Caffeine Effects on Risky Decision Making After 75 Hours of Sleep Deprivation

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Introduction: Recent research indicates that sleep deprivation impairs decision making. However, it is unknown to what extent such deficits are exacerbated in a dose-response manner by increasing levels of sleepiness, and the extent to which such sleep-loss-induced deficits can be reversed by caffeine. ***Methods:*** At three time points, 26 healthy subjects completed alternate forms of the Iowa Gambling Task (IGT): rested baseline, 51 h awake, and 75 h awake. Every 2 h each night, 12 volunteers also received 4 200-mg doses of caffeine, with the last dose occurring 3 h prior to the IGT. ***Results:*** At baseline, volunteers readily learned to avoid disadvantageous high-risk card decks while progressively choosing more frequently from advantageous low-risk card decks. When sleep deprived, however, these same subjects showed impaired performance, choosing more frequently from the disadvantageous high-risk card decks, particularly during the latter half of the game. Contrary to expectations, the severity of performance impairment did not increase significantly from 51 to 75 h of wakefulness, and caffeine had no significant effects on IGT performance during sleep deprivation. ***Discussion and Conclusions:*** As a provisional extension of our previous study, these preliminary findings further suggest that the ability to integrate emotion with cognition to guide decision making, a capacity believed to be mediated by the ventromedial prefrontal cortex, may be particularly vulnerable to sleep loss. Moreover, these capacities may not be significantly improved by moderate doses of caffeine, suggesting that they may function separately from simple arousal and alertness systems.

Keywords: Iowa Gambling Task, risk-taking, executive function, prefrontal cortex, wakefulness, sleep loss, somatic marker hypothesis.

IT HAS LONG BEEN known that sleep deprivation produces deficits in elementary cognitive processes such as alertness, attention, concentration, and psychomotor vigilance (12,39). However, recent interest has been more specifically focused on how sleep loss may affect higher order cognitive processes such as judgment (27), decision making (17), and cognitive control (14,18). These types of cognitive processes rely heavily on the functional integrity of the prefrontal cortex (21).

This focus on higher order executive functions is warranted, since the prefrontal cortex appears to be especially vulnerable to the effects of prolonged wakefulness. Even as little as 24 h of continuous sleep deprivation is associated with significant reductions in metabolic activity within the prefrontal cortex (37) and activity in affected brain regions continues to wane as the duration of wakefulness is extended up to 72 h (38). Similarly, sleep deprivation impairs some aspects of executive functions that are believed to be mediated by the prefrontal cortex, including divergent thinking, problem solving, mental flexibility, cognitive set shifting, and inhibitory capacity (14,19). Although a number of studies have failed to find performance impairments on executive function tasks following sleep deprivation (9), it is difficult to determine whether such negative results actually reflect the relative imperviousness of some mental capabilities to the effects of sleep loss, since the sensitivity of tests can be altered by manipulating parameters like feedback and duration of the test (3). Nevertheless, because of the heterogeneous nature of the prefrontal cortex and the capacities it mediates, the variability in findings across studies examining the effects of sleep deprivation on executive function raises the possibility that specific prefrontal systems may be adversely affected while others may remain intact during prolonged wakefulness.

Some recent evidence suggests that executive capacities that rely heavily upon the integration of affective processing with ongoing cognition may be particularly degraded by sleep deprivation (26,27). In a recent study, we demonstrated that 49 h of continuous sleep deprivation impaired a specific type of executive function involving the ability to make advantageous decisions under conditions of uncertainty on the Iowa Gambling Task (IGT) (26). In that study, we found that over a period of 100 trials on the IGT, healthy rested volunteers learned to avoid risky alternatives that ultimately led to a net loss in favor of less risky alternatives that ultimately led to a net gain. Once sleep deprived for 2 nights, however, these same subjects had difficulty making advantageous decisions, showing a pattern of performance that was not unlike that seen among patients with lesions to the ventromedial prefrontal cortex (4). Specifically, while the sleep-deprived subjects initially

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appeared to learn to avoid disadvantageous choices on the first half of the trials, they subsequently shifted their decisions away from these good choices and adopted a more risky strategy for the second half of the task (26). Although the deficit was not as severe as that seen in neurological patients, the notable similarity in the pattern of responses supports the notion that sleep deprivation is associated with a temporary dysfunction of the emotional decision-making processes mediated predominantly by the ventromedial prefrontal cortex.

It remains unknown, however, whether the decision-making deficits produced by sleep deprivation are exacerbated by additional sleep loss beyond 49 h. Based on functional neuroimaging studies that show progressive declines in regional cerebral metabolism with periods of sleep deprivation ranging from 24 to 72 h (37,38), it might be expected that decision-making deficits should likewise continue to decline as the duration of wakefulness is extended. Furthermore, it is not known whether the detrimental effect of sleep deprivation on decision making can be mitigated by commonly used stimulants such as caffeine. Longstanding evidence suggests that caffeine is effective at restoring simple alertness and vigilance during sleep loss, and it is commonly (albeit informally) used in operational and other environments to improve performance and safety. However, its effectiveness for reversing the effects of sleep loss on some aspects of higher order executive functioning is questionable (15).

The present study was conducted as a provisional extension of our earlier study to replicate and extend our findings on the effects of sleep deprivation on IGT performance by lengthening the duration of the sleep deprivation period and administering caffeine to some subjects. Healthy subjects were assessed using the IGT at rested baseline, again following 51 h of sleep deprivation, and finally following 75 h of sleep deprivation. Additionally, approximately half of the sample received multiple double-blind administrations of caffeine during the overnight period, with the final dose given 3 h prior to the IGT. It was hypothesized that: 1) at rested baseline, subjects would learn the IGT, showing a linear trend toward better performance as the game progressed; 2) sleep deprivation would be associated with impairment of IGT performance characterized by a quadratic function (i.e., initial increase in advantageous decisions, followed by a shift toward disadvantageous decisions in the second half of the task, replicating previous findings); 3) caffeine would improve performance on the IGT relative to placebo; and 4) greater impairment of IGT performance would be evident at 75 h relative to 51 h of sleep deprivation.

METHODS

Subjects

There were 26 healthy volunteers (21 men; 5 women), ranging in age from 20 to 35 yr (M age = 25.3, SD = 4.1) with an average of 14.1 yr of formal education (SD = 1.6), who participated. Volunteers were all native English speakers who read at a 6th grade level or better, as assessed by the Wide Range Achievement Test, 3rd edition (Psychological Assessment Resources, Inc., Lutz, FL). These data were collected as part of a larger study on the effects of caffeine on alertness and vigilance. While some data from these subjects have already been published elsewhere (27,28), the present study presents novel and previously unpublished findings related to the effects of caffeine on risky decision making. Exclusion criteria included high caffeine use (> 300 mg $\cdot$ d^{-1}), current tobacco use, or any notable history of medical, neurological, or psychiatric problems during a screening physical examination by a physician. Subjects were also excluded if they scored 10 or higher on the Beck Depression Inventory (8) and/or above 40 on either scale of the Spielberger State/Trait Anxiety Inventory (34). Urine drug screens were collected on the first day of the study to confirm the absence of any illicit substances or stimulant medications. Subjects were paid for their time in the study plus a bonus for good effort on the tasks. Subjects were informed that the bonus would require adequate performance on the IGT, although the exact criterion used to determine bonus payment was left vague in order to ensure sustained motivation. In actuality, the criterion for the bonus was set low enough that all subjects were virtually guaranteed to receive the maximum payment. The protocol and procedures of this study were approved by the Walter Reed Army Institute of Research Human Use Review Committee and the U. S. Army Human Subjects Research Review Board.

Iowa Gambling Task (IGT)

The IGT assesses an individual's ability to learn to avoid short-term high-risk choices and modify decision making to maximize long-term gains (5). Briefly, four identically appearing decks of cards were presented on the computer screen (labeled A′, B′, C′, D′ at baseline, K′, L′, M′, N′ following 51 h of sleep deprivation, and Q′, R′, S′, T′ following 75 h of sleep deprivation). Subjects attempted to win as much money as possible by selecting a total of 100 cards, one at a time, from among the four decks. Two of the decks provided relatively large wins, with occasional extremely large losses, while the other two decks provided small wins with even smaller overall losses. Subjects were informed that "some decks are better than others" but were not given any other clues as to which decks to choose. Greater detail on the administration of the IGT is provided elsewhere (26).

Study Design and Procedures

Four volunteers participated during each study run. On the acclimation day (Day 0), volunteers arrived at 1900 and were briefed on the study procedures, trained on the use of equipment, and given a full night (i.e., 8 h) of uninterrupted time in bed to obtain sleep. Subjects remained in a private sleep laboratory bedroom with enforced darkness from 2300 to 0700. Actigraphy measurements were obtained during the acclimation night using a trimode actograph (Precision Control Design, Inc., Fort Walton Beach, FL) and scored for sleep using

the Action-W scoring program (Ambulatory Monitoring, Inc., Ardsley, NY). Subjects obtained an average of 6.84 h of sleep (SD = 0.71) during the acclimation night (ranging from 5.27 to 7.68 h). After arising the following morning (Day 1), volunteers remained awake for the next 77 h. During this time, subjects engaged in regular psychomotor vigilance testing and completed occasional cognitive tasks and personality inventories. When not being tested, subjects were free to engage in leisure activities (e.g., watch movies, play video or board games, read books), as long as they remained within the confines of the sleep laboratory. The baseline IGT was completed at 1000 (after 3 h awake). The second IGT was administered at 1000 on Day 3, following 51 h awake. The final IGT was administered at 1000 on Day 4, following 75 h awake. Due to unforeseen time constraints, some subjects were not able to complete all three testing sessions. Overall, 25 subjects completed the baseline testing, 23 completed the 51-h sleep deprivation testing, and 22 completed the 75-h sleep deprivation testing session.

In a double blind manner, approximately half of the sample (N = 12) received 4 repeated doses of caffeine throughout the night in a commercially available chewing gum (200 mg, Stay Alert™ Gum, MMI Federal Marketing Services, Montgomery, AL). At this dosing, the gum has been shown to be absorbed into the blood stream more rapidly than pills, sustains plasma concentrations in an effective range (36), and is effective at sustaining psychomotor vigilance performance during 1 night of sleep deprivation (24). The other group (N = 14) received an identical tasting placebo chewing gum. Gum was administered every 2 h each night (at 0100, 0300, 0500, and 0700) for a total of 800 mg of caffeine across each 8-h overnight period.

Data Analysis

Performance on the IGT was scored in a manner identical to that described in our previous report (26). A net score was calculated for each block by subtracting the number of cards chosen from the disadvantageous decks from the number of cards chosen from the advantageous decks [e.g., net score = (# of selections from "good" decks) − (# of selections from "bad" decks)]. Positive net scores indicated advantageous responding whereas negative net scores indicated disadvantageous (i.e., risky) decision making (6).

An unanticipated computer malfunction resulted in partial loss of data for several subjects. This data loss occurred for 3 of 26 (11.5%) subjects on the baseline day, 3 of 26 (11.5%) on the 51-h sleep-deprived day, and 4 of the 26 (15.4%) on the 75-h sleep deprivation day. No subject lost more than one session of data. Because an omnibus repeated measures design incorporating all three sessions simultaneously would exclude missing cases in a list-wise manner, the data were instead analyzed using a series of three hypothesis-specific repeated measures ANOVAs to minimize the loss of data. Two ANOVAs were used to compare each sleep deprivation session to baseline and one ANOVA compared the two sleep deprivation sessions to one another. Statistical analysis proceeded in the following stages: 1) to replicate the normal pattern of improving performance over the course of the game when well-rested, the baseline performance was tested for linear trend using a repeated measures analysis of variance (ANOVA) in SPSS 12.0; 2) to test the effects of 51 h of sleep deprivation and caffeine, IGT performances from Day 1 and Day 3 were subjected to a 2 (Day) × 5 (Block) × 2 (Drug) mixed model ANOVA; 3) to test the effects of 75 h of sleep deprivation and caffeine, IGT performances from Day 1 and Day 4 were subjected to a 2 (Day) × 5 (Block) × 2 (Drug) mixed model ANOVA; and finally, 4) to compare differences between 51 and 75 h of sleep deprivation, Day 3 and Day 4 were compared directly using a 2 (Day) × 5 (Block) repeated measures ANOVA. Based on findings from our previous study, planned comparisons were undertaken to evaluate the differences between the conditions at each block.

RESULTS

Baseline Performance

It was hypothesized that net score performance would increase according to a monotonic trend, replicating previously published findings that healthy normal subjects progressively learn to select from "good" decks and learn to avoid "bad" decks as the game progresses. As evident in **Fig. 1A**, a repeated measures test of linear trend clearly demonstrated that subjects learned to make advantageous decisions on the baseline day [$F(1, 22) = 25.79$, $P < 0.001$]. Although not hypothesized, there was also a significant quadratic trend [$F(1, 22) = 4.75$, $P = 0.04$], suggesting that the rate of learning was most rapid in the first half of the IGT. Cubic and quartic trends were not significant.

51 Hours of Sleep Deprivation

Effects of caffeine on IGT: It was hypothesized that caffeine would improve performance on the IGT following 2 nights of sleep deprivation. A 2 (Baseline vs. Day 3) × 5 (Block 1-5) × 2 (caffeine vs. placebo) mixed-model ANOVA indicated that there was no main effect of caffeine on IGT performances [$F(1, 18) = 2.39$, $P = 0.14$]. Furthermore, caffeine did not interact significantly with any of the other conditions (Day, Block, Day × Block), suggesting that at 51 h of continuous wakefulness, the regimen of caffeine administration was ineffective at improving performance on the IGT (see Fig. 1A).

Effects of sleep deprivation on IGT: Because caffeine had no significant effect in the previous analysis, 51-h data from the drug groups was pooled for subsequent analyses for this time point. Based on previously published findings (26), it was predicted that sleep deprivation would lead to a quadratic pattern of performance across the five Blocks of the task, with subjects showing a gradual preference for "good" decks initially, followed by a reversal of that pattern toward more frequent preferences for "bad" decks, starting approximately halfway through the task. It was further hypothesized that the difference between baseline and sleep deprived sessions would be significant by the final Block of the task.

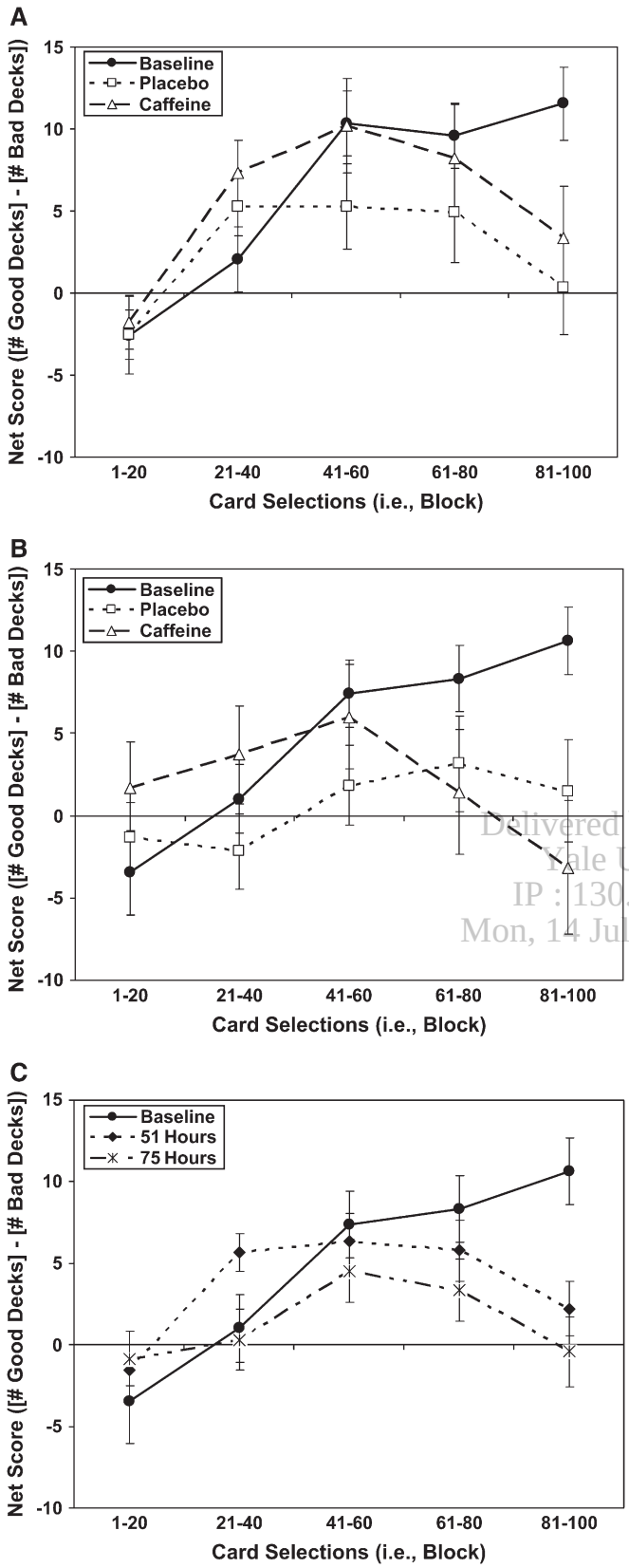

Fig. 1. Net scores, reflecting the number of good deck choices minus the number of bad deck choices, are plotted for each block of 20 cards in the Iowa Gambling Task. Lines represent the performance of the caffeine and placebo groups and pooled baseline performance for all subjects included in the comparison. Comparisons are plotted separately for placebo and caffeine groups at A) 51 h awake, B) 75 h awake, and C) 51 h versus 75 h awake when drug groups are collapsed. Error bars represent 1 standard error.

As evident in Fig. 1A, a repeated measures test of quadratic trend clearly demonstrated that the data followed the predicted quadractic trend [$F(1, 22) = 27.93$, $P < 0.001$]. Although the overall performance on the IGT did not differ between baseline and 51-h sleep-deprived sessions [$F(1, 72) = 2.49$, $P = 0.13$], when the baseline and sleep-deprived sessions were compared separately by Block, significantly worse (than baseline) performance was evident only for Block 5 [$F(1, 18) = 16.07$, $P < 0.001$].

75 Hours of Sleep Deprivation

Effects of caffeine on IGT: Similar to the findings at 51 h of wakefulness, a 2 (Baseline vs. Day 4) × 5 (Block 1-5) × 2 (caffeine vs. placebo) mixed-model ANOVA revealed no main effect of caffeine on IGT performances after 75 h of sleep deprivation [$F(1, 17) = 0.01$, $P = 0.94$]. Likewise, caffeine did not interact significantly with any of the other conditions (Day, Block, Day × Block), suggesting caffeine at the dosing schedule used here was ineffective at improving performance on the IGT even following 75 h of continuous sleep deprivation (see **Fig. 1B**).

Effects of sleep deprivation on IGT: Because caffeine had no significant effect at 75 h, data from the drug groups were pooled for subsequent analyses. Again, IGT performance at each Block was tested for the hypothesized quadratic trend. However, after 75 h of sleep deprivation, the quadratic trend across Blocks was no longer significant [$F(1, 21) = 2.79$, $P = 0.11$]. There was, however, a significant main effect of Day [$F(1, 68) = 5.82$, $P = 0.027$], indicating that volunteers performed more advantageously at baseline than they did following 75 h of sleep deprivation. Furthermore, when the baseline and 75-h sleep-deprived sessions were compared separately by Block, worse performance following sleep loss was evident for both Block 4 [$F(1, 17) = 5.097$, $P = 0.037$] and Block 5 [$F(1, 17) = 12.95$, $P = 0.002$] (see Fig. 1B).

51 vs. 75 Hours of Sleep Deprivation

Finally, it was also of interest to examine whether there was a dose dependent effect of sleep deprivation. Specifically, we hypothesized that performance on the IGT would be significantly worse following 75 h of sleep deprivation than following 51 h of sleep deprivation. However, a repeated measures ANOVA comparing the two test days failed to reveal a significant decline in performance on the IGT from 51 to 75 h of sleep deprivation [$F(1, 72) = 2.74$, $P = 0.12$] (see **Fig. 1C**).

DISCUSSION

As predicted, decision-making performance on the IGT was significantly impaired by sleep loss in this preliminary extension of our previous work (26). Relative to the well-rested baseline, impaired performance was evident at 51 h of sleep deprivation, replicating our previous finding that 2 nights without sleep produces deficits on this task. No sleep dose/response effect was evident, however, with IGT performance at 75 h of sleep deprivation showing no significant difference from performance at

51 h. Moreover, the observed deficits in decision making during sleep deprivation were not significantly enhanced by caffeine administered during the overnight sleep deprivation period preceding the IGT. Regardless of whether administered caffeine or placebo, sleep-deprived volunteers were impaired in their ability to evaluate the relative value of immediate gains and long-term penalties when compared to their own baseline. These preliminary findings suggest that the complex cognitive and affective processes required for successful IGT performance were adversely affected during two or more nights of sleep deprivation, and these decrements were not meaningfully reversed by the present dosing regimen of caffeine.

The IGT is sensitive to the integrity and functioning of the ventromedial prefrontal cortex. For example, performance on the IGT is associated with increased functional activity in the ventromedial prefrontal cortex in healthy volunteers (31) and is severely impaired by lesions to this same region (7). Interestingly, the pattern of performance decrements on the IGT during sleep loss appear similar to the deficits seen among neurological patients with lesions to the ventromedial prefrontal cortex (4,10), though generally less severe in magnitude. The finding that IGT performances decline with sleep loss is consistent with functional neuroimaging research that shows that sleep deprivation is associated with reduced metabolic activity within the prefrontal cortex (37,38) and altered prefrontal activity patterns during executive function tasks (13). It is also consistent with the assertions of Harrison and Horne that the cognitive processes mediated by the prefrontal cortex may be particularly vulnerable to the adverse effects of sleep deprivation (17). While preliminary and in need of replication, these findings suggest that sleep deprivation may have a particularly adverse effect on the functioning of this region of the brain and its associated cognitive-affective processes (26), possibly by producing a temporary but reversible functional lesion to the ventromedial prefrontal cortex or its associated systems.

The ventromedial deficit hypothesis proposed here is bolstered by findings from several other studies examining the effects of sleep deprivation on processes believed to be mediated by the ventromedial and orbital regions of the prefrontal cortex. For example, we have found that sleep deprivation significantly hinders the ability of healthy volunteers to identify elements of humor in cartoons and written jokes (25), reduces the efficiency and quality of moral reasoning (27), and impairs the ability to correctly identify odors (29), all of which are capacities that rely heavily on the functioning of ventral regions of the prefrontal cortex (16,33,40). These findings, in conjunction with other data suggesting that sleep deprivation is associated with alterations in a variety of affective processes including mood (12), affective symptoms of psychopathology (22), responses to frustration (23), and the evaluation of emotional events (41), suggest that continuous sleep deprivation has a particularly detrimental effect on the ability to integrate emotion with other cognitive processes, possibly via a common dysfunction of the ventromedial prefrontal cortex.

The primary goal of the present study was to evaluate the effectiveness of caffeine at reversing the decision-making deficits on the IGT that may be produced by sleep loss. When administered on the present dosing regimen, caffeine was not effective at restoring performance on the IGT, despite the fact that equivalent doses have been shown to effectively sustain alertness and psychomotor vigilance during a single night of sleep deprivation (24). However, further research is needed with different dosing regimens to more definitively answer this question since it is possible that potentially beneficial effects of caffeine had dissipated by the time subjects completed the IGT. This explanation is unlikely, because the IGT was administered well within the 4- to 6-h half-life of caffeine (35). Nevertheless, it is possible that the plasma levels of caffeine at this point were insufficient to reverse the functional deficits in decision making produced by sleep loss. Greater sensitivity may result from shortening the time interval between caffeine and test administration, so that testing occurs nearer to the point of peak plasma concentration.

The present preliminary findings replicate and provisionally extend our earlier work on the effects of sleep deprivation on risky decision making with the IGT, but some limitations should be noted. First, because no non-sleep-deprived control group was included (all subjects served as their own controls) it is possible that the changes in performance on the second and third administrations of the IGT reflected practice effects. However, recent data from the laboratory of Bechara and colleagues show no significant difference in performance across the three alternate forms of the IGT when administered in serial order (A. Bechara. Personal communication; 22 July 2005), thus reducing the likelihood that this was a factor in the present findings. Nevertheless, future studies would probably benefit by including a non-sleep-deprived control group that also receives the test article (i.e., placebo versus caffeine) to fully evaluate the effects of sleep loss and stimulants on IGT performance.

Second, it is noteworthy that the significant differences between baseline and sleep-deprived conditions occur only in the final blocks of the task, raising the possibility that sleep-deprived subjects may simply become bored or impatient with the long task. Consequently, they may prefer to select riskier decks when sleep deprived in order to increase the level of stimulation and excitement. However, these behaviors themselves may reflect declines in executive control, as it is well established that symptoms of distractibility (1,2), apathy and poor motivation (30,32), boredom susceptibility (20), and difficulty sustaining goal-directed behavior (11) are all hallmarks of executive function deficits seen in neurological patients suffering from prefrontal dysfunction. Furthermore, we believe that the subjects put forth their best effort, as they were highly motivated to earn the performance bonus on this task. Future methods that analyze the consistency of responses may be able to address this concern directly. Finally, the present study was limited by the absence of a post-recovery sleep administration of the IGT. Consequently, the extent to which the impairments

in decision making induced by sleep deprivation were reversed by a full night of sleep could not be determined in this study. Despite these limitations, the present results suggest that prolonged sleep deprivation is particularly disruptive to the normal cognitive-affective integration processes thought to be mediated by the ventromedial prefrontal cortex and these deficits appear unaffected by moderate doses of caffeine. Because caffeine is currently the most widely used fatigue countermeasure in the world, further work should be focused on delineating its efficacy for reversing sleep-loss induced deficits of executive mental functions, and assessing the implications of such findings as they relate to efficiency and safety in operational settings.

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