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Research report

Sleep deprivation impairs performance in the 5-choice continuous performance test: Similarities between humans and mice

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HIGHLIGHTS

- The 5-choice continuous performance test assesses attention across species.
- 36 h total sleep deprivation impairs attentional performance in humans.
- 36 h REM sleep deprivation impairs performance in mice similarly.
- The 5C-CPT may be used to test putative cognitive enhancers after sleep deprivation.

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ABSTRACT

Several groups undergo extended periods without sleep due to working conditions or mental illness. Such sleep deprivation (SD) can deleteriously affect attentional processes and disrupt work and family functioning. Understanding the biological underpinnings of SD effects may assist in developing sleep therapies and cognitive enhancers. Utilizing cross-species tests of attentional processing in humans and rodents would aid in mechanistic studies examining SD-induced inattention. We assessed the effects of 36 h of: (1) Total SD (TSD) in healthy male and female humans ($n = 50$); and (2) REM SD (RSD) in male C57BL/6 mice ($n = 26$) on performance in the cross-species 5-choice continuous performance test (5C-CPT). The 5C-CPT includes target trials on which subjects were required to respond and non-target trials on which subjects were required to inhibit from responding. TSD-induced effects on human psychomotor vigilance test (PVT) were also examined. Effects of SD were also examined on mice split into good and poor performance groups based on pre-deprivation scores. In the human 5C-CPT, TSD decreased hit rate and vigilance with trend-level effects on accuracy. In the PVT, TSD slowed response times and increased lapses. In the mouse 5C-CPT, RSD reduced accuracy and hit rate with trend-level effects on vigilance, primarily in good performers. In conclusion, SD induced impaired 5C-CPT performance in both humans and mice and validates the 5C-CPT as a cross-species translational task. The 5C-CPT can be used to examine mechanisms underlying SD-induced deficits in vigilance and assist in testing putative cognitive enhancers.

1. Introduction

All species, including humans, require some state of sleep [1]. Despite the ubiquity of this phenomenon, much of the underlying mechanisms, long-term effects, and the actual function that sleep provides are still poorly understood. Nevertheless, it is well known that deprivation from sleep negatively affects general health and cognition in humans [2–4]. The extent to which sustained wakefulness impairs cognitive performance in particular seems to depend on the task at hand. For example, sleep deprivation (SD) has a more profound effect in tasks requiring the maintenance of attention than in tasks assessing working memory and executive functions [5].

The increasingly fast-paced nature of society requires people to work longer hours resulting in sleeping fewer hours per day with irregular patterns of sleep [6]. For example, several professions

Abbreviations: 5C-CPT, 5-Choice Continuous Performance Test; 5CSRTT, 5-Choice Serial Reaction Time Task; CR, Correct rejection; FA, False alarm; FAR, FA rate; HR, Hit rate; ITI, Inter-trial interval; PVT, Psychomotor Vigilance Test; REM, Rapid eye movement; RI, Responsivity index; RSD, REM sleep deprivation; RT, Reaction time; SD, Sleep deprivation; TSD, Total sleep deprivation; vRT, variable RT.

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including piloting or the military require vigilance (attending to relevant stimuli over time), yet involve extended periods without sleep, which impairs vigilance [7,8]. Moreover, certain psychiatric populations exhibit abnormal sleeping patterns, which may further impact their already deficient cognitive performance and possibly impair efficacy of some treatments (*e.g.*, cognitive behavioral therapy). Patients with bipolar disorder for instance are well known for experiencing disrupted sleep patterns, SD, and concomitantly suffer from cognitive symptoms [9]. Furthermore, SD can precipitate manic and hypomanic episodes [10], yet benefit patients in depressive episodes [11,12]. Investigating the mechanisms of SD-induced effects on behaviors including vigilance would aid in developing cognition-enhancing pharmaceuticals or behavioral countermeasures to cognitive deficits for certain professions and psychiatric disorders. While humans can be experimentally sleep deprived, animal models are more suitable for investigating underlying mechanisms of SD-induced deficits in vigilance. Additionally, SD may serve as an environmental challenge in animal models of psychiatric disorders [13,14]. The limited cross-species tests of attention/vigilance in humans and animals hampers such investigations however.

Attentional performance during SD in humans has commonly been assessed using the psychomotor vigilance test (PVT) [15]. This reaction time (RT) task requires responding to a visual cue (target stimulus) presented at pseudo-random intervals. Generally, RTs are slowed and more variable, while omissions are increased in humans subjected to SD [7]. SD-induced impaired performance has been observed in rats in a PVT analog [16] and the 5-choice serial reaction time task (5CSRTT), the latter of which requires responding in varied locations [17]. These tasks require only responses to target stimuli however, despite the important and distinct role that inhibiting from responding to irrelevant (non-target) stimuli has in attentional processes [18]. Specifically, with only target stimuli, separating attentional lapses from response fatigue is difficult. By including non-target stimuli, one can determine whether response rates are globally or specifically diminished due to inattention to relevant stimuli. Likewise, treatments that increase global responsiveness may not be useful when one's environment is littered with irrelevant (non-target) stimuli. Hence, cross-species studies are required on the effects of SD on attentional performance that is specific to responding to relevant (target) stimuli.

The combination of both target and non-target stimuli is the hallmark of tests labeled as continuous performance tests (CPT; [18]). With the inclusion of non-target stimuli, CPTs measure vigilance and are the gold-standard tests of attention in psychiatric populations [19]. In the limited studies conducted on the effects of SD on CPT performance, several days of sleep restriction increased misses to target stimuli and reduced responses to non-target stimuli, thereby overall impairing vigilance and reducing responsiveness [20,21]. Other studies using total SD (TSD) report modest but non-significantly increased misses to targets but no change in non-target responses after TSD in healthy subjects; however stronger attentional disruption is reported in methadone-maintained subjects [22,23]. TSD primarily increased non-target responses compared to target responses in a go/no-go task however, despite this task not being a true CPT [24]. Determining the effects of SD on a cross-species vigilance task is required however, for examining putative underlying mechanisms.

The 5-choice (5C-CPT), based on the 5CSRTT, was developed to assess vigilance in mice [25–27] and rats [28,29], and is now available in humans [30], including in an fMRI setting [31]. Consistent with other CPTs, the 5C-CPT presents target stimuli to which the subject is required to respond as well as non-target stimuli, to which the subject is required to inhibit from responding. To date, no studies have assessed whether SD affects mouse or human performance in this cross-species CPT. Thus, the present studies investigated whether SD would affect 5C-CPT performance similarly in both mice and humans. We hypothesized that: (a) 36 h of TSD in humans; and (b) 36 h of rapid eye movement (REM) SD (RSD) in mice would similarly impair 5C-CPT performance. Since inter-individual differences were expected on mice 5C-CPT performance [27], and treatments can affect rodent performance differentially dependent upon baseline performance [32,33], we split the animals in good and poor performers. Finally, to ensure the validity of our TSD protocol, we also assessed TSD-induced effects in the human PVT.

2. Methods

2.1. Humans

Fifty human subjects (23 female) aged between 18 and 39 years were recruited through flyers, newspaper, and radio from the general San Diego community to participate in this study. Subjects were initially screened via telephone for eligibility. Informed consent was signed at an in-person screen, which included a complete medical history and a Structured Clinical Interview for DSM-IV. Inclusion criteria were at least 12 years of education, a consistent sleep-wake schedule (7–9 h sleep each night), and for women to be tested in the early follicular phase of their menstrual cycle. Exclusion criteria were history of any sleep disorder, Axis I psychopathology or immediate family history of mood or psychotic disorders; head injury followed by unconsciousness, migraine headaches requiring treatment, seizures, neurological symptoms of the hand, wrist, or arm; current use of nicotine or in the past 2 years; current use of psychotropic medications, hormone-based birth control; high caffeine (>400 mg/day) or alcohol (>2 ounces/day) use; positive urine toxicology screen for illegal substances; hearing threshold above 45 dB(A) at 500–6000 Hz; non-responsiveness to startling stimuli or any other medical condition which might pose a health risk for the subject. Subjects were instructed to maintain a regular sleep-wake schedule at home for at least one week prior to the study, which was monitored with sleep diaries and actigraphy. Sleep monitoring on the first night of the study screened for unreported sleep disorders. This study was conducted at the VA San Diego with the approval of the IRBs of UCSD and VA and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

2.1.1. Total sleep deprivation

Subjects spent four nights and days in the laboratory: (a) adaptation to the lab (night/day 0); (b) normal sleep followed by a battery of testing including the PVT and then the 5C-CPT (night/day 1); (c) sleep or TSD followed by a similar battery of testing (night/day 2); and (d) sleep or TSD followed by a similar battery of testing as night/day 2 (night/day 3). Subjects were randomly assigned to one of three groups. Group 1 received normal sleep throughout the study; group 2 was sleep deprived for 36 h prior to day 2; and group 3 was sleep deprived for 36 h prior to day 3. Subjects assigned to group 1 were included in the 'normal sleep' group ($n = 18$). Post-deprivation night data for subjects in groups 2 and 3 were collapsed into the TSD group ($n = 32$). The data from group 1 used for analysis was taken from day 2 or 3 in order to match with subjects from groups 2 and 3 therefore minimizing practice effects as a putative confound. Sleep schedules were made as similar to those maintained at home as possible with sleep being monitored with a standard overnight polysomnogram, including EEG, EOG, and EMG. At each point, subjects were free to engage in activities such as reading, watching television, or socializing. No exercise more strenuous than walking was allowed, nor any form of stimulant. Light snacks and meals were provided. Lights were kept at a constant low