Sleep duration is associated with Caudate volume and executive function

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Abstract
The ineligible role of the caudate nucleus in sleep has been implicated. Previous literature showed that the caudate volume is associated with longer habitual sleep duration in older adults. However, the association between sleep duration and caudate volume remains unknown in the younger population. In this study, we examined the caudate volume in youth to older adults (10 to 85 years old) with a greater sample size (N=464). The volumetric size of the caudate nucleus showed significantly positive association with habitual sleep duration, especially in younger population. Sleep duration showed a significant association with executive function performance. However, caudate volume did not significantly predict executive function. Our results suggested that sleep duration is associated with the caudate volume and executive function. It is also suggested that there are some external mechanisms that modulate executive function which prevent the caudate-sleep relation’s effect on executive function.

Keywords Caudate Nucleus · Sleep duration · Executive functions · Structural imaging

Introduction
The caudate nuclei have been suggested to be a key region for sleep which may be accounted for by their role in reward/sensory processing and regulation of cortical excitability (Stoffers et al., 2014). Anatomically, caudate volume has been found to be associated with sleep duration. In older adult humans (ages 55–80), larger caudate volume was related to both longer total sleep time and the shorter Stroop response times, i.e. enhanced executive functioning, induced by mild exercise (Won et al., 2019). In a PET study, the caudate showed significant increase in activity during REM and a notable decrease in activity from pre-sleep wakefulness to slow wave sleep (Braun, 1997). While the majority of neurons in the caudate have been found most active during REM and wakefulness, a small sector of caudate neurons demonstrated heightened activity during slow wave sleep, regulating the sleep-wakefulness cycle, along with involuntary movements (Oniani et al., 2009). These findings together suggest that sleep stages may be modulated by the caudate nucleus in some way.

Caudate disruption resulting in unsuccessful sleeping patterns has been repeatedly shown. EEG results after implementing destruction of the caudate via uni- and bilateral injections of kainic acid on rats induced a constant state of alertness and inability to sleep for two days (Vataev & Oganesyan, 2000). In humans, diminished caudate recruitment was found to be associated with sleep impairment and also with subjective report of hyper-arousal, a key element of insomnia (Stoffers et al., 2014). During an awake executive function task in fMRI, the caudate showed less activity in subjects with insomnia and control subjects assigned to experience slight sleep disruption (Stoffers et al., 2014). In addition, an association was found between increased subjective reports of hyper-arousal and the decreased caudate engagement in subjects with insomnia (Stoffers et al., 2014).

The caudate nuclei are also suggested to be involved in obstructive sleep apnea (OSA). Symptoms of depression and anxiety which can accompany OSA were found to show increased correlation to substandard resting-state functional connectivity (FC) of the caudate with other areas of the brain. The bilateral caudate showed smaller
FC to the bilateral inferior frontal gyrus and right angular gyrus in OSA patients who were additionally more prone to episodes of anxiety and depression, compared to healthy controls (Song et al., 2018). These results suggest the possibility that deprived sleep due to OSA may be a result of disrupted caudate functionality. Indeed, caudate functional disconnectivity was induced by sleep deprivation in male subjects (ages 18–24 years) with healthy sleeping patterns who were subjected to 36 h of total sleep deprivation, resulting in defective functional connectivity of the left caudate with the postcentral gyrus and inferior temporal gyrus of the cortex (Wang et al., 2021). On the other hand, it has been demonstrated that stimulation of the caudate can show sedative effects. Stimulation of the caudate on cats during calm wakefulness resulted in notable behavioral changes, including drowsiness, from low frequency stimulation, and even sleep, from extended moderate stimulation (Gogichadze et al., 2017).

Sleep has been found to influence executive function. Sleep continuity has been shown to be associated with better executive function across age groups, while total sleep duration was found to only affect cognition in the younger age range (Wilckens et al., 2014). In adolescents, sleepiness but not sleep duration has been found to be associated with executive function (Anderson et al., 2009). However, while caudate recruitment was smaller in those with sleep disturbance in an executive function task, sleep disturbance did not significantly affect performance in executive function (Stoffers et al., 2014).

Previous literature strongly suggests the possible role of the caudate on sleep duration. To our best knowledge, however, the association between the caudate volume and sleep duration in other age ranges (i.e. less than 50) have not been studied. In this study, we aimed to examine the association between caudate volume and sleep length, as well as executive functioning across a wide age range in adult human MRI data. We employed a large data set (67 subjects, 10–85 years old) to assess the association.

### Table 1 Demographic information of the subjects

| N | Age ± SD (Range) | female: male | PSQI sleep hours ± SD (Range) | Rule Violation Ratio in Tower of London ± SD (Range) |
|---|------------------|-------------|-----------------------------|-----------------------------------------------|
| 464 | 42.30 ± 20.31 (10–85) | 287:177 | 6.88 ± 1.36 (3–12) | 10.03 ± 1.25 (1–11) |

#### Methods

The MRI images and the demographic data of the enhanced Nathan Kline Institute-Rockland Sample (Nooner et al., 2012) were obtained from Collaborative Informatics and Neuroimaging Suite (Biswal et al., 2010). This data subset consisted of 467 individuals (42.10 ± 20.38 years old; 288 females and 179 males; Table 1) without known neurological preconditions (such as stroke, tumor and traumatic brain damage) and MRI contraindications and with Delis-Kaplan executive function system (D-KEFS) Tower of London (Delis et al., 2001) scores as well as Pittsburgh Sleep Quality Assessment index (PSQI) scores, which measures sleep quality over the previous month through self-reporting (Buysse et al., 1989). The participants were screened for psychiatric, neurological, and chronic medical illnesses before being included. High-resolution structural T1 volume was acquired as 176 sagittal slices of 1 mm thickness (voxel size = $1 \times 1 \times 1$ mm, TR = 1900ms and TE = 2.52ms, FOV = 256). Caudate volume, as well as putamen volume, was estimated using the Freesurfer image analysis suite (version 7.2.0; http://surfer.nmr.mgh.harvard.edu). A multiple linear regression was tested to predict the PSQI (sleep length) based on bilateral caudate volume, age and sex. As a comparison test, multiple linear regression was tested to predict the PSQI (sleep length) based on bilateral putamen volume, age and sex. In order to measure executive function, rule violations per item ratio in the Tower of London task was used (Stoffers et al., 2014). To examine the association between sleep duration and executive functions, a linear regression was tested to predict the rule violations based on the PSQI (sleep length), age, and sex. In order to examine the association between the caudate volume and executive functions, a multiple linear regression was tested to predict the rule violations based on bilateral caudate volume, age, and sex. In order to test whether the relationship between age and sleep duration is mediated by caudate volume, mediation analysis was conducted using MBESS package (Kelley, 2020) on R 4.1.2. We tested the significance of this indirect effect using bootstrapping procedures. Unstandardized indirect effects and partially standardized indirect effects were computed for each of 10,000 bootstrapped samples, and the 95% confidence interval was computed by determining the indirect effects at the 2.5th and 97.5th percentiles. In order to assess the associations in different age ranges, the participants were classified into four groups: younger than 30 years old ($N=171$), 30–50 years old (110), 50–70 years old (134), and 70 years and older (48). In each age group, a linear regression was tested to predict the rule violations based on the PSQI (sleep length) based on bilateral caudate volume, age and sex. Also, a multiple linear
regression was tested to predict the rule violations based on bilateral caudate volume and age.

**Results**

Between sleep duration and caudate volume, a significant regression equation was found ($F(3, 460) = 6.67, p < 0.001$, Fig. 1) with an adjusted $R^2$ of 0.035. The predicted sleep length (hours) was equal to $5.83 + 0.00016$ (caudate volume) $- 0.0088$ (age) $+ 0.2$ (sex). Caudate volume ($p=0.017$) and age ($p<0.01$) significantly predicted sleep length. A significant regression was found in the multiple regression to predict sleep duration based on putamen volume, age and sex ($F(3, 460) = 4.76, p<0.0028$) with an adjusted $R^2$ of 0.024. However, putamen volume did not show a significant association with sleep duration ($p=0.64$), while age did ($p=0.014$).

Sleep length predicted rule violations. A significant regression equation was found ($F(1, 460) = 8.92, p<0.001$) with an adjusted $R^2$ of 0.048. The predicted rule violations were $10.02 - 0.087$ (sleep length) $+ 0.012$ (age) $+ 0.068$ (sex). Sleep length negatively ($p=0.04$) and age positively ($p<0.01$) predicted rule violations.

Although age significantly predicted rule violations, caudate volume did not predict rule violations (Fig. 2). A significant regression was found ($F(1, 463) = 7.05, p<0.001$) with an adjusted $R^2$ of 0.037, where the predicted rule violations were $9.29 + 0.000015$ (caudate volume: $p=0.79$) $+ 0.013$ (age: $p<0.001$) $+ 0.062$ (sex: $p=0.61$).

The relationship between age and sleep duration was partially mediated by caudate volume (Fig. 3). There was a significant direct effect between age and sleep duration ($\beta = -0.17, p<0.001$). The standardized regression coefficient between age and caudate volume was statistically significant, as was the standardized regression coefficient between caudate volume and sleep duration. The standardized indirect effect was $(-0.39)*(-0.12) = 0.047$. The bootstrapped partially standardized indirect effect was $-0.00076$, and the 95% confidence interval ranged from $-0.0042 : -0.00012$. Thus, the indirect effect was statistically significant.

Among four age groups, only the group of younger than 30 years old showed significant association between caudate volume and sleep length. A significant regression equation was found ($F(3, 167) = 8.32, p<0.001$) with an adjusted
6.31 + 0.00024 (caudate volume) – 0.0082 (age) + 0.53 (sex). 

\[ R^2 \text{ of 0.11. The predicted sleep length (hours) was equal to} \]

\[ 6.31 + 0.00024 \times \text{(caudate volume)} - 0.0082 \times \text{(age)} + 0.53 \times \text{(sex)} \]
No other group showed a significant association between caudate volume and sleep length. No group showed a significant association between caudate volume and executive function.

Discussion

This study examined the associations among caudate volume, sleep duration, and executive functions. (1) The caudate volume showed a significant positive association with sleep duration. (2) The sleep duration predicts executive function performance. However, (3) the caudate volume did not predict executive function performance. Also, (4) caudate volume - sleep association was limited to younger age range failing to replicate previous study.

Although previous literature is limited for the association between caudate volume and sleep duration, existing literature is consistent with suggesting positive association between the caudate and sleep length. Previously, a significant relationship between longer habitual total sleep time and greater caudate volume was found in older adults (Won et al., 2019). Our results initially replicated this relation in a wider age range, supporting the link between greater caudate volume and longer sleep duration. Additionally, insomnia and induced sleep disruption, i.e. smaller total sleep duration, results in lower caudate activity (Stoffers et al., 2014). Induced shorter sleep leads to reduced caudate activity. This may potentially account for the link between caudate volume and sleep duration, through which greater caudate activity by greater mass is associated with longer sleep. In addition, the lack of association between putamen volume and sleep duration suggests the specificity of the caudate nucleus in its relationship with sleep.

Whereas age showed significant associations with caudate volume (Fig. 1B) and also with sleep duration (Fig. 1C), mediation analysis indicated a subtle but significant effect of age on sleep duration through caudate volume (Fig. 3), as well as the direct effect between age and sleep duration. It is also suggested that caudate volume has its own effect on habitual sleep duration. Although age has a far greater direct influence on sleep duration, it is suggested that caudate volume is partly involved in age-related change in sleep duration.

The caudate volume - sleep duration association was limited to the younger population of less than 30 years old. Although the association was significant across the all-age range, the association is deemed to come from the younger population. Although division into groups would have reduced statistical power, it would not account for the diminished association. The overall findings may strongly be influenced by the younger population. Sleep continuity has been associated with executive function across all age groups, and older adults were found to have higher wake after sleep onset (WASO) measurements, i.e. minutes spent awake after sleep onset, compared to younger adults (Wilckens et al., 2014). Although the caudate may not play roles in this asymmetry between younger vs. older population in sleep continuity and executive functions, the different age-influenced effects of fragmented sleep introduce a possible explanation to our similarly age-influenced caudate volume-sleep results. As our study did not include sleep disruption indices, further studies investigating a caudate-sleep continuity relationship may connect interrupted sleep to the diminished caudate-volume sleep relationship found in older adults.

Previous findings showed that longer sleep duration was associated with exercise-induced improvements in executive function for older adults, but no significant relationship was found between caudate volume and executive functioning responses in general (Won et al., 2019). Our study also found a subtle but significant association between longer sleep and enhanced executive function across all age ranges. In contrast, a significant influence of sleep on executive function was not detected when insomnia or one night of induced sleep disruption facilitated less sleep time. Specifically the rule violations per item ratio in the Tower of London task were not affected by the sleep disruption (Stoffers et al., 2014). This may suggest that habitual sleep length influences executive function performance but not pathological and short term induced sleep deprivation. Indeed previous literature also reported that total sleep time, specifically too much or too little sleep in the previous seven days, was negatively associated with cognitive performance but only in younger age ranges (Wilckens et al., 2014). Our results used sleep duration in the previous month, compared to seven days, which may again suggest that longer termed habitual sleep influences executive function for all ages.

No significant direct association was found between caudate volume and executive function, whereas the sample size in our study is not small (N=464). While subjects with insomnia and controls subjected to sleep disruption showed less functional activity of the caudate during executive functioning, the attenuated caudate activity did not affect their task performance (Stoffers et al., 2014). As previously stated, these results may be more representative of the caudate-sleep length relationship rather than a caudate volume-executive function relationship, since insufficient sleep related to reduced caudate recruitment, but the lack of recruitment had no effect on task performance. This may suggest that an external mechanism such as the orbitofrontal cortex regulates executive function independent of the association between sleep duration and executive functions, or insufficient recruitment in one area may invoke
compensation via activation of other areas. (Stoffers et al., 2014). It may be suggested that caudate-executive function relationship may be more involved in acute sleep disruptions, rather than habitual sleep length.

There are a few limitations of this study that need to be addressed. First, this study is not able to determine the causal relationship between the caudate volume and sleep. Greater caudate volume results in longer habitual sleep or longer habitual sleep results in greater caudal volume. Second, this study did not examine activities of the caudate but instead tested the size of the anatomical apparatus. Examining the caudate activity and sleep duration as well as executive function may elucidate mechanisms behind these associations. Third, it has to be noted that the sleep duration used in this study is based on questionnaires, not the direct measurement of sleep duration. Therefore, the sleep duration may be influenced by self-perception of sleep length and other factors. In addition, $R^2$ reported in this study is relatively small. It is implied that these associations account for a very small portion of sleep duration and executive functions, while these associations are significant.

This study demonstrated that the caudate volume is associated with habitual sleep length, especially in the younger population, but not with executive function performance, while habitual sleep length is associated with executive functions. It was also found that caudate volume is more strongly influenced by age and may partially mediate age-related change in sleep duration.

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Data availability The original data is available at the NKI-RS website.

Code availability The tractography code will be available at https://olemiss.edu/projects/dnl/ upon publication.

Declarations

Conflicts of interest/competing interests None.

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Ethics approval This study is not considered to be a human subject study.

Consent to participate N/A (No direct participation to this study).

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