Title:

Unbalanced resting-state networks activity in psychophysiological insomnia

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Compliance with Ethical Standards:

- *Conflict of Interest:* Daniel Ruivo Marques, Ana Allen Gomes, Vanda Clemente, José Moutinho dos Santos, Isabel Catarina Duarte, Gina Caetano and Miguel Castelo-Branco declare that they have no conflict of interest.

- *Ethical approval:* All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

- *Informed consent:* Informed consent was obtained from all individual participants included in the study.

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Abstract

Psychophysiological Insomnia (PI) is a clinical condition characterized by sleep-related disturbing cognitive activity and biased self-related information processing. This hypothetical cognitive arousal has been hypothesized to be associated with overactivation within different brain areas and networks, especially when individuals are at rest, e.g., in the absence of any attention-demanding task. In this study, we carried out a resting-state fMRI experiment aimed at investigating activity of the different resting-state networks in PI. Our pool of participants was compound of 5 PI patients and 5 sex- and age-matched healthy controls recruited from the community. Participants from both groups also completed a set of self-report measures, including the Sleep Diary, Insomnia Severity Index (ISI), Dysfunctional Beliefs and Attitudes About Sleep (DBAS-30), and the World Health Organization Quality of Life Measure (WHOQOL-Bref). Our results showed that insomnia patients presented altered activation in the default mode network (DMN), visual and auditory networks, and bilateral fronto-parietal networks. In the DMN, the patients presented a pattern of both decreased (right superior frontal gyrus, left medial frontal gyrus, and right middle temporal gyrus) and increased activation (left superior frontal gyrus, left anterior and posterior cingulate, right precuneus, left cingulate gyrus, and left middle temporal gyrus). Our findings on unbalanced resting-state networks in PI, with special emphasis on the DMN, may lay grounds to better understanding of the cognitive arousal experienced by PI patients and might help to further improve the clinical management of insomnia.

Keywords: Insomnia, resting-state networks, neural activation, default-mode network, neuroimaging, fMRI

Introduction

Advances in neuroimaging have enabled to characterize brain function at rest, when no external tasks or stimuli are present, and to identify inherent functional connectivity between brain regions known to be involved in cognition or sensory processing – during the so called resting-state. This activity is organized in networks, and the integrity of these seems to play a pivotal role in health and well-being in general [1].

Within these resting-state networks, the brain "default mode network" (DMN) has been of particular interest [2,3]. The DMN neural network is characterized by a set of brain regions that increase their activity when an individual is not performing any attention or cognitive demanding task [4]. Diverse studies have identified a set of brain regions which constitute core hubs of DMN. Among them, we emphasize the dorsal medial prefrontal cortex (MPFC), the ventral MPFC, the posterior cingulate cortex/retrosplenial cortex (PCC/resp cortex), the precuneus, the inferior parietal lobes, and some parts of medial temporal lobes [5]. A core feature seems to be the involvement of the self in the cognitive content underlying the activation of this network. The functions that have been ascribed to the DMN relate to episodic memory, prospective memory, theory of mind, and decision-making [6]. These functions are supported by previous studies – even before the pithy interest in resting-states and DMN in particular – derived from the field of cognitive neuropsychology as focused on episodic and autobiographical memory research (Buckner, 2012). For example, it has been shown that autobiographical memories activate similar brain regions to the DMN [6,7].

The DMN is therefore well suited as a subject of investigation both in healthy and clinical populations [5,6,8,9,10,]. Dysfunction of the DMN has been found in diverse neuropsychiatric disorders such as major depression, obsessive-compulsive disorder, social anxiety disorder, posttraumatic stress disorder and other related anxiety disorders, autism,

schizophrenia and bipolar disorder, attention deficit and hyperactivity disorder, personality disorders, alcoholism, drug abuse, Alzheimer´s disease, Parkinson´s disease, mild cognitive impairment, Huntington´s disease, and non-neuropsychiatric disorders such as failed back surgery syndrome, chronic pain, obesity, dyspepsia, and migraine among others [8,9].

One of the clinical disorders where DMN´s study has not been extensively researched is psychophysiological insomnia (PI). PI is one of the most common sleep disorders [11-13] whose key feature is hyperarousal [14]. This construct encompasses abnormal levels of arousal at neurobiological, affective, and cognitive-behavioral domains. In this sense, it seems useful to investigate deeper the functional integrity of the default network in PI given the clinical phenomenology of the disorder [15].

In general, neuroimaging studies on insomnia are lacking [16-18]. Although there are some studies on DMN activity across sleep stages and sleep-wakefulness transitions [19-21], only a few published studies consider the DMN or resting-state neural activity in insomnia. The investigation led by Hasler and colleagues [22] explored the DMN functional connectivity in insomnia across sleep-wake states through 18-fluorodeoxyglucose positron emission tomography. The authors found that during the evening wakefulness and NREM sleep, the insomnia patients had attenuated mPFC-PCC activity. The researchers posited that this finding may be related to the dysfunctional self-related cognitions that PI patients frequently refer to. Another study, despite not directly addressing the DMN as the main research topic, observed that insomnia patients performed a memory task at the same level as healthy controls inside the fMRI scanner [23]. However, the former did not deactivate so significantly the neural areas related to DMN when performing the cognitive task, thus showing that the patients would have difficulties in stopping or at least coping with self-related thoughts. It was also observed, during rest,

that insomnia patients showed an abnormal connectivity among amygdala and other brain regions such as the insula [24]. Despite the limited empirical studies on DMN´s (dys)function in PI, it is important to highlight that some literature has already recognized its potential importance in research and clinical practice purposes [15-25]

Finally, a resting-state fMRI study in jet lagged individuals found that some nodes within DMN such as bilateral mPFC and anterior cingulate cortex (ACC) presented decreased connectivity comparatively to control individuals [26]. These type of studies, in particular, within the scope of sleep disorders, will certainly help to differentiate the clinical phenomenology of the different sleep disorders, thereby showing promise concerning the increase in accuracy of the differential diagnosis.

To our knowledge there is no available literature concerned in studying the remaining resting-state networks, beyond the DMN, such as the visual network, fronto-parietal network, sensory-motor network and auditory network in PI. The only study published on this matter used a sample of healthy participants and correlated sleep-onset and sleep maintenance difficulties with brain regions of interest extracted from a resting-state fMRI experiment [27].

In the current study, our aim is to assess the functional integrity of DMN and other networks during the resting-state such as the visual network (VN), fronto-parietal network (FPN), and auditory network (AN) in patients with insomnia using an fMRI resting-state paradigm. We hypothesize that there might be a dysfunction (manifested as patterns of unbalanced activity across the network) related to both an increase and a decrease activation of (at least) some structures within the DMN. Regarding VN, FPN and AN, we hypothesize that these networks might be impaired based on the overall hyperarousal hypothesis; however, as there is no systematic studies on this topic, no specific predictions were conceptualized. Drawing on evidence that insomnia patients frequently report an

increase in negative self-referential cognitive contents while trying to fall asleep, we expect to find an overall pattern of hyperarousal in mPFC and PCC hubs compared to a healthy-control group; this is expected since PI is considered a 24-hour disorder [14] and the resting-state might be an excellent simulator of what happens whenever the individual goes to bed every night in order to sleep [15]. We hypothesize further, within the hyperarousal conceptual framework, that other resting-state networks may as well show disrupted or altered activity in PI patients.

Method

Participants

For this study we recruited 5 participants diagnosed with PI (mean age=41.6± 8.7; education years=16.6±3.0; 3 females) and 5 sex- and age- matched healthy controls (mean age=38.6±7.1; education years=18.0±1.5; 3 females). All the participants were right-handed. The clinical sample was selected from the sleep psychology consultation at a Sleep Medicine Centre. To be eligible for the study, insomnia patients had to meet the criteria for PI according to ICSD-2 manual [12], having an age between 18-60 years, and should not meet criteria for an untreated comorbid disorder such as psychiatric, neurological or other chronic one. The distribution of the major insomnia subtypes in our clinical sample were: initial insomnia (60%), intermediate insomnia (100%), terminal insomnia (60%), and non-refreshing sleep (60%). In terms of the frequency of complaints, insomnia patients had in average 4.20 (1.79) insomnia nights per week whilst the duration of the complaints was 55.2 (39.2) months in average.

The healthy group was constituted by individuals from the community who accepted to take part in this study. Participants had normal or corrected to normal visual acuity. None of the individuals was paid to participate in this study. Before the fMRI examination,

all participants completed a signed informed consent form containing a brief rational about the experiment goals. The first author responded to all participants´ questions. The study was performed in accordance to the Declaration of Helsinki and with permission from the medical ethical committee of Coimbra University Hospital Center (CHUC).

Psychological measures

In addition to the fMRI examination, all participants completed the following measures:

- *Dysfunctional Beliefs and Attitudes About Sleep (DBAS-30)* – This scale is intended to assess attitudes regarding sleep behaviour and is constituted by 30 items. Higher scores are related with more dysfunctional beliefs about sleep [28,29];

- *Insomnia Severity Index* (ISI) – The ISI is one of the most known scales on insomnia which evaluates the severity of self-reported complaints (Morin, 1993). The standard scoring guidelines are: 0-7 = no clinically significant insomnia; 8-14 = subthreshold insomnia; 15-21 = moderate insomnia; and 22-28 = severe insomnia [30,31];

- *Sleep Diary* – The sleep diary enables to obtain important indicators of subjective sleep perception [29,32]. In this study we obtained data along 7 consecutive days concerning sleep latency (SL), wake after sleep-onset (WASO), total sleep time (TST), and sleep efficiency (SE);

- *World Health Organization Quality of Life measure* (WHOQOL Bref – Portuguese version: Vaz-Serra et al. [33]) – This instrument is a self-reported overall quality of life

measure. It is possible to extract results from 4 domains (i.e., physical health, psychological health, social relationships, and environment). Moreover, it gives a general quality of life score composed by the joint of the two first items of the scale [33]. Higher scoring is associated with better self-perceived quality of life.

We did not compute internal consistency indexes such as the Cronbach´s alphas for any of the scales since the sample size was significantly small for that purpose.

Resting-state fMRI experiment

The experimental paradigm consisted of 12 minutes of acquisition time whilst participants remained at rest. That period was separated onto two conditions (resting-state with eyes open and resting-state with eyes closed) each one lasting 2 minutes and repeated 3 times, interspersed. The instructions were given by a recorded voice that participants listened through headphones; they were instructed to relax while fixating the central point of the screen, or close their eyes.

Image data acquisition

Imaging was performed on a Siemens *MAGNETON Trio 3.0 Tesla* at ICNAS (Institute of Nuclear Sciences Applied to Health, Coimbra, Portugal). The participants underwent structural imaging and functional fMRI with a 12 channel head coil. Participants were fitted with earplugs, padding was used to minimize involuntary head movements, and they were also provided with a command button that they could push whether they felt uncomfortable at any time of image collection.

T1-weighted structural images were collected with an MPRAGE (magnetization prepared rapid gradient echo) sequence: 176 slices, echo time (TE) = 3.42 ms, repetition

time (TR) = 2530 ms, Flip angle 7.0º, 1 mm^3 voxel size, and Field-of-View (FoV) = 256 x 256 mm^2. Functional MRI was performed with a gradient echo-planar imaging pulse sequence: 38 slices, echo time (TE) = 30 ms, repetition time (TR) = 2500 ms, Inter slice time = 65 ms, slice thickness = 3.0 mm, mosaic 7x7 matrix; resolution or slice matrix size = 84 x = y 84, interleaved, voxel resolution = 3.0x3.0 mm^2, FOV = 256 x 256 mm^2, and Flip angle 90º. In total, we acquired 288 volumes.

Data preprocessing and analysis

Data were pre-processed and analyzed using BrainVoyager QX 2.6 (Brain Innovation BV, Maastricht, The Netherlands). The analysis of functional data included slice-scan-time corrections (cubic spline interpolation and ascending interleaved slice scanning order), temporal filtering (High-pass GLM Fourier 2 sines/cosines), motion-correction (trilinear interpolation), and spatial smoothing (kernel with FWHM=8mm). The translation and rotation parameters estimated for each volume during motion correction were inspected, and did not exceed 2mm. Functional data were further co-registered to same-session structural images, and both structural and functional scans were transformed into Talairach space. The functional volumes were re-sampled to a voxel size of 3 mm^3.

For the data analysis we considered covariates of motion (translation and rotation), white matter (WM) and cerebrospinal fluid signal (CSF). The covariates were derived by averaging voxels' mean signal time courses for each participant: a brain segmentation was applied to derive WM masks and estimate the WM covariate, and CSF signal was estimated from a region of interest consisting on the third ventricle. Finally, a cortical mask was created to restrict the number of voxels, based on brain segmentation, and inflated by +/- 3mm.

There are different methods to analyze resting-state in a functional magnetic resonance imaging (fMRI) study. One of the most suitable is the independent component analysis (ICA), which enables the segregation of distinct neural networks, including DMN, according to their independent spatial patterns [1,5,34]. ICA is a model-free or data-driven method unlike the seed-based analysis which is a hypothesis-driven approach [1].

In this study, we performed a cortex-based independent component analysis (cbICA). We performed a concatenated analysis of both resting conditions as was implemented by Andrews-Hanna, Reidler, Sepulcre, Poulin, and Buckner [35]. Firstly, at the single individual level, 48 independent components were extracted for each data set and scaled to spatial *z*-score maps with a deflation approach and Tahn nonlinearity [36]. This option was based on the rule of thumb that suggests keeping a number of components approximately around one sixth of the number of time points, thus ensuring these components account for more than 99.9% of the total variance. Individual ICs were inspected to identify the presence, within each subject, of components with higher spatial correlation with known and validated RSN templates [1], with an emphasis on the DMN, whilst ensuring these ICs derived from BOLD signal through the ICA fingerprint method, as implemented in BrainVoyager QX. Thus, we used the fast ICA approach deflation algorithm for single-subject level and the self-organizing group ICA (SogICA) algorithm for group-level analyses [37-40]. At group-level analyses we extracted 38 ICs components from each individual data set without loss of the dimensionality of the data [41]. The resulting ICs from the SogICA group level analysis, which showed high spatial similarity to RSNs [1-42], were further inspected at subject-level. Group-level statistics maps were obtained recurring to two-factor ANOVA analysis (38 clusters as within-subjects factor and 2 groups as between-subjects factor). The False Discovery Rate (FDR) correction ($q < 0.05$) was used to correct for multiple comparisons. For each identified resting-state

network, between-group differences were assessed by means of a voxel-wise one-way ANOVA *z*-values obtained from individual ICA group maps. In order to identify and label the Talairach coordinates of the brain´s peak activation clusters, we used the Talairach Client - Version 2.4.3 application. Whilst all presented statistical maps were superimposed on a Talairach template, the brain used to display the rs-fMRI results pertains to one control participant whose brain was the best representative brain of the "average brain" of all the participants in this study.

Results

Psychological and sleep measures

In general, the PI group showed, as expected, worse sleep subjective parameters according to sleep diaries. Besides, patients endorsed more sleep and insomnia biased attitudes, more self-reported insomnia severity and worst subjective self-reported quality of life than the control group (cf. Table 1).

INSERT TABLE 1 HERE

Neuroimaging measures

In participants of both groups, using ICA analysis, we identified the most known sub-networks during rest [42]: aDMN (anterior default-mode network), pDMN (posterior default-mode network), VN (visual network), AN (auditory network), rFPN (right fronto-parietal network), lFPN (left fronto-parietal network).

Insomnia patients´ resting-state networks functional activation

Figure 1 displays the significant clusters of neural activity in PI patients for all of the resting-states examined in this study. The aDMN showed increased activity in the medial

prefrontal cortex; the pDMN showed higher activation in precuneus, cingulate posterior and bilateral inferior parietal lobules; the VN presented increased activation in primary visual areas of the occipital cortex; the AN showed bilateral superior temporal cortex higher activation; and the FPNs presented higher activation in dorsolateral prefrontal cortices and superior parietal cortices.

INSERT FIGURE 1

Healthy controls´ resting-state networks functional activation

Figure 2 displays the significant clusters of neural activity in healthy-controls for all of the resting-states examined in this study. Like the clinical group, in control sample, the aDMN showed increased activation in the medial prefrontal cortex; the pDMN showed increased activation in precuneus, cingulate posterior and bilateral inferior parietal lobules; the VN presented higher levels of activation in primary visual areas of the occipital cortex; the AN showed bilateral superior temporal cortex increased activation; and the FPNs shown higher activation in dorsolateral prefrontal cortices and superior parietal cortices.

INSERT FIGURE 2

Contrasts between the patients group and the control group

In order to understand potential differences in DMN activation and all other brain resting-state networks between the clinical and the control groups, we performed a contrast analysis (see Methods). The visualization of the neuronal patterns can be seen in Figure 3; a detailed specification of the brain regions can be seen in Table 2.

INSERT FIGURE 3

Regarding the aDMN, we found that PI patients showed increased activation compared with healthy volunteers in the right superior frontal gyrus and in the left medial frontal gyrus, and decreased activation within the left superior frontal gyrus and left anterior cingulate.

In the pDMN, insomnia patients exhibited increased activation in the right middle temporal gyrus compared with the control group; in left posterior cingulate, right precuneus, left cingulate gyrus and left middle temporal gyrus, the clinical group showed decreased functional activation.

Concerning the VN, the insomnia group showed more activation in the right cuneus and less activation in the right cuneus and left cuneus.

In the AN, patients showed more activation in two different sites within the left superior temporal gyrus.

With regard to rFPN, insomnia patients presented increased activation in the right inferior parietal lobule and decreased activation in the right inferior parietal lobule, compared with healthy volunteers.

Finally, concerning the lFPN, we found that PI patients presented increased activity in the left middle frontal gyrus and left inferior parietal lobule compared to control group individuals.

INSERT TABLE 2 HERE

Discussion

Thus far, little is known on how resting-state networks might be impaired in PI. It was our aim in the current research to examine this question. We extracted and identified the

main resting-state network in clinical and control groups, to which we applied contrast analysis to explore putative differences in neural activation in particular in the DMN.

In our study, the DMN could be separated in anterior and posterior independent components. This division of the DMN into anterior and posterior components has also been frequently reported in former studies [43]. Regarding aDMN, it was found that PI patients showed increased activation, compared with healthy individuals, in the right superior frontal gyrus and in the left medial frontal gyrus, and decreased activation within the left superior frontal gyrus and left anterior cingulate. It is well known that insomnia patients recur to cognitive strategies in order to control thinking processes, namely the self-reported ones. The absence of any external task might aggravate this scenario, exacerbating the cognitive arousal. A recent study found that voluntary cognitive appraisal of emotional distressing stimuli worsens the arousal of the patients [44]. Besides, the effort to suppress any thoughts or implementing distraction techniques in order to not think in a particular topic has in fact, a paradoxical effect [45]. The mindfulness and acceptance-based approaches of the so called “third wave-generation” of cognitive-behavioral therapies may have an important role in the clinical management of insomnia [46] and this work may help provide a biological basis for such approaches.

For the pDMN component, PI patients exhibited increased activation in the right middle temporal gyrus. In several studies, medial temporal regions are considered key regions of the DMN [1,6] so this finding appears to be in line with an eventual memory self-processing dysfunction [47]. On the other hand, the patients displayed decreased activity in the posterior cingulate, precuneus, cingulate gyrus, and left middle temporal gyrus. All of these regions are important hubs of the DMN. The consequent impaired connection or communication among these brain regions with activation unbalance might help to explain the persistence of the symptomatology.

Our findings on VN suggest there is a consistent pattern of differential activation in the insomnia group compared with healthy individuals. Namely, PI patients exhibited an increased activation in the right cuneus (BA 17) and a decreased activation in the bilateral cuneus (BA 19). One should note that the increased activation of the cuneus in both groups refers to distinct parts within the right cuneus. A study by Wang et al. [48] demonstrated that primary visual cortex appears to be implicated in memory-related mental imagery and/or visual memory consolidation. In the study by Killgore et al. [27], it was found also that primary visual cortex was hyperconnected in a sample of individuals with insomnia complaints (although not a clinically diagnosed sample).

Regarding AN, insomnia patients showed more activity in the left superior temporal gyrus. This brain region (BA 22) is an associative area which among other functions is implicated in in pitch discrimination, sound intensity processing and nonverbal sound processing. In the literature the most closest study resembling our finding is the one by Killgore et al. [27]; they found that primary auditory cortex in resting-state is functionally hyperconnected with the supplementary motor cortex in a group of individuals with insomnia complaints. This finding is interesting and seems to reinforce the notion that hyperarousal in insomnia is widespread and may affect all the sensory and executive systems.

Finally, when we analyze the FPN (also known in the literature as “executive-control network”) it is evident that insomnia patients presented increased activation in the right inferior parietal lobule and decreased activation in the right inferior parietal lobule with regard to rFPN. The rFPN seems to be related with language processes and working memory. Concerning to lFPN, PI patients presented increased activation in the middle frontal gyrus and the inferior parietal lobule comparatively to the control group. The lFPN is specially related with cognitive control and attention [43]. This finding is in line with the

overall hypothesis of hyperarousal in insomnia [14]. The cognitive performance of PI patients and healthy individuals are identical, however, the neural underlying mechanisms appears to be altered [23].

The obtained subjective self-report data from both groups is in line with our expectations. Descriptive analysis suggests that insomnia patients report higher levels of insomnia severity according to ISI results, endorse more dysfunctional beliefs and attitudes regarding sleep and insomnia, and present overall worse quality of life. Besides, the sleep parameters extracted from sleep diaries suggest worse results for the insomnia group.

Despite of the encouraging results, we should acknowledge some limitations in our study. The reduced sample size is one of the main limitations; perhaps some group differences might have gone undetected in our study. Although the clinical sample has been recruited at a National Sleep Medicine Centre, several factors explain the reduced sample size: (1) this Sleep Medicine Centre is the unique accredited centre existing in the Health National System, thus, several patients with several sleep disturbances have to be evaluated; besides there is only one clinical psychologist/somnologist responsible for the sleep psychology consultation; (2) some patients had fear of the fMRI machine; some older patients were more reluctant in participating in the study; (3) as the place where the fMRI was performed was away from the Sleep Medicine Centre, for some patients this dislocation was impractical (i.e., schedules management). However, even with this small sample the results were strongly significant, which seems to be an indicator that these data are robust. Another limitation is related with the fact that one of the insomnia patients was taking medication at the time of the scanning session. Although there is no literature about the effects of psychotropic drugs on DMN activation, it appears to be reasonable to accept this influence. In addition, it is difficult to generalize these results to insomnia patients' population since there is no sufficient power in terms of sample size and our sample

included patients with several phenotypes concerning PI. Even so, it is important to note that our PI patients were recruited at the unique Sleep Medicine Center in our country from the public health service. In this case, there are good indicators of ecological validity. Other key topics that should be investigated in the future are the correlations between specific regions of interest (e.g., precuneus) and clinical features of insomnia (e.g., ISI, DBAS scores, sleep diary parameters) that we cannot study due to the small sample size. The study of correlations with structural alterations may also be relevant. Finally, one should be aware that resting-state functional activation data should be interpreted with caution, as even the detection of intrinsic networks and unbalance of activity across brain areas does not imply necessarily a (dys)function of a specific brain region.

In sum, our study supports the new perspective that PI might be seen as a "self-processing disorder" [15]. Furthermore, it seems to be a disorder in which the main resting-state networks are impaired, namely through a heightened sensory processing, supporting the hyperarousal theory of insomnia [17,27]. Similar to other clinical conditions, PI might be conceptualized also as a disorder that disrupts brain networks rather than single brain regions [1].

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Table 1. Psychological self-reported measures and sleep diary indexes

	Insomnia group (n=5)	Healthy controls (n=4)*
	M ± SD	M ± SD
SL_minutes	28.0 ± 23.3	6.75 ± 4.2
WASO_minutes	54.0 ± 33.8	12.7 ± 12.5
TST_minutes	356.0 ± 105.6	402.5 ± 71.0
TIB_minutes	511.0 ± 51.2	461.5 ± 86.2
SE_% (week)	0.68 ± 0.15	0.87 ± 0.01
SL_minutes (week)	30.8 ± 30.1	6.2 ± 4.3
WASO_minutes (week)	54.6 ± 35.5	16.2 ± 15.5
TST_minutes (week)	333.2 ± 123.2	395.2 ± 75.5
TIB_minutes (week)	496.4 ± 63.6	457.0 ± 82.2
SE_% (week)	0.65 ± 0.16	0.86 ± 0.0
SL_minutes (weekend)	22.0 ± 18.9	7.2 ± 5.3
WASO_minutes (weekend)	52.8 ± 37.0	4.5 ± 4.6
TST_minutes (weekend)	412.8 ± 75.8	421.2 ± 65.0
TIB_minutes (weekend)	549.2 ± 56.4	472.5 ± 109.2
SE_% (weekend)	0.75 ± 0.12	0.90 ± 0.07
ISI	17.6 ± 5.0	1.7 ± 1.5
DBAS-30 total	5.2 ± 1.2	2.8 ± 1.5
DBAS-30 [F1]	6.1 ± 1.7	3.7 ± 2.4
DBAS-30 [F2]	4.9 ± 0.8	1.7 ± 1.7
DBAS-30 [F3]	6.0 ± 1.5	3.8 ± 1.9
DBAS-30 [F4]	2.6 ± 1.9	2.0 ± 2.1
DBAS-30 [F5]	4.9 ± 1.3	2.8 ± 1.2
WHOQOL-Bref overall	70.0 ± 14.2	84.3 ± 15.7
WHOQOL-Bref [D1]	45.0 ± 3.1	66.9 ± 3.4
WHOQOL-Bref [D2]	74.1 ± 5.4	76.0 ± 5.2
WHOQOL-Bref [D3]	65.0 ± 29.9	75.0 ± 18.0
WHOQOL-Bref [D4]	66.2 ± 10.9	83.5 ± 17.9

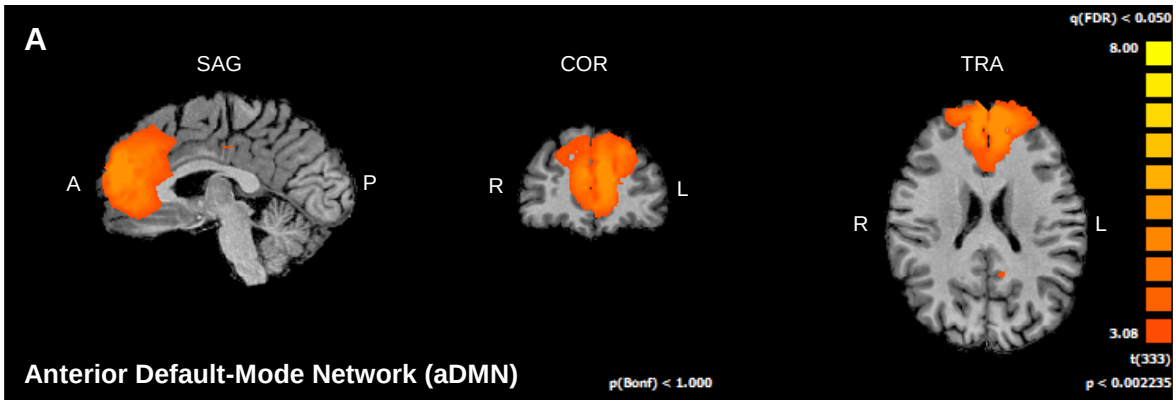
* The data of one healthy-control participant is missing.

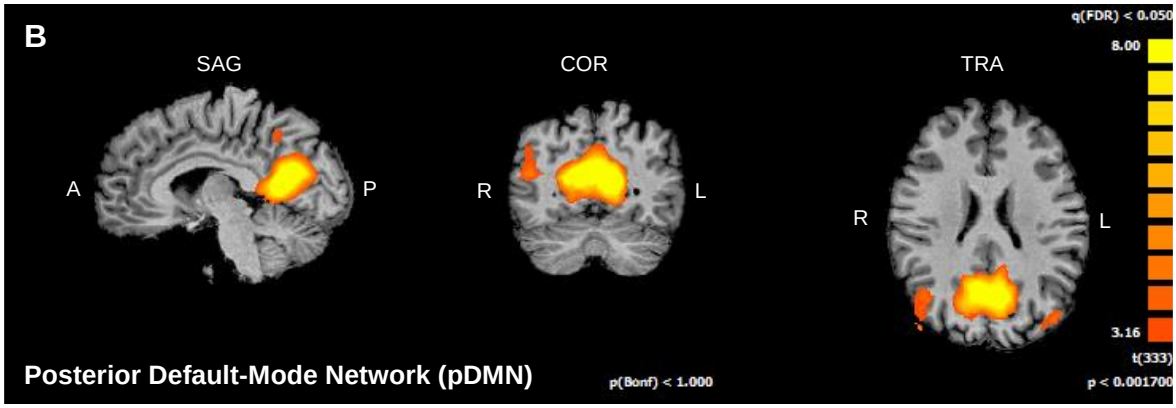
Note. M = Mean; SD = Standard deviation; SL = Sleep latency; WASO = Waking after sleep-onset; TST = Total sleep time; TIB = Time in bed; SE = Sleep efficiency; ISI = Insomnia Severity Index; DBAS-30 = Dysfunctional Beliefs and Attitudes About Sleep; DBAS-30[F1] = Beliefs about the effects of insomnia; DBAS-30[F2] = Beliefs about the loss of control over sleep and the unpredictability of sleep; DBAS-30[F3] = Perceived sleep needs and sleep expectations; DBAS-30[F4] = Misattributions about causes of insomnia , DBAS-30[F5] = Expectations about sleep-promoting habits ; WHOQOL-Bref = World Health Organization Quality of Sleep measure; WHOQOL-Bref [D1] = Physical health; WHOQOL-Bref [D2] = Psychological health; WHOQOL-Bref [D3] = Social relationships; WHOQOL-Bref [D4] = Environment.

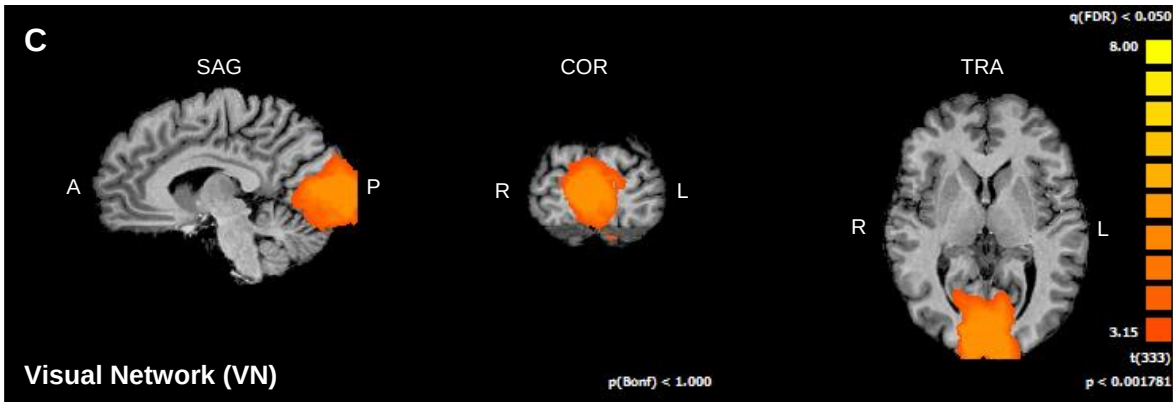
Table 2. Contrast maps between clinical and control groups

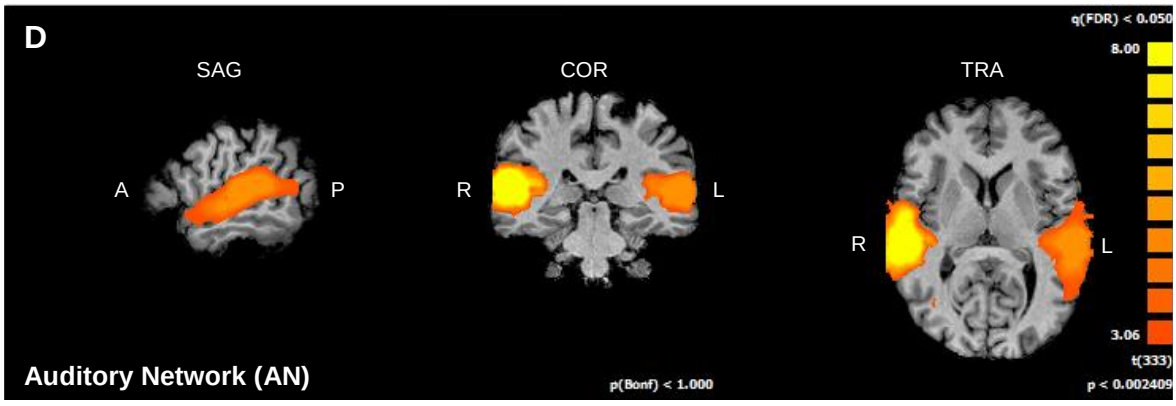
Region	Hemisphere	BA	x	Y	z	*t*-value	*p*-value
Insomnia > Controls							
aDMN							
Superior frontal gyrus	R	10	20	49	18	7.1226602	0.000000
Medial frontal gyrus	L	9	-25	40	18	5.529262	0.000000
pDMN							
Middle temporal gyrus	R	39	47	-74	21	5.705650	0.000000
VN							
Cuneus	R	19	11	-86	9	10.608647	0.000000
AN							
Superior temporal gyrus	L	22	-55	-26	6	7.767006	0.000000
Superior temporal gyrus	L	22	-49	-38	12	5.275382	0.000000
rFPN							
Inferior parietal lobule	R	40	40	-35	45	7.003407	0.000000
lFPN							
Middle frontal gyrus	L	47	-46	46	-6	8.346044	0.000000
Inferior parietal lobule	L	40	-53	-47	51	6.808233	0.000000
Controls > Insomnia							
aDMN							
Superior frontal gyrus	L	9	-7	55	30	-8.378763	0.000000
Anterior cingulate	L	32	-10	37	15	-4.745625	0.00000
pDMN							
Posterior cingulate	L	31	-7	-68	15	-8533331	0.000000
Precuneus	R	31	11	-50	27	-6.549892	0.000000
Cingulate gyrus	L	31	-13	-20	42	6.542913	0.000000
Middle temporal gyrus	L	39	-37	-68	30	-4.631860	0.000000
VN							
Cuneus	R	19	26	-83	24	-4.772088	0.000000
Cuneus	L	19	-22	-92	27	-5.197095	0.000000
rFPN							
Inferior parietal lobule	R	40	40	-50	45	-6.053132	0.000000

Note. aDMN = anterior default-mode network; pDMN = posterior default-mode network; VN = visual network; AN = auditory network; rFPN = right fronto-parietal network; lFPN = left fronto-parietal network; R = Right hemisphere; L = Left hemisphere; BA = Brodmann Area.


A
SAG
COR
TRA
A
P
R
L
R
L
q(FDR) < 0.050
8.00
3.08
t(333)
p < 0.002235
Anterior Default-Mode Network (aDMN)
p(Bonf) < 1.000


B
SAG
COR
TRA
A
P
R
L
R
L
q(FDR) < 0.050
8.00
3.16
t(333)
p < 0.001700
Posterior Default-Mode Network (pDMN)
p(Bonf) < 1.000


C
SAG
COR
TRA
A
P
R
L
R
L
q(FDR) < 0.050
8.00
3.15
t(333)
p < 0.001781
Visual Network (VN)
p(Bonf) < 1.000


D
SAG
COR
TRA
A
P
R
L
R
L
q(FDR) < 0.050
8.00
3.06
t(333)
p < 0.002409
Auditory Network (AN)
p(Bonf) < 1.000

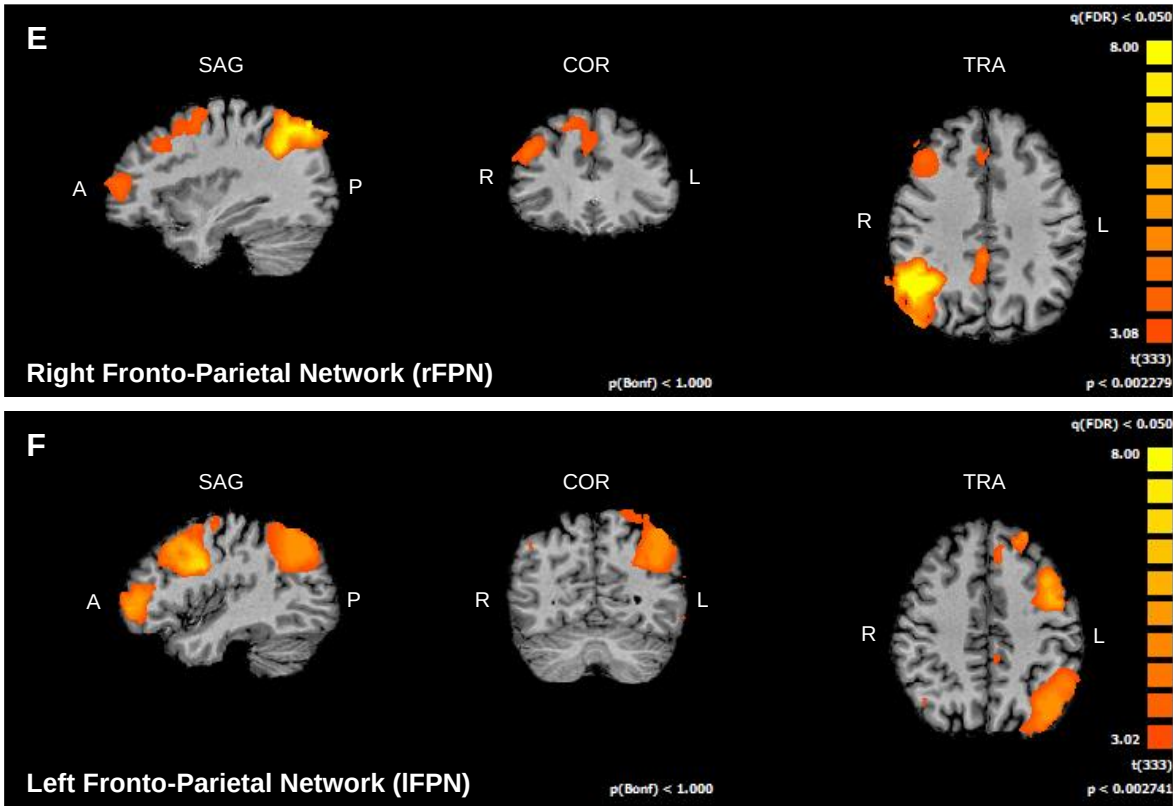
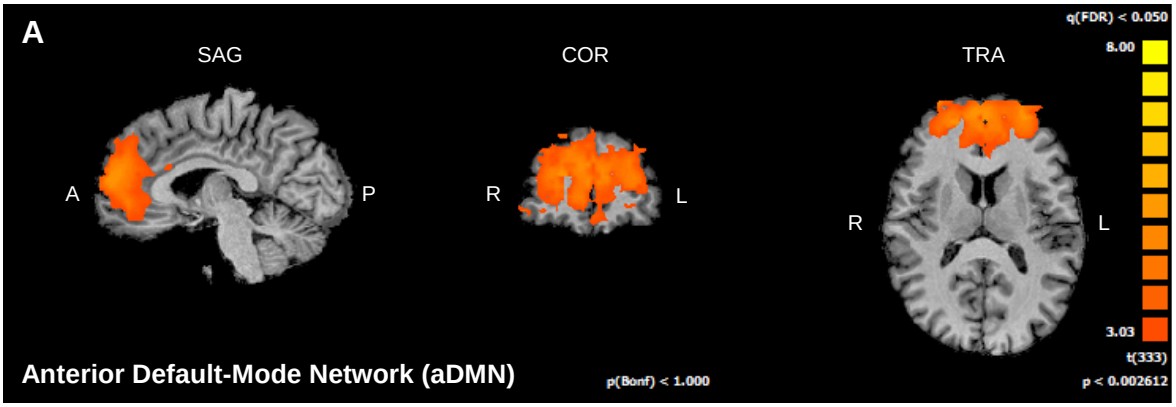
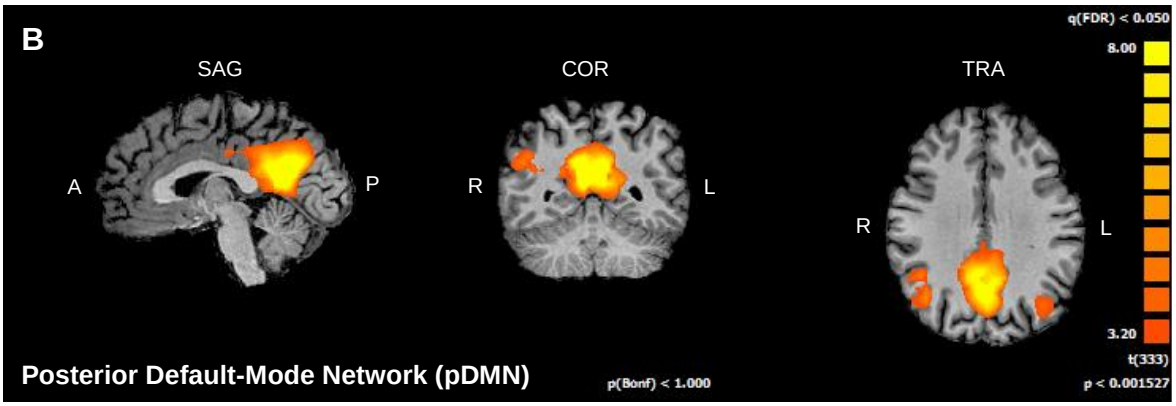
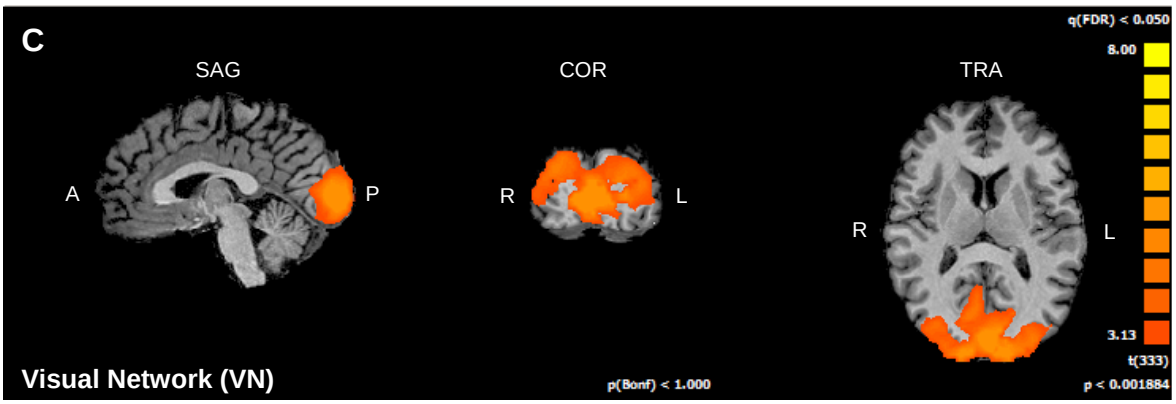
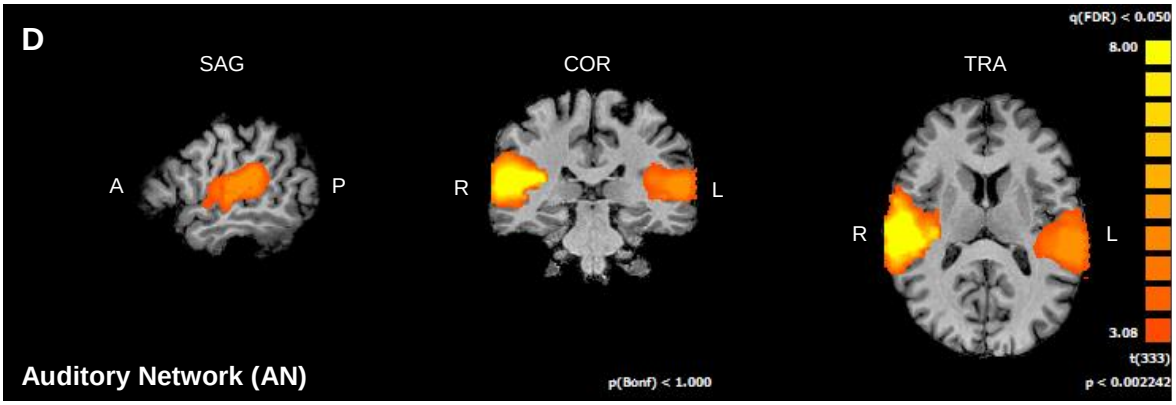


Figure 1. Resting-state networks´ activation in PI patients. A=aDMN, B=pDMN, C=VN, D=AN, E=rFPN, F=lFPN


A
SAG
COR
TRA
A
P
R
L
R
L
q(FDR) < 0.050
8.00
3.03
t(333)
p < 0.002612
Anterior Default-Mode Network (aDMN)
p(Bonf) < 1.000


B
SAG
COR
TRA
A
P
R
L
R
L
q(FDR) < 0.050
8.00
3.20
t(333)
p < 0.001527
Posterior Default-Mode Network (pDMN)
p(Bonf) < 1.000


C
SAG
COR
TRA
A
P
R
L
R
L
q(FDR) < 0.050
8.00
3.13
t(333)
p < 0.001884
Visual Network (VN)
p(Bonf) < 1.000


D
SAG
COR
TRA
A
P
R
L
R
L
q(FDR) < 0.050
8.00
3.08
t(333)
p < 0.002242
Auditory Network (AN)
p(Bonf) < 1.000

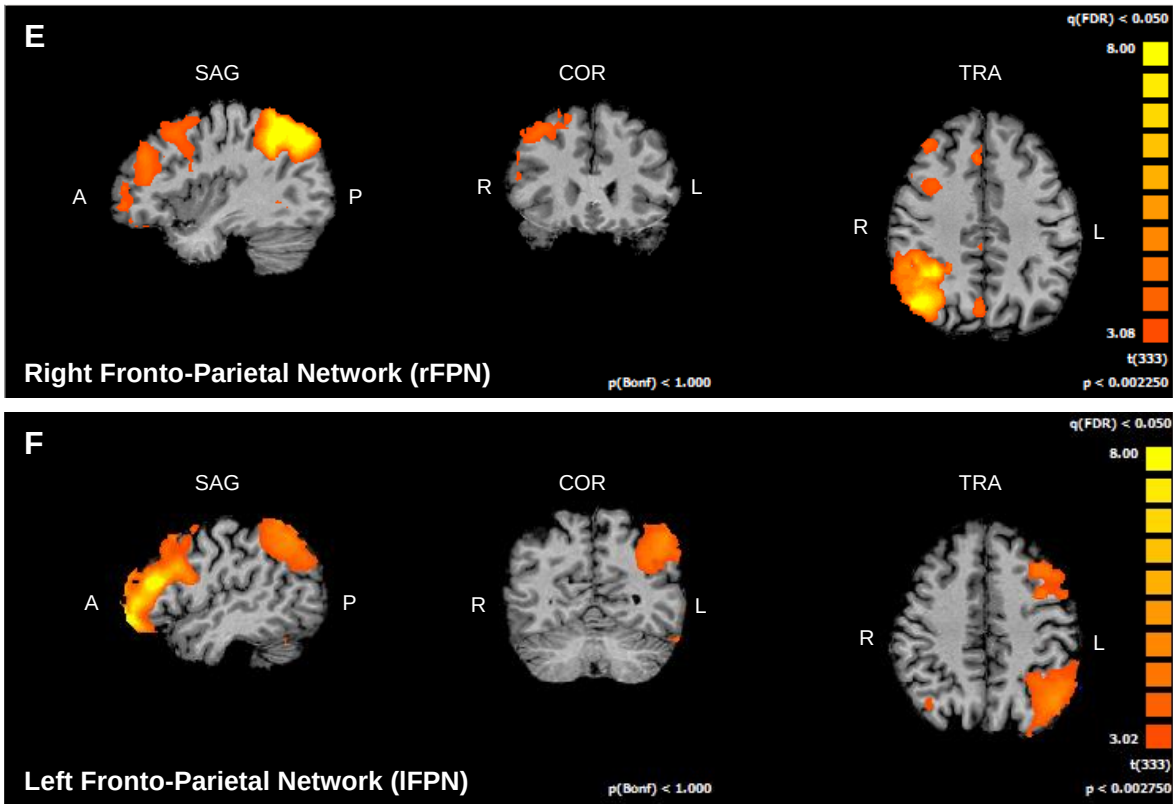
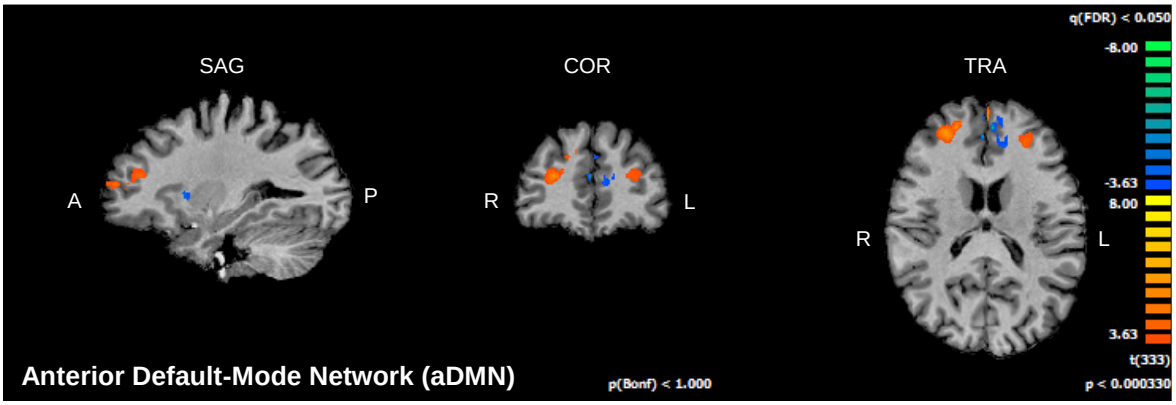
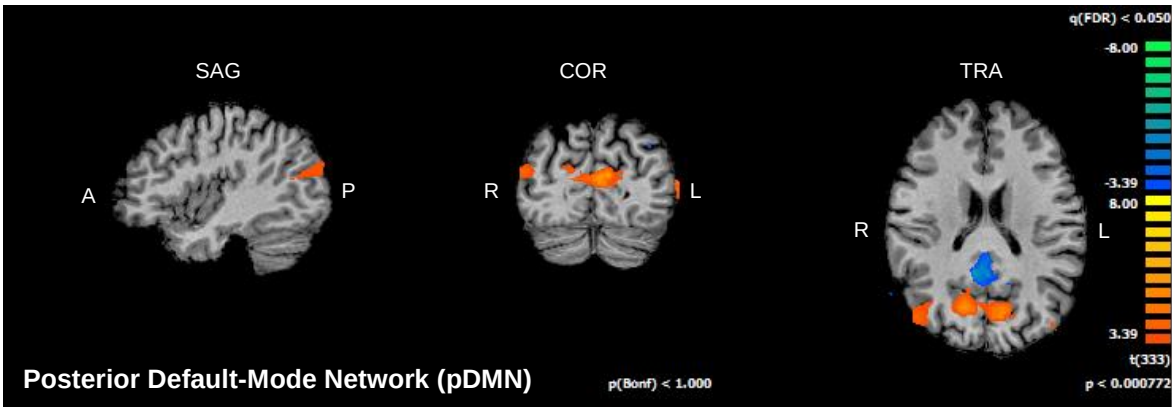
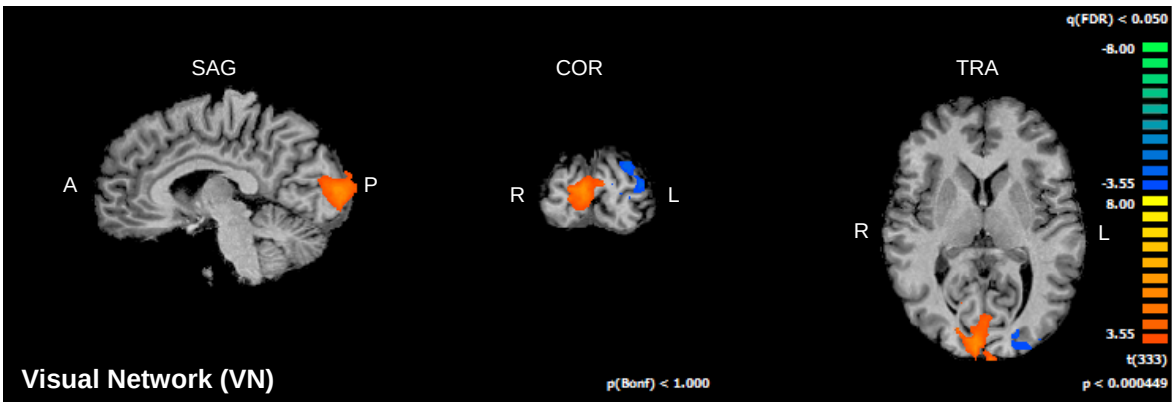
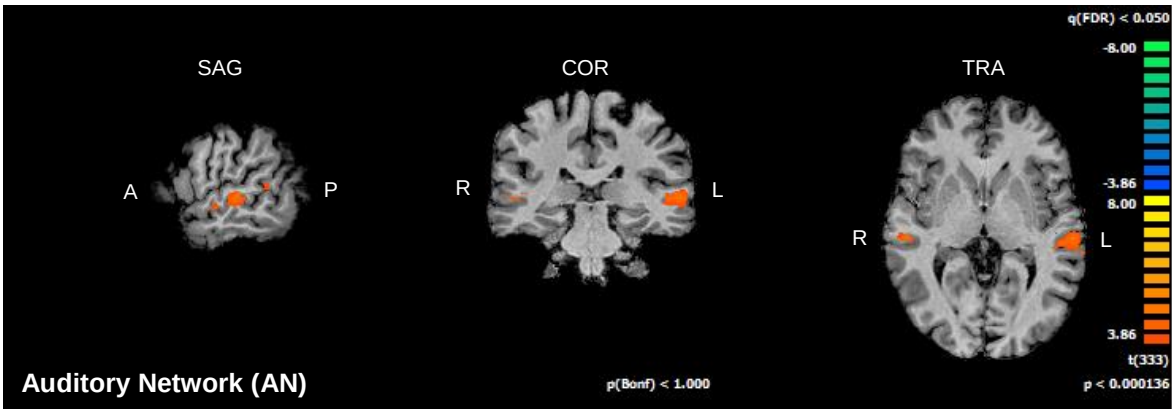


Figure 2. Resting-state networks´ activation in healthy-controls. A=aDMN, B=pDMN, C=VN, D=AN, E=rFPN, F=lFPN


SAG
COR
TRA
A
P
R
L
R
L
q(FDR) < 0.050
-8.00
-3.63
8.00
3.63
t(333)
p < 0.000330
Anterior Default-Mode Network (aDMN)
p(Bonf) < 1.000


SAG
COR
TRA
A
P
R
L
R
L
q(FDR) < 0.050
-8.00
-3.39
8.00
3.39
t(333)
p < 0.000772
Posterior Default-Mode Network (pDMN)
p(Bonf) < 1.000


SAG
COR
TRA
A
P
R
L
R
L
q(FDR) < 0.050
-8.00
-3.55
8.00
3.55
t(333)
p < 0.000449
Visual Network (VN)
p(Bonf) < 1.000


SAG
COR
TRA
A
P
R
L
R
L
q(FDR) < 0.050
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-3.86
8.00
3.86
t(333)
p < 0.000136
Auditory Network (AN)
p(Bonf) < 1.000

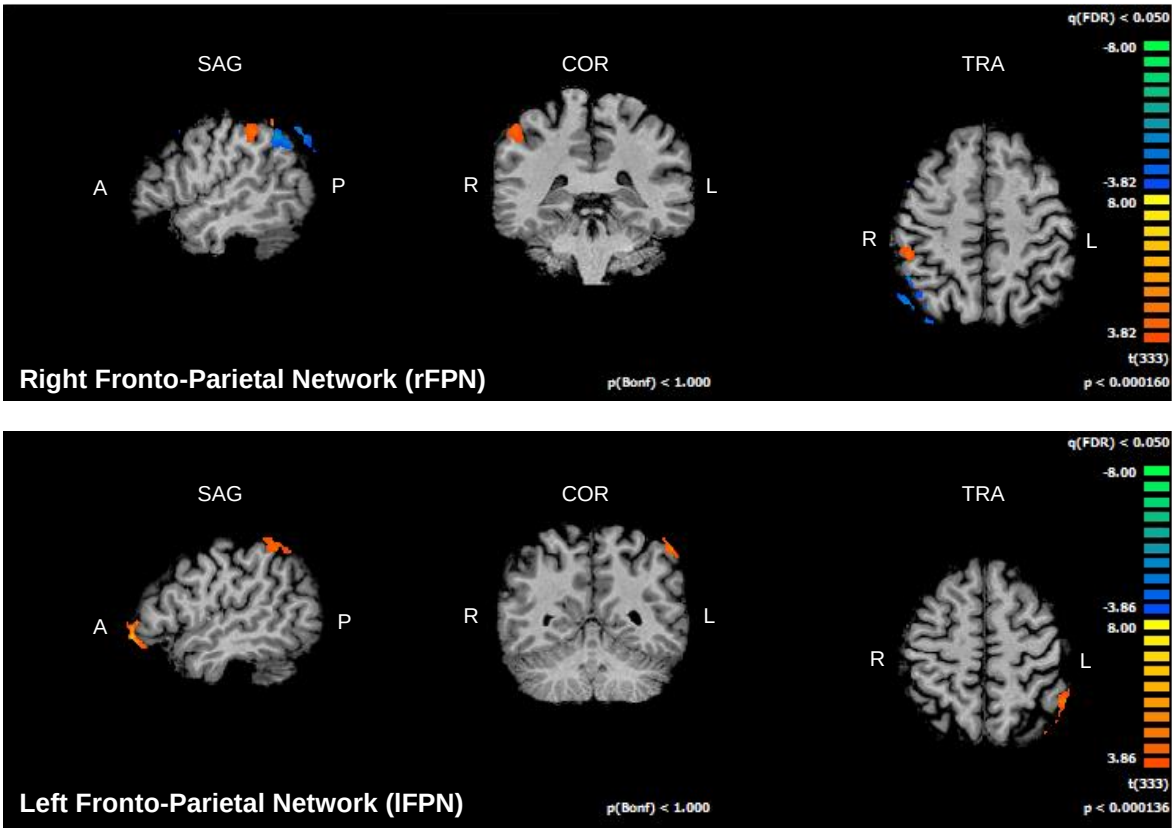

Figure 3. Contrast maps of different resting-state networks´ activation between PI patients and healthy-control participants. In warm colors are displayed the brain regions that are functionally more connected in PI patients compared to healthy participants; in cool colors are displayed the brain regions that are functionally more connected in healthy participants compared to PI patients.