Received: 22 May 2019 | Revised: 28 June 2019 | Accepted: 8 July 2019

DOI: 10.1111/jsr.12901

REGULAR RESEARCH PAPER

Journal of Sleep Research

Reduced structural connectivity in Insomnia Disorder

Kira V. Jespersen[1] | Angus Stevner[1,2] | Henrique Fernandes[1,2] | Stine D. Sørensen[1] | Eus Van Someren[3,4,5] | Morten Kringelbach[1,2] | Peter Vuust[1]

[1]Department of Clinical Medicine, Center for Music in the Brain, Aarhus University & the Royal Academy of Music Aarhus/Aalborg, Aarhus, Denmark

[2]Department of Psychiatry, University of Oxford, Oxford, UK

[3]Department of Sleep and Cognition, Netherlands Institute for Neuroscience, Institute of the Royal Netherlands Academy of Arts and Sciences, Amsterdam, The Netherlands

[4]Department of Integrative Neurophysiology, Center for Neurogenomics and Cognitive Research, Amsterdam Neuroscience, VU University Amsterdam, Amsterdam, The Netherlands

[5]Department of Psychiatry, Amsterdam UMC, Amsterdam Neuroscience, VU University Amsterdam, Amsterdam, The Netherlands

Correspondence
Kira V. Jespersen, Center for Music in the Brain, Noerrebrogade 44, build. 1A, 8000 Aarhus C, Denmark.
Email: kira@clin.au.dk

Abstract

Insomnia Disorder is the most prevalent sleep disorder, and it involves both sleep difficulties and daytime complaints. The neural underpinnings of Insomnia Disorder are poorly understood. Several existing neuroimaging studies focused on local measures and specific regions of interests, which makes it difficult to judge their whole-brain significance. We therefore here applied a data-driven approach to assess differences in whole-brain structural connectivity between adults with Insomnia Disorder and matched controls without sleep complaints. We used diffusion tensor imaging and probabilistic tractography to assess whole-brain structural connectivity, and examined group differences using network-based statistics. The results revealed a significant difference in the structural connectivity of the two groups (p = .014). Participants with Insomnia Disorder showed reduced connectivity in a sub-network that included mainly fronto-subcortical connections with the insula as a key region. By taking a whole-brain network perspective, our study enables the integration of previous inconsistent findings. Our results reveal that reduced structural connectivity of the left insula and the connections between frontal and subcortical regions are central neurobiological features of Insomnia Disorder. The importance of these areas for interoception, emotional processing, stress responses and the generation of slow-wave sleep may help guide the development of neurobiology-based models of the prevalent condition of Insomnia Disorder.

KEYWORDS

diffusion tensor imaging, insomnia, insula, neuroimaging, sleep, structural connectivity

1 | INTRODUCTION

Insomnia is the most common sleep disorder, reported in 6%–22% of the general population (Ohayon, 2002; Roth et al., 2011). The diagnostic criteria involve prolonged difficulties initiating or maintaining sleep, including early morning awakenings, and significant impairments in important areas of daytime functioning (e.g. occupational, social or behavioural; Riemann et al., 2015). Unfortunately, insomnia is often a persistent condition, and it is associated with reduced quality of life as well as deficiencies in cognitive and emotional functioning (Morin et al., 2015). There is a high rate of co-morbidity with medical and psychiatric disorders, and insomnia confers an increased risk for depression and anxiety (Riemann et al., 2015).

Even though the burden of insomnia is heavy for both individuals and society, the pathophysiology of the disorder is poorly understood. The most prevailing theory of insomnia is the hyperarousal theory, which conceptualizes insomnia as the result of increased physiological and cortical arousal that interferes with the normal sleep processes (Bonnet & Arand, 2010; Riemann et al., 2010). Most neuroimaging studies have been interpreted within this framework. However, not all studies fit this model, and a more complex

understanding may be needed, for example, including awareness (Kay & Buysse, 2017; Tagliazucchi & Van Someren, 2017).

So far, no reliable biological marker for insomnia has been identified. Modern neuroimaging methods allow for a non-invasive mapping of structural and functional brain networks, and provide a promising way to shed light on the neurobiological foundations of insomnia to achieve clinically relevant information that can help target interventions. An increasing number of studies have investigated functional connectivity alterations related to insomnia but, as a number of recent reviews point out, the results are relatively inconsistent so far (Kay & Buysse, 2017; Spiegelhalder et al., 2015; Tagliazucchi & Van Someren, 2017). This inconsistency may stem from the variety of methods used (Spiegelhalder et al., 2015), but may also be influenced by sleep confounds (Tagliazucchi & Laufs, 2014) and insomnia heterogeneity (Blanken et al., 2019).

Other studies have approached the neurobiological basis of insomnia by looking at structural differences between persons with Insomnia Disorder and good sleeper controls. In terms of grey-matter alterations, neuroimaging studies have linked insomnia to grey-matter decreases in the orbitofrontal cortex (Altena, Vrenken, Van Der Werf, Van Den Heuvel, & Van Someren, 2010; Stoffers et al., 2012) and hippocampus (Koo, Shin, Lim, Seong, & Joo, 2017; Riemann et al., 2007). In addition, a few studies have used diffusion tensor imaging (DTI) to evaluate differences in white-matter tracts in persons with Insomnia Disorder compared with matched controls. One study found reduced fractional anisotropy in the anterior internal capsule, suggesting disturbed fronto-subcortical connectivity in patients with insomnia (Spiegelhalder et al., 2014). Similarly, Li and colleagues found reduced fractional anisotropy in the right anterior and posterior internal capsule, as well as in white-matter tracts of the superior corona radiate, longitudinal fasciculus and the corpus callosum (Li et al., 2016). Kang and colleagues specifically investigated the neural connectivity of the left thalamus and inferior frontal gyrus, and found that patients with insomnia had reduced fractional anisotropy and axial diffusivity in the tract connecting these two regions (Kang et al., 2018). Furthermore, disturbances of fronto-subcortical white-matter integrity were also found to be related to poor sleep quality in a large study with community-dwelling older adults (Sexton et al., 2017). A recent DTI study assessed topological alterations in Insomnia Disorder, and found changes of the regional organization of frontal and subcortical areas as well as reduced connectivity in frontal networks (Wu et al., 2018). In summary, studies assessing structural alterations related to insomnia have generally reported reductions in frontal and subcortical areas and the white-matter tracts connecting these areas.

Across functional and structural studies, a recent coordinate-based meta-analysis integrating neuroimaging findings showed limited consistency in identifying "where" in the brain findings on insomnia converge (Tahmasian et al., 2018). Therefore, a more integrated approach may be required to better understand the brain mechanisms of insomnia. Most studies on brain structure have assessed insomnia-related differences in specific regions and white-matter tracts, and the few studies that have assessed insomnia-related structural connectivity (SC) have focused mainly on graph-theoretical measures (Lu et al., 2017a; Wu et al., 2018). Thus, it is still unclear how whole-brain SC is affected by these regional changes. The brain is an extraordinarily complex system, and modern understandings of neuropathology have evolved from an emphasis on specific brain regions to evaluating the disturbances of inter-connected neural networks (Fornito & Bullmore, 2015). State-of-the-art neuroimaging methods reflect this refined understanding of brain structure and function by applying data-driven connectivity approaches at the whole-brain level. This is particularly relevant to disorders such as insomnia that affect a large range of functions not plausibly explained by alterations of single brain structures. Uncovering the large-scale network alterations in insomnia could prove essential for a better understanding of this highly prevalent disorder and the widespread dysfunctions associated with it. However, this perspective has not gained sufficient attention in insomnia research.

The objective of this study was to investigate the changes in SC associated with Insomnia Disorder. SC forms the anatomical backbone of functional brain connectivity, and DTI techniques have enabled us to non-invasively assess the white-matter tracts connecting brain areas and their alterations in neurological and psychiatric disorders (Griffa, Baumann, Thiran, & Hagmann, 2013). We employed a data-driven approach that allowed us to assess whole-brain SC in adults with Insomnia Disorder compared with healthy controls with no sleep complaints. Based on the before-mentioned studies, we hypothesized that Insomnia Disorder would be characterized by reduced SC among frontal and subcortical areas, and that individual differences in connectivity would correlate with insomnia severity.

2 | METHODS

2.1 | Participants

We included 30 adult participants in the study (age 18–65 years); 16 persons with Insomnia Disorder and 14 matched controls without sleep complaints. Insomnia participants were recruited from the sleep clinic at the Department of Clinical Neurophysiology, Aarhus University Hospital (Denmark) or via newspaper announcements. Age- and gender-matched controls with no sleep problems were recruited through local announcements. All participants underwent a clinical interview, and inclusion criteria for the insomnia group were Insomnia Disorder according to the DSM-5 criteria, largely equivalent with the diagnosis of Chronic Insomnia according to the ICSD3. That is, difficulties initiating or maintaining sleep, including early morning awakenings, with adequate opportunity for sleep. The sleep problems had to be present for at least three nights per week for the last 3 months, and had to be associated with significant impairments in important areas of daytime functioning, such as occupational, educational or social functioning (Morin et al., 2015). Participants with Insomnia Disorder were screened for other sleep disorders, and underwent 1 night of ambulatory polysomnography. Polysomnography montage and scoring was done in accordance with the AASM

manual (Iber, Ancoli-Israel, Chesson, & Quan, 2007) by an experienced technician trained in sleep scoring, and the scoring was re-examined by a neurologist specialized in sleep medicine. Participants were excluded if they had more than mild symptoms of other sleep disorders, such as sleep-disordered breathing, sleep-related movement disorder or circadian rhythm disorder. Exclusion criteria for all participants were the use of psychotropic or hypnotic medications, sleep-disruptive medical disorders, psychiatric disorders, alcohol or substance abuse, as well as any standard magnetic resonance imaging (MRI) incompatibility. All participants completed the Pittsburgh Sleep Quality Index (PSQI; Buysse, Reynolds Iii, Monk, Berman, & Kupfer, 1989) and the Insomnia Severity Index (ISI; Bastien, Vallieres, & Morin, 2001). The characteristics of the participants are shown in Table 1. The study was approved by the Ethical Committee of the Central Denmark Region, and participants signed informed consent prior to inclusion in accordance with the Declaration of Helsinki.

2.2 | Image acquisition and analysis

All participants underwent the same imaging protocol using a Siemens Trio 3T MRI scanner with a 12-channel head coil at Aarhus University Hospital, Denmark. The T1-weighted sequence was performed with the following parameters: voxel size 1 × 1 mm, slice thickness 1 mm, matrix size 256 × 256, FoV 256 × 256, repetition time 2,000 ms, echo time 3.7 ms, pixel bandwidth 150 Hz/Px, and flip angle of 9°. The diffusion-weighted sequence was acquired using echo-planar imaging (SE-EPI) with a voxel size 2 × 2 mm, slice thickness 2.4 mm, matrix size 96 × 96, FoV 192 × 192, repetition time 5,900 ms, echo time 84 ms, *b*-value 1,000 s mm^{-2}, 71 diffusion directions (9 *b*0 scans, acquired every eight volumes), two phase-encoding directions (anterior-posterior and posterior-anterior), pixel bandwidth 2004 Hz/Px.

For each participant, probabilistic tractography was applied to the DTI data to produce a map of whole-brain SC and thus characterize the strength of physical binding between all brain regions. We used the FDT pipeline in FSL (FMRIB Software Library, Oxford, version 5.0, www.fmrib.ox.ac.uk/fsl/), combined with in-house written scripts, to run the multiple preprocessing steps for SC estimation. These included correction for head movements and eddy currents using the EDDY and TOPUP algorithms with the dual phase-encoding directions, to reconstruct a single set of data with significantly reduced distortions. We fitted a tensor model to each voxel of the brain and visually inspected the coding of the fibre-tracts, followed by estimation of crossing fibres using a Markov-Chain-Monte-Carlo algorithm. Brain parcellation was performed using the Automated Anatomical Labeling (AAL) brain atlas (Tzourio-Mazoyer et al., 2002), where the brain is parcellated into 90 cortical and subcortical regions. The AAL atlas is widely used in connectivity studies and can thus facilitate comparison between studies. The estimation of SC was done using probabilistic tractography at the voxel level with a sampling of 5,000 streamlines per voxel. For each region, the connectivity to the remaining 89 regions was calculated and normalized by the volume of each region, to control for the area size effect. A threshold of 1% of the maximum number of streamlines from seed to target region was set to remove spurious connections. Because the connectivity probability from region 1 to region 2 is highly correlated with the connectivity probability from region 2 to region 1, we defined the unidirectional connectivity between two regions by averaging these two probabilities. For each participant, a 90 × 90 connectivity matrix was constructed, representing the participant-specific SC network of the brain. Figure 1 illustrates the analysis pipeline.

2.3 | Group analysis

Between-group statistical comparison was performed using network-based statistics (NBS; Zalesky, Fornito, & Bullmore, 2010). This is a non-parametric method used to identify significant differences between groups of networks, while controlling for multiple comparisons that arise from comparing a large number of connections. The NBS method controls the family-wise error rate by making the assumption that relevant differences in connectivity between groups are confined to connections that are connected with each other and thus form sub-networks in the larger network. The method is analogous to cluster-based correction strategies used in standard parametric mapping (Hayasaka & Nichols, 2004), but rather than clusters in volumetric data it identifies sub-networks in the topological space. NBS is based on the General Linear Model combined with non-parametric permutations of the design matrix. Here, we used a design corresponding to

TABLE 1 Demographic and clinical characteristics of the participants

	Insomnia disorder	Normal sleepers	t/χ^2	*p*-value
Age (years)	46.9 (3.26)	48.6 (3.71)	$t(28) = 0.36$	.722
Gender (M/F)	5/11	4/10	$\chi^2(1) = 0.03$	.873
Body mass index	22.4 (3.4)	23.9 (3.1)	$t(28) = 1.31$	.200
Handedness (R/L)	12/4	12/2	$\chi^2(1) = 0.54$	.464
Education (years)	14.5 (2.2)	15.3 (2.2)	$t(28) = -0.92$	.368
PSQI score	12.3 (0.84)	3.5 (0.31)	$t(28) = -9.27$	< .000
ISI score	18.8 (5.18)	2.8 (2.52)	$t(28) = -10.53$	< .000

Note: Values are listed as mean (*SD*).
Abbreviations: ISI, Insomnia Severity Index; PSQI, Pittsburgh Sleep Quality Index; *SD*, standard deviation.

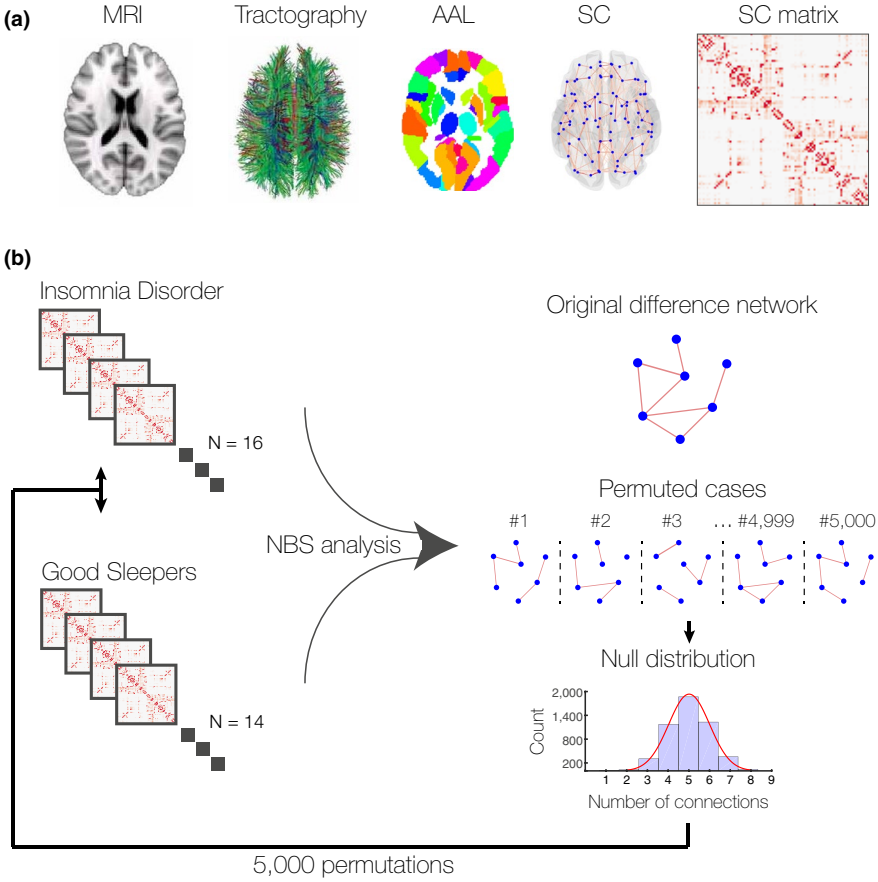

FIGURE 1 Analysis pipeline. (a) Using standard anatomical magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI), structural connectivity (SC) was determined for each participant by applying probabilistic tractography. The brain regions were defined using the Automated Anatomical Labeling (AAL) template. The SC of each participant can be visualized as a connectivity matrix reflecting the strength of the connectivity between each of the 90 AAL regions. (b) We used network-based statistics (NBS) to compare the connectivity matrices of the two groups. This method creates a null distribution of the largest sub-network by permuting participants across the two groups

unpaired *t*-tests between the group diagnosed with Insomnia Disorder and the group of matched controls with no sleep problems. The NBS method relies on a specification of the *t*-statistic (*t*-stat) level above which connected sub-networks will be identified, while the permutations control for the family-wise error rate. We tested a range of *t*-stat thresholds from 2 to 3.4. A high *t*-stat threshold implies that only the connections with most pronounced differences between groups are included, while lower thresholds allow more subtle differences to form the sub-networks. For all thresholds we regarded sub-networks of corrected *p*-values as significant if $p < .05$. In all cases, significance was an attribute of the sub-network in question and never individual connections.

2.4 | Associations between structural connectivity and clinical scores

We used Pearson's correlations to assess the relationship between the properties of the identified network and clinical scores of disturbed sleep (PSQI) and insomnia severity (ISI).

3 | RESULTS

The difference between the groups in PSQI and ISI scores (both $p < .000$) shows that the two groups are clearly distinct with regard to disturbed sleep and insomnia severity. The PSQI scores ranged from 8 to 19 in the insomnia group, and from 2 to 5 in the control group. The ISI scores ranged from 9 to 24 in the insomnia group, and from 0 to 9 in the control group. The groups did not differ in terms of age, gender and education (Table 1). The participants in the insomnia group reported onset of insomnia symptoms between 1 and 20 years ago, with a group mean of 11 years (*SD* 1.62). According to the polysomnography data, it took about 17 min for the participants in the insomnia group to fall asleep. The average total sleep time was 6 hr and 20 min, and the mean awake time after sleep onset was 40 min. On average, insomnia participants were asleep 85% of the time spend in bed. Participants in the control group did not undergo polysomnography. According to the PSQI ratings, the insomnia participants slept somewhat less. The scores showed an average total sleep time of 5 hr and 6 min, with a mean sleep-onset latency of 35 min and an average awake time after sleep onset of 109 min. According to the PSQI scores, the average sleep efficiency of the insomnia participants was 68%.

3.1 | Structural connectivity

Compared with matched controls with no sleep complaints, the NBS analyses showed that participants with Insomnia Disorder had reduced SC in a brain network including 34 regions and 39 structural links between them (*t*-threshold 2.6, $p = .014$). Figure 2 shows a visualization of the network of reduced connectivity in the insomnia group, and Table 2 gives an overview of the difference network ordered by the degree, i.e. the number of connections linking one node to other nodes within the significant network.

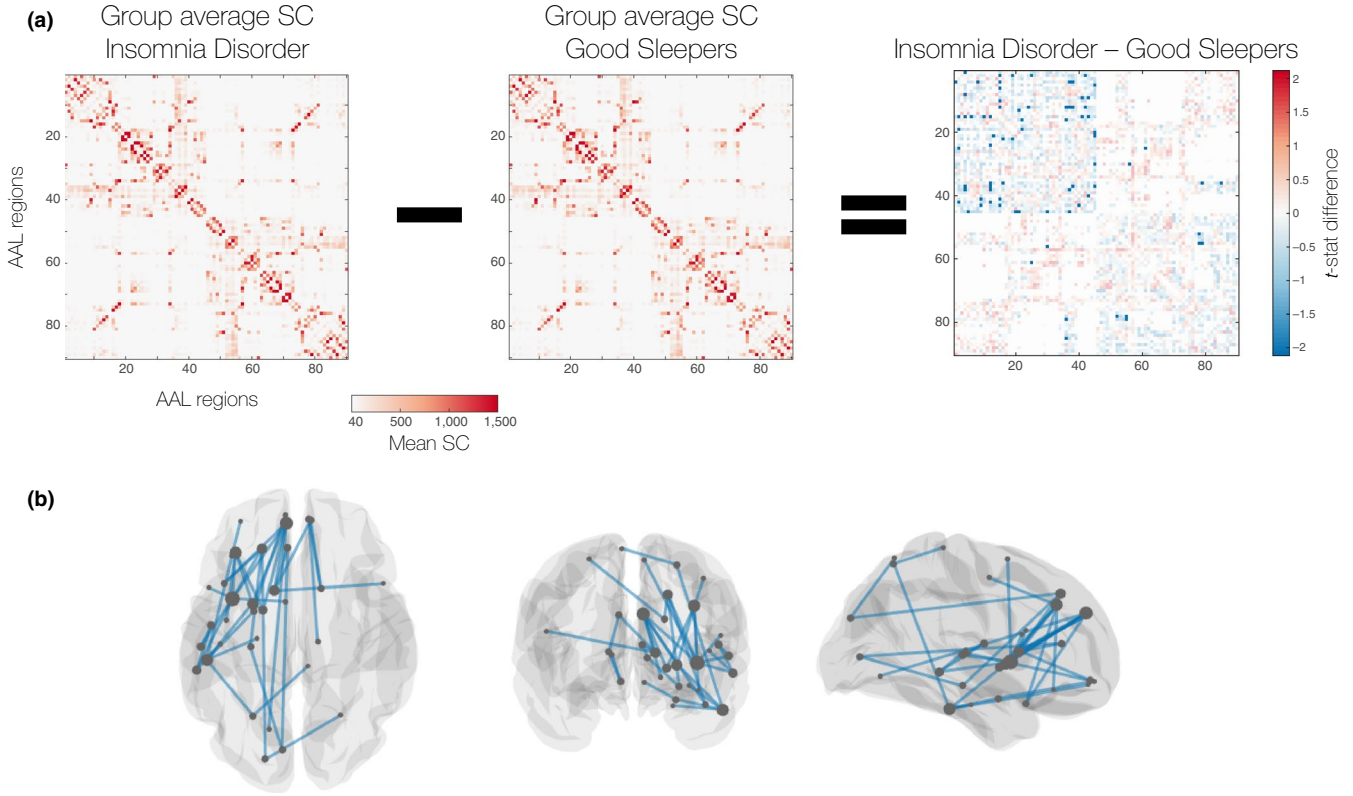

FIGURE 2 Reduced structural connectivity (SC) in Insomnia Disorder. (a) When comparing the connectivity matrices of the participants with Insomnia Disorder with the Good Sleeper Controls, we found a sub-network of significantly reduced connectivity in the insomnia group. (b) A visualization shows the regions and connections involved in the network of reduced connectivity in Insomnia Disorder. Thickness of connection reflects the amplitude of the difference (absolute of *t*-stat) and node size is scaled to the degree within the significant network

The altered network identified with NBS was largely left-lateralized and predominantly involved fronto-subcortical connections. The region of the network with the largest degree was left insula followed by left medial superior frontal gyrus, left middle frontal gyrus, left inferior temporal gyrus, left superior frontal gyrus, left caudate and left putamen (Table 2). The findings were robust to other NBS settings (Supporting Information, Figure S1). The NBS analyses revealed no networks of increased connectivity in the insomnia group.

3.2 | Correlation with clinical measures

Across all participants, there were significant negative correlations of the mean connection strength of the identified network with the PSQI scores ($r = -.71$, $p < .000$) and with the ISI scores ($r = -.71$, $p < .000$; Figure 3). There were no significant correlations with the PSQI or ISI scores when looking at correlations within the groups separately.

4 | DISCUSSION

We found that Insomnia Disorder is associated with reduced SC in a network including mainly fronto-subcortical connections in the left hemisphere with particularly impaired connectivity of the left insula. Moreover, we found a clear relationship between mean connection strength of the network and insomnia severity (ISI) and sleep quality (PSQI) across all participants. The findings suggest either that Insomnia Disorder could lead to reduced SC in fronto-subcortical areas or, alternatively, that people with pre-existing low SC in these areas have an increased risk of developing Insomnia Disorder. The mean duration of the insomnia symptoms was 11 years in this sample (range 1–20 years), so it would be possible that the disorder could have caused changes in SC. However, we cannot determine the causality from the present study.

4.1 | A key role of the insula

The present findings indicate that reduced connectivity of the left insula plays a key role in insomnia disorder. This is consistent with a number of resting-state functional MRI (fMRI) studies suggesting a role of the insula in insomnia. Reduced functional connectivity between the left insula, amygdala, striatum and thalamus was found in an early resting-state fMRI study comparing persons with Insomnia Disorder with matched controls without sleep complaints (Huang et al., 2012). Similarly, Chen and colleagues reported altered insula activation using a resting-state paradigm with simultaneous electroencephalogram (EEG) and fMRI. They found increased co-activation of insula with salience networks in persons with Insomnia Disorder

TABLE 2 Network of reduced structural connectivity in Insomnia Disorder (NBS, *t*-thresh = 2.6)

AAL region 1	AAL region 2	*t*-value
Insula L	Mid temporal gyrus L	3.38277
Insula L	Mid frontal gyrus L	3.31802
Insula L	Sup temporal gyrus L	3.28373
Insula L	Suppl motor area L	3.21040
Insula L	Sup frontal gyrus, medial L	3.03876
Insula L	Sup frontal gyrus L	2.91902
Insula L	Inf frontal gyrus, operc part L	2.75371
Sup frontal gyrus, medial L	Putamen L	3.49883
Sup frontal gyrus, medial L	Ligual gyrus	2.92450
Sup frontal gyrus, medial L	Temporal pole: sup temp gyrus L	2.89226
Sup frontal gyrus, medial L	Pallidum L	2.79188
Sup frontal gyrus, medial L	Caudate L	2.70861
Mid frontal gyrus L	Putamen L	3.27051
Mid frontal gyrus L	Precentral gyrus L	3.12777
Mid frontal gyrus L	Pallidum L	3.02592
Mid frontal gyrus L	Inf frontal gyrus, orb part L	2.60041
Inf temporal gyrus L	Putamen L	3.61412
Inf temporal gyrus L	Sup parietal gyrus L	3.07406
Inf temporal gyrus L	Amygdala L	2.86488
Inf temporal gyrus L	Parahippocampal gyrus L	2.82760
Inf temporal gyrus L	Mid frontal gyrus, orb part L	2.68540
Sup frontal gyrus L	Sup occipital gyrus L	3.02766
Sup frontal gyrus L	Temporal pole: sup temp gyrus L	2.70466
Sup frontal gyrus L	Hippocampus L	2.66740
Caudate L	Anterior cingulate L	3.60375
Caudate L	Sup frontal gyrus, medial R	2.81492
Caudate L	Inf frontal gyrus, operc part R	2.61736
Putamen L	Pallidum L	2.83568
Mid temporal gyrus L	Rolandic operculum L	2.86214
Mid temporal gyrus L	Heschl gyrus L	2.77894
Caudate R	Sup frontal gyrus, medial R	2.91264
Caudate R	Sup frontal gyrus, medial orb R	2.72567
Sup frontal gyrus, med orb R	Thalamus R	3.67602
Rolandic operculum L	Sup temporal gyrus L	4.23588
Anterior cingulate L	Calcarine fissure L	2.74708
Amygdala L	Sup frontal gyrus, medial orb L	3.05236
Hippocampus L	Calcarine fissure L	3.09335
Sup occipital gyrus L	Sup parietal gyrus R	3.04965
Sup parietal gyrus L	Paracentral lobule R	2.61789

Note: All connections and their *t*-value ordered by degree.
Abbreviations: AAL, automated anatomical labelling; *t*-thresh, *t*-threshold; degree = number of connections linking this node to other nodes of the network.

when instructed to fall asleep (Chen, Chang, Glover, & Gotlib, 2014). The salience networks of this study involve different areas than the connections found in our study, and the relationship between structural and functional connectivity is not simple (Cabral, Kringelbach, & Deco, 2017), but both studies point to insula connectivity as an important factor for understanding the neural circuitry underlying Insomnia Disorder. Furthermore, aberrant insula activity in persons with insomnia was reported in resting-state fMRI studies applying analyses of regional homogeneity (Wang et al., 2016) and fractional amplitude of low-frequency fluctuations (Liu et al., 2016). Even though the relationship between functional and SC is not yet fully understood (Mollink et al., 2019), the results of these previous studies on functional connectivity seem to support the findings of the present study suggesting disrupted insula connectivity in Insomnia Disorder.

Structural neuroimaging studies have also pointed to insular involvement in insomnia complaints. A recent DTI study of healthy adults with insomnia symptoms reported a negative correlation between nodal efficiency in the left insula and insomnia severity (Lu et al., 2017a). Nodal efficiency is a graph theoretical term reflecting how well a brain region connects with other regions of the network. As such, these results seem in line with our findings, even though the study provides no information on the specific nature of the connections. In addition, a voxel-based morphometry study reported an inverse association of early morning awakening with grey-matter density in the area bordering the left insula and orbitofrontal cortex (Stoffers et al., 2012).

The insula is thought to play an essential role for human awareness, and it is involved in a number of functions, such as interoception, emotional salience, time perception and decision-making (Namkung, Kim, & Sawa, 2017). Studies suggest that insula is important for integration of information on our feeling state (Craig, 2002). It is involved in visceral and somatic sensory processing, and the integration of these processes into conscious emotional experience (Namkung et al., 2017). Insular activity is particularly linked to interoceptive awareness (Craig, 2002), and a recent study showed alterations in EEG-markers of interoception in Insomnia Disorder (Wei et al., 2016). The reduced insula connectivity observed in this study may be key to altered interoception in Insomnia Disorder.

Insula function is not limited to interoception and affective processes. It is also a key region in the detection and processing of salient stimuli across multiple cognitive and sensory domains (Namkung et al., 2017). The insula is uniquely positioned deep within the lateral sulcus of the brain, widely connected to frontal, temporal, parietal and subcortical areas (Ghaziri et al., 2017). This position enables a key function in the so-called salience network involved in the orientation towards both external and internal stimuli and the generation of appropriate responses to these (Menon & Uddin, 2010; Namkung et al., 2017). These responses also include the modulation of autonomic reactivity to salient stimuli (Menon & Uddin, 2010), and as such, disturbed insula connectivity may be a primary target for studies on brain mechanisms underlying hyper-arousal, the enigmatic key feature of Insomnia Disorder. In

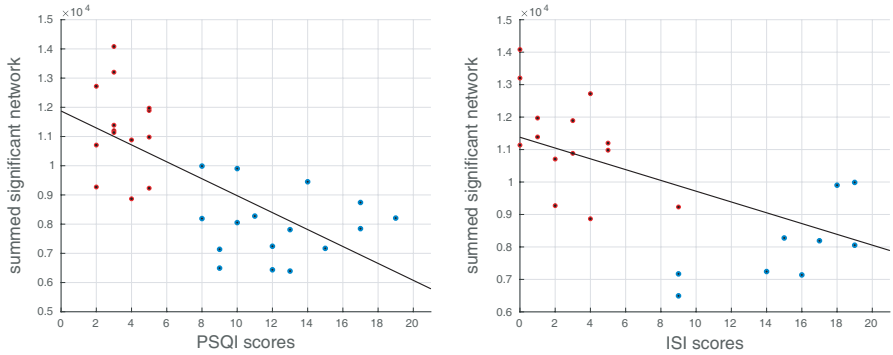

FIGURE 3 Correlation with clinical measures. Significant correlations were found between mean connection strength of the identified network and clinical measures of sleep quality (Pittsburgh Sleep Quality Index; PSQI) and insomnia severity (Insomnia Severity Index; ISI) of all participants. In both scales, higher scores indicate poorer sleep (PSQI) or more severe insomnia (ISI). The insomnia participants are represented in blue and the control group in red

summary, the reduced connectivity of the insula suggests that insomnia is associated with impairments in interoception, emotional processing, and the generation of appropriate internal and external responses to salient events.

The insular cortex is very closely apposed to the claustrum, a thin subcortical sheet of neurons. Given their proximity, we cannot exclude a possible involvement of claustrum connectivity where we interpret connections as having the insular cortex as origin or destination. Interestingly, a recent genome-wide association study, combined with cell-type-specific gene-set analyses, showed significant enrichment of insomnia risk genes in pyramidal neurons of the claustrum (Jansen et al., 2019).

In a meta-analysis, insula grey-matter reductions have been found as a shared feature of psychopathology, including depression, anxiety and schizophrenia (Goodkind et al., 2015). This is consistent with the present results as sleep disturbances are highly prevalent in most psychiatric disorders (Morin et al., 2015). Neuroimaging studies investigating these should take care to control for the impact of insomnia. The exclusion criteria of the present study ensured that participants did not suffer from psychiatric disorders. Still, the question remains if insula dysfunction is in any way specific to insomnia or may be a more general vulnerability factor that is involved in a number of diseases. A recent large-scale study reported a role of the insula in the functionally connected structures mediating the association between depressive symptoms and sleep quality (Cheng, Rolls, Ruan, & Feng, 2018), and future studies should aim at disentangling the role of insula in insomnia and psychiatric disorders.

We found that participants with Insomnia Disorder showed a network of reduced connectivity with the left insula being connected to seven other regions within this network (primarily frontal regions, Table 2). It would be relevant to know if these connections are afferent, efferent or bi-directional connections, but it is not possible to determine the nature of the connections from our data. In general, we still have a limited understanding of the SC of the human insula, even though recent progress has been made (Ghaziri et al., 2017). Therefore, we need future research to assess whether Insomnia Disorder is related to the output of the insula not reaching downstream areas sufficiently, or if the input to the insula is impeded and therefore insula activity is not modulated optimally.

4.2 | Reduced fronto-subcortical connectivity in Insomnia Disorder

Another key feature of the present findings is the reduced fronto-subcortical connectivity. Fronto-subcortical network dysfunction has been identified in several neurological and psychiatric disorders (Tekin, 2002), and it is also consistent with previous studies on Insomnia Disorder. Studies looking at white-matter integrity found reduced fractional anisotropy in the anterior internal capsule in persons with Insomnia Disorder compared with good sleeper controls, indicating disturbed fronto-subcortical connectivity (Li et al., 2016; Spiegelhalder et al., 2014). Our results are also in line with a recent DTI study that found reduced fronto-subcortical connectivity in Insomnia Disorder (Wu et al., 2018). However, this study also reported other networks of reduced SC and one network of increased connectivity. The reasons for the divergence of the results may be found in the data quality of the study, the use of deterministic tractography and unclear NBS settings.

The reduced connectivity in the present study includes connections between frontal areas and classical limbic areas, such as amygdala, hippocampus and thalamus, and alterations in these regions have previously been reported in persons with Insomnia Disorder (Huang et al., 2012; Koo et al., 2017; Riemann et al., 2007). Together with the insula hypoconnectivity, the reduced connectivity of these brain regions may contribute to the cognitive and emotional dysfunctions experienced by persons with Insomnia Disorder.

Interestingly, what is even more pronounced is the reduced connectivity of frontal regions, including the orbitofrontal and medial frontal cortex with basal ganglia structures, such as the putamen, caudate and pallidum. A recent genome-wide association study, combined with tissue-specific gene-set analyses, showed strong enrichment of insomnia risk genes across the basal ganglia (Jansen et al., 2019), and altered activity in basal ganglia structures has previously been associated with Insomnia Disorder. A recent study

reported that structural changes of the putamen were related to higher arousal indices in participants with persistent insomnia (Koo et al., 2017). Likewise, differences in the local topology of the putamen were found to be related to increased insomnia scores in a recent study using resting-state fMRI in healthy adults with insomnia symptoms compared with controls with no insomnia complaints (Lu et al., 2017b). In a task-based fMRI study, Stoffers and colleagues found reduced recruitment of the head of the left caudate in persons with Insomnia Disorder during an executive task and argued that the caudate was an essential structure for the abnormalities related to insomnia (Stoffers et al., 2013). This suggestion is supported by a seed-based resting-state fMRI study by Huang and colleagues, which had amygdala as primary region of interest. They reported reduced connectivity between the left amygdala and bilateral caudate as well as between the right amygdala and the left pallidum (Huang et al., 2012). In summary, these studies are consistent with our findings that point to an essential role of the basal ganglia in Insomnia Disorder.

A recent meta-analysis of neuroimaging studies on post-traumatic stress disorder (PTSD) found that persons with PTSD differed from trauma-exposed persons without PTSD mainly in altered activity in basal ganglia regions (Stark et al., 2015). It may be that basal ganglia dysfunction is involved when stress responses turn into a clinical syndrome, such as PTSD. Our results suggest that reduced basal ganglia connectivity with frontal regions is an important component of the pathophysiology of insomnia and the risk it imposes on the development of other mental disorders.

4.3 | Left hemisphere lateralization

A prominent feature of the present findings is the high degree of left hemisphere lateralization. The left hemisphere has not previously been emphasized in relation to insomnia as most studies find bilateral alterations of brain activity. The lateralization is not explained by handedness, as we ran the NBS analysis with handedness as co-variate and found the same results. In contrast to our findings, two previous studies reported insomnia-related reductions in white-matter integrity that were largely right-lateralized (Li et al., 2016; Sexton et al., 2017). However, left hemisphere alterations in relation to insomnia symptoms have also been reported previously, including reduced volume of the left orbitofrontal cortex (Altena et al., 2010) and of the area bordering the left insula and orbitofrontal cortex (Stoffers et al., 2012). In addition, reduced nodal efficiency of the left insula and putamen has also been associated with Insomnia Disorder (Wu et al., 2018). These findings show reductions in left hemisphere structures that are part of the network of reduced connectivity found in the present study.

Furthermore, altered functional connectivity of the left insula seems to be one of the most consistent findings of resting-state fMRI studies (Chen et al., 2014; Huang et al., 2012; Liu et al., 2016; Wang et al., 2016). Based on asymmetries in the peripheral autonomic nervous system, a neurobiological model has proposed that the left insula is primarily activated by parasympathetic activity and the right insula is activated predominantly in relation to sympathetic input (Craig, 2002). According to this model, reduced SC of the left insula, as seen in our results, would be expected to impair the neural processing of parasympathetic input and as such interfere with sleep.

In a different line of work, high-density EEG research on slow waves during sleep has shown a higher involvement of the left hemisphere in the origin and propagation of slow waves during sleep (Murphy et al., 2009). Particularly, slow waves often originate in the left insula, and involve the middle, medial and inferior frontal gyri significantly more in the left hemisphere than in the right. These areas are exactly the key regions of reduced connectivity identified in our study. An extensive meta-analysis shows that persons with insomnia have significantly reduced slow-wave sleep compared with controls with no sleep problems (Baglioni et al., 2014), and the network of reduced connectivity identified in this study may be one of the mechanisms behind the reduction in slow-wave sleep in insomnia. Furthermore, a recent study shows that the sleep EEG of Insomnia Disorder is characterized most by a difficulty to transition from N2 sleep to the deeper sleep stage N3 characterized by slow waves (Wei et al., 2017). Concertedly, these previous findings and the current results make it tempting to suggest involvement of the reduced connectivity of the left insula and frontal regions in persons with Insomnia Disorder in their difficulty to enter slow-wave sleep.

In the interpretation of the present results, a number of limitations should be considered. First, this is a cross-sectional study, and we can draw no causal conclusions from the results regarding whether the observed differences in structural brain connectivity are the cause or result of insomnia disorder. Future studies should use longitudinal designs to clarify the causal direction of structural alterations in Insomnia Disorder. Second, the present study included a relatively small sample size. The two groups, however, are well matched and at the same time clearly distinct with regard to insomnia measures. In addition, the insomnia group is very well defined, as all the participant groups underwent polysomnography to rule out common co-morbid sleep disorders, such as sleep-disordered breathing and sleep-related movement disorders. Finally, we could not assess subdivisions of the relevant network regions, such as anterior or posterior insula, as the AAL atlas used for brain parcelation includes only relatively large brain regions. We chose this atlas because it is commonly used and thereby facilitates comparison between studies, but a different brain parcellation strategy might allow for a more nuanced view of the brain regions.

In conclusion, our results show that Insomnia Disorder is related to significantly reduced SC in a network involving left insula as well as fronto-subcortical connections. This study adds to the existing knowledge by taking a data-driven whole-brain perspective on brain connectivity. The findings demonstrate changes in brain connectivity at the structural level that form the anatomical "backbone" of functional connectivity in areas related to interoception, emotional processing, stress responses and the initiation of travelling slow waves. These findings can improve the understanding of the

neurobiological foundations of insomnia and may assist the development of efficient treatment strategies.

ACKNOWLEDGEMENTS

Thanks to Tim Van Hartevelt, Dora Zeidler, Marit Otto and Kristina Bacher Svendsen for assistance with this project. Center for Music in the Brain is funded by the Danish National Research Foundation (DNRF117).

CONFLICT OF INTEREST

KVJ, AS, HF, SDS, EVS, MK, PV: no conflicts of interest declared.

AUTHOR CONTRIBUTIONS

This study was designed by KVJ, PV, MK and EVS. KVJ and SDS did assessment and data collection. KVJ, AS and HF analysed the data. KVJ drafted the manuscript. AS, HF, SDS, MK, EVS and PV revised the manuscript.

ORCID

Kira V. Jespersen https://orcid.org/0000-0002-7183-3849

REFERENCES

Altena, E., Vrenken, H., Van Der Werf, Y. D., Van Den Heuvel, O. A., & Van Someren, E. J. (2010). Reduced orbitofrontal and parietal gray matter in chronic insomnia: A voxel-based morphometric study. *Biological Psychiatry*, *67*, 182–185. https://doi.org/10.1016/j.biopsych.2009.08.003

Baglioni, C., Regen, W., Teghen, A., Spiegelhalder, K., Feige, B., Nissen, C., & Riemann, D. (2014). Sleep changes in the disorder of insomnia: A meta-analysis of polysomnographic studies. *Sleep Medicine Reviews*, *18*, 195–213. https://doi.org/10.1016/j.smrv.2013.04.001

Bastien, C. H., Vallieres, A., & Morin, C. M. (2001). Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Medicine*, *2*, 297–307. https://doi.org/10.1016/s1389-9457(00)00065-4

Blanken, T. F., Benjamins, J. S., Borsboom, D., Vermunt, J. K., Paquola, C., Ramautar, J., …, Van Someren, E. J. W. (2019). Insomnia disorder subtypes derived from life history and traits of affect and personality. *The Lancet Psychiatry*, *6*, 151–163. https://doi.org/10.1016/s2215-0366(18)30464-4

Bonnet, M. H., & Arand, D. L. (2010). Hyperarousal and insomnia: State of the science. *Sleep Medicine Reviews*, *14*, 9–15. https://doi.org/10.1016/j.smrv.2009.05.002

Buysse, D. J., Reynolds Iii, C. F., Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The Pittsburgh sleep quality index: A new instrument for psychiatric practice and research. *Psychiatry Research*, *28*, 193–213. https://doi.org/10.1016/0165-1781(89)90047-4

Cabral, J., Kringelbach, M. L., & Deco, G. (2017). Functional connectivity dynamically evolves on multiple time-scales over a static structural connectome: Models and mechanisms. *NeuroImage*, *160*, 84–96. https://doi.org/10.1016/j.neuroimage.2017.03.045

Chen, M. C., Chang, C., Glover, G. H., & Gotlib, I. H. (2014). Increased insula coactivation with salience networks in insomnia. *Biological Psychology*, *97*, 1–8. https://doi.org/10.1016/j.biopsycho.2013.12.016

Cheng, W., Rolls, E. T., Ruan, H., & Feng, J. (2018). Functional connectivities in the brain that mediate the association between depressive problems and sleep quality. *JAMA Psychiatry*, *75*, 1052–1061. https://doi.org/10.1001/jamapsychiatry.2018.1941

Craig, A. D. (2002). How do you feel? Interoception: The sense of the physiological condition of the body. *Nature Reviews Neuroscience*, *3*, 655–666. https://doi.org/10.1038/nrn894

Fornito, A., & Bullmore, E. T. (2015). Connectomics: A new paradigm for understanding brain disease. *European Neuropsychopharmacology*, *25*, 733–748. https://doi.org/10.1016/j.euroneuro.2014.02.011

Ghaziri, J., Tucholka, A., Girard, G., Houde, J. C., Boucher, O., Gilbert, G., …, Nguyen, D. K. (2017). The corticocortical structural connectivity of the human insula. *Cerebral Cortex*, *27*, 1216–1228. https://doi.org/10.1093/cercor/bhv308

Goodkind, M., Eickhoff, S. B., Oathes, D. J., Jiang, Y., Chang, A., Jones-Hagata, L. B., …, Etkin, A. (2015). Identification of a common neurobiological substrate for mental illness. *JAMA Psychiatry*, *72*, 305–315. https://doi.org/10.1001/jamapsychiatry.2014.2206

Griffa, A., Baumann, P. S., Thiran, J.-P., & Hagmann, P. (2013). Structural connectomics in brain diseases. *NeuroImage*, *80*, 515–526. https://doi.org/10.1016/j.neuroimage.2013.04.056

Hayasaka, S., & Nichols, T. E. (2004). Combining voxel intensity and cluster extent with permutation test framework. *NeuroImage*, *23*, 54–63. https://doi.org/10.1016/j.neuroimage.2004.04.035

Huang, Z., Liang, P., Jia, X., Zhan, S., Li, N., Ding, Y., …, Li, K. (2012). Abnormal amygdala connectivity in patients with primary insomnia: Evidence from resting state fMRI. *European Journal of Radiology*, *81*, 1288–1295. https://doi.org/10.1016/j.ejrad.2011.03.029

Iber, C., Ancoli-Israel, S., Chesson, A., & Quan, S. (2007). *The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications* (pp. 48–49). Westchester, IL: American Academy of Sleep Medicine.

Jansen, P. R., Watanabe, K., Stringer, S., Skene, N., Bryois, J., Hammerschlag, A. R., …, Posthuma, D. (2019). Genome-wide analysis of insomnia in 1,331,010 individuals identifies new risk loci and functional pathways. *Nature Genetics*, *51*(3), 394–403. https://doi.org/10.1038/s41588-018-0333-3

Kang, J. M., Joo, S. W., Son, Y. D., Kim, H., Ko, K. P., Lee, J. S., & Kang, S. G. (2018). Low white-matter integrity between the left thalamus and inferior frontal gyrus in patients with insomnia disorder. *Journal of Psychiatry & Neuroscience*, *43*, 366. https://doi.org/10.1503/jpn.170195

Kay, D. B., & Buysse, D. J. (2017). Hyperarousal and beyond: New insights to the pathophysiology of insomnia disorder through functional neuroimaging studies. *Brain Sciences*, *7*(3), 23. https://doi.org/10.3390/brainsci7030023

Koo, D. L., Shin, J.-H., Lim, J.-S., Seong, J.-K., & Joo, E. Y. (2017). Changes in subcortical shape and cognitive function in patients with chronic insomnia. *Sleep Medicine*, *35*, 23–26. https://doi.org/10.1016/j.sleep.2017.04.002

Li, S., Tian, J., Bauer, A., Huang, R., Wen, H., Li, M., …, Jiang, G. (2016). Reduced integrity of right lateralized white matter in patients with primary Insomnia: A diffusion-tensor imaging study. *Radiology*, *280*, 520–528. https://doi.org/10.1148/radiol.2016152038

Liu, C. H., Liu, C. Z., Zhang, J., Yuan, Z., Tang, L. R., Tie, C. L., …, Liu, Q. Q. (2016). Reduced spontaneous neuronal activity in the insular cortex and thalamus in healthy adults with insomnia symptoms. *Brain Research*, *1648*, 317–324. https://doi.org/10.1016/j.brainres.2016.07.024

Lu, F. M., Dai, J., Couto, T. A., Liu, C. H., Chen, H., Lu, S. L., …, Yuan, Z. (2017a). Diffusion tensor imaging tractography reveals disrupted white matter structural connectivity network in healthy adults with

insomnia symptoms. *Frontiers in Human Neuroscience*, *11*, 583. https://doi.org/10.3389/fnhum.2017.00583

Lu, F. M., Liu, C. H., Lu, S. L., Tang, L. R., Tie, C. L., Zhang, J., & Yuan, Z. (2017b). Disrupted topology of frontostriatal circuits is linked to the severity of insomnia. *Frontiers in Neuroscience*, *11*, 214.

Menon, V., & Uddin, L. Q. (2010). Saliency, switching, attention and control: A network model of insula function. *Brain Structure and Function*, *214*, 655–667. https://doi.org/10.1007/s00429-010-0262-0

Mollink, J., Smith, S. M., Elliott, L. T., Kleinnijenhuis, M., Hiemstra, M., Alfaro-Almagro, F., …, Miller, K. L. (2019). The spatial correspondence and genetic influence of interhemispheric connectivity with white matter microstructure. *Nature Neuroscience*, *22*, 809–819. https://doi.org/10.1038/s41593-019-0379-2

Morin, C. M., Drake, C. L., Harvey, A. G., Krystal, A. D., Manber, R., Riemann, D., & Spiegelhalder, K. (2015). Insomnia disorder. *Nature Reviews Disease Primers*, *1*, 15026. https://doi.org/10.1038/nrdp.2015.26

Murphy, M., Riedner, B. A., Huber, R., Massimini, M., Ferrarelli, F., & Tononi, G. (2009). Source modeling sleep slow waves. *Proceedings of the National Academy of Sciences*, *106*, 1608–1613. https://doi.org/10.1073/pnas.0807933106

Namkung, H., Kim, S.-H., & Sawa, A. (2017). The Insula: An underestimated brain area in clinical neuroscience, psychiatry, and neurology. *Trends in Neurosciences*, *40*, 200–207. https://doi.org/10.1016/j.tins.2017.02.002

Ohayon, M. M. (2002). Epidemiology of insomnia: What we know and what we still need to learn. *Sleep Medicine Reviews*, *6*, 97–111. https://doi.org/10.1053/smrv.2002.0186

Riemann, D., Nissen, C., Palagini, L., Otte, A., Perlis, M. L., & Spiegelhalder, K. (2015). The neurobiology, investigation, and treatment of chronic insomnia. *The Lancet Neurology*, *14*, 547–558. https://doi.org/10.1016/s1474-4422(15)00021-6

Riemann, D., Spiegelhalder, K., Feige, B., Voderholzer, U., Berger, M., Perlis, M., & Nissen, C. (2010). The hyperarousal model of insomnia: A review of the concept and its evidence. *Sleep Medicine Reviews*, *14*, 19–31. https://doi.org/10.1016/j.smrv.2009.04.002

Riemann, D., Voderholzer, U., Spiegelhalder, K., Hornyak, M., Buysse, D. J., Nissen, C., …, Feige, B. (2007). Chronic insomnia and MRI-measured hippocampal volumes: A pilot study. *Sleep*, *30*, 955–958. https://doi.org/10.1093/sleep/30.8.955

Roth, T., Coulouvrat, C., Hajak, G., Lakoma, M. D., Sampson, N. A., Shahly, V., …, Kessler, R. C. (2011). Prevalence and perceived health associated with insomnia based on DSM-IV-TR; international statistical classification of diseases and related health problems, tenth revision; and research diagnostic criteria/international classification of sleep disorders, criteria: Results from the America insomnia survey. *Biological Psychiatry*, *69*, 592–600. https://doi.org/10.1016/j.biopsych.2010.10.023

Sexton, C. E., Zsoldos, E., Filippini, N., Griffanti, L., Winkler, A., Mahmood, A., …, Ebmeier, K. P. (2017). Associations between self-reported sleep quality and white matter in community-dwelling older adults: A prospective cohort study. *Human Brain Mapping*, *38*, 5465–5473. https://doi.org/10.1002/hbm.23739

Spiegelhalder, K., Regen, W., Baglioni, C., Nissen, C., Riemann, D., & Kyle, S. D. (2015). Neuroimaging insights into insomnia. *Current Neurology and Neuroscience Reports*, *15*, 9. https://doi.org/10.1007/s11910-015-0527-3

Spiegelhalder, K., Regen, W., Prem, M., Baglioni, C., Nissen, C., Feige, B., …, Riemann, D. (2014). Reduced anterior internal capsule white matter integrity in primary insomnia. *Human Brain Mapping*, *35*, 3431–3438. https://doi.org/10.1002/hbm.22412

Stark, E. A., Parsons, C. E., Van Hartevelt, T. J., Charquero-Ballester, M., McManners, H., Ehlers, A., …, Kringelbach, M. L. (2015). Post-traumatic stress influences the brain even in the absence of symptoms: A systematic, quantitative meta-analysis of neuroimaging studies. *Neuroscience & Biobehavioral Reviews*, *56*, 207–221. https://doi.org/10.1016/j.neubiorev.2015.07.007

Stoffers, D., Altena, E., van der Werf, Y. D., Sanz-Arigita, E. J., Voorn, T. A., Astill, R. G., …, Van Someren, E. J. (2013). The caudate: A key node in the neuronal network imbalance of insomnia? *Brain*, *137*, 610–620.

Stoffers, D., Moens, S., Benjamins, J., van Tol, M. J., Penninx, B. W., Veltman, D. J., …, Van Someren, E. J. (2012). Orbitofrontal gray matter relates to early morning awakening: A neural correlate of insomnia complaints? *Frontiers in Neurology*, *3*, 105.

Tagliazucchi, E., & Laufs, H. (2014). Decoding wakefulness levels from typical fMRI resting-state data reveals reliable drifts between wakefulness and sleep. *Neuron*, *82*, 695–708. https://doi.org/10.1016/j.neuron.2014.03.020

Tagliazucchi, E., & Van Someren, E. J. (2017). The large-scale functional connectivity correlates of consciousness and arousal during the healthy and pathological human sleep cycle. *NeuroImage*, *160*, 55–72. https://doi.org/10.1016/j.neuroimage.2017.06.026

Tahmasian, M., Noori, K., Samea, F., Zarei, M., Spiegelhalder, K., Eickhoff, S. B., …, Eickhoff, C. R. (2018). A Lack of consistent brain alterations in insomnia disorder: An activation likelihood estimation meta-analysis. *Sleep Medicine Reviews*, *42*, 111–118. https://doi.org/10.1016/j.smrv.2018.07.004

Tekin, S. (2002). Frontal–subcortical neuronal circuits and clinical neuropsychiatry. *Journal of Psychosomatic Research*, *53*, 647–654. https://doi.org/10.1016/s0022-3999(02)00428-2

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., …, Joliot, M. (2002). Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *NeuroImage*, *15*, 273–289. https://doi.org/10.1006/nimg.2001.0978

Wang, T., Li, S., Jiang, G., Lin, C., Li, M., Ma, X., …, Tian, J. (2016). Regional homogeneity changes in patients with primary insomnia. *European Radiology*, *26*, 1292–1300. https://doi.org/10.1007/s00330-015-3960-4

Wei, Y., Colombo, M. A., Ramautar, J. R., Blanken, T. F., van der Werf, Y. D., Spiegelhalder, K., …, Van Someren, E. J. W. (2017). Sleep stage transition dynamics reveal specific stage 2 vulnerability in insomnia. *Sleep*, *40*(9). https://doi.org/10.1093/sleep/zsx117

Wei, Y., Ramautar, J. R., Colombo, M. A., Stoffers, D., Gómez-Herrero, G., van der Meijden, W. P., …, Van Someren, E. J. (2016). I keep a close watch on this heart of mine: Increased interoception in insomnia. *Sleep*, *39*, 2113–2124. https://doi.org/10.5665/sleep.6308

Wu, Y., Liu, M., Zeng, S., Ma, X., Yan, J., Lin, C., …, Jiang, G. (2018). Abnormal topology of the structural connectome in the limbic cortico-basal-ganglia circuit and default-mode network among primary insomnia patients. *Frontiers in Neuroscience*, *12*, 860. https://doi.org/10.3389/fnins.2018.00860

Zalesky, A., Fornito, A., & Bullmore, E. T. (2010). Network-based statistic: Identifying differences in brain networks. *NeuroImage*, *53*, 1197–1207. https://doi.org/10.1016/j.neuroimage.2010.06.041

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Jespersen KV, Stevner A, Fernandes H, et al. Reduced structural connectivity in Insomnia Disorder. *J Sleep Res*. 2019;00:e12901. https://doi.org/10.1111/jsr.12901