Social Jet lag Has Detrimental Effects on Hallmark Characteristics of Adolescent Brain Structure, Circuit Organization and Intrinsic Dynamics

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Abstract

Study Objectives: To investigate associations between social jet lag and the developing adolescent brain.

Methods: N = 3507 youth (median (IQR) age = 12.0 (1.1) years; 50.9% females) from the Adolescent Brain Cognitive Development (ABCD) cohort were studied. Social jet lag (adjusted for sleep debt (SJL_{SC}) versus non-adjusted (SJL)), topological properties and intrinsic dynamics of resting-state networks, and morphometric brain characteristics were analyzed.

Results: Over 35% of participants had SJL_{SC} ≥2.0 h. Boys, Hispanic and Black non-Hispanic youth, and/or those at later pubertal stages had longer SJL_{SC} (β=0.06 to 0.68, CI=[0.02, 0.83], p≤0.02), which was also associated with higher BMI (β=0.13, CI=[0.08, 0.18], p<0.01). SJL_{SC} and SJL were associated with lower strength of thalamic connections (β=-0.22, CI=[-0.39, -0.05], p=0.03). Longer SJL_{SC} was also associated with lower topological resilience and lower connectivity of the salience network (β=-0.04, CI=[-0.08, -0.01], p=0.04), and lower thickness and/or volume of structures overlapping with this and other networks supporting emotional and reward processing and social function (β=-0.08 to -0.05, CI=[-0.12, -0.01], p<0.05). Longer SJL was associated with lower connectivity and efficiency of the dorsal attention network (β=-0.05, CI=[-0.10, -0.01], p<0.05). Finally, SJL_{SC} and SJL were associated with alterations in spontaneously coordinated brain activity, and. lower information transfer between regions supporting sensorimotor integration, social function and emotion regulation (β=-0.07 to -0.05, CI=[-0.12, -0.01], p<0.04).

Conclusions: Misaligned sleep is associated with widespread alterations in adolescent brain structures, circuit organization and dynamics of regions that play critical roles in cognitive (including social) function, and emotion and reward regulation.

Keywords: Social Jet lag; Adolescence; Brain Development: Network organization, Structural characteristics; Resting-state fMRI; Intrinsic dynamics

Statement of Significance

Social jet lag is common in adolescence and may have widespread but incompletely understood adverse effects on fundamental aspects of developing brain circuit organization and structural characteristics of constituent regions, with detrimental implications for cognitive function. In over 3,500 adolescents, this is the first study to investigate associations between social jet lag and hallmark structural, topological and dynamic properties of brain networks that play ubiquitous roles in cognitive function. The study provides mechanistic knowledge on adverse impacts of social jet lag on brain regions that play fundamental regulatory roles, such as the thalamus, and networks that together support emotional and reward processing and regulation, social function and cognitive control. Findings suggest that social jet lag may also disrupt normative neural maturation and plasticity.

1. INTRODUCTION

Adolescence is characterized by profound changes in sleep duration, quality, and timing, as a result of maturating regulatory processes and social environmental factors. [1] Adolescents often sleep less than recommended for optimal development, and have substantial differences in their wake times between weekdays and weekends [1-4] Their mismatch in sleep timing between school and free days results in misalignment between their biological clock and social schedule, termed social jet lag. [5]

Social jet lag in school-aged children is typically defined as a greater than 2-hour disparity in sleep timing between school days and free days. Almost half of all adolescents experience social jet lag, which has been linked to adverse physical, cognitive, and mental health outcomes in youth. Prior studies have reported associations, especially in girls, with elevated BMI and weight gain over time, [6-8] likely resulting from decreases in physical activity, higher screen time, and metabolic and endocrine dysregulation, [9-11] but also changes in food-related behaviors, including irregular meal timing, reduced intake of nutrient-dense foods, and elevated sugar intake, [12-14] and poor fitness. [15] Social jet lag has also been associated with sleep disturbances in youth, including poor sleep quality, insomnia, fatigue, and daytime sleepiness. [12, 16-20]

Social jet lag may also adversely impact cognitive function in youth, including worse academic performance, lower crystallized intelligence, poor reading performance, and memory and attention deficits, especially in girls. [19-28]

Common mental health disorders commonly emerge during adolescence, likely as a result of profound environmental, physiological and brain changes. Although their underlying causes are incompletely understood, [29, 30] inadequate (including misaligned) sleep may increase risk for these disorders. Social jet lag has been associated with higher risk of anxiety, depression, social dysfunction and antisocial behaviors, mood changes, conduct issues, and risky behaviors especially in girls. [19, 20, 31-37] Social jet lag has also been linked to higher screen time (both throughout the day and before sleep), which affects mental health and emotion regulation in youth. [9, 38-42]

Relatively few studies have examined the impact of social jet lag on the developing brain, especially during adolescence and young adulthood, as high-level cognitive function and its neural substrates continue to maturate. A recent study in young adults reported links between social jet lag and widespread alterations in functional connectivity of brain networks involved in attention, reward processing, and executive control. [43] Longer social jet lag was associated with weaker connections between the ventral striatum and inferior orbitofrontal cortex, and changes in connectivity between the dorsolateral prefrontal cortex (DLPFC) and frontal, parietal, and occipital lobes. Another recent study based on the large Adolescent Brain Cognitive Development (ABCD) study cohort, [44] reported inverse associations between social jet lag and resting-state connectivity between the right hippocampus and cingulo-opercular network. [27] Social jet lag has also been associated with lower gray matter volume of the medial prefrontal cortex, amygdala, and hippocampus. [45] Additional studies, focusing on the effects of circadian disruption and irregular sleep patterns have reported

widespread brain alterations, especially in regions supporting emotional and sensory processing. [46, 47] These studies have also shown that the prefrontal cortex, which undergoes heightened maturation in adolescence, is particularly sensitive to changes in sleep patterns, with potentially long-term implications for emotional regulation and mental health. [48]

Despite their insights, prior studies on detrimental effects of social jet lag on cognitive development have provided limited knowledge on its neuromodulatory mechanisms. To date, there are no investigations that have examined its effects on fundamental brain characteristics that play central roles in cognitive function, including the organization of developing networks (i.e., beyond just the strength of their connections) and their spontaneous (intrinsic) dynamics, morphometric characteristics of their constituent structures, and communication between their regions, and their dynamics. Extensive prior work has linked these characteristics to developmental processes, cognitive function, and mental health in youth. [49-60] However, none of these studies have examined the impact of social jet lag, which increases with age in adolescence, [61] in parallel with neural maturation and profound reorganization of brain circuits, and may amplify the risk of miswiring, resulting in cognitive deficits and mental health issues.

To address this critical gap in knowledge, this study investigated associations between social jet lag and brain characteristics (topological, morphometric, and dynamic). For this purpose, data from a sample of over 3,500 adolescents from the ABCD cohort at the two-year follow-up (ages ~11-12 years) were analyzed. The study leveraged available multimodal sleep and brain data, and used cutting-edge computational

approaches to comprehensively characterize the topological organization of resting-state brain networks and information flow between their constituent regions, as well as regional and network intrinsic dynamics. The study tested the following hypotheses: 1) Social jet lag adversely impacts hallmark topological and structural characteristics of underdeveloped (and thus vulnerable) brain networks, including their efficiency, resilience, and strength of their connections; 2) It disrupts normative communication between brain regions and information transfer, including in hubs, i.e., highly connected, domain-general regions that receive extensive domain-specific information, synthesize and distribute the output to specially distributed areas, in response to cognitive demands; 3) It impairs the spontaneous coordination of brain networks, including the underdeveloped Default-Mode Network (DMN), which is active at rest and maturates significantly adolescence, [62] plays a ubiquitous role in cognitive function, [63, 64] and is adversely affected by irregular sleep patterns and poor quality sleep [65-67]; 4) Social jet lag also disrupts pubertal changes in temporal fluctuations of the DMN's and other networks' intrinsic coordination patterns and regional activity, i.e., it impairs the increased consistency of these patterns, which reflects normative development. [53]

2. METHODS

The study analyzed fully anonymized, publicly available data, and was approved by the Boston Children's Hospital Institutional Review Board.

2.1 Participants

Effects of social jet lag on the brain were investigated in a sample of n = 3507 typically developing adolescents (median age = 12.0 years, interquartile range (IQR) = 1.1 years; 50.9% girls). All participants had at least one high-quality 5-minute resting-state fMRI

scan that was minimally affected by motion in the scanner. Neurodevelopmental and neuropsychiatric disorders can have significant adverse effects on sleep, and brain structure and circuitry. To minimize associated confounding effects, youth with a diagnosis of Attention Deficit Hyperactivity Disorder (ADHD), Autism Spectrum Disorder (ASD), any neuropsychiatric disorder (including schizophrenia, bipolar disorder and any psychotic disorder) or mood disorders were excluded. In addition, those with identified anomalies in their structural MRI were also excluded.

2.2 Social Jet lag Measures

Two measures of social jet lag were derived from the youth-reported Munich Chronotype Questionnaire (MCTQ). [68] Similar to prior work, [27] the primary measure used in this study corrected for sleep debt (e.g., shorter sleep on school days versus oversleeping on free days), using the correction [69]:

$$Social\ Jet\ lag\ (SJL)_{SC} = (SOW + 0.5*SD_{week}) - (SOF + 0.5*SD_{week}) = |SOW - SOF|$$

This measure corresponds to the absolute difference between sleep onset on school (SOW) and free (SOF) days. Results were also analyzed based on the classic social jet lag measure, which includes sleep debt (SJL), [5] i.e., the absolute difference between sleep midpoints (the time halfway between sleep onset and wake time) on school and free days, which includes weekend oversleep due to sleep debt. Both measures are expressed in hours.

2.3 Neuroimaging data

Structural and functional (resting-state) MRI data were collected in 3.0T scanners (GE, Siemens, Philips; repetition time (TR) = 0.8 s; isotropic voxel size = 2.4 mm) at 21

ABCD study sites across the United States. Scanner parameters are summarized in [105]. Resting-state fMRI was acquired while participants kept their eyes open and fixated on a crosshair. The fMRI protocol included up to four, 5-min runs, separated by short videos to ensure that participants did not fall asleep in the scanner. Prior to sharing with the community, data undergo at least minimal preprocessing at the ABCD study's Data Analysis, Informatics & Resource Center (DAIRC) to correct for head movement, B0 distortions, and gradient nonlinearities. [70] Minimally processed fMRI, (which were then further processed using the custom Next Generation Neural Data Analysis (NGNDA) platform), and fully processed structural MRI were analyzed in this study. Details on processing fMRI data using NGNDA are provided in Supplemental Materials and Brooks et al., 2021. [65] As part of this processing, data were harmonized in order to account for signal differences associated with the acquisition systems (three different manufacturers and 32- vs 64-channel head coils) [104]. Primary analyses focused on the highest-quality fMRI run, selected based on the lowest median connectivity (given that the brain at rest is weakly coordinated) and typically coinciding with the run with the lowest percent of frames censored for motion, using a 0.3 mm threshold (median (IQR) = 1.1 (4.0)%). For participants with more than one high-quality run, a second run was also analyzed for replication purposes (n = 2687; ~77% of the cohort; median (IQR) percent of frames censored for motion = 1.3 (3.7)%).

2.3.1. Time-independent and dynamic topological properties

Time-independent (non-directional and directional (effective)) and time-dependent (dynamic) connectivity matrices were estimated. Non-directional time-compressed matrices were estimated at a resolution of 1088 parcels, while effective and dynamic

matrices were estimated at a lower resolution of 100 regions (for computational tractably analyses). Time-independent connectivity was measured via the peak cross-correlation of fMRI signal pairs, and resulting matrices were thresholded to obtain corresponding adjacency matrices (see Supplemental materials for details). Time-dependent connectivity was estimated using a covariance-based approach, witha 16-s sliding window (20 frames), similarly to our prior work [53, 65]. A covariance matrix was estimated in each window, and was transformed to a correlation matrix. Brain-specific thresholds were then estimated from time-dependent correlation matrices, using an entropy-based approach, to obtain weighted adjacency matrices. Additional details on their estimation are provided in Supplemental Materials. Topological properties from time-compressed and dynamic connectivity matrices were estimated at three spatial scales: a) the entire brain (connectome), b) large-scale resting-state networks, [71] and additional ones, including the reward, [72] prefrontal cortical (and its projections, as separate circuits), social, [73] and central executive networks, [74] and c) individual brain regions (network nodes). These properties included measures of connection strength (median connectivity within and between networks), community structure (modularity and clustering), topological resilience (robustness of the network to perturbations that could lead to loss of connections), efficiency (an overall measure assessing how efficiently information is transferred through the brain), fragility (vulnerability to network perturbations), and eigenvector centrality (topological importance of a region in the network). Further details on their estimation are provided in Supplemental Materials.

2.3.2 Temporal variability of spontaneous brain activity and coordination

The coefficient of dispersion was selected as the estimator of topological property variability over time.

Temporal fluctuations of regional activity were also estimated. Following the approach in Sydnor et al., 2023, [75] the frequency power spectrum of each parcel signal was estimated, and the median square root of low-frequency spectral power (0.01 - 0.10 Hz) was used to quantify signal amplitude fluctuations. Then, parcel-level estimates were downsampled to 100 regional fluctuation amplitudes by taking the median over all parcels within a region. [53]

2.3.3 Information transfer between brain regions

Information flow in and out of a region, was measured using Phase transfer entropy (PTE) [76-78]. PTE is calculated from the instantaneous phase of pairs of signals (i,j), based on which transfer entropy is estimated, to assess the impact of of signal i phase at time t on signal j phase at time t+1. A time delay of three time points (~2.5 s) was assumed in the estimation [111-112]. For each region, three measures were estimated: a) median flow of information out of a region (median taken over all values across each row of the PTE matrix); b) median flow of information into a region (median taken over all values across each column of the PTE matrix); c) net flow as the difference between outflow and inflow. In addition, directed PTE (dPTE), was calculated by normalizing the PTE values to the range 0-1, to reflect the preferential direction of information flow (Hillebrand et al., 2016). Values >0.5 indicated higher outflow, and those <0.5 higher inflow.

2.3.4 Morphological brain properties

Cortical thickness, white matter intensity (potentially reflecting developmental white matter differences), and cortical and subcortical gray matter volume were estimated from fully processed T1-weighted MRI scans, and provided by the ABCD. These morphometric measures were estimated in 68 cortical and 30 subcortical and cerebellar regions. Two atlases were used for parcellation, the Desikan-Killiany atlas [79] for the cortex, and one based on probabilistic classification, [80] for subcortical regions and the cerebellum.

2.4 Statistical analysis

Linear mixed-effect models that included random effects (intercept and slope) for ABCD site, to account for potential site effects, were developed for all analyses. In addition, these sites are geographically diverse and vary substantially as a function of population density. Thus, all analyses also accounted for sampling bias using propensity scores provided by the ABCD study. Age, sex, pubertal stage, race-ethnicity, family income, and BMI (z-scores stratified by sex) [81] were included in all models. Due to insufficient statistical power for comparisons of racial groups, race-ethnicity was combined into a binary variable: white non-Hispanic (0) versus racioethnic minority (1). Pubertal stage ranged from pre-puberty (1) to late/post-puberty (4). The ABCD uses the Pubertal Development Scale (from pre-puberty = 1, early puberty = 2, mid puberty = 3, late puberty = 4, post-puberty = 5) [107], to determine pubertal stage based on physical changes. Stage is calculated based on parent responses to questions on their child's body and facial hair, skin changes, height spurt, breast development and menarche

(females), deepening voice (males). A very small number of youth were in post-puberty, and thus for modeling purposes they were combined with those in late puberty in a single category (= 4). In addition, secondary analyses were conducted using pubertal stage as a 3-category variable, i.e., collapsing pre- and early puberty into one category (= 1), mid puberty = 2, and late and post puberty as a single category as well (= 3). Recent work has shown that agreement between Tanner staging (the clinical standard) and the Pubertal Development Scale is low, but increases substantially when categories are combined as outlined above [113]. Models that included brain parameters were also adjusted for time of day of the scan [82] and percent of frames censored for motion. In these models, SJL_{SC} or SJL were the independent variable of interest, and brain characteristics the dependent variables. Additional models assessed relationships between social jet lag and demographic and other individual characteristics, as well as total weekly screen time (in hours). In these models, SJL_{SC} or SJL were the dependent variable. The statistical significance level was set at $\alpha = 0.05$. Given multiple comparisons (for example, multiple topological or morphometric properties, all p-values were corrected for the False Discovery Rate (FDR) [83]. At the connectome, network levels and structural region levels, corrections were done over all topological (or morphometric) properties of the entire brain, a network or a region. At the node/region level, p-values were corrected over all nodes in a particular network.

Model validation used predictive power as the relevant metric. The sample was randomly split into training and testing sets (75:25), and model parameters were estimated from the training set. The process was repeated 100 times, and at each iteration the Coefficient of Variation of the Root Mean Square Error (CV[RMSE]) was

estimated (using the testing set) as a measure of the model's predictive power. Models with CV[RMSE] ≤0.2 were considered to have good predictive power.

3. RESULTS

Almost 40% of participants were in pre or early puberty (n = 1383 (39.4%)), and ~30% in mid-puberty (n = 1133 (32.3%)). The distribution of race and ethnicity, and family income of the sample reflected that of the ABCD study. Over 50% of participants were white and non-Hispanic (n = 1820 (51.9%)), ~15 were black and non-Hispanic (n = 507 (14.5%), and ~20% were Hispanic (n = 771 (22.0%)). About 47% of families (n = 1646 (46.6%)) had a yearly household income of <$100,000. Median BMI was 19.3 kg/m^2 (IQR = 5.6). Participant characteristics are summarized in Table 1.

Median (IQR) SJL_{SC} was 1 (1) h (and 1.5 (1.5) h based on SJL). About 74% of the sample had SJL_{SC} ≥1 hour, and ~36% had ≥2 hours. The distribution of these measures is shown in Figure 1. Girls, white non-Hispanic youth, and those from families with higher family income had shorter SJL_{SC} (β = -0.11, CI = [-0.23, -0.0003], p = 0.05; β = -0.45, CI = [-0.55, -0.35], p < 0.01; β = -0.11, CI = [-0.13, -0.08], p < 0.01, respectively). In contrast, Hispanic and Black non-Hispanic youth had longer SJL_{SC} (β = 0.14, CI = [0.02, 0.25], p = 0.02; β = 0.68, CI = [0.53, 0.83], p < 0.01), and so did those at later pubertal stages (β = 0.06, CI = [0.01, 0.12], p = 0.03, respectively). BMI was positively associated with SJL_{SC} (β = 0.13, CI = [0.08, 0.18], p < 0.01), and similarly for total weekly screen time (β = 0.008, CI = [0.006, 0.011], p < 0.01). Model statistics are provided in Table 2. Corresponding statistics for the model that used pubertal stage as a 3-category variable are provided in Supplemental Table S2.

3.1 Associations between social jet lag and time-independent topological characteristics

3.1.1 Network topological properties

Longer SJL_{SC} was associated with lower median connectivity between the right thalamus and the rest of the brain (β = -0.22, CI = [-0.39, -0.05], p = 0.03). It was also associated with lower median within-network connectivity (β = -0.04, CI = [-0.08, -0.01], p = 0.04), and higher fragility (β = 0.05, CI = [0.01, 0.09], p = 0.04) of the right salience network. In addition, longer SJL was associated with lower median connectivity (within- and across-network) of the right thalamus (β = -0.29, CI = [-0.48, -0.10], p < 0.01), I.e, weaker connections between the thalamus and the rest of the brain, and lower efficiency of information processing, and both within- and cross-network connectivity of the right dorsal attention network (β = -0.052 to -0.047, CI = [-0.10, -0.01], p < 0.05) In summary, longer SJL and SJL_{SC} were associated with altered topological characteristics of multiple brain networks. Model statistics are provided in Table 3. All models had good predictive power (CV[RMSE] < 0.20)).

3.1.2 Local (regional) topological properties

At the parcel (node) level, and based on the best run, SJL was associated with lower local clustering within the bilateral central and peripheral visual networks (β = -0.09 to -0.05, CI = [-0.13, -0.01], p < 0.05), higher centrality of the left somatomotor network (β = 0.05 to 0.08, CI = [0.01, 0.12], p < 0.05) and lower centrality of the bilateral dorsal attention and central and peripheral visual networks (β = -0.09 to -0.05, CI = [-0.13, -0.01], p < 0.05). These associations are shown in Figure 2. There were no

corresponding statistical associations with SJL_{SC}. At both the regional and network scales, reported associations were overall consistent irrespective of whether pubertal stage was represented by a 3-category or 4-category variable. Figure S1 shows associations between SJL and regional topology based on these models.

3.2 Associations between social jet lag and morphometric regional properties

SJL_{SC} was associated with lower thickness of multiple structures of the temporal lobe (including the banks of the left superior temporal sulcus, bilateral superior temporal gyrus and right medial temporal gyrus) and the bilateral lingual gyrus (β = -0.07 to -0.05, CI = [-0.12, -0.01], $p < 0.04$). It was also associated with lower volume of the banks of the left superior temporal sulcus, bilateral middle and left inferior temporal gyri, left entorhinal cortex, bilateral inferior parietal gyrus, left insula, left hippocampus, and bilateral caudate nucleus, putamen, amygdala, and nucleus accumbens (β = -0.08 to -0.05, CI = [-0.12, -0.01], $p < 0.05$). These associations were overall consistent for SJL as well. Additional negative associations were estimated between SJL and volume of multiple regions, including lateral and medial orbitofrontal cortices and several brain hubs, such as the bilateral precuneus and the right cingulate cortex. In summary, longer SJL and SJL_{SC} were associated with altered structural characteristics of distributed brain regions, including ones that continue to develop in adolescence. All models had good predictive power (CV[RMSE] < 0.20). Model statistics are provided in Table 4.

3.3 Associations between social jet lag and signal and topological dynamics

SJL_{sc} was associated with higher local clustering fluctuations in bilateral somatomotor areas (β = 0.05, CI = [0.01, 0.10], $p < 0.04$). SJL was also associated with higher

clustering fluctuations in a left somatomotor region (β = 0.06, CI = [0.02, 0.10], p = 0.02) and lower clustering fluctuations in the salience, dorsal attention, and basal ganglia regions (β = -0.07 to -0.05, CI = [-0.12, -0.01], p < 0.03). The spatial distributions of these associations are shown in Figure 3. In addition, SJL_{SC} was associated with higher fluctuation amplitude in left somatomotor areas (β = 0.04 to 0.05, CI = [0.004, 0.09], p < 0.04) and lower fluctuation amplitude in bilateral dorsal attention, left frontoparietal control, and left default mode areas (β = -0.06 to -0.04, CI = [-0.11, -0.01], p < 0.05). SJL was also associated with higher fluctuation amplitude of bilateral somatomotor areas (β = 0.05 to 0.08, CI = [0.01, 0.12], p < 0.05) and lower fluctuation amplitude of bilateral dorsal attention, bilateral frontoparietal control, bilateral default mode, and right salience areas (β = -0.08 to -0.05, CI = [-0.13, -0.01], p < 0.05). In summary, longer summary, SJL and SJL_{SC} were associated with higher variability of spontaneous brain activation and/or coordination patterns in some regions (especially those of the somatomotor network) and lower variability in others. All related statistical models had good predictive power (CV[RMSE] < 0.13). The spatial distribution of these associations is shown in Figure 4.

3.4 Associations between social jet lag and regional information flow

SJL was associated with lower median outflow from the left amygdala, bilateral temporoparietal, right peripheral visual, and right somatomotor regions (β = -0.07 to -0.04, CI = [-0.11, -0.003], p < 0.05). It was also associated with lower median net flow in the right temporoparietal, peripheral visual, and somatomotor areas (β = -0.07 to -0.05, CI = [-0.12, -0.01], p < 0.04). All related models had good predictive power (CV[RMSE]

< 0.09). The spatial distributions of these associations are shown in Figure 5. No corresponding associations were estimated for SJL_{SC}.

3.5 Mappings between structural and functional correlates of social jet lag

Associations between structural and functional findings were also examined. Connectivity between the right dorsal attention and the rest of the brain, and morphometric properties of the right lingual gyrus () were positively associated (β = 0.15, CI = [0.09, 0.21], p < 0.01), and both were negatively associated with SJL_{SC}. Also, higher fluctuation amplitude in the right somatomotor network was negatively associated with out and net flow in its constituent regions, (β = -0.22 to -0.12, CI = [-0.26, -0.07], p < 0.01), with both properties being negatively impacted by SJL_{SC} (higher fluctuation amplitude and lower information flow). Model statistics are provided in Table S1.

4. DISCUSSION

Insufficient, poor quality and/or misaligned sleep during development has profound and often long-lasting detrimental effects on brain health [24, 107-109]. During sensitive periods, such as adolescence, these effects may be amplified, leading to cognitive deficits (including impaired learning) and mental health issues [4, 18, 27, 35-37]. Although the effects of insufficient and disrupted/disordered sleep on cognitive and mental health have been extensively studied, those of misaligned sleep (and social jet lag) remain incompletely understood. In this study we have addressed this gap in knowledge and, in a sample of over 3,500 adolescents, have investigated associations between social jet lag and comprehensive brain properties across multiple domains, including topology, morphology, and dynamics. It examined and compared both SJL_{SC}

and SJL, i.e., social jet lag excluding sleep debt (to minimize effects of insufficient sleep on school days and oversleeping on free days), and social jet lag that included sleep debt. To the best of our knowledge this is the first study to examine impacts of social jet lag on the evolving organization and dynamics of adolescent resting-state networks - the backbone of the functional connectome, properties of their constituent structures, and information flow through the brain, which is critical to information processing and cognitive function.

Over a third of participants had social jet lag of 2 or more hours, an alarming statistic given its links to increased risk for mental health problems, [84] cardiovascular, metabolic, and hormonal issues, and obesity [6, 85-87]. Longer social jet lag was also associated with longer weekly screen time, as well as BMI, in agreement with prior studies that have reported associations between screen time and social jet lag, [40] a sedentary lifestyle, lower physical activity and higher BMI [9, 88]. In addition, Black and Hispanic youth had longer social jet lag, again a finding that is aligned with a number of prior studies that have reported significant sleep disparities, including misaligned and poor quality sleep in racial and ethnic minorities [89-92].

Equally alarming are the identified associations between social jet lag and fundamental aspects of brain structure, organization of its circuitry, and intrinsic dynamics, all of which play critical roles in cognitive function. Longer social jet lag (both excluding and including sleep debt) was associated with weaker connections between the thalamus and the rest of the brain. The thalamus plays a critical role in the regulation of the sleep-wake cycle and circadian rhythm, which may be disrupted by social jet lag. [93,

94] Our results suggest a potential mechanistic relationship between social jet lag and the regulation of the sleep-wake cycle, through the former's impact on the thalamus. In addition, prior studies have associated social jet lag with alterations in brain networks that include the thalamus, and support motor function and posture control, but are also involved in reward processing, emotion regulation and eating behaviors, as well as mental health [32, 95, 96]. Our findings suggest another potential mechanistic relationship between social jet lag and these processes, through its adverse effects on networks that regulate them and/or support mental health.

SJL was also associated with weaker and less efficient connections of the dorsal attention network, while SJL_{SC} was associated with weaker connections within the ventral attention/salience network. The two networks share brain structures, have overlapping functions and interact significantly to control attention, with the ventral network filtering out important information (and signals a need for attentional switching), which the dorsal network requires for goal-directed attention [114,115]. It is possible that the associations between SJL and the dorsal network are partly due to mismatch in sleep schedules and partly due to sleep debt (which significantly impacts goal-directed attention [116]), whereas the association with the ventral network is solely due to mismatch in sleep timing. Studies on both adults and adolescents have reported negative effects of social jet lag on attention [117,118], thus our findings provide new knowledge on its negative associations with underlying circuits.

Social jet lag was also associated with lower fluctuations of spontaneous brain activity and coordination patterns in some regions, and higher fluctuations in others. Prior work,

including our own, has shown that intrinsic topological and BOLD signal fluctuations represent markers of brain development, and broadly decrease with age and neuroanatomical maturation, i.e., spontaneous coordination patterns become increasingly consistent. [53, 75] Prior studies have also shown that higher spontaneous BOLD fluctuations in sensorimotor areas may be associated with impaired plasticity [97]. Both social jet lag measures were associated with higher signal and topological fluctuations in these areas. It would, therefore, be important to follow youth longitudinally, in order to identify potential detrimental effects of social jet lag on fundamental developmental processes that facilitate adaptation and learning. During development, changes in intrinsic brain dynamics are spatially heterogeneous, and may be disrupted by social jet lag, likely through its adverse effects on underlying structures, resulting in less consistent coordination patterns and higher signal variability in some areas, and abnormally lower fluctuations in others. This potential mechanism of action is partially supported by identified negative associations between social jet lag and cortical and subcortical volume of spatially distributed brain areas, overlapping with regions and networks in which topological and dynamic properties were adversely impacted by social jet lag. These included structures of the salience network (in which negative topological associations with social jet lag were also estimated) that are involved in multisensory processing and integration, such as the insula, as well as the amygdala and the nucleus accumbens. These structures play central roles in reward and emotion processing. Social jet lag was also associated with morphometric alterations in regions of the DMN, dorsal attention and frontoparietal networks. Together, these networks support cognitive processes that develop significantly in adolescence, including executive control and decision-making, but also reward and emotion regulation [98-101].

Thus, social jet lag may have detrimental effects on these processes through its neuromodulatory effects on brain structures, circuits and their intrinsic dynamics.

We have also identified distributed negative associations between social jet lag that included sleep debt and information flow through the brain, including hubs, which receive, synthesize and output information in support of cognitive demands. Communication between brain regions is critical to cognitive processing. Some domain-specific regions may receive more information (for example external (sensory) inputs) than they output, and others may output more information than they receive, with cognitive and/or topological hubs often receiving and outputting equal amounts of information [102-103]. Social jet lag was associated with lower flow of information from the amygdala to the rest of the brain, and similarly from temporoparietal, peripheral visual, and right somatomotor regions. This implies that it may adversely affect distributed interactions between brain regions that support sensory processing, motor function, sensorimotor interactions, but also high-level social function and emotional processing. These associations were specific to social jet lag that included sleep debt, and could thus be associated with it as well. However, they were specific to regions where other negative associations were identified for both measures of social jet lag. Together with its topological, structural, and dynamic correlates, these findings suggest that social jet lag may have extensive detrimental effects on the adolescent brain, affecting the strength, resilience and the consistency of spontaneous coordination patterns of its circuits, information transmission through them, and their underlying structures. Given the vulnerability of the brain during this sensitive period, these findings have important implications for both mental health and cognitive function across

domains, and academic performance, as highlighted in prior work on another sample from the ABCD study cohort [24].

Despite its many strengths, including the large sample, and comparisons of measures of social jet lag with and without sleep debt with comprehensive measures of brain structure, topology, and dynamics, the study also had some limitations. First, this was a cross-sectional study of youth in a narrow age range. Thus, associations between social jet lag and age-related changes in brain characteristics over a longer period could not be established. By design, the ABCD study restricts age to a narrow range at each assessment, to limit overlap in age between assessments. A future investigation could extend this analysis to multiple assessments and thus a wider age range. Second, social jet lag was estimated from the MCTQ, which is a subjective instrument, and thus less accurate than actigraphy-based estimates. Although the ABCD study is collecting actigraphy data, they are only available for a substantially smaller sample at the two-year follow-up, which may limit the statistical power of some analyses. Nevertheless, a future investigation could compare subjective and objective measures of social jet lag and its brain correlates in this smaller sample, similarly to Yang et al., 2023 [27]. Although the study investigated two measures of jet lag, including and excluding sleep debt, respectively, other aspects of sleep, for example quality, could also affect brain characteristics. In prior work on the baseline ABCD cohort, we have reported associations between topological network properties and In addition, this study was retrospective, and was thus inherently limited by the decisions made by the ABCD investigators. However, the ABCD is the only adolescent study to collect both sleep (and related measures) and multimodal neuroimaging data from such a large cohort.

Thus, leveraging these data provides unique opportunities to study impacts of sleep misalignment on brain development and generate findings that may be generalizable to the larger adolescent population. Finally, this study has focused exclusively on associations between social jet lag and brain circuits, structural characteristics and information transfer between regions. Each of these aspects of brain function plays important roles in cognitive function. The ABCD study collects extensive neurocognitive data. A future investigation could examine direct and indirect (brain-mediated) associations between social jet lag and cognitive function.

This study makes a significant contribution to the field's incomplete understanding of the neural correlates of social jet lag in the adolescent brain. It provides novel mechanistic insights into how misaligned sleep, which is common in adolescence (almost 40% of youth in this study experienced social jet lag of at least 2 h), may impact fundamental biological processes, such as the sleep-wake cycle, through its impact on the thalamus and its connections with the rest of the brain, and evolving cognitive functions, such as reward processing and emotional regulation, through its impact on the organization and strength of brain networks that support them. Social jet lag may also modulate the brain's task-independent (intrinsic) dynamics, and spontaneous coordination of its regions, a process that plays a ubiquitous role in cognitive function and is impaired in mental health disorders, and may disrupt developmental changes in these dynamics. Finally, social jet lag may also impair information transfer between brain regions that together support sensory processing, sensorimotor integration, emotional regulation and social function.

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Data Availability Statement

The data underlying this article are publicly available through the National Institute of Mental Health, National Data Archive (NDA): https://nda.nih.gov/

Computer codes associated with the analyses are available at:

https://github.com/cstamoulis1/Social-Jetlag-Brain

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FIGURE CAPTIONS

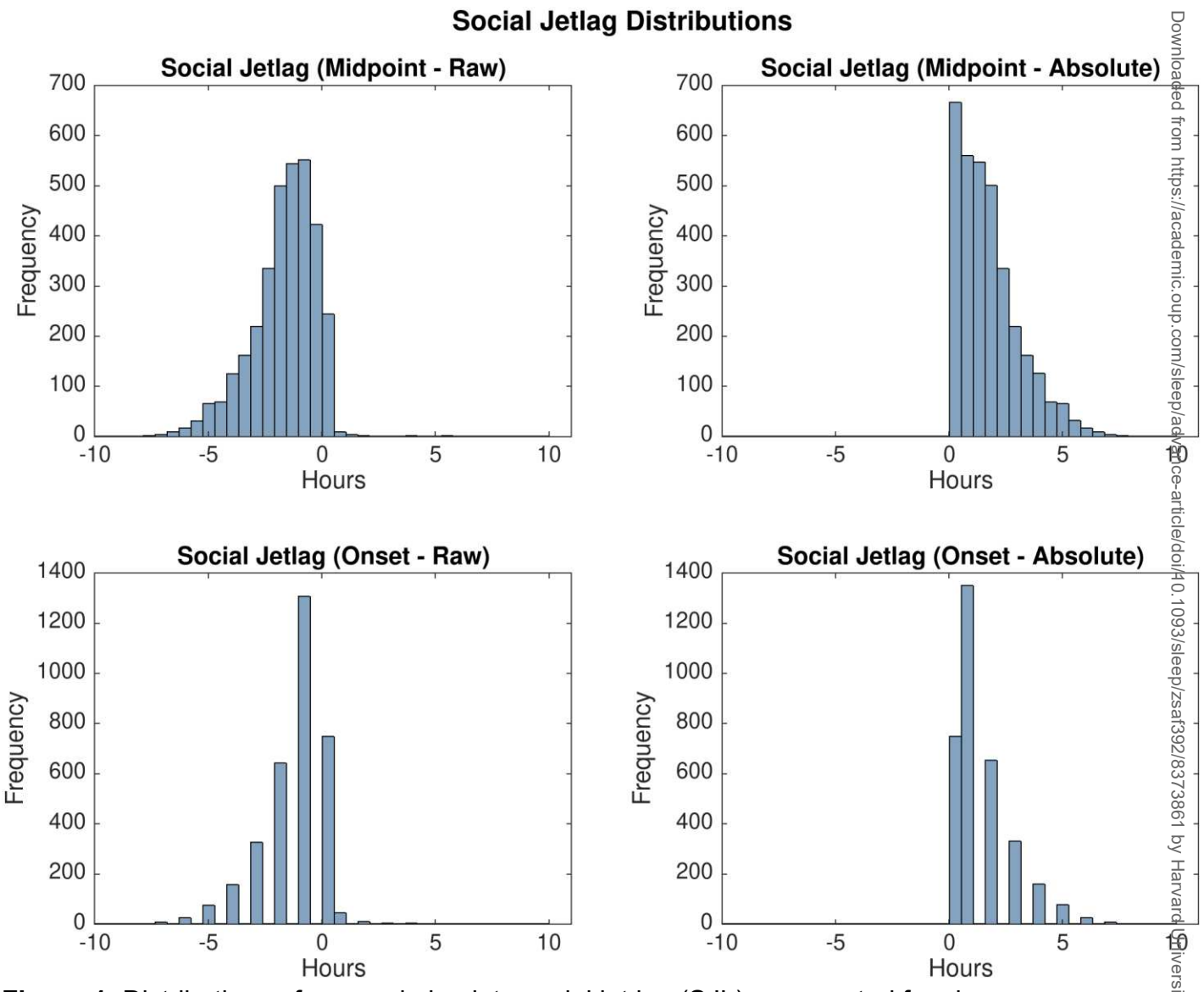


Figure 1. Distributions of raw and absolute social jet lag (SJL) uncorrected for sleep debt (midpoint-based, top row) and sleep debt-corrected SJL_{SC} (bottom row).

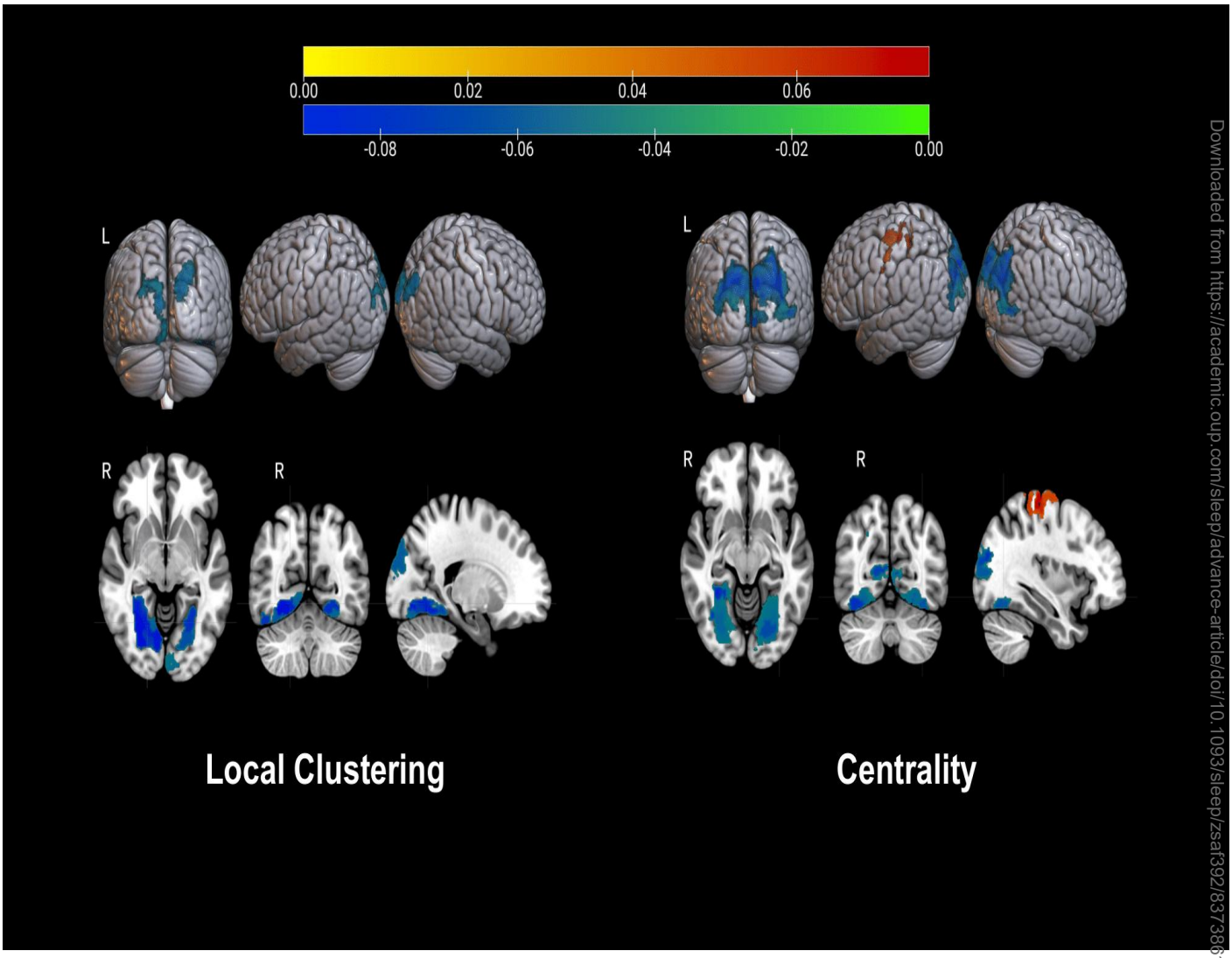


Figure 2. Associations between SJL (including sleep debt) and local clustering (left panels) and node centrality (right panels). The color map represents the values of model regression coefficients. Yellow to red corresponds to positive values and blue to green to negative values.

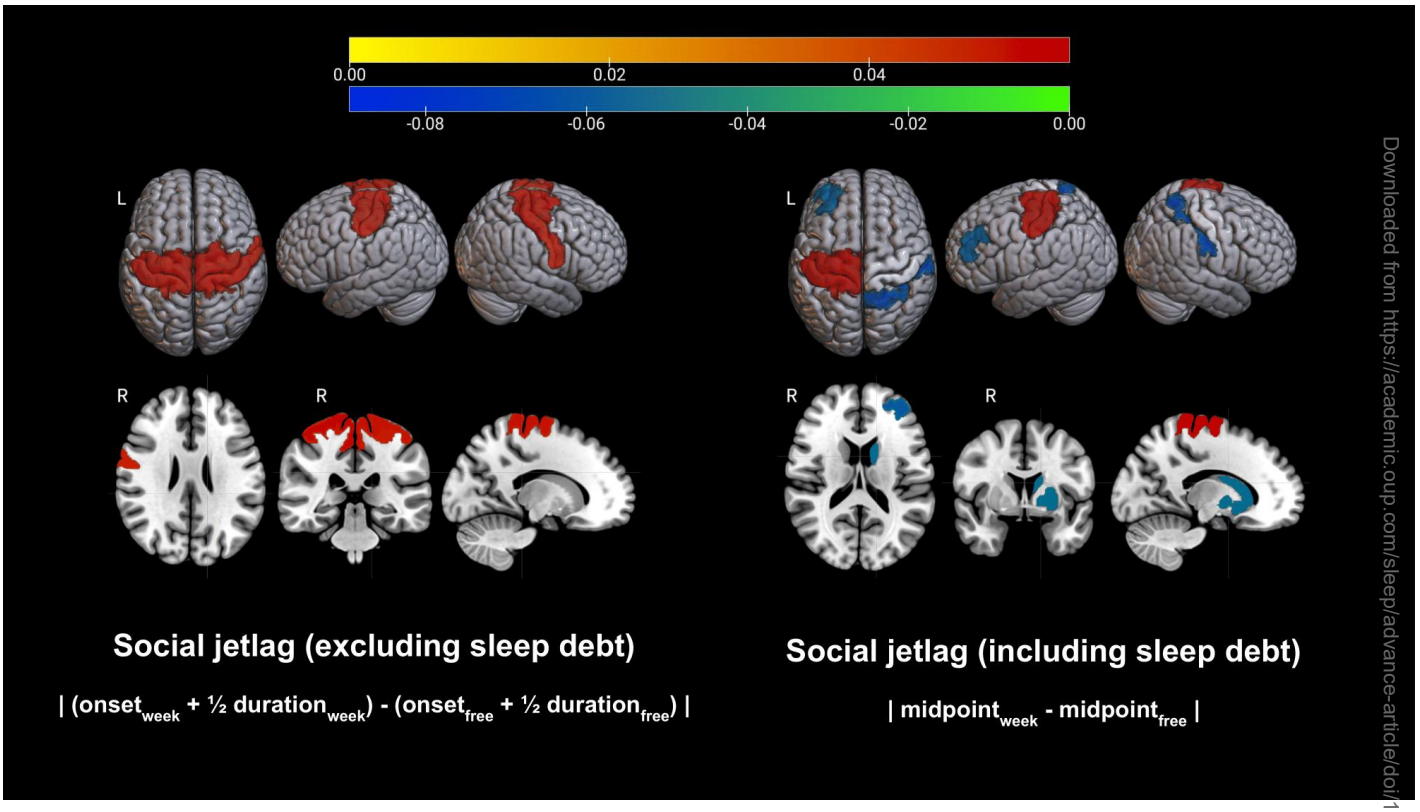


Figure 3. Associations between social jetlag and local clustering fluctuation. The color map represents the values of model regression coefficients. Yellow to red correspond to positive values and blue to green to negative values.

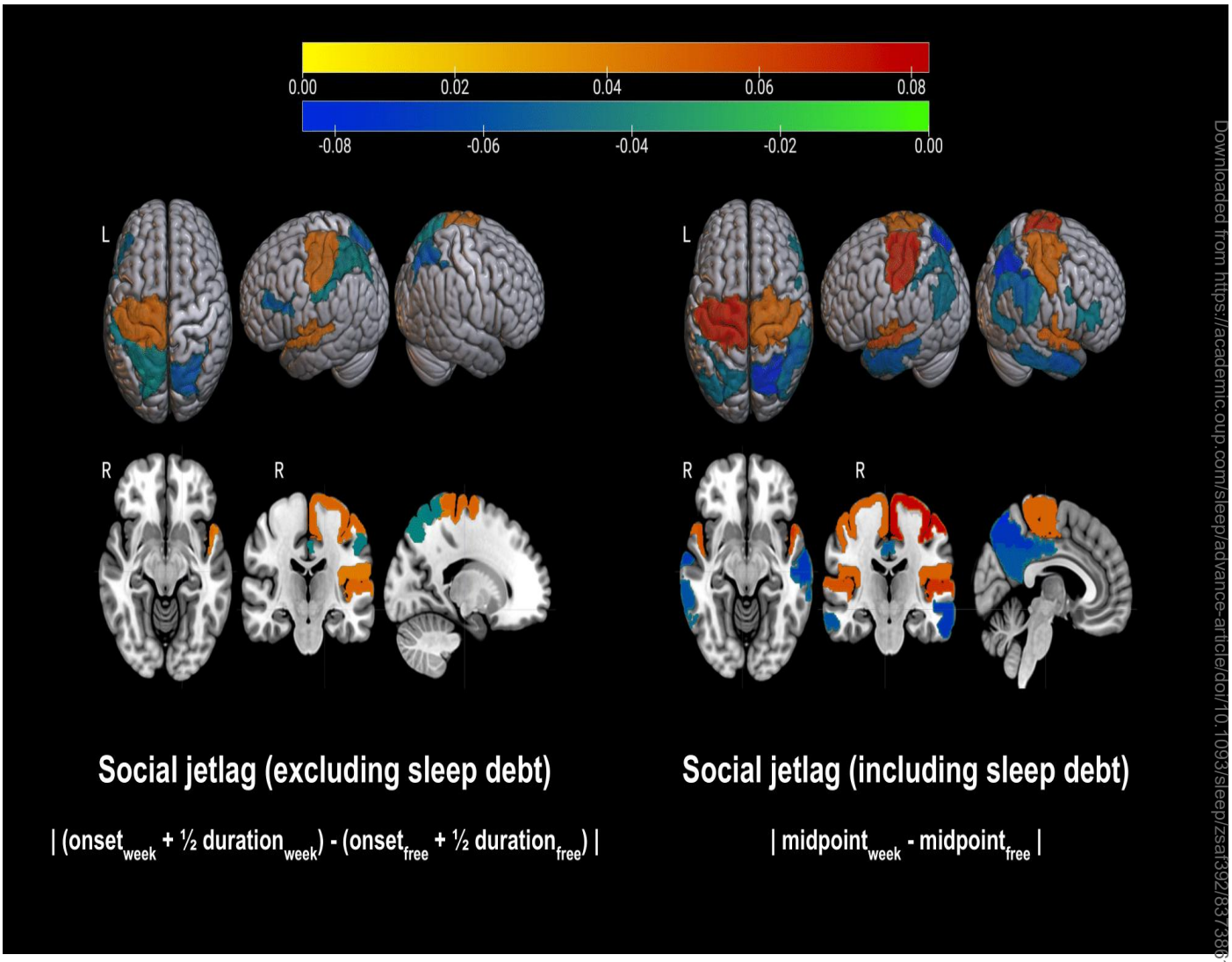


Figure 4. Associations between SJL_{SC} (excluding sleep debt) – left panels, and SJL (including sleep debt) – right panels, and fluctuation amplitude. The color map represents the value of model regression coefficients. Yellow to red corresponds to positive values and blue to green to negative values.

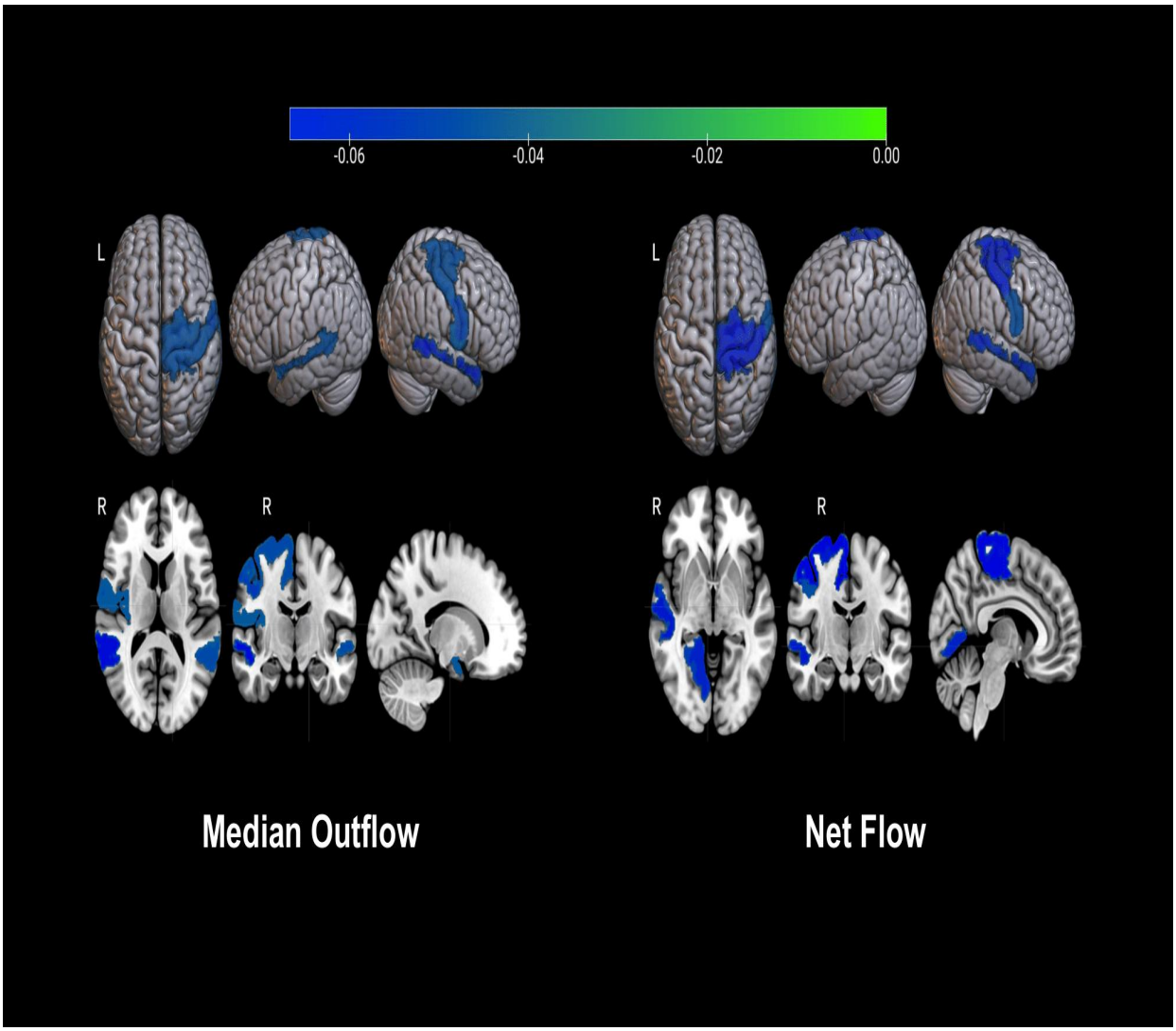
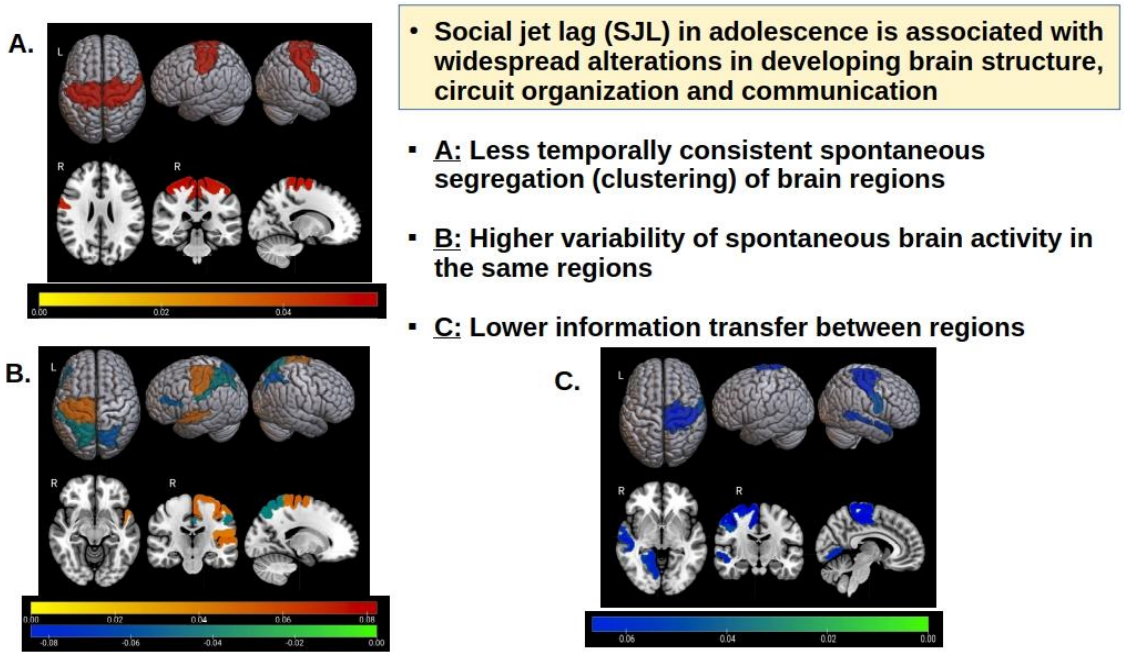


Figure 5. Associations between SJL (including sleep debt) and information flow. The color map represents the value of model regression coefficients (all were negative).



Graphical Abstract

TABLES

Table 1. Participant characteristics (n = 3507). The racioethnic category “Other Non-Hispanic” combines small racial categories: Filipino, Vietnamese, Alaska Native, American Indian, Asian Indian, Chinese, Guamanian, Hawaiian, Japanese, Korean, Native Samoan, other Pacific Islander, other Asian, multiracial, other race.

Characteristic	Statistic/Category	Value
Age (years)	**Median (IQR)**	12.00 (1.08)
Sex	**Male**	1720 (49.04%)
	Female	1785 (50.90)
	Missing	2 (0.06%)
Race/Ethnicity	**White Non-Hispanic**	1820 (51.90%)
	Black Non-Hispanic	507 (14.46%)
	Asian Non-Hispanic	68 (1.94%)
	Other Non-Hispanic	330 (9.41%)
	Hispanic	771 (21.98%)
	Missing	11 (0.31%)
Family Income ($)	**<25,000**	344 (9.81%)
	25,000 - 49,999	416 (11.86%)
	50,000 - 74,999	426 (12.15%)
	75,000 - 99,999	450 (12.83%)
	100,000 - 199,999	1094 (31.19%)
	≥200,000	508 (14.49%)
	Missing	269 (7.67%)
BMI	**Median (IQR)**	19.33 (5.58)
	Missing	27 (0.77%)
Pubertal Stage	**Pre-Puberty**	634 (18.08%)
	Early Puberty	749 (21.36%)
	Mid-Puberty	1133 (32.30%)
	Late/Post-Puberty	801 (22.84%)
	Missing	190 (5.42%)

Table 2. Statistics of models testing associations between social jetlag excluding sleep debt (SJL_{SC}) and demographic and other characteristics. All p-values have been adjusted for the False Discovery Rate. CI: Confidence interval. Exact p-values are reported to the third decimal place. Smaller values are indicated as p<0.001.

Covariate	Beta	95th % CI	P-value
Pubertal stage	0.063	[0.006, 0.121]	0.032
Sex	-0.113	[-0.227, -0.001]]	0.049
White non-Hispanic	-0.446	[-0.546, -0.345]	<0.001
Black non-Hispanic	0.680	[0.528, 0.833]	<0.001
Hispanic	0.135	[0.023, 0.248]	0.018
Family income	-0.107	[-0.133, -0.082]	<0.001
BMI	0.127	[0.078, 0.176]	<0.001
Screen time	0.008	[0.006, 0.011]	<0.001

Table 3. Statistics of models testing associations between SJL_{SC} (excluding sleep debt) and topological properties of individual networks, and similarly for SJL (including sleep debt) Results are based on the best-quality run. All p-values have been adjusted for the False Discovery Rate. CI: Confidence interval. Exact p-values are reported to the third decimal place. Smaller values are indicated as p<0.001. When p-values for multiple properties are reported together, the range is reported as ≤ to the largest one (meeting significance).

Network	Property	Beta	95th % CI	P-value
	SOCIAL JETLAG EXCLUDING SLEEP DEBT (SJL_{SC})			
Salience (R)	**Median connectivity (within-network)**	-0.044	[-0.083, -0.005]	0.043
	Fragility	0.052	[0.012, 0.0927]	0.043
Thalamus (R)	**Median connectivity (across-network)**	-0.219	[-0.393, -0.045]	0.028
	SOCIAL JETLAG INCLUDING SLEEP DEBT (SJL)			
Thalamus (R)	**Median connectivity (within-network)**	-0.292	[-0.480, -0.104]	0.004
	Median connectivity (across-network)	-0.289	[-0.474, -0.104]	0.004
Dorsal Attention (R)	**Median connectivity (across-network)**	-0.052	[-0.096, -0.009]	0.036
	Median connectivity within network	-0.05	[-0.090, -0.010]	0.048
	Global efficiency	-0.047	[-0.087, -0.008]	0.036

Table 4. Statistics of models testing associations between SJL_{SC} (excluding sleep debt)and morphometric brain properties, and similarly for SJL (including sleep debt). All p-values have been adjusted for the False Discovery Rate. CI: Confidence interval. Exact p-values are reported to the third decimal place. Smaller values are indicated as p<0.001. When p-values for multiple properties are reported together, the range is reported as ≤ to the largest one (meeting significance).

Property	Region	Beta	95th % CI	P-value	Region	Beta	95th % CI	P-value
	SOCIAL JETLAG EXCLUDING SLEEP DEBT (SJL_{SC})				**SOCIAL JETLAG INCLUDING SLEEP DEBT (SJL)**			
Thickness	**Banks of the superior temporal sulcus (L)**	-0.062	[-0.105, -0.019]	0.013	**Banks of the superior temporal sulcus (L)**	-0.060	[-0.106, - 0.014]	0.015
	Lingual gyrus (bilateral)	-0.073 to -0.053	[-0.117, -0.014]	≤0.017	**Lingual gyrus (L)**	-0.059	[-0.098, -0.020]	0.008
	Superior temporal gyrus (bilateral)	-0.063 to -0.051	[-0.101, -0.011]	≤0.036				
	Middle temporal gyrus (R)	-0.059	[-0.099, -0.019]	0.005				
					Medial orbitofrontal cortex (L)	-0.047	[-0.087, -0.008]	0.020
Volume	**Banks of the superior temporal sulcus (L)**	-0.052	[-0.090, -0.013]	0.013	**Banks of the superior temporal sulcus (L)**	-0.081	[-0.120, -0.042]	<0.001
	Middle temporal gyrus (bilateral)	-0.077 to -0.056	[-0.115, -0.019]	≤0.010	**Middle temporal gyrus (bilateral)**	-0.069 to -0.056	[-0.108, -0.015]	≤0.022
	Inferior temporal gyrus (L)	-0.049	[-0.084, -0.014]	0.020	**Inferior temporal gyrus (L)**	-0.072	[-0.108, -0.035]	<0.001
	Entorhinal cortex (L)	-0.059	[-0.102, -0.016]	0.022	**Entorhinal cortex (L)**	-0.051	[-0.093, -0.010]	0.043
	Inferior parietal gyrus (bilateral)	-0.073 to -0.057	[-0.110, -0.018]	≤0.014	**Inferior parietal gyrus (L)**	-0.080	[-0.121, -0.040]	<0.001
	Insula (L)	-0.057	[-0.096, -0.017]	0.014	**Insula (L)**	-0.053	[-0.094, -0.013]	0.030
	Caudate nucleus (bilateral)	-0.054 to -0.046	[-0.102, -0.0002]	≤0.049	**Caudate Nucleus (bilateral)**	-0.049	[-0.092, -0.007]	≤0.024

	Putamen (bilateral)	-0.052 to -0.047	[-0.092, -0.006]	≤0.024			
	Hippocampus (L)	-0.045	[-0.082, -0.009]	0.015	**Hippocampus (bilateral)**	-0.051 to -0.042	[-0.088, -0.004]	≤0.032
	Amygdala (bilateral)	-0.052 to -0.050	[-0.089, -0.014]	≤0.007	**Amygdala (bilateral)**	-0.063 to -0.055	[-0.100, -0.018]	≤0.004
	Nucleus accumbens (bilateral)	-0.056 to -0.046	[-0.096, -0.006]	≤0.026	**Nucleus accumbens (bilateral)**	-0.068 to -0.056	[-0.106, -0.010]	≤0.018
					Lateral orbitofrontal cortex (bilateral)	-0.052 to -0.050	[-0.093, -0.011]	≤0.041
					Medial orbitofrontal cortex (bilateral)	-0.063 to -0.043	[-0.111, -0.007]	≤0.031
					Precentral gyrus (L)	-0.062	[-0.099, -0.025]	0.003
					Precuneus (bilateral)	-0.050 to -0.048	[-0.086, -0.012]	≤0.029
					Superior parietal gyrus (bilateral)	-0.066 to -0.053	[-0.104, -0.016]	≤0.016
					Superior temporal gyrus (L)	-0.050	[-0.089, -0.011]	0.034
					Postcentral gyrus (R)	-0.049	[-0.086, -0.011]	0.034
					Rostral anterior cingulate cortex (R)	-0.054	[-0.093, -0.016]	0.018
White matter intensity					**Entorhinal cortex (L)**	-0.027	[-0.050, -0.003]	0.043
					Insula (L)	0.022	[0.002, 0.041]	0.046