Reduced dynamic functional connectivity between salience and executive brain networks in insomnia disorder

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Received: 6 August 2019 | Revised: 6 November 2019 | Accepted: 6 November 2019

DOI: 10.1111/jsr.12953

SHORT PAPER

Reduced dynamic functional connectivity between salience and executive brain networks in insomnia disorder

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Funding information
ZonMw, Grant/Award Number: Neuropsychoanalysis Fund 16.561.0001; H2020 European Research Council, Grant/Award Number: ERC Advanced Grant 671084 INSOMNIA; Fundação Bial, Grant/Award Number: 190/16 and 253/12; Nederlandse Organisatie voor Wetenschappelijk Onderzoek, Grant/Award Number: VICI-453.07.001

Summary

Research into insomnia disorder has pointed to large-scale brain network dysfunctions. Dynamic functional connectivity is instrumental to cognitive functions but has not been investigated in insomnia disorder. This study assessed between-network functional connectivity strength and variability in patients with insomnia disorder as compared with matched controls without sleep complaints. Twelve-minute resting-state functional magnetic resonance images and T1-weighed images were acquired in 65 people diagnosed with insomnia disorder (21–69 years, 48 female) and 65 matched controls without sleep complaints (22–70 years, 42 female). Pairwise correlations between the activity time series of 14 resting-state networks and temporal variability of the correlations were compared between cases and controls. After false discovery rate correction for multiple comparisons, people with insomnia disorder and controls did not differ significantly in terms of mean between-network functional connectivity strength; people with insomnia disorder did, however, show less functional connectivity *variability* between the anterior salience network and the left executive-control network. The finding suggests less flexible interactions between the networks during the resting state in people with insomnia disorder.

KEYWORDS

dynamic functional connectivity, insomnia disorder, resting-state functional magnetic resonance imaging, salience network

Y.W. and J.L. contributed equally to this study.

1 | INTRODUCTION

Insomnia disorder (ID) is a chronic sleep disorder of high prevalence and tremendous socioeconomic burden. To date, treatment options for ID have been limited. Cognitive-behaviour therapy is effective in reducing symptoms but still leaves room for improvement (Harvey & Tang, 2003). Pharmacological interventions are usually effective only in the short term and can incur several side-effects. There is an urgent need of developing novel interventions for ID, which in turn depends on a better understanding of its neural pathophysiology.

Recently, resting-state functional connectivity (FC) in ID has been increasingly studied and suggests involvement of distributed brain systems ("functional networks"). However, findings from different studies are not always consistent (Tahmasian et al., 2018). Multiple reasons could explain discrepancies across studies. For instance, small sample sizes and heterogeneity of ID in combination with different selection criteria might result in study populations corresponding to distinct clinical characteristics. Another reason specific to FC could be that it fluctuates over time and did not "average out" equally in all studies. This latter consideration is important as it has been recognized that not only FC but also its dynamics are crucially engaged in brain functions.

Aberrant FC of the salience network (SN) with other brain regions has often been implicated in ID (Khazaie et al., 2017). Interactions between the SN and other cognitive systems are nonetheless highly variable (Chen, Cai, Ryali, Supekar, & Menon, 2016). It has been proposed that dysregulated dynamic interactions among cognitive networks underlie pathological mentation in psychiatric disorders, and that the SN represents a major source of automatic (e.g. affective) constraints on mental activities (Christoff, Irving, Fox, Spreng, & Andrews-Hanna, 2016). Given the key role of cognitive and affective control in ID (Schmidt, Harvey, & Linden, 2011), we hypothesized that people with ID would exhibit alterations in FC dynamics among functional networks, especially in those involving the SN. To test this hypothesis, we evaluated between-network resting-state FC strength and variability in patients with ID as compared with matched controls without sleep complaints. To our knowledge, this is the first study on dynamic FC in ID.

2 | METHODS

2.1 | Participants

We analysed resting-state functional magnetic resonance imaging (fMRI) data of 65 people meeting the DSM-5 criteria for ID (21–69 years, 48 female) and 65 age- and sex-matched controls without sleep complaints (22–70 years, 42 female) from a previously reported study (Leerssen et al., 2019). Exclusion criteria for all participants were: (a) diagnosed current or past neurological or psychiatric disorders other than ID; (b) current sleep disorders other than ID, including signs of frequent hypopnea or leg movements during 2 nights of laboratory polysomnography; (c) shift work; (d) use of sleep medications within the prior 2 months; (e) MRI contraindications; (f) excessive head movements (> 3 mm) or video-monitored eye closure indicative of falling asleep during fMRI acquisition. Assessments were part of more elaborate studies, which were approved by the Ethics Review Board of the University of Amsterdam. All participants provided written informed consent.

2.2 | Imaging protocol

Participants were scanned on 3-Tesla MRI scanners of the same brand and type (Achieva, Philips Medical Systems, Best, The Netherlands) with 32-channel head coils at two different sites of the Spinoza Centre for Neuroimaging, Amsterdam, The Netherlands. On the assessment days, participants were asked to refrain from alcohol and drugs. Participants were not allowed to consume caffeinated beverages for at least 6 hr before the MRI scanning sessions. Scans were made between 09:00 and 20:00 hours. Twelve-minute (288 volumes) resting-state functional images were acquired from a single-shot echo-planar imaging (EPI) gradient echo sequence with the following scanning parameters: repetition time = 2,500 ms; echo time = 28 ms; phase-encoding direction = AP/RL; flip angle = 77.2°; field of view = 240 × 240 × 118 mm^3 (AP × RL × FH); voxel size = 2.5 × 2.5 × 2.5 mm^3; slice gap = 10%; SENSE factor = 2 (AP). During acquisition, participants were instructed to look at a fixation cross, lie still, keep their eyes open, think of nothing in particular, and try not to fall asleep. Additionally, T1-weighted images were acquired from a 3D Turbo Field Echo sequence with the following scanning parameters: repetition time = 8.3 ms; echo time = 3.8 ms; phase-encoding direction = RL; flip angle = 8°; field of view = 240 × 188 × 220 mm^3 (AP × RL × FH); voxel size = 1 × 1 × 1 mm^3; SENSE factors = 2.5 (RL), 2 (FH).

2.3 | Image preprocessing

The fMRI Expert Analysis Tool in FMRIB's Software Library (FSL) version 5.0.9 was used for: (a) brain extraction; (b) removal of the first five volumes to exclude T1 saturation effects; (c) motion correction; (d) B_0 inhomogeneity-induced distortion correction; (e) boundary-based registration (BBR) with the T1-weighted image; and (f) spatial smoothing (FWHM = 5 mm). Motion artefacts were subsequently removed by ICA-AROMA followed by nuisance regression (mean white-matter and cerebrospinal-fluid signals and a linear trend) and high-pass filtering (60 s cutoff; Pruim et al., 2015).

2.4 | Between-network static and dynamic functional connectivity

The current study investigated the interactions between 14 well-known functional networks (Shirer, Ryali, Rykhlevskaia, Menon,

& Greicius, 2012). We registered the standard MNI152 structural image to each participant's T1-weighted image using the non-linear Symmetric Normalization (SyN) algorithm implemented in the Advanced Normalization Tools (ANTs) version 2.1.0. The non-linear SyN transformation and the BBR transformation matrix were concatenated so as to register the network maps to the EPI space. Each fMRI volume was spatially regressed on the 14 registered network maps. The resulting regression coefficients, representing network activity at each timeframe, were concatenated into 14 network activity time series. Between-network FC strength was quantified by pairwise Pearson correlation coefficients between the network activity time series.

To study dynamic FC, pairwise Pearson correlation coefficients were calculated for each 1-min window (24 volumes) sliding in steps of one volume. We used 1-min sliding windows so that reasonably reliable correlation coefficients could be estimated. The length of the correlation coefficient time series for each network pair was thus 283 − 24 + 1 = 260 (number of sliding windows). The correlation coefficients were Fisher-transformed (to obtain normally distributed values), after which their standard deviations over time were taken to quantify between-network FC variability.

2.5 | Statistical analyses

Group differences in FC strength and variability were evaluated according to the following steps. First, Wilcoxon rank-sum Z statistic for each network pair was computed separately within each scanning site. Next, the Stouffer–Lipták method was used to combine the Z-values from each site into a final set of Z-values, which were then converted to p-values. Finally, Benjamini–Hochberg false discovery rate (FDR) correction was applied to account for multiple comparisons over 14 × 13/2 = 91 network pairs. Associations with clinical characteristics were evaluated with Spearman correlation coefficients in follow-up analyses.

3 | RESULTS

Figure 1a shows the mean FC strength over 12 min for each network pair, averaged over people with ID and controls. It can be seen that people with ID and controls exhibited highly similar between-network FC patterns. Statistical comparisons confirmed that there was no significant group difference with respect to static between-network FC ($-2.00 < Z < 2.28$, $p_{FDR} > .94$ for all network pairs).

Figure 1b shows the variability of FC for each network pair, averaged over people with ID and controls. Statistical comparisons revealed that people with ID had significantly less FC variability between the anterior salience network (aSN) and the left executive-control network (LECN; $Z = -3.80$, $p_{FDR} = .01$) as well as less FC variability between the aSN and the dorsal default-mode network (dDMN) at a trend level ($Z = -3.20$, $p_{FDR} = .06$). The effects were in the same direction within each scanning site (Table 1), confirming the robustness of group differences. No significant or trend-level group difference in FC variability was observed for any other network pair ($p_{FDR} > .32$).

The self-reported Insomnia Severity Index (ISI; Bastien, Vallières, & Morin, 2001) and Hyperarousal Scale (HAS; Pavlova et al., 2001) as well as polysomnographic sleep parameters (2nd night) were available in the majority of the participants (Table 2). Correlation analyses indicated that aSN–LECN FC variability was significantly and negatively associated with the ISI ($r_s[127] = -.34$, $p = .0001$; Figure 2) and not significantly associated with the other clinical characteristics.

4 | DISCUSSION

The current study assessed static and dynamic FC of brain functional networks in people with ID and matched controls without sleep complaints. By focusing on network–network interactions, we found that while mean between-network FC strength remains similar in patients and controls, aSN–LECN FC *variability* is significantly reduced in ID.

Although we did not observe significant group differences in static between-network FC, we do not exclude that static FC differences might exist at more fine-grained spatial scales (Leerssen et al., 2019). Previous resting-state fMRI studies have suggested that hyperarousal in ID involves the SN (Khazaie et al., 2017). These studies only examined mean FC strength over several minutes and did not evaluate possible FC fluctuations occurring at faster time-scales. Interestingly, a recent study utilizing electroencephalographic microstates to assess sub-second network dynamics during the resting state found in people with ID shortened mean microstate duration for a particular microstate class commonly associated with the SN (Wei, Ramautar, Colombo, Lindert, & Someren, 2018). The finding together with the current results strengthens the notion of impaired SN dynamics in ID, which could be observed at both sub-second and minute-by-minute time-scales.

One important function of the SN is modulating the activation and deactivation of the default-mode network (DMN) and the executive-control network (ECN). Proper functioning of the SN thus entails its flexible interactions with the DMN and the ECN. Reduced dynamic FC of the SN in ID may indicate a compromised capability of people with ID to switch between networks in response to changing environments and needs. This implication is supported by previous task-based fMRI studies showing hypoactivation of the left inferior frontal gyrus (part of the LECN; Altena et al., 2008) and failure to deactivate the DMN (Drummond et al., 2013) in people with ID during demanding cognitive tasks.

Furthermore, it has been demonstrated that the FC dynamics of the SN predict individual differences in cognitive flexibility (Chen et al., 2016). Recent neuroimaging studies have found that the affective signatures of negative emotional memories persist through extinction learning (Seo et al., 2018) and over the long term (Wassing et al., 2019) in ID, pointing to deficient adaptation as a result of emotional inflexibility. With respect to spontaneous

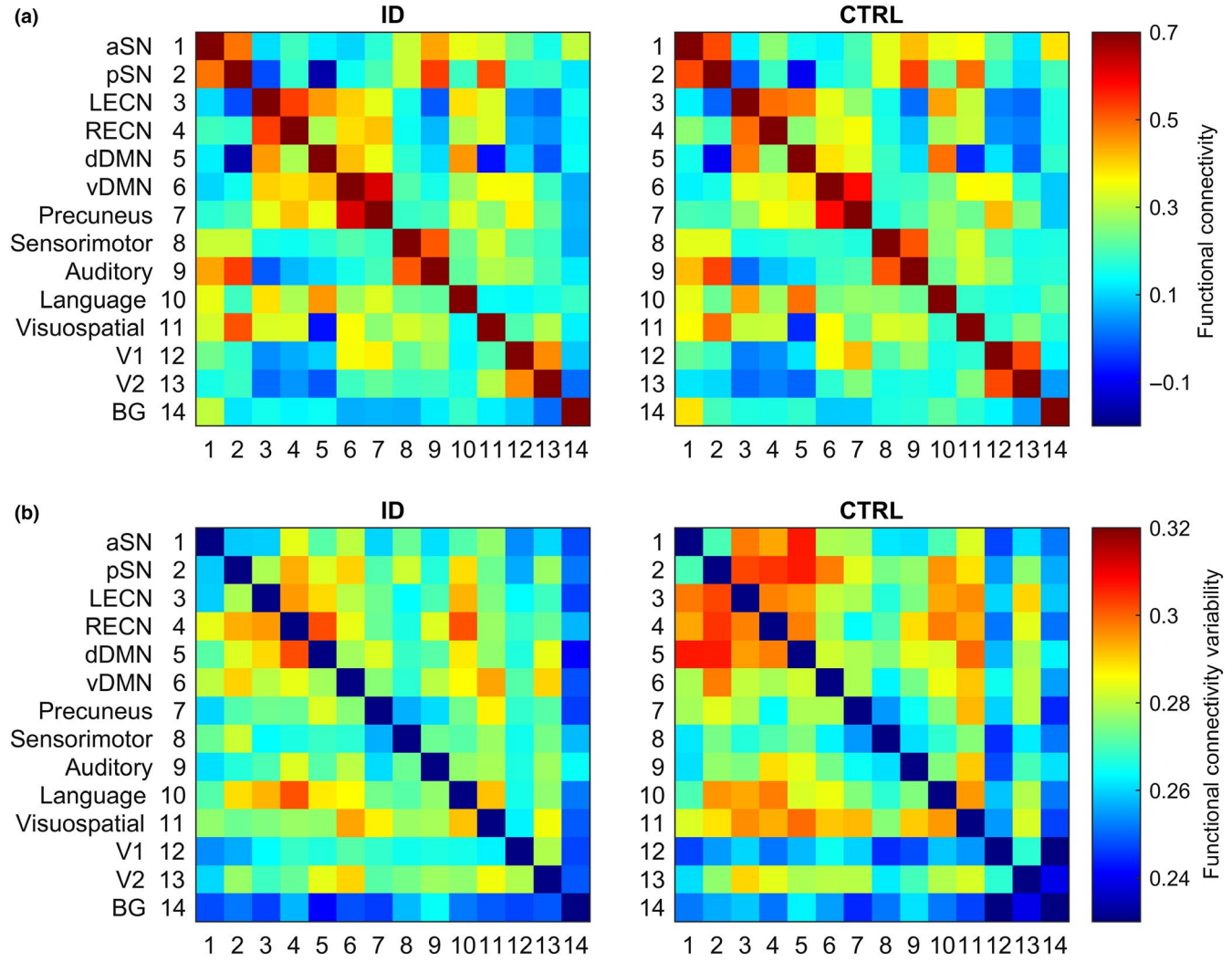

FIGURE 1 (a) Mean between-network functional connectivity (FC), and (b) variability of between-network FC, in people with insomnia disorder (ID) and matched controls (CTRL). aSN, anterior salience network; BG, basal ganglia network; dDMN, dorsal default-mode network; LECN, left executive-control network; pSN, posterior salience network; RECN, right executive-control network; vDMN, ventral default-mode network; V1, primary visual network; V2, higher visual network

	Site 1 (*N* = 58)			Site 2 (*N* = 72)		
	Control (*n* = 29)	ID (*n* = 29)	*Z*	Control (*n* = 36)	ID (*n* = 36)	*Z*
aSN–LECN	0.30 ± 0.06	0.27 ± 0.05	−2.04	0.30 ± 0.06	0.25 ± 0.04	−3.27
aSN–dDMN	0.32 ± 0.07	0.28 ± 0.06	−2.22	0.29 ± 0.06	0.26 ± 0.05	−2.30

Abbreviations: aSN, anterior salience network; dDMN, dorsal default-mode network; ID, insomnia disorder; LECN, left executive-control network.

TABLE 1 Functional connectivity variability between the aSN and the LECN/dDMN (mean ± *SD*) within each scanning site and the associated Wilcoxon rank-sum *Z* statistics

mental activity, deficient cognitive-affective flexibility may in particular manifest in the form of negatively-toned repetitive thoughts (e.g. rumination; Christoff et al., 2016). As dysfunctional thought control has long been considered a key factor that causally contributes to chronic insomnia symptoms (Schmidt et al., 2011), our results suggest that cognitive-affective flexibility may represent a promising venue for ID management.

5 | LIMITATIONS

As articulated above, we regarded between-network FC dynamics, especially those pertaining to the SN, as most relevant to the pathophysiology of ID. Possible alterations in FC strength and variability between more fine-grained brain regions may be left undetected by our analytic strategy. In addition, we focused on only one

TABLE 2 Self-reported and polysomnographic measures (mean ± *SD*) and their correlations with functional connectivity variability between the aSN and the LECN

	Control	ID	r_s, *p*
Subjective complaints	*n* = 64	*n* = 65	
ISI	4.19 ± 4.28	16.29 ± 5.16	−.34, .0001
HAS—Introspectiveness	10.81 ± 3.72	12.65 ± 4.26	−.15, .09
HAS—Reactivity	3.75 ± 2.42	4.42 ± 2.58	.00, .99
Objective sleep parameters	*n* = 57	*n* = 56	
TST, min	430.93 ± 54.47	380.68 ± 102.45	.01, .94
SOL, min	23.25 ± 20.07	23.41 ± 21.70	.10, .28
WASO, min	39.51 ± 27.56	72.40 ± 58.19	−.11, .26
SE, %	87.31 ± 6.97	78.49 ± 18.72	.04, .67
Stage N1, %	3.56 ± 2.09	6.47 ± 8.82	−.01, .93
Stage N2, %	45.29 ± 10.32	46.38 ± 14.08	−.08, .41
Stage N3, %	27.30 ± 10.75	25.07 ± 13.41	−.07, .47
Stage R, %	23.85 ± 7.50	22.08 ± 12.39	.16, .10

Abbreviations: HAS, Hyperarousal Scale; ID, insomnia disorder; ISI, Insomnia Severity Index; r_s, Spearman correlation coefficient with aSN–LECN functional connectivity variability; SE, sleep efficiency; SOL, sleep-onset latency; TST, total sleep time; WASO, wake after sleep onset.

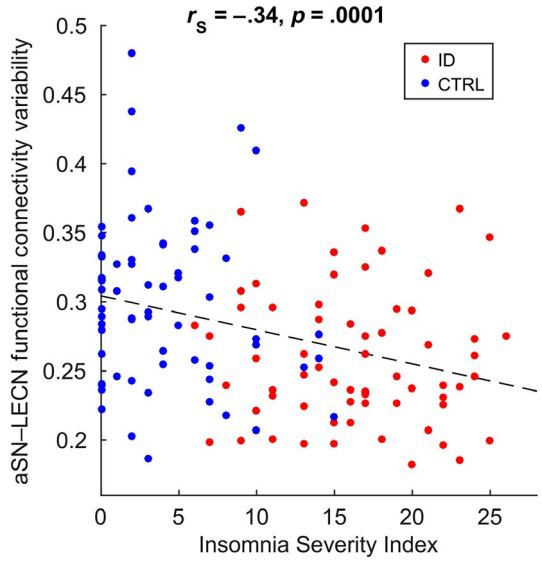

FIGURE 2 Association of functional connectivity variability between the anterior salience network (aSN) and the left executive-control network (LECN) with the Insomnia Severity Index. Red and blue dots denote people with insomnia disorder (ID) and controls (CTRL), respectively. The dashed line depicts the least squares linear fit

aspect of brain dynamics, namely FC variability. Future studies may apply other analytic strategies, such as "brain state"-based analyses, to gain a more detailed understanding of dynamic FC in ID. The temporal resolution of the fMRI was low. Preprocessing effectively mitigated but could not completely rule out signal contamination by (aliased) physiological noises. In future studies, accelerated fMRI may be adopted, which would more reliably capture brain dynamics at fast time-scales and allow easier separation of physiological noises (LeVan, Akin, & Hennig, 2018).

ACKNOWLEDGEMENTS

Research leading to these results has received funding from the Bial Foundation grants 253/12 and 190/16, the Netherlands Organisation of Scientific Research (NWO) grant VICI-453.07.001, the Netherlands Organisation for Health Research and Development (ZonMw) Neuropsychoanalysis Fund 16.561.0001, and the European Research Council Advanced Grant 671084 INSOMNIA.

CONFLICT OF INTERESTS

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AUTHOR CONTRIBUTIONS

YW, JL: information processing and management; writing; revision of the manuscript. RW, DS, JP, EJWVS: planning and design; data collection; revision of the manuscript.

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How to cite this article: Wei Y, Leerssen J, Wassing R, Stoffers D, Perrier J, Van Someren EJW. Reduced dynamic functional connectivity between salience and executive brain networks in insomnia disorder. *J Sleep Res*. 2019;00:e12953. https://doi.org/10.1111/jsr.12953