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# Reduced resting-state thalamostriatal functional connectivity is associated with excessive daytime sleepiness in persons with and without depressive disorders

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ABSTRACT

*Background:* Excessive daytime sleepiness (EDS) is a common and significant problem encountered in affective illness, however, the biological underpinnings of EDS in persons with psychiatric disorders are not clear. This study evaluated the associations between thalamic connectivity with cortical and subcortical brain regions with EDS in persons with and without depressive disorders (DD).

*Methods:* Resting-state functional connectivity magnetic resonance imaging scans from 67 unmedicated young to middle-aged women with current DD (n = 30), remitted DD (n = 13), and healthy controls (n = 24) were utilized to examine the associations between thalamic connectivity with cortical/subcortical structures and EDS.

*Results:* After correction for multiple comparisons and adjustment for age, habitual sleep duration, and depressive symptomatology, reduced resting-state connectivity between the bilateral thalamus and left rostral striatum (caudate/putamen) was significantly associated with EDS.

*Limitations:* Causal inferences between thalamostriatal connectivity and EDS could not be determined.

*Conclusions:* These results further implicate the role of the striatum and thalamus as central components of the experience of EDS. Further research is indicated to clarify the specific role these structures play in EDS in psychiatric disorders.

## 1. Introduction

Excessive daytime sleepiness (EDS) is a common symptom experienced across the spectrum of psychiatric disorders, particularly affective illness. EDS has been associated with treatment resistance, symptomatic relapse, increased risk of suicide, and functional impairment in mood disorders (Plante, 2015), underscoring the need to more fully understand the neurobiological mechanisms underlying this symptom. Unfortunately, hypersomnolence in mood disorders remains poorly understood, with standard clinical measures of sleep propensity, such as the multiple sleep latency test, failing to identify EDS in the majority of patients with psychiatric disorders (Plante, 2017). Thus, technologies that utilize non-electroencephalographic measures of brain function may be more fruitful methods to evaluate the neurophysiological underpinnings of EDS in psychiatric illness.

Resting-state functional connectivity magnetic resonance imaging (rs-fcMRI) is a neuroimaging technique that estimates functional connectivity between brain regions when the subject is at "rest," and not actively engaged in any specific task (Biswal et al., 1995; Shehzad et al., 2009). In rs-fcMRI, correlated fluctuations between different parts of the brain result from synchronized spontaneous low-frequency fluctuations in the activity of neuronal networks (Biswal et al., 1995; Fox and Raichle, 2007). Recently, rs-fcMRI has demonstrated an association between daytime sleepiness and reduced connectivity between the thalamus and sensorimotor cortex in non-sleep deprived healthy persons (Killgore et al., 2015). Similar cortical areas are associated with a widely-replicated fMRI signature associated with falling asleep, in which an increase in the blood-oxygen-level-dependent signal occurs primarily in motor and sensory cortices as humans transition from wakefulness to sleep (Davis et al., 2016). Thus, this investigation sought to extend this line of inquiry to psychiatric illness, and clarify whether alterations in connectivity between the thalamus and other cortical/subcortical structures are associated with EDS in persons with and without depressive disorders (DD).

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## 2. Methods

### 2.1. Participants

Rs-fcMRI data from baseline scans conducted in 67 unmedicated (not taking psychotropic medications or hormonal contraceptives) young to middle-aged women were drawn from the Depression, Adversity, & Stress Hormones (DASH) study conducted at the University of Wisconsin (UW)-Madison. Consistent with the NIMH Research Domain Criteria (RDoC) framework (Insel, 2014), potential candidates with a range of depressive symptomatology and diagnoses were recruited. In-person assessment included the Structured Clinical Interview for DSM-IV Axis I disorders (SCID) (First et al., 2002), as well as additional questions to assess DSM-5 criteria (American Psychiatric Association, 2013). Exclusion criteria included lifetime history of mania or psychosis, substance use disorder within the preceding 6 months, significant risk for suicide, claustrophobia, or regular nicotine use. As part of the assessment battery, participants were queried regarding their habitual sleep duration, and also completed the Beck Depression Inventory-II (Beck et al., 1996) (BDI-II) and Epworth Sleepiness Scale (Johns, 1991) (ESS), to quantify the severity of depressive symptoms and daytime sleepiness, respectively. All participants provided informed consent and the UW Health Sciences Institutional Review Board approved all study procedures.

### 2.2. Rs-fcMRI

A series of magnetic resonance (MR) images were acquired using a 3-Tesla General Electric MR750 MRI scanner with an 8-channel RF coil. All scans were conducted at approximately 18:00 h. High-resolution structural T1-weighted images were obtained using a 3D IR-prepped fast gradient-echo pulse sequence (TI:600 ms, TR/TE/flip:9 ms/1.8 ms/10°, matrix:256 × 192 × 134, FOV:240 mm, slice thick:1 mm, acq time: ~ 7.5 min). Functional activation and connectivity were determined from a series of T2*-weighted echo-planar images (TR/TE/flip: 2000 ms/25 ms/60°, matrix: 64 × 64 × 40, FOV: 224 mm, slice thickness: 3.5 mm). Acquisition time was 10 min. Resting-state MR images were preprocessed using established methods that included correction for subject motion, B0-field map correction, slice-time offsets, spatial smoothing (fwhm:6 mm), and band-pass temporal filtering (0.01–0.1 Hz) (Jo et al., 2013). Resting-state MRI data was aligned to the structural T1 data prior to spatial smoothing, and warped to Talairach space based on an affine 12-parameter alignment of the structural T1-weighted data to the MNI brain. Time points in the resting-state MRI data affected by motion were censored (Power et al., 2012). The sum-squared difference between successive image volumes was < 0.2 mm. Time course of estimated subject motion and signal changes from ventricular cerebrospinal fluid and white matter were used as additional nuisance regressors (Jo et al., 2010). Functional connectivity was estimated using a seed-based approach (Biswal et al., 1995). Seed regions (left and right thalamus) were defined using the Talairach Daemon atlas (Lancaster et al., 2000). Signal intensity time courses were averaged within each seed region and then correlated against time courses from the rest of the brain. Associations between functional connectivity and daytime sleepiness scores were assessed, with adjustment for self-reported habitual sleep duration, depressive symptoms (square root of BDI score to reduce negative skew and undue influence of extreme scores), and age. Given the heterogeneous nature of diagnoses among active and remitted DD, correction for depressive symptom severity rather than evaluation of group interactions was employed. The individual voxel p-value used to define regions of interest for this analysis was 0.001. After cluster-based correction for multiple comparisons, the corrected p-value was less than 0.01 for significance (Cox et al., 2017a, b). All analyses were conducted using Analysis of Functional NeuroImages (AFNI) (Cox, 1996). The functional connectivity and multilinear regression analyses were performed using AFNI's 3dDeconvolve program.

**Table 1**
Demographic data.

| | Active DD | Remitted DD | Healthy Controls | F-statistic | p-value |
|---|---|---|---|---|---|
| N | 30 | 13 | 24 | – | – |
| Age (years) | 28.3 (7.4) | 27.6 (6.0) | 27.5 (8.1) | 0.1 | 0.90 |
| BDI-II | 19.6 (10.3) | 0.8 (1.5) | 0.9 (1.5) | 59.1 | < 0.0001 |
| ESS | 9.1 (4.3) | 5.6 (3.5) | 5.8 (3.2) | 6.6 | 0.002 |
| HSD (hours) | 7.5 (1.4) | 7.6 (0.8) | 7.0 (1.3) | 1.2 | 0.31 |

DD = depressive disorders; BDI = Beck Depression Inventory; ESS = Epworth Sleepiness Score; HSD = habitual sleep duration.

## 3. Results

Participants with active DD consisted of 15 persons with major depressive disorder (MDD), 13 persons with persistent depressive disorder (PDD), and 2 with other specified depressive disorder (OSDD; 1 short-duration depressive episode, 1 depressive episode with insufficient symptoms). Among remitted DD, 8 met criteria for prior MDD, 4 for past PDD, and 1 for prior OSDD (depressive episode with insufficient symptoms). Participants from the three groups were of similar age with comparable habitual sleep duration (Table 1). Active DD participants had significantly greater BDI-II scores relative to both remitted DD and healthy controls ($p < 0.001$, both bonferroni corrected post hoc comparisons). In addition, ESS scores were significantly higher in active DD group relative to both remitted ($p = 0.02$) and healthy control ($p = 0.006$) participants.

Functional connectivity analysis demonstrated a significant association between ESS score and connectivity between the thalamus and left rostral striatal region, including portions of the caudate and putamen (corrected p-value < 0.01). This relationship was observed using both left and right thalamic seed regions (Fig. 1), showing that reduction in thalamostriatal connectivity was associated with increased daytime sleepiness. However, associations between ESS scores and connectivity between the thalamus and neither the right putamen nor any cortical regions met study threshold for statistical significance after correction for multiple comparisons.

## 4. Discussion

This study demonstrates a significant association between resting-state thalamostriatal functional connectivity and EDS in a heterogeneous sample of patients with and without depressive illness. The implication of two subcortical areas, the thalamus and rostral striatum (caudate and putamen) in the experience of EDS is consistent with prior literature that has demonstrated these structures are critically related to the experience of hypersomnolence in humans.

The thalamus plays an important role in the maintenance of wakefulness, and is richly innervated by components of the arousal mechanism including the locus coeruleus, pedunculopontine and lateral dorsal tegmental nuclei, and orexin-containing neurons in the lateral hypothalamus (Scammell et al., 2017). Consistent with this role, cerebrovascular accidents that damage the thalamus can result in significant hypersomnolence (Bassetti et al., 1996). Moreover, the degree of reduction of glucose metabolism in the thalamus is related to the severity of daytime sleepiness induced by benzodiazepines (Volkow et al., 1995). Finally, the magnitude of dopamine receptor availability in the thalamus resulting from sleep deprivation has been associated with the degree of subsequent tiredness/sleepiness (Volkow et al., 2008).

The putamen and caudate are connected to the thalamus functionally and anatomically, and have also been implicated as important structures in EDS. In animal models, caudoputamen lesions result in

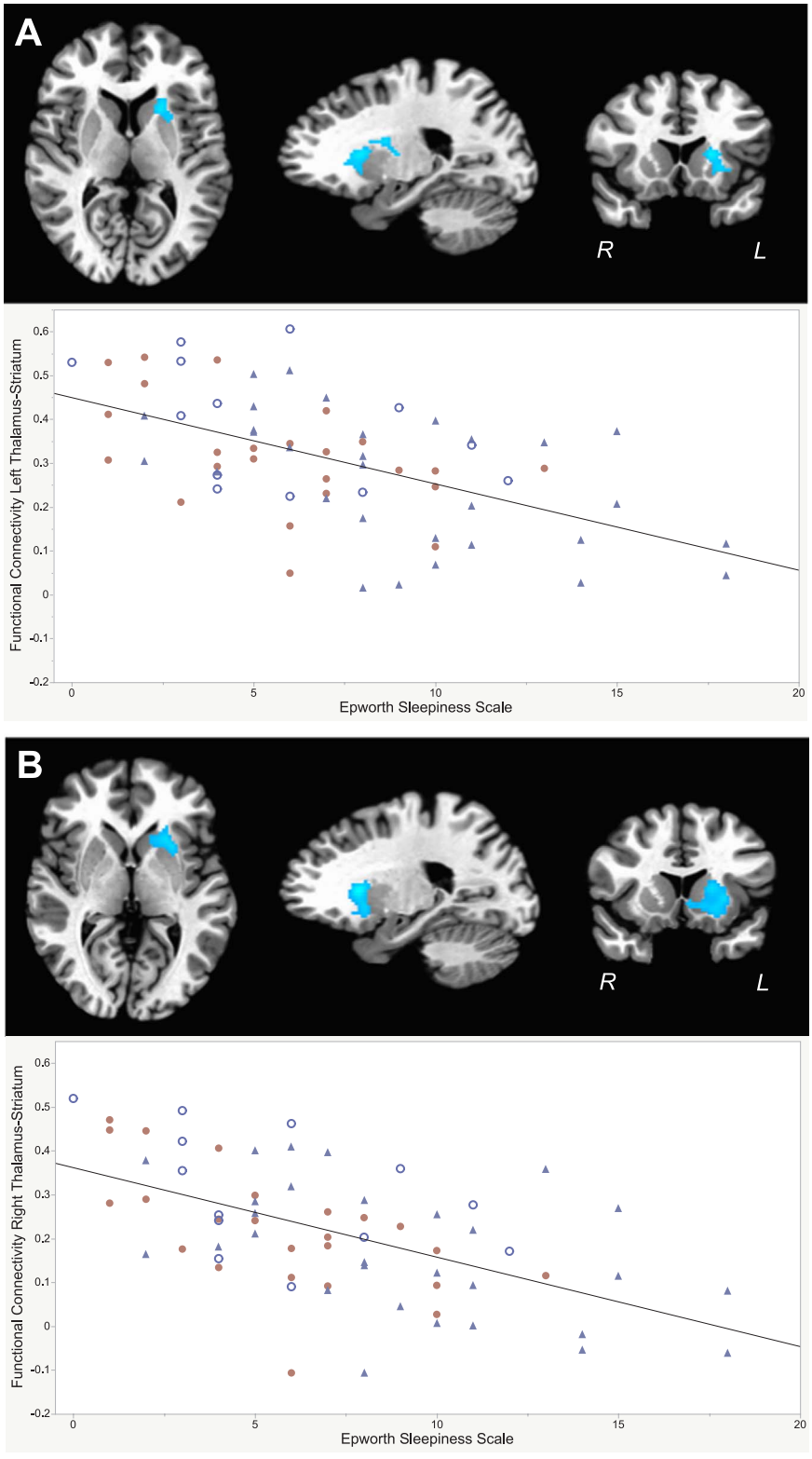


**Fig. 1.** Association between severity of daytime sleepiness and thalamostriatal functional connectivity using A) left and B) right thalamic seed regions. Blue areas displayed on magnetic resonance images denote rostral striatal regions in which functional connectivity with the thalamus were negatively associated with excessive daytime sleepiness, after adjustment for age, depression severity, and habitual sleep duration as well as correction for multiple comparisons. Scatterplots depict individual thalamostriatal functional connectivity values for each participant. Blue triangles = active DD; blue open circles = remitted DD; red closed circles = healthy controls. Increasing ESS score reflective of increased subjective daytime sleepiness.

significant reductions in wakefulness and increased sleep duration (Qu et al., 2010). In humans, the severity of daytime sleepiness that occurs in Parkinson's disease is associated specifically with the degree of dopamine transporter uptake in the bilateral caudate and putamen (Happe et al., 2007). Sleep deprivation also results in dopamine receptor downregulation in the caudate and putamen, which is in turn associated with increased sleepiness and decreased alertness in healthy persons (Volkow et al., 2008). Finally, increases in dopamine in the caudate and putamen induced by the stimulant methylphenidate are specifically correlated with increased vigilance and decreased somnolence resulting from the drug (Volkow et al., 2012).

Although we did not replicate findings of an association between reduced thalamocortical connectivity and EDS previously demonstrated in healthy persons (Killgore et al., 2015), it is noteworthy that the thalamus, rostral striatum, and pre/motor cortex are anatomically and functionally connected in a well-characterized brain circuit (Haber,

2016). This cortico-striatal-thalamic-cortical loop has long been known to be involved in motor control, however, the last several decades of work have led to significant advances in understanding how the cortex, basal ganglia, and thalamus interact to also integrate information across other domains of function including reward and cognition, as well as the control of sleep and wakefulness (Lazarus et al., 2013). Thus, our results suggest that future research that clarifies how this brain circuit is involved in the experience of EDS, particularly in mood disorders, is indicated.

## 5. Limitations

There are limitations of our study that merit discussion. First, data were gathered from a sample of convenience, for which we did not have concurrent electroencephalographic monitoring during fMRI procedures to determine if participants were awake or asleep in the scanner, which may have affected results. Since the transition from wake to sleep has been associated with increased functional connectivity between the thalamus and sensorimotor cortex (Hale et al., 2016), if somnolent participants did fall asleep in the scanner, it may have contributed to our null finding regarding relationships between EDS and thalamocortical connectivity. Second, the generalizability of results is impacted by a sample that only consisted of female participants. Finally, our data are associative in nature, and not able to demonstrate causal relationships between thalamostriatal connectivity and EDS, which would require prospective experiments that use targeted methods that modulate connectivity between these subcortical structures.

## 6. Conclusions

In conclusion, we have demonstrated a significant relationship between excessive daytime sleepiness and functional connectivity between the thalamus and rostral striatum in persons with and without depressive illness. These findings are consistent with prior literature that implicates these brain structures in the experience of EDS in humans. Future controlled research designed to test the causal role of thalamostriatal connectivity in daytime sleepiness in depression is indicated, to develop more targeted treatments for EDS in affective illness.

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