Title

Self-referential dysfunction and default mode hyperactivation in psychophysiological insomnia patients: A case-control fMRI study

Running Title

Self-referential dysfunction in insomnia

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Abstract

Psychophysiological insomnia (PI) is one of the most frequent sleep disorders. In this study we tested whether differences in terms of neural activation are present between a group of PI patients group and a healthy-control group while they are exposed to idiosyncratic ruminations and worries, evoked visually by words, so as to explore their hypothetical link with default-mode network (DMN) dysfunction in PI. We recruited 5 PI patients diagnosed according to ICSD-2 of AASM and 5 age- and sex-matched healthy-controls. Patients were recruited at the outpatient Sleep Medicine Centre of the Coimbra University Hospital Centre. We used an fMRI block-design paradigm where the participants visualized lists of words related to past/present and future concerns and also emotionally neutral words. The results suggested that the PI patients showed a failure of the DMN to deactivate. Moreover, when these patients were exposed to words concerned to both past/present ruminations and future worries, there was a pronounced and significant over-recruitment of brain areas related to DMN and self-referential processing when they were compared to healthy volunteers. The differences between the patient and control groups were also evident in self-report measures. In sum, despite the relatively small sample size, our study clearly suggests that in PI there is a dysfunction in brain regions pertaining to self-referential processing which is corroborated by an overall pattern of hyperarousal in brain regions comprising the DMN. These data may be useful in the improvement of pathophysiological models, diagnostic and therapeutic interventions for insomnia.

Keywords: Psychophysiological insomnia, hyperarousal, rumination, worry, default-mode network.

Introduction

Psychophysiological insomnia (PI) is one of the most common sleep disorders [1-4], with a prevalence ranging from 3 to 5% in the general population [5]. Two cardinal features of this disorder are the negative conditioning between habitual sleep cues (e.g., bedroom, bedtime) and detrimental behaviors for sleeping (e.g., watching television, worrying or using computer in bed/bedroom), and a widespread hyperarousal of different systems – physiological, emotional, and cognitive – along the 24 hours of the day [1,2,6]. Cognitive hyperarousal seems to be the most compromised mechanism [7]. Generally, cognitive arousal in PI pertains to the intrusive thoughts about sleep and other themes, which have the potential to disturb individuals. Rumination and worry are two important psychological processes associated with cognitive arousal. According to some authors, PI patients are ten times more likely to report their perceived pattern of cognitive arousal as more disturbed than the physiological one [8]. Additionally, there is evidence suggesting that PI patients are more vulnerable to evaluate stressing/threatening stimuli as more negative compared with healthy individuals [9]. Even so, the reported frequency of these same negative events is similar between the two groups. For example, a recent neuroimaging study found that although there were no noticeable differences between a group of PI patients and a control group when passively viewing negative pictures, the clinical group did show an increased amygdala activation during cognitive reappraisal of the negative stimuli [10]. According to several models on the understanding of PI and the current clinical practice, it seems evident that dysfunctional cognitive-affective patterns related to rumination and worry foster the maintenance of PI [11,12]. In the psychology literature it is usual to distinguish the concept of rumination from worry [13]. Although both relate to a kind of repetitive and persistent cognitive activity with respect to the self and characterized by a negative

focus [14], they differ mainly with regard to the temporal dimension – rumination is focused mostly on the cognitive activity concerning the past or present life events, whereas worry is related to anticipated threats with direct implications to the self [15]. Further, rumination is more related with depressive states whilst worry is more associated with anxiety states [13]. This is relevant to insomnia research as depression and anxiety disorders are the most prevailing clinical comorbid conditions [1,15,16]. One of the most relevant symptoms of PI patients is the excessive preoccupation about sleep.. However, preoccupations pertaining to other life themes emerge in cognitive activity as well, and are likely to cause sleep disruption [10,17,18]. In this sense, Watts, Coyle, and East [19] distinguished “worrying insomniacs" and “non-worrying insomniacs". The former would comprise the patients concerned with numerous topics (e.g., trivial issues, plans, work issues, familiar relationships, bodily sensations, and daily hassles), whereas the latter group would include patients predominantly anxious with respect to their own sleep and its related deficits. In summary, in both “insomnia types” the self seems to play a central role in cognitive processing activity.

In recent decades, cognitive neuroscience began to study the brain structures that are hypothetically underlying the “self”, supported by modern technologies such as positron emission tomography (PET) and thereafter functional magnetic resonance imaging (fMRI) [20]. It has been suggested that the medial prefrontal cortex (MPFC), posterior cingulate cortex (PCC), and precuneus are key brain regions linked with self-referential cognition and self-reflection in healthy individuals [21-24]. For example, these brain regions are particularly activated during the visualization of self-related stimuli [25].

However, neuroimaging studies of insomnia using fMRI technology in particular, are scarce in the literature [26,27]. Research concerning neuroimaging and disrupted

self-related information processing in neuropsychiatric disorders has known some advances recently [28]. Given the lack of studies on insomnia about this topic, we reviewed the research carried out in anxiety disorders and major depressive disorder since the anxious and depressive components in insomnia are important [29]. In a study by Paulesu et al. [30], with generalized anxiety disorder (GAD) patients and healthy subjects, it was shown that the same network of brain regions was similarly recruited in both groups , when listening to worry-inducing sentences and when generating worry-like mental thoughts. However, when both groups were at rest, the cortical regions recruited by the worry condition – anterior cingulate cortex and dorsal MPFC - remained significantly activated in GAD individuals. Zhao et al. [31] studied a sample of patients with different anxiety disorders against a healthy group in an fMRI experiment. They observed that while both groups deactivate MPFC and PCC when they were exposed to neutral words, comparatively to rest, the clinical group deactivate more the PCC and into a lesser extent the MPFC than the control group. An fMRI study on major depressive disorder (MDD)found, in the context of ruminative stimuli, that patients showed increased activation in the orbitofrontal cortex, subgenual anterior cingulate, and dorsolateral prefrontal cortex comparatively to healthy controls. Furthermore, they exhibited more neural activity in the amygdala, rostral anterior cingulate/MPFC, dorsolateral prefrontal cortex, PCC, and parahippocampus when contrasting induced rumination against abstract distraction conditions [32]. Finally, in an fMRI study aimed to examine neural modifications induced by cognitive-behavioral therapy for depression, an MPFC hyperactivation was found in depressive patients, before the clinical intervention, compared to a group of healthy participants - The experiment consisted in a self-referential task recurring to emotional trait words as stimuli [33].

Several studies have suggested that when healthy individuals are exposed to visual or auditory stimuli related to their own worries, there is an overall neural activation of cortical areas comprising the default mode network (DMN). This neural network appears to be related to self-referential processing: mind-wandering, retrieval of episodic memories, envisioning the future, relevant decision-making, and theory of mind [34-36]. The DMN comprises the cortical medial areas of the brain, including the ventral MPFC, the dorsal MPFC, the medial temporal lobe, the inferior parietal lobe, the precuneus, the PCC/retrosplenial cortex, and the hippocampal formation [37-38]. There are some studies suggesting that the DMN, beyond representing a cohesive and coherent organization, can be divided into specific sub-organizations or sub-systems. In an attempt to dissociate subsystems within the DMN, Andrews-Hanna, Reidler, Sepulcre, Poulin and Buckner [39] found that this network may be divided into two main components, once taking into account the self-reference and temporal orientation variables. These authors reported that one of the components is the *dorsal medial subsystem,* which includes the dorsal prefrontal medial dorsal, the temporo-parietal junction, the lateral temporal cortex and the temporal pole - this subsystem is engaged when people make self-relevant affective decisions. The other component is the *medial temporal subsystem* which includes the medial prefrontal cortex ventral medial, the posterior inferior parietal lobe, the retrosplenial cortex, the parahippocampal cortex and the hippocampal formation – this subsystem is mobilized when individuals engage in decisions that require mental constructions based on memory (past-present focus). In future-oriented cognitions the two subsystems appears to be simultaneously mobilized, presumably to enable the construction of mental models of significant events for the self. In short, default-mode of brain function and self-referential stimuli induces an engagement of several overlapping brain regions, particularly ventral MPFC and PCC

[40-44]. However, there are specificities regarding each one. Whitfield-Gabrieli et al. [45] found that an explicit self-reference task activated preferentially the dorsal MPFC, whereas rest activated preferentially the precuneus.

In the current study, we intend to study the pattern of neural activation when the subjects visualize idiosyncratic past/present, future worries, and neutral words. The idiosyncratic stimuli will enable to study the neural emotional signatures for each individual while fostering ecological validity of the measures. For that purpose, we recruited a clinical (n = 5) and a sex- and an age- matched healthy control group (n = 5), and tested whether different neural signatures according to temporal orientation of the concern could be outlined. Moreover, we investigated whether there was a significant difference in activity in brain regions, comprising the DMN, between both groups. We hypothesized that more pronounced activity in self-related brain regions would be present in PI patients when they are exposed to the idiosyncratic specific stimuli, comparatively to the healthy control group.

Methods

Participants

Five individuals diagnosed with PI in a sleep medicine center (three women, 2 men; 29–53 years-old, mean age 41.6 ± 8.7) and 5 right-handed sex- and age- matched healthy adults, recruited from the community, volunteered for this study. The study was performed after permission from the medical ethical committee of Coimbra University Hospital Center (CHUC) (See Table 1), and in accordance to the Declaration of Helsinki. Subjects from the clinical group were invited to take part in our study if they met the following criteria: (1) having a PI diagnosis according to ICSD-2 (AASM, 2005) criteria made by a team of professionals at the Sleep Medicine Center at CHUC,

accredited by the European Sleep Research Society, namely a clinical psychologist/somnologist and a pneumologist/somnologist. At this Sleep Medicine Centreall cases are evaluated in a general sleep consultation at first; after this process, the patient is forwarded to a specific specialty; (2) having an age ranging from 18 to 60 years; and (3) not having an untreated psychiatric or sleep disorder that could fully explain the PI diagnosis. All the participants had normal or corrected to normal visual acuity. None of the subjects was paid to participate in this study. Informed consent was obtained from all individual participants included in the study. Individuals from the clinical group reported having 4 nights of insomnia per week in average, and a symptom duration of 55 months approximately. One of the PI patients was taking psychiatric drugs for insomnia (a neuroleptic and a benzodiazepine) at the time of the study. However, in this latter case, it was certified that PI was an independent diagnosis. Control participants were all selected from community sample and have no history of psychiatric, sleep, or other relevant clinical disorders. Besides the demographic data, all subjects were assessed in terms of insomnia severity, dysfunctional beliefs about sleep, and self-reported quality of life through the Insomnia Severity Index – ISI [47,47], the Dysfunctional Beliefs and Attitudes About Sleep – DBAS-30 [48,49], and the World Health Organization Quality of Life measure – WHOQOL–Bref [50], respectively. Finally, it was requested to all participants to complete a sleep diary during 1 week (7 nights) [48,51].

INSERT TABLE 1 HERE

Stimuli and task

The experimental paradigm consisted on a block-design, compounded of three condition blocks – neutral words, words related with past/present worries, and words

related with future worries – each repeated ten times over the experiment, and presented on an MR compatible screen. Each condition block had a duration of 30 seconds and was intercalated by a resting period of 30 seconds, in which subjects were asked to fixate a cross located at the screen centre. In each condition block, 15 previously self-generated words were presented for 2 seconds each. The total duration of each condition was: rest (15 minutes), neutral words (5 minutes), words related with past/present concerns (5 minutes), and words related with future worries (5 minutes). The order of each word within each condition was randomized (see Figure 1). The visual stimuli (i.e., words) were programmed using the software Matlab© (MathWorks, 2012a).

The lists of idiosyncratic words were generated by each participant. Notwithstanding, in order to guarantee that the task was successfully performed, the principal researcher was always available to help participants. Each participant was requested to fill 3 lists (neutral words, past/present worries, and future worries), with 15 blank spaces each, according to the following rules: “each space should be completed with a minimum of two words and a maximum of three words since in the latter case the additional word is a binding one (e.g., from, the, at, …)”. We chose to join past and present words in a single list for two reasons: (1) the words that people chose could be related to past situations, but when they were recalled, they could yet induce some significant arousal – present concern; and (2) the words could pertain to past activating events but that currently do not have any emotionally charged repercussion (albeit recognized as important to the self).

One must note that the passive viewing of the words constitutes an explicit task which involves at least recruitment of attentional resources that is, reading mechanisms [52]. Our experimental design was based on previous published studies performed by Hoehn-Saric, Schlund and Wong [53] and Zhao and Wang [31].

INSERT FIGURE 1 HERE

Image data acquisition

Imaging was performed on a Siemens MAGNETON Trio 3.0 Tesla at the ICNAS (Institute of Nuclear Sciences Applied to Health, Portugal). The participants underwent structural T1-weighted imaging and fMRI with a standard 12 channel head coil. Before examination, all participants were submitted to a safety questionnaire, after careful assessment of a radiology technician. Participants were fitted with earplugs, and padding was used to minimize involuntary head movements. Participants were also provided with a knob that they could push if they felt uncomfortable at any time of image acquisition.

The structural scan (MPRAGE - magnetization prepared rapid gradient echo) had the following parameters: 176 slices; echo time (TE) = 3.42 ms; repetition time (TR) = 2530 ms; flip angle = 7.0º; Field-of-View (FOV) = 256 mm. Blood Oxygenation Level Dependent images were collected. Our functional paradigm was acquired using a gradient echo-planar imaging (EPI) pulse sequence with the following parameters: 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 = 3x3x3 mm^3; FOV = 256 x 256; flip angle = 90º. In total, 725 volumes were collected.

Data preprocessing and analysis

Data were pre-processed and analyzed using BrainVoyager QX 2.6™ (Brain Innovation BV, Maastricht, The Netherlands) [54]. Structural volumes were corrected

for intensity inhomogeneities, the brain was segregated from head tissue, and transformed into Talairach stereotaxic space [55]. The preprocessing of fMRI data included: the slice scan time corrections (cubic spline interpolation and ascending interleaved slice scanning order), 3D motion correction (trilinear interpolation), temporal filtering (High-pass GLM Fourier 2 sines/cosines), and spatial smoothing (kernel with FWHM=8mm). For each subject, pre-processed fMRI volumes were co-registered to the corresponding structural volume, and transformed into Talairach space. VTC files were re-sampled to 3mm^3.

For the whole-brain analysis, we ran a fixed effects general linear model (FFX-GLM) analysis: in a first-level analysis, a standard GLM was used to estimate beta values for each subject and condition, then entered into the second-level analysis as a dependent variable. Baseline was defined as the average activity during the *Rest* periods, and the analysis included six confound predictors for each subject (three rigid-body translations and three rotations). Correction for multiple comparisons was performed with a False Discovery Rate (FDR) correction ($q < 0.05$). The Talairach coordinates and the information about the brain clusters were extracted recurring to NeuroElf (http://neuroelf.net), with labeling of brain peak activation clusters via the Talairach Client application (Version 2.4.3). The parameters used were: ('minsize'=20, 'localmax'=500 and 'localmin'=300). All the analyses were carried out in the 3D Talairach space, and were later projected onto a brain surface mesh for visualization purposes. The surface mesh corresponds to the cortex inflation of a control participant whose brain was the most identical to the average brain of the whole sample.

To compute descriptive statistics from self-reported measures we used IBM SPSS Statistics™ Version 22 (IBM, SPSS, Chicago, IL).

Results

Sleep log results

The clinical group presented worse results in all the sleep measures extracted from the sleep log, compared to healthy-controls (See Table 2 for details). PI patients had longer sleep latency, more nocturnal awakenings duration, less total sleep time duration, and they spent more time in bed compared to the control group. Furthermore, insomnia patients obtained significantly lower sleep efficiency than controls.

Self-report measures results

PI patients reported more insomnia severity and endorsed more dysfunctional beliefs regarding sleep and insomnia compared to healthy individuals. Moreover, the general quality of life indicator and the four domains related to it were more compromised in the PI group (See Table 2).

INSERT TABLE 2 HERE

fMRI results

Contrast between PI patients and healthy controls regarding the neural activation induced by past/present self-related words

Several cortical brain regions shown to be significantly more activated in PI patients than in the control group when all the participants were exposed to visual stimuli (words) depicting idiosyncratic past/present activating self-related words (see Figure 2). Within these areas are included the bilateral middle occipital gyri, the bilateral cuneus, the bilateral posterior cingulate, the cerebellum´s declive, the left postcentral gyrus, the bilateral superior frontal gyri, the left superior temporal gyrus, the right fusiform gyrus and the right temporal middle gyrus (see Table 3). Within the areas

that shown more activation in control group compared to PI group are the bilateral inferior occipital gyri, the right cuneus, the left middle occipital gyrus, the bilateral middle frontal gyri, the left middle temporal gyrus, the left precuneus and the left cingulate gyrus.

INSERT FIGURE 2 HERE

INSERT TABLE 3 HERE

Contrast between PI patients and healthy controls regarding the neural activation induced by future self-related words

Several cortical brain regions were significantly more activated in PI patients than in the control group when all the participants were exposed to visual stimuli (words) depicting idiosyncratic future activating self-related words (see Figure 3). Within these areas are included the right superior frontal gyrus, the left middle occipital gyrus, the bilateral cuneus, the bilateral precuneus, the left posterior cingulate, the left parahippocampal gyrus, the left inferior parietal lobule, the left precentral gyrus, the right fusiform gyrus and the right temporal gyrus (see Table 4). Within the areas that shown more activation in control group compared to PI group are the left lingual gyrus, the right cuneus, the bilateral middle frontal gyrus, and the right superior parietal lobule.

INSERT FIGURE 3 HERE

INSERT TABLE 4 HERE

Contrast between PI patients and healthy controls regarding the neural activation induced by neutral self-related words

Several cortical brain regions shown to be significantly more activated in PI patients than in the control group when all the participants were exposed to visual

stimuli (words) depicting idiosyncratic neutral words (see Figure 4). Within these areas are included the left middle occipital gyrus, the bilateral cuneus, the left lingual gyrus, the left posterior cingulate, the cerebellum´s declive, the right precuneus, the left superior parietal lobule, the bilateral middle frontal gyri, the right superior frontal gyrus, the left inferior parietal lobule, the left precentral gyrus, the left insula, the right postcentral gyrus, the right middle temporal gyrus, the left cingulate gyrus, the left anterior cingulate, the right inferior frontal gyrus, the left superior temporal gyrus, and the right caudate (see Table 5).Within the areas that shown more activation in control group compared to PI group are the left lingual gyrus and the right cuneus.

INSERT FIGURE 4 HERE

INSERT TABLE 5 HERE

Contrast [neutral vs. baseline] in PI patients and healthy controls separately

Finally, we studied independently the contrast between neutral words condition and the baseline for both groups. As can be observed in Figure 5-A, the control group deactivated significantly brain regions related to DMN (e.g., bilateral precuneus, bilateral medial frontal gyri, bilateral inferior parietal lobules, and bilateral middle temporal gyri) when they were visualizing neutral words. Activated brain areas included, for example, the superior temporal gyri, the middle frontal gyri, the inferior frontal gyrus, and the inferior parietal lobule (see Table 6). On the other hand, PI patients do not deactivate significantly any brain regions (see Figure 5-B). However, when patients visualized neutral words, several cortical areas became activated beyond the visual areas – e.g., bilateral medial frontal gyri and bilateral superior parietal lobules (see Table 6).

INSERT FIGURE 5 HERE

INSERT TABLE 6 HERE

Discussion

PI is a sleep disorder characterized by conditioned bedtime arousal and disturbing thoughts about the self [56]. The results of our study suggest that PI patients present a widespread pattern of increased neural activation compared to a group of healthy individuals. These findings support the well-known "hyperarousal hypothesis" in PI [6]. In this study, it was our aim to explore neurobiological correlates of psychological constructs such as worry and rumination in PI patients.. According to the hyperarousal theory, the patients are more prone to stress-reactivity and the hypothetical abnormal levels of arousal may be studied across several methods and focusing on disparate human systems (cognitive, behavioral, affective, and neurobiological). Besides, PI is considered a 24-hr disorder so the daytime studies appear to be an important asset to investigate this sleep disorder [6].

It is well known in previous literature that the processing of stimuli or information directly implicated with the self activates a relatively well established set of brain regions, many of them comprising the DMN. Notwithstanding, beyond these core regions that stand out in the majority of the studies, other important brain areas with implications for the "self" might be differently highlighted by other experimental paradigms.

In our study, when neural activation pattern related to past/present concerns is compared between both groups, it is noticeable that PI patients also show a significant higher activation from brain regions linked to DMN and self-referential processing.

Within the main brain regions, we highlight the bilateral posterior cingulate, the bilateral superior frontal gyri, the left superior temporal gyrus, and the right temporal middle gyrus. The posterior cingulate is a brain area directly implicated in episodic memory and self-awareness [57-58]. There is some evidence associating superior frontal gyri with self-referential processing [59]. The superior and medial temporal cortices are intimately linked to retrieval of autobiographical memories [60]. The visual areas such as middle occipital gyri, cuneus or fusiform, which are related with processing of visual stimuli, have been also discussed as having a role in self-referential processing. For example, the occipital medial cortex is a brain region which frequently is shown activated in affective neuroscience fMRI studies and appears to be related to attentional modulation to the inputs or stimuli presented to the participants [53]. Many of the regions we discussed also have a role in the theory of mind function; this seems coherent with our results, as some of the words (past/present and futures concerns) contained in the lists generated by the participants implied also situations related with family members or friends (e.g., diseases, unemployment, etc) [61]).

In turn, when neural activation related to future concerns is compared between both groups, it is noticeable that PI patients show a similar pattern of activation to the past/present words, and activate significantly more brain regions linked to DMN and self-referential processing than normal controls. This finding is in accordance with other studies suggesting that there is an overlapping of brain areas when individuals are exposed to self-referential stimuli related to both their past and their future [42]. PI patients display a pattern of general increased activation both with regard to the past/present and future concerns. This is in accordance with some literature that posits that within PI patients there are individuals where the dysfunctional cognitive activity is more attached to the past/present concerns, whereas in others patients the future domain

seems to be more compromised. Of course, there are patients in which both domains are relevant and are impaired [62].

Finally, when the neutral words contrast is performed between the clinical and control groups, PI patients show a generalized pattern of activation in brain areas very similar to those found in past/present and futures concern conditions.. Within these areas are included the left posterior cingulate, the right precuneus, the bilateral middle frontal gyri, the left inferior parietal lobule, the left insula, the right middle temporal gyrus, the left cingulate gyrus, and the left anterior cingulate. Besides, even more regions associated with DMN and self processing emerged. For example, in this contrast we observe the activation of brain regions such as the insula, inferior parietal lobe and middle frontal gyrus, all of them intrinsically associated with self-processing and DMN [35]. Similarly to what has been found in anxiety disorders, the neutral stimuli activated brain areas related to emotional arousal such as the posterior cingulate, the precuneus, the middle frontal gyri, the insula, and the middle temporal gyrus [30-31]. This finding is in line with the hypothetical state of arousal and hypervigilance typical of insomnia disorder - itmight be related with overall higher responsivity or sensitivity (i.e., a trait), regardless of the content of the stimuli.

An additional interesting finding deserves further discussion. In all of the contrasts we performed, it was noticeable that some visual areas in the occipital lobes (e.g., cuneus, lingual gyrus, occipital medial cortex) were systematically more activated in control individuals than in PI patients [63,64]. This finding might relate to the easiest detachment from introspective mode by healthy individuals. One should note that a study by Schlochtermeier et al. [65] found that the activation of cortico-emotional networks is identical for visual stimuli and verbal stimuli. Thus, the sensory modality by which we presented the stimuli may not account for these results.

Complementarily, we performed a contrast separately for each of the samples between neutral words and baseline conditions in order to explore a hypothetically dysfunction in DMN de(activation) in PI patients. Our results show that healthy-control group displays an expected pattern of deactivation in regions comprising DMN (but not only) when they are instructed to pay attention to the neutral words (attention-demanding task). In turn, PI patients do not show any significant cortical deactivation as is expected in normal samples. On the contrary, brain regions such as the bilateral medial frontal gyri and bilateral superior parietal lobules were significantly activated when PI patients were exposed to neutral words compared to the baseline. This result is interesting, and goes in line with a recent study that posits that beyond an overlap between brain regions related to resting-state and self-referential processing, some differential patterns do exist [45]. In this case, and in accordance with the results already discussed, the neutral condition for PI patients functioned as a "threatening" condition in an identical way as the other experimental conditions. However, one should note that we cannot discard also the possibility (or potential contribution) of low disengagement from worry-thoughts from the other two conditions, as all do occur in the same experimental session.

These results are therefore in line with our hypotheses: PI patients cannot disengage themselves from disturbing cognitive contents, which might intensify at bedtime (when the patient is likely less involved in external tasks and more aware of her/his thoughts). According to neurobiological findings, it is congruent that prefrontal cortex, PCC and parietal lobes are highly activated in insomnia individuals. Buysse, Germain, Hall, Monk, and Nofzinger [66] posit that it is expected that brain regions involved in self-awareness such as the precuneus, to be over-activated both during bedtime and NREM

sleep in PI patients. Our results suggest that perhaps this arousal might extend also to the daytime.

Apart from the direct and obvious implications of the obtained results for the hyperarousal hypothesis, we posit that cognitive and metacognitive models of insomnia are important in discussing of these findings [67,68]. It seems that the manner in which PI patients cope with their negative cognitions might be more relevant than the content of their own thoughts. When the participants of both groups filled out the list of words for the fMRI protocol, it was notorious that the core concerns were not significantly different.

Overall, the main strengths of this study are:: a novel way to collect evoked responses at the fMRI scanner; the utilization of idiosyncratic words presented visually, not a standardized list of predefined traits or words that participants would have to decide whether applied to themselves or not; finally, the total time the individuals were inside the fMRI machine accounted for the robustness of the data..

Limitations of the study

Notwithstanding, some important limitations should be noted: *i)* small sample size, due to strict inclusion criteria; *ii)* one of the patients was taking medication at the time of the study, whereby we do not know whether the results may be explained (at least in part) by this confounding variable; and *iii)* some patients report that the time inside the fMRI scanner was too long and this factor might have contaminated the collected neuroimaging data. Nevertheless, we stress the relevance that the prolonged time inside the fMRI scanner might bring in terms of ecological validity of the study. Finally, as we recruit patients who sought help only in one sleep center, we cannot assure that this

sample may represent the larger population on adult patients with PI, even if this is one of the largest centres of the country [69].

The continuity of this research line appears to be important. As such, for future studies we suggest to replicate these findings in a larger sample, contrasting other patients groups such as GAD or depression, and observe whether there are significant differences among them. Additionally, it would be interesting to compare an insomnia sample against a sleep-deprived one – either acute or chronic – to explore the idea that insomnia patients might not be necessarily sleep-deprived; collecting simultaneous EEG data would enable to assess effects on brain rhythms. One other point to be studied could be the administration of more psychological assessment measures so as to identify possible correlations with neural activity in key regions-of-interest, such as MPFC or precuneus – in this case, one must have a large sample size to assure careful interpretation of the data to avoiding overinterpretation of correlational data [70]. Finally, we stress the possibility of replicating this study adding a list of positive words according to the same temporal orientations we privileged. This topic may be interesting to investigate since the cognitive arousing activity which is likely to disturb the PI patients´ sleep may be positive as well, although this is not the most frequent scenario.

In conclusion, our study may help to improve neurobiological models of insomnia, in particular, in studying the hypothesis underlying DMN brain dysfunction and hyperactivity [66].

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Conflict of Interest Statement

The authors declare that there are no conflicts of interest.

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Table 1 – Demographic and psychological characteristics of the sample

	PI patients (n=5) Median (P25 | P75)	Healthy controls (n=5) Median (P25 | P75)
Age (years)	43.0 (34.0 | 48.5)	38.0 (32.5 | 45.0)
Education (years)	15.0 (10.5 | 16.0)	18.0 (16.5 | 19.5)
Sex	3 F / 2 M	3 F / 2 M

Note. SD = Standard deviation; F = Female; M = Male

Table 2 – Sleep log and self-report measures

	PI patients (n=5)	Healthy controls (n=4)*	Mann-Whitney test	
	Median (P25 | P75)	Median (P25 | P75)	*z*	*p*
SL (minutes)	14.0 (7.5 | 55.5)	7.0 (2.5 | 10.7)	-1.470	0.142
WASO (minutes)	69.0 (17.5 | 83.0)	13.0 (1.0 | 24.2)	-1.470	0.142
TST (minutes)	300.0 (271.5 | 468.5)	418.0 (328.2 | 461.2)	-0.735	0.462
TIB (minutes)	524.0 (457.5 | 558.0)	476.0 (372.5 | 536.0)	-1.225	0.221
SE (%)	0.65 (.54 | .84)	.88 (.85 | .89)	-1.968	0.49
ISI	15.0 (13.5 | 23.0)	1.0 (1.0 | 3.25)	-2.491	0.013
DBAS-30	5.30 (4.26 | 6.16)	2.51 (1.53 | 4.40)	-2.205	0.027
WHOQOL-Bref overall	75.0 (56.2 | 81.2)	87.5 (68.7 | 96.8)	-1.382	0.167
WHOQOL-Bref [D1]	42.8 (42.8 | 48.2)	66.0 (64.2 | 70.5)	-2.502	0.012
WHOQOL-Bref [D2]	75.0 (68.7 | 79.1)	75.0 (71.8 | 81.2)	-0.377	0.706
WHOQOL-Bref [D3]	58.3 (41.6 | 91.6)	79.1 (56.2 | 89.5)	-0.618	0.537
WHOQOL-Bref [D4]	65.6 (57.8 | 75.0)	87.5 (64.8 | 98.4)	-1.359	0.174

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

Note. 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; 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 3 - Talairach coordinates of activation clusters between both groups regarding the past/present condition

		Talairach coordinates					
Region	Hemisphere	BA	x	y	z	Cluster size (k)	*t*-value
Past/present words							
PI patients > *Healthy controls*							
Middle Occipital Gyrus	L	18	-21	-94	19	2489	8.391832
Cuneus	R	18	9	-94	10		6.918135
Cuneus	L	18	-6	-76	28		5.532022
Posterior Cingulate	L	31	-18	-61	16		5.108182
Lingual Gyrus	L	18	-3	-70	-2		4.745942
Middle Occipital Gyrus	L	19	-45	-82	13		8.131234
Cuneus	L	18	-24	-85	25		7.745584
Cuneus	R	18	9	-91	19		6.973338
Cuneus	R	18	21	-79	28		5.829484
Declive	L	-	-27	-67	-14		5.031836
Posterior Cingulate	R	23	9	-58	13		4.127951
Cuneus	L	18	-6	-73	19		5.670094
Postcentral Gyrus	L	2	-63	-22	25	173	5.839907
Superior Frontal Gyrus	R	10	18	62	1	109	5.689000
Superior Temporal Gyrus	L	22	-57	8	1	235	4.591518
Fusiform Gyrus	R	19	21	-67	-8	54	4.379697
Postcentral Gyrus	R	2	63	-22	31	70	4.372968
Superior Frontal Gyrus	L	6	-9	-1	61	35	3.893251
Superior Frontal Gyrus	L	10	-21	59	-8	44	3.666368
Superior Parietal Lobule	L	7	-6	-70	58	28	3.591783
Middle Temporal Gyrus	R	39	39	-73	19	20	3.583133
Healthy controls > PI patients							
Inferior Occipital Gyrus	L	17	-12	-91	-5	912	-8.202089
Cuneus	R	17	18	-94	-2		-7.869256
Middle Occipital Gyrus	L	19	-27	-88	7		-7.786157
Inferior Occipital Gyrus	R	18	27	-88	-8		-5.773417
Middle Frontal Gyrus	L	46	-36	20	22	52	-4.659845
Middle Temporal Gyrus	L	21	-66	-34	-8	89	-4.414620

Precuneus	L	39	-36	-61	37	206	-4.169694
Middle Frontal Gyrus	R	9	33	26	22	21	-3.745999
Cingulate Gyrus	L	31	-6	-52	31	44	-3.599144

Note. R=Right hemisphere; L=Left hemisphere; BA=Brodmann Area. Minimum size of clusters=20.

Table 4 - Talairach coordinates of activation clusters between both groups regarding the future condition

		Talairach coordinates					
						Cluster size	
Region	Hemisphere	BA	x	y	z	(k)	*t*-value
Future words							
PI patients > *Healthy controls*							
Superior Frontal Gyrus	R	10	18	65	-2	411	7.584518
Middle Occipital Gyrus	L	19	-45	-79	16	3176	7.577302
Cuneus	L	19	-24	-85	28		6.306173
Middle Occipital Gyrus	L	18	-21	-94	19		5.836624
Precuneus	R	19	9	-85	43		5.596190
Cuneus	R	18	9	-97	10		5.578913
Posterior Cingulate	L	30	-3	67	10		6.166642
Precuneus	R	31	21	-73	31		4.864830
Cuneus	R	18	6	-94	19		6.160268
Posterior Cingulate	L	30	-15	-55	10		5.906564
Parahippocampal Gyrus	L	30	-15	-46	1		5.760088
Precuneus	L	19	-15	-82	40		5.164919
Inferior Parietal Lobule	L	40	-66	-28	25	156	5.742141
Precentral Gyrus	L	44	-57	11	4	100	5.187091
Inferior Parietal Lobule	R	40	57	-25	31	87	4.103082
Fusiform Gyrus	R	19	21	-67	-8	35	4.086811
Middle Temporal Gyrus	R	39	42	-73	25	33	3.753589
Healthy controls > PI patients							
Lingual Gyrus	L	17	-15	-91	-2	317	-8.129291
Cuneus	R	17	21	-94	-2	234	-7.668869
Middle Frontal Gyrus	L	9	-36	17	25	37	-4.004123
Medial Frontal Gyrus	R	10	21	50	7	60	-3.619098
Superior Parietal Lobule	R	7	36	-67	46	22	-3.550972

Note. R=Right hemisphere; L=Left hemisphere; BA=Brodmann Area. Minimum size of clusters=20.

Table 5 - Talairach coordinates of activation clusters between both groups regarding the neutral condition

		Talairach coordinates					
Region	Hemisphere	BA	x	y	z	Cluster size (k)	*t*-value
Neutral words							
PI patients > *Healthy controls*							
Middle Occipital Gyrus	L	19	-24	-97	19	3745	7.514253
Middle Occipital Gyrus	L	19	-24	-97	19		7.514253
Middle Occipital Gyrus	L	19	-24	-97	19		7.514253
Cuneus	L	18	0	-97	16		7.117648
Lingual Gyrus	L	-	-12	-61	1		5.078488
Posterior Cingulate	L	30	-15	-55	10		4.960924
Middle Occipital Gyrus	L	19	-45	-79	13		6.521839
Cuneus	R	18	9	-88	22		6.170494
Cuneus	L	30	-3	-70	10		6.052876
Cuneus	L	19	-6	-79	31		5.743964
Lingual Gyrus	L	18	-6	-73	-2		5.343783
Declive	L	-	-27	-64	-20		5.260688
Precuneus	R	19	12	-85	43		4.898978
Superior Parietal Lobule	L	7	-3	-64	58		4.678679
Culmen of Vermis	R	-	6	-61	1		4.608467
Middle Frontal Gyrus	L	10	-24	56	-8	797	6.168018
Superior Frontal Gyrus	R	10	21	62	-2		5.608289
Lentiform Nucleus (putamen)	L	-	-18	8	-5		3.938770
Medial Frontal Gyrus	R	11	9	50	-11		3.641579
Inferior Parietal Lobule	L	40	-66	-28	25	530	5.897815
Precentral Gyrus	L	44	-60	8	10		4.873219
Inferior Frontal Gyrus	L	44	-51	2	19		4.004919
Insula	L	13	-42	-1	-2		3.811280
Postcentral Gyrus	R	2	66	-19	28	94	4.105882
Middle Temporal Gyrus	R	39	42	-76	13	88	4.089099
Middle Frontal Gyrus	L	9	-30	47	37	65	4.074358
Cingulate Gyrus	L	24	-3	-1	43	35	3.742775
Anterior Cingulate	L	24	0	17	22	28	3.492516
Inferior Frontal Gyrus	R	47	39	29	-5	33	3.487157

Sub-Gyral	L	6	-21	2	55	31	3.347102
Superior Temporal Gyrus	L	38	-51	17	-23	37	3.178977
Caudate (Caudate Head)	R	-	12	17	-2	28	3.082626
Healthy controls > PI patients							
Lingual Gyrus	L	17	-15	-91	-2	387	-8.343771
Cuneus	R	17	18	-94	-2	186	-7.773012

Note. R=Right hemisphere; L=Left hemisphere; BA=Brodmann Area. Minimum size of clusters=20.

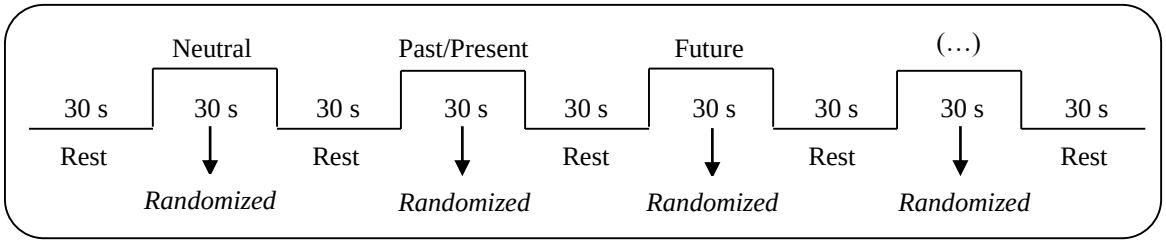

Figure 1 – Experimental fMRI block-design of the study

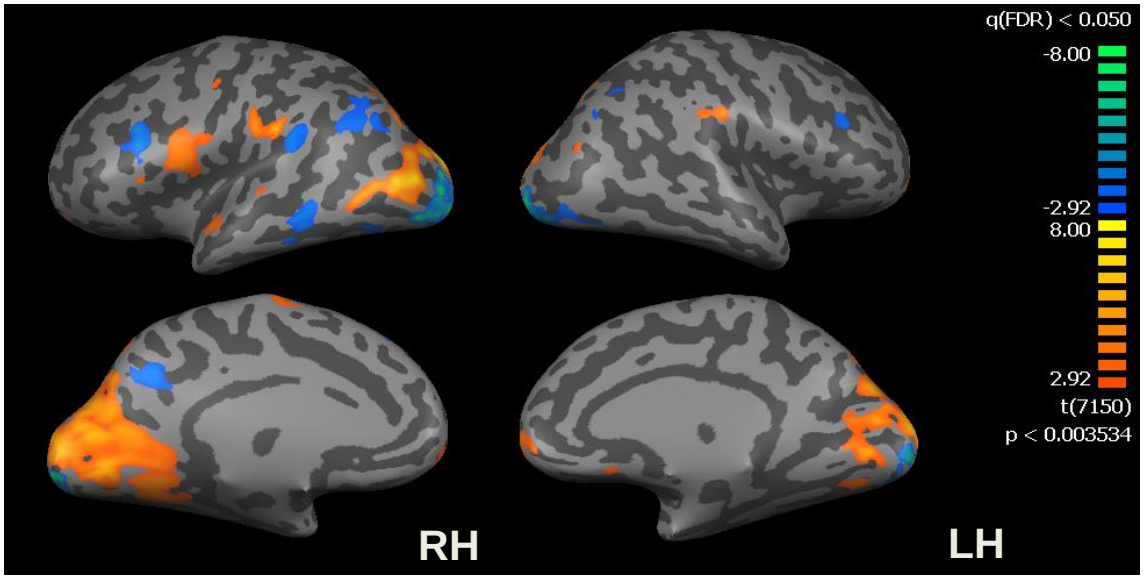

Figure 2 –Group contrast between PI patients and controls for the condition past/present self-related words. Brain regions more activated in PI patients are shown in warm colors. . Top panel: the lateral views of both hemispheres are depicted. Bottom panel: the medial views of both hemispheres are displayed. RH=right hemisphere; LH=left hemisphere. Radiological display convention was used.

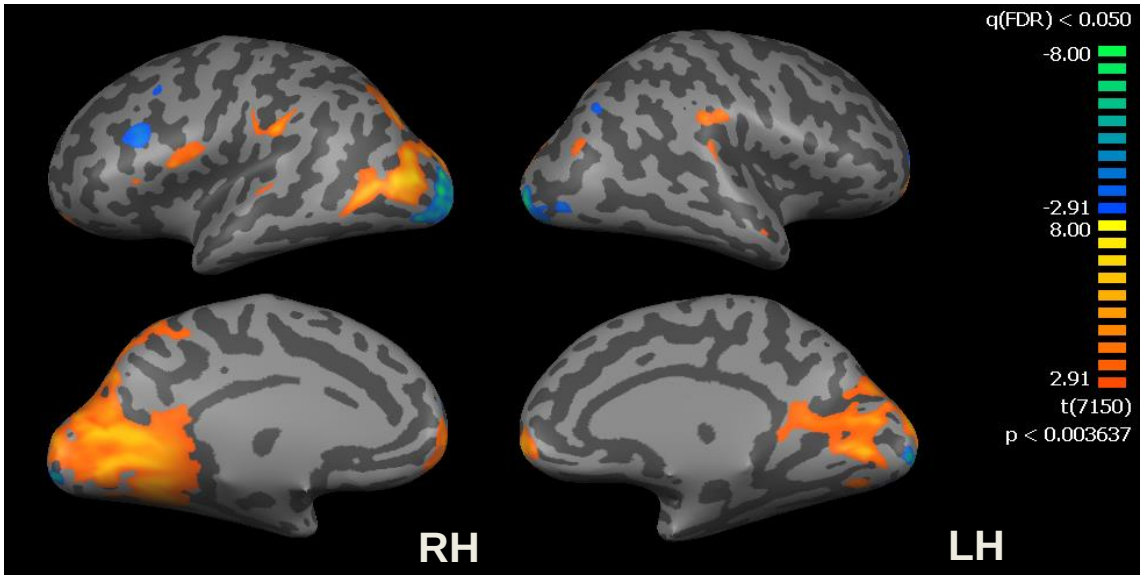

Figure 3 – Group contrast between PI patients and controls for the condition future self-related words. Brain regions more activated in PI patients are shown in warm colors . Top panel: the lateral views of both hemispheres are depicted. Bottom panel: the medial views of both hemispheres are displayed. RH=right hemisphere; LH=left hemisphere. Radiological display convention was used.

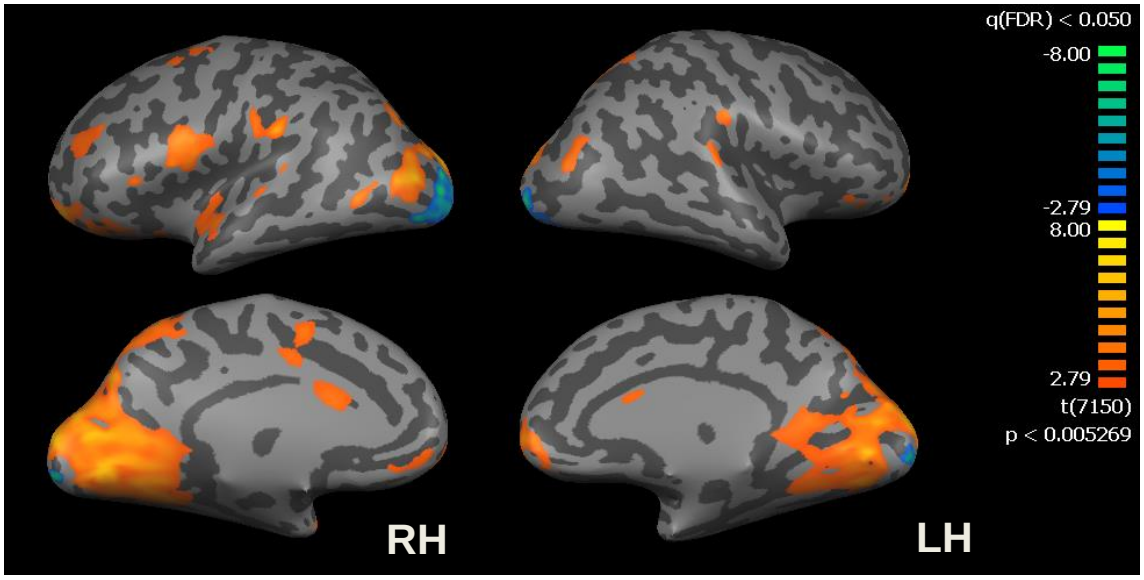

Figure 4 – Group contrast between PI patients and controls for the condition neutral self-related words. Brain regions more activated in PI patients are shown in warm colors . Top panel: the lateral views of both hemispheres are depicted. Bottom panel: the medial views of both hemispheres are displayed. RH=right hemisphere; LH=left hemisphere. Radiological display convention was used.

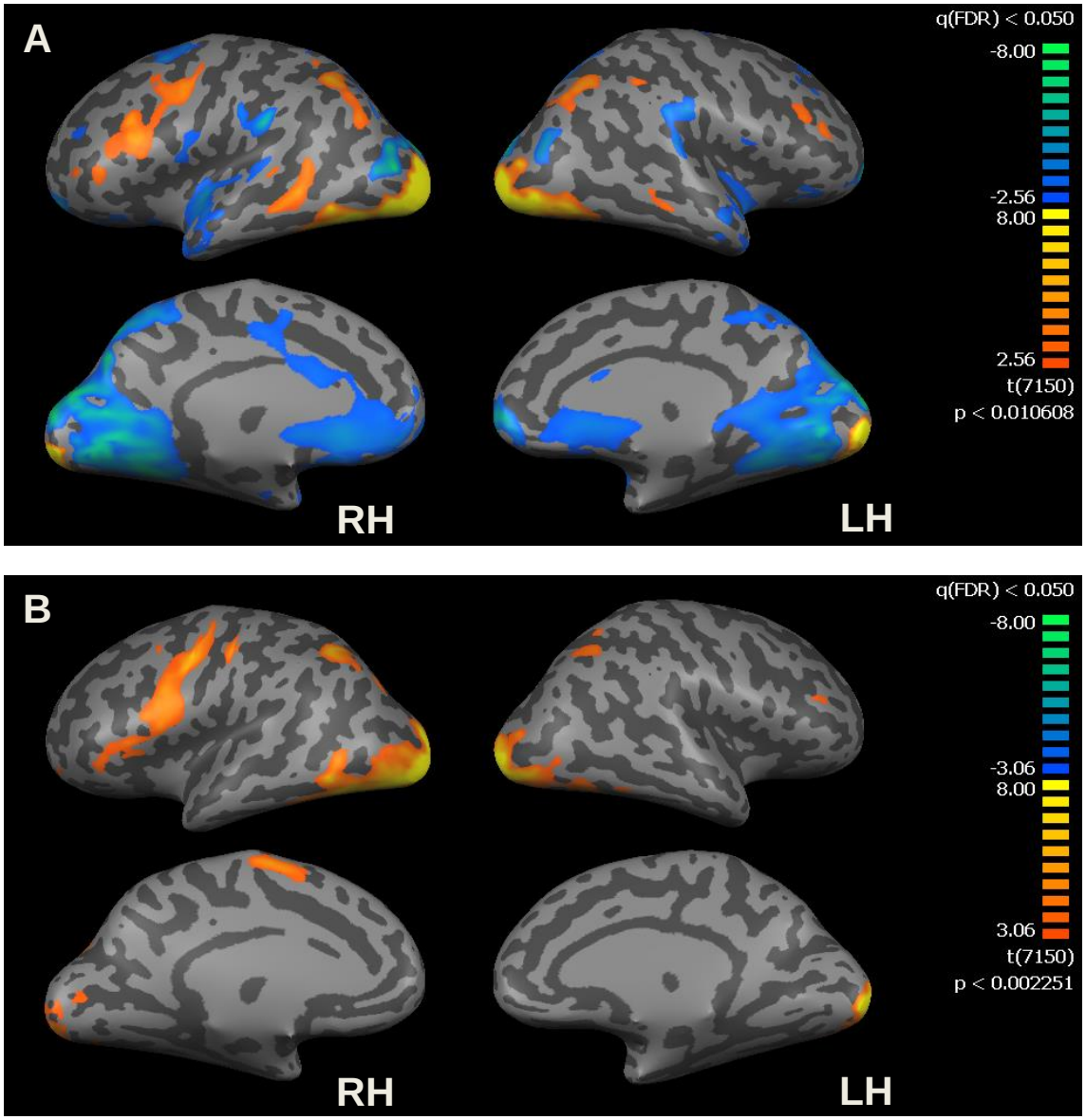

Figure 5 – Contrast between neutral words and baseline for the control group (A) and PI patients (B). Cool colors display brain deactivations when the individuals visualized self-related neutral words. Top panel: the lateral views of both hemispheres are depicted; Bottom panel: the medial views of both hemispheres are displayed. RH=right hemisphere; LH=left hemisphere. Radiological display convention was used.