Behavioral/Systems/Cognitive

Sleep Deprivation Decreases Binding of [^{11}C]Raclopride to Dopamine D_2/D_3 Receptors in the Human Brain

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Sleep deprivation can markedly impair human performance contributing to accidents and poor productivity. The mechanisms underlying this impairment are not well understood, but brain dopamine systems have been implicated. Here, we test whether one night of sleep deprivation changes dopamine brain activity. We studied 15 healthy subjects using positron emission tomography and [^{11}C]raclopride (dopamine D_2/D_3 receptor radioligand) and [^{11}C]cocaine (dopamine transporter radioligand). Subjects were tested twice: after one night of rested sleep and after one night of sleep deprivation. The specific binding of [^{11}C]raclopride in the striatum and thalamus were significantly reduced after sleep deprivation and the magnitude of this reduction correlated with increases in fatigue (tiredness and sleepiness) and with deterioration in cognitive performance (visual attention and working memory). In contrast, sleep deprivation did not affect the specific binding of [^{11}C]cocaine in the striatum. Because [^{11}C]raclopride competes with endogenous dopamine for binding to D_2/D_3 receptors, we interpret the decreases in binding to reflect dopamine increases with sleep deprivation. However, we cannot rule out the possibility that decreased [^{11}C]raclopride binding reflects decreases in receptor levels or affinity. Sleep deprivation did not affect dopamine transporters (target for most wake-promoting medications) and thus dopamine increases are likely to reflect increases in dopamine cell firing and/or release rather than decreases in dopamine reuptake. Because dopamine-enhancing drugs increase wakefulness, we postulate that dopamine increases after sleep deprivation is a mechanism by which the brain maintains arousal as the drive to sleep increases but one that is insufficient to counteract behavioral and cognitive impairment.

Key words: **dopamine transporters; striatum; thalamus; visual attention; PET; circadian rhythms**

Introduction

Across species, the drive to maintain a regular sleep–wake cycle is profound. Disruption of the sleep–wake cycle adversely affects an individual's daily performance, safety, and health (Colten and Altevogt, 2006). The public health implications of sleep deprivation (SD) are enormous and include the deleterious health consequences of SD, which is associated with risks for a wide variety of medical conditions (e.g., hypertension, obesity, diabetes, depression, and compromised immunological function) (Colten and Altevogt, 2006). SD also accounts for 20% of all serious car accidents, which is equivalent to those attributed to alcohol (Connor et al., 2002). Accidents associated with SD are partially attributed to fatigue related performance failures (Colten and Altevogt, 2006). Indeed, SD adversely affects cognitive performance interfering with attention and reaction time (Durmer and Dinges, 2005). This can impair judgment and decision making (Durmer and Dinges, 2005). The mechanisms associated with impaired cognitive function with SD are poorly understood.

Multiple neurotransmitters are implicated in regulating the sleep–wake cycle (Siegel, 2004). The role of dopamine (DA) has been controversial because electrical activity of DA cells does not change during the wake–sleep cycle (Miller et al., 1983). However, there is increasing evidence of the importance of DA in sleep–wake states (Dzirasa et al., 2006; Lu et al., 2006; Monti and Monti, 2007) including the fact that medications used to maintain wakefulness increase brain DA activity (Boutrel and Koob, 2004). Moreover, patients with Parkinson's disease who have degeneration of DA pathways suffer from sleep disturbances including excessive daytime sleepiness (Happe et al., 2007). Also, mutations in the gene that encodes for the dopamine transporter (main molecular target that regulates extracellular DA concentration in brain) (Gainetdinov et al., 1998) in the fly markedly reduce sleep (Kume et al., 2005). However, the effects of SD on DA activity in the human brain and its relationship to cognitive performance have not been evaluated.

We therefore set to assess the effects of SD on DA neurotransmission in the human brain and its relationship to cognitive performance. We used positron emission tomography (PET) and [^{11}C]raclopride, a radiotracer that is sensitive to competition with endogenous DA to measure changes in DA (Volkow et al., 1994), and [^{11}C]cocaine to measure DA transporters (DATs)

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(Volkow et al., 1995) during non-sleep deprivation (non-SD) and after one night of SD. We measured DATs because they regulate extracellular DA (Gainetdinov et al., 1998) and are the targets of medications used to promote wakefulness (Boutrel and Koob, 2004). Moreover, because the cell surface expression of DAT can be rapidly regulated (minutes) this could be a mechanism for modulating DA neurotransmission (Hoover et al., 2007). We measured performance on visual attention (VA) (Pylyshyn and Storm, 1988) and working memory (WM) (Gevins et al., 1987), which are tasks sensitive to SD (Durmer and Dinges, 2005). Our working hypotheses were as follows: (1) SD would result in DA increases (evidenced by decreases in D_2 receptor availability) to maintain arousal; (2) DA increases would correlate with behavioral reports of fatigue (tiredness, desire to sleep, decreases in rested) and with cognitive performance; (3) SD would result in DAT downregulation to enhance DA neurotransmission.

Materials and Methods

Subjects. Fifteen healthy, nonsmoking, right-handed men (mean ± standard deviation, age 32 ± 8 years; education, 16 ± 2 years) participated in the study. Participants were screened carefully with a detailed medical history, physical and neurological examination, electrocardiogram, breath CO, routine blood tests and urinalysis, and urine toxicology for psychotropic drugs to ensure they fulfilled inclusion and exclusion criteria. Inclusion criteria were as follows: (1) ability to understand and give informed consent; and (2) 18–50 years of age. Exclusion criteria were as follows: (1) urine positive for psychotropic drugs; (2) present or past history of dependence on alcohol or other drugs of abuse (including current dependence on nicotine); (3) present or past history of neurological or psychiatric disorder; (4) use of psychoactive medications in the past month (i.e., opiate analgesics, stimulants, sedatives); (5) use of prescription (nonpsychiatric) medication(s), i.e., antihistamines; (6) medical conditions that may alter cerebral function; (7) cardiovascular and metabolic diseases; (8) history of head trauma with loss of consciousness of >30 min; (9) history of sleep disorders (if they responded affirmatively to having problems falling asleep, staying asleep, feeling tired after wakening, and/or required medications to help them sleep and/or if they had a past or present history of sleep apnea or restless leg syndrome; and (10) work that required shift hours. Subjects were asked to keep a diary of the number of hours slept per night for the 2 weeks duration of the study (from evaluation to completion of PET scans) and this corresponded to an average of 7 ± 1 h per night (range, 5–8 h). Signed informed consents were obtained from the subjects before participation as approved by the Institutional Review Board at Brookhaven National Laboratory.

Behavioral and cognitive measures. Subjects were asked to rate self-reports for descriptors of "desire to sleep," "tiredness," and "rested" on a scale of 1–10, with 1 being not at all and 10 being very intense. They also rated their "mood" with 1 being very low and 10 very high. Self-reports were obtained before radiotracer injection.

Visual attention. We used a VA task (Pylyshyn and Storm, 1988). For this task subjects viewed a display of moving balls and used only their attention to keep track of two, three, or four of 10 balls that had been briefly cued. To avoid eye movements while following the balls subjects were asked to fixate on a cross at the center of the display. At the end of each trial, the balls stopped moving and a new set of balls was highlighted; the subject presses a button if these balls were the same as the target set.

Working memory. We used the "n back" WM task (Gevins et al., 1987). For this task, subjects viewed a display where single alphabetical letters were sequentially presented in random order at a rate of 1/s. The subjects were instructed to press a response button whenever the current letter was the same as the current (zero-back), the one (one-back task), or the two (two-back task) before.

Performance accuracy was estimated as follows: (successful event − false alarms)/total events. These tasks were performed after the PET scans were completed.

SD and rested wakefulness (non-sleep deprivation) procedures. Subjects were kept overnight at Brookhaven National Laboratory before their scheduled SD or non-SD session to ensure that subjects stayed awake for the SD (one night of sleep deprivation) or had a good night of rest for the non-SD (mean, 6.7 ± 0.9 h slept; range, 5–8.5 h) conditions. A research assistant remained with them throughout the night to ensure that they did not fall asleep for the SD or that they slept properly for the non-SD condition. On the day of the non-SD condition, the subjects were woken at 7:00 A.M. and brought to the imaging suit where a nurse remained with the subjects to ensure that they stayed awake throughout the study. No food was given after midnight and caffeinated beverages were discontinued 24 h before the study.

Imaging. PET studies were done with a Siemens HR+ tomograph (resolution, 4.5 × 4.5 × 4.5 mm full-width at half-maximum). Each subject was tested on two separate days: 1 d after non-SD and another after one night of SD. The order of the conditions (non-SD or SD) was randomized to control for order effects. On each day, subjects underwent two sets of scans: first, a [^{11}C]cocaine scan (performed between 10 A.M. and 11:00 A.M.; ~3–4 h after awakening for the non-SD condition and 27–31 h after awakening for the SD condition) followed 2 h later by a [^{11}C]raclopride scan (performed between 12 P.M. and 1:00 P.M.; ~5–6 h after awakening for the non-SD condition and 29–33 h after awakening for the SD condition). The [^{11}C]cocaine scans were done to monitor changes in DAT and the [^{11}C]raclopride scans to monitor changes in endogenous DA after SD. For [^{11}C]cocaine, sequential dynamic scans were started immediately after intravenous injection of 4–8 mCi of [^{11}C]cocaine (specific activity, >0.2 Ci/μmol at time of injection) for a total of 60 min as described previously (Volkow et al., 1995). For [^{11}C]raclopride, sequential dynamic scans were started immediately after intravenous injection of 4–10 mCi of [^{11}C]raclopride (specific activity, >0.25 Ci/μmol at time of injection) for a total of 60 min as described previously (Volkow et al., 1994). To ensure that subjects would not fall asleep during the study, they were asked to keep their eyes open and a nurse remained by their side to ensure compliance. If the subjects closed their eyes, the nurse would ask them to open them again.

Image analysis and statistics. Regions of interest (ROIs) were obtained directly from the [^{11}C]raclopride and [^{11}C]cocaine images as described previously (Volkow et al., 1994, 1995). Briefly, we identified and selected the ROIs on summed images (dynamic images taken from 10–54 min) that were resliced along the intercommisural plane (anterior cingulate–posterior cingulate line). The caudate, putamen, and cerebellum were measured on four, three, and two planes respectively, and right and left regions were delineated. These regions were then projected to the dynamic scans to obtain concentrations of ^{11}C versus time, which were used to calculate the distribution volumes using a graphical analysis technique for reversible systems that does not require arterial blood sampling (Logan et al., 1996). We computed the ratio of the distribution volume in the caudate and putamen to that in the cerebellum. The distribution volume ratio (DVR), which corresponds to $B_{max}/K_d + 1$, was used as an estimate of D_2/D_3 receptor availability ([^{11}C]raclopride images) and of DA transporter availability ([^{11}C]cocaine images).

For [^{11}C]raclopride and for [^{11}C]cocaine differences between non-SD and SD were tested with paired t tests on the B_{max}/K_d measures (left and right regions were averaged into one measure). Pearson's product moment correlations were used to assess the association between the changes in B_{max}/K_d measures for [^{11}C]raclopride and for [^{11}C]cocaine (SD − non-SD/non-SD × 100) and the change in the behavioral and cognitive measures (SD − non-SD). To test the two main hypotheses of the study (SD would increase DA) and that these differences would be associated with fatigue (increased desire to sleep and tiredness and decreases in rested) and deterioration in cognitive performance (visual attention and working memory tests), we set significance at $p < 0.05$.

To corroborate the location where the changes in the specific binding of [^{11}C]raclopride and of [^{11}C]cocaine occurred and to assess whether there were regions other than the striatum where SD changed specific binding, we also analyzed the distribution volume ratio images using statistical parametric mapping (SPM), which enabled us to make comparisons on a pixel by pixel basis (Friston et al., 1995). Paired *t* tests were performed to compare the non-SD and the SD conditions ($p < 0.005$, uncorrected; cluster threshold >100 voxels).

Table 1. Self-reports for behavioral descriptors and for the accuracy scores on the visual attention and the working memory tasks for the non-SD and SD conditions

	Non-SD	SD	*t* test
Behavioral measures			
Desire to sleep	3.5 ± 3	7.7 ± 2	$p < 0.001$
Tired	3.0 ± 2	6.5 ± 3	$p < 0.003$
Rested	7.5 ± 2	3.6 ± 3	$p < 0.0003$
Mood	6.7 ± 2	6.5 ± 2	NS
Cognitive measures			
Visual attention			
Two balls	95 ± 8	86 ± 16	$p < 0.06$
Three balls	96 ± 4	79 ± 21	$p < 0.009$
Four balls	86 ± 10	66 ± 20	$p < 0.006$
Working memory			
Zero back	99 ± 2	92 ± 10	$p < 0.04$
One back	97 ± 4	94 ± 8	NS
Two back	86 ± 7	83 ± 8	NS

The scores for the performance on visual attention and working memory tasks for the three levels of difficulty are shown. Values represent mean ± standard deviation. Significance levels for the comparisons are shown (paired two-tail *t* tests).

To assess whether regions other than the striatum that were identified as differing between SD and non-SD by SPM were significant, we extracted ROIs independently from those identified by SPM using an automated method as described previously (Volkow et al., 2003). This automated method projects the individual's images (distribution volume ratio images) into the Talairach brain and then uses an inverse mapping procedure to extract the coordinates of the voxels located in the thalamus and the occipital regions (as defined by the Talairach Daemon database), which were the regions identified as significant by SPM. Because these were a posteriori comparisons, we set the level of significance for comparison between SD and non-SD conditions to $p < 0.005$. Significance for the correlations between changes in behavioral measures and DA changes in extrastriatal regions (a posteriori analysis) was set at $p < 0.005$, and p values < 0.05 are reported as trends. We also used SPM to compute the pixel by pixel correlations between the changes in the behavioral measures and the changes in radioligand binding, which were done to corroborate the ROI findings.

Results

Behavioral and cognitive effects of SD

SD significantly increased self-reports for "desire to sleep" and "tired" and significantly decreased self-reports of "rested." Self-reports of "mood" did not differ in SD and non-SD conditions (Table 1). SD significantly decreased performance accuracy on the VA task (all difficulty levels), whereas it decreased performance on the WM task only for the zero-back level (Table 1). SD did not change reaction times in these tests (data not shown). The correlations between the SD-induced changes in the behavioral and the cognitive measures were not significant.

Effects of SD on [^{11}C]raclopride and [^{11}C]cocaine binding

SD did not change the specific binding of [^{11}C]cocaine (B_{max}/K_d measures) in the caudate or putamen (Fig. 1). In contrast, SD significantly decreased the specific binding of [^{11}C]raclopride (B_{max}/K_d measures) in the caudate and putamen when compared with non-SD (Fig. 1).

The results obtained using SPM on the [^{11}C]cocaine images (transformed to DVR) revealed no differences in the striatum but showed decreases ($p < 0.005$) in an area in the left thalamus ($t = 2.92$; $p < 0.002$; Talairach coordinates: −18, −8, 10). However, this thalamic region did not achieve significance after correction for cluster size ($p = 0.27$) (Fig. 2).

SPM analysis of the PET [^{11}C]raclopride images (transformed to DVR) corroborated the significant decreases in binding in the striatum and also revealed decreases in the thalamus ($t = 4.9$; $p < 0.001$; Talairach coordinates: −18, −22, 0) and in a small area in the occipital cortex ($t = 5.0$; $p < 0.001$; Talairach coordinates: 14, −84, 4). The thalamic region remained significant after cluster correction but the occipital region did not, which suggests that it most likely reflected statistical noise (Fig. 2). The ROI analysis corroborated the significant decreases in B_{max}/K_d in the thalamus with SD ($t = 3.8$; $p < 0.002$).

Correlations between changes in [^{11}C]raclopride binding and behavior

The correlation analysis between the changes in D_2 receptor availability (B_{max}/K_d) with SD and the changes in the behavioral self-reports were significant, showing a negative correlation of "tired" and D_2 availability in the caudate ($r = 0.83$; $p < 0.0001$) and putamen ($r = 0.59$; $p < 0.02$). For "desire to sleep," the correlation was negative for D_2 availability in the caudate ($r = 0.72$; $p < 0.003$). For "rested," the correlation was positive for changes in D_2 availability in the caudate ($r = 0.7$; $p < 0.002$) and showed a similar trend in the thalamus ($r = 0.55$; $p < 0.04$) (Fig. 3). The pixel by pixel correlations done with SPM corroborated these associations; the results for the correlations with changes in "tired" (negative) and "rested" (positive) are shown in Figure 2.

Correlations between changes in specific binding of [^{11}C]raclopride and cognitive measures

The correlations between changes in D_2 receptor availability and changes in performance in the VA task were significant for putamen (two and three-ball levels of difficulty) for the caudate (four-ball level) and thalamus (three levels of difficulty): the greater the changes in specific binding, the greater the deterioration (Table 2). The correlations with WM were much weaker and were significant only in putamen (one-back level). Averaging the scores across the three levels of difficulty yielded stronger correlations both for the VA task showing significant correlations with the putamen ($r = 0.79$; $p < 0.001$), thalamus ($r = 0.80$; $p < 0.001$), and caudate ($r = 0.56$; $p < 0.05$), and for WM showing significant correlations with putamen ($r = 0.71$; $p < 0.004$), and a trend in the thalamus ($r = 0.57$; $p < 0.03$) (Fig. 4). The correlations on the changes in binding of [^{11}C]raclopride between the regions were significant between the caudate and putamen ($r = 0.68$; $p < 0.006$) and between the caudate and thalamus ($r = 0.67$; $p < 0.006$), which would indicate that these findings do not allow us to determine whether the association of the cognitive measures with the regional changes in [^{11}C]raclopride binding were regionally specific.

Discussion

Here, we show that SD decreased the specific binding of [^{11}C]raclopride in the striatum and thalamus, but not that of [^{11}C]cocaine, and that the decreases in [^{11}C]raclopride binding were associated with subjective measures of fatigue and with deterioration in cognitive performance.

Decreases in binding of [^{11}C]raclopride with SD

We interpret the findings of decreases in the specific binding of [^{11}C]raclopride as an indication of increases in DA release with SD. This is consistent with findings from a pilot single-photon emission-computed tomography study in depressed patients that showed decreases in striatal binding of the D_2 receptor radioligand [^{123}I]iodobenzamide (also sensitive to competition with endogenous DA) in five patients that reported a beneficial effect of SD in their mood, although it showed no changes in patients that

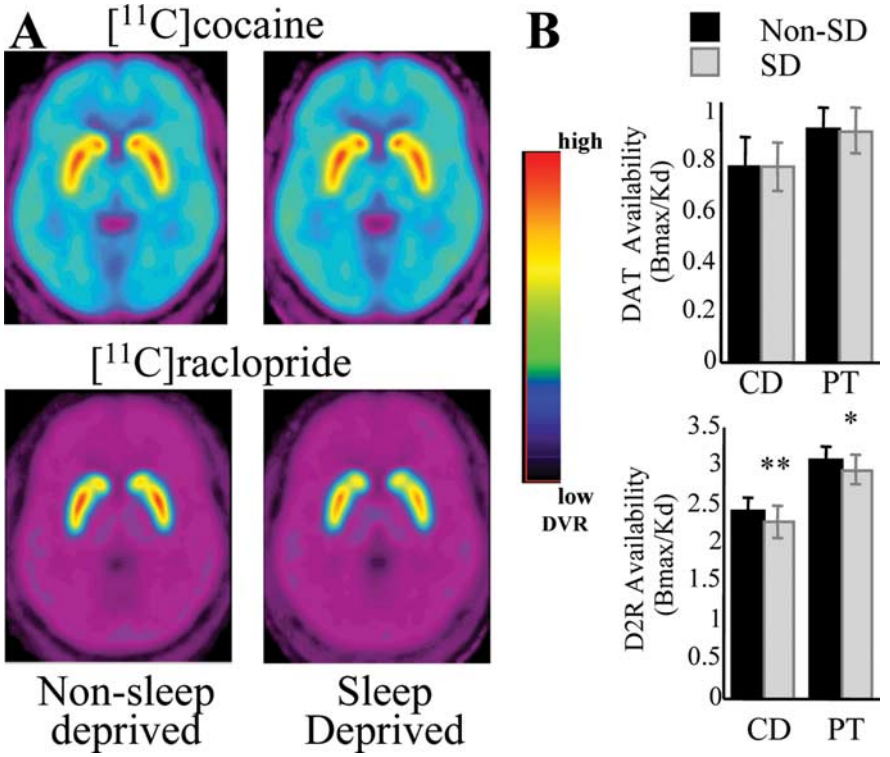

Figure 1. ***A***, Averaged brain images of the distribution volume ratio for [^{11}C]cocaine and for [^{11}C]raclopride at the level of the striatum for the non-SD and SD conditions. ***B***, B_{max}/K_d in the caudate (CD) and putamen (PT) for [^{11}C]cocaine (measure of DAT availability) and for [^{11}C]raclopride (measure of D_2 receptor availability) for non-SD and SD. Values represent mean ± standard deviation. Comparisons correspond to paired *t* tests (2 tail): $*p < 0.05$; $**p < 0.01$.

did not improve (Ebert et al., 1994). These findings are also consistent with clinical studies that used indirect measures of brain DA activity to assess SD effects. Specifically, studies measuring prolactin, which is inhibited by DA (Jaber et al., 1996), reported significant reductions after SD (Calil and Zwicker, 1987; Kasper et al., 1988), and studies measuring spontaneous eye blink rate, which is considered a positive central marker of DA activity (Ebert and Berger, 1998), reported increases after SD (Barbato et al., 1995, 2007) in proportion to the hours subjects had been awake (Barbato et al., 2007). Moreover, DA increases with SD have been postulated to underlie the therapeutic effects of SD in major depression (Ebert and Berger, 1998).

Medications used to promote wakefulness (methylphenidate, amphetamine, and modafinil) increase extracellular DA in the striatum (Boutrel and Koob, 2004), and the potency of amphetamine to maintain wakefulness is associated with its potency to increase DA in the striatum (Kanbayashi et al., 2000). Therefore, DA increases after SD could reflect a compensatory response to maintain wakefulness and counteract a rising sleep drive (Barbato et al., 1995, 2007). Thus, the correlations between decreases in the specific binding of [^{11}C]raclopride (interpreted as DA increases) and "desire to sleep" and "tiredness" could reflect the stronger DA stimulation needed to maintain wakefulness with increasing levels of fatigue. These findings are consistent, although for the opposite state, from those reported in controls after caffeine administration, which showed that the decreases in tiredness were correlated with increases in [^{11}C]raclopride (Kaasinen et al., 2004).

The notion that DA increases with SD could reflect a sleep opposing process is consistent with a sleep/wake model that posits a dual process: a sleep drive (mediated in part through adenosine accumulation in brain) (Basheer et al., 2004) and a wakefulness-promoting process (circadian component mediated by the suprachiasmatic nucleus) (Edgar et al., 1993). DA activation could be one of the mechanisms through which the suprachiasmatic nucleus opposes the increased sleep drive that follows prolonged wakefulness (Basheer et al., 2004). The suprachiasmatic nucleus could modulate DA release in the striatum through thalamostriatal projections or via direct projections into mesencephalic DA cells (Geisler and Zahm, 2005), where it regulates expression of tyrosine hydroxylase (rate limiting enzyme in DA synthesis) (Sleipness et al., 2007). Increases in DA tone after SD could also promote arousal via its regulation of orexin/hypocretin neurons (Alberto et al., 2006) or by activation of DA cells in ventral periaqueductal gray (Lu et al., 2006).

Contrary to our hypothesis, we saw no changes in DA transporters. This suggests that DA increases with SD are driven by increased DA release, but not by reduced DA reuptake into the terminal. This is consistent with studies showing that the effects of DA on sleep/wakening are modulated by mesencephalic DA cells and not by their terminals (Bagetta et al., 1988).

Although medications that increase DA are used to maintain wakefulness, some have proposed that increases in DA could induce sleepiness. This is because clinical studies have reported that DA agonists increase somnolence in patients with Parkinson's disease (Pal et al., 2001) and in controls (Andreu et al., 1999). However, the effects of DA agonists are most likely mediated by D_2 autoreceptors (Andreu et al., 1999), which would result in DA decreases rather than increases.

However, the methodology does not allow us to exclude the possibility that decreases in [^{11}C]raclopride binding reflect a downregulation of D_2 receptors and/or changes in affinity rather than DA increases (Gjedde et al., 2005). Preclinical studies on the effects of SD on striatal D_2 receptor levels report increases (Nunes Júnior et al., 1994) as well as no changes (Wirz-Justice et al., 1981; Farber et al., 1983); although, to our knowledge, none has reported decreases. However, extrapolation is limited because most of these studies evaluated rapid eye movement SD rather than total SD.

Changes in DA D_2 receptor availability in thalamus with SD

In this study, we found a significant reduction in binding of [^{11}C]raclopride in the thalamus with SD. DA cells project into several thalamic nuclei (Freeman et al., 2001) and [^{11}C]raclopride has been used to measure D_2 receptors in the thalamus (Volkow et al., 1997; Kaasinen et al., 2004). Thus, decreases in [^{11}C]raclopride binding could reflect changes in DA neurotransmission in the thalamus with SD. The thalamus is considered a key region in modulating sleep and wakefulness and is a target of the suprachiasmatic nucleus (McCormick and Bal, 1997). Changes in [^{11}C]raclopride binding in the thalamus were associated with cognitive impairment (VA and WM). This is also consistent with findings from a recent study in nonhuman primates

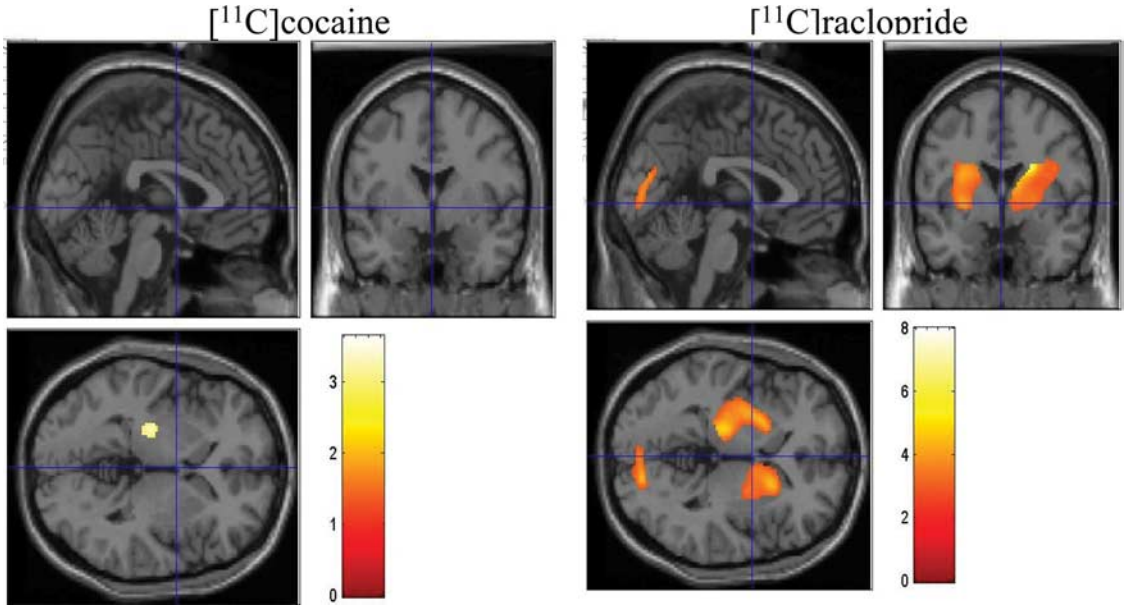

Figure 2. Brain maps obtained with SPM showing the difference in the distribution volume ratio of [^{11}C]cocaine and of [^{11}C]raclopride between non-SD and SD (non-SD > SD; $p < 0.005$, uncorrected; cluster, >100 pixels). There were no regions where specific binding was greater for the SD than the non-SD condition. Decreases in the specific binding of [^{11}C]raclopride are interpreted to reflect increases in DA.

that showed that the reduced metabolic activity in the thalamus with SD was reverted by orexin-A (potent arousal peptide) along with the behavioral impairment (Deadwyler et al., 2007). However, because the sensitivity of [^{11}C]raclopride for measuring thalamic D_2 receptors is low, we interpret this finding as preliminary. Although SD is likely to have decreased cerebral blood flow (CBF) in the thalamus, this is unlikely to account for the reduction in the specific binding of [^{11}C]raclopride in the thalamus because the distribution volume, which was used to estimate the distribution volume ratio (DV in thalamus to DV in cerebellum) does not depend on CBF (Zubieta et al., 1998).

Relationship between SD-induced changes in DA and cognitive performance

The impairment in performance in VA (and to a lesser degree in WM) with SD is consistent with previous studies (Durmer and Dinges, 2005). We also show that deterioration in performance in VA (and to a lesser degree in WM) was associated with decreased [^{11}C]raclopride binding (interpreted as DA increases). This association could reflect the involvement of DA in these tasks (Goldman-Rakic, 1995; Chudasama and Robbins, 2004). Although this may seem paradoxical, because DA agonists in preclinical models have been shown to improve cognitive performance (Goldman-Rakic, 1995), others have shown that stimulant medication can impair performance on WM and attention tasks (Murphy et al., 1996; Chudasama and Robbins, 2004). Similarly, in healthy humans, medications that increase DA (i.e., stimulants) can improve cognitive performance with SD (Bonnet et al., 2005), but this is not always the case (Bray et al., 2004) and in some subjects stimulants impair performance (Mattay et al., 2000). The fact that DA stimulation in some instances improves cognitive performance but that excessive stimulation impairs it has led some to propose a model that posits an "inverted-U-shaped curve" for the relationship between DA stimulation and cognitive performance (Mattay et al., 2000). This model proposes a lower and an upper threshold level of DA stimulation required for optimal performance. Indeed, preclinical and clinical studies have shown improvement in cognitive performance with low doses of amphetamine but impairment with higher doses (Aultman and Moghaddam, 2001; Tipper et al., 2005).

However, because modulation by DA of WM and attention is mediated in part through the prefrontal cortex (Goldman-Rakic, 1995; Chudasama and Robbins, 2004), we cannot exclude the possibility that DA changes in the striatum and thalamus may be an epiphenomenon (e.g., fatigue-induced increases that are proportional but not causal to the deterioration in cognitive function).

Study limitations

The limited sensitivity of the [^{11}C]raclopride methodology restricted our measures to regions with relatively high concentrations of D_2 receptors (striatum and thalamus), but were unable to measure regions with relatively low concentrations (prefrontal cortex). The restricted spatial resolution of PET did not allowed us to measure small regions such as the ventral periaqueductal gray where damage to DA cells results in decreased wakefulness (Lu et al., 2006).

As discussed, the [^{11}C]raclopride method does not allow us to ascertain whether changes in binding reflect changes in DA, in D_2 receptor levels, or in affinity (Gjedde et al., 2005).

We did not obtain electroencephalographic measures, which would have provided us with quantitative measures of duration of sleep (non-SD condition) and assurance that subjects did not fall asleep (SD condition or during scanning). However, a research assistant remained with the subjects during both nights (to ensure they went to bed for the non-SD condition and that they stayed awake for the SD condition), and a nurse remained by the side of the subjects throughout all of the imaging procedures to ensure that they would not fall asleep.

Summary

Here, we show that one night of SD increases DA in the striatum and thalamus. Because DA enhancing drugs help to maintain

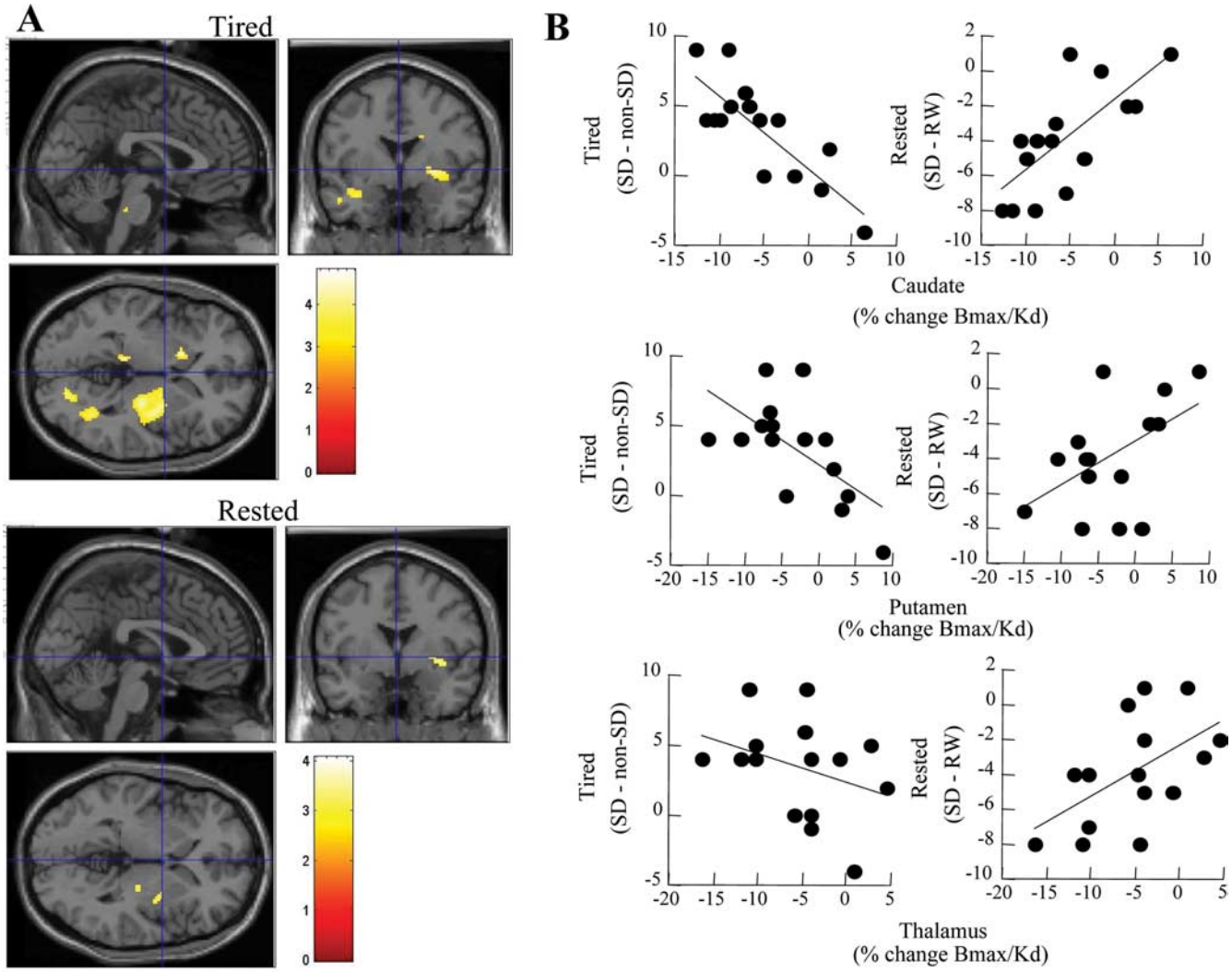

Figure 3. ***A***, SPM maps of the correlations between changes in the specific binding of [^{11}C]raclopride with SD (percentage changes from non-SD) and changes with SD in self-reports of "tiredness" (negative correlations) and "rested" (positive correlations) with respect to the non-SD condition ($p < 0.005$, uncorrected). ***B***, Regression slopes between the changes in the specific binding of [^{11}C]raclopride (percentage changes in B_{max}/K_d from non-SD) and changes in "tiredness" in the caudate ($r = 0.83$; $p < 0.0001$), putamen ($r = 0.59$; $p < 0.02$), and thalamus ($r = 0.34$; $p = 21$), and for changes in "rested" and caudate ($r = 0.7$; $p < 0.002$), putamen ($r = 0.49$; $p < 0.06$), and thalamus ($r = 0.55$; $p < 0.04$).

Table 2. Correlations between the changes (non-SD − SD) in the behavioral measures and the accuracy scores on the VA and WM tasks and percent changes in the specific binding of [^{11}C]raclopride (non-SD − SD/non-SD × 100) in caudate, putamen, and thalamus

	Caudate	Putamen	Thalamus
VA			
Two balls	NS	$r = 0.72, p < 0.004$	$r = 0.58, p < 0.03$
Three balls	NS	$r = 0.72, p < 0.004$	$r = 0.70, p < 0.005$
Four balls	$r = 0.53, p < 0.05$	NS	$r = 0.65, p < 0.01$
WM			
Zero back	NS	NS	NS
One back	NS	$r = 0.54, p < 0.04$	NS
Two back	NS	NS	NS

wakefulness, we postulate that the DA increases serve to maintain arousal as the drive to sleep increases.

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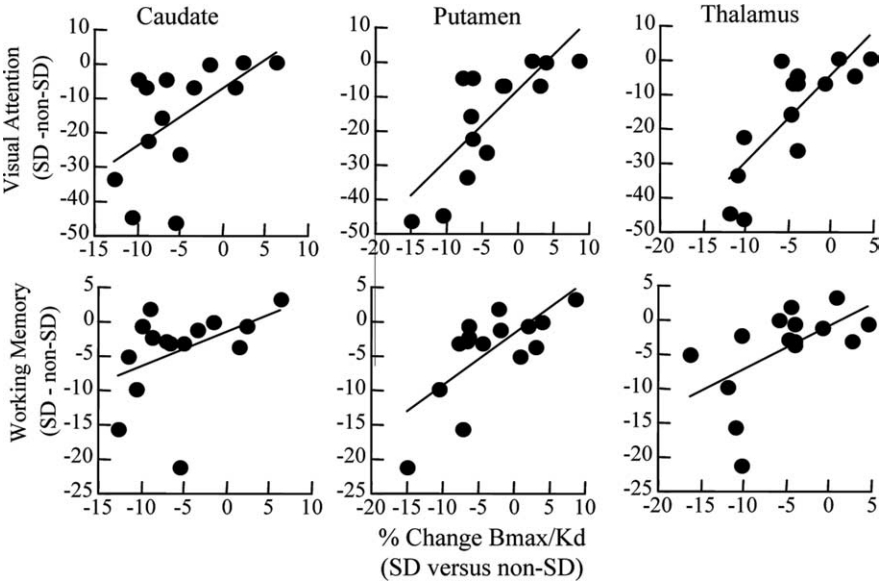

Figure 4. Regression slopes between the changes in the specific binding of [^{11}C]raclopride (percentage changes in B_{max}/K_d from non-SD) and changes in cognitive performance (SD − non-SD) for the visual attention task in the caudate ($r = 0.56$; $p < 0.05$), putamen ($r = 0.79$; $p < 0.001$), and thalamus ($r = 0.79$; $p < 0.001$), and for the working memory task in the putamen ($r = 0.71$; $p < 0.004$) and thalamus ($r = 0.57$; $p < 0.03$).

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