable, and frequently co-occurring stressors in high-risk professions. Both stressors are known to acutely induce inflammatory responses and an increasing body of literature suggests this may lead to cognitive impairment. This study examined the combined effects of total SD and acute social stress on cognitive performance and took a comprehensive approach to explore their (shared) underlying mechanism leading to cognitive decline.
Method: We recorded cognitive performance on a response inhibition task and a multitask and monitored a range of inflammatory, psychophysiological and self-reported markers in 101 participants, both before and after one night of either sleep (control group: N = 48) or SD (N = 53), and both before and after a social stressor (Trier Social Stress Test).
Results: SD decreased cognitive performance. The social stress test also results in cognitive performance decline in the control group on the response inhibition task, but improved rather than decreased performance of sleep deprived participants on both tasks. The subjective ratings of mental effort also reflect this antagonistic interaction, indicating that the social stressor when sleep-deprived also reduced mental effort. In the inflammatory and physiological measures, this pattern was only reflected by IL-22 in blood. SD reduced blood IL-22 concentrations, and the social stress reduced IL-22 in the control group as well, but not in sleep-deprived participants. There were no interactive effects of SD and social stress on any other inflammatory or psychophysiological measures. The effects of the social stress test on autonomic measures and subjective results suggest that increased arousal may have benefited sleep-deprived participants' cognitive performance.
Discussion: SD generally decreased cognitive performance and increased required mental effort. By contrast, the isolated effects of a social stressor were not generic, showing a positive effect on cognitive performance when sleep deprived. Our study is the first that studied combined effects of sleep deprivation and acute social stress on cognitive performance and inflammatory markers. It provides a comprehensive overview of effects of these stressors on a range of variables. We did not show unequivocal evidence of an underlying physiological mechanism explaining changes in performance due to (the combination of) sleep deprivation and social stress, but consider IL-22 as a possible cytokine involved in this mechanism and certainly worth following up on in future research.

1. Introduction

A range of professions require performing cognitive challenging tasks in multi-stressor environments. For instance, military aircrew have to stay alert, multitask, and make quick decisions during their mission while dealing with stressors such as heat, cold, sleep deprivation, noise, or mental stress. We know that single stressors can impair or improve cognitive functioning (Alhola and Polo-Kantola, 2007; Hudson et al., 2020), but our understanding of how combined stressors interact and affect cognitive performance is limited. In general, there are three main

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interaction types; (1) *Additive:* the combined effect is the sum of the individual effects, implying no interaction in a statistical sense; (2) *Synergistic:* the combined effect is more than the sum of the individual effects, and (3) *Antagonistic:* the combined effect is less than the sum of the individual effects. Interaction effects can be further subdivided based on the direction and strength of each stressor effect (Bottenheft et al., 2023).

The type of interactive effect of multiple stressors on cognitive performance likely depends on the extent and manner to which the underlying mechanisms that mediate the impact of each stressor overlap. According to Lloyd and Havenith (2016), the stressor interaction (synergistic or antagonistic) is stronger when they share the same underlying physiological mechanism. Therefore we here examine how a combination of stressors may affect cognitive performance and used a comprehensive approach to explore (shared) mechanism(s) underlying the effect of stressors on cognitive performance. More specifically, the present study focuses on total sleep deprivation (SD) and acute social stress for several reasons. First, both are common, often unavoidable, and frequently co-occurring stressors for high-risk professionals (Schwarz et al., 2018a). Second, sleep deprivation and (high) stress generally negatively impact functioning (Goel et al., 2009; Rodrigues et al., 2018). More specifically, both of these stressors impair similar aspects of cognitive functioning (Hudson et al., 2020; Sandi, 2013). Third, both stressors are known to acutely induce inflammatory responses. An increasing body of literature suggests this may lead to cognitive impairment (Irwin et al., 2016; Shields et al., 2017). Separate lines of research have explored the link between stressors and inflammatory responses, as well as the link between inflammation and cognitive functioning. As of yet, there are no studies including all three elements: sleep deprivation and other acute stressors, markers of acute inflammatory responses and cognitive performance. Such studies are required to examine whether sleep deprivation and other stressors possibly affect cognition through inflammation. In the following sections we elaborate on the effects of sleep deprivation on cognition and on inflammatory responses and do the same for acute social stress. Subsequently, we discuss research on immune system components that are involved in inflammation that can impact cognitive processes.

1.1. Sleep deprivation, cognition and the role of inflammation

Sleep deprivation is known to mainly impair prefrontal cortex (PFC) dependent functions (Chuah et al., 2006; Nilsson et al., 2005; Plieger and Reuter, 2020), such as sustained attention (Kusztor et al., 2019; Lim and Dinges, 2010) and executive functioning (Aidman et al., 2019; Killgore et al., 2009; Kusztor et al., 2019; Nilsson et al., 2005). Impairment of sustained attention is exemplified by slowed reaction times in simple sustained attention tasks (Killgore et al., 2009). Executive functioning are top-down processes that are responsible for goal-directed behavior (Hofmann et al., 2012) and can be divided in three main executive functions: inhibitory control, working memory (WM) and task switching (Friedman and Miyake, 2004). In particular the least complex functions of executive functioning have been found to be affected, with reduced inhibitory control and impaired task switching following sleep deprivation (Aidman et al., 2019). Inconsistent results were found on more complex executive functioning tasks (Aidman et al., 2019; Killgore et al., 2009; Tucker et al., 2010).

One explanation links sleep deprivation and its effect on cognitive functioning to inflammation. Research shows that already a single night of total SD leads to higher amounts of proinflammatory cytokines in the blood (Irwin et al, 2016; Shields et al., 2017). Furthermore, these effects become stronger after multiple nights of (partial) sleep deprivation or in people with chronic poor sleep (Irwin et al., 2015, 2016). Cytokines may cross the blood-brain barrier and negatively affect central inflammatory processes, resulting in cognitive performance decline (Trapero and Cauli, 2014). However, there is no research yet that directly investigates the potential effect of sleep deprivation-induced inflammation on cognitive performance through linking effects of total SD on inflammation and cognitive performance as measured in the same study.

1.2. Social stress, cognition and the role of inflammation

Stress is also known to influence cognition, though the direction depends on the type and intensity of stress as well as on the specific cognitive function (Sandi, 2013). While mild stress may improve cognitive function, high levels of stress impair hippocampus- and prefrontal cortex-related cognitive functions, such as memory formation and complex, flexible reasoning (Sandi, 2013). Furthermore and comparable to SD, acute social stress is known to impair executive functions, including impaired task switching and response inhibition (Plessow et al., 2012; Rodrigues et al., 2018).

Acute social laboratory stressors have also been shown to elicit an immune response, as reflected by circulating proinflammatory cytokines (IL-1β, IL-6, IL-10 and TNF-α) in blood (Marsland et al., 2017; Prather et al., 2014). This response is mediated by activation of the sympathetic nervous system (SNS) which is associated with increased adrenaline and other catecholamines, resulting in an increased production of cytokines (Marsland et al., 2017; Rohleder, 2019). With a later onset, acute stress also elevates cortisol levels which normally inhibits cytokine production (Dantzer et al., 2018).

1.3. Inflammation effects on cognition

In turn, a stress-induced immune response has been shown to affect cognitive performance. For example, Barrientos et al. (2002) found that acutely elevated levels of IL-1β in the brain of rats reduce memory consolidation for a learning task. Regarding human research, Shields et al. (2017) also indicated that acute stress-induced IL-1β in saliva is associated with changes in memory processes. Furthermore, Quinn et al. (2020) found that impairment in executive control after acute social stress induction was associated with elevated levels of stress-induced IL-6. Although cytokine expression might affect the central nervous system (Trapero and Cauli, 2014), the exact pathway in case of acute stressors remains unclear.

Besides these possible acute stress-induced immune effects on cognition, it is known that chronic inflammation negatively affects cognition (Marsland et al., 2016; McAfoose and Baune, 2009; Shields et al., 2017; Trapero and Cauli, 2014). For example, Marsland et al (2016) found that increased peripheral inflammation markers (IL-6 and C-reactive protein) were associated with poor spatial reasoning, short term memory, verbal proficiency, and learning and memory. Furthermore, McAfoose & Baune (2009) found that chronic increased cytokine levels affect brain regions that play an important role in hippocampal-dependent learning and memory. Although the exact role of cytokines in higher cognitive functioning such as attention and executive functioning remains unknown, learning and memory processes also depend on these functions (McAfoose and Baune, 2009). Moreover, Shields et al. (2017) concluded in their review that chronic elevated proinflammatory cytokine levels may also impair prefrontal cortex functioning, as illustrated by poorer performance on tasks that require executive functioning.

1.4. Effects of combined stressors

These findings suggest that both sleep deprivation and acute social stress may affect cognitive performance via a mechanism that involves the immune system. Poor or limited sleep may alter the responsiveness of the immune system (Schwarz et al., 2018b), and even more during an acute social stressor (Massar et al., 2017; Minkel et al., 2014). Previous studies found inconsistent results regarding combined effects on other psychophysiological stress responses. Minkel et al. (2014) found that salivary cortisol was increased after a social stressor in a one night sleep-deprived group compared to a control group. Massar et al. (2017)

also found that prolonged poor sleep increases the psychophysiological reactivity to social laboratory stressors. Schwarz et al. (2018) found increased cortisol and subjective stress levels after one night of sleep deprivation, while the reactivity of these markers to a social stressor did not change after sleep deprivation compared to a control group. Note that these studies focused on the combined effects on physiological stress responses while effects on cognitive performance have not yet been studied.

The present study examined the isolated and combined effects of total SD and acute social stress on cognitive performance and took a comprehensive approach to explore the possible (shared) underlying mechanism, and specifically the role of the immune system. Besides biochemical markers of inflammation also including anti-inflammatory cytokines, this comprehensive approach comprises measures from other domains, including cortisol in saliva, autonomic and subjective measures. Autonomic responses and salivary cortisol were included because these measures are a non-invasive and reliable way to investigate an induced stress response. We hypothesize that each individual stressor will reduce cognitive performance, and induce inflammatory, autonomic and subjective responses. We will explore whether effects on inflammatory responses and cognition are associated since this would be consistent with a causal effect. As both stressors may share a mechanism affecting cognitive performance through the immune system, we hypothesize that total SD and acute social stress combined will result in the strongest reduction (synergistic) in cognitive performance.

2. Material and methods

2.1. Participants

A total of 105 participants were included in this study, of which 101 participants completed the whole two-day study. They were randomly assigned to the total sleep deprivation (N = 53) or control group (N = 48). Participants were recruited through the TNO participant pool. Approval for this study was granted by an accredited medical research ethics committee (MREC Brabant, reference number: P2045, approval number NL74961.028.20). All participants gave written informed consent. Exclusion criteria were: smoking, drugs use in the last three months, signs of flue or viral infection in the last ten days, pregnancy, history of psychiatric illness, including sleep disorders, autoimmune disease and/or hyperactive thyroid and known heart, kidney or liver disease or neurological complaints. BMI ranged from 18 to 30 kg/m2. Ages ranged from 19 to 55 years old (M = 28.5, SD = 10.3). No serious adverse events were reported.

2.2. Study design and brief setup

The study encompassed two consecutive test days (see Fig. 1). The design was a mixed design with **sleep deprivation** (*total sleep deprivation (TSD) group* vs. *control group*) as between-subjects independent variable and the **social stress test** (*before vs. after* the social stress test) as within-subjects independent variable. In the morning of day one and two and again after the social stress test, both groups performed a cognitive test battery to assess cognitive performance. Before and after each social stress test, capillary blood and saliva were collected and mood states were assessed. Heart rate and electrodermal activity were assessed during the social stress tests.

2.3. Materials

2.3.1. Social stress tests

On the first test day acute social stress was induced using the Sing-a-Song Stress Test (SSST) developed by Brouwer and Hogervorst (2014). The responses to the SSST on day one are not used in this paper.

On the second test day, the Trier Social Stress Test (TSST) was used to induce stress (Kirschbaum et al., 1993). The TSST is a standardized protocol that is sensitive for studying acute stress responses in a laboratory setting (Dickerson and Kemeny, 2004; Allen et al., 2014). Before undergoing the social stress test, a relaxation period of 3 min took place to ensure minimum stress. The test consisted of three phases, each lasting 5 min: 1) anticipation, 2) presentation, and 3) mental arithmetic. During the anticipatory stress phase, participants were asked to prepare a 5 min presentation about themselves for an imaginary job interview. They had to talk about their own personality and convince the jury member that they are best candidate for the job. The participants were told that during the presentation, a camera recorded their performance for later evaluation of their performance. Next, the participants gave the presentation during the second phase in front of one jury member. The jury member was trained to maintain neutral expressions throughout the test and also to motivate the participant to keep talking for 5 min.

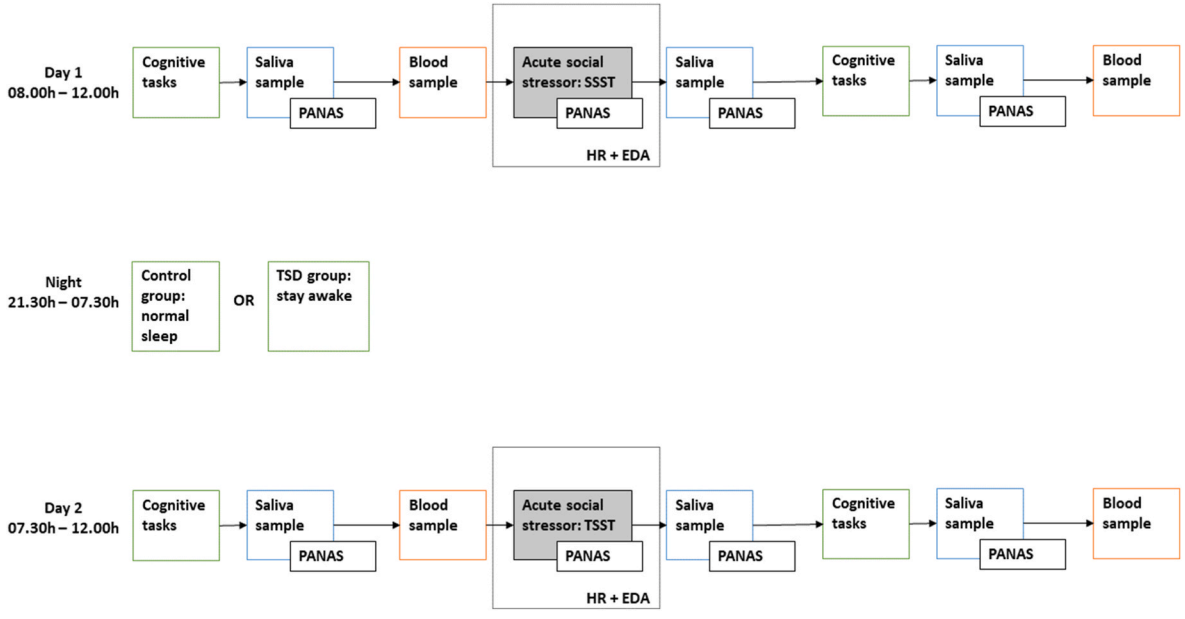

Fig. 1. Overview of measurements during each test day. PANAS = Positive and Negative Affect Scale, SSST = Sing-a-Song Stress Test, TSST = Trier Social Stress Test, HR = Heart Rate and EDA = Electrodermal Activity.

Participants were told that the jury member could not answer questions or give feedback. The participants were oriented towards the camera. They were told that the videotapes would be shown to the experts to judge their performance (adapted from Yim et al., 2010). In the third phase the participants had to respond verbally to a challenging arithmetic problem in the presence of the same observers.

2.3.2. Cognitive task measures

Each morning, participants performed cognitive test batteries before and after the social stressor. Not all cognitive tasks that were performed before the stressor were also performed after. For this paper, we only examine data from the tasks that were performed both before and after each social stress test: the Go/No-go task and the SYNWIN. These tasks are suitable for measuring cognitive performance multiple times.

The Go/No-go task (GN) was used to measure participant's capacity for sustained attention and response inhibition (Young et al., 2018). Participants looked at a screen and pressed a key as fast as possible when the word 'GO' appeared on the screen and withhold from pressing when 'NO GO' was shown. The task had a duration of 5 min and the inter-stimulus interval was 0.450 s. The probability of a 'GO' being presented was 80%. Performance was defined by means of two outcomes; mean reaction time of all the 'GO' trials and the probability of a false alarm (FA %) (response during 'NO GO').

The SYNWIN is a computer-based task with multiple tasks to perform simultaneously (Elsmore, 1994). It has been used in studies of human-computer interaction and the impact of environment on cognitive performance (Hambrick et al., 2010). It represents different cognitive skills required in complex task situations. SYNWIN includes four tasks; a simple memory task, an arithmetic computation task, a visual monitoring task (checking a fuel gauge), and an auditory monitoring task. The task had a duration of 10 min. Performance was defined by a composite score and accuracy on each individual task. The composite score represents performance across all four tasks by including points earned minus penalties for incorrect responses, namely incorrect or missed identification in the memory task, incorrect calculation, allowing the fuel gauge to expire, and auditory false alarms or misses.

2.3.3. Physiological measures

2.3.3.1. Inflammatory responses. In order to assess the inflammatory tone at baseline and the response of the immune system, capillary blood (130 μL) was collected by a finger prick approximately 5 min before and 50 min after stress onset (Shields, 2020). The test leader collected capillary blood according to a protocol developed by the Laboratory for Human Biology Research Department of Antropology (McDade, 2014). Blood samples were collected in EDTA-coated vials and kept on ice prior to centrifugation at 4 °C (14,000 rpm for 15 min). The obtained EDTA plasma was stored at −70 °C until use. The frozen plasma samples were transferred to TNO Metabolic Health Research (Leiden, Netherlands) for biomarker analysis following protocols described in previous literature (Schutte et al., 2022; Vreeken et al., 2022). This included an assessment of systemic inflammation using cytokine multiplex panels (Human 10plex Cytokine Panel 1, Quanterix, Billerica, USA). For this analysis the following cytokines (among which interleukins (ILs)) were used: IL-1β, IL-6, IL-10, TNF-alpha and IL-22. The first four have been found to increase in response to acute stress in a meta-analysis by Marsland et al. (2017). The anti-inflammatory cytokine IL-22 has not been studied before in the context of acute stress in humans, but may be of interest given its recently demonstrated sensitivity to acute stress (Shaler et al., 2021) and sleep deprivation (Gao et al., 2020) in mice. For each cytokine, the baseline plasma concentration before the social stress test on day two was subtracted from the concentration measured after stress onset on that day, to obtain a delta value which reflects the inflammatory stress response. A higher delta score would be consistent with a higher stress response (Marsland et al., 2017; Shaler et al., 2021).

2.3.3.2. Endocrine responses. Saliva was collected in saliva collection containers (Passive Drool using the Saliva Collection Aid, Salimetrics, USA). The obtained samples were immediately stored at −20 °C and, at the end of each test day, transferred to a −70 °C freezer for further storage until use in assays. Salivary cortisol was determined using assay number #KGE008B (R&D Systems, Abingdon, United Kingdom) once before (baseline) and twice after each social stress test. Salivary cortisol is often used as a biomarker of psychological stress and stress-related diseases (Hellhammer et al., 2009). In line with recommendations by Shields (2020) to capture cortisol reactivity to stress we collected one sample approximately 10 min before stress onset, one sample 15 min after, and one sample 30 min after. The 'Area Under the Curve with respect to increase' (AUC_I) as a measure of cortisol stress response (Pruessner et al., 2003) was computed:

$$AUC_I = \left(\sum_{i=1}^{n-1} \left(\frac{(m_{(i+1)} + m_i)}{2} \right) \right) - (n-1) \bullet m_1$$

with m_i meaning the individual measurements and n denoting the total amount of measurements (i.e., three in our case).

2.3.3.3. Autonomic nervous system. Heart rate (HR) data was obtained through the use of Tickr (Wahoo Fitness LLC, Atlanta, Georgia, USA), which is a HR measuring chest band with built-in electrodes to capture the electrocardiogram. The HR data was sent via the Wahoo Fitness Workout Tracker application (version 1.33.0.115) to an Android mobile phone. This phone was connected to the Tickr via Bluetooth and carried by the participants throughout the experiment. Electrodermal activity (EDA) responses were measured through two disposable electrodes placed on the palm of the non-dominant hand of the participant, which were connected to the EdaMove4 wrist band (Movisens GmbH, Karlsruhe, Germany). EDA was processed to obtain the fast-changing phasic part, also referred to as skin conductance response (SCR), using Ledalab for MATLAB (Benedek and Kaernbach, 2010). This phasic response is considered to be an index of sympathetic nervous system activity (Benedek and Kaernbach, 2010; Boucsein, 2012). In the following parts of this manuscript EDA refers to the phasic part of the response electrodermal response. Mean HR and EDA baseline values were computed over the 3 min rest period prior to the social stressors on each day (the SSST and TSST). For the TSST, the baseline values were subtracted from the mean HR and EDA computed over the 1 min after stress onset during the anticipation phase of the TSST. This generates a delta ANS TSST stress response without the influence of motion while talking in the presentation phase. A higher delta score indicates a greater stress response.

2.3.4. Subjective measures

Subjective affect was rated through the Positive and Negative Affect Scale (PANAS; Watson et al., 1988). The PANAS consists of the question "To what extent do you now feel … ?" followed by ten negative and ten positive emotions. Participants indicate to what extent they feel affiliated to that emotion on a five point Likert-scale, ranging from "Very slightly or not at all" (1) to "Extremely" (5). Outcomes are two total scores, one for positive affect (PA) and one for negative affect (NA), ranging from 10 (very low) to 50 (very high). The PANAS was administered four times on each day; before the social stress test (baseline), directly after the social stress test (measuring direct responsivity), approximately 25 min after social stress onset and at the end of the day. In this study only PANAS ratings before and directly after the social stress test were used.

After each cognitive task, the participants rated their subjective mental effort on the Rating Scale of Mental Effort (RSME) (Zijlstra and van Doorn 1985). The RSME scale ranges from 0 to 150, with higher values reflecting higher workload. It has nine descriptors along the axis, e.g., 'not effortful' at value 2 and 'rather effortful' at value 58.

2.4. Procedures

This study consisted of four visits: 1) a training visit, 2) morning day one, 3) night at home or at TNO and 4) morning day two.

2.4.1. First training visit

Participants were informed about the outline and procedure of the study, and practiced the cognitive tasks to eliminate possible learning effects. They were not informed about the social stress tests, as this could affect stress reactivity measures. Participants were instructed to not consume any caffeine containing substances (e.g. coffee, chocolate, tea) from 6 p.m. the night prior to the morning they were expected to start the experiment.

2.4.2. Morning day one

Participants arrived at 08:00 a.m. at the test location. After explanation of the procedures, sensors for EDA and HR measurement were attached. Next, a baseline assessment with the cognitive task battery took place (GN and SYNWIN). The order of cognitive tasks was counterbalanced. After performing these cognitive tasks, a 15 min rest period took place, followed by a baseline cortisol saliva sample. Participants were also asked to assess their affect by filling in the PANAS questionnaire. Next, capillary blood samples were collected by using a finger prick, followed by a 10 min rest period of which 5 min in front of a computer screen. These 5 min were part of the Sing-a-Song stress test. After this social stress test a second subjective affect rating was assessed followed by a rest period of 15 min. This rest period was necessary for collection of the second cortisol saliva sample, and was followed by a third affect rating. Participants were asked to not tell about the social stress test to other participants in the study. The participants performed the cognitive tasks for the second time, followed by the a third cortisol saliva samples and fourth affect rating. After this morning day one visit, the participants in both groups went home. Participants were not allowed to sleep at home during the day. They were also not allowed to do any kind of intensity training. Consuming caffeine (coffee, tea, chocolate) was allowed till 6 p.m.

2.4.3. Night

Participants in the control group stayed at home to sleep. Subjective sleepiness was assessed with the Stanford Sleepiness Scale (SSS; Hoddes et al., 1973). The sleep deprived group came back to the test location at 9:00 pm Participants from this group wore the wearable EDA and HR sensors continuously from that moment on. They were situated in a spacious experimental room, where they were free to move around in between tests and could perform reading, watch movies, play board games or interact with other participants and experimental leaders. During the night, participants could not perform any kind of intense bodily activity. From 21:30 pm until 7:30, every 60 min participants were instructed to watch short movie clips, rate their sleepiness using the SSS and perform a simple attentional task (Psychomotor Vigilance Task). Participants were designated a desk with a computer where they could perform these hourly tasks. Standardized snacks during the night and standardized breakfast for both groups in the morning of day two were served at the test location. The results of the measurements conducted during the night are discussed in another paper by Stuldreher et al. (in revision).

2.4.4. Morning day two

The next morning, the control group had to be present on location at 8 a.m. for breakfast and the second set of measurements. This group started the morning with applying the sensors for EDA and HR measures. Next, the procedures described in morning day one were repeated. To reduce possible habituation effects, a different social stress test was used, i.e. the TSST.

2.5. Analysis

For statistical data analysis IBM SPSS (Statistical Package for the Social Sciences) version 26.0 was used. All statistical tests were performed using a significance level of alpha = .05. Missing data is not replaced, but removed from analysis. For the inflammatory and psychophysiological markers non-parametric techniques were used because ranks and medians are more robust to outliers. See Fig. 2 for a schematic overview of the statistical tests. To test three hypotheses, we performed the following three analyses.

1) The main effect of sleep deprivation (*TSD group, control* group), assessed with a *t*-test for independent samples on pre-stress cognitive performance day two and a Mann-Whitney *U* test on all other dependent variables. To correct for individual differences, we subtracted scores of day one from those of day two.
2) The main effect of the social stress test (*before, after*), analyzed using only data from the control group on day two (i.e. to isolate the main effect from possible effects of sleep deprivation). The effects on cognitive performance were assessed with paired-sample t-tests and all other dependent variables with Wilcoxon Matched-Pairs Signed Rank tests. For cortisol, AUC_I deviation from zero was also determined using a Wilcoxon Matched-Pairs Signed Rank tests.
3) The interaction sleep deprivation x social stress test, assessed by a generalized linear model (GLM) with sleep deprivation as a between-subjects independent variable and the social stress test as within-subjects independent variable for the cognitive performance measures. For both groups, cognitive performance *after* versus *before* the social stress test on day two was analyzed with post-hoc comparison tests. Please note that the main effects from the GLM are not interpreted. The interaction effect on inflammatory and psychophysiological markers was determined with Mann-Whitney U tests and Wilcoxon Matched-Pairs Signed Rank tests to compare the stress response levels (difference between *after* and *before* the social stress tests) between the groups.

Spearman's rank tests were computed to explore for correlations between sleep deprivation effects on cognitive measures against inflammatory markers, psychophysiological markers and subjective

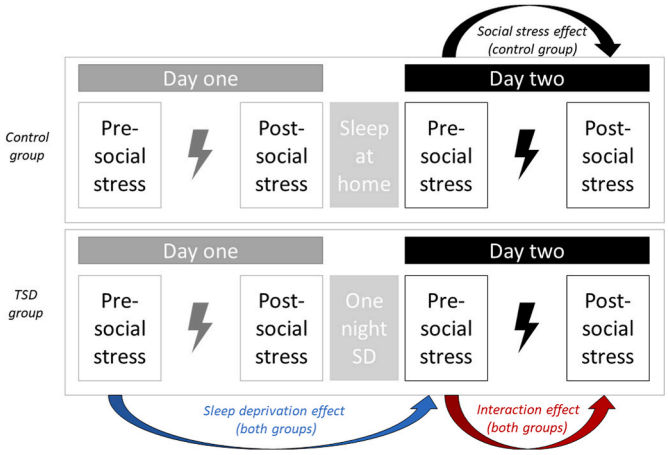

Fig. 2. Schematic overview of (non)parametric tests. The blue arrow represents testing the effect of groups on pre-stress cognitive performance and markers day two, the black arrow represents testing the effect of the social stress test on day two on cognitive performance and markers in the control group and the red arrow represents testing whether the effect of social stress test day two on cognitive performance and markers differs between control and TSD group. Measurements after the social stress test on day one are not used in this paper. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

measures. Only participants from the *TSD group* were included in this analysis. Spearman's rank correlations were also computed to assess the relationship between social stress effects combined with effects of sleep deprivation on cognitive measures on the one hand, and on the other hand inflammatory markers, psychophysiological markers and subjective measures. Only participants from the *TSD group* were included in the analysis.

3. Results

3.1. Cognitive performance

Data of the SYNWIN from one participant was missing because this participant did not seem to perform the task correctly resulting in a negative score. The parametric tests statistics of the main effects of sleep deprivation, the social stress test, and their interaction on cognitive performance measures on day two can be seen in Table 1.

3.1.1. Sleep deprivation

The main effect of sleep deprivation was significant for all performance measures, showing lower performance in the *TSD group* compared to the *control group* (see Fig. 3A, B and C).

3.1.2. Social stress test

The main effect of the social stress test was only significant for GN – FA % (t (47) = 2.348, p = .023, blue line in Fig. 3F) indicating lower performance *after* the social stress test than *before* the social stress test. No effect of the social stress test was found for SYNWIN composite score (t (46) = 1.64, p = .108, blue line in Fig. 3D) or for GN – mean RT go responses (t (47) = −1.86, p = .070, blue line in Fig. 3E).

3.1.3. Interaction sleep deprivation x social stress test

The interaction between sleep deprivation and the social stress test was significant for the SYNWIN composite score (F (1,97) = 6.77, p = .011, Fig. 3D), and the GN – FA % (F (1, 99) = 9.03, p = .003, Fig. 3F). The interaction showed a trend on GN – mean RT go responses (F (1, 99) = 3.77, p = .055, Fig. 3E). Pairwise comparisons on the SYNWIN composite score showed that the scores *after* the social stress test significantly increased for the *TSD group* only (p < .001). For the GN – mean RT go responses, pairwise comparisons showed that the RT *after* the social stress test was lower for the *TSD group* (p < .001), but not for the *control* group. For the GN – FA %, pairwise comparisons showed that the percentage false alarms after the social stress test was significantly higher for the *control group* (p = .016), while a trend was found for a lower percentage false alarms for the *TSD group* (p = .076).

Table 1
The main effects of sleep deprivation (independent *t*-test on pre-stress cognitive performance day two), the social stress test (paired sample *t*-test for the control group on day two) and the interaction effect between sleep deprivation and the social stress test (between-within GLM) on cognitive performance. Increased cognitive performance is indicated by + and decreased cognitive performance by -.

	Effect of sleep deprivation	Effect of social stress test (control group)	Interaction effect of sleep deprivation x social stress test
SYNWIN composite score	t (90.87) = 5.34, p = <.001** –	t (46) = 1.64, p = .108	F (1,97) = 6.77, p = .011* + *for SD group*
GN – mean RT go responses	t (86.70) = −3.56, p = <.001** –	t (47) = −1.86, p = .070	F (1, 99) = 3.765, p = .055 + *for SD group*
GN – FA %	t (99) = −5.35, p = <.001** –	t (47) = 2.348, p = .023* –	F (1, 99) = 9.032, p = .003* + *for SD group*

*p < .05, **p < .001.

3.2. Inflammatory markers

Data of inflammatory markers at different timepoints from seven participants were missing due to insufficient plasma. Furthermore, data of IL-1β on day one from one more participant has been excluded due to a technical error. The main effects of sleep deprivation and the social stress test and their interaction on inflammatory markers can be seen in Table 2. Significant results are discussed in the text and shown in Fig. 4.

3.2.1. IL-6

The main effect of sleep deprivation was significant for IL-6, showing increased IL-6 concentrations in blood in the *TSD group* compared to the *control group* ($U(N_{sd} = 50, N_c = 44) = 600$, $z = -3.789$, p < .001, see Fig. 4A). There was no main effect of the social stress test on IL-6 concentrations (Z = −0.302, p = .763). A Mann-Whitney *U* test indicated that IL-6 stress response concentrations did not significantly differ between the groups, indicating no interaction effect of sleep deprivation and the social stress test ($U(N_{sd} = 53, N_c = 43) = 1103$, $z = -0.269$, p = .788). These findings imply that sleep deprivation affected the IL-6 concentrations in blood, while the social stress test did not result in such an effect.

3.2.2. IL-22

The main effect of sleep deprivation was significant for IL-22, showing lower IL-22 concentrations in blood in the *TSD group* compared to the *control group* ($U(N_{sd} = 50, N_c = 44) = 744$, $z = -2.698$, p = .007, see Fig. 4B). The main effect of the social stress test was also significant, with lower IL-22 concentrations in blood *after* the social stress test on day two compared to *before* (Z = −2.688, p = .007, see blue line in Fig. 4C). The interaction between sleep deprivation and the social stress test was also significant for IL-22 concentrations ($U(N_{sd} = 53, N_c = 43) = 814$, $z = -2.398$, p = .016, see Fig. 4C). In the *TSD group* IL-22 concentrations remained unchanged *after* the social stress test, while it decreased for the *control group*. These findings imply that TSD reduced IL-22 concentrations, and that social stress reduced IL-22 in well rested participants, but not in sleep-deprived participants.

3.3. Psychophysiological markers

Data of baseline HR values from 30 participants, data of HR stress responses from 16 participants, data of baseline EDA values from 27 and data of EDA stress responses from 23 participants is missing due to technical recording issues. Data of cortisol in saliva at different timepoints from a total of three participants is missing due to technical issues. The same non-parametric tests that are used for the inflammatory markers are used for the psychophysiological markers (shown in Table 3). Significant results are reported in the text and shown in Fig. 5.

3.3.1. HR

The main effect of sleep deprivation was not significant for HR ($U(N_{sd} = 37, N_c = 34) = 528$, $z = -1.163$, p = .245). The main effect of the social stress tests on HR was significant, with increased HR *during the stress test* compared to HR *before the stress test* (Z = −5.096, p < .001, see Fig. 5C). The interaction between sleep deprivation and the social stress test was not significant for HR ($U(N_{sd} = 42, N_c = 43) = 829$, $z = -0.650$, p = .515).

3.3.2. EDA

The main effect of sleep deprivation was significant for EDA, showing increased EDA in the *TSD group* compared to the *control group* ($U(N_{sd} = 40, N_c = 34) = 390$, $z = -3.145$, p = .002, see Fig. 5A). The main effect of the social stress test on EDA was also significant, with increased EDA *during the stress test* compared to EDA *before the stress test* (Z = −4.085, p < .001, see Fig. 5D). The interaction between sleep deprivation and the social stress test was not significant for EDA ($U(N_{sd} = 42, N_c = 36) = 680$, $z = -0.762$, p = .446).

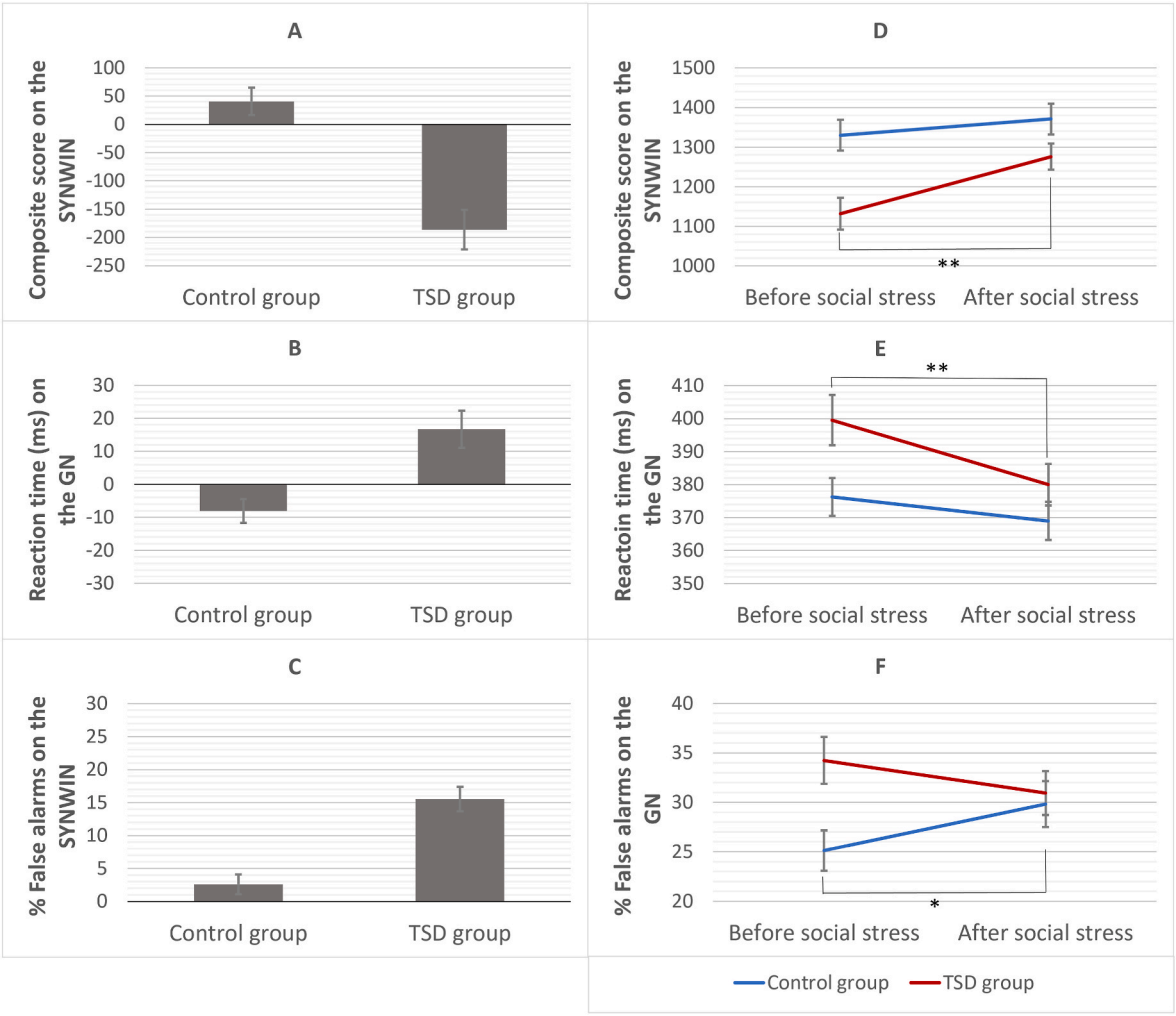

Fig. 3. Main effect of sleep deprivation on cognitive measures (A, B and C), main effect of social stress test on cognitive measures (blue lines in D, E and F) and interaction effect of sleep deprivation and social stress test on cognitive measures (blue and red lines in D, E and F). Error bars are ±1 standard error. For interaction effects, significant pairwise comparisons are indicated by * p < .05, **p < .001. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

3.3.3. *Cortisol in saliva*

The main effect of sleep deprivation was not significant, but a trend was found for cortisol, showing lower cortisol concentrations in the *TSD group* compared to the *control group* ($U(N_{sd} = 51, N_c = 47) = 930$, $z = -4.246$, p = .056, see Fig. 5B). There was no main effect of the social stress test on the AUC_I as a measure of cortisol stress response (Z = −0.942, p = .346). The interaction between sleep deprivation and the social stress test was not significant for cortisol stress response levels (AUC_I) ($U(N_{sd} = 52, N_c = 47) = 1025$, $z = -1.380$, p = .167).

3.4. *Subjective markers*

Data of the RSME during both the SYNWIN and GN from two participants was missing because of technical recording issues. For the same reason, data of the PANAS on different time points from a total of four participants was missing. Non-parametric tests were also used for the subjective markers and shown in Table 4. Significant results are reported in the text and shown in Fig. 6.

3.4.1. *Mental effort*

The main effect of **sleep deprivation** was significant for RSME ratings of the SYNWIN, showing increased ratings in the *TSD group* compared to the *control group* ($U(N_{sd} = 52, N_c = 47) = 745$, $z = -3.343$, p < .001, see Fig. 6A). Also the RMSE ratings of the GN task were significantly increased in the *TSD group* compared to the *control group* ($U(N_{sd} = 52, N_c = 47) = 661$, $z = -3.932$, p < .001, see Fig. 6B). There was no main effect of the **social stress test** on RSME ratings of the SYNWIN (Z = −1.111, p = .266), or GN task (Z = −0.011, p = .991). The interaction between **sleep deprivation** and the **social stress test** for RSME ratings of the SYNWIN was significant ($U(N_{sd} = 52, N_c = 47) = 821.00$, $z = -2.811$, $p = .005$, see Fig. 6F). More specifically, the RSME stress response decreased for the *TSD group* ($p = .005$), while it did not changed for the *control group*. The interaction between **sleep deprivation** and the **social stress test** for RSME ratings of the GN task was also significant ($N_{sd} = 52, N_c = 47) = 920.50$, $z = -2.114$, $p = .035$, see Fig. 6G). This RSME stress response decreased for the *TSD group* ($p = .013$), while it did not changed for the *control group*.

3.4.2. *Affect ratings*

The main effect of **sleep deprivation** was significant for positive affect ratings, showing decreased ratings in the *TSD group* compared to the *control group* ($U(N_{sd} = 53, N_c = 46) = 597$, $z = -4.372$, p < .001, see Fig. 6C), while a trend for negative affect ratings indicated increased ratings in the *TSD group* compared to the *control group*, $U(N_{sd} = 53, N_c = 46) = 973.500$, $z = -1.743$, p = .081. The main effect of the **social stress test** on positive affect ratings was also significant, showing

Table 2
Main effects of sleep deprivation (Mann-Whitney *U* test on pre-stress inflammatory markers day two), the social stress test (Wilcoxon Signed-Ranks test for the control group on day two) and the interaction effect between sleep deprivation and the social stress test (Mann-Whitney *U* test for both groups) on inflammatory markers. Corresponding nonparametric test statistics are shown. Increased inflammatory response is indicated by + and decreased inflammatory response by -.

	Effect of sleep deprivation	Effect of social stress test (control group)	Interaction effect of sleep deprivation x social stress test
IL-1β	$U(N_{sd} = 50, N_c = 43) = 1051, z = -.185$, p = .853	Z = −.229, p = .819	$U(N_{sd} = 53, N_c = 43) = 1063, z = -.564$, p = .573
IL-6	$U(N_{sd} = 50, N_c = 44) = 600, z = -3.789$, p < .001** +	Z = −.302, p = .763	$U(N_{sd} = 53, N_c = 43) = 1103, z = -.269$, p = .788
IL-10	$U(N_{sd} = 50, N_c = 44) = 1022.50, z = -.587$, p = .557	Z = −1.002, p = .316	$U(N_{sd} = 53, N_c = 43) = 1114, z = -.188$, p = .851
IL-22	$U(N_{sd} = 50, N_c = 44) = 744, z = -2.698$, p = .007* -	Z = −2.688, p = .007* -	$U(N_{sd} = 53, N_c = 43) = 814, z = -2.398$, p = .016* *- for control group*
TNFa	$U(N_{sd} = 50, N_c = 44) = 1028.50, z = -.542$, p = .588	Z = −.966, p = .334	$U(N_{sd} = 53, N_c = 43) = 1133.50, z = -.044$, p = .965

*$p < .05$, **$p < .001$.

increased ratings *after the stress test* compared to *before* (Z = −4.291, p < .001, see Fig. 6D). Also the main effect of the **social stress test** on negative affect ratings was significant, showing increased ratings *after the stress test* compared to *before* (Z = −2.869, p = .004, see Fig. 6E). The interaction between **sleep deprivation** and the **social stress test** was not significant for positive affect ratings ($U(N_{sd} = 52, N_c = 46) = 1171.00, z = -0.178$, p = .859), or for negative affect ratings ($U(N_{sd} = 52, N_c = 46) = 2384.00, z = -1.361$, p = .173).

3.5. Correlations between cognitive measures and biomarkers

There were no significant correlations between sleep deprivation effects on cognitive measures (baseline value on day two minus baseline value on day one) and inflammatory markers, psychophysiological markers and subjective measures. Also no significant correlations were found between social stress effects combined with effects of sleep deprivation on cognitive measures and any of the inflammatory markers, psychophysiological markers and subjective measures.

4. Discussion

4.1. Cognitive performance and stressors

The main aim of the current study was to examine isolated and combined effects of TSD and acute social stress on cognitive

Table 3
Main effects of sleep deprivation (Mann-Whitney U-test on pre-stress psychophysiological markers day two), the social stress test (Wilcoxon Signed-Ranks test for the control group on day two) and the interaction effect between sleep deprivation and the social stress test (Mann-Whitney U-test for both groups) on psychophysiological markers. Corresponding nonparametric test statistics are shown. Increased psychophysiological response is indicated by + and decreased psychophysiological response by -.

	Effect of sleep deprivation	Effect of social stress test (control group)	Interaction effect of sleep deprivation x social stress test
HR	$U(N_{sd} = 37, N_c = 34) = 528, z = -1.163$, p = .245	Z = −5.096, p < .001** +	$U(N_{sd} = 42, N_c = 43) = 829, z = -.650$, p = .515
EDA	$U(N_{sd} = 40, N_c = 34) = 390, z = -3.145$, p = .002* +	Z = −4.085, p < .001** +	$U(N_{sd} = 42, N_c = 36) = 680, z = -.762$, p = .446
Cortisol (AUC_I)	$U(N_{sd} = 51, N_c = 47) = 930, z = -1.909$, p = .056 –	Z = −.942, p = .346	$U(N_{sd} = 52, N_c = 47) = 1025, z = -1.380$, p = .167

*$p < .05$, **$p < .001$.

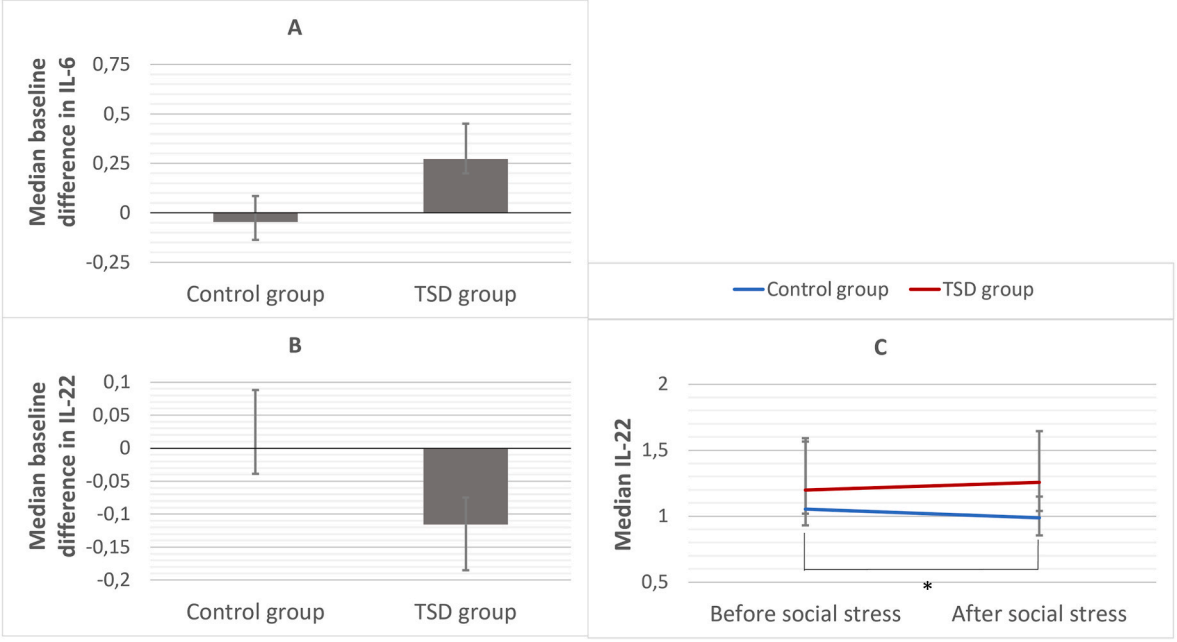

Fig. 4. Main effects of sleep deprivation on inflammatory markers (A and B) and interaction effect of sleep deprivation and social stress test on IL-22 (C). Error bars are 95% confidence interval of the median. For the interaction effect, significant pairwise comparisons are indicated by * p < .05.

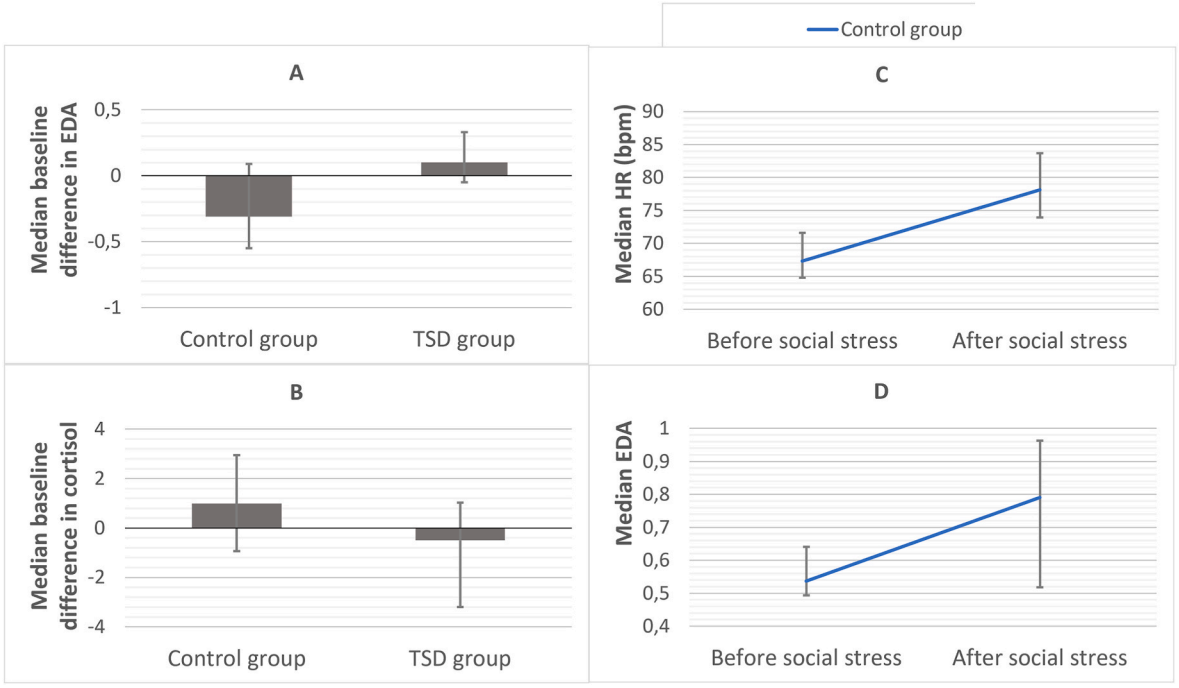

Fig. 5. Main effects of sleep deprivation on psychophysiology (A and B) and main effects of the social stress test on HR and EDA (C and D). Error bars are 95% confidence interval of the median.

Table 4
Main effects of sleep deprivation (Mann-Whitney U-test on pre-social stress subjective markers on day two), the social stress test (Wilcoxon Signed-Ranks test for the control group on day two) and the interaction effect between sleep deprivation and the social stress test (Mann-Whitney *U* test for both groups) on subjective markers. Corresponding nonparametric test statistics are shown. Increased subjective rating is indicated by + and decreased subjective rating by -.

	Effect of sleep deprivation	Effect of social stress test (control group)	Interaction effect of sleep deprivation x social stress test
RSME ratings during the SYNWIN	$U(N_{sd} = 52, N_c = 47) = 745$, $z = -3.343$, $p < .001$** +	$Z = -1.111$, $p = .266$	$U(N_{sd} = 52, N_c = 47) = 821.00$, $z = -2.811$, $p = .005$* *- for SD group*
RSME ratings during the GN	$U(N_{sd} = 52, N_c = 47) = 661$, $z = -3.932$, $p < .001$** +	$Z = -.011$, $p = .991$	$U(N_{sd} = 52, N_c = 47) = 920.50$, $z = -2.114$, $p = .035$* *- for SD group*
Positive affect ratings	$U(N_{sd} = 53, N_c = 46) = 597$, $z = -4.372$, $p < .001$** −	$Z = -4.291$, $p < .001$** +	$U(N_{sd} = 52, N_c = 46) = 1171.00$, $z = -.178$, $p = .859$
Negative affect ratings	$U(N_{sd} = 53, N_c = 46) = 973.500$, $z = -1.743$, $p = .081$ +	$Z = -2.869$, $p = .004$* +	$U(N_{sd} = 52, N_c = 46) = 2384.00$, $z = -1.361$, $p = .173$

*$p < .05$, **$p < .001$.

performance. We took a comprehensive approach to explore possible (shared) underlying mechanisms. Our results confirm earlier reported main effects of both stressors, but we are the first to report an interaction between sleep deprivation and a social stress test on cognitive performance. In line with our expectations, sleep deprivation led to performance decline on both a complex multitask and a response inhibition task. The social stress test in isolation also resulted in cognitive performance decline on the response inhibition task. However, the interaction shows that the social stressor improved rather than decreased performance of sleep deprived people. This implies that there is an antagonistic interaction, with the stressors combined resulting in opposite effects on cognitive performance.

At first sight, the finding that the social stress test did not result in further performance decline after sleep deprivation seems counter-intuitive. However, similar results have been found for sensory rather than social stressors in the context of fatigued or bored participants (Corcoran, 1962). An explanation for this can be grounded in the adapted version of a performance-effort model proposed by Bottenheft et al. (2023). This model describes four phases as function of increasing task load: low task load with reduced performance due to an inattentive state, normal task load with optimal performance, high task load with optimal performance through investment of additional effort, and overload where there are no (attentional) resources available. A stressor can occupy cognitive resources that are required for the task, resulting in performance decline. The same happens when task load increases; the performance starts to decline (i.e. the transition from high load to overload, see right side of Fig. 7). However, the impact of a stressor can be different at lower task load levels, where performance can increase instead of decrease due to higher arousal with a stressor (see left side of Fig. 7). Sleep deprivation can cause a state of inattentiveness, resulting in a decrease in performance (Alhola and Polo-Kantola, 2007). In our study, the social stress test increased arousal resulting in an increase of performance in sleep deprived people. This corresponds with our findings of expected increased autonomic responses (both HR and EDA) after the social stress test. Besides this, we found that sleep deprivation also increased EDA responses, which is indicative of a higher state of arousal when sleep deprived. Although this may sounds contradictory to a state of inattentiveness, sleep deprivation is known to be associated with increased sympathetic nervous system arousal when performing a task or being emotionally challenged (Meerlo et al., 2008). This can be explained by higher autonomic activation, i.e. increase in phasic arousal, that is required to maintain alert when sleep deprived (Alhola and Polo-Kantola, 2007; Meerlo et al., 2008).

Furthermore, our subjective results confirmed that sleep deprivation increased subjective mental effort on both cognitive tasks, implying that it took more effort to maintain task performance after sleep deprivation. However, the social stress test decreased subjective ratings of mental

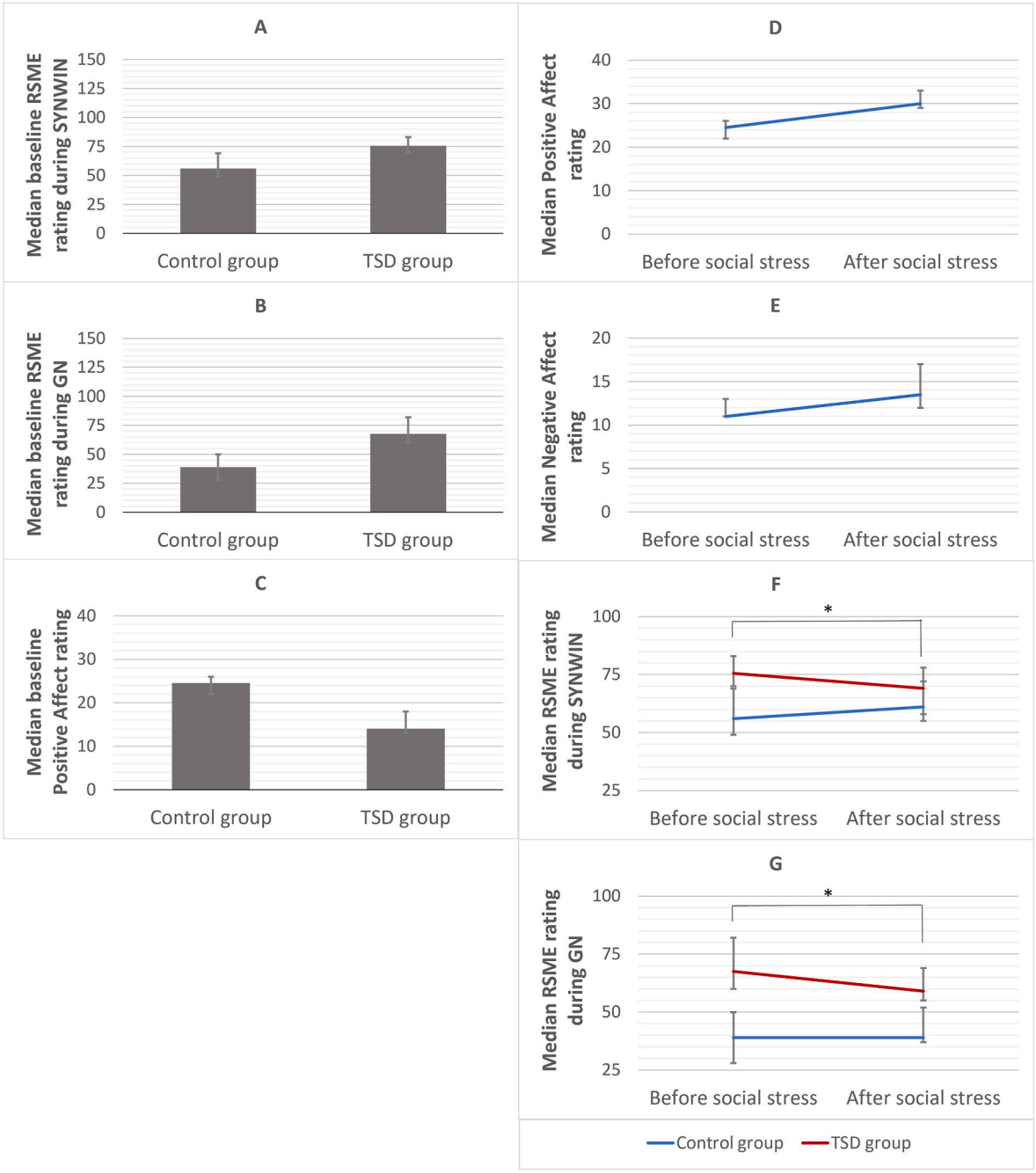

Fig. 6. Main effects of sleep deprivation on subjective markers (A, B and C), effect of the social stress test on Positive- and Negative Affect (D and E) and interaction effect of sleep deprivation and social stress test on RSME ratings (F and G). Error bars are 95% confidence interval of the median. For interaction effects, significant pairwise comparisons are indicated by * $p < .05$.

effort of sleep deprived people. This is consistent with an improved cognitive performance that required less mental effort due to the arousing effect of a social stressor.

4.2. The effects of sleep deprivation on physiological and metabolic-inflammatory parameters

Physiological and metabolic-inflammatory parameters were collected allowing us to associate these markers with i) cognitive decline after TSD and ii) cognitive improvement after acute social stress for sleep deprived people. We found that sleep deprivation caused an increase in the blood concentrations of the pro-inflammatory cytokine IL-6. This corresponds to studies suggesting that IL-6 is a sleepiness-mediating cytokine which increases during the day after partial or total sleep deprivation (Vgontzas et al., 1999, 2004). In this study we showed that the anti-inflammatory cytokine IL-22 decreased after sleep deprivation. The observed decrease in blood IL-22 concentrations upon sleep deprivation has not been reported in humans so far but is supported by Gao et al. (2020), who also reported a decrease of IL-22 in sleep-deprived mice. IL-22 has emerged over the past decade as a protective cytokine required for tissue repair, wound healing and homeostasis promoting self-renewal of neural stem cells in the brain (Coronas et al., 2023). While the protective role of IL-22 against pathogens has been well-established many questions exist regarding its role under non-inflammatory conditions (Zenewicz and Flavell, 2011) including the response to stressors, such as sleep deprivation.

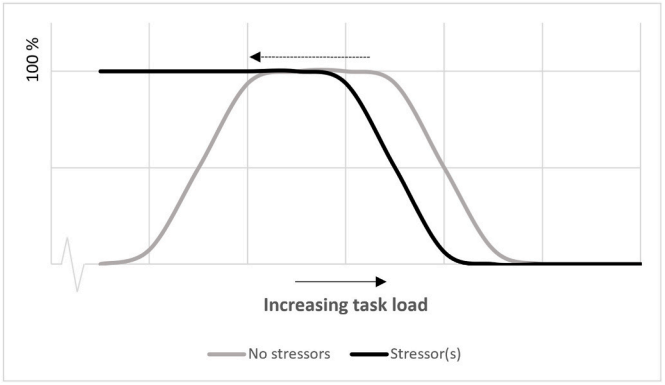

Fig. 7. Shift in expected performance curves for conditions without stressors (grey) and with stressor(s) (black) as function of increasing task load.

Contrary to our expectation, morning salivary cortisol was reduced after sleep deprivation. A possible explanation is that the cortisol awakening response (CAR) is disturbed after sleep deprivation. Normally there is a sharp increase of cortisol levels after awakening (Pruessner et al., 1997), but literature showed that cortisol in the morning is blunted after total sleep deprivation (Vargas and Lopez-Duran, 2020). The circadian dynamics of cortisol and the high variability of measures like the CAR advocates alternative measures and reinforces the search for other biomarkers of stress responses.

Sleep deprived people subjectively indicated that positive emotions were decreased, while negative emotions were not affected. Although it was expected that negative emotions increase after sleep deprivation, Talbot et al. (2010) also found no effect of sleep deprivation on negative emotions. The authors explain that the questionnaire being used (PANAS) may not assess the type of negative emotions experienced when sleep deprived.

4.3. The effects of the social stress test on physiological and metabolic-inflammatory parameters

Not only sleep deprivation, but also the social stress test resulted in a decrease of IL-22 concentrations in blood, while the other cytokines in our study were unaffected by the social stressor. This may indicate that IL-22 is a more sensitive (or more specific) biomarker of stress than the other cytokines. To our knowledge there are no published studies about the effects of acute social stressors on IL-22, let alone mechanistic explanations how IL-22 may affect cognitive performance in humans. It is possible that the effects on performance are associated to low-grade infections elsewhere in the body. Shaler et al. (2021) showed that psychological stress reduces IL-22 mediated protection against infections in the gut in mice.

The significant increase of autonomic responses after the social stress test confirm a successful stress induction by the social stress test. Subjectively, the social stress test increased both negative emotions and positive emotions. On the contrary, no increase of salivary cortisol was found for the well-rested people and therefore was not a responsive marker for social stress in our study. This is inconsistent with a meta-analysis by Dickerson and Kemeny (2004), who found that most of the studies with a comparable public speaking task as social stress test lead to an increase in cortisol response. Therefore our findings may be explained by methodological factors that have influenced the results, such as using only one jury member during the TSST, getting used to the laboratory setting and, given the other type of social stress test on day one, in particular getting used to a social stress test.

4.4. Combined effects of sleep deprivation and social stress on biomarkers

Although some literature shows that poor or limited sleep increased the cortisol and immune reactivity to a social stressor (Minkel et al., 2014; Prather et al., 2014), this study found no evidence for increased immune reactivity to a social stressor after sleep deprivation, but rather the opposite - a stronger IL-22 response to the social stressor in the control group than in the TSD group. This may be caused by the fact that Prather et al. (2014) focused on lower self-rated chronic sleep quality, instead of acute TSD. Minkel et al. (2014) focused on one night of TSD like we did, but the timing of the social stress test was different from our study. Participants in their study were exposed to the social stress test at 5 p.m. instead of in the morning.

We found a uniform decline of blood IL-22 concentrations in response to both total sleep deprivation and acute social stress suggesting reduced protection under both stressors and that cytokines such as IL-22 may account for the higher vulnerability of persons that are exposed to stress in general. We do not think that IL-22 did not decrease in sleep deprived participants because a further decrease below the level already achieved after total sleep deprivation is not possible. Data presented in Fig. 4C argues against such a floor effect: while sleep deprivation reduced IL-22, overall levels of IL-22 in the TSD group are not extremely low and even tend to be higher than in the control group, suggesting that we are not looking at floor levels.

4.5. Exploration of possible (shared) mechanisms

The (antagonistic) interaction between the stressors confirms the possibility that they share the same mechanism through which they affect cognitive performance. The pattern of changes in cognitive performance and IL-22 are exactly the same. Besides this possible mechanism of immune response, the level of arousal caused by the social stressor can also act as mechanism to regulate sleep deprived changes. We further explored possible mechanisms by calculating the correlations between the cognitive performance scores and the physiological and metabolic-inflammatory parameters. None of these correlations reached significance. This lack of correlations, as well as the scarcity of research involving IL-22 in humans, prohibits us from drawing firm conclusions on the possibility that IL-22 plays a causal role in stressor induced cognitive decline. We do think these findings warrant follow-up research on IL-22 in relation with sleep deprivation, social stress and cognitive performance because reductions in IL-22 may predispose individuals to pathogen infection as well as chronic inflammatory and neurodegenerative disorders.

4.6. Conclusions

To our knowledge, this is the first study that took a comprehensive approach to characterize the inflammatory, psychological and autonomic state at baseline and under acute social stress conditions. We can conclude that both sleep deprivation and the social stressor have a negative effect on cognitive performance, while social stress partly compensates the cognitive performance decline in sleep-deprived people by increasing their arousal level. The subjective ratings of mental effort also reflect this interaction between sleep deprivation and social stress, indicating cognitive performance improvement that required less mental effort. From all inflammatory and physiological measures, this pattern was matched specifically by IL-22. Both SD and the social stress test reduce IL-22 concentrations in blood, but in particular for the well-rested people. There were no interactive effects of the two types of stressors in any other inflammatory or psychophysiological measure. These findings warrant further studies on the as-of-yet, understudied IL-22, a cytokine with protective anti-inflammatory properties. Specifically, whether IL-22 could constitute a biomarker of detrimental stress responses and investigate whether a preventive decline in IL-22 can provide protection against stress. Besides IL-22, the social stressor strongly increased HR and EDA. Together with the subjective results, this indicates that an arousal effect was involved, whereby the social stress test improves performance of sleep deprived people.

Ethics statement

The studies involving human participants were reviewed and approved by the MREC Brabant (reference number P2045, approval number NL74961.028.20). The participants provided their written informed consent to participate in this study.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The authors do not have permission to share data.

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