A Lack of consistent brain alterations in insomnia disorder: an activation likelihood estimation meta-analysis

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Abbreviations

ACC: anterior cingulate cortex

ALE: activation likelihood estimation

ALFF: amplitude of low frequency fluctuations

CBMA: coordinate-based meta-analysis

DMN: default mode network

DSM-IV: diagnostic and statistical manual of mental disorders-fourth edition

DSM-5: diagnostic and statistical manual of mental disorders-fifth edition

FC: functional connectivity

FWE: family wise error

GWAS: genome wide association studies

ICA: independent components analysis

ICSD-3: international classification of sleep disorders

ID: insomnia disorder

IFG: inferior frontal gyrus

LPBA40: LONI probabilistic brain atlas

MA: modeled activation

MDD: major depressive disorder

MNI: Montreal neurological institute

OFC: orbitofrontal cortex

PET: positron emission tomography

PTSD: posttraumatic stress disorder

ReHo: regional homogeneity

ROI: region of interest

rs-fMRI: resting-state functional magnetic resonance imaging

TFCE: threshold-free cluster enhancement

t-fMRI: task-based functional magnetic resonance imaging

Summary (198/200 words)

Insomnia disorder is a prevalent sleep disorder, which affects about 10% of general population. However, its neural mechanisms are poorly understood. Recently, several structural and functional neuroimaging studies have been conducted in patients with insomnia disorder, but these studies have yielded diverse findings. Here, we aimed to identify consistent patterns of abnormal brain alterations in insomnia disorder by performing a quantitative coordinate-based meta-analysis. Following the preferred reporting for systematic reviews and meta-analyses statement, we searched PubMed database and used reference tracking and finally retrieved 19 eligible studies (6 task-based functional magnetic resonance imaging, 8 resting-state functional magnetic resonance imaging, 3 voxel-based morphometry, and 2 positron emission tomography). We extracted peak coordinates from these studies and tested for convergence using the activation likelihood estimation method. Using this method, we found no significant convergent evidence for combination of structural atrophy and functional disturbances across previous studies (p= 0.914). Inconsistencies across these studies might be related to heterogonous clinical populations, the explorative nature of these studies in combination with small sample sizes, different experimental designs, and various preprocessing and statistical approaches. Future neuroimaging studies on insomnia disorder should include larger well-characterized samples, as well as standard imaging and analysis protocols.

Introduction

Insomnia disorder (ID) is the most common sleep disorder in adults with a prevalence range from about 4-22%, and an average of at least about 10% in the general population (1-3). The Diagnostic and statistical manual of mental disorders-fifth edition (DSM-5) and the third edition of International classification of sleep disorders (ICSD-3) criteria (1, 4) define ID as difficulties in falling and/or maintaining sleep or early morning awakening occurring for at least three times per week over a period of at least three months, not attributable to sleep-disrupting external conditions, and accompanied by subjective daytime complaints, for example fatigue, mood disturbance, poor concentration or memory impairment (5-7). People with ID experience a lower quality of life, and may have an increased risk of road and motor vehicle accidents (5, 6, 8). In addition, ID is a common comorbid condition in several psychiatric disorders including major depressive disorder (MDD), posttraumatic stress disorder (PTSD), anxiety, alcohol or drug abuse, bipolar disorder, eating disorder, obsessive compulsive disorder, and psychotic disorders (9-15). Annual costs associated with ID-related absenteeism and productivity losses in Canada were estimated at $970.6 million and $5 billion, respectively (16). ID has a strong association with days-out-of-role, which is independent from comorbidity (17). Results from the America insomnia survey demonstrated that insomnia was associated with substantial workplace costs and lost work performance due to presenteeism (18). Also, it accounts for 4.6% of injuries requiring medical attention (19). Neurobiological and psychological studies have suggested various genetic, behavioral, cognitive, and emotional risk factors for the development and maintenance of insomnia symptoms (1). Impaired daytime functioning due to insomnia is associated with cognitive deficits, interpersonal distress, low work productivity, and high sick leave (20-22). However, despite the high socioeconomic burden (23), the neurobiology of ID remains poorly understood (1, 24).

Over the last decade, a number of structural and functional neuroimaging studies, including voxel-based morphometry (VBM), positron emission tomography (PET), task-based functional magnetic resonance imaging (t-fMRI), and resting-state functional magnetic resonance imaging (rs-fMRI) have been conducted on patients with ID. For review see: (24-26). Structural MRI studies demonstrated grey matter atrophy in the orbitofrontal cortex, temporal cortex, precuneus and hippocampus, as well as grey matter volume increase in the anterior cingulate cortex (ACC) in patients with ID compared to good sleepers (27-31). Functional differences have also been reported in studies on ID. PET studies revealed an altered neural metabolism in the general arousal system including the ascending reticular activating system and hypothalamus, in the emotion-regulating system including the hippocampus, amygdala and ACC, and in the cognitive system including the prefrontal cortex (32, 33). Task-based fMRI studies suggested abnormal activation in various regions including the amygdala, temporal lobe, and frontostriatal networks including the caudate nucleus and inferior frontal gyrus (34-39). Rs-fMRI studies reported abnormal connectivity patterns in ID (40-46) e.g. increased functional connectivity between the insula and salience network (47) and between hippocampi and the left middle frontal gyrus (48). Thus, the available neuroimaging findings in ID are divergent. The variability of the findings has been suggested to be due to the explorative nature of the studies in combination with relatively small sample sizes and due to heterogeneous patient groups that differed in several key aspects including diagnostic criteria, duration and severity of disease, age, gender, imaging acquisition, preprocessing, and analysis methods (24, 49-51), and a plea for subtyping insomnia to reduce heterogeneity has been made recently (8).

In order to find convergence in structure and function across the heterogeneity of patients, modalities and methods, activation likelihood estimation (ALE) has been proposed as an objective technique for coordinate-based meta-analyses (CBMA) to quantitatively gain a more unified investigation of neurobiological changes in neuropsychiatric disorders (52-54). In particular, the CBMA method uses statistical inference by integrating neuroimaging findings to

identify “where” in the brain the convergence between reported foci is more than expected by chance (55). We here report a CBMA on published neuroimaging studies reporting functional and structural deviations in patients with ID.

Methods

Search strategies and study selection

We conducted our search in the PubMed database in December 2017 to identify studies that contain the following keywords: ("insomnia" OR "insomnia disorder") AND ("functional magnetic resonance imaging" OR "fMRI" OR "Positron Emission Tomography" OR "PET" OR "Voxel-based morphometry" OR "VBM"). Following the Preferred reporting items for systematic reviews and meta-analyses statement (56), two researchers (K.N. & M.T.) independently screened the 313 retrieved abstracts and checked for their eligibility to be included. English peer-reviewed neuroimaging publications that compared a group of ID patients with healthy subjects were included, i.e. studies reporting within-group contrasts only or data from healthy subjects with insomnia symptoms were excluded. Diagnosis of ID patients in all included papers was based on DSM-IV or DSM-IV-TR or DSM-5 criteria. We excluded editorial letters, case-reports, systematic reviews, meta-analyses, methodological studies, studies that did not report standard space coordinates, longitudinal/interventional studies, and studies with a sample size of less than 7 subjects in each group as suggested previously (49, 53, 54). Moreover, all included data came from voxel-wise whole brain analysis, because including heterogeneous region of-interest (ROI) analyses may lead to inflated significance for those ROIs (49). In cases in which coordinates were not reported in the eligible studies, we contacted the authors to obtain the relevant information.

Data extraction

Our screening process yielded 19 studies consisting of 6 task-based fMRI, 8 rs-fMRI, 3 VBM, and 2 PET publications comprising 404 patients with ID and 395 good sleepers (27, 30-47) (Table 1, S1). Recorded data includes the first author's name, year of publication, age, gender, number of subjects, scanning modality, and the peak coordinates (x,y,z) in Talairach (57) or Montreal neurological institute (MNI) (58) stereotactic space. Coordinates reported in Talairach space were transformed into MNI space for ALE analysis (59). We used the extracted stereotactic coordinates for conducting the ALE meta-analysis. Of note, “study” reflects a single scientific publication and “experiment” represents an individual analysis or contrast of interest in a given study yielding localization information (i.e., ID > Controls or ID < Controls). Our dataset containing the coordinates of the extracted experiments was arranged based on the pooling approach (60). In this approach, Turkeltaub and colleagues proposed that data should be organized by dependent subject groups rather than by individual experiments to minimize within group effects. This means that if several papers were published based on the same group of subjects and reported several experiments, we combined them (60).

Activation Likelihood Estimation

CBMA was performed with the revised version of ALE (61). ALE estimates convergence and compares this with a random topography. ALE employs three steps: *i)* extracted coordinates are modeled as center of three-dimensional Gaussian probability distribution confirming uncertainty results from between-subject variations and technical differences; *ii)* creation of a modeled activation map (MA map) from combination of the probability distributions of all foci in the considered experiment. Then, incorporation of MA maps yields the final ALE map that reflects the likelihood convergence of results across all experiments; *iii)* statistically comparing the ALE

map with a random distribution to discern random convergence from true convergence between experiments (52, 61, 62). Significant statistical threshold set at $p < 0.05$ family-wise error in cluster level (cFWE) (49).

Confirmatory ROI-based analysis

In addition to the whole brain ALE approach, we performed ROI analysis using the LONI Probabilistic Brain Atlas (LPBA40) (63) in order to indicate potential regions in which there is above-chance convergence. Here, we compared the sum of all ALE values in the particular region to their distribution order null, which tests for the maximum convergence for the average across the entire ROI. Afterwards, we corrected the results for multiple comparisons using FWE threshold in cluster level to avoid false-positive results (49, 64).

Results

From 313 retrieved papers, 19 fulfilled the criteria (Figure 1), including 10 “patients < controls” contrasts and 9 “patients > controls” contrasts resulting in 115 peak foci (Figure 2 A). Included studies were consisting of eight rs-fMRI studies, which applied various methods. For example, one study performed whole brain functional connectivity, one study applied independent components analysis (ICA), two studies performed regional homogeneity (ReHo), and four studies applied the amplitude of low frequency fluctuations (ALFF) method. We also included four task-fMRI studies including letter fluency, category fluency, working memory, tower of London, and emotional tasks. In addition, two PET experiments were included in our analysis.

Analyses across all experiments including both grey matter atrophy and functional abnormalities revealed no significant convergence between different neuroimaging studies performed in ID patients compared to healthy controls (p= 0.914, cFWE) (Figure 2 B).

Repeating analysis with a more liberal statistical threshold (i.e. threshold-free enhancement (TFCE) demonstrated no significant findings as well (p= 0.807). Separate analyses for different imaging modality or increased versus decreased structural/functional alterations were not possible because they would each require at least 17 independent contrasts (49, 65). Analysis of the ALE integral within brain ROIs within the LPBA40 atlas demonstrated clusters within the right amygdala and hippocampus (p= 0.008), left inferior frontal gyrus (IFG) (p= 0.012), right IFG (p= 0.032), left orbitofrontal cortex (OFC) (p = 0.019), and right cingulate cortex (p= 0.030). However, none of these findings survived after corrections for multiple comparisons.

Discussion

The current meta-analysis provided no significant convergent evidence for structural atrophy and functional impairment across 19 published ID studies. The number of experiments using each neuroimaging modality was not high enough to perform analyses for fMRI, PET and VBM separately as at least 17 experiments are necessary to achieve 80% power for moderate effects (65). Our inconsistent findings might be related to heterogonous clinical populations, the explorative nature of the studies in combination with small sample sizes of participants, and various experimental design, preprocessing and statistical approaches. It has been demonstrated that low statistical power of individual studies decreases the chance of detecting true effects in neuroscience research (50). The heterogeneity in experimental designs across task-based fMRI experiments might be another of the potential reasons of inconsistent findings.

Paradigm diversity of tasks performed in fMRI experiments in ID include a working memory task, a spatial working memory, letter or category fluency task, a tower of London task, emotional task, and passive viewing tasks (emotional, sleep-related and neutral pictures) (34-39). The number of experiments with similar tasks was not sufficient to conduct sub-analyses for specific cognitive domains. Moreover, applied rs-fMRI methods in ID were also diverse e.g. independent component analysis (ICA), amplitude of low-frequency fluctuations (ALFF), regional homogeneity, and whole brain functional connectivity (40-47). Similarly, although there is no experimental variability in the included structural MRI (27, 30, 31) and PET studies (32, 33), analytical heterogeneity such as various statistical thresholds or spatial transformation of the brain images is an important issue in such studies.

CBMA using the ALE approach is an unbiased method to integrate multiple neuroimaging studies. ALE quantifies consistency across studies and thus aims to overcome limitations of individual studies with respect to generalizability and robustness (49, 55, 61). ALE establish consensus to identify consistent brain regions in various cognitive and emotional domains (66, 67) or to indicate the spatial locations of functional and/or structural disruptions in neuropsychiatric disorders (53, 54, 68, 69). In the present study, we followed the recently suggested standard protocols of neuroimaging meta-analysis (49). Firstly, our dataset was organized based on the pooling approach introduced by Turkeltaub and colleagues to minimize within-group effects (60). Here, the foci have been organized according to groups of participants rather than experiments to optimize the degree to which ALE values represent concordance of results (60). Secondly, we performed cluster-level FWE correction, which is superior to false discovery rate (FDR) correction to provide maximum statistical rigor (65, 70). In addition, previous experiments based on the ROI analyses were excluded to avoid inflating significance for those particular regions (49). We also repeated the analyses with TFCE as a more liberal statistical threshold and found no significant consistent region again, which support the observed null findings using cluster-level FWE correction.

Beside the whole-brain ALE approach, the regional ALE analysis showed small effects (uncorrected p-values) in the right amygdala and hippocampus, bilateral IFG, left OFC and right cingulate cortex. These small effects might be due to low number of included experiments. The accumulative findings from previous reviews suggest that ID-related structural and functional disruptions are distributed across various intrinsic brain networks e.g. the salience network and default mode network (DMN) (24, 71). The salience network detects emotional stimuli and mediates the switching between activation of the central executive network and the DMN to guide appropriate responses to salient stimuli (72). Chen and colleagues found higher insula coactivation with salience networks in patients with ID (47). Patients with ID also demonstrated higher functional connectivity between the dorsal attention and frontoparietal control networks and lower functional connectivity between the anterior and posterior parts of DMN (73). Recently, we also highlighted the key role of the salience network in hyperarousal and affective symptoms in ID (71). Moreover, Nie and colleagues found impaired region-to-region functional connectivity between the main hubs of DMN in ID (74). Disrupted structural covariance between the anterior and posterior parts of DMN was observed in the ID patients, which could be related to abnormal transition from wake to sleep (75). Recent Genome wide association studies (GWAS) on ID have suggested a few cortical and subcortical areas where gene expression profiles show above-chance resemblance to the genetic risk profile of ID (76-78). Identified areas included the caudate nucleus and Brodmann areas 9 and 24**.** The GWAS studies also found enriched insomnia risk gene expression in specific types of neurons that are located in the striatum, claustrum and hypothalamus (76-78). Seed-based analyses, as well as fMRI employing tasks that specifically targeting these areas, may be used to evaluate whether the gene variants that add to the risk of insomnia, also lead to changes that are detectable with our current methods for structural and functional MRI. We did not find any of the mentioned regions in the whole-brain ALE analysis. Moreover, our ROI analysis was also unable to find significant regions after corrections for multiple comparisons. Taken together, the effects of ID

may be distributed across the whole brain and heterogeneity of available experiments did allow us to find consistent abnormal brain regions in ID. Hence, further neuroimaging studies with larger sample size, homogenous clinical presentation of participants, and using standard preprocessing and analysis protocols are needed. Moreover, future human or animal studies could focus on cellular or molecular mechanism of insomnia.

ID is clinically described as a heterogeneous disorder, which includes different subtypes of pathophysiology in terms of cognitions, mood, traits, history of life events and family history and not necessarily due to sleep complaints only (8). Previous meta-analyses and systematic reviews have reported ID as a heterogeneous disorder with both sleep-related and non-sleep symptoms including poor cognitive performance (79), and emotional deficits (5). ID is also associated with mood disturbance and depression (9, 80), attention-deficit/hyperactivity symptoms (81), personality traits (82), mental illness (83). These studies suggest that ID triggers several functional domains and therefore various brain regions are involved. Interestingly, it has been shown that depression risk and differential behavioral profiles of patients with ID are linked to the objective sleep duration phenotype (84). This wide range of symptoms and limited consistency might be also due to different subtypes of ID with specific multivariate profile of characteristics. A recent data-driven approach in a large sample identified novel robust subtypes of ID and illustrated marked differences on a neurophysiological biomarker (85). The relative representation of each subtype in a sample was moreover shown highly dependent on exclusion criteria that have been applied differentially across individual neuroimaging studies (85). Unaccounted for heterogeneity may thus be involved in discrepancies and failure of replication in neuroimaging studies on discerning characteristics of ID.

Conclusion

To the best of our knowledge, this study is the first neuroimaging meta-analysis of structural and functional alterations in patients with ID and we observed no significant convergent regional alterations. This heterogeneity might be due to differences in clinical populations, experimental design and statistical inference procedures. Of note, inconsistency across neuroimaging studies is not limited to ID, and has e.g. also been observed in depression and attention-deficit/hyperactivity symptoms (68, 86). Whereas the current findings only summarize the studies on people with a diagnosis of insomnia, it could prove useful to run a similar analysis on the more extensive literature on brain correlates of insomnia complaints. Here, quality assessment of studies and pre-registration of analysis protocol were not performed, which should be considered in future meta-analyses.

Improving reproducibility in neuroimaging studies should be considered as a high priority to deliver valid findings (50). Hence, we suggest focusing on replication studies in ID using well-characterized, subtype-homogeneous samples and including moreover a comprehensive description of recruitment strategy, comorbidities, gender, age, and medication status of patients. Moreover, standard preprocessing and statistical analysis should be followed. Our results might inspire future individual neuroimaging studies, as well as mega-analyses and emphasis on standardization of designs, analysis and reporting of the results.

Conflicts of interest

The authors do not have any conflicts of interest to disclose.

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Practice Points

- We found no significant convergent structural and functional alterations in patients with insomnia disorder compared to healthy subjects across previous publications.
- The observed heterogeneity might be due to heterogeneity within small samples of participants, various experimental design, preprocessing and statistical approaches.
- Recent works highlighted that insomnia disorder is clinically described as a heterogeneous disorder, which includes different subtypes. This is an important point to recruit homogeneous samples in future studies.

Research Agenda

- Future neuroimaging individual studies, as well as mega-analyses on insomnia disorder should use larger number of participants, well-characterized, and subtype-homogeneous samples.
- Standard preprocessing and statistical analysis should be followed in individual neuroimaging studies of insomnia disorder.
- By expansion of insomnia literature, further neuroimaging meta-analysis is needed following the suggested standard protocols of neuroimaging meta-analysis in terms of in-/exclusion criteria, data organization, and statistical inference.

Figures' legends

Figure 1. Study selection strategy flow chart.

Figure 2. A) Reported coordinates reflecting structural/functional brain alterations in patients with insomnia disorder compared to healthy subjects (red = increased, blue = decreased); B) ALE maps relevant to meta-analysis, reflecting spatial uncertainty associated with each peak coordinate by modeling Gaussian probability distributions around each peak coordinate (p = 0.914, family-wise error in cluster level).

Table 1. Studies entered into the meta-analysis are listed based on the year of publication. VBM: voxel-based morphometry; fMRI: functional magnetic resonance imaging; Rs-fMRI: resting-state fMRI, FC: functional connectivity, ALFF: amplitude of low frequency fluctuation, GM: gray matter, WM: white matter, BDI: beck depression inventory

	Author, year	**Number of subjects (Insomnia/controls)**	**Number of males (Insomnia/controls)**	**Age of patients/ controls (Mean ± SD)**	**Imaging modality**	**Covariates**
1	Son et al, 2017 (36)	21/26	9/11	36.6 ± 9.8/33.2 ± 7.1	t-fMRI	–
2	Kim et al, 2017 (39)	14/18	4/4	49.0 ± 12.3/42.7 ± 12.3	t-fMRI	Six motion parameters
3	Huang et al, 2017 (45)	27/26	10/10	40.07 ± 11.62/41.19 ± 11.69	rs-fMRI (whole-brain FC)	Age and gender
4	Zhou et al, 2017 (41)	27/27	17/17	42.59 ± 11.59/40.92 ± 11.46	rs-fMRI (ALFF)	gender, age and the mean frame-wise displacement
5	Ran et al, 2017 (40)	21/20	5/6	40.62 ± 7.52/38.65 ± 7.40	rs-fMRI (ALFF)	Grey matter
6	Kay et al, 2016 (32)	44/40	20/15	37/38	PET	–
7	Li et al, 2016 (35)	30/30	17/NS	39.36 ± 8.53/36.15 ± 8.61	t-fMRI	–
8	Li et al, 2016 (43)	55/44	24/11	39.18 ± 10.34/39.91 ± 9.43	rs-fMRI (ALFF)	sex, age and education level
9	Dai et al, 2016 (44)	42/42	15/18	49.21 ± 10.96/49.14 ± 10.2	rs-fMRI (ALFF)	age, sex, and years of education
10	Wang et al, 2015 (46)	59/47	21/14	39.3 ± 10.7/40.0 ± 9.1	rs-fMRI (ReHo)	head-motion measures

11	Dai et al, 2014 (42)	24/24	7/12	54.8 ± 9.8/52.5 ± 6.6	rs-fMRI (ReHo)	age, years of education, and/or sex
12	Baglioni et al, 2014 (34)	22/38	7/17	40.7 ± 12.6/39.6 ± 8.9	t-fMRI	six motion estimates, BDI scores
13	Chen et al, 2014 (47)	17/17	0/0	27.16 ± 6.67/27.56 ± 6.83	rs-fMRI (ICA)	–
14	Stoffers et al, 2014 (37)	24/13	7/4	60.3 ± 6.0/60.1 ± 8.3	t-fMRI	caudate region of interest baseline perfusion
15	Joo et al, 2014 (30)	27/30	2/2	51.2 ± 9.6/50.4 ± 7.1	Surface-based-analysis	BDI-II
16	Joo et al, 2013 (31)	27/27	2/4	52.3 ± 7.8/51.7 ± 5.4	VBM	age and sex and intracranial volume
17	Altena et al, 2010 (27)	24/13	7/4	60.3 ± 6.0/60.2 ± 8.4	VBM	Total GM or WM and age
18	Altena et al, 2008 (38)	21/12	4/3	61 ± 6.2/60 ± 8.2	t-fMRI	–
19	Nofzinger et al, 2004 (33)	7/20	3/7	34.2 ± 8.9/32.6 ± 8.4	PET	global metabolism and age

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