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Insomnia Subtypes Have Differentiating Deviations in Brain Structural Connectivity

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ABSTRACT

BACKGROUND: Insomnia disorder is the most common sleep disorder. A better understanding of insomnia-related deviations in the brain could inspire better treatment. Insufficiently recognized heterogeneity within the insomnia population could obscure detection of involved brain circuits. In the current study, we investigated whether structural brain connectivity deviations differed between recently discovered and validated insomnia subtypes.

METHODS: Structural and diffusion-weighted 3T magnetic resonance imaging data from 4 independent studies were harmonized. The sample consisted of 73 control participants without sleep complaints and 204 participants with insomnia who were grouped into 5 insomnia subtypes based on their fingerprint of mood and personality traits assessed with the Insomnia Type Questionnaire. Linear regression correcting for age and sex was used to evaluate group differences in structural connectivity strength, indicated by fractional anisotropy, streamline volume density, and mean diffusivity and evaluated within 3 different atlases.

RESULTS: Insomnia subtypes showed differentiating profiles of deviating structural connectivity that were concentrated in different functional networks. Permutation testing against randomly drawn heterogeneous subsamples indicated significant specificity of deviation profiles in 4 of the 5 subtypes: highly distressed, moderately distressed reward sensitive, slightly distressed low reactive, and slightly distressed high reactive. Connectivity deviation profile significance ranged from $p = .001$ to $p = .049$ for different resolutions of brain parcellation and connectivity weight.

CONCLUSIONS: Our results provide an initial indication that different insomnia subtypes exhibit distinct profiles of deviations in structural brain connectivity. Subtyping insomnia may be essential for a better understanding of brain mechanisms that contribute to insomnia vulnerability.

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Insomnia disorder is a common sleep disorder that affects approximately 10% of the adult European population (1,2). Patients with insomnia are affected by persistent difficulty falling asleep, staying asleep, and/or early morning awakening with subjectively impaired daytime functioning (3). Insomnia disorder has severe consequences, including an increased risk of cardiovascular disorders (4), obesity (5), and mental disorders (6,7). Cognitive behavioral therapy for insomnia can alleviate the burden of insomnia complaints (8,9) and contribute to prevention of other mental disorders (10–12). However, cognitive behavioral therapy for insomnia does not bring sufficient relief for all patients, even if complemented with hypnotics (8,9). To innovate and improve treatment, we need a better understanding of the brain circuits involved in insomnia vulnerability. Brain imaging studies have so far failed to pinpoint consistent, specifically localized, brain regional deviations. Therefore, it has been proposed that insomnia more likely involves distributed deviations, which may be revealed by studying structural connectivity between brain regions (13,14). Structural connectivity deviations could impact the vulnerability to develop and maintain insomnia (15). Reviews of structural and functional imaging studies comparing people with insomnia disorder and people without sleep complaints have suggested potential involvement of the default mode network and salience network in insomnia (16–20). Nevertheless, the explained variance and consistency across studies have been limited (21,22). It has been proposed that inconsistency in neuroimaging results could be due in part to unrecognized heterogeneity within the affected population; differently distributed deviations in brain structure or function may present as the same disease phenotype (23,24).

If more homogeneous subtypes could be recognized within such a heterogeneous population, corresponding deviations in structural connectivity might be determined with better consistency. How to define different insomnia subtypes is an ongoing discussion. Various insomnia subtype classifications have focused on dominant sleep complaints (3,25–28). Unfortunately, sleep feature–related classifications may not be very robust (25,27). More recently, a bottom-up, data-driven approach revealed 5 more robust subtypes of insomnia disorder. Instead of focusing on sleep features only, the subtypes could be distinguished based on their level of distress as well

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as their unique profile of personality and mood traits (24). These subtypes can be assessed with the Insomnia Type Questionnaire (ITQ) (24). It can be hypothesized that ITQ-based insomnia subtypes also differ with respect to deviations in the brain circuits involved in these distinguishing mood and personality traits.

Therefore, in the current study, we aimed to compare the structural connectivity of the 5 ITQ-based insomnia subtypes. Based on brain region-to-function mappings reported in the literature (29) and subtype-specific mood and personality traits, we selected frontal, orbitofrontal, and temporal brain regions for inclusion in analyses. White matter microstructure of connections between the selected regions was assessed using fractional anisotropy (FA), streamline volume density (SVD), and mean diffusivity (MD) (30,31). Analysis of 204 subtyped people with insomnia disorder and 73 people without sleep complaints provided the first indication that insomnia subtypes can have different structural connectivity deviation profiles and sometimes even opposing deviations. We further contextualized our findings by identifying the major functional networks that were most affected for each subtype.

METHODS AND MATERIALS

Participants

Data were acquired during 4 studies performed between 2014 and 2021 by the Sleep & Cognition group at the Netherlands Institute for Neuroscience, Amsterdam (32–34). Participants were recruited through the Netherlands Sleep Registry (http://www.slaapregister.nl), advertisements, and media. Across all studies, applicants were eligible if they were between ages 18 and 70 years. Screening occurred via telephone, online questionnaires, and a subsequent intake interview. Depending on the original study sample, insomnia disorder was diagnosed in accordance with the International Classification of Sleep Disorders (26) and DSM-IV (35) or DSM-5 (3). Exclusion criteria for applicants varied across the original studies but consistently included a current diagnosis of severe sleep apnea; severe restless leg syndrome; narcolepsy; any other severe neurological, psychiatric, or somatic disorders; current shift work; or any magnetic resonance imaging (MRI) contraindication such as non–MR compatible metal implants, claustrophobia, or pregnancy (see the Supplement for additional details). In addition, 3 studies recorded a polysomnogram that was inspected for undiagnosed severe sleep disorders other than insomnia. All studies were approved by the ethical board of the Vrije Universiteit Medical Center or the University of Amsterdam. Written informed consent was obtained from all participants.

Measures

Sample characteristics were described using the Insomnia Severity Index (range 0–28) (36), Pittsburgh Sleep Quality Index (range 1–21) (37), Inventory of Depressive Symptomatology – Self Report (range 0–84) (38), and Hospital Anxiety and Depression Scale (anxiety and depression subscale both range 0–21) (39). Higher scores on these questionnaires indicate more severe symptoms. In participants with a diagnosis of insomnia disorder, we determined the insomnia type using the ITQ (24). T1-weighted and diffusion-weighted images were acquired using 2 Philips Achieva 3T scanners (see the Supplement for MRI acquisition details).

Structural Connectome Reconstruction

Preprocessing and reconstruction of structural connectivity networks were performed separately for each sample. T1-weighted scans were preprocessed and segmented using the recon-all function of FreeSurfer (stable version 6.0.1) (40). Synb0-DISCO (version 3.0) (41,42), CATO version 3.2.2 (43), and FSL version 6.0.4 (44) were used to preprocess diffusion-weighted data and reconstruct structural connectivity matrices. For network reconstruction, we used the fine-grained Cammoun subparcellation of the Desikan-Killiany atlas consisting of 114 cortical regions (43,45). To validate our findings, we also used the Desikan-Killiany combined cortical and subcortical atlas as present in FreeSurfer (46), which consists of 82 regions, and the cortical parcellation by Schaefer *et al.* consisting of 100 regions (47). For each atlas, the weight of a connection between regions was computed as the weighted average FA or MD value over all voxels that the streamlines passed or as SVD reflecting the number of streamlines between 2 regions divided by the mean volume of the connected regions. To ensure sufficient data points for each connection, analyses only included connections that were present in at least 70% of the participants (48). To account for multisite and multisample effects, we harmonized the connection weights for each pairwise connection between all brain regions for sample differences using the NeuroCombat (49) R package version 1.0.13 (https://github.com/Jfortin1/ComBatHarmonization) in R version 4.0.4 (see the Supplement for more details).

Regions-of-Interest Selection

The fact that insomnia subtypes differed with respect to their profile of mood and personality traits allowed for data-driven selection of brain regions of interest representing these traits (Figure 1A). To do this, we made use of the Neuro Knowledge Engine (NKE) (29), a functional neuroimaging database that links brain structures to function based on rigorous neuroimaging meta-analysis of 18,155 positron emission tomography and MRI articles. NKE consists of functional terms and brain activation coordinates extracted from functional neuroimaging studies. By combining functional terms, NKE describes clusters that represent neurobiological domains, e.g., arousal. We matched the mood and personality traits that distinguish ITQ-based insomnia subtypes to NKE functional terms to identify NKE neurobiological domains where insomnia subtypes differ (see the Supplement for a list of the used terms). NKE neurobiological domains were included if at least 40% of the NKE functional terms matched terms distinguishing insomnia subtypes. Next, the brain coordinate data of included NKE neurobiological domains were registered to atlas space, and the frequency of insomnia subtype–related NKE neurobiological domains per atlas region was determined. NKE offers an arbitrary granularity from as little as 2, up to as many as 50, different NKE neurobiological domains. We focused on the finer granularity of 25 up to 50 NKE neurobiological domains for more specific neurobiological domains, smaller associated brain regions, and higher sensitivity due to more NKE

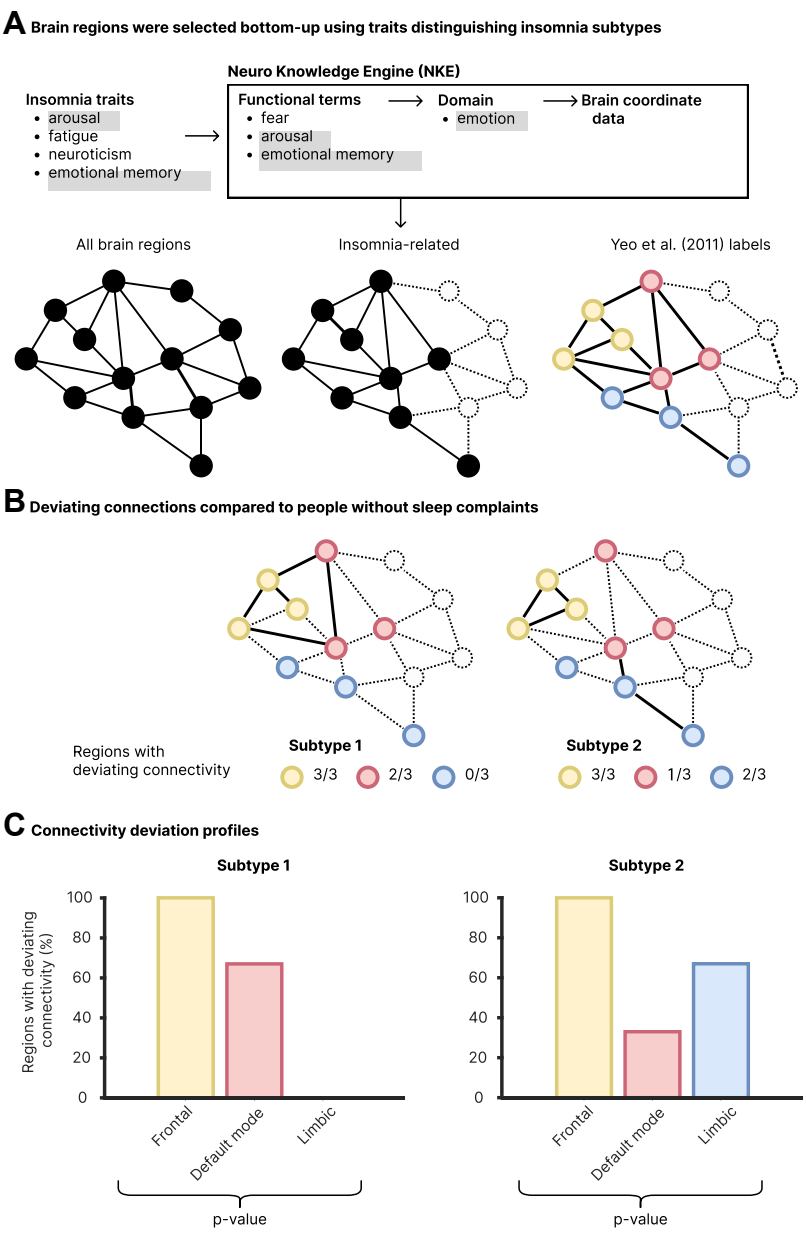

Figure 1. Procedure of brain region selection and obtaining connectivity deviation profiles. **(A)** Brain regions involved in traits distinguishing insomnia subtypes were selected using the Neuro Knowledge Engine database and functionally annotated according to the Yeo *et al.* (51) intrinsic functional resting-state networks. **(B)** Examples of deviating (solid lines) and nondeviating (dashed lines) connections of insomnia subtypes 1 and 2 compared with people without sleep complaints. **(C)** Example connectivity deviation profiles based on the proportion of brain regions with deviating structural connectivity in each functional network. The *p* value indicating significance of the specificity of the connectivity deviation profile of each subtype is obtained by permutation testing with drawing groups randomly from all heterogeneous insomniacs irrespective of their subtype, while keeping the control group the same.

functional terms. Repeating the steps described above for the different NKE clustering granularities allowed us to build a heat map indicating the involvement of brain regions in insomnia (Figure S1). We selected regions of interest that linked at least 10 times to any neurobiological domain associated with insomnia subtype traits.

Deviating Structural Connectivity

After selecting brain regions involved in traits that distinguished insomnia subtypes (Figure 1A), connection-wise deviations in white matter microstructure were assessed 3 times based on FA, SVD, and MD. For every connection, group differences in the standardized deviation of FA, SVD, and MD were estimated by running 2 multivariate regression models on *z*-transformed data including the covariates age and sex. An initial model compared the heterogeneous insomnia group combining all subtypes with the group of control participants without sleep complaints. A second model compared all 5 insomnia subtypes as separate groups with people without sleep complaints. Subsequent analyses focused on deviating connections, defined as all deviations exceeding a primary (*t* statistic) threshold of $|t| \geq 2$ (Figure 1B).

Functional Annotation and Connectivity Deviation Profiles

The resulting matrices with deviating structural connections between the selected brain regions were functionally annotated to evaluate whether insomnia subtypes differed in the

functional systems involved. Brain regions were annotated based on the 7 intrinsic functional resting-state networks described by Yeo *et al.* (50). Next, we calculated the percentage of regions with deviating connectivity within each functional network by dividing the number of regions with at least 1 deviating connection exceeding a t statistic $|t| \geq 2$ by the number of regions present in the functional network (Figure 1B, C). This approach provided, both for the heterogeneous insomnia group and for each subtype, a profile of the proportion of brain regions with deviating structural connectivity in each functional network.

Connectivity Deviation Profile–Based Statistics

Permutation testing of the connectivity deviation profiles was used to evaluate subtype specificity. This approach tests the probability of obtaining similar results if we took random subsamples of the total heterogeneous insomnia sample to compare with the control group without sleep complaints. We ran 10,000 permutations in which subtype labels were shuffled across participants with insomnia while taking covariates into account (51). In short (also see Figure 1B, C), for each permutation, we repeated the analysis steps described above by estimating connection-wise deviations in the randomly shuffled subtype groups and computing the number of brain regions with deviating structural connectivity in each annotated functional network. Based on the estimated null distributions, p values for the connectivity deviation profiles were obtained by calculating how often at least the same number of brain regions with deviating connectivity were present for all 5 functional network annotations in the randomly labeled groups. The p values represent the likelihood of finding the subtype-specific connectivity deviation profile in randomly labeled subsamples of heterogeneous insomnia. Unless stated otherwise, all analyses were performed in MATLAB (version 2019b; The MathWorks, Inc.). Figures use an accessible qualitative color scheme (52). Preprocessed connectivity matrices (http://osf.io/zjkcb) and the analysis code (http://github.com/tombresser/Deviating-structural-connectivity-in-insomnia-subtypes) are available.

RESULTS

Participants

The total sample consisted of a reference group of 73 people without sleep complaints and 204 people with insomnia. In the insomnia sample, 31 were subtyped as highly distressed, 89 as moderately distressed reward sensitive, 30 as moderately distressed reward insensitive, 34 as slightly distressed high reactive, and 20 as slightly distressed low reactive, as described by Blanken *et al.* (24). Table S2 shows all demographics.

Insomnia Subtype Traits Map to Frontal, Orbitofrontal, and Temporal Brain Regions

NKE was used to map mood and personality traits that distinguished insomnia subtypes to the Cammoun subparcellation of the Desikan-Killiany cortical atlas (45). The resulting heat map (Figure S1) indicated involvement of frontal, orbitofrontal, and temporal regions. Based on this heat map, 43 regions of interest (Table S3) that linked at least 10 times to any NKE neurobiological domain associated with insomnia subtype traits were included (Figure 2A) in subsequent analyses.

Insomnia Subtypes Differ in Structural Connectivity Deviations

Focusing on the FA-weighted structural connectivity of the selected regions of interest relevant to insomnia subtypes, we contrasted people without sleep complaints with the heterogeneous insomnia disorder group first and subsequently with each of the 5 subtypes separately. For both the heterogeneous sample of participants with insomnia and the subtypes, deviations in structural connectivity of the 43 regions of interest were visualized as red and blue lines representing higher and lower FA values, respectively, relative to control participants (Figure 2B). These deviating connectivity maps indicate differentiating patterns for different subtypes compared with people without sleep complaints, including some opposing deviations. For example, compared with people without sleep complaints, the heterogeneous insomnia group showed only increased connectivity strength between cortical regions, whereas all subtypes showed one or multiple deviating connections with reduced connectivity strength.

Structural Connectivity Deviations of Insomnia Subtypes Concentrate in Different Functional Networks

To place our findings in a functional perspective, we annotated the regions of interest in accordance with the functional networks described by Yeo *et al.* (50). The frontal, orbitofrontal, and temporal brain regions related to mood and personality traits that distinguished subtypes were part of 5 of the 7 functional networks described by Yeo *et al.* (50), i.e., the limbic (8 regions), ventral attention (11 regions), somatomotor (8 regions), default mode (13 regions), and frontoparietal (3 regions) networks (Figure 2A). The annotated deviating structural connectivity maps show how the involved functional systems differ depending on the subtype of insomnia (Figure 2B). To obtain a more globally integrated interpretation of these subtype-specific deviations, we quantified the percentage of brain regions with deviating structural connectivity in each functional network for every group (Figure 3A). The resulting connectivity deviation profiles show that in the heterogeneous total sample, connectivity deviations occurred in the somatomotor network, ventral attention network, frontoparietal network, and default mode network. Profiles of the insomnia subtypes revealed differential degrees of involvement of these networks as well as involvement of the limbic network. Insomnia subtypes differed in how deviations in structural connectivity were concentrated in 5 functional networks. The highly distressed subtype distinguished itself from the other subtypes by showing more brain regions with structural connectivity deviations in the default mode network (8/13 regions, 62%). In the moderately distressed reward-sensitive subtype, only a few connectivity deviations were within the ventral attention network (1/11 regions, 9%). In the slightly distressed low-reactive subtype, deviations were concentrated within the ventral attention network (5/11 regions, 45%). It should be noted that only 3 of

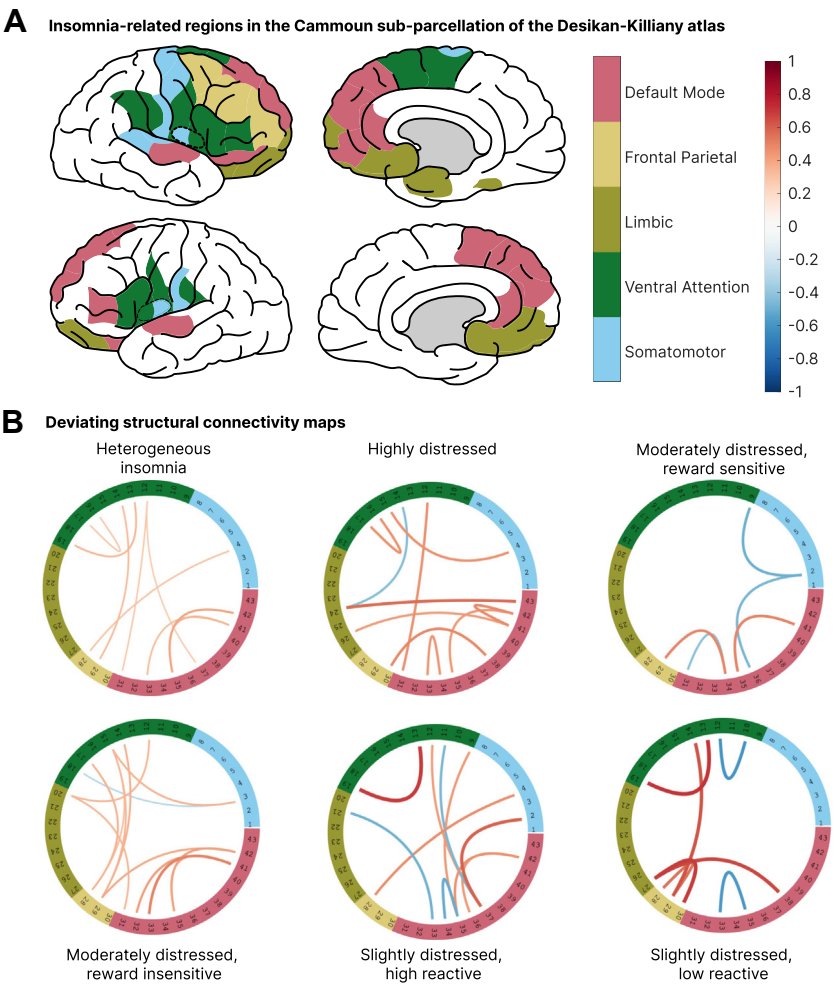

Figure 2. Deviating structural connectivity maps with functional annotation. **(A)** Representation of brain regions of the Cammoun subparcellation of the Desikan-Killiany cortical atlas that are, according to the Neuro Knowledge Engine database, involved in insomnia subtype-distinguishing mood and personality traits. Colors indicate the functional networks that the regions belong to according to Yeo *et al.* (50). **(B)** Circular representations of deviating structural connections based on fractional anisotropy. Ring numbers indicate cortical area (Table S3) and colors indicate the functional networks [as in **(A)**]. Thickness and color of the connecting lines represent the standardized effect size of the deviation relative to the control group, which varied between −0.80 and 0.77.

the 43 regions of interest for insomnia belong to the frontoparietal system, so that the resolution of perceptual involvement visualized in Figure 3 is not optimal for this network. For the absolute number of deviating connections in each functional network, we refer the reader to the Supplement (see Tables S5–S13 and Figures S11–S16).

Testing Subtype Specificity

So far, visual inspection suggested that deviating connectivity was differentially represented in functional systems depending on the subtype of insomnia. To test whether deviating patterns were subtype specific and would not occur with random sampling from the heterogeneous sample of people with insomnia, we ran 10,000 permutations by shuffling subtype labels across all participants with insomnia while keeping the control labels of the group without sleep complaints the same. We found that the connectivity deviation profile of the highly distressed subtype (p = .044, Bonferroni-corrected p = .220) differed significantly from random subsamples drawn from the heterogeneous pool of mixed insomnia subtypes.

Subcortical Brain Regions

To validate our findings and include subcortical regions, we reconstructed the heat map, repeated the connectivity map analysis, and repeated the connectivity deviation profile analysis using the 82-parcel Desikan-Killiany combined cortical and subcortical atlas in FreeSurfer (46). The heat map analysis selected 38 regions of interest resembling the cortical regions selected by the approach using the Cammoun 114-cortical parcel approach and also subcortical structures, i.e., the left putamen and bilateral hippocampus, amygdala, and nucleus accumbens area. The deviating connectivity maps again showed differentiating patterns in different subtypes compared with people without sleep complaints, with sometimes opposing deviations (Figure 4B). Visual inspection of the connectivity deviation profiles showed distinct differences between subtypes and indicated involvement of subcortical regions in all subtypes, especially the slightly distressed low-reactive subtype (Figure 3B). Permutation testing revealed that the profile of the slightly distressed, low-reactive subtype (p = .021, Bonferroni-corrected p = .105) differed significantly from randomly labeled subsamples drawn from the heterogeneous pool of mixed insomnia subtypes.

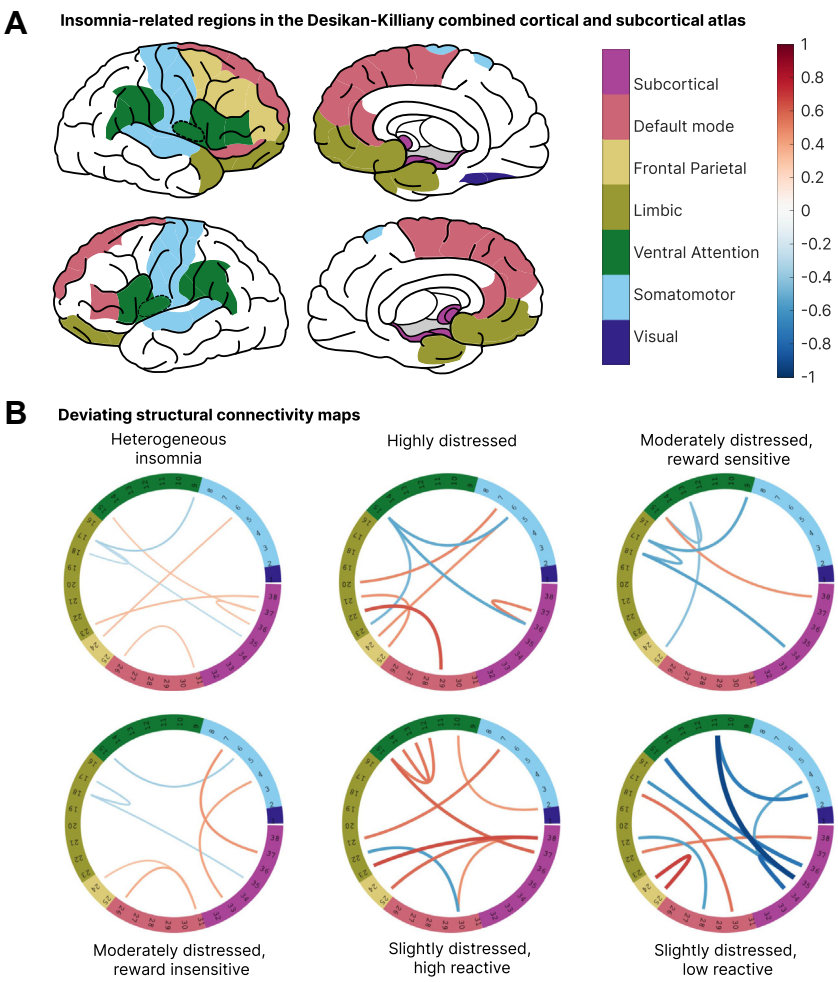

Figure 3. Deviating structural connectivity maps within functional networks including subcortical regions. **(A)** Representation of brain regions of the Desikan-Killiany combined cortical and subcortical atlas that are, according to the Neuro Knowledge Engine database, involved in insomnia subtype-distinguishing mood and personality traits. Colors indicate the functional networks that the regions belong to according to Yeo *et al.* (50). **(B)** Circular representations of deviating structural connections based on fractional anisotropy. Ring numbers indicate cortical area (Table S4), and colors indicate the functional networks [as in **(A)**]. The thickness and color of the lines represent the standardized effect size of the deviation relative to the control group, which varied between −0.67 and 0.67.

Consistency of the Connectivity Deviation Profiles

In addition to the FA-weighted structural connectivity findings reported, we also analyzed MD-weighted and SVD-weighted structural connectivity in both atlases and the cortical parcellation by Schaefer *et al.* (47). Table 1 shows the permuted *p* value for the connectivity deviation profile of each insomnia subtype across the different brain parcellations and connectivity weights. The analyses show some variance depending on brain parcellation and connectivity weight; however, the connectivity deviation profile of the highly distressed, moderately distressed reward-sensitive, and slightly distressed high-reactive subtypes were significant in multiple analyses. See the Supplement and Tables S14 to S16 for additional validation analyses regarding reconstruction method, scanner site, brain volume, and region of interest.

DISCUSSION

This study shows that specific subtypes of insomnia have different patterns of deviating structural connectivity. Deviations in structural connectivity associated with insomnia disorder differ depending on the specific subtype of insomnia and may even be in opposing directions. For regions of interest defined by the circuits associated with subtype-distinguishing personality and mood traits, deviating structural connectivity was predominantly found in limbic, default mode, and ventral attention networks. The extent to which brain regions within these networks showed deviating structural connectivity differed between subtypes. We demonstrated the robustness of these findings across 3 brain atlases, 3 connectivity weights, and by permutation testing. Our findings indicate that insomnia subtypes have distinct profiles of structural connectivity deviations, some of which would dilute or even cancel each other out in insomnia samples that are heterogeneous with unknown proportional representation of the different subtypes.

Heterogeneous Insomnia Disorder

Across the atlases, the heterogeneous insomnia sample showed deviating connectivity of frontal regions with limbic, ventral attention, default mode, and frontoparietal networks. Deviating connections in the limbic network were only

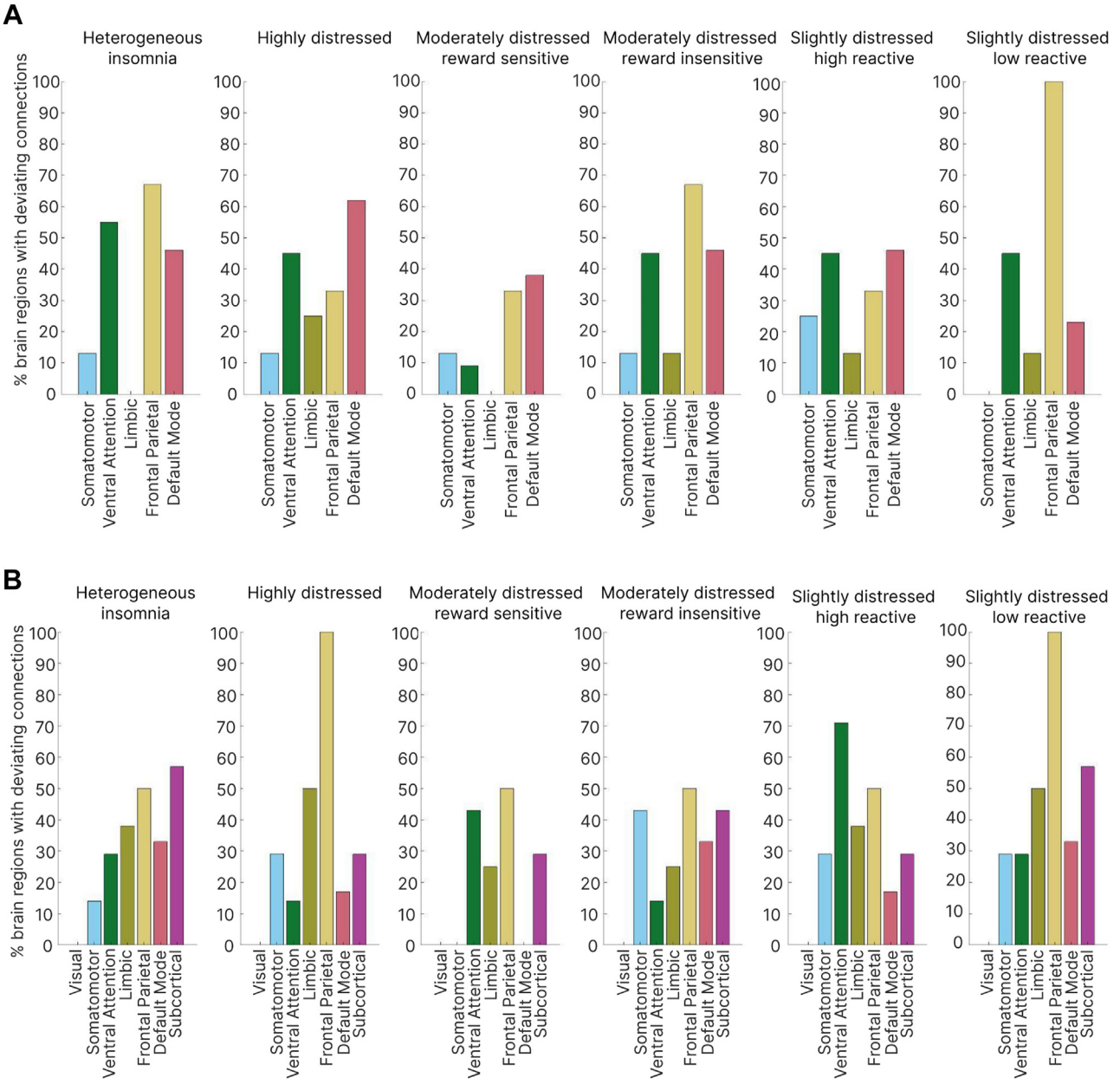

Figure 4. Connectivity deviation profiles. Subtype-specific deviations quantified as the percentage of insomnia-related brain regions with deviating structural connectivity in each functional network. **(A)** Brain regions defined by the Cammoun subparcellation of the Desikan-Killiany cortical atlas. **(B)** Brain regions defined by the Desikan-Killiany combined cortical and subcortical atlas. Connectivity deviations concern fractional anisotropy.

observed in the combined cortical and subcortical atlas of Desikan-Killiany. Previous studies in heterogeneous samples of people with insomnia disorder have reported similar deviating structural connectivity in regions such as the orbital frontal gyrus, superior frontal gyrus, cingulate gyrus, and insula, as well as the limbic and default mode networks (16,18,19,32,53–55). It is important to emphasize that the current study focused on finding differences in connectivity deviations between subtypes and therefore might have missed connectivity deviations that may be generic for all people with insomnia irrespective of subtype. For example, the angular gyrus was not part of the regions of interest that we defined based on subtype-distinguishing personality and mood traits; thus, we did not evaluate a previously suggested deviation of angular gyrus connectivity (32). Differences from previous studies may therefore be partially related to the regions-of-interest approach that we applied, but they could also result from different distributions of subtypes within different study samples. For example, while diluted and not significant in our larger but heterogeneous total sample, subtype samples

Table 1. *p* Values of the Connectivity Deviation Profiles

	Cammoun			Desikan-Killiany			Schaefer		
Subtypes	FA	SVD	MD	FA	SVD	MD	FA	SVD	MD
Highly Distressed	.044[a]	.234	.145	.058	.001[a,b]	.075	.086	.143	.063
Moderately Distressed, Reward Sensitive	.376	.053	.245	.240	.012[a]	.390	.106	.001[a,b]	.480
Moderately Distressed, Reward Insensitive	.181	.241	.295	.070	.112	.600	.094	.632	.361
Slightly Distressed, High Reactive	.143	.260	.01[a,b]	.052	.068	.021[a]	.046[a]	.263	.008[a,b]
Slightly Distressed, Low Reactive	.080	.689	.278	.021[a]	.181	.171	.049	.520	.231

Permutation-based *p* values showing to what extent connectivity deviation profiles differed from randomly labeled subsamples drawn from the heterogeneous pool of mixed insomnia subtypes across different brain parcellations and connection weights. Cammoun indicates Cammoun subparcellation of Desikan-Killiany; Desikan-Killiany indicates combined cortical and subcortical Desikan-Killiany parcellation; and Schaefer indicates cortical parcellation by Schaefer *et al.* (47).

FA, fractional anisotropy; MD, mean diffusivity; SVD, streamline volume density.

[a]$p < .05$.

[b]$p < .05$ after Bonferroni correction.

showed specific deviating structural connectivity of the limbic network in the Cammoun subparcellation of the Desikan-Killiany cortical atlas. These findings suggest that the unknown differences in the proportional representation of subtypes in heterogeneous insomnia samples could have contributed to inconsistent findings (21,22).

Insomnia Subtypes

Different ways to subtype insomnia have been proposed. We chose to use the classification that has proven to be most robust so far: at 5-year follow-up, 87% maintained their original subtype (24). Insomnia subtypes have also been proposed based on sleep characteristics like sleep onset insomnia or on specific predisposing, precipitating, and perpetuating processes. Most of the earlier subtypes were abandoned from the major nosologies due to a lack of reliability and validity [for review, see (14)]. One sleep-based subtyping method that has shown value is to distinguish between insomnia with short sleep (<6 hours) from insomnia in individuals who have a normal sleep duration (≥6 hours) using single-night polysomnography (56). However, we considered the robustness of this method to be suboptimal for our purposes; when recorded for a second night, only 32% of the short-sleeping insomniacs maintained their subtype, and only 14% fulfilled the criterion for short sleep across 2 nights (57,58).

For 4 of 5 insomnia subtypes, their specific connectivity deviation profile based on either FA, SVD, or MD differed significantly from profiles of randomly labeled subsamples of heterogeneous insomnia. Subtypes differed with respect to the predominantly affected functional networks. In the highly distressed subtype, deviating structural connectivity was predominantly concentrated in brain regions linked to the default mode, ventral attention, and limbic networks. In the slightly distressed low-reactive subtype, deviations predominantly concerned connectivity of the limbic and default mode networks. Finally, the slightly distressed high-reactive subtype was characterized by deviating MD-weighted connectivity in the somatomotor, ventral attention, limbic, and default mode networks. Our results show, for at least 4 of 5 insomnia subtypes, that connectivity deviation profiles were specific and diluted in randomly labeled subsamples of heterogeneous insomnia. The findings support the notion of different neural correlates underlying insomnia subtypes.

Functional Networks

Functional annotation showed that deviations in structural connectivity were concentrated in the ventral attention network, limbic network, default mode network, and subcortical regions, which have all previously been linked to insomnia disorder or traits relevant to insomnia.

The ventral attention network described by Yeo *et al.* is likely an aggregate of the salience and cingulo-opercular networks (50). This network is important for identifying and responding to salient stimuli, as well as shifting attention following unexpected stimuli (59,60). Previous studies have reported deviating structural (32,53) and functional (61) connectivity of the ventral attention network or salience network in insomnia. Altered salience network connectivity has also been reported in other psychiatric disorders (62,63) characterized by insomnia complaints and polygenic risks that overlap strongly with the polygenic risk for insomnia (64,65)—notably depression and anxiety. With its involvement in internal thought (66,67) and maladaptive rumination (68,69), the default mode network is of interest due to its potential role in dysfunctional forms of cognitive control in insomnia (61,70–72). Early-life experiences could play a role because they have long-lasting effects on functional connectivity including the default mode network (73,74) and contribute to the risk of developing insomnia (75,76).

Within the regions of interest defined by their involvement in the personality and mood traits that distinguish insomnia subtypes, the limbic network comprised orbitofrontal regions and the right frontal pole. Orbitofrontal brain regions are important in emotion, processing reward value, decision making, and problem-solving abilities (77,78). Alterations in structure and/or function of the orbitofrontal cortex have been described in insomnia (79–83) and depression (78). Several studies have even suggested the orbitofrontal cortex as a region where deviations link insomnia and depression (84–86). The degree of deviating limbic structural connectivity potentially reflects the degree of reduced subjective happiness, reduced positive affect, and higher prevalence of depression across the insomnia subtypes (24). On the other hand, the slightly distressed low-reactive subtype also showed disturbed limbic connectivity in the Desikan-Killiany combined cortical

and subcortical atlas but is not characterized by similarly excessive deviations in traits characteristic of depression (24). A possible explanation for this could be that disturbed limbic connectivity is likely to occur in all people with insomnia, while the deviating connections and direction of deviations may differ between subtypes (see Figures 2B and 4B). The observed deviating subcortical connectivity is consistent with previously described altered frontal-subcortical connectivity (53,54,87). The number of subcortical regions with deviating structural connectivity differed between the 5 subtypes and was the highest in the slightly distressed low-reactive subtype.

Limitations

Limitations of the current study have to be considered. First, group sizes were conventional for neuroimaging studies, but the required power for brainwide association studies remains an ongoing debate (88–91). To avoid underpowered comparisons, we integrated deviating structural connections into connectivity deviation profiles before performing statistical testing. Therefore, the findings should be interpreted at the profile level. Second, our study focused on a data-driven selection of cortical and subcortical regions. As a result, some regions and connections reported on in previous studies of insomnia were outside the scope of the current study.

Conclusions

Our study provides an initial indication that insomnia subtypes show differentiating, subtype-specific structural connectivity deviation profiles. The subtype-specific structural connectivity deviation profiles of 4 of 5 subtypes differed significantly from what would be expected in randomly drawn subsamples of heterogeneous insomnia. Our findings support the notion of insomnia subtypes with possibly different underlying brain mechanisms and show that subtyping of insomnia could be essential to discover more robust structural brain correlates and gain a better understanding of the brain mechanisms involved.

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