A Genetic Polymorphism of the Human Dopamine Transporter Determines the Impact of Sleep Deprivation on Brain Responses to Rewards and Punishments

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Abstract

■ Despite an emerging link between alterations in motivated behavior and a lack of sleep, the impact of sleep deprivation on human brain mechanisms of reward and punishment remain largely unknown, as does the role of trait dopamine activity in modulating such effects in the mesolimbic system. Combining fMRI with an established incentive paradigm and individual genotyping, here, we test the hypothesis that trait differences in the human dopamine transporter (DAT) gene—associated with altered synaptic dopamine availability—govern the impact of sleep deprivation on neural sensitivity to impending monetary gains and losses. Consistent with this framework, markedly different striatal reward responses were observed following sleep loss depending on the DAT functional polymorphisms, such that only participants with elevated trait-synaptic dopamine expressed amplified striatal response during anticipation of monetary gain following sleep loss. Moreover, significantly different neural reactivity to impending monetary punishment was also observed following sleep deprivation based on the DAT functional polymorphisms: only participants with reduced trait-synaptic dopamine suffered a blunting in anterior insula responses during anticipation of monetary loss following sleep loss. Together, these data support a mechanistic role of trait dopaminergic function in determining the interaction between sleep deprivation and neural processing of rewards and punishments. These findings may have clinical implications in disorders where the DAT genetic polymorphism presents a known risk factor with comorbid sleep disruption, including attention hyperactive deficit disorder and certain symptoms of substance abuse. ■

INTRODUCTION

Dopamine-related brain circuits modulate the approach toward rewards and avoidance of punishments, thus guiding motivated behaviors (Knutson & Greer, 2008; Nitschke, Sarinopoulos, Mackiewicz, Schaefer, & Davidson, 2006). Dopaminergic projection areas in the nucleus accumbens (NAcc) and anterior insula have consistently been implicated in the anticipation of gains and losses. Furthermore, abnormal responses in these neural circuits—due to genetics, disease, or environmental factors—have been linked to a range of disadvantageous outcomes, including suboptimal risk-taking, deficits of attention, mood disturbance, and addiction (Knutson & Greer, 2008).

Independent of these findings, emerging evidence indicates that sleep deprivation can disrupt dopaminergic function by modifying dopamine receptor sensitivity and availability in animal models (Volkow et al., 2012; Tufik, 1981). However, neural evidence that sleep deprivation alters human brain activity during incentive processing, particularly in the NAcc and anterior insula, has been inconsistent. Some reports have demonstrated significant disruptions (Mullin et al., 2013; Venkatraman, Huettel, Chuah, Payne, & Chee, 2011; Venkatraman, Chuah, Huettel, & Chee, 2007), but others indicate a lack of significant difference (Libedinsky et al., 2011, 2013; Menz, Buchel, & Peters, 2012).

At least two possible, yet currently unexplored, factors might account for these inconsistent findings. First, experiments reporting significant effects focused on tasks that employed mixed gamble stimuli, which combine both gains and losses in the same trial. This may limit the ability to identify unique differences in processing of gain or loss independently, an issue of special relevance considering that the neural representations of gains and losses are at least partially distinct (Knutson & Greer, 2008). Second, individual differences (including genetic polymorphisms that alter incentive brain processing) may interact with sleep deprivation, obscuring differences when not explicitly considered.

One candidate for individual differences in dopamine function involves the polymorphism on the dopamine transporter (DAT) gene, which has been associated with altered dopamine availability (Aarts et al., 2010). Individual differences in this genetic polymorphism may modulate incentive brain processing during sleep deprivation due to the functional influence of the DAT polymorphism on (a) synaptic dopamine function, (b) brain reactivity to

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doi:10.1162/jocn_a_00939

reward (Aarts et al., 2010), and (c) sleep homeostasis (Holst et al., 2014). Furthermore, characterizing the interaction between trait dopamine genetics, sleep deprivation, and reward brain activity has potential clinical importance, because sleep disruption is highly comorbid with numerous psychiatric and neurological conditions associated with dysregulated dopaminergic reward processing, including Parkinson's disease, attention hyperactive deficit disorder (ADHD), and substance abuse (Moreau, Rouleau, & Morin, 2013; Perogamvros & Schwartz, 2012)

Motivated by this evidence, we examined the effects of sleep deprivation on brain activity in the context of an established incentive paradigm that independently elicits anticipation of gain and loss. Specifically, we tracked differential effects of sleep deprivation on NAcc activity during gain anticipation and on anterior insula activity during loss anticipation. Furthermore, we tested whether individual trait differences in the DAT gene—associated with altered dopamine availability—interacted with sleep deprivation in altering neural activity during anticipation of gains and losses.

METHODS

Participants

Written informed consent was obtained from all participants, with the experimental protocol approved by the Institutional Review Board of the University of California, Berkeley. All participants were free of general medical, neurological, psychiatric, or sleep disorder diagnoses and did not report any history of drug abuse or head trauma and were free from MRI contraindications. Participants kept a regular sleep schedule (7–9 hr in bed between the hours of 10 p.m. and 10 a.m.) and abstained from drugs, alcohol, and caffeine for 3 days before each experimental session. Twenty-nine participants took part in the experiment (17 women; mean age = 20.5, SD = 1.8, three participants were left handed) and were separated into four groups according to sleep condition (rested or deprived) and genotype status (9R or 10R/10R; see Genetic Analysis below for details): (1) Sleep rested and 10R/10R: n = 7, age = 20.86, SD = 2.9, two women; (2) Sleep deprived and 10R/10R: n = 7, age = 20.86, SD = 1.8, six women; (3) Sleep rested and 9R: n = 8, age = 19.63, SD = 1.2, five women; and (4) Sleep deprived and 9R: n = 7, age = 20.57, SD = 1.3, four women.

Genetic Analysis

One method used to assess individual differences in dopaminergic function involves examining functional genetic polymorphisms, which constitute naturally occurring variations in alleles that can lead to altered gene expression and thus function (Dreher, Kohn, Kolachana, Weinberger, & Berman, 2009). Although several genes affect dopamine action, the DAT gene polymorphism is particularly well suited for examining the interaction between striatal dopamine function and sleep loss. DAT is a protein that clears synaptic dopamine after release in the striatum, homeostatically governing the fidelity of dopamine signaling (Williams & Galli, 2006). Evidence from human radioligand studies (Mill, Asherson, Browes, D'Souza, & Craig, 2002; Heinz et al., 2000; see Jacobsen et al., 2000) and in vitro models (VanNess, Owens, & Kilts, 2005; Mill et al., 2002) demonstrates that carrying at least one allele characterized by nine tandem repeats of a nucleotide base pair sequence on the 3′ untranslated region of the DAT gene ("9R carriers") results in lower levels of DAT protein and therefore higher dopamine synaptic availability. In contrast, having homozygous alleles with 10 tandem repeats ("10R homozygotes") results in lower dopamine synaptic availability. Moreover, the highest concentrations of DAT are found within the striatum (Williams & Galli, 2006; Ciliax et al., 1999), and human neuroimaging studies have demonstrated alterations in both striatal activity and mesolimbic and related cortical functional connectivity that depends on the DAT polymorphism (Zhong, Chark, Ebstein, & Chew, 2012; Aarts et al., 2010; Dreher et al., 2009). Offering a further motivated link with sleep, DAT function is necessary for the wake-promoting properties of stimulants such as cocaine and modafinil, including under sleep deprivation (Wisor et al., 2001), and recent evidence demonstrates that the DAT polymorphism has functional effects on sleep homeostasis (Holst et al., 2014).

Thus, investigating individuals with trait differences in the DAT polymorphism offers a unique human in vivo opportunity (advocated when studying candidate gene targets; Meyer-Lindenberg, 2012) to examine dopamine-related incentive brain functioning following sleep deprivation.

To assess this genetic variation, saliva samples were collected from participants using Oragene kits (DNA Genotek, Inc., Ottawa, Ontario, Canada) after the experimental session. DNA extraction was then carried out by the Functional Genomics laboratory at the University of California, Berkeley, and genotyping was performed by the Institute for Human Genetics at the University of California, San Francisco. The polymorphism on *SLC6A3/DAT1* includes a 40-bp variable number of tandem repeats (VNTR) in the 3′ untranslated region of the gene that is repeated between 3 and 13 times, with the greatest frequency being either 9 repeats (9R) or 10 repeats (10R; Dreher et al., 2009). This information was used to classify participants into two groups: (1) those who were homozygous for the 10R allele and (2) those who were either homozygous for the 9R allele or who had one copy of the 9R allele and one copy of the 10R allele (i.e., 9R carriers). No participants carried any other number of VNTR alleles. The percentage of 10R homozygotes and 9R carriers in our sample is consistent with percentages of these allele frequencies reported previously (Holst et al., 2014; Stice, Yokum, Burger, Epstein, & Smolen, 2012; Dreher et al., 2009).

Sleep Conditions

Participants completed one of two experimental sessions: (1) a night of normal sleep in the lab or (2) a night of total sleep deprivation. All participants completed an fMRI scanning session the morning after the experimental night, with an average scan start time of 9:06 a.m. ± 46 min for the sleep deprivation group and 10:04 a.m. ± 49 min for the sleep rested group. Participants were required to keep a regular sleep schedule for 3 days before each experimental session (7–9 hr time in bed between 10 p.m. and 10 a.m.), verified by daily sleep diaries and wrist actigraphy. On average, participants obtained 8.15 hr (*SD* = 1.0) time in bed across each of the three nights preceding the sleep deprivation and 8.03 hr (*SD* = 1.0) in the three nights preceding the sleep rested condition. On the experimental night in the sleep deprivation group, participants were monitored using wrist actigraphy throughout the day and then additionally monitored in lab by trained personnel from 9 p.m. until the experiment was complete. Sleep-deprived participants accrued 24.9 hr (*SD* = 1.2) of continue wakefulness before the scan session. On the experimental night in the sleep rested condition, polysomnography sleep monitoring was recorded in the laboratory using 19-channel EEG (locations according to international 10–20 system), together with EOG at right and left outer canthi and EMG via three chin electrodes (Klem, Luders, Jasper, & Elger, 1999). Sleep-staging was performed in accordance with standardized techniques (Rechtschaffen & Kales, 1968) from the C3-A2 electrode derivation. During this polysomnography rested session, participants obtained an average of 8.4 hr (*SD* = 0.80) time asleep (average minutes ± *SD*): 48.02 ± 19.4 NREM Stage 1; 264.33 ± 51.3 NREM Stage 2; 80.83 ± 45.6 NREM SWS (Stages 3 and 4); 112.21 ± 32.8 REM sleep. Note that one participant was excluded from this sleep summary because of a technical problem in the sleep recording resulting in missing data.

Monetary Incentive Delay Task

The monetary incentive delay task included both a gain condition (where money could be won) and loss condition (where money could be lost) and associated with discrete neural responses (Knutson & Greer, 2008). Each trial begins with a cue indicating potential monetary gain (circle symbol) or loss (square symbol) of a certain amount of money (Figure 1), followed by an anticipatory fixation. Next, during a 2000-msec time window, a target briefly appears (180–280 msec), and participants attempt to press a button before the target is replaced by a fixation cross. Finally, participants see the outcome of their performance (whether they "hit" or "missed" the target) and their cumulative session earnings. The target duration is individually set for each participant, based on a practice session before the scan, and adapted throughout the task so that

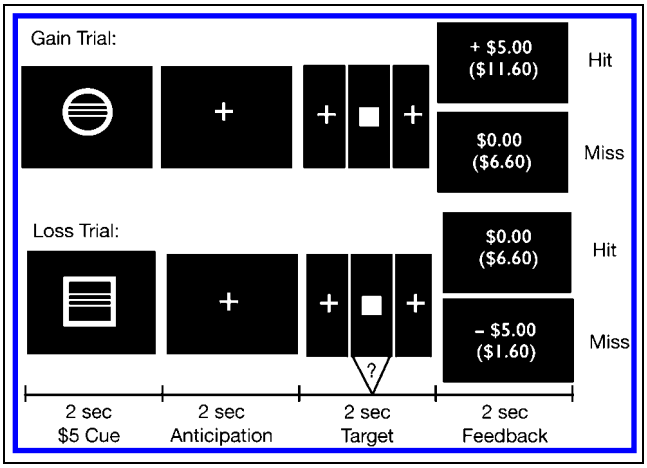

Figure 1. Monetary incentive delay task trials. One of eight monetary cues (gain: $0, $0.20, $1, $5; loss: $0, −$0.20, −$1, −$5) is followed by a fixation and then a jittered target presentation. The participant must respond as quickly as possible to the target in order to win (or avoid losing) the cued incentive, with outcome success signaled thereafter.

the overall success rate is ~66% for each cue type. This importantly ensures that the difficulty (and end payout) is approximately equivalent across participants and across the sleep rested and sleep-deprived states.

Eight cue types were used (gain: $5, $1, $0.20, $0 and loss: $5, $1, $0.20, $0), providing a parametric manipulation of the extent of potential gains and losses (Knutson & Greer, 2008). The value of each cue was explicitly told to the participants before the session and participants completed a short "quiz" on cue values before scanning to ensure that they understood the cue meanings. A total of 120 trials were administered in pseudorandom order, divided evenly among gain and loss trials, as well as the four incentive magnitudes.

fMRI Scanning Acquisition

BOLD contrast functional images were acquired with echo-planar T2*-weighted imaging using a Siemens 3-T MRI scanner with a 12-channel head coil. Each image volume consisted of 32 ascending 3.5 mm slices (96 × 96 matrix; repetition time = 2000 msec; echo time = 28 msec; voxel size 2.5 × 2.5 × 3.5 mm, field of view = 224 mm, flip angle = 90°). One high-resolution, T1-weighted structural scan was acquired at the end of the sleep rested session (256 × 256 matrix; repetition time = 1900; echo time = 2.52; flip angle = 9°; field of view = 256 mm; 1 × 1 × 1 mm voxels). Concurrent eye tracking was utilized to further verify wakefulness during all scans. The scan session was split into two scanner acquisition runs with 60 trials each.

fMRI Scanning Preprocessing

Preprocessing and data analysis were performed using Statistical Parametric Mapping software implemented in

Matlab (SPM8; Wellcome Department of Cognitive Neurology, London, UK). First, scan-to-scan variance was assessed for quality assurance using time-series difference analysis (imaging.mrc-cbu.cam.ac.uk/imaging/DataDiagnostics) and individual scans with suprathreshold shifts (indicating high subject movement) were removed and replaced with the average of surrounding scans, these time points were subsequently modeled out with "dummy" regressors (this affected six participants in total). Images were then corrected for slice timing, and time series were linearly detrended, motion-corrected, and smoothed using a 6-mm FWHM Gaussian kernel. Time series for each voxel were high pass filtered (width of 128 sec) before submission to statistical analysis.

General Linear Model

A separate general linear model was constructed for each participant, which included (1) all gain anticipation period onsets for each trial convolved with a canonical hemodynamic response function with a 4-sec duration, (2) a parametric regressor of increasing reward value (for gains from \$0 to \$5) convolved with a canonical hemodynamic response function with a 4-sec duration (this was the regressor of interest), (3) all gain outcome period onsets for each trial convolved with a canonical hemodynamic response function with a 2-sec duration, (4) a parametric regressor of gain trial outcomes (hits = +1; misses = −1) convolved with a canonical hemodynamic response function with a 2-sec duration, (5–8) the same regressors described for 1–4 were also defined for the loss condition, and (9) six movement-related covariates (three rigid body translations and three rotations determined from the realignment preprocessing step). Separate regressors were used within the same model for each of the two scanner acquisition runs. All canonical hemodynamic response functions refer to the default hemodynamic response function in SPM8. First-level general linear models were run on the functional scans in participant space, and coordinate maps were transformed to standardized MNI space before implementation of the second-level analysis.

ROI Analysis

In accordance with recommended ROI reporting policies (Poldrack, 2007), ROIs were taken as the average parameter estimates from 4-mm spheres centered around MNI coordinates from previous literature on reward-motivated action (Harsay et al., 2011) for the ventral striatum (L: −12, 18, −8; R: 6, 10, −6) and loss anticipation (Wu, Bossaerts, & Knutson, 2011) for the right anterior insula (R: 36, 27, −1). Both of these regions have substantial dopaminergic innervation and have been reliably linked to motivated behavior (Haber & Knutson, 2010). The parameter estimates from the voxels in these ROIs were averaged for each participant and then entered into a two-way ANOVA across participants using the MATLAB (The MathWorks, Inc., Natick, MA) function anova2 with factors of sleep condition (rested or deprived) and DAT status (10R homozygous or 9R carriers).

RESULTS

Effects of Sleep Deprivation and Dopamine Polymorphism on Gain Anticipation

Consistent with several previous reports (Libedinsky et al., 2011, 2013; Menz et al., 2012), sleep deprivation did not have a significant main effect on NAcc ROI activity during the anticipation of monetary gain, relative to the rested condition (Figure 2A). This was also true when using a whole-brain analysis rather than the a priori ROI approach, even at a liberal threshold (Table 1). However, supporting the experimental hypothesis, there was a significant Sleep condition by Genotype interaction for NAcc activity during anticipation of monetary gain (p = .01; Figure 2B). Post hoc t tests revealed that the 9R carriers—associated with elevated phasic striatal dopamine—expressed significantly amplified reward responsively relative to the 10R homozygotes following sleep deprivation (p = .005), as well as the 9R carriers in the sleep rested

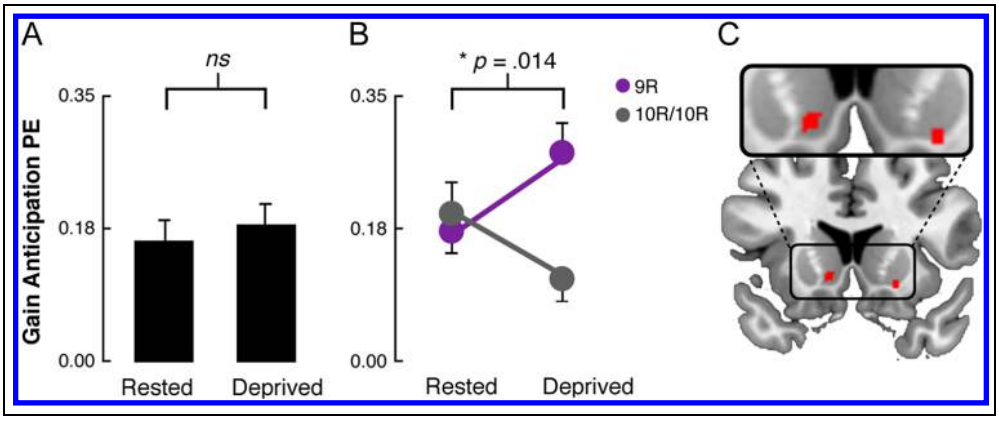

Figure 2. Neural responses to gain anticipation in the NAcc by sleep condition and genotype. Overall, NAcc activity showed no sleep condition differences during gain anticipation (A); however, there was a significant sleep condition (rested or deprived) by DAT genotype (9R or 10R/10R) interaction of activity during gain anticipation (p = .01; B and C). Brain image is threshold at p < .005 uncorrected for display purposes.

Table 1. Exploratory Whole-brain Analysis Showing All Peak Activations (MNI Coordinates) Significant at $p < .001$ Uncorrected (20 mm^3 Cluster Criteria) for Paired Comparison (Sleep Rested <> Sleep Deprived) of the Parametric Contrast of Gain Anticipation and Loss Anticipation

Region	*T*	*Cluster Size*	*X*	*Y*	*Z*
Rested > Sleep Deprived: Gain Anticipation					
R lingual gyrus	4.57	144	16	−62	10
	3.74		22	−68	18
L cerebellum	4.33	40	−40	−40	−44
L inferior frontal lobe	4.27	32	−46	12	18
L inferior frontal lobe	4.20	30	−32	10	22
	3.59		−24	20	22
L cerebellum vermis	3.98	44	−2	−70	−16
Rested > Sleep Deprived: Loss Anticipation					
R fusiform gyrus	4.26	57	24	−78	−10
	3.64		12	−82	−6
L inferior frontal opercular	4.23	38	−26	2	26
R lingual gyrus	3.80	26	4	−60	12
L middle frontal	3.77	22	−24	16	30
Sleep Deprived > Rested: Gain Anticipation					
R frontal middle gyrus	4.32	69	48	16	52
	3.94		46	24	50
	3.64		42	12	58
L frontal middle gyrus	4.16	26	−48	26	46
Sleep Deprived > Rested: Loss Anticipation					
None					

condition ($p = .05$). No significant changes in NAcc reward reactivity were observed across sleep conditions in the 10R homozygotes ($p = .13$).

Therefore, markedly different NAcc reward responses were observed following sleep deprivation depending on the DAT functional polymorphism, with elevated trait-synaptic dopamine (represented by the 9R carriers) leading to heightened striatal reward reactivity under conditions of sleep deprivation, relative to the 10R homozygotes.

Effects of Sleep Deprivation and Dopamine Polymorphism on Loss Anticipation

As with monetary gain, no significant main effects of sleep deprivation were identified during monetary loss anticipation in anterior insula activity, either using the a priori ROI approach (Figure 3A) or a whole-brain investigation (Table 1). However, there was a significant Sleep condition by Genotype interaction in anterior insula activity during loss anticipation, consistent with the experimental hypothesis ($p = .01$; Figure 2B). Although similar to the interaction for gain reactivity in the NAcc, post hoc *t* tests revealed that the loss-dependent anterior insula interaction was driven by the 10R homozygous group—those associated with reduced synaptic striatal dopamine—expressing a significant reduction in loss anticipation reactivity under sleep deprivation compared with the sleep rested condition ($p = .03$). There were no significant differences in loss activity in the anterior insula between the rested and deprived conditions in the 9R carrier group and nonsignificant trends in response difference between the two genetic groups in the sleep rested condition ($p = .075$) and between the two genetic groups in the sleep-deprived condition ($p = .085$).

Thus, significantly different anterior insula response profiles were observed following sleep deprivation depending on the DAT functional polymorphism, as was the case for gain-associated NAcc activity. Specifically, reduced trait-synaptic dopamine (represented by the 10R homozygotes) resulted in a blunted anterior insula activity in response to monetary losses following sleep deprivation, relative to the sleep rested condition.

DISCUSSION

This study provides an initial exploration of interactions between sleep deprivation and genetics on incentive processing. Despite a relatively modest sample size, these findings (1) independently characterize the impact of sleep loss on distinct neural substrates of reward (monetary gain) and punishment (monetary loss) processing, thereby helping to reconcile findings of previous sleep deprivation studies in which these opposing incentive factors were combined in the same trial, and (2) determine the interactive influence of genetic trait dopaminergic variants and sleep deprivation on neural processing of rewards and punishments.

Distinct Processing of Gain and Loss following Sleep Deprivation

To date, investigations into the neural consequences of sleep deprivation on incentive processing have largely focused on paradigms that combine potential gain and loss outcomes to assess risk taking behavior (Mullin et al., 2013; Venkatraman et al., 2007, 2011; Killgore, Balkin, & Wesensten, 2006). These studies attributed observed neural and behavioral shifts in risk taking to changes in valuation of gains (specifically, increases) and losses (specifically, decreases). However, more recent reports have questioned the gain/loss valuation hypothesis because

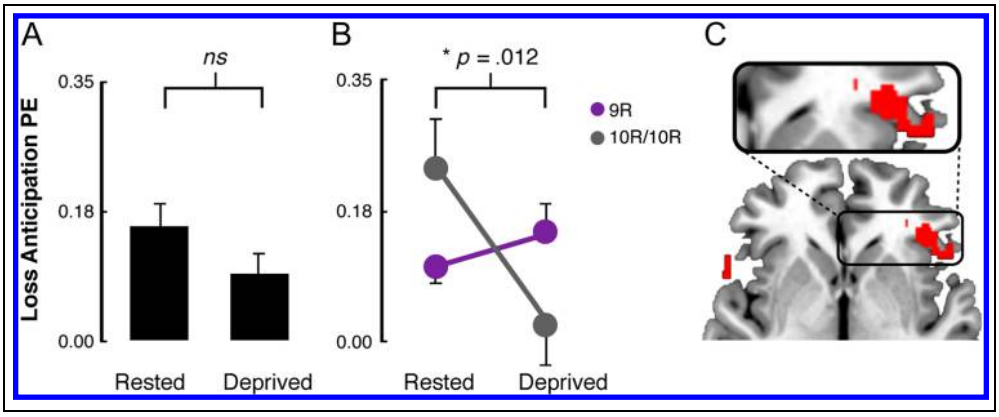

Figure 3. Neural responses to loss anticipation in the anterior insula by sleep condition and genotype. Overall, anterior insula activity showed no sleep condition differences during loss anticipation (A); however, there was a significant sleep condition (rested or deprived) by DAT genotype (9R or 10R/10R) interaction of activity during loss anticipation (p = .01; B and C). Brain image is threshold at $p < .005$ uncorrected for display purposes.

of new contradictory evidence (Libedinsky et al., 2013; Menz et al., 2012).

After distinguishing anticipation of gains and losses in distinct trials, we did not observe group-level effects of sleep deprivation on neural activity during anticipation of either monetary gains or monetary losses. Therefore, a more parsimonious explanation for previous findings may be that sleep deprivation reduces the ability to integrate competing incentives (i.e., gains and losses), rather than a biased perception of either gain or loss individually. Such an account is additionally consistent with evidence that responses to conflict (i.e., cognition associated with processing conflicting options) are decreased under sleep deprivation (Menz et al., 2012). Importantly, although effects may not be evident at the group level, trait differences may still bias incentive processing on the individual level. Combined, these effects might suggest group level deficits of incentive integration under sleep deprivation in combination with individual differences in the direction of incentive bias (i.e., increased sensitivity to either gains or losses) that may depend upon dopamine genetics.

Interactions between DAT and Sleep Deprivation on Incentive Processing

Although sleep deprivation did not significantly alter incentive brain processing at the group level, when dopamine genotype subgroup was considered, significant interactions emerged. For NAcc activity during gain anticipation, sleep-deprived individuals with 9R DAT polymorphism (associated with more phasic dopamine) showed enhanced responses, relative to either 9R carriers under sleep rested conditions, or to 10R/10R carriers (associated with less phasic dopamine). Therefore, the impact of sleep loss on striatal reward processing was not universal but, instead, depended on the trait dopamine-regulating genotype status of individuals.

This finding offers several mechanistic insights into reward brain processing under conditions of sleep loss. First, sleep deprivation has previously been shown to reduce the availability of dopamine D2/D3 receptors in the human striatum (Volkow et al., 2012), which could suggest a potential mechanism underlying the current findings. Specifically, the unique combination of elevated phasic dopamine (here, the 9R carriers) and reduced availability of D2/D3 receptors after sleep deprivation (Volkow et al., 2012) may consequently increase the availability or receptivity of remaining D1 receptors, resulting in enhanced reward reactivity in the striatum. This appears further tenable considering that activation of postsynaptic D1 receptors may preferentially increase striatal fMRI signal (Knutson & Gibbs, 2007). Second, because D2 receptors can facilitate DAT functioning (Williams & Galli, 2006), sleep loss-related reductions of D2 receptors may impair the efficacy of the DAT protein on an individual genotype-specific basis. As a consequence, sleep deprivation may exaggerate deficits of the DAT protein in the 9R group, thereby resulting in increased phasic dopamine availability that increases NAcc reward reactivity following sleep deprivation. Third, sleep deprivation may decrease tonic dopamine (Miller, Farber, Gatz, Roffwarg, & German, 1983), "unmasking" individual differences in phasic dopamine. Although each of these mechanisms is distinct, they could also interact to produce the observed findings. Some combination of these accounts might provide a mechanistic explanation of how changes in dopamine function due to sleep deprivation can ultimately lead to individual level interactions with DAT genotype.

Genotype interactions with sleep deprivation were not limited to reward processing but also occurred in the context of punishment. Specifically, although sleep deprivation did not influence anterior insula activity during anticipation of loss at the group level, a significant interaction again emerged after accounting for individual differences in the DAT polymorphism. In contrast to the interaction of NAcc activity during gain anticipation and sleep deprivation in the 9R carriers, this interaction was driven by diminished anterior insula activity during loss anticipation in sleep-deprived 10R carriers, relative to rested conditions. In contrast, 9R carriers displayed no significant changes in anterior insula activity during loss anticipation, suggesting resilience to the impact of sleep deprivation.

Several lines of evidence may offer mechanistic insights explaining the genotypic difference between the 9R carriers and 10R homozygotes during loss anticipation. The insula, particularly the anterior (agranular) region, receives especially dense dopamine innervation from brainstem nuclei. Furthermore, dopaminergic projections to this area appear necessary for certain forms of avoidance (rather than approach) behavior (Treadway et al., 2012; Zito, Bechara, Greenwood, & van der Kooy, 1988). Therefore, the increased phasic dopaminergic activity within the 9R carriers may confer a protective benefit to the effects of sleep deprivation during loss anticipation, in contrast to enhanced phasic dopaminergic activity in the striatum during gain anticipation. As a consequence, elevated phasic dopamine action in the anterior insula of 9R carriers may negate the normal blunting of loss sensitivity caused by sleep loss seen in 10R homozygotes.

When considered together, these data indicate opposing sleep deprivation alterations in neural responses during anticipation of gains and losses on the basis of genotype. Specifically, DAT 9R carriers show increased neural responses during gain anticipation (with no changes during loss anticipation), whereas 10R homozygotes show decreased neural responses during loss anticipation (with little change during gain anticipation). Interestingly, both of these profiles could promote reward seeking in the face of mixed incentives (i.e., gain and loss trade-offs, combined), consistent with behavioral findings (McKenna, Dicjinson, Orff, & Drummond, 2007; Killgore et al., 2006). However, the current findings suggest that these two genetic subgroups may express a similar behavioral phenotype through different underlying mechanisms.

Clinical Implications

More generally, these findings may be of clinical relevance when considering disorders in which the DAT genetic polymorphism presents a known risk factor with concomitant sleep disruption. This would include ADHD (Sharp, McQuillin, & Gurling, 2009) and symptoms related to the condition of substance abuse (i.e., cue-induced craving and withdrawal; van der Zwaluw et al., 2009). In these cases, sleep disruption presents a potentially compounding risk factor, which may generate divergent pathological profiles, and thus different therapeutic responses to sleep restorative interventions, depending on an individual's dopaminergic genotype. For example, NAcc activity during reward anticipation is blunted in individuals with ADHD (e.g., Scheres, Milham, Knutson, & Castellanos, 2007), and the representation of 9R carriers is increased in ADHD (Franke, Neale, & Faraone, 2009). NAcc activity during reward anticipation, however, is not significantly influenced by DAT genotype in children with ADHD (Hoogman et al., 2013). Given recognized sleep disruptions in ADHD (Moreau et al., 2013), the present results imply that sleep deprivation might "unmask" genetic influences on the striatal function of individuals afflicted with ADHD. If correct, such findings might indicate that sleep disruption and dopaminergic genotype are interactive risk factors as well as therapeutic targets for relevant disorders.

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