Universidade de Aveiro Departamento de Educação e Psicologia
2016

Daniel Ruivo Marques

A hipótese da hiperativação na insónia psicofisiológica. Estudo da default-mode network e sua modificação após TCC

The hyperarousal hypothesis in psychophysiological insomnia. Study of default-mode network and its modification after CBT

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Tese apresentada à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Doutor em Psicologia, realizada sob a orientação científica da Doutora Ana Cardoso Allen Gomes, Professora Auxiliar do Departamento de Educação e Psicologia da Universidade de Aveiro, do Doutor Miguel de Sá e Sousa de Castelo Branco, Professor Associado com Agregação da Faculdade de Medicina da Universidade de Coimbra e da Doutora Gina Maria Costa Caetano, Investigadora no Instituto de Imagem Biomédica e Ciências da Vida (IBILI) da Faculdade de Medicina da Universidade de Coimbra

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Para Francisco, Zulmira e Zé.

o júri

presidente

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palavras-chave

Insónia psicofisiológica, hiperativação, *default-mode network*, *resting-state*, terapia cognitivo-comportamental, IRMf.

resumo

A insónia primária é a perturbação do comportamento de sono mais prevalente quer na população clínica quer na comunidade. Uma das formas mais comuns é a insónia psicofisiológica (IP). A hiperativação neuropsicofisiológica, afetiva, cognitiva e comportamental assim como o condicionamento mal-adaptativo entre estímulos associados ao sono e à cama com estímulos indutores de ativação são duas das características mais diferenciadoras desta patologia. Tendo por base a importância que esta perturbação assume em termos de saúde pública, levou-se a cabo 4 estudos empíricos com recurso a ressonância magnética funcional: No primeiro estudo comparou-se a ativação neurobiológica entre um grupo de doentes com IP (*n*=5) e um grupo de indivíduos saudáveis (*n*=5) emparelhado quanto ao sexo e à idade quando eram confrontados com palavras que remetiam para preocupações do passado/presente, preocupações do futuro e palavras neutras; no segundo estudo, explorou-se as diferenças na ativação referente à *default-mode network* (DMN) e outras *resting-states* nos mesmos grupos do estudo 1; no terceiro e quarto estudos, repetiram-se os mesmos procedimentos para um grupo clínico (*N*=2) após estes terem sido submetidos a terapia cognitivo-comportamental para a insónia (TCC-I). No geral, verificou-se que os doentes com IP exibiram um padrão generalizado de hiperativação em áreas associadas à DMN quer quando confrontados com estímulos ativadores quer em repouso; em termos de ativação nas resting-states, constatou-se que, em repouso, o grupo clínico apresentou disfunções significativas. Após TCC-I, observou-se que os indicadores disfuncionais verificados nos estudos anteriores se esbateram tendendo a aproximar-se do perfil de ativação dos indivíduos saudáveis. Os resultados obtidos reforçam assim a ideia da hiperativação na insónia ao longo das 24 horas do dia assim como do papel fundamental que a ativação cognitiva parece ter na etiopatogenia e no tratamento da insónia. Para além disso, este trabalho contribui para um melhor entendimento da neurobiologia da insónia e sugere que se podem identificar mecanismos neuronais subjacentes às modificações operadas pela TCC-I.

keywords

Psychophysiological insomnia, hyperarousal, default-mode network, resting-state, cognitive-behavioral therapy, fMRI.

abstract

Primary Insomnia is the more prevalent sleep disorder both in clinical and community samples. One of the most frequent subtypes is psychophysiological insomnia (PI). The hyperarousal at different levels – biological, affective, cognitive, and behavioral – and the maladaptive conditioning between sleep-related stimuli and arousal are two major features of PI. Since this is a disorder which assumes an important role in public health, we performed 4 empirical studies recurring to fMRI: In the first study, we compared neurobiological activation between a group of PI patients (*n*=5) and a sex- and age-matched control group (*n*=5) when they were exposed to words concerning to past/present worries, future worries and neutral words; in the second study, we explored the activity of default-mode network (DMN) and other brain resting-states in the same groups as study 1; in the third and fourth studies, we repeated both experiments in a clinical group of patients with PI (*N*=2) after they underwent cognitive-behavioral therapy for insomnia (CBT-I). In general, it was observed that PI patients exhibited a generalized pattern of hyperarousal in several brain areas associated with DMN when they were confronted with affective stimuli and when they were resting in the fMRI scanner. In terms of activation of brain resting networks, we observed that the clinical group presented significant dysfunctions. After CBT-I, it was detected that the dysfunctional indicators observed in previous studies normalize, approaching the activation patterns typical of healthy individuals. The obtained results enhance the idea that the hyperarousal in PI is present during the 24-hours of the day; besides, the key role that cognitive arousal may be in the etiology and therapy of insomnia is also highlighted. In conclusion, this work contributes to a better understanding of neurobiology of insomnia and suggests that it might be possible to identify neural mechanisms underlying modifications accounted by CBT-I.

Insónia

Não durmo, nem espero dormir.
Nem na morte espero dormir.

Espera-me uma insónia da largura dos astros,
E um bocejo inútil do comprimento do mundo.

Não durmo; não posso ler quando acordo de noite,
Não posso escrever quando acordo de noite,
Não posso pensar quando acordo de noite —
Meu Deus, nem posso sonhar quando acordo de noite!

(...)

Não durmo, jazo, cadáver acordado, sentindo,
E o meu sentimento é um pensamento vazio.
Passam por mim, transtornadas, coisas que me sucederam
— Todas aquelas de que me arrependo e me culpo;
Passam por mim, transtornadas, coisas que me não sucederam
— Todas aquelas de que me arrependo e me culpo;
Passam por mim, transtornadas, coisas que não são nada,
E até dessas me arrependo, me culpo, e não durmo.

(...)

Não durmo. Não durmo. Não durmo.
Que grande sono em toda a cabeça e em cima dos olhos e na alma!
Que grande sono em tudo excepto no poder dormir!

(...)

Que horas são? Não sei.
Não tenho energia para estender uma mão para o relógio,
Não tenho energia para nada, para mais nada…

Álvaro de Campos, *in* “Poemas”

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Abbreviations

AASM	American Academy of Sleep Medicine
AN	Auditory Network
ANOVA	Analysis of Variance
APA	American Psychiatric Association
APA	American Psychological Association
BA	Brodmann Area
BOLD	Blood Oxygenation Level Dependent
BV	BrainVoyager
cbICA	Cortex-Based Independent Component Analysis
CBT	Cognitive-Behavioral Therapy
CBT-I	Cognitive-Behavioral Therapy for Insomnia
CID	Chronic Insomnia Disorder
DBAS-30	Dysfunctional Beliefs and Attitudes about Sleep
DMN	Default-Mode Network
DSM	Diagnostic and Statistical Manual of Mental Disorders
EEG	Electroencefalography
EKG	Electrocadiogram
EMG	Electromyogram
EOG	Electro-oculogram
EPI	Echo-Planar Imaging
FDR	False Discovery Rate
FFX	Fixed-Factor Analysis
fMRI	Functional Magnetic Resonance Imaging
FOV	Field of View
GAD	Generalized Anxiety Disorder
GLM	General Linear Model
ICD	International Classification of Diseases
ICA	Independent Component Analysis
IPL	Inferior Parietal Lobule
ISI	Insomnia Severity Index
lFPN	Left Fronto-Parietal Network
LH	Left Hemisphere
M	Mean
MDD	Major Depression Disorder
MPFC	Medial Prefrontal Cortex
MPRAGE	Magnetization Prepared Rapid Gradient Echo
MRI	Magnetic Resonance Imaging
MSLT	Multiple Sleep Latency Test
NIH	National Institute of Health
NREM	Non-Rapid Eye Movement
p	Statistical Level of Significance
PCC	Posterior Cingulate Cortex
PET	Positron Emission Tomography
PI	Psychophysiological Insomnia / Primary Insomnia
PSG	Polysomnography
rFPN	Right Fronto-Parietal Network
RCT	Randomized Controlled Trial

REM	Rapid Eye Movement
RH	Right Hemisphere
SD	Standard Deviation
SE	Sleep Efficiency
SPECT	Single Photon Emission Computed Tomography
SPSS	Statistical Package for the Social Sciences
SL	Sleep Latency
SogICA	Self-Organizing Group Independent Component Analysis
TE	Echo Time
TIB	Time in Bed
TR	Repetition Time
TST	Total Sleep Time
VN	Visual Network
WASO	Waking After Sleep-Onset
WHOQOL-Bref	World Health Organization Quality Of Life Questionnaire

Introductory Note

This PhD thesis comprises different types of papers that were published or are currently under review by some scientific journals.

When our research project started, we assumed “Psychophysiological Insomnia” designation according to the criteria posited by ICSD-2, AASM (2005). Other times, we assumed the “Primary Insomnia” designation as was adopted by the majority of specialized experts in the field and the DSM-IV-TR (2000). However, over the past few years, there were significant developments in insomnia´s research and clinical classifications. Some of the reviewers of our manuscripts demanded that we change the designation to “Insomnia Disorder” to be consistent with DSM-5, for example, or to “Chronic Insomnia Disorder” to be consistent with ICSD-3 (2014).

This explains why different terminologies for insomnia disorder appear along the different chapters of this work.

In sum, in this thesis, “Insomnia”, “Insomnia Disorder”, “Chronic Insomnia Disorder” and “Primary Insomnia”, should all be seen as synonymous of “Psychophysiological Insomnia” (ICSD, AASM, 2005).

INTRODUCTION

"Today, neuroscience, social sciences and humanities need to consider that disciplines do not exist per se, but are contingent and limited ways of knowing reality and understanding real life problems."

[Panese, 2009, p. 2]

A brief note on sleep

The problems related to sleep behavior constitute significant complaints presented to health professionals (Buysse, 2011). Insomnia, in particular, is the most frequent complaint in the context of primary health care after acute pain (Ferreira et al, 2001; Clemente, 2006; Morin, 1993). The symptoms of insomnia which often coexist with different clinical syndromes and the variety of possible insomnia diagnoses that the professionals may draw have motivated clinical and health psychologists to develop specific assessment and treatment strategies that scientific research has shown to be effective and efficient (Clemente, 2006; Schutte-Rodin, Broch, Buysse, Dorsey & Sateia, 2008; Morgenthaler, 2006; Morin et al., 2006; Morin et al., 2009; Sivertsen, 2006; Wilson et al, 2010).

From a historical point of view, it can be considered that it is with Aristotle in the fourth century BC that it arises a more systematic questioning onto sleep. This philosopher suggested that it was the cooling of the heart which would cause sleeping; Plato and Galen assigned a prominent role to the brain; in subsequent years, including the period of the Renaissance, it was postulated that sleep would be caused either by a deficit or by an excess of blood in the brain. In the nineteenth century, emerged the theory of hipnotoxines, substances that hypothetically would poison the brain causing therefore the sleep; Kleitman in the twentieth century, writes the "bible" of sleep study proposing a mechanism of fatigue at the level of the muscular and nervous systems. After this milestone, Von Economo proposes a brain center which was responsible for controlling sleep, and Bremer outline sleep as a passive process. Researchers as Moruzzi and Magoun, Aserinsky, Jouvet, and Hobson argue that sleep is rather an active process. These investigators contributed with valuable discoveries and most of them still current in the field of sleep medicine (Dement, 2011; Espie & Morin, 2012; Gomes, 2005; Hobson, 1995).

Briefly, we can say that sleep behavior goes through several stages during the night. There are often distinguished the NREM sleep (non-rapid eye movements) from the REM sleep (rapid eye movements) (Morin & Espie, 2003). Within the first, it were separated four stages - S1, S2, S3, and S4 - the first two are called “light sleep” and the last two are called “deep sleep” or slow/delta waves sleep (Dement, 2011; Espie & Morin, 2012; Gomes, 2005).[1] The REM phase is the one that is usually associated with more emotional

[1] In 2007, it was proposed by the AASM (American Academy of Sleep Medicine) a connection between stages 3 and 4 forming a single composite stage called henceforth S3 (Afonso, 2012; Paiva & Penzel, 2011).

and bizarre character dreams. During human development, sleep behavior changes in a significant way, either in quality or in quantity (Carney &, Edinger 2006; Dement, 2011).

Sleep is thus a shared behavior with the majority of living organisms albeit the researchers currently do not fully understand their associated functions and roles (Morin & Espie, 2012; Wickens, 2005). However, it can be said that sleep fits a key role in physical and mental restoration of body, memory consolidation and learning, cell renewal as well as a wide range of biophysiological and biochemical changes that allow the body to adapt to the environment in an efficient manner (Morin, 1993; Morin & Espie, 2003; Möller-Levet, 2013; Penzel & Paiva, 2011; Xie et al., 2013.). The studies conducted with participants who underwent sleep deprivation, either partially or chronic, have concluded that many of the higher psychological functions are compromised; in turn, the consequences on emotional, social, professional and even traffic behavior, among many other domains have led experts to alert that the sleep problems translate a serious public health problem (Boonstra, Stins, Daffertshofer, & Beek, 2007; Durmer & Dinges, 2005; Ohayon & Reynolds III, 2009; Paiva & Penzel, 2011).

One of the most simple and more clarifying definitions about sleep is the one by Hobson (1995) which states that "... is a dynamic behavior. Not simply the absence of waking, sleep is a special activity of the brain, controlled by elaborate and precise mechanisms. Not simply a state of rest, sleep has its own *specific, positive functions* "(p.1). It should be noted that the relationship between sleep and wakefulness is bidirectional, as difficulties during the day can be reflected at night during sleep, and difficulties during sleep may likewise have major repercussions in wakefulness (Gomes, 2005). This close association points to the need to consider the sleep as an essential factor to the promotion of quality of life, regardless of the age range considered (Carney & Edinger, 2008; Hamilton & Taylor, 2012, Pandi-Perumal, Monti, & Monjan, 2010; Richardson & Monjan, 2007).

Reasons to choose current dissertation´s theme

We identify three additional major reasons underlying the choice of our dissertation research topic, which was developed based on the initial idea of studying the imagiology of psychophysiological insomnia as suggested by the two main supervisors:

1 – The investment on new fields for research and practice in psychology - sleep disorders are frequently a relegated study domain in any initial training or postgraduate plan in Portuguese psychologists´ curricula (Gomes, 2005). Consequently, there is no significant interest in this subject by these professionals. In this sense, we chose to select for study a specific sleep disorder (i.e., psychophysiological insomnia - PI) whose first-line treatment choice is a psychotherapeutic methodology (i.e., cognitive-behavioral therapy - CBT). Many relevant authors, especially psychologists, have made contributions of great value. Research into the PI becomes even more impressive given that there is a consensus in the literature, considering that this is a disorder that covers 24 hours of the day (Kyle, Morgan, & Espie, 2010; Riemann et al., 2010; Wilson et al., 2010). Besides, our choice was also influenced by the scientific training received in Psychology, Integrated Master Degree in Psychology, Faculty of Psychology and Educational Sciences of the University of Coimbra (FPCE-UC), with specialization in Cognitive-Behavioral Therapy. The opportunity to have clinical training in the curricular internship at the Hospitals of University of Coimbra (HUC), allowed me to understand, among other things, that the difficulties related to sleep behavior are evident and significant in a considerable group of people who recur to mental health services. This training was also complemented by a Postgraduate Diploma in Cognitive and Behavioral Psychotherapy concluded with the recognition and accreditation of the Portuguese Association of Behavior Therapy (APTC) and the publication of some papers focusing on topics related to practical aspects concerning the implementation of this type of psychotherapy (Marques, 2009; Marques, 2010a; Marques, 2010b) or its relationship with the neurosciences (Pocinho, Madeira, Marques, Relvas, & Bettencourt, 2011);

2 – *Combination of methods and practices derived from psychology (experimental) with the modern techniques stemming from neurosciences, such as imaging functional magnetic resonance imaging (fMRI)* - taking into account the recent developments made in the field of structural and functional imaging of the brain, and taking into account the current state of the art research in neuroscience in the international arena, it emerges as relevant to join the traditional methods of data collection from psychology with neuroscience. The current state of the art research on the brain and behavior of organisms requires that psychologists, now more than ever, know the basic and fundamental concepts within the scope of neurobiology, neurophysiology, and genetics (Raichle & Snyder, 2007);

3 – *The research should have a strong focus on clinical practice* - that is the role of research as a basis and an aid in the process of decision making and solving practical problems (Salkovskis, 2002). The rationale is to give a further contribution to psychological clinical practice by providing data about the changes (mechanisms) which are operated in the brain as a result of the application of evidence-based psychotherapies. From our point of view, this topic of research, will contribute to close psychology and psychological treatments. We believe that it cans strength the confidence of the layperson and the patients in the psychological treatments (Marques, 2010a).

In this sense, the theme of this work meets the three aforementioned guiding lines. The sleep medicine is currently an interdisciplinary field of study, including clinicians and researchers of several specialties inside medicine such as neurology, psychiatry, otolaryngology, pulmonology specialists, and non-medical fields such as psychology, nursing, biomedical engineering, and others. In the specific case of psychology, there is a marked influence on the emergence of so-called Behavioral Sleep Medicine, which is based, in essence, in the application of principles and laws derived from the learning theories connecting areas of specialization such as health psychology and sleep medicine itself and eventually constitute a subspecialty within the latter (Stepanski & Perlis, 2000; Smith & Neubauer, 2003). Around the same time, the Monitor magazine, owned by the American Psychological Association (APA) published an article entitled "Sleep psychologists in demand: The success of cognitive behavioral therapy behavioral sleep

medicine has made the fast-growing field" that focus on the advances made possible by psychology and psychologists in the study of sleep behavior. It should be outlined that sleep psychology is since 2013 considered officially a specialty of Psychology (APA, 2013). Given the above scenario, we chose to relate several current and important issues both in the field of clinical psychology and in the field of neuroscience.

As stated above, one of the issues that has lately interested researchers in the field of neuroscience and clinical psychology is to study and understand hypothetical neural changes that occur in individuals after undergo to various forms of psychotherapy or psychological interventions (Scrimali, 2012). In this line, experimental paradigms have been created using a variety of methodologies, such as positron emission tomography (PET) imaging or structural magnetic resonance imaging (MRI) and functional (fMRI) (Linden, 2006; Pocinho et al., 2011). Currently, the contribution of neuroscience for the investigation of basic psychological processes is unquestionable and can also be argued that the strategies and experimental research paradigms derived from experimental psychology gave rise to a refinement of research methodologies in the field of neuroscience, in particular in the design of stimulation or symptom-provocation experiments (Jokic-Begic, 2010; Linden, 2006).

In the field of neuroscience, encompassing disciplines as diverse as psychology, neurology, psychiatry, philosophy of mind and even some branches of engineering, for example, is essential to establish protocols for collaboration between research centers and human resources from different backgrounds, to join forces, boosting up learning and using the know-how competently of each area of knowledge (Kolb & Wishaw, 2003). It is on this basis that many of the studies that are published in prestigious international journals work. Trying to reconcile the interest in an area and a sleep disorder intrinsically related to clinical psychology, and with the ambition to work in the light of what is done today by groups and reference research centers worldwide we thought it would be appropriate to operationalize the interest in this subject with something germane in the field of neuroscience.

In this sense, we proposed to focus in one of the resting-state brain networks, (i.e., what happens in terms of regional brain activity when the brain is in apparent "rest" or, in other words, when the individual is not performing any particular task which mobilizes their attentional resources in an explicit manner) (Greicius, Krasnow, Reiss, & Menon,

2003; Raichle et al., 2001; Raichle & Snyder, 2007). The behavior of this resting-state brain seems significantly to activate a set of interconnected brain areas that constitute a network that researchers have agreed to call "default mode network" (DMN) (Buckner & Vincent, 2007; Greicius & Menon, 2004; Raichle, 2009; Raichle & Snyder, 2007; Raichle et al., 2001). Reputed authors in the field of sleep medicine recently begun to suggest that studies that relate the behavior of the DMN in the field of sleep disorders and cognitive activities underlying it are needed (Hasler et al., 2013; Stickgold, personal communication, March 29, 2012; van Someren et al., 2013). The relevance of studying the sleep behavior from the neurobiological point of view is a current topic in the field and led to the development of an European network which has as its ultimate goal the creation of integrated databases with records of investigations carried out about sleep and its disorders. These methodologies allow visualization of brain activity to study the components of the DMN in participants diagnosed with PI and evaluate the respective activation levels, allowing also understanding whether there are relevant and meaningful neuroanatomical and neurofunctional modifications induced by CBT-I (Bastien, 2011). This study has not yet been performed according to our knowledge. We would like to stress that for the successful preparation of this thesis it was crucial the opportunity to have clinical practice and supervision at the Sleep Psychology Consultation at the University of Aveiro, and at the Sleep Clinical Psychology Consultation at the Sleep Medicine Centre of University Hospital Centre of Coimbra. All this activity enabled the publication of other sleep-related works as well.

It should be noted that this PhD research project only was possible due to the collaboration among researchers and professionals from the University of Aveiro, CMS-CHUC (Coimbra) and IBILI (University of Coimbra).

The PI is a disorder which in its assessment, treatment and research received large contributions of many internationally recognized psychologists. In this regard there are already defined the skills and criteria that physicians and nonmedical specialists (e.g., psychologists) should meet to be recognized as sleep medicine specialists (Penzel et al., 2014).

✦✦✦

This dissertation is structured in four different parts. The first part titled "Theoretical overview" comprises four chapters. In chapter 1 *"An overview regarding insomnia disorder: Conceptualization, assessment and treatment"* we present the main features of PI and explore the assessment and treatment techniques; in chapter 2 *"Hyperarousal and failure to inhibit wakefulness in primary insomnia: Birds of a feather?"* we critically discuss the existing comprehensive models of insomnia and propose an integrative approach; the chapter 3 *"Neurobiological correlates of psychological treatments for insomnia – A review"* is concerned in discussing the major advantages in considering neuroimaging techniques complementarily to the traditional ones (e.g., self-report measures) when one assesses the CBT-I results; the chapter 4 *"Default-mode network activity and its role in comprehension and management of psychophysiological insomnia: A new perspective"* provides our new ideas within the field that will serve as the theoretical framework to the empirical studies that were conducted.

The second part concerning "Methods" is constituted by a short single chapter - chapter 5 - that we named *"General considerations on methodology"* where are described overall methodological options pertaining to the empirical studies, and where one can find some information not detailed in the corresponding articles.

The third part encompasses the three empirical studies we carried out. Chapter 6 *"Self-referential dysfunction and default mode hyperactivation in insomnia patients: A case-control fMRI study"* explores the neural self-referential differences regarding rumination and worry in insomnia patients and healthy-controls, and chapter 7 *"Unbalanced resting-state networks activity in psychophysiological insomnia"* investigates whether the DMN is disrupted in insomnia patients comparatively to healthy-controls; The chapter 8 *"The effect of tailored cognitive-behavioral therapy on neurobiological function in insomnia patients: an fMRI study"* contains two studies that are extensions of the aforementioned studies (Chapters 6 and 7), as we were interested in observing whether there were significant modifications induced by tailored CBT-I in a small group of insomnia patients.

Lastly, part four "Concluding Remarks", is composed by a unique chapter – chapter 9 – titled *"Discussion and Conclusions"* where we endeavor to integrate the obtained empirical findings with the literature we reviewed in the first chapters of the dissertation.

In the end, one may access to an additional part labeled *"Appendices"* where it can be found research materials and other relevant (even if supplementary) documentation.

We are aware that a Ph.D dissertation composed by independent papers (published or submitted for publication to different academic journals) constitutes a major challenge. Our major challenge was perhaps to stablish a coherent and logical sequence along the various papers. Please note that the manuscript style of each chapter is consistent with the guidelines of the journals where they were published or submitted for publication. Therefore, there are slight differences in the format presentation of chapters due to this fact.

I deeply hope you enjoy reading this work as much as I enjoyed writing it.

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PART I

THEORETICAL OVERVIEW

CHAPTER 1: An overview regarding insomnia disorder: Conceptualization, assessment and treatment

CHAPTER 2: Hyperarousal and failure to inhibit wakefulness in primary insomnia: "Birds of a feather?"

CHAPTER 3: Assessing the neurobiological correlates of psychological treatments for insomnia

CHAPTER 4: Default-mode network activity and its role in comprehension and management of psychophysiological insomnia: A new perspective

Chapter 1

An overview regarding insomnia disorder: Conceptualization, assessment and treatment*

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Abstract

Insomnia Disorder (ID) constitutes one of the most frequent sleep disorders and one of the most distressing disorders in modern societies. Besides, it affects largely the quality of life of the individuals. Also for this reason it is considered a public health problem. It is frequently associated with psychiatric disorders – in particular anxiety and depressive disorders – and other medical disorders such as chronic pain. Because of the clinical relevance of insomnia for several contexts (e.g., applied health settings, clinical training), it is important to have a realistic and useful framework of insomnia. Our aim for this chapter is to present a brief but actual overview over the main issues pertaining to the diagnostic classification of insomnia, reporting the DSM-5, the ICSD-AASM-3 and ICD-10 diagnostic criteria; the assessment – focusing the most recommended available techniques to evaluate insomnia – and the evidence-based interventions discussing the most recent approaches, outlining the practical aspects, as well as their benefits and limitations.

Key-words: Insomnia; Diagnostic; Assessment; Psychological Therapies; Sleep

Introduction

Insomnia Disorder (ID) is one of the most prevalent sleep disorders. It concerns to difficulties in sleep-onset, nocturnal awakenings, early awakenings, or non-repairing sleep which cannot be attributed to other medical or psychiatric comorbid disorder (AASM, 2005). Moreover, there are two key features specifically related to ID: the hyperarousal of different human systems such as cognitive or neurobiological ones, and the maladaptive conditioning between sleep responses and arousal-provoking stimuli (Morin & Espie, 2003).

The word "insomnia" comes from Latin *in* which means "no" and *somnus* which means "sleep", thus expressing an inability to obtain sleep either in quantity or quality. Approximately 10 to 15% of general population presents insomnia complaints, being the most frequent sleep disorder. It is estimated an incidence of 3-5% new cases every year (Drake & Roth, 2006)[2].

From a historical point of view we identify that the first reflections on insomnia begin by the year 300 B.C. when Democritus associates the insomnia complaints with a poor and unhealthy diet. In the Bible, it is suggested that sleep inability would be related to an excessive worry with material possessions. In the arts and literature, Shakespeare makes numerous references to insomnia in his plays leading us to assume, according to the interpretation of some authors, that he himself would suffer from this problem (Head, 1886). In 1869 Hammond writes the first structured book dedicated to insomnia. However, it will be in 1920, after the introduction of the first hypnotic drugs, that research concerning insomnia will assume more relevance, particularly the proposal of therapeutic techniques to relieve it (Espie & Morin, 2012).

The specific designation "psychophysiological insomnia" first appears in a paper by Hauri and Fischer (1986) and according with these authors, points to a type of insomnia which "develops secondary to chronic, somatized tension and negative conditioning'' (p.38). The conceptual deconstruction of the term (i.e., psychophysiological) refers to an interplay between psychological and biophysiological factors, outlining the features related

[2] One must note that the values may be different according to the insomnia definition adopted by the authors of the studies (Buysse et al. 2006; Schwartz & Carney, 2012).

with learning mechanisms which decades earlier had been studied in a systematic manner by experimental psychologists.

1. Conceptualization of insomnia

In terms of sleep disorders classification, more specifically regarding insomnia, one should stress that there are three main manuals: The Diagnostic and Statistical Manual of Mental Disorders (DSM-5, APA, 2013), The International Classification of Sleep Disorders (ICSD-2, AASM, 2005) and the International Classification of Diseases (ICD-10, WHO, 1992). However, in the majority of studies the DSM-IV, now updated to DSM-5 and ICSD-2 are the ones more used. In tables 1 and 2 are presented the respectively diagnostic criteria. In the table 3, we present the diagnostic criteria of the more recent International Classification of Sleep Disorders (ICSD-3, AASM, 2014). One should note that in this new updated manual from AASM (2014) the sub-types of insomnia (e.g., psychophysiological insomnia) are only clinically classifiable, not presenting specific diagnostic criteria.

Table 1. Diagnostic criteria for insomnia disorder (DSM-5)

DIAGNOSTIC CRITERIA FOR INSOMNIA DISORDER [780.52]
(A) A predominant complaint of dissatisfaction with sleep quantity or quality, associated with one (or more) of the following symptoms: 1. Difficulty initiating sleep. (In children, this may manifest as difficulty initiating sleep without caregiver intervention.) 2. Difficulty maintaining sleep, characterized by frequent awakenings or problems returning to sleep after awakenings. (In children, this may manifest as difficulty returning to sleep without caregiver intervention.) 3. Early-morning awakening with inability to return to sleep. **(B)** The sleep disturbance causes clinically significant distress or impairment in social, occupational, educational, academic, behavioral, or other important areas of functioning: **(C)** The sleep difficulty occurs at least 3 nights per week. **(D)** The sleep difficulty is present for at least 3 months. **(E)** The sleep difficulty occurs despite adequate opportunity for sleep. **(F)** The insomnia is not better explained by and does not occur exclusively during the course of another sleep-wake disorder (e.g., narcolepsy, a breathing-related sleep disorder, a circadian rhythm sleep-wake disorder, a parasomnia). **(G)** The insomnia is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication). **(H)** Coexisting metal disorders and medical conditions do not adequately explain the predominant complaint of insomnia. Specify if: **With non-sleep disorder comorbidity**, including substance use disorders **With other medical comorbidity** **With other sleep disorder** Specify if: **Episodic:** Symptoms last at least 1 month but less than 3 months. **Persistent:** Symptoms last 3 months or longer. **Recurrent:** Two (or more) episodes within the space of 1 year. **Note:** Acute and short-term insomnia (i.e., symptoms lasting less than 3 months but otherwise meeting all criteria with regard to frequency, intensity, distress, and/or impairment) should be coded as another specified insomnia disorder.

Table 2. Diagnostic criteria for psychophysiological insomnia (ICSD-2)

ICSD-2 INSOMNIA DIAGNOSTIC CRITERIA

(A) The patient´s insomnia symptoms meet the criteria for insomnia*.

(B) The insomnia is present at least one month.

(C) The patient has evidence of conditioned sleep difficulty and/or heightened arousal in bed as indicated by one or more of the following:

a. excessive focus on and heightened anxiety about sleep;

b. difficulty falling asleep in bed at the desired bedtime or during planned naps, but no difficulty in falling asleep during other monotonous activities when not intending to sleep;

c. ability to sleep better away from home than at home;

d. mental arousal in bed characterized by either intrusive thoughts or a perceived inability to volitionally ceases sleep-preventing mental activity;

e. heightened somatic tension in bed reflected by a perceived inability to relax the body sufficiently to allow the onset of sleep.

(D) The sleep disturbance is not better explained by another sleep disorder, mental disorder, medication use, or substance abuse disorder.

*** General criteria for insomnia**

(A) A complaint of difficulty initiating sleep, difficulty maintaining sleep, or waking up too early, or sleep that is chronically nonrestorative or poor in quality.

(B) The above sleep difficulty occurs despite adequate opportunity and circumstances for sleep.

(C) At least one of the following forms of daytime impairment related to the nighttime difficulty is reported by the patient:

a. fatigue;
b. attention, concentration; memory impairment;
c. social or vocational dysfunction or poor school performance;
d. mood disturbance or irritability;
e. daytime sleepiness;
f. motivation, energy, or initiative reduction;
g. proneness for errors or accidents at work or while driving;
h. tension, headaches, or gastrointestinal symptoms in response to sleep loss.
i. concerns or worries about sleep.

Table 3. Diagnostic criteria for chronic insomnia disorder (ICSD-3)

ICSD-3 INSOMNIA DIAGNOSTIC CRITERIA
A. The patient reports, or patient's caregiver observes on or more of the following: 1. Difficulty initiating sleep 2. Difficulty maintaining sleep 3. Waking up earlier than desired 4. Resistance to going to bed on appropriate schedule 5. Difficulty sleeping without parent or caregiver **B.** One or more of the following related to the nighttime sleep difficulty: 1. Fatigue/malaise 2. Attention, concentration, or memory impairment 3. Impaired social, familial, occupational, or academic performance 4. Mood disturbance/irritability 5. Daytime sleepiness 6. Behavioral problems (e.g. hyperactivity, impulsivity, aggression) 7. Reduced motivation / energy / initiative 8. Proneness for errors / accidents 9. Concerns about or dissatisfaction with sleep **C.** The reported sleep/wake complaints cannot be explained purely by inadequate opportunity (i.e., enough time allotted for sleep) or inadequate circumstances (i.e., the environment is safe, dark, quiet, and comfortable) for sleep **D.** The sleep disturbance and associated symptoms occur at least three times per week. **E.** The sleep disturbance and associated daytime symptoms have been present for at least three months. **F.** The sleep/wake difficulty is not better explained by another sleep disorder
Clinical subtypes: - Psychophysiological insomnia - Idiopathic Insomnia - Paradoxical insomnia - Inadequate sleep hygiene - Behavioral insomnia of childhood - Insomnia due to (another) mental disorder - Insomnia due to (a) medical condition - Insomnia due to drug or substance

One must note that a few decades ago some authors as Patricia Lacks established other additional criteria to operationalize ID, namely: sleep onset >30 minutes; total sleep time awake >30 minutes; a maximum of 6,5 hrs of total sleep per night, diurnal fatigue with mood oscillations, and deficits in work performance during at least 3 night per week (Silva, 1990). By definition, insomnia is associated with sleep efficiency inferior to 85%[3]. However, one must note that this is a guide, not necessarily a defining quality that must be used.

A useful distinction one can draw in ID is concerning the temporal course, contributing to distinguishing insomnia subtypes (Perlis et al., 2011). Initial insomnia concerns to the difficulties in initiating sleep being associated with anxiety and tension states; intermediary insomnia regards to frequent awakenings during the course of the night being implicated in several psychiatric, neurologic, and other medical conditions in general; finally, terminal insomnia concerns to early-awakening and experiencing difficulties to falling asleep again. This latter relates mostly with depressive disorders (Paiva & Penzel, 2011). It can also be distinguished mixed insomnia which pertains to the combinations of the aforementioned subtypes. ID may be also differentiated regarding duration and severity. In terms of duration, the most common division is between acute and chronic insomnia. In general, acute insomnia does not last more than a month and is intrinsically related to a well-defined precipitant such as a stress situation, substance use, or experiencing acute pain. When this period is exceeded, the insomnia becomes chronic and points to a prototypical case of ID. Perlis, Benson-Jungquist, Smith, and Posner (2005) suggest a germane "rule of thumb" useful to clinical practice: they refer that when the patients stop relate their complaints with the originating precipitants, and indicate that insomnia seems to have "a life on its own", it is adequate consider a case of ID. In terms of severity, it is frequent to distinguish light, moderate, and severe insomnia.

Insomnia diagnosis is actually based mainly on the criteria from *International Classification of Sleep Disorders* (2.ª ed.) of *American Academy of Sleep Medicine* (ICSD-2, AASM, 2005) (cf. Table 3). Regardless from the preferred classification criteria, there is a significant group of insomnia patients which do not fit into them. Thus, there is necessity

[3] The sleep efficiency is a well-known measure used in sleep clinics and research. It refers to the quotient between the total sleep time (i.e., time that the individual effectively sleeps) and the total time spent in bed multiplied by 100 (Paiva & Penzel, 2011).

of improving the criteria and privilege more dimensional classifications, rather than categorical ones (Ohayon & Reynolds III, 2009).

In terms of prevalence, it is well documented that ID increases with age, being more frequent in women, divorced and widow individuals, and people with low economical and educational levels. It is a disorder which begins approximately at the adulthood affecting about $^{1}/_{3}$ of the population (Morgenthaler et al., 2006). The AASM (2005) points that it is a rare disorder in children, however, more common in teenagers, young-adults and adults from all the ages. Only 13% of the individuals who has complaints of insomnia seek clinical help, although this percentage tends to increase with age and insomnia severity (Buysse, 2011; Morin, 2011).

From the familial incidence point of view, we refer one of the main researches where it was studied a group of 285 patients comprising several types of insomnia, albeit the ID was the most frequent one. The main findings suggested that 35% of the insomnia patients evidenced a positive familiar history of sleep disturbances, being ID the most prevalent one (75%). Besides, the mother was the principal signalized person (Bastien & Morin, 2000). This finding was also observed in a study by Dauvilliers et al. (2005). The authors argued that despite ID has a multifactorial genesis, the presence of a positive familiar history of sleep disturbances/insomnia cannot at the current moment reveal whether this is due to a genetic predisposition or a social learning mechanism. In the same line, in a study with teenagers and their caregivers, it was observed that it seems to have a hereditary basis for insomnia, apart from (caregiver) modelling (Wing et al., 2012).

In general clinical practice (as in sleep medicine practice) the comorbidity scenario is the rule. That is, the co-occurrence of distinct disorders in the same individual which consequently complicates the clinical management of the disorder(s)[4]. In ID scope, this is the more common scenario as well. The comorbid complaints which are most salient in insomnia patient are depressive major disorder and anxiety disorders such as generalized anxiety disorder, panic disorder, and posttraumatic stress disorder. Insomnia patients are three times most likely to develop psychological disorders than individuals without sleep disturbances history. On the other hand, some psychological disorders such as depression or anxiety disorders are associated also with the development of insomnia disturbance

[4] Since 2005, the designation "secondary insomnia" was replaced by the term "comorbid insomnia" (National Institute of Health [NIH], 2005). This demands that the clinical strategies are used taking into account the other problems that patients present – transdiagnostic utility (Cougle, 2012; Harvey, 2006).

(Krystal, 2006). ID may co-occur also with other medical conditions (e.g., chronic pain, fibromyalgia) or other sleep disorders (e.g., restless legs syndrome, sleep apnea). Although the frequent comorbidity, it is important to highlight as referred by Roth, Rohers, and Pies (2007) that "insomnia is not merely a symptom of another disorder but a disorder of hyperarousal. Hence, treatment should be directed at the insomnia as well as the comorbid disorder" (p.77). Of the same opinion is Allison Harvey (2006) when she mentions that comorbid insomnia should not be considered as an epiphenomenon of other clinical conditions, as insomnia tends to remain when the other "primary" disorder is successfully treated.

In summarizing, ID is characterized as a sleep disorder which demands specific and idiosyncratic assessment and intervention techniques.

1.1. Consequences of insomnia

As already mentioned, poor sleep nights will influence the daytime period of the individuals. Therefore, it is comprehensible that insomnia impairs different life domains.

In terms of emotional behavior it is protruding the decreasing of self-esteem and self-efficacy levels leading to a sense of lack of control over the self and the own life. Allied to this aspect is the experience of not being understood by other people, frequently causing frustration, anxiety, anger, and even interpersonal and marital problems (Rogojanski, Carney, & Monson, 2013).

In the cognitive domain, there is evidence which supports the decreasing of attention, vigilance, memory, ability to perform calculations, increasing of reaction times with repercussions in diurnal functioning. There is also evidence suggesting that the fatigue appears to be more dysfunctional than diurnal sleepiness according to self-report measures (Shekleton, Rogers, & Rajaratnam, 2010).

Additionally, there is also economical costs associated with ID as performance is not maximized leading to higher rates of absenteeism and hospital visits. These patients are more prone to use maladaptive coping strategies to deal with insomnia (e.g., drinking alcohol beverages, consuming medical or non-medical drugs abusively) (Paiva & Penzel, 2011).

Sleep deprivation, either partial or total, increase the likelihood of having traffic and work accidents, comparatively to good sleepers (Chuah & Chee, 2008).

Finally, we highlight a particular point concerning the self-report quality of life of insomniac patients. There is compelling evidence showing that quality of life of these patients tends to decrease (LeBlanc et al., 2007; Kyle, Morgan & Espie, 2010; Wilson et al., 2010; Specchio et al., 2004). However, when the ID patients are treated (medical or psychological treatments) the quality of life tends to improve along with insomnia symptoms per se. These effects are experienced subjectively as improvements by the patients (Kyle, Morgan, & Espie, 2010; Léger, Scheuermaier, Philip, Paillard, & Guilleminault, 2001).

1.2. Insomnia in the scope of sleep disorders

We already have mentioned that ID is the more common sleep disorder making 12.5 to 15% of the total insomnia complaints (DSM-5, APA, 2013; Cervena et al., 2004). In the DSM-5 the insomnia disorder is integrated within the sleep-wake disorders; in the ICD-10, the insomnia diagnosis is possible in the sleep disorders chapter. According to our point of view the best medical classification, and the most used for insomnia (Arnedt, Conroy, Posner, & Aloia, 2006) is the one by *International Classification of Sleep Disorders* of *American Academy of Sleep Medicine* (ICSD-2, AASM, 2005)[5]. In this classification, unlike the other manuals, insomnia encompasses a whole chapter with eleven possible insomnia diagnostics.

Accordingly, there are listed adjustment insomnia, psychophysiological insomnia, paradoxical insomnia, idiopathic insomnia, insomnia due to mental disorder, inadequate sleep hygiene, behavioral insomnia of childhood, insomnia due to drug or substance, insomnia due to medical condition, insomnia not due to substance or known physiological condition, and physiological insomnia.

2. Assessment of insomnia: Methods and instruments

In sleep medicine there are a variety of indicators that the clinician can obtain from the patients. Conventionally, there is a distinction between subjective measures and objective measures. Within subjective measures there are clinical interviews, sleep diaries and self-report questionnaires; within objective measures there are polysomnography (PSG) and

[5] The diagnostic classifications of DSM-IV-TR and CID-10 are more used in primary health and psychiatric settings, whereas ICSD-2 is more used in sleep medicine centers (Arnedt, Conroy, Posner, & Aloia, 2006).

actigraphy; moreover, the measures may be short- and long-term (Azevedo, 1980, 1988; Gomes, 2005). All of these methodologies can be used for insomnia assessment and treatment purposes.

In short, we highlight that in 2006 a group of sleep experts published an article comprising a set of recommendations for assessment in insomnia disorder (Buysse, Ancoli-Israel, Edinger, Lichstein, & Morin, 2006). Additionally, in the sleep medicine field, some authors have differentiated the "hard" measures – objective, from the "soft" ones - subjective (Moul, Morin, Buysse, Reynolds III, & Kupfer, 2007).

2.1. Subjective measures

Subjective measures encompass self-report clinical interviews, questionnaires (for collecting data in the short-term) and sleep diaries (for collecting data in the long-term).

Clinical interviews are the gold standard in insomnia´s assessment. Insomnia Interview Schedule (Morin, 1993) is one of the most well-known clinical interviews (Arnedt, Conroy, Posner, & Aloia, 2006). General assessment of sleep includes the following topics: (1) definition of the sleep problem, (2) duration, (3) severity, (4) sleep patterns, (5) efficacy of the previous treatments and (6) worries and expectations of the patient regarding treatment. The standard cognitive-behavioral clinical guide is a useful script which supports the entire assessment and intervention both within the scope of sleep disorders and other disorders (Dudley & Kuyken, 2006). Self-report questionnaires are an important complementary in insomnia´s assessment. They can be administered to large groups of individuals and enable to interpret the individual scores of the patient (Spielman, Yang, Glovinsky, 2011). Some of the most used and well-known scales in this domain are the Insomnia Severity Index [ISI] (Morin, 1993; Bastien, Vallières, & Morin, 2001), the Dysfunctional Beliefs and Attitudes about Sleep [DBAS-16] (Morin, Vallières & Ivers, 2007), the Pre-Sleep Arousal Scale [PSAS] (Nicassio, Mendlowitz, Fussell, & Petras, 1985), the Glasgow Content of Thoughts Inventory [GCTI] (Harvey & Espie, 2004), the Glasgow Sleep Effort Scale [GSES] (Broomfield & Espie, 2005), the Athens Insomnia Scale (Soldatos, Dikeos, & Paparrigopoulos, 2000), the Brief Insomnia Questionnaire (Kessler et al., 2010), and the Ford Insomnia Response to Stress Test [FIRST] (Drake, Richardson, Rohers, Scofield, & Roth, 2004).

Sleep diaries are a self-report measure completed normally during 1 or 2 weeks. Through them, it can be computed sleep onset latency, wake after sleep onset, total sleep time, total sleep time spent in bed, and sleep efficiency indices (Arnedt, Conroy, Posner & Aloia, 2006; Morin & Espie, 2003). There are different versions of sleep diaries, see for example Morin (1993) or Morin and Espie (2003). Recently, it was defined a "standard form" of sleep diary (Carney et al., 2012). There are some drawbacks related with sleep diaries: they require the collaboration of the individual; they are a retrospective tool and thus sensitive to memory distortions; they demand considerable time to be filled in; and they require manual calculations from the clinician / researcher.

2.2. Objective measures

The objective measures comprise PSG (for collecting data in the short-term) and actigraphy (for collecting data in the long-term).

The PSG represents the "gold standard" of sleep behavior assessment. It permits the conjunction of several physiological indicators such as electroencephalography (EEG), electromyography (EMG), electrocardiogram (EKG), electro-oculogram (EOG), and measures of oxygen saturations enabling an overall evaluation of an individual with some sleep disorder. For a basic PSG study, it is need at least an EEG, an EOG, and an EMG measures. In some sleep disorders such as sleep apnea, this evaluation is essential. However, in ID, this is a dispensable exam, albeit may be useful for screening of other sleep disorders (i.e., differential diagnosis), and of course, for scientific research purposes (Parrino et al., 2004). Nonetheless, there are authors who pinpoint that a routine PSG should be carried out even in insomnia cases (Buysse et al., 2006; Paiva & Penzel, 2011).

Actigraphy consists in wearing an object similar to a wrist clock or to an arm-band containing an accelerometer which enables to study the rest-activity pattern over a week or two (it enables registering more time, but usually this is the time-span most studied). After this, the data can be downloaded to a computer and it can be calculated several sleep parameters (Carvalho, 2002). Notwithstanding, the actigraphy is not a mandatory instrument in insomnia as we aforementioned. However, several clinicians find its use germane in treatment, namely when they are using cognitive restructuring-based techniques (Tang & Harvey, 2004). In terms of research settings it became an important

tool to study sleep objective parameters in ecological contexts (Afonso, 2012; Littner et al., 2003).

Recently, some investigators are trying to define criteria to study ID recurring to actigraphy. Preliminary findings suggest an agreement rate between PSG and actigraphy pertaining to total sleep time, sleep onset, and number of nocturnal awakenings > 5 minutes indicators (Lichstein et al., 2006; Natale, Plazzi, & Martoni, 2009; Vallières & Morin, 2003) Therefore, actigraphy is a nonintrusive and comfortable tool (Ancoli-Israel et al., 2003). In cases where the PSG is not available, actigraphy seems to be a good alternative (Edinger & Carney, 2008).

In sum, it should be noted that according to evidence-based guidelines from the American Academy of Sleep Medicine (AASM), insomnia is primarily diagnosed by clinical evaluation considering a thorough sleep history and detailed medical, substance and psychiatric history, as a standard which reflects high degree of clinical certainty (cf. e.g., Schutte-Rodin et al., 2008). Moreover, according to the same academy, "polysomnography and daytime multiple sleep latency testing (MSLT) are not indicated in the routine evaluation of chronic insomnia, including insomnia due to psychiatric or neuropsychiatric disorders" (Schutte-Rodin et al., 2008, p. 487).

3. Psychological treatment of insomnia

Psychological treatments of insomnia are one of the most important aspects of insomnia management. CBT-I (cognitive-behavioral therapy for insomnia) is actually the "working horse" of the psychological treatments for insomnia (Wilson et al., 2010). The research supports its efficacy and effectiveness in short- and long-term surpassing the limited effects of medication whose recommendation is limited (4-8 weeks) (Morin, 2002; Morin & Benca, 2012; Sivertsen, 2006). The increasing interest in insomnia´s psychological treatment outcomes derives from the dissatisfaction with the psychotropic drugs and the fact that insomnia is the second most prevalent mental health problem (Harvey & Tang, 2006). Within the evidence-based set of techniques, the research has shown that there are some of them more effective than others (Verbeek, Schreuder, & Declerck, 1999). Even so, there are studies suggesting about $^{1}/_{3}$ of the patients is medicated when they start CBT-I.

In 1988, in a famous conference in Stanford, it was concluded that 3 in 4 insomnia patients could improve with CBT-I. Actually, about 70-80% of insomnia patients benefit from CBT-I (Morin, 2002). Moreover, this particular form of treatment seems to be more useful and beneficial than psychopharmacological one, according to patients´ perspective (Morin et al., 1992, Clemente, Ferreira, Fernandes, César, & Azevedo, 1996, Haynes & Bootzin, 2010). Despite the good results, Harvey and Tang (2003) argue that CBT-I´s efficacy is lower compared to CBT for other psychological disorders such as depression or anxiety.

Non-pharmacological or psychosocial treatments for insomnia emerged in the 30s of the last century coinciding with the application of relaxation training. Since 1970 there has been a revolution in the psychological treatment of various psychopathologies and from then on, this is also reflected in the field of insomnia resulting in a set of clinical procedures such as stimulus control therapy or cognitive therapies (Perlis et al, 2011; Riemann et al., 2009, 2010.). Thus, it was found a viable alternative to the traditional insomnia´s symptomatic approach (i.e., with unique and privileged use of hypnotic drugs) and exclusively oriented for psychological disorders treatment (Clemente, 2006; Pigeon, 2010; Morin & Peek, 2003).

The first psychological interventions for insomnia were based on two assumptions: (1) insomnia may be conceptualized as a "learning disorder" and consequently is governed by principles of learning theories or laws, and (2) the patients may learn to cope with insomnia applying the strategies derived from those theories and models (Silva, 1990).

Blind placebo-controlled randomized clinical trials have suggested that, on average, cognitive-behavioral interventions demonstrate efficacy within six weeks of treatment and follow-up measures, for example, six months after CBT-I (Edinger , Wohlgemuth, Radtke, Marsh, & Quillian, 2001; Morin et al, 2009). Although in the current work our interest lies within the adult population, it is important to note that in pediatric clinical practice CBT have shown effectiveness, and is also recommended as a first-line treatment for behavioral insomnia of childhood (i.e., pediatric behavioral insomnia or childhood behavioral insomnia) (Owens, 2006; Owens, France, & Wiggs, 1999). CBT-I with older adults has also shown empirical evidence of efficacy (Fiorentino & Martin, 2010; Morgenthaler et al., 2006).

Another point that deserves attention is the issue of combined treatments, i.e., the junction in the same therapeutic plan of psychopharmacological and psychotherapeutic strategies. Although it may be intuitive to think that the combination of both treatments may enhance therapeutic outcomes, it is certain that there is no secure and robust evidence that such possibility is the better one (Morin, 2006b). Some studies suggest that in insomnia the psychological interventions alone tend to be more effective than when combined with pharmacological therapy (Lichstein, Turcotte, & St-Jean, 2012). There are no criteria, for example, on the dosage of the drug and treatment duration. Morin (2006a) identifies three essential key points that clinicians should bear in mind when considering combination of treatments: (1) there is no single treatment that is effective per se for all the patients with insomnia; (2) the preference for a specific treatment - a patient who describe her/his insomnia as a disease/medical condition is more likely to adhere to a psychopharmacological treatment, whereas another patient who describes its complaints in a psychological frame might adhere better to a psychosocial treatment; and (3) the patient may not be motivated to follow behavioral prescriptions. Complementing this scenario is the fact that approximately 60% of people who suffer from insomnia do not mention this difficulty to her/his doctor, particularly in the primary health care context (Cortoos, Verstraeten, & Cluydts, 2006). There is no doubt that there are effective and efficient treatments for insomnia. However, there remain some difficulties in accessing and implementation of appropriate treatments, namely: (1) lack of training of doctors and clinical psychologists in management of sleep disorders, particularly insomnia, (2) the lack of time in medical and psychological consultations to work out issues pertaining to sleep, (3) the disregard for sleep complaints of the patients, (4) the belief among technicians and patients that sleep complaints are not important, (5) the perception that available treatments are ineffective and are associated with several risks, and (6) the belief that there is no evidence that the resolution of the sleep problems lead to an improvement of comorbid medical conditions and quality of life in general (Benca, 2005; Edinger & Wohlgemuth, 1999;).

Next, we will briefly describe the main cognitive and behavioral techniques that have been used for insomnia treatment.

3.1. Techniques and behavioral and cognitive therapies for insomnia

3.1.1. Stimulus control

The stimulus control technique encompasses a set of instructions that are provided to the patient in order to re-associate stimuli like bed or bedroom with sleep itself. This technique involves five basic requirements: (1) going to bed only when the patient feels drowsiness; (2) getting out of bed if he/she does not fall asleep within 10 minutes (Harvey & Tang, 2006) or 20 minutes (Morin et al., 2006), going to another room, occupying him/herself with a monotonous activity and only return to bed when he/she feels sleepy again; and (3) using the bed / bedroom only for sleep or sexual activity (e.g., it were not allowed reading activities, eating or watching television in the bedroom). Together with these indications - which define the stimulus control technique - the following recommendations are also provided: (4) waking-up in the morning, about the same time regardless of the amount of sleep (duration) obtained in the previous night, and (5) avoiding taking naps during the day or during wakefulness. The rationale behind this procedure is that there is a negative or maladaptive conditioning between sleep-related behaviors and sleep-incompatible behaviors. Therapists should be especially cautious when prescribing this procedure to older adults, especially because it can involve getting out of bed and as such do increase the likelihood of falls, especially when they are medicated, which is the most common situation (Morin 2011).

3.1.2. Time in bed restriction

Sleep restriction technique (or restriction of time in bed) is aimed to reduce the time spent in bed in order to adapt it to the current (average) amount of time the patient spend objectively sleeping plus 30 additional minutes; this 30 minutes period encompasses the time associated with normal sleep onset latency and eventual nocturnal awakenings of the "good sleeper" (Troxel et al., 2012).. The central point is to maximize sleep efficiency and the association "bed→sleep." One should note, however, that the minimum number of hours "prescribed" for the patient to remain in bed should not be less than 6 hours (Troxel et al. 2012). This step is important because patients spend many hours a day in bed trying to fall asleep, and the actual hours of sleep are less, so there is a significant lag. In terms of method, they are generally followed the next steps: (1) the patient is instructed to fill in the

sleep diaries for 2 weeks to get the average duration of slept hours per night (e.g., 05h:45m)[6] - this will be the "sleep window"; (2) then, the clinician in collaboration with the patient settle a “rising time” which should be strictly followed each morning (e.g., 7:00); the "threshold time" is then calculated by subtracting the average sleep effective duration from the combined “rising time” (e.g., 7:00 - 5:45 = 1:15 → “threshold time”). The patient is instructed not to go to bed before this "time limit" (i.e., 1:15 am) and get up in the next morning at the previously scheduled time. Individuals should follow this prescription every night including at weekends. Weekly, there are made some adjustments to the "sleep window", which are based on the sleep efficiency indices. If the sleep efficiency is equal or greater than 90%, the clinician should increase the "sleep window" in 15 minutes; if the sleep efficiency is lower than 85%, the clinician should decrease the "sleep window" in 15 minutes (Espie & Kyle, 2012).

Sleep restriction in bed is a technical procedure that can create some resistance on the part of some patients as produces a moderate sleep deprivation, which contributes therapeutically to the increase in sleep pressure and to adjust homeostasis and the circadian sleep-wake cycle. As main contraindications are the use in individuals suggestible to seizures, bipolar patients and patients with some types of parasomnias (Morin, 2011). Other authors point to other contraindications such as the presence of mood disorders, sleep apnea, delayed sleep phase and shift work (Glovinsky & Spielman, 1991). A recent exploratory study comparing the efficacy of sleep restriction against the stimulus control strategy indicated that although the two techniques have been somewhat different, in general, there was a slight superiority of sleep restriction pertaining to improvements in sleep latency, sleep efficiency, and self-reported severity of insomnia (Armstrong, Sidani, & Bootzin, 2013).

3.1.3 Relaxation training

The relaxation training encompasses a variety of procedures aimed at reducing tension or somatic anxiety and / or cognitive or psychophysiological arousal before sleep or after awakenings after sleep onset (Bonnet, 1997; Harvey & Tang, 2006; Vaz-Serra, 2002). This family of strategies includes progressive muscle relaxation, autogenic training, yoga,

[6] The calculations are always rounded at intervals of 15 minutes.

hypnosis, and biofeedback[7]. The patients learn to control functions related to the autonomic nervous system linked to prototypical activation of insomnia, for example. Although there are many relaxation procedures such as Schultz autogenic training, the most studied method in the field of insomnia is the progressive muscle relaxation (i.e., Jacobson Relaxation Training). One must note, however, that at least initially, it is a procedure susceptible of increasing the levels of anxiety of individuals with perfectionist personality traits (Morin, 2011).

3.1.4 Cognitive therapy

Cognitive therapy refers to a psychological or psychotherapeutic method intended to identify, challenge and modify dysfunctional beliefs and attitudes (in the case of insomnia, deeply related to the sleep behavior). There are no available current data to justify its use as a single treatment for insomnia (Morgenthaler et al., 2006). However, recent studies have suggested that both behavior and cognitive therapy have shown efficacy when evaluated in an independent manner (Morin, Harvey & Bélanger, 2011). In this line, some authors have posited that cognitive restructuring is inherent to the implementation of behavioral-based techniques (Cougle, 2012); they closely related to the method of cognitive restructuring. This perspective assumes that individuals are not disturbed by the events themselves, but by their personal vision or perception about these. In other words, the cognitive model is based on the idea that they are not the stimuli or situations themselves that disturb the individuals, but rather the view that people have on these (Beck, 1976, Beck & Emery, 1985). Basically, cognitive therapy for insomnia problems relates to the identification, evaluation and modification of cognitions related to fear of not being able to fall asleep / or daytime consequences derived from sleepless nights (Carney et al., 2010; Turcotte, St-Jean, & Bastien, 2011). As empirical tests or behavioral experiences associated with them often involve sleep short-term sleep deprivation, it is a procedure that is contraindicated for patients with certain professions such as industrial machines operators or airline pilots. Although there are not sufficient evidence as monotherapy for insomnia, there is evidence suggesting that there is an improvement in the

[7] This procedure has been subject to some studies indicating that may be an effective strategy for insomnia – guideline; put simply, it is a strategy derived from the psychophysiology and which enable individuals the opportunity to receive and process retroactive information (feedback) about their bio-physiological functions (bio) through visual or auditory stimuli.

effectiveness of psychological treatment for insomnia whether cognitive components are included (Harvey & Eidelman, 2011). One of the most useful strategies embedded in the cognitive restructuring method is the self-monitoring recordings; these are sheets divided into several columns and containing topics such as day / situation, negative automatic thoughts, emotions and consequent intensity, alternative thoughts and intensity evaluation emotions after the generation or development of alternative cognitions (Beck, 1995; Morin & Bélanger 2011; Perlis & Gehrman, 2011).

In sum, cognitive therapies rely heavily on the cognitive restructuring paradigm, including, in a simplified manner, the identification of dysfunctional automatic thoughts, the classification of these cognitions in terms of information processing errors (i.e., cognitive distortions) and challenging of cognitions and beliefs (Beck, 1995). The initial application of cognitive restructuring methods to insomnia was initially suggested by Morin (1993). As previously mentioned (cf. 2.1. subjective measures) there is a well-known questionnaire used in both clinical and research settings, aimed to identifying dysfunctional beliefs about sleep and insomnia (Morin, 1993; Morin et al., 2007).

Within the recommendations of international associations of sleep medicine it is common to include two specific cognitive techniques that can be used, though directed to very particular cases: “stop thinking” (i.e., the patient identify dysfunctional cognitions and contingently should exclaim "STOP!” in order to break the chain of thoughts and cease the ruminative activity) and “paradoxical intention” (i.e., a technique that aims to reduce the anxiety associated with sleep effort at bedtime through the instruction to go to bed and try to not fall asleep – guideline. This latter strategy has the disadvantage of being specific only for sleep onset problems (Espie & Kyle, 2012). In addition to these two strategies there is the “cognitive control” technique. It is an extension of stimulus control therapy, but more focused on cognitive content, with the goal of decreasing the probability of having activating mental activity in the usual sleeping environment of the patient. The instructions consist of: (1) providing 20 minutes every day for this activity using a notepad and a pen; (2) discussing the day's events as well as plans for the next days; (3) listing the disturbing cognitions and problems and outline possible solutions to each one; (4) these 20 minutes will help to organize activating cognitions of the patient decreasing their intensity; (5) if the patient is already in bed trying to fall asleep and these activating thoughts occur, the patient should remember that he/she already "dealt with the issue" and (6) if new images or

thoughts that prevent him/her from falling asleep appears, the person should register these new cognitions in the paper kept at the bedside table) (Espie & Lindsey, 1987).

One other technique that might be useful in insomnia is based on "opening-up" strategy by Pennebaker. In this technique patients have to write strong emotional situations that prevent the process of falling asleep. This exercise should last for 3-5 days at least. Individuals should be honest and explore thoughts and emotions that are being stressful at the present time (not only in relation to complaints of insomnia). This is a strategy aimed to help reorganize cognitive dysfunctional processes with a strong emotional charge in a cathartic way. It is expected that the intensity and frequency of cognitive activity before sleep decrease (Harvey & Farrell, 2003).

Finally, Levey, Aldaz, Watts and Coyle (1991) suggest a strategy derived from the classical works within cognitive psychology of memory by Alan Baddeley. Based on the idea that working memory (sometimes called short-term memory) has a temporary and limited capacity storage, the authors point out that if one takes the short-term system with meaningless phonemes, the projection of activating and dysfunctional cognitions loses intensity. This technique was known as "articulatory suppression" and is based on the following instructions: (1) the patient should lie in bed and close his/her eyes; (2) repeat a meaningless word every 1-2 seconds (e.g., "the"); (3) whisper or utter the selected word; and (4) remain in this task for 5 minutes or until he/she feels drowsy (Morin & Espie, 2003).

It is worth mention one of the latest developments regarding cognitive techniques for insomnia: the cognitive refocusing treatment (Gellis, 2012). In summary, this strategy is brief (can be discussed only in a single session). The patient, with the help of clinician, should identify three different categories of thoughts (contents) strong enough to hold the attention of the patient at bedtime. These categories must comply with two features: the thoughts should be non-emotional and non-physiological activators and should be catchy enough to keep the attention of the patient. For example, one can think about new recipes or an excerpt from a favorite TV program. Following this, the patient is instructed to focus attention on these stipulated thoughts at bedtime or when experiencing nighttime awakenings. If other thoughts arise (i.e., intrusive thoughts), individuals are instructed not to attach particular importance and focus attention to the fixed cognitive contents previously listed. The ultimate goal of the strategy is to encourage the learning of the

association between a specific category of thought and sleep behavior. In preliminary studies, the duration considered for the use of this procedure is around 30 minutes (Gellis, Arigo, & Elliot, 2013).

3.1.5 Sleep education / Sleep hygiene

Sleep education/sleep hygiene though being presented as the last strategy in this list, is usually the first step in intervention in insomnia and, in general, in all disorders related to sleep behavior. Briefly, this strategy comprises a set of guidelines on aspects related with sleep (e.g., sleep architecture, changes in sleep patterns associated with development, etc) and general health practices that may interfere with sleep. Psychoeducation or education about the rules of sleep hygiene as well as the explanation of basic concepts about sleep characteristics are a non-specific ingredient of the therapeutic plan, as it should be a common and widespread practice in psychotherapy sessions but also in medical consultations. On the other hand, there are studies that refer that psychoeducation may be necessary but not sufficient *per se* to resolve the most cases of chronic insomnia. However, there are descriptions of some authors who reported that sleep education sessions were sufficient to resolve ID cases classified as moderate (Morin, 2011; Silva, 1990). In the most recently international published recommendations, there are no data to support this strategy as singly "therapy" in insomnia (Morgenthaler, 2006). The requirements related to sleep hygiene frequently consist of: 1 - always wake up at the same time every day in order to adjust the biological clock (it is explained to the patient in a simple manner some notions of applied chronobiology with relevance for her/his particular case); 2 - regular physical exercise, albeit not close to bedtime (e.g., up to 3 hours before) - this regular activity decreases sleep latency and enhances deep sleep; 3 - Check if there are appropriate and facilitating conditions for sleeping, i.e. mattress and pillows quality, checking for noise, exposure to light and, where appropriate, in particular cases, creation of alternatives that do not greatly disturb sleep as in the case of individuals caring for an infant child; 4 - investigate if the bedroom has a proper and comfortable temperature (too hot or cold can hinder the sleep continuity and increase the number of nighttime awakenings); 5 - practice of a regular diet and avoid going to bed with appetite (one should make small but regular meals - when the organism feels appetite the individual's attention tends to focus on the physiological sensations causing discomfort, and consequently, causing sleep onset

difficulties); 6 - Avoid drinking large amounts of liquids late in the day/early evening (the rationale is that if there is less intake of fluids, the kidneys do not produce so much urine, which would fill the bladder and it would indicate to the brain the need to urinate during the night); 7 - avoid using products that contain caffeine, such as coffee, cola soft drinks chocolate, energy drinks and some types of tea, because caffeine is a stimulant and therefore helps to increase the level of excitability of the nervous system; 8 - Avoid drinking alcohol (it should be explained to the patient that although alcohol facilitate sleep, it will fragment the sleep and will contribute to a poor quality of sleep); 9 - Avoid smoking (as it contains nicotine and it is a stimulant); 10 – Do not "take problems to bed" (while acknowledging that such practice is not easy to perform, the clinician may resort to strategies or exercises applied in other clinical conditions such as generalized anxiety disorder - one of these strategies which is commonly used is the "worries chair"); 11 – Do not force sleep (this requirement reinforces the idea that the more the patient makes efforts to rest or sleep the worst outcome he/she gets contributing to a vicious cycle of performance anxiety); 12 - Put the clock out of sight and not look at it during nocturnal awakenings, as it will signal to the individual the hours that have passed and fuel the worry cascade; 13 - Avoid naps or lying in bed / sofa during the day (in patients with insomnia this is a cardinal rule - do not realize will create sleep pressure and lead to sleep regulation and homeostatic equilibrium); and 14 - To avoid sleeping with pets (as they often move during the night they may cause sleep interruptions). As can be seen, these requirements related to sleep hygiene have some overlapping with some of the indications accompanying sleep restriction and stimulus control techniques (Morin & Espie, 2003) and as such sometimes it becomes complex the task of distinguish the different strategies for insomnia. On the other hand, discussion of sleep hygiene habits can be considered as inseparable from cognitive restructuring strategies according to several authors (Perlis et al., 2011; Silva, 1990).

3.1.6 Multi-modal cognitive-behavioral therapy for insomnia (CBT-I)

The CBT sets the more generic term used to encompass the combination of cognitive and behavioral techniques (Morgenthaler et al, 2006; Morin, 1993, 2011; Morin & Benca, 2012). Currently, many authors prefer to use this more comprehensive and integrated modality in their interventions with patients with ID (Morin & Espie, 2003; Perlis et al.,

2005). In the words of Espie (2007) CBT "is based on the concept that cognition, emotion and behavior all interact and that maladaptive thoughts can cause negative feelings which can result in changes in behavior" (p.4). Still, it must be considered that behavioral strategies continue to show up as the most effective (Epstein, Sidani, Bootzin, & Belyea, 2012).

A general strategy related to education and sleep hygiene and following the principles of respondent and operant conditioning is the establishment of "pre-sleep routines", which implies that the patient sets systematic daily routines (i.e., behavioral repertoires, for example, before going to bed the individual can take a hot bath, brush teeth, going into the WC, watch TV, etc) related with sleep behavior. With consistent training, these associations between pre-sleep routines and subsequent sleep become habits and induce drowsiness (Wickwire, Schumacher, & Clarke, 2009).

Similarly to whatever therapeutic process, insomnia treatment should comprise at least one session devoted to “relapse prevention” and future problems that it can be predicted (Morin & Espie, 2003). In this session, it is usually discussed ways of dealing with lapses and relapses that can occur in the future through "role-playing", analyzing the cognitive contents and emotional activation that might arise. This is an opportunity to assess and monitor the learning gains and to adjust some technical procedures.

A good practice is to jot down the main points worked in the sessions (Harvey, 2005). After this phase, the patient should be followed in longer intervals in time, following the therapeutic regimen over the long-term (i.e., follow-up).

3.1.7 New developments in CBT-I

A more recent development in the psychosocial treatment of insomnia is the application of mindfulness and acceptance-based techniques. These approaches integrate empirically validated procedures derived from behavioral and cognitive albeit having as background the principles of mindfulness strategies. One of the core tenets is that to facilitate sleep is necessary to experience cognitive deactivation and an attitude of non-judgment and acceptance from one's own mental events, such as negative automatic thoughts (NATs) and mental image.

Quite simply, it can be said that it "should be practiced with an attitude of nonjudgmental acceptance. That is, perceptions, cognitions, emotions or sensations that

enter the individual's awareness during mindfulness practice are observed carefully but are not evaluated as good or bad, true or false, healthy or sick, or important or trivial" (Lundh, 2005, p.34). One type of more structured intervention proposes for instance, a short protocol (around 8 weeks) and includes group sessions consisting of 6-8 participants (Ong & Manber, 2011). This new approaches to insomnia aims to change the relationship that individuals have with their own sleep rather than working directly with the explicit modification of the amount of sleep obtained per night (Lundh, 2005; Ong & Scholts, 2010). Although there are few systematic studies on the application of this methodology in the field of insomnia, some studies have pointed to positive results pertaining to patients´ satisfaction (Ong & Manber, 2011). A brief intervention (i.e., 3 sessions) based on mindfulness, particularly in acceptance and commitment therapy (ACT), suggests to be of importance in the reduction of symptomatology and improving in self-reported quality of life (Peters, Junge, Cunnington, Ong & Greenwood, 2012). There is already some evidence indicating that the addition of mindfulness strategies in traditional cognitive-behavioral protocols enhances the clinical effectiveness of the interventions (Ong, Shapiro, & Manber, 2008). In line with what is recommended by these new cognitive-behavioral approaches, a strategy that is often used is "thought suppression", initially proposed by Harvard psychologist Daniel Wegner. The classic example of the "white bear exercise" may be considered an important behavioral experiment (Ree & Harvey, 2004). This exercise can be very useful in the very first sessions when discussing with the patient the advantages and disadvantages of "having or not having control over mental processes" (Espie et al., 2006). Put simply, what this psychological theory of Wegner (i.e., Ironic Processes of Mental Control) is suggesting is that the more conscious or voluntary effort an individual makes to avoid thinking about something, the greater the probability of failure in this task (Wegner, Schneider, Carter III, & White, 1987). This process is visible, for example, when individuals attempt not to think on a given stimulus/object. This process increases the probability that the avoided content appears during the dreaming activity of the individual in the same day (Wegner, Wenzlaff, & Kozak, 2004).

3.2. Indications, benefits and drawbacks

From the foregoing, it is clear that cognitive and behavioral strategies are effective in management of ID (Morin & Benca, 2012). As main indications for the use of this techniques are cases of primary and comorbid insomnias. In the case of short-term insomnia, there is evidence of effectiveness similar to those achieved with pharmacologic therapies; in the case of chronic insomnia, CBT-I is recommended as first-line treatment (Morgenthaler et al., 2006; Morin & Benca, 2011; Morin & Espie, 2003). After CBT-I, usually there is a number of significant changes, such as a decrease in the dissociation between subjective and objective measures and an improvement in sleep patterns measured through sleep diaries and actigraphy (Sato, Yamadera, Matsushima, Itoh, & Nakayama, 2010).

It is relevant to note that it is advisable to discontinue the medication before starting CBT-I in order to establish a baseline for the patient ("free of medication"); it also avoids problems associated with discontinuation/withdrawal of the drug after psychological treatment; moreover, concomitant use of hypnotic or other kind of medication may cause biased attributions regarding treatment outcomes by patients (Perlis et al., 2005). It is noteworthy to outline that the medication might difficult the successful implementation of psychological strategies. Some authors suggest that CBT "is most likely to be successful if the medications are discontinued before treatment" (Perlis et al., 2005; p. 45) and this is a data supported in empirical evidence (Lichstein et al., 2012). The CBT-I assumes a set of benefits: maintenance of the long-term gains; does not have a negative interaction with other known medical treatment approaches, and it seems to be relatively innocuous in terms of adverse effects. On this last point it should be noted that many authors have already identified some negative effects and treatment failure associated with psychological treatments, including the empirically supported or validated treatments (Barlow, 2010). The disadvantages that may be related to the implementation of CBT in patients with insomnia are mainly its cost (i.e., as other psychological interventions and CBT applied to other disorders, psychosocial treatment requires a greater number of sessions compared pharmacological interventions); the response latency (i.e., unlike some drugs that have almost an immediate effect, CBT-I usually requires a few weeks in order the patient can experience some beneficial effect); it requires time and motivation (i.e., it requires that patients have time in their schedule to implement the procedures, such as

relaxation training and requires that the patient adheres to the treatment protocol and be collaborative); it can create daytime sleepiness during sleep restriction procedure (which therefore may contribute to deviations in implementation of techniques); and difficulties in access to a trained and qualified clinical (i.e., currently, there are still few psychologists, psychiatrists, neurologists and possibly other professionals who have consistent training in the assessment and treatment of insomnia) and, as such, it is not yet a sufficiently widespread and pervasive practice (Morin, 2006a; Moul et al, 2007).

It should also be noted that, despite the results / therapeutic successes with CBT-I, only about 20 to 30% of patients returning to a "normal" sleep pattern, that is, the sleep pattern that was habitual before the disorder onset (Moul et al., 2007).

As challenges for the future it is pointed out that it is necessary to disseminate this type of intervention in various settings in order to make the practice of CBT-I more known; it is essential to invest in the training of doctors and psychologists at the primary care level (Ellis, 2012). According to Buysse (2011), the biggest challenge for psychological therapies for insomnia is its spread in the scientific community.

Conclusion

ID is a sleep disorder that can be identified through different diagnostic systems. The classification of AASM (2005; 2014) is the one that specifies more dysfunctional behaviors with implications for psychological clinical formulation of the cases. There are several methodologies to assess insomnia, however, the most useful are subjective ones such as the clinical interviews. Besides, there are well-established treatments for ID that should te priviledged, particularly psychological therapies.

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Chapter 2

Hyperarousal and failure to inhibit wakefulness in primary insomnia: "Birds of a feather?"*

***** Marques, D., Gomes, A., Castelo-Branco, M., Clemente, V., & Santos, J. (2015). Hyperarousal and failure to inhibit wakefulness in primary insomnia: "Birds of a feather?". *Sleep and Biological Rhythms, 13*(3), 219-228. doi:10.1111/sbr.12115

Abstract

Primary insomnia (PI) is one of the most prevalent sleep disorders. For this reason, over the last decades, several comprehensive and etiological theories have been proposed. In this paper we review some of the main theoretical models of insomnia and discuss the two most studied processes for comprehension of insomnia: the hyperarousal and the failure to inhibit wakefulness or psychobiological inhibition hypotheses. Some clinical implications of the models are described. In the end, we propose that the two processes are complementary and both are relevant to the understanding of clinical insomnia.

Key-words: primary insomnia, hyperarousal hypothesis; psychobiological inhibition hypothesis

Introduction

Primary insomnia (PI) is a clinical condition characterized by a marked difficulty in initiating or maintaining sleep, waking up too early and cannot go back to sleep or experiencing non-restorative sleep that is not due to a comorbid medical or psychiatric disorder.[1,2] Briefly, it results on a pathological reduction of sleep time at night or experiencing a non-restorative sleep. Insomnia is a highly prevalent health complaint afflicting approximately 50% of the general population.[3] Prevalence of PI in general population ranges from 3 to 5%.[4] PI is one of the most common clinical entities within all sleep disorders.[1,4,5]

Models of insomnia and its relationship to the concept of hyperarousal

The set of theories about the etiology and pathophysiology of PI has led researchers and clinicians to propose integrated approaches. From the mid-80s of the twentieth century the emphasis was put mainly on the psychological, emotional, and psychopathological variables. However, from the 90's and with the advent of neuroimaging techniques, theoretical approaches started to highlight the role of neurobiological variables. Following these developments, the concept of hyperarousal became popular as a predisposing factor for insomnia, which combined with other constructs such as personalistic traits or genetic components would make individuals more or less vulnerable to develop an insomnia disorder.[4,3] The comprehensive list of the models we present follows a hybrid orientation, although with a more behavioral focus. For a brief review of the main physiological models see other references.[6,7] For a review of the Drosophila model of insomnia and the cage exchange model see Perlis et al.[8] The list of models we present in the current paper (i.e., internalization of conflict´s model; behavioral perspective of Spielman; stimulus control model; microanalytic model of Morin; hybrid cognitive-behavioral model of Lundh and Broman; neurocognitive theory of insomnia; Espie´s psychobiological inhibition model; the cognitive model of Harvey; and bottom-up model of Riemann) is entirely from our responsibility and tries whenever possible to follow chronological criteria. Similarly, it should be noted that some of these models are different in their explanation level. For

example, some theoretical approaches are more interested in understanding of the maintenance factors in insomnia rather than on etiological ones.[9] According to the literature review we have performed, the models selected in this paper seemed to be the most comprehensive and appropriate ones for the purposes of the present work. For a brief explanation of each of the models see Table 1.

Table 1. An overview on insomnia models

Insomnia model	Description
Internalization of conflict´s model [10,11]	• A pioneer model that focused on the personality features of insomnia patients.
Behavioral perspective of Spielman [21]	• The behavioral theory of insomnia states that in insomnia there are three factors that one should understand: predisposing factors, precipitating factors and maintenance factors.
Stimulus control model [24]	• Initially conceptualized by Richard Bootzin. It assumes that there are a maladaptive conditioning between stimuli that causes arousal and stimuli that are sleep-inducing. It is the theoretical support of the most efficacious treatment for insomnia (i.e., stimulus control technique).
Microanalytic model of Morin [20]	• One of the most studied and well-known theories about insomnia. It originated several useful psychological assessment instruments. Although centered on maintenance factors of insomnia, this perspective suggest three levels of arousal: cognitive, emotional and physiological.
Hybrid cognitive-behavioral model of Lundh and Broman [27,28]	• This is a perspective which differentiates processes that interfere with sleep-related levels of cognitive, emotional and physiological arousal and processes that make the individual prone to perceive or interpret their sleep patterns in a distorted or dysfunctional way; besides, this perspective tries to include concepts derived from mindfulness approaches.
Neurocognitive theory of insomnia [29,30]	• The first behavioral-based model which emphasizes neurobiological variables in insomnia and operationalizes the cortical arousal concept.
Espie´s psychobiological inhibition model [31]	• Psychobiological inhibition model posits that one of the most critical issues in insomnia is the difficulty regarding inhibit the arousal typical or normal from wakefulness period. Further, this conceptualization tries to understand the "insomnia experience" from the normal sleep parameters.
The cognitive model of Harvey [36,37]	• Cognitive model by Harvey is a model centered on cognitive aspects of insomnia such as underlying critical beliefs, ruminations, worries and misperception of sleep deficits.
Bottom-up model of Riemann et al. [3]	• This is not in fact a theory about insomnia. However, it represents an integrated and critical view emphasizing the genetic and neurobiological vulnerabilities in causing insomnia. Notwithstanding, the behavioral and psychological variables are equally considered by the authors.
The instability hypothesis of REM sleep [41]	• It is suggested that one of the major causes of insomnia might be an instability in REM sleep. The micro- and macro- awakenings during REM sleep in insomnia patients appear to be an important topic to study in the next years.
Metacognitive model of insomnia [26]	• The metacognitive model is the most recent model on insomnia. It is the first structured perspective based on mindfulness and acceptance approaches. The aim is to give a mindfulness perspective of insomnia, but in a complementary way to the classical models.

Internalization of conflict´s model

The first attempt to relate empirically insomnia with psychological constructs comes with the internalization model of conflicts.[10] Based on the input from psychodynamic and psychosomatic medicine insights dominant at the time, the authors used a psychological assessment tool widely used for studying the personality, the MMPI (Minnesota Multiphasic Personality Inventory), and assessed hundreds of people. The results showed significantly higher levels of depression, conversion hysteria and psychasthenia in individuals with PI compared to control groups without sleep complaints. Following this, it was defined a "typical" personality type for the PI patient: a person with a more pronounced tendency to internalize problems and emotions (e.g., depression) than to externalizing (e.g., acting-out). This predisposition to internalize conflicts would lead to increased levels of emotional activation, which in turn would lead to physiological hyperarousal, transforming the person into someone less prone to sleep.[11] Another study, with 528 subjects (428 insomniacs and 100 controls) using the same psychological measure confirmed the initial pioneering study. The profile of individuals with insomnia was homogeneous between people from rural areas and semi-urban areas being characterized by high levels of neurotic depression, rumination, anxiety, chronic inhibition of emotions, and an inability to express hostile feelings (e.g., anger).[12]

In terms of implications for treatment, these authors suggested that:

(…) [it] should primarily center around psychotherapeutic treatment to elicit emotional discharge during the day to minimize emotional arousal at night and to deal directly with the fear of sleeplessness itself by means of supportive psychotherapy or behavioral techniques. Adjunctive short-term use of hypnotic drugs may be utilized to diminish physiologic arousal in insomniacs, which is a result of their unexpressed and internalized negative emotionality (p. 354).

These data were supported by another study using the MMPI, which found a “psychosomatic profile” in patients with insomnia.[13] There are still few investigations on personality characteristics of patients with insomnia, and as such it is proposed by several authors as an issue to invest in the future.[9] Some recent studies that are trying to follow this direction are worth mentioning.

A research of Spiegelhalder et al. reinforced the idea that there is a personalistic pattern, containing obsessive traits, in patients with insomnia compared to patients with other sleep

disorders. The authors assessed/operationalized this construct using an original construct: punctuality.[14] The recent studies about personality traits of individuals with insomnia have brought new data, specifically about the fact that patients with PI seem to differentiate themselves from other patients with other subtypes of insomnia. There are researches which emphasize there is no particular pathognomonic profile related to PI while others suggest that PI patients are more pessimistic, fearful, shy and reveal higher fatigue level compared to general population samples.[15] Other studies point to a similar profile in insomnia patients and individuals with various psychosomatic diseases.[16] A recent research concluded that there is a negative correlation among the severity of insomnia and personality related variables such as looking for new sensations ("novelty seeking"), dependence for rewards ("reward dependence") and cooperation ("cooperativeness"). Moreover, the same research found a positive relationship among "harm avoidance", "self-transcendence" and "sleep-related cognitions" and insomnia severity.[17] Other studies have investigated also the association between sleep/insomnia and perfectionism.[18,19] In summary, the studies concerning the profile of individuals with insomnia are within what many authors consider to be emotional hyperarousal.[20]

Behavioral perspective of Spielman

The approach regarding PI by Arthur Spielman may be considered one of the most important ones, since it will influence subsequently further psychological (i.e., cognitive-behavioral models) and biological approaches.[9] This model suggests that there are three factors related to the etiology and maintenance of PI: a) *predisposing factors* - that refer to behavioral traits of vulnerability prior to insomnia, encompassing biopsychosocial spectrum variables such as biological (e.g., hyperarousal of different neurobiological systems), psychological (e.g., tendency to worry and ruminate excessively), and social (e.g., bed companion with inconsistent sleep schedule, social pressures to sleep without respecting the sufficient hours of sleep) variables; b) *precipitating factors* - which concerns life situations perceived and interpreted by the person as threatening and stressful, and as such, inducing insomnia symptoms (e.g., death in the family, sudden illness); and finally, c) the *maintenance factors* - which relate roughly with the maladaptive strategies that

people develop to cope with insomnia (e.g., excessive time in bed, staying in bed although not sleeping.[9,21] This model turns out to explain why people with PI sleep well in new environments, even in the first night on a sleep laboratory. This is known as "reverse first night effect".[22] The environment is new, has few visual and temporal cues for activation (arousal) and allows transitory improvement in the patient's complaints. This also explains the fact that many patients fall asleep, for example, in the living room watching TV, and consequently when they go to the room/bed, drowsiness disappears and a scenario of widespread arousal installs. It should be noted that alternative views have been develop over the years about the role of these different factors, in particular, regarding the role of the predisposing factors that seem not to be as static as previously thought.[23] This perspective is also known as the model of the 3 P's, since the designation of the three factors begins with the letter "P" - predisposing, precipitating and perpetuating.[7]

Stimulus control model

The stimulus control model proposed by Bootzin is based on the conditioning history of individuals.[24] Starting from the assumption that the same stimulus can generate varied responses, this author suggests that the PI develops when the sleep-related stimuli (e.g., bedtime, bed or room) failed to generate responses associated (only) to sleep, yielding alternatively responses inconsistent with the sleep behavior or sleep induction, such as reading, working or concerning about not being able to fall asleep. In this sense, because there is a learned association between stimuli and responses that is not conducive to sleep, the clinician can help patients to inhibit, strength or promote new learning conditions.[25]

Microanalytic model of Morin

The Canadian psychologist Charles Morin proposed in the early 90s of the last century a guiding multifactorial and integrative model to understand how the vicious cycle related with PI installs and becomes autonomous and independent from the precipitating factor that might have originated it. This theory stresses psychosocial aspects, namely cognitive

arousal, but also includes biophysiological variables, being the first model to suggest a more articulated concept of hyperarousal covering affective, behavioral and physiological domains. Thus, according to this author, there are four major categories of maintenance factors that, together, explain how a person cannot to get rid of insomnia: (1) *activation*, characterized by an abnormal and excessive activity in physiological (i.e., activity related to the central and peripheral nervous system that maintains arousal and is incompatible with, or interferes with the process of inducing sleep), cognitive (i.e., related to an intense activity in terms of alertness, intrusive thoughts related to own sleep behavior, daily concerns, eager anticipations, ...), and emotional systems (i.e., related with stressors which induce a permanent state of activation, personality traits such as neuroticism and perfectionism, or psychopathology); (2) *dysfunctional cognitions* (i.e., which relate to cognitive arousal and that crystallize in a more profound way forming core beliefs or cognitive schemes that once activated or hypervalent they will guide the subsequent processing of information); (3) *maladaptive habits* (i.e., excessive time in bed, napping); (4) and the *pernicious consequences of the interaction of all these factors*.[20] It is due to Morins` works and his theoretical model that cognitive techniques (developed initially for depressive and anxiety disorders) targeted for therapeutic intervention become frequently used in clinical practice. This author, in addition to his many important contributions to the insomnia´s study, investigated two fundamental cognitive errors or distortions in patients with PI: catastrophizing and probability over estimation.[26] This theoretical model by Morin, together with behavioral models such as the Spielman´s theory, is one of the most cited in the literature, underlying most of contemporary clinical practice in the field of insomnia.

Hybrid cognitive-behavioral model of Lundh and Broman

The Lundh and Broman´s model is clearly an approach that gives more prominence to insomnia´s maintenance processes.[27] The authors note that there are two types of psychological processes forming the core of the experience of insomnia: (1) *processes that interfere with sleep-related levels of cognitive, emotional and physiological arousal*, which may be moderated by personality characteristics such as neuroticism, and (2)

processes that make the individual prone to perceive or interpret their sleep patterns in a distorted or dysfunctional way - usually linked to inaccurate beliefs that people hold about sleep in general, causal attributions associated with partial or total sleep deprivation, or attentional biases (among others). Despite this distinction, the authors suggest that in practice there is a bidirectional relationship between these two processes, influencing each other. High levels of arousal often leads to biased interpretations or cognitive distortions regarding own sleep difficulties; in turn, ruminations, worries, and negative beliefs and attitudes regarding sleep, often lead to exacerbation of arousal. In short, this is an approach with important clinical implications, which allows that treatment strategies will be selected depending on the identification of the process more compromised to each individual.[28] If the sleep-interfering processes are the most predominant, then the treatment may focus on strategies such as relaxation, stimulus control, restriction of time in bed, or techniques derived from cognitive-behavioral paradigms of third generation such as mindfulness and acceptance; if on the other hand the processes involved are essentially those that lead the individual to perceive or interpret their sleep patterns in a distorted or dysfunctional way, then cognitively oriented methodologies may be more relevant. Nonetheless, in most cases, both processes are compromised.

Neurocognitive theory of insomnia

The neurocognitive theory represents an advance in conceptualization of insomnia, extending the behavioral or psychological classical models to put in evidence biophysiological variables, which have been understudied by previous models. This model highlights the concept of hyperarousal, and divides it into the three distinct components considered by previous models, namely: somatic, cognitive, and cortical. *Somatic hyperarousal* corresponds to high rates of metabolism; *cognitive hyperarousal* concerns psychological constructs such as rumination or worry; and *cortical hyperarousal* concerns to cortical high activity recorded by electroencephalography or event-related potentials (e.g., EEG and ERP, respectively) or other measures related to the activity of central nervous system (e.g. structural and functional neuroimaging – MRI and fMRI, respectively).[29,30] These authors call attention to the "paradoxes of insomnia" maintained

by patients (i.e., perceiving hypnotic treatment as being more effective than it actually is; overestimating sleep latency and underestimating total sleep time; and perceiving sleep, as recorded by polysomnography, as awakefulness). Traditionally, somatic activation is seen as something physical/corporal - thus studied preferentially with physiological or biological methods, while the cognitive activation is regarded as a "matter of mind," being privileged for this purpose by traditional psychological records.[29] The same investigators stresses that the approach should not be orthogonal but integrated, and the cortical activity may be interpreted as a correlate of cognitive activity, for example.

Espie´s psychobiological inhibition model

Colin Espie, an experienced clinical psychologist and researcher in the domain of insomnia, proposes that the circadian and homeostatic processes are inhibited in chronic insomnia. He and his colleagues developed the AIE model (A-attention; I-intention; E-effort) which consists of a cognitive model aiming to further understand the development and maintenance of chronic insomnia.[31,3] This model may even represent, according to its proponents, a subtype of PI that may be called AIE syndrome.[32] This perspective focuses on the cognitive mechanisms related to the general hyperarousal underlying PI, and it tries to explain insomnia symptomatology by the same mechanisms underlying normal or standard sleep. For sleep to occur, there must be a general dearousal (i.e., decreased activation / deactivation), at the cognitive and physiological levels, together with a set of automated actions concerning stimulus control or practices related to good sleep hygiene. In this sense, this model states that the three main components of cognitive dysfunction in PI are: *selective attention to sleep*, *explicit intention to sleep*, and *effort to fall asleep*. However, in contrast: 1) normal sleep is an automatic and involuntary process that can be inhibited by selectively directing attention to itself - according to Troxel, German and Buysse is the same as saying that "trying to sleep is not only frustrating, but biologically impossible: Sleep is not a volitional behavior, but the state that the brain switches into when it is ready to do so, based on homeostatic and circadian factors" (p. 273)[33]; 2) automaticity is committed to a self-implicit instruction to sleep, and 3) the explicit effort to try to sleep results in the development of maladaptive or dysfunctional behaviors, such as

alcohol intake.[31,34] From a pragmatic way, it may be assumed that the selective attention, the explicit intention and the effort to sleep represent three distinct, albeit related, modes: the "scanning mode", the "planning mode" and the "performing mode", respectively. This model proposed by Espie et al. although more focused on cognitive processes, supports the probable mechanisms by which cognitive-behavioral strategies used in the treatment of insomnia are effective, that is, precisely because they would facilitate the disinhibition of neurobiological structures responsible for inducing sleep.[8] This model further explains why individuals with insomnia tend to obtain better sleep outside the usual sleeping place: because they do not have the specific goal or explicit intent to sleep. Furthermore, it gives strength to the use of the paradoxical intention´s technique. In sum, these authors elaborated an alternative explanation to the classical hyperarousal hypothesis, which despite its value needs more research.

The cognitive model of Harvey

The cognitive model of Allison Harvey is a more faithful approach to the classic cognitive theories of psychopathology.[35] According to Harvey and her team, insomnia is maintained by a profusion of cognitive processes that operate either at night or during the day. These cognitive processes relate to (1) *worry*, (2) *selective attention and monitoring*, (3) *misperception of sleep and daytime dysfunction*, (4) *dysfunctional beliefs*, and (5) *dysfunctional safety behaviors*.[36] Briefly, this cognitive model emphasizes an individualized case formulation-driven treatment, and it considers that the worries (Harvey & Greenall, 2003), for instance, at bedtime, will lead the nervous system to rise sympathetic arousal and physiological distress.[37] This arousal state, similar to what occurs in threat, harm or challenge situations (i.e., stress in general), will decrease the attentional field turning the person more aware of possible clues or threatening stimuli (monitoring), and preventing her/him from relaxing. The attention and monitoring are typically directed to stimuli signalizing potential threats related to sleep (or lack of it), such as internal stimuli, such as certain bodily sensations, or external environment stimuli, such as the clock displaying the hours.[38] Therefore, it will strengthen unrealistic or dysfunctional beliefs that maintain the vicious cycle of insomnia. To deal with the perceived threat, the

person performs certain open or covert behaviors (i.e., safety behaviors) which aim to reduce anxiety and decrease sleep latency. Generally, these are dysfunctional behaviors (e.g., taking psychotropic drugs, alcohol abuse, trying hard to sleep – sleep effort) in the sense that they prevent the patient from having experiences that challenge their beliefs, thus making it more likely that the fears of patients persist.[39] A very important component in this model in terms of therapeutic protocol design is the emphasis on behavioral experiments.[37] This cognitive model allows for a flexible treatment for many patients because the intervention options and sequence are adjusted depending on the analysis of the most relevant maintenance factors for each patient.

Bottom-up model of Riemann

In an article published in 2010, Riemann and colleagues gathering input from various scientific fields, organized the literature so far supporting the hypothesis of hyperarousal in insomnia. The authors' initial thesis was that there is empirical evidence organized in the literature that converges to the hypothesis of hyperarousal in insomnia, gathering input from various scientific domains (e.g., neuroendocrine, neuroimagiologic, neuroimmunologic, and electrophysiological).[3] The bottom-up model proposes that PI results partially from a genetically determined dysfunction in sleep–wake regulating neural circuitries. However, this approach does not ignore the relevance of perpetuating factors or maintenance mechanisms, such as tendency to ruminating both during the night and during the day. In terms of comprehensive models of PI, it is suggested that there should be a balance between a top-down approach (which focus on the importance of cognitive processes on the physiological activation, such as Perlis et al. or Espie models)[29,31] and a bottom-up approach privileging an explanation based on a genetically determined dysfunction of the neural mechanisms that regulates the sleep-wake cycle, essentially located in the brainstem, hypothetically causing cognitive and emotional disturbances. The authors state that it is necessary to integrate data from neurobiological research (including genetic studies that have shown robust in understanding the hyperarousal of PI in order to complement (but not to neglect) psychological or behavioral models.[3] Although there are conflicting data and it is currently impossible to determine cause-effect relationships,

Riemann et al. suggest that it is reasonable to assume that only those individuals with a certain genetic vulnerability for insomnia are likely to develop chronic insomnia.[5] Still, we should recognize that "(…) there is no definitive evidence that supports any single theory of insomnia. Likewise, the biological or neurophysiological markers have adequate sensitivity and specificity demonstrated" (p. 256).[40]

The instability hypothesis of REM sleep

A complementary view to the hypothesis of hyperarousal in insomnia establishes that what causes sleep complaints in these patients is the instability occurring during REM sleep. This hypothesis has been based on studies that point to the existence of common micro and macro-awakenings in these patients during REM sleep. This is the sleep stage where there is greater neuropsychophysiological activation. In this way, researchers suggest that this stage is where individuals with a more pronounced degree of activation are more sensitive to arousals and sleep fragmentation. Also according to this model, concerns about sleep difficulties and their consequences are common themes in the dreams of insomnia patients. Arousals occurring in REM sleep make dream cognitions more accessible to conscious perception, to memorizing and its retrieval upon waking in the morning, resulting in an experience of interrupted and not restorative sleep. This fragmentation in REM sleep seems to point to a dysfunction in the limbic and paralimbic areas of the brain that are especially active at this sleep stage.[41] REM sleep appears to be particularly vulnerable to pre-sleep concerns, which might lead therefore to a retrospective memory of this phase as waking time, and to perceive sleep quality as poor. In short, for these authors, the hyperarousal in PI is expressed primarily as a pronounced change in REM sleep.

Metacognitive model of insomnia

The model of two levels of arousal related with sleep (metacognitive model of insomnia) by Ong et al. represents an attempt to develop a conceptual framework of insomnia within the third generation models of cognitive-behavioral therapies.[26] This theoretical proposal clearly emphasizes the role played by metacognitions (referred in this model as secondary activation). Put it simply, this model concerns to how one relates to thoughts about sleep and not directly to cognitive activity directly related to the inability to sleep. It denotes a marked influence of Lundh and Broman´s model.[27] This perspective, despite the satisfactory results found/obtained until now, is still an exploratory one, as it lacks more systematic research. It is the first model that attempts to develop a theoretical explanation on the mechanisms that underlie the promising results that treatments based on mindfulness and acceptance have achieved.

Discussion

The hyperarousal´s hypothesis

It should be noted that in this paper was chosen the term "hyperarousal hypothesis" like Bonnet and Arand suggest to refer to hyperactivation.[42] Other authors use alternative designations as "hyperactivation perspective", "hyperactivation theory" or "hyperarousal model".[3,5]

PI is one of the sleep disorders included in the International Classification of Sleep Disorders (AASM, 2005) and is currently regarded as a “psychobiological disorder”.[5] Consequently, hypotheses about its etiology and pathophysiology have been generated trying to reconcile the traditional psychological models with the findings within the modern neuroscience. In this line, the hyperarousal proposal emerges as representing an integrated perspective of insomnia, and corresponding to an increased level of overall stimulation in the organism, affecting physiological, cognitive, and emotional systems.[43,42,44] The most recent studies, as mentioned by Pejovic & Vgontzas, suggest that

“insomnia is a disorder of hyperarousal present throughout the 24-hour sleep/wake cycle, rather than a disorder of sleep loss" (p. 65).[45]

Many insomnia understanding models have attempted, since their beginning, to incorporate the concept of hyperarousal. However, one aspect that can be criticized in some models that explain this construct is that there seems to be no consensus about what the boundaries are to this hypothetical hyperactivation. That is, there are authors who discuss disparate systems (e.g., cognitive, emotional, ...), subdivide other systems that might fit together into other subsystems such as the physiological activation and cortical activation, others suggest that hyperarousal concerns essentially to neurobiological activation, and there are also researchers who refer to hyperarousal as a concept that meets any kind of arousal, regardless of the system. Thus, we are witnessing a paradoxical situation in this field. If on the one hand the view that there is a hyperarousal in PI seems to be consensual, on the other, there is no consensus on what the term covers. Riemann et al. report that even after about 20 years from the initial conceptualization of PI by Hauri and Fischer (1986) there was little accumulation of studies on the physiological component (i.e., somatic tension) of insomnia.[3,46] In this study, for operationalization purposes, we assume the definition of hyperarousal as any significantly pronounced activity in neurobiological, cognitive and/or emotional systems, either self-reported or objectively observed by different methods, and which differs from the average of a group without major sleep problems or disorders. As a complement to the suggested models we should invest in the study of affective and personalistic variables.[9,47] For instance, it would be germane to realize to which extent neuroticism predisposes to, or it results from PI. Contextual and environmental factors should likewise be further investigated. Regardless of the comprehensive model on the etiology and maintenance of insomnia, it should be noted that the psychophysiological stress plays a major role, similar to what occurs in other neuropsychiatric disorders.[48] Although the study of the hyperarousal in insomnia represents a field eminently useful and advantageous, it should be recognized that despite the extensive research to date, one cannot discern whether it is due to hyperarousal that individuals develop insomnia or vice versa, i.e., whether the activation of various biological systems is due to a clinical manifestation of insomnia *per se*. Still, there are authors who point out that probably the relationship is bidirectional.[3] Moreover, the evidence is still insufficient to discern whether the hyperarousal itself is constant/stable or

variable/floating throughout the night (and day).[31] However, Riemann et al. state that "given the cyclic nature of the sleep process itself with well-known oscillations between slow-wave and REM sleep and other dynamic changes with even shorter period lengths during sleep, it seems reasonable to assume that the hypothetical hyperarousal also fluctuates, which might explain that neuroimaging methods with different sampling times may produce divergent results "(p. 26).[3]

In sum, in the scope of insomnia research, there are two possible processes involved: the hyperarousal and the failure to inhibit wakefulness. Note, however, that these mechanisms are not necessarily opposites, but rather complementary.[8] The hyperarousal hypothesis states that PI patients have significantly higher levels of general arousal than good sleepers. Although this hyperarousal is generalized, the cognitive component should be emphasized. Several PI patients refer that the presence of dysfunctional thoughts – overactivity of the cognitive system – is the most disturbing feature of insomnia.[49,50] Besides, one must note that this dysfunctional activity albeit very frequent at bedtime, it is also common during the daytime.[3] On the other hand, the failure to inhibit wakefulness process posit that as bedtime approaches, PI patients have difficulty in their ability to relax; the typical arousal levels of the daytime wakefulness tend to remain constant, not allowing the action of neurobiological structures and neurobiochemical mediators responsible for inducing sleep.[31] Espie´s model is clearly a perspective that fits in the process of failure in inhibiting wakefulness.

Is there room for more theories of insomnia?

As stated by Harvey, we also think that there are still many contributions to be made to theory and intervention in PI.[37] Although very satisfactory results are obtained with the techniques derived from the models generated so far, we believe that with refinement and improvement of brain imaging techniques, among others, the behavioral models will establish themselves in a more solid and consistent way. Secondly, and based on new paradigms of neuroscience, our group is very interested in studying the default mode network (DMN) in these patients. One of our tasks is to understand whether the DMN is relevant to insomnia and to enrich the existing empirically well-established insomnia

models. With the help of neuroimaging techniques and developments in clinical psychology and psychiatry research, we believe that the two processes for insomnia addressed in this paper, will be both improved. We hope in the future to further understand how the simultaneous action of both processes may lead to better insomnia treatments.

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Chapter 3

Neurobiological correlates of psychological treatments for insomnia – A review*

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Highlights:

- Effects at neurobiological level of psychological treatment for insomnia are analyzed.
- The first integrative study about the topic.
- Despite the promising results, more studies are needed.

Abstract

Sleep disorders and sleep disturbances are considered nowadays a major public health problem. Within sleep problems, insomnia is the most common health complaint. The maintenance of insomnia symptoms may lead to a clinical disorder – Insomnia Disorder (ID). A significant amount of literature has shown the efficacy and effectiveness of psychological treatments for ID. Often, the evaluation of therapeutic processes and outcomes focus on subjective measures such as sleep diaries. In this work, we review the few published studies that evaluate modifications in neurobiological domain related to evidence-based psychological interventions, namely cognitive-behavioral therapy for insomnia (CBT-I). The search was carried out consulting Scopus, PubMed, and ISI Web of Knowledge databases. Only 12 studies were found. From the reviewed papers it was observed that the results are diverse, perhaps due to significantly differences pertaining the methodologies used. However, one interesting finding emerged: daytime experiments on insomnia comprising mainly cognitive tasks denoted hypofunction in ID patients, whereas nighttime experiments mainly associated with affective/emotional tasks denoted hyperarousal. We suggest that the study of the neural changes prompted by CBT-I is a major topic in the domain of psychotherapy and sleep medicine. Despite the scarce studies on neurobiological mechanisms of CBT-I, the results achieved until now are promising and should be taken into account in the future. Nonetheless, more research on this topic are needed.

Keywords: Insomnia, CBT-I, Neurobiology, Neuroimaging, Sleep

Introduction

Insomnia is the most frequent complaint in the context of sleep problems (AASM, 2005). Furthermore, it is a frequent problem co-occurring with anxiety and mood disorders. It is estimated that 30% of adults report symptoms of insomnia, and 6% to 10% meet the diagnostic criteria for the disorder (Roth, 2007).

Insomnia Disorder (ID) refers to a clinical disorder concerning difficulties in sleep-onset, sleep maintenance, early awakenings, and/or poor quality of sleep resulting in some form of daytime impairment (APA, 2013). In the new classification of American Association of Sleep Medicine, it is proposed the "chronic insomnia" designation (AASM, 2014). Notwithstanding, we will use ID designation throughout the whole manuscript.

Insomnia (henceforth, we will use the terms "insomnia" and "insomnia disorder" as synonyms) is an oscillating sleep disorder since there are "good" and "bad nights" intermittently. Because of this, the clinical assessment task is challenging. This is evident when we analyze the amount of pathophysiologic models that have been proposed to explain insomnia over the years (for a review, see Buysse, Germain, Hall, Monk, & Nofzinger, 2011; Espie, Broomfield, MacMahon, Macphee, & Taylor, 2006; Harvey, 2002; Lundh & Broman, 2000; Morin, 1993; Ong, Ulmer, & Manber, 2012; Perlis, Giles, Mendelson, Bootzin, & Wyatt, 1997). All these models, mainly psychological in their theoretical frameworks, gave consistency to the two hypotheses explaining the development and maintenance processes of insomnia: the hyperarousal (Marques, Gomes, Clemente, Santos, & Castelo-Branco, 2015; Riemann et al., 2010), and the failure to inhibit wakefulness (Marques et al., 2015; Perlis, Shaw, Cano, & Espie, 2011). The *hyperarousal hypothesis* in insomnia pertains to a widespread activation of several systems (e.g., cognitive, physiological, emotional, cortical), which consequently prevents the person from relaxing (Riemann et al., 2010). Put simply, the hyperarousal process assumes that ID patients have a general overactivity compared to healthy individuals (even during the daytime), and this excessive activity is more pronounced at bedtime and during sleep. Hyperarousal is one of the most studied processes within ID (Perlis et al., 2011). Although one may consider this level of high generalized arousal as regarding the cognitive and emotional components, it is certain that there is a closer relationship with the biological domain both in wakefulness and during sleep (Bastien, St-Jean, Morin, & Turcotte Carrier, 2008; Cortoos, Verstraeten, & Cluydts, 2006; Dang-Vu et al., 2007; Chuah & Chee, 2008;

Desseilles et al., 2008; Drummond, Smith, Orff, & Perlis Chengazi, 2004; Nofzinger, 2004, 2010, 2013; Riemann, Kloepfer, & Berger, 2009; Varkevisser, Dongen, & Kerkhof, 2005). Thus, this has been the inspiration to many investigators who have studied insomnia according to a neurobiological approach. On the other hand, *the failure to inhibit wakefulness hypothesis* suggests that the most prominent feature of insomnia is a difficulty in inhibiting the typical activation of the wakefulness period (Espie et al., 2006). Put simply, this hypothesis does not necessarily assumes hyperactivity but rather the maintenance of the normal wakefulness activation. In practice, it is feasible to accept a complementarity of both hypotheses (Perlis et al., 2011). Probably these two processes may relate to two distinct profiles of patients with ID. This seems plausible according to the clinical practice. However, until now, there is insufficient empirical evidence to support these assumptions.

Following the developments in insomnia´s conceptualization, several techniques have been proposed over the years. There is growing evidence supporting that cognitive-behavioral therapy is effective for insomnia (CBT-I) (Trauer, Qian, Doyle, Rajaratnam, & Cunnington, 2015). CBT-I is based on the standard general cognitive and behavioral strategies which outline the key role of maladaptive thoughts and behaviors in insomnia´s etiology and perpetuation (Morin & Espie, 2003). Within the main techniques that are part of the psychological intervention package, we outline stimulus control procedure, sleep restriction, relaxation techniques, cognitive therapy, and multimodal CBT-I comprising behavioral and cognitive techniques (Morgenthaler et al., 2006). The CBT-I has shown excellent results with diverse populations – children (e.g., Paine & Gradisar, 2011), adults (e.g., Edinger et al., 2001), older adults (e.g., Sivertsen et al., 2006), comorbid insomnia (e.g., Talbot et al., 2014), and hypnotic-dependent insomnia (e.g., Lichstein et al., 2013). The hypnotic medication (i.e., benzodiazepines and nonbenzodiazepine "Z drugs"), which is often prescribed for insomnia patients, is only recommended for a short period of time (2-4 weeks).

Psychologists are amongst the main professionals who provide the suitable treatment for insomnia, and naturally they use several measures to monitor the progress of the intervention. The common methods for measuring the baseline (i.e., before the beginning of the treatment) and the impact of therapy in insomnia are essentially self-report measures. More recently, there has been an interest in using actimetry, a more objective

measure of sleep (Natale, Léger, Martoni, Bayon, & Erbacci, 2014). Unlike other sleep disorders, polysomnography may be dispensable in insomnia, although it may be useful both for differential diagnosis and research purposes (Martin & Ancoli-Israel, 2002).

The conjunction of psychotherapy and neuroscience is an area of current research (Linden, 2006). In a more systematic way, some authors like Walter et al. (2009) recovered the term "neuropsychotherapy", introduced by Klaus Grawe in 2004 to foster the research concerning the neurobiological study of psychotherapy. Those researchers expanded the concept suggesting that it would include: (1) the identification of targets and neural mediators of the functional effects of psychotherapy; (2) the determination of new ways of psychotherapeutic interventions using neurotechnology; and (3) planning or designing of those interventions based on available scientific knowledge. The interest to study the neural mechanisms of psychological interventions has mainly focused on anxiety disorders and major depression (Almeida et al., 2013; Linden, 2006). In this paper, we will focus on the research that assessed some kind of neurobiological correlate before and after a psychological or non-pharmacological treatment for insomnia. Afterwards, we will discuss some of the applied and practical implications that neurobiological studies related to the efficacy and effectiveness of CBT-I may bring in a foreseeable future. Although the aim of this paper is centered in structural and dynamic changes in the brain after psychological interventions for insomnia, it is crucial to be aware of the literature regarding structural and functional brain studies in PI (Nofzinger, 2010, 2013; Riemann et al., 2010; Spiegelhalder et al., 2013).

Method

We searched the databases of Scopus, PubMed, and ISI Web of Knowledge. Furthermore, we manually searched studies and references in journals, books and conferences´ proceedings. In order to retrieve publications on databases, we constrained the search to the period of time between 1980 and 2014. This option was based in the fact that the majority of techniques in which we were interested arose only in the end of last century. Our inclusion criteria were: 1- to have been published after 1980; 2- to have used some kind of neurobiological measure either structural or dynamic (EEG, ERP, PSG, PET, MRI, fMRI, DTI, etc) before and after a psychological intervention (preferentially CBT-I); 3- to report studies on ID (or other alternative designations such as “primary insomnia” or

"psychophysiological insomnia"), thus excluding comorbid insomnia; and 4- to have been written in languages known to the authors (i.e., English, Portuguese, Spanish, and French). The inclusion criteria were purposely broad as we expected to find few articles. We have also included studies which were published in abstract form when there was no full paper published or available. The entry keywords were searched according to article title, abstract, and keywords criteria. We have organized our search based on three joint categories that were all crossed:

- insomnia; insomnia disorder; primary insomnia; psychophysiologic* insomnia; chronic insomnia;
AND
- neural; neurobiological*; neurophysiologic*; neuroimag*; fMRI; functional MRI; MRI; PET; DSI; SPECT; PSG; EEG; ERP;
AND
- cognitive-behavi* therapy; CBT-I; CBT; psychosocial intervention; nonpharmacological therapy; nonpharmacological intervention;

After our (electronical and manual) search, we selected 12 works including some published abstracts that complied with the requirements for analysis in this work.

Results

In the scarce existing literature assessing neurobiological changes in insomnia patients before and after CBT-I, we observe a trend showing significant functional alterations in some core brain areas, suggesting plausible benefits resulting from psychological interventions. Those studies we found are presented below, following the neurobiological technique criterion.

EEG / PSG studies

Jacobs, Benson and Friedman (1993) found that a multifactorial intervention comprising sleep restriction, modified stimulus control, and relaxation training reduced the levels of β activity - a frequency band related to wakefulness and measured by EEG

(electroencephalography) - in a group of insomnia patients (n = 12) from pre to post-test concerning sleep-onset latency, compared to a sex- and age-matched (n = 14) control group without any sleep complaints. The treatment consisted of 5 sessions scheduled every 2 weeks (10 weeks in total) and it was based on a treatment manual developed by one of the authors. This finding suggested that the cortical arousal observed close to bedtime and when subjects were trying to sleep might be successfully reduced through psychological techniques. Noteworthy, improvement in mood and sleep self-report measures were also observed. These results strengthened the (cortical) hyperarousal hypothesis in ID.

A study by Morin, Kowatch, Barry, and Walton (1993) found that CBT-I delivered in group format for 8 weeks reduced wake-after sleep-onset (WASO) percentage (51.3%) in a sample of older adults according to PSG measure, compared to a waiting list condition. The follow-up period over 12-month showed improvement.

A research by Edinger, Wohlgemuth, Radtke, Marsh, and Quillian (2001) compared CBT-I, progressive muscle relaxation, and a placebo intervention, and found that CBT-I was a more effective treatment in WASO reduction than relaxation or placebo interventions. Although not so significantly as the sleep logs' outcomes, WASO PSG measures followed this trend as well.

Cervena et al. (2004) studied the neurophysiological effects of CBT-I (using high density EEG recording) on sleep architecture. Based on the existing data showing an increase in the high frequency electrical brain waves close to bedtime and during NREM sleep, the authors decided to test the efficacy of psychological intervention on some of these impaired neurophysiological parameters. Although the sample of patients with insomnia was small (n = 9), it was found that CBT-I improved the quality of sleep in terms of objective and subjective indicators, contributing to a decrease in CNS (central nervous system) hyperarousal (even during sleep), a reduction in high frequency EEG wave (i.e., β frequencies), therefore favoring sleep pressure and regulating its homeostasis. The CBT-I consisted of 8 sessions for a period of 8 weeks.

A study by Miller et al. (2014) assessed physiological markers of arousal related to the sleep restriction technique for 6 weeks. The clinical sample comprised 10 ID participants. The authors found that from pre- to post-treatment the objectively-defined total sleep time improved, the plasma cortisol did not show significant differences, but there were higher levels in the early morning, and the core body temperature decreased.

A different study investigated the effects of multi-modal CBT-I – 6-week course – on a clinical sample of patients with sleep maintenance insomnia (n = 16) compared to a placebo-controlled group (n = 14). Indices obtained through PSG and sleep diaries were used as outcome measures. There were modifications in sleep-diary measures – decrease of WASO, increase of sleep efficiency (SE), and decrease of time in bed (TIB) – and in polysomnographic parameters such as decrease of WASO and increase of SE. Furthermore, it was observed that CBT-I led to a more rapid decline in EEG delta power over the night. This progressive decline is related to an improvement in homeostatic function (Krystal & Edinger, 2010).

SPECT studies

In another research, Smith et al. (2005) evaluated the effects of behavioral therapy on cerebral blood flow in a group of PI patients during NREM (n = 4) using SPECT (single-photon emission computed tomography). The treatment consisted in 8 sessions for 8 weeks comprising sleep restriction and stimulus control. Interestingly, from pre- to post-treatment, a pronounced activation of basal ganglia was observed. It is known that basal ganglia have different roles on behavior, namely that they appear to be associated with automatic behavior, and with regulation of motor and premotor functions, among others (Lazarus, Chen, Urade, & Huang, 2013). It has also been observed that basal ganglia appear to have an important role in the regulation of sleep-wake behavior; a possible explanation for the association between the basal ganglia activation after therapy and the improvement in PI patients´ symptoms might be the fostering of dopamine production in the basal ganglia via D2 receptors, thus promoting the sleeping behavior (Vetrivelan, Qiu, Chang, & Lu, 2010). This finding was also associated with improvements in PSG measures and subjective patients´ perceptions. However, one must note that the results obtained in this study may probably indicate that two disparate but interdependent phenomena might occur in ID involving different brain regions and neural networks: on the one hand, brain structures such as reticular ascending system, thalamus or limbic areas, which do not deactivate, therefore causing the widespread hyperarousal (Nofzinger et al., 2004); on the other hand, brain areas which are reduced "by default" in insomnia, and that interfere with performance in several domains as in the basal ganglia's case.

PET studies

Nofzinger (2013) mentions a not yet published [^{18}F] Fluorodeoxyglucose positron emission tomography (FDG-PET) study by Milgron, Buysse, Hall, Nofzinger, and Germain, which evaluated the effects of CBT-I on relative regional metabolic rate of glucose on a group of ID patients (n = 5) during morning wakefulness and NREM sleep. After the intervention, a decrease in dorsal frontoparietal areas, limbic and paralimbic areas, thalamus, and basal ganglia was observed. Unfortunately, we could not obtain any more details about this study.

fMRI studies

Altena et al. (2008) used fMRI to compare a group of subjects with PI (n = 21) to a wait list control group (n = 12) in the performance of verbal fluency tasks (i.e., categories and letters). Afterward, the clinical sample was subjected to a non-pharmacological treatment for insomnia for a period of 6 weeks. The treatment included multi-modal CBT-I, body temperature and bright light interventions, and physical activity counseling. The aim of this study was to assess post-intervention neuroimaging modifications, that is, the assessment of neurofunctional reversibility. Results indicated that prior to therapeutic intervention the ID patients displayed a pattern of hypoactivation in the inferior and medial prefrontal cortex compared to the control group. This pattern changed after therapeutic intervention, with the clinical group obtaining identical results to those of the participants who constituted the control group. Once again, evidence that supports neural hypoactivation in PI improved through psychological treatment was found.

Van der Werf, Stoffers, Altena, and Van Someren (2012) concluded, in a study using fMRI before and after non-pharmacological intervention for insomnia, that in cognitive tasks associated with verbal fluency, visual memory, and executive functions (i.e., Tower of London), the patients with insomnia (n = 25) obtained similar levels of behavioral performance compared to individuals in the control group (n = 13) without any sleep problems. Still, a decrease was observed in the neural activation of brain regions such as the prefrontal cortex, and the right caudate nucleus. The authors interpreted this result as evidence that cognitive complaints reported by these patients are realistic, even in the absence of a noticeable effect in behavioral performance. This is suggestive that the performance is suboptimal in patients. However, after some of the ID patients underwent

non-medicated sleep therapy, it was found that the prefrontal cortex activation increased. The same was not observed in the caudate nucleus area. Once again, a hypoactivation pattern was verified.

In an fMRI study with a group of PI individuals (n = 18), Franzen, Siegle, Buysse, and Jones (2013) found that the conscious re-evaluation process of previously visualized negative stimulus activated significantly more the amygdala when compared to the condition where the patients saw the stimuli passively without any attempts to modify them. Put it simply, the voluntary or conscious effort to regulate emotion (i.e., cognitive reappraisal of the negative emotional stimuli) appears to harm the ID patients. In the group comprising subjects without sleep problems (n = 30), the use of cognitive reappraisal strategies decreased the amygdala activation when they were confronted with the same emotionally activating images. This hyper-reactivity pattern seems to agree with the overall hyperarousal theory. Nevertheless, we should note that this was not a study focused on a structured treatment program, though based on an important cognitive technique often used in clinical practice (within cognitive restructuring method of cognitive therapies).

More recently, in the functional neuroimaging study by Stoffers et al. (2014) it was found that the attenuated activity of the left caudate nucleus that had been observed when ID patients (n = 25) were compared with control subjects (n = 14) while performing cognitive tasks did not change after a successful 6-week treatment program for insomnia (multi-modal CBT-I and chronotherapy). The authors pinpointed that the reduced caudate recruitment capacity already observed in the study by Van der Werf et al. (2012) might be an important endophenotypic trait or a predisponent factor that makes the individuals more or less prone to develop insomnia problems. Given the neuroanatomical and neurofunctional features of the caudate nuclei, the existing hypoactivation might support the general inability to regulate arousal states. It seems important to refine treatments which may reverse this pattern.

For an overview of the main findings see Table 1.

Table 1. Overview of reviewed studies

Authors	N	Neurobiological technique	Tested psychological treatment / psychological technique	Main neurobiological findings
Jacobs, Benson and Friedman (1993)	12 patients 14 healthy controls	EEG, PSG	Multifactorial intervention comprising sleep restriction, modified stimulus control, and relaxation training (10 weeks)	↓ levels of β activity
Morin et al. (1993)	12 patients 12 wait-list	EEG, PSG	Group CBT-I (8 weeks)	↓ wake-after sleep-onset
Edinger et al. (2001)	12 patients (CBT-I) 12 patients (Relaxation training) 12 patients (placebo)	EEG, PSG	CBT-I (6 weeks)	CBT-I was a more effective treatment in WASO reduction than relaxation or placebo interventions
Cervena et al. (2004)	9 patients	EEG (high density)	CBT-I (8 weeks)	↓ levels of β activity even during sleep
Miller et al. (2014)	25 patients	EEG, PSG	Sleep restriction (6 weeks)	From pre- to post-treatment the objectively-defined total sleep time improved, the plasma cortisol did not show significant differences, but there were higher levels in the early morning, and the core body temperature decreased
Krystal & Edinger (2010)	16 patients (CBT-I) 14 patients (placebo)	PSG	Multi-modal CBT-I (6 weeks)	↓ WASO ↑ SE

Note. EEG=electroencefalography, PSG=polysomnography, fMRI=functional magnetic resonance imaging, PET=positron emission tomography, SPECT=single-photon computed tomography, CBT-I=cognitive-behavioral therapy for insomnia, WASO=wake-after sleep-onset, SE=sleep efficiency.

Table 1. Overview of reviewed studies (continued)

Authors	N	Neurobiological technique	Tested psychological treatment / psychological technique	Main neurobiological findings
Smith et al. (2005)	4 patients	SPECT	Behavioral therapy (stimulus control and sleep restriction) (8 weeks)	Pronounced activation of basal ganglia was observed
Milgron et al. (cited by Nofzinger, 2013)	5 patients	[^{18}F] Fluorodeoxyglucose positron emission tomography (FDG-PET)	CBT-I (no data available regarding treatment duration)	↓ relative regional metabolic rate of glucose in dorsal frontoparietal areas, limbic and paralimbic areas, thalamus, and basal ganglia
Altena et al. (2008)	21 patients (CBT-I) 12 wait-list	fMRI	Multi-modal CBT-I, body temperature and bright light interventions, and physical activity counseling (6 weeks)	The pattern of hypoactivation in the inferior and medial prefrontal cortex observed in insomnia patients before therapy was normalized
Van der Werf, Stoffers, Altena, and Van Someren (2012)	25 patients 13 healthy controls	fMRI	Non-pharmacological intervention for insomnia – CBT-I-based intervention (6 weeks)	After the intervention, it was observed an increase in the prefrontal cortex activity
Franzen et al. (2013)	18 patients 30 healthy controls	fMRI	Cognitive reappraisal	The voluntary or conscious effort to regulate negative emotions appears to harm the insomnia patients

Note. EEG=electroencefalography, PSG=polysomnography, fMRI=functional magnetic resonance imaging, PET=positron emission tomography, SPECT=single-photon computed tomography, CBT-I=cognitive-behavioral therapy for insomnia, WASO=wake-after sleep-onset, SE=sleep efficiency.

Table 1. Overview of reviewed studies (continued)

Authors	N	Neurobiological technique	Tested psychological treatment / psychological technique	Main neurobiological findings
Stoffers et al. (2014)	25 patients 14 healthy controls	fMRI	Multi-modal CBT-I and chronotherapy (6 weeks)	The attenuated activity of the left caudate nucleus that had been observed when ID patients (n=25) were compared with control subjects (n=14) while performing cognitive tasks did not change after a successful 6-week treatment program for insomnia

Note. EEG=electroencefalography, PSG=polysomnography, fMRI=functional magnetic resonance imaging, PET=positron emission tomography, SPECT=single-photon computed tomography, CBT-I=cognitive-behavioral therapy for insomnia, WASO=wake-after sleep-onset, SE=sleep efficiency.

Discussion and Conclusions

Recently there seems to be a growing interest by many researchers towards the understanding of the biological mechanisms which make CBT effective. However, it seems vital not to overlook the role of neuroscience in the field of CBT or psychotherapy in general. Moreover, we should not expect that the neurosciences might in the future validate any psychotherapy per se. To study the effectiveness and validation of psychotherapies we must always use the classical and stringent experimental designs such as the RCTs (Beck, 2010). Insomnia seems to be an appropriate disorder for the study of neural mechanisms of psychological treatments. For this purpose, one should review the current findings about neurobiology, and specifically, the neuroimaging studies on insomnia as well as other studies using additional methodologies. Furthermore, it is essential to compare the individuals who are "responders" and "non-responders" to CBT-I, and check if there is a neural distinct pattern between them. This line of research complies with the subject about harmful effects related to the practice of psychotherapies (Barlow, 2010).

In broad terms, we described studies that found evidence which supports both the hyperarousal hypothesis, and a hypoactivation pathway in insomnia. A cursory glance at these findings allows one to perceive that studies using cognitive tasks in the experiments found essentially an overall pattern of hypofunction in some brain areas; in turn, studies using affective or emotional paradigms have verified an overall pattern of hyperactivation or increased arousal (Spiegelhalder et al., 2013). Thus, beyond the relevant differences in the ways of collecting data - which may account for differences in results in the studies - we should care about how the experimental designs are drawn, and we should analyze the data bearing in mind that important assumption. We posit that both cognitive and affective paradigms are relevant to the comprehension of PI. The great challenge is to integrate them, and explain how they interact.

This formulation may fit into the new models on insomnia, such as the neurobiological one by Buysse et al (2011). In the neurobiological model of insomnia, it is assumed that there are multiple brain sleep-wake regulators which in the case of the insomnia patients may not be well coordinated.

Studies on the neurobiology of insomnia have pinpointed an interesting variability pattern of (dys)function regarding the different moments of the day. For example,

prefrontal cortex appears to be overactive at bedtime, and during NREM sleep, but it shows hypoactivation during daytime (Van Someren et al., 2013). Therefore, it is germane to explore if the time of the day influences the results that are observed either before intervention or in the posttest. In the meantime, it seems particularly useful to investigate if the implementation of CBT-I interventions respecting the individuals´ chronotype might potentiate therapeutic gains (Adan et al., 2012). Although there are already studies in chronotherapeutics, particularly pertaining to the optimal timing of drug administrations (Ohdo, 2010), in the broad area of psychotherapy this matter lacks research.

Finally, it seems interesting to carry out studies using other neurobiological methods of data collection beyond EEG or fMRI (e.g., molecular biology, neurochemistry).

To summarize it, we think that the systematic study of this subject might change the way psychotherapies are theorized, and particularly, the way psychological treatments for ID are conceptualized.

Foundations for a new research topic

Since a few decades ago, there has been a growing interest in assessing the results of psychological interventions and psychotherapies (Margison et al., 2000). In order to complement the traditional "paper and pencil" methods, some researchers have begun to rely on biomedical imaging technologies (particularly fMRI) so as to unravel the neuronal changes that are processed in the brain after psychosocial interventions. Thus, some authors have proposed methods and adaptations of experimental paradigms to study this matter. Linden (2006) has written a paper briefly but clearly summarizing the "state of the art" on this subject by reviewing the major studies on anxiety and depressive disorders. Similarly to what has been done with these, we believe that ID is a disorder that justifies being studied according to these new paradigms.

Then why should psychologists systematically study the neural repercussions of their therapies in insomnia? What are the benefits? Within this paradigm, we argue that this step must be carried out carefully and only after the interventions are already established according to the standard paradigms widely used in efficacy studies in psychotherapy (e.g., randomized clinical trials - RCTs). The validation of the psychological techniques, including the more idiosyncratic ones used in applied contexts, must be behavioral-guided (Goldfried, 2013). In fact, the validity of the psychosocial techniques in the treatment of

insomnia is already well-established (Morgenthaler et al., 2006). Still, research should be continued for at least two main reasons: in the future, further strategies may be included in the package of the well-established techniques; and even within the recommended techniques there have been some fluctuations (e.g., the relaxation training, though nowadays a *standard* strategy for insomnia treatment, was once considered a *guideline* technique). In this sense, we believe that the anatomical and functional neural experiments in the psychotherapy field will bring new insights onto psychotherapy efficacy and effectiveness (Linden, 2006). Moreover, we would like to stress that this is not a biological or reductionist point of view on psychological interventions (Fonagy, 2004). In graduate and postgraduate training programs, psychologists are taught to monitor the impact of their interventions based essentially on self-reported measures (e.g., questionnaires or subjective perception of own patients). That procedure remains important and in most cases it is the best and the most appropriate practice, mainly in terms of cost-benefit ratio. We defend that in the research domain, gaining knowledge about the neural repercussions of the therapy will benefit our comprehension of the etiological models of insomnia. Understandably, that will bring consequences for the clinical practice. Furthermore, it might help us to understand the possible differential neural pathways related to psychological therapies and psychopharmacological treatments. These studies may, for instance, help to understand different sub-types of insomnia (Van Someren, 2014; Van Someren et al., 2013), taking into account variables related to personality (Laar, Verbeek, Pevernage, Aldenkamp, & Overeem, 2010), individual differences regarding sleep effort (Broomfield & Espie, 2005; Espie et al., 2006), and dysfunctional beliefs about sleep (Morin, 1993; Morin, Vallières, & Ivers, 2007). They may also foster a deeper knowledge of the clinical phenomenology of insomnia and its treatment. This perspective will benefit the field as it is beyond the well-known and fundamental differences among initial, intermediate, and terminal insomnia (Perlis, Benson-Jungquist, Smith, & Posner, 2005).

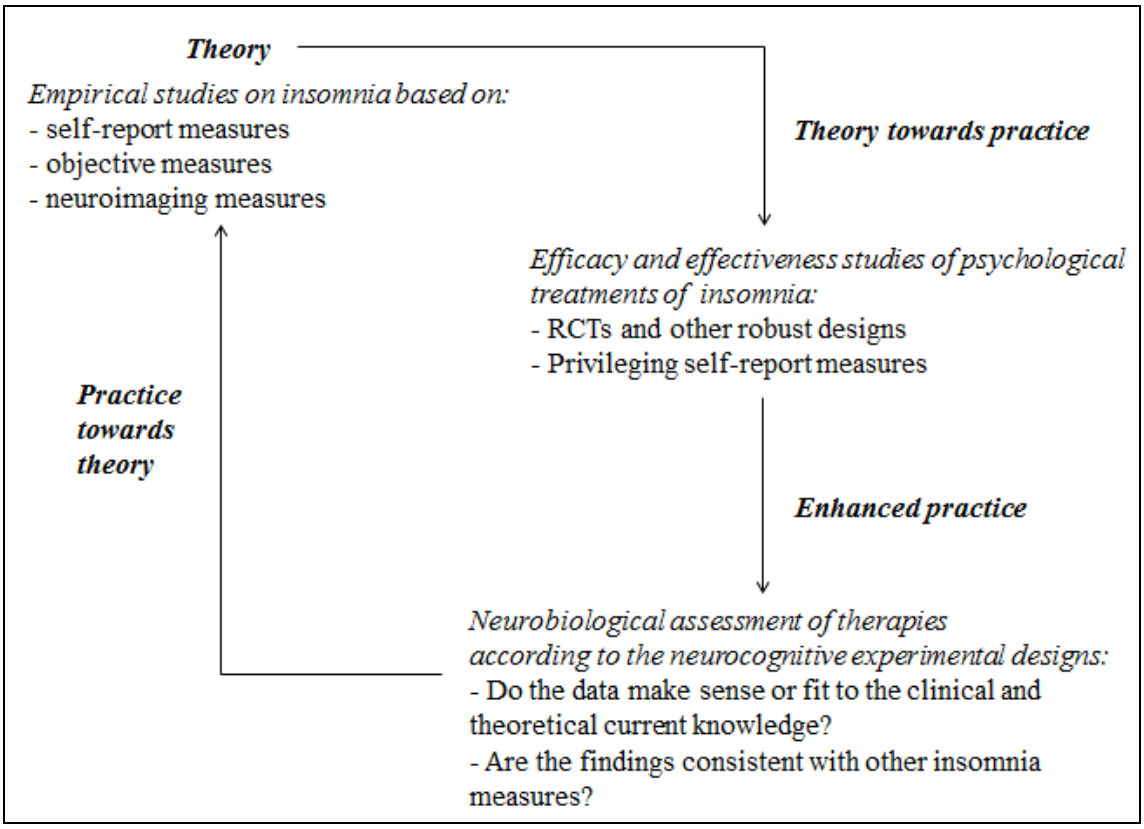

Figure 1. A conceptual framework displaying the relevance of studying the neural changes induced by psychological treatment for insomnia.

In Figure 1, we assert that the background theory and the comprehensive models on insomnia derive mainly from studies using self-report instruments, especially questionnaires, and eventually polissonography, or actimetry measures. The neuroimaging studies are highlighted in our figure albeit they are scarce in insomnia research comparatively to other disorders (cf. Spiegelhalder et al., 2013). Furthermore, the set of theoretical models have fostered and supported clinical strategies used in the psychological management of insomnia. The latter are tested and validated according several research designs such as randomized clinical trials. The most common outcome measures are self-report ones. In this line, aiming to enhance the consistency and reliability of the psychological techniques, we argue that the cognitive neuroscience paradigms will add inquestionable value to the traditional ways of thinking about insomnia and, in particular, its treatment. Knowing the brain areas and the networks whose activity is responsive to psychotherapy for insomnia might help us to understand, for instance, in which patients the frequently prescribed psychiatric drugs may or may not be useful. Likewise, it might benefit our understanding of the most useful behavioral-based models.

The methods of neuroscience may be important to reveal the mechanisms by which psychotherapeutic interventions work (Folensbee, 2007). Any psychotherapeutic intervention may be conceptualized as a more or less structured - depending on the theoretical orientations - systematic learning process (Coutanche & Thompson-Schill, 2012). The cumulative evidence regarding neuroplasticity of the brain enhances this perspective. Perhaps the best example to this crux is the ability of the brain to structurally and functionally change when organisms learn. For instance, in fields such as sports and music several studies have shown that some brain areas change their structure and function in response to the skills they acquire (Chang, 2014). One of the most comprehensive meta-analysis regarding the evaluation of brain modifications after training cognitive and motor skills suggested that as one becomes more of an expert at a skill, the attentional networks decrease their activity, and the brain areas comprising the default-mode network (DMN) become more prominent (Patel, Spreng, & Turner, 2013). That is, the learned skills will progressively demand less effort to be performed over the course of time. In this respect, we emphasize the role that a hypothetical dysfunction in DMN might represent towards insomnia and its treatment (Buysse et al., 2011; Drummond et al., 2013; Marques et al., 2015; Van Someren et al., 2013). It is germane to remember that this resting-state network seems to be related to episodic memory, and self-referential information processing functions. Future research should clarify this matter. So psychotherapy may be conceptualized as a process concerning the learning and practice of new skills. As stated by Lundh (2005), the insomnia patient “may be instructed that treatment is a matter of learning new skills - which is a process that takes time - and not a matter of finding techniques that can be used instantly to fall asleep" (p.35). In this sense, new learning skills prompted by psychotherapy will become part of the behavioral repertoire of the PI patients. Those skills become habits over time, mingling with the personality of the individuals. We assume those are precisely the behavioral changes which will consequently be reflected in the anatomical and functional (re)organization of the brain when the individuals are scanned in an fMRI machine, or other methodology after psychological treatment.

In short, it can be posited that assessing the skills which patients develop after psychological treatments through neuroscience tools will aid in the complex task of monitoring the genuine effects of those treatments (Bastien, 2011).

Disclosure Statement

None of the authors has any potential conflict of interest.

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Chapter 4

Default-mode network activity and its role in comprehension and management of psychophysiological insomnia: A new perspective*

***** Marques, D., Gomes, A., Clemente, V., Santos, J., & Castelo-Branco, M. (2015). Default-mode network activity and its role in comprehension and management of psychophysiological insomnia: A new perspective. *New Ideas in Psychology, 36*, 30-37. doi:10.1016/j.newideapsych.2014.08.001

Highlights

- Default network function: new insights on insomnia´s comprehension and therapy.
- Insomnia might be conceptualized as a self-referential processing disorder.
- A conceptual insomnia framework based on default network abnormalities is possible.

Abstract

Psychophysiological insomnia (PI) is a common sleep disorder in which numerous variables interact. The mechanisms responsible for the etiology and maintenance of PI, though far from completely understood, point to the existence of hyperarousal of several systems. The frequent occurrence of ruminations and worries with a self-referential component (related or not with sleep complaints) during the pre-sleep period, and daytime wakefulness, seems to relate to the functions which have been associated with default-mode network (DMN) activity. This neural network seems to be involved in introspective thinking as well as emotional and episodic memory processing, among others. In this paper, we propose that PI may be conceptualized as a disorder associated with overactivity of some brain areas of DMN. Accordingly, it is also suggested that cognitive-behavioral therapy for insomnia (CBT-I), a kind of non-pharmacological treatment, may alter the function of this network, improving symptoms of patients, and overall quality of life.

Key-words: Insomnia; Hyperarousal; Default-mode network; Cognitive-behavioral therapy for insomnia

1. Introduction

Approximately 10-15% of the general population has insomnia and this is considered as being one of the most common sleep disorders with an estimated incidence of 3-5% of new cases each year (Drake & Roth, 2006). Psychophysiological insomnia (PI) is a sleep disorder with clear-cut classification criteria in terms of medical diagnosis and covers complaints in starting, maintaining sleep, or experiencing non-restorative sleep. According to the second edition of International Classification of Sleep Disorders - ICSD-2 of the American Academy of Sleep Medicine (AASM, 2005), this is a diagnosis that includes high cognitive, physiological, and emotional arousal levels associated with negative conditioning between some stimuli or spatial/temporal cues and sleep behaviors.

As suggested in the literature, insomnia (particularly conditioned insomnia) seems to be a fluctuating disorder. This is evident when we analyze the amount of pathophysiologic models that have been proposed to explain it (Bootzin, 1972; Espie, Broomfield, MacMahon, Macphee, & Taylor, 2006; Harvey, 2002; Kales, Caldwell, Preston, Healey, & Kales, 1976; Lundh & Broman, 2000; Morin, 1993; Ong, Ulmer, & Manber, 2012; Perlis, Giles, Mendelson, Bootzin, & Wyatt, 1997; Spielman, Caruso, & Glovinsky, 1987). All these models, mainly psychological in their origins, gave consistency to the two hypotheses explaining insomnia development and maintenance processes: hyperarousal and failure to inhibit wakefulness, respectively (Perlis, Shaw, Cano, & Espie, 2011). The hyperarousal hypothesis states that in patients with insomnia there is a widespread activation of several systems (e.g., cognitive, physiological, emotional, cortical), which consequently prevents the person to relax. The concept of hyperarousal was recognized to be of major importance in the understanding of PI. However, sleep researchers have not yet reached a consensus on which dimensions this concept covers (Riemann et al., 2010).

On the other hand, the failure to inhibit wakefulness account suggests that the difficulty in inhibiting activation typical of wakefulness period is the principal disturbing process in PI (Espie et al., 2006). In practice, it is feasible to accept the complementarity of both hypotheses (Perlis et al., 2011). It is likely that these two processes may relate to two distinct profiles of patients with insomnia. Although interesting, we do not have yet evidence to support this claim.

Many studies have concluded that bedtime is the period of day in which individuals are more available to deal with emotionally arousing cognitions (Harvey, 2005). For example, people tend to focus on the concerns regarding the organization and management of the following day, to elaborate a retrospective of the past day, to remember past traumatic events, or to anxiously anticipate the future, or generate negative expectations related to own sleep behavior, among many others (Watts, Coyle, & East, 1994). Accordingly, it is easy to understand that intrusive and dysfunctional thoughts related with the self play a key role in PI.

As already mentioned, there are many models proposed for understanding the etiology and maintenance of PI. Nevertheless, it should be noted that the behavioral or psychological models are the most studied and well-known ones, with the added advantage, but also the challenge, of integrating neurobiological, biochemical, physiological, and even immunological variables (Talbot & Harvey, 2010).

In this article, we will present some provisional ideas suggesting that the new developments in neuroscience, in particular, pertaining to the brain´s default-mode network (DMN) study will bring important advances for insomnia´s conceptualization and treatment.

2. The default-mode network

The function of the DMN is currently one of the most studied topics in the field of cognitive neuroscience. In general, it concerns to a relatively well-defined set of brain areas which have a higher level of activation when the subjects are not focused on a specific external task mobilizing their explicit attentional resources (i.e., goal-oriented task or attention demanding task). For this reason, it is also called a task-negative network (Raichle & Snyder, 2007). In spite of this, it is relevant to stress that DMN brain regions are also generally activated in attention demanding tasks albeit in a lesser extent (the exception is when the individuals perform tasks requiring self-referential processing).

The DMN has captured the interest of many scholars since during this “state of rest” the brain consumes identical energy resources compared with solving arithmetic problems tasks, for example (Snyder & Raichle, 2012).

Several studies using the resting-state paradigm and focused particularly in DMN have shown that there are basic psychological functions associated with this neural network. The

DMN is involved in behaviors such as mind-wandering, recovery of past memories, planning/projection of future events, and consideration of perspective/point of view of other individuals (theory of mind). All of these functions activate multiple regions within the DMN (Buckner, Andrews-Hanna, & Schacter, 2008). Overall, they represent what the researchers refer to as the "internal modes of cognition". The resting-state experiments (i.e., in which the participant is asked to simply relax with eyes closed or open, as appropriate) allow to obtain an overview of the most active brain regions that a growing number of studies have shown to be related with each other (i.e., work interdependently), when the subject is focused only on their own psychological processes (Raichle & Snyder, 2007). However, we must note that DMN constitutes just one of the many resting networks observed in the brain.

Although there is no full understanding about the functions inherent to DMN, several studies have converged in identifying the underlying brain structures. These regions include medial areas of the brain, comprising the ventral medial prefrontal cortex (MPFC), dorsal MPFC, medial temporal lobule, inferior parietal lobule (IPL), precuneus, posterior cingulate cortex (CPP)/retrosplenial cortex, and the hippocampal formation (Buckner et al., 2008). Nonetheless, it is worth noting that the current consensus is on MPFC, including anterior cingulate cortex (AAC), PCC, and IPL (Whitfield-Gabrieli and Ford, 2012).

There are some studies suggesting that the DMN, instead of representing a cohesive and coherent organization, can be divided into specific sub-organizations. In an attempt to dissociate subsystems within DMN, Andrews-Hanna, Reidler, Sepulcre, Poulin and Buckner (2010) observed that this network can be subdivided into two main components, taking into account the self-reference and temporal orientation variables. These authors reported that one component is the *medial prefrontal cortex system* - including the dorsal prefrontal medial dorsal, the temporo-parietal junction, the lateral temporal cortex, and the temporal pole; the other component is the *temporal lobe subsystem* which includes the medial ventral prefrontal cortex, posterior inferior parietal lobe, retrosplenial cortex, parahippocampal cortex and the hippocampal formation, and is mobilized when individuals engage in decisions that require mental simulations based on memory. In future-oriented cognitions the two subsystems are simultaneously mobilized, presumably to facilitate the construction of mental models that enable people to adapt to the environment.

Since the last decade, many scholars have sought to understand the patterns of response of the DMN in various neuropsychiatric disorders such as Alzheimer's disease, autism spectrum disorders, schizophrenia, attention deficit hyperactivity disorder, depressive disorders, anxiety disorders, among others (Whitfield-Gabrieli & Ford, 2012; Broyd et al., 2009).

In the case of sleep disorders and PI, in particular, the study of the functional impact of DMN activity seems to be of utmost importance. Resting-state studies appear to be a very reliable and valid biological paradigm to examine the "rest activity" of these patients because it simulates what appears to happen every evening (e.g., in a typical night) prior to sleep-onset, for instance.

3. Insomnia as a self-referential processing disorder: The DMN dysfunction pathway

Until now, we enlightened that DMN has an important role in many human functions and may be disrupted in several disorders. The most studied disorders have been the Alzheimer's disease, major depression, anxiety disorders, schizophrenia, autism, and attention-deficit/hyperactivity disorder. However, the DMN dysfunction hypothesis has been examined also in other disorders beyond neuropsychiatric ones (e.g., Kornelsen et al., 2013; Liu et al., 2013; Tregellas et al., 2011; Violante et al., 2012; Wolf et al., 2012). For this article purpose, we will outline major depression and anxiety disorders findings since depressive and anxiety symptoms are common in PI patients (AASM, 2005).

In major depression it has been observed a general pattern of activation in DMN areas (Greicius et al., 2007; Marchetti, Koster, Sonuga-Barke, Raedt, 2012), even when the patients are performing an attention demanding task (Sarsam, Parkes, Roberts, Reid, & Kinderman, 2013). This may explain the dysfunctional cognitive rumination reported by these individuals (Anticevic, Cole, Murray, Corlett, Wang, & Krystal, 2013). In patients with varied anxiety disorders it has been found a failure in normal DMN deactivation, and maintenance of intense DMN activity when these individuals are exposed to neutral stimuli (Zhao et al., 2007). In posttraumatic stress disorder, it was observed an impairment in DMN according to a connectivity functional analysis (Daniels et al., 2010). In a study encompassing a group of generalized anxiety disorder patients, a frequent comorbid

disorder in PI (Bélanger, Morin, Langlois, & Ladouceur, 2004), it was found that either patients or healthy controls activated the MPFC and AAC – pivotal areas of DMN – when they were exposed to anxiogenic stimuli; however, the clinical group kept the activation in these brain regions when in resting-state (Paulesu et al., 2009). All the studies cited were performed with functional magnetic resonance imaging (fMRI).

Notwithstanding, we must stress that the results of the studies mentioned so far are largely dependent of sample sizes, experimental designs, data analysis techniques, among many other factors.

In healthy individuals it seems that DMN plays a key role in mood regulation as well. A study by Killingsworth and Gilbert (2010) reinforced the idea that there is an emotional cost associated with DMN activity (regardless of its benefits and evolutionary/adaptive advantages). This cost refers to the negative correlation that seems to exist between levels of self-reported happiness and activity in this neural network. In summary, the more the activity in the DMN (i.e., self-referential processing), the greater the likelihood of individuals reporting psychological distress.

Before we put forward some hypotheses based on our proposed "DMN dysfunction pathway in insomnia", we will refer some studies that recently have emerged on DMN, sleep and insomnia relationships.

Larson-Prior et al. (2006) studied the association between cerebral electrical activity related to introspective and relaxing states (i.e., alpha waves) and BOLD (blood oxygenation level dependent) signal during two resting-state conditions (eyes closed during 5 and 20 minutes periods) in a sample of 34 healthy individuals. The results showed a significant association between these two signal types, particularly located in PCC. In another study with 10 healthy participants, the same authors studied the functional connectivity between DMN in wakefulness state and NREM sleep stages using fMRI and simultaneous EEG (electroencephalography). The main conclusion was that functional connectivity patterns within DMN from wakefulness to sleep is maintained (Larson-Prior et al., 2009). On the other hand, a study by Horovitz et al. (2009) with healthy individuals found that during normal sleep there are significant modifications in DMN activity, in particular, a reduced correlation between anterior and posterior components. It may happen that this pattern does not occur in PI patients.

Gujar, Yoo, Hu and Walker (2010) recognized that sleep deprivation in non-clinical populations altered activity in the DMN. Sämann et al. (2011) recruited a sample of 25 healthy volunteers and investigated brain's default mode network from wakefulness to slow wave sleep. They found that as sleep depth increases, some DMN´s brain areas such as PCC, retrosplenial cortex, parahippocampal gyrus, and MPFC, decreased their activity. Other research by De Havas, Parimal, Soon and Chee (2012) evaluated functional connectivity among DMN regions before and after 24 hours sleep deprivation (n=26). After sleep deprivation, there was a reduction in functional connectivity in DMN. Rao (2012, October) verified that it only takes one sleepless night to disrupt the way in which hippocampus and DMN regions communicate. In the meantime, when the subjects recovered the "lost sleep", the pattern becomes normal again.

The only published studies we found specifically about DMN and its relationship to insomnia (at least to our knowledge) were the ones by Hasler et al. (2013) and Drummond et al. (2013).

Hasler et al. (2013) investigated the functional connectivity between areas of the DMN in a sample of patients with PI (n=53) and in a sample of good sleepers (n=52) in four different times of the day: in the morning after waking-up; in wakefulness at the end of the day/early evening; during NREM sleep; and during NREM sleep after sleep restriction. It was verified that both groups were not distinct regarding functional connectivity in the morning period after waking-up. However, in the other three moments of the day the groups showed differences. The control group evidenced higher correlation values between PCC and MPFC during wakefulness at evening and NREM sleep. The clinical group showed higher magnitude correlations in these brain regions after sleep restriction, comparatively to the control group. Finally, insomnia patients revealed higher magnitude associations between PCC and inferior parietal cortex, except for post-sleep restriction NREM sleep. This research was performed through [18F]fluorodeoxyglucose positron emission tomography.

The other study on insomnia (albeit not focused explicitly in DMN) aimed to compare the performance on a test of working memory (n-back working memory test) in a group of patients with PI (n=25), and a group of matched individuals from the general population (n=25). Although there have been no differences between the groups in behavioral performance, it was found that patients with PI did not recruit successfully the same brain

regions involved in the memory task compared to the control group. Interestingly, it was also found that insomnia patients were not so able to deactivate brain regions related to the DMN when compared to the control group. This effect was more pronounced when the difficulty of the memory task increased (Drummond et al., 2013). This research was performed through fMRI.

Finally, it should be mentioned a study using simultaneous fMRI and EEG by Chen et al. (2014) concerned with resting-states study on insomnia. They analyzed the functional connectivity of 17 PI patients and 17 healthy control participants during rest and during the time the participants tried to fall asleep. It was found that there was an aberrant activation of the insula in PI patients. Besides, this insula activity was related to gamma activity in EEG and negative affect.

Noteworthy, we must underscore that the inclusion of actual sleep stages into the DMN model is problematic. It has been shown that there is a general metabolic decrease from waking to sleeping (not restricted to DMN areas); thus, brain activity and connectivity patterns differ fundamentally between waking and sleeping.

3.1. Integrating DMN in current approaches to insomnia

According to the still scarce literature on the role of the DMN in insomnia and sleep, we can draw some provisional explanatory links which shall be validated by future studies.

When the individual is in bed preparing for sleep it seems plausible that by the absence of tasks/external stimuli that require focused attention, the person focuses on its internal functioning by "default". According to the most well-known explanatory processes in insomnia (see Introduction), we can delineate two types of possible trajectories: (1) there is a significantly high level of arousal in DMN brain areas even during the day, and which tends to persist at night, and possibly during sleep stages – *hyperarousal hypothesis* (Riemann et al., 2010); (2) there is pronounced activation at bedtime particularly; with the approaching of night, and in the absence of explicit tasks to mobilize the attention of the subject, the attentional focus will be on self-referential processes (Harvey, 2005) which involve the activation of the DMN. That is, the other neural networks will reduce their activity, whereas DMN will not be so deactivated. The activity in DMN might inhibit brain structures underlying sleep induction – *failure to inhibit wakefulness hypothesis* (Espie et al., 2006). According to these considerations, ruminations and concerns will occupy

attentional resources of the individuals, thereby disrupting their sleep. The way the person copes with these pathophysiological processes will depend on several variables commonly referred in the literature such as sleep anxiety, sleep effort, cognitive and behavioral coping strategies, among others (Espie et al., 2006; Harvey, 2002, 2005; Morin, 1993; Perlis et al., 2011).

In insomnia disorder it is conceivable that one can interpret the dysfunction of DMN in two complementary ways (which may reflect the different cluster categories of patients with PI): (1) lack of suppression of irrelevant processes when performing demanding tasks (as also observed in schizophrenia, for instance), and (2) lack of suppression primarily assigned to abnormally intense cognitive activity (as suggested in the context of depression) (Anticevic et al., 2013; Whitfield-Gabrieli & Ford, 2012). We hope that future research can shed light on these hypotheses.

3.2. The "head button" that never switches off

In clinical practice it is common to hear insomnia patients saying that they should have a button/switch in their heads that they could shut down to fall asleep quickly (i.e., avoiding the flood of thoughts related to the self, and generally with a negative emotional valence). Perhaps research regarding the DMN may shed light on understanding of these cognitive activation complaints in two ways: First, this "button" would not necessarily be categorical (i.e., only with two options: *on* - wakefulness and *off* - sleep), but instead it would be something more like a dimensional continuum; on the other hand, could be a set of "buttons" as represented by various brain structures constituting DMN. These hypotheses seem to fit in the new theoretical developments of insomnia disorder (see, for example, the neurobiological model by Buysse, Germain, Hall, Monk, & Nofzinger, 2011).

3.3. One step ahead in insomnia

We have discussed the putative interplay between insomnia disorder and DMN hitherto. However, a caveat should be underlined. We would like to stress that the perspective we propose (i.e., DMN dysfunction in insomnia) should be seen as a useful theoretical framework (though complementary) to the existing models and theories. In this vein, the hypothesized DMN dysfunction in insomnia resembles the insomnia´s REM sleep instability account for insomnia proposed by Riemann et al. (2012). This hypothesis

establishes that insomnia patients are prone to more nocturnal micro- and macro-awakenings because REM sleep is the most aroused state that individual experience when they are sleeping. This account reinforces the hyperarousal concept in insomnia. One must note that the authors stated carefully that this is not a new theory but rather a new hypothesis that may contribute to a better understanding of insomnia alongside with the current models.

Given the foregoing, it can be hypothesized that persistent arousal in PI may be due to in part a hyperactivation in brain areas related to DMN, before or during sleep, and even during the period of wakefulness (i.e., during the day) (Nofzinger, 2010). We assume that this hyperarousal mechanism relates with behavioral characteristics that cover many domains (i.e., cognitive, physiological, emotional) which are interdependent. Although we are interested in measuring its neurobiological correlates, we argue that the cognitive arousal experienced by insomnia patients is inextricably linked to the biological underpinnings (Perlis et al., 1997), and the respective need to be studied as directly as possible, because of the mental or psychological functions which have been attributed to the DMN. This would allow, as is done for other disorders, to more closely test if activity patterns within the DMN are responsive to different kinds of treatment, particularly cognitive-behavioral therapy for insomnia (CBT-I) which is a well-established clinical intervention for insomnia (Whitfield-Gabrieli & Ford, 2012; Morgenthaler et al., 2010). Currently, and taking into account the putative functions of the DMN, we are interested in objectively testing into which extent autobiographical activating stimuli generated by the subjects and related to different temporal orientations (i.e., past/present and future) drive different areas of the DMN. In insomnia research, this issue seems to be relevant since there are significant inter-individual differences, and some patients report many activating cognitions related to what they have to do next day (future), while others patients refer more aspects related with situations about past and/or present events (ruminations). In addition, in accordance with what we mentioned earlier, we will explore the impact of eye opening and closure on patterns of neuronal activation in areas related to the DMN, given that this affects the ongoing alpha rhythm (reflecting visual idleness) state level and the link between visual processing and the DMN (Barry, Clarke, Johnstone, Magee, & Rushby, 2007; Knyazev, Slobodskoj-Plusnin, Bocharov, & Pylkova, 2011; Xu et al., 2014). Consequently, these results should be compared with a control group without sleep

problems. It is also possible that there may be an association between cortical areas that mediate the different types of temporal orientation, the fact that the participants have their eyes closed or not, and the related physiological state. In the context of the clinical phenomenology of insomnia this seems very relevant. We think that there may be important differences in temporal patterns of activity related to introspection over time in patients with PI compared to other neuropsychiatric disorders and control samples. It was already mentioned that the DMN hyperactivation observed in major depression disorder seems to relate to ruminative activity. Given that depressive disorders are one of the most common comorbid conditions associated with PI, we wonder if the PI pattern will be the same or if, on the other hand, the component relating to the processing of "future" concerns will be more active, giving consistency to what seems to be more apparent in clinical practice (cf. Integrating DMN in current approaches to insomnia) (Buckner et al., 2008; Whitfield-Gabrieli & Ford, 2012). Additionally, a relevant topic to explore in the future is to analyze whether DMN abnormalities observed in insomnia might also explain DMN abnormalities verified in patients with psychiatric disorders.

4. Specificities regarding the study of the DMN in insomnia

Taking into account some main characteristics of PI (e.g., intrusive thoughts/cognitive arousal) and the functions that appear to be hypothetically related to the DMN, we think it is very important in clinical practice and neurobiological research to study how the regions of DMN modulate their activity in these patients compared with matched control samples taken from general population, without sleep complaints or other neuropsychiatric disorders. It should be outlined that the scientific literature indicates that patients with insomnia are ten times more likely to report their pattern of cognitive arousal as more disturbing than the physiological one (Lichstein & Rosenthal, 1980). Moreover, studies of functional connectivity (i.e., assessment of direction and magnitude of relationships among different brain areas) allow us to understand how the different brain structures communicate with each other. Further, the use of active task paradigms enabling the study of neural activation according to different blocks of stimuli, for example, is also an important avenue for research. To achieve this, it is essential the use of neuroimaging techniques such as fMRI complemented with other traditional measures used in sleep

medicine, including self-response questionnaires, actigraphy, and polysomnography (Whitfield-Gabrieli & Ford, 2012).

Although it is important to evaluate the DMN in insomnia patients prior to bedtime or even during all sleep stages, we emphasize that the same studies must be performed during daytime, since PI seems to be a 24-hour disorder (Riemann, et al. 2010). As Lundh (2005) states: "there is evidence that people's cognitive-emotional processes at restful moments during the day are representative of their presleep processes. This finding makes it possible to study the relevant cognitive-emotional processes by having the individual lie down on a bed for short periods in the laboratory during the day" (p.31).

In fMRI neuroimaging studies participants have to lie down for data acquisition. Contrary to the usual fMRI scannings, we posit that in insomnia patients the measurement time in the scanner should be extended (e.g., 60 minutes). This is important because the prolonged exam may favors boredom – and insomnia patients may or may not fall asleep. However, it is important to underline that this extended duration of scans may bring confounds to the data as the brain states vary over time even in healthy control individuals (Tagliazucchi & Laufs, 2014). Whenever possible, one should control this issue through collecting EEG data simultaneously or using simple tasks such as psychomotor vigilance tests (Sämann et al., 2010). On the other hand the scanning environment might lead to higher levels of arousal. In this vein, it may be considered as a "stimulus provocation paradigm" variant (Linden, 2006). Other cluster of insomnia patients where the maladaptive conditioning principles between their habitual bed/bedroom and sleep behavior are most evident may actually sleep in the scanner. It is therefore no surprise that some of these patients may at least doze in fMRI experiments since it is a new environment. One must note that this paradigm is well suited for research questions that are not focused in studying the performance of the individuals in attention-demanding tasks. In the latter case, the scanning times must be curtailed.

In insomnia, it seems to make sense to study the DMN either with eyes open or eyes closed during the resting-state, since even before falling asleep, when individuals are in bed, there is an inter-individual variability in the tendency for attempting to sleep (i.e., sleep effort) and, as such, keeping eyes closed. On the other hand, given the cognitive load hypothetically mediated by DMN, there might be a tendency to keep eyes open as a reflex

response to daydreaming/mindwandering, even if the external environment remains dark or without any light source.

Given the particularities of insomnia, several experimental design strategies are viable. Insomnia groups should be compared against control groups (i.e., groups without sleep complaints or disorders), and if possible paired *case-control studies* (whenever possible). The aim will be to compare each patient sample against her/his paired control participant. According to the extent literature and our own clinical experience it seems plausible that in PI there is a considerable variability in many important processes among patients (e.g., cognitive processes as selective attention, dysfunctional beliefs, coping strategies, among many others).

In short, as major advantages and limitations of DMN research in insomnia we highlight:

Advantages:

(i) It may account to explain at least partially sleep-onset complaints, intermediate awakenings, and daytime (dys)function;

(ii)It suits for the research during daytime, nighttime and sleep periods;

(iii) It might help to clarify and discriminate the role of the two main processes in PI (i.e., hyperarousal and failure to inhibit wakefulness);

(iv) It will help in the validation of evidence-based psychotherapies according to a neurobiological approach, resembling what is being studied in other disorders (e.g., anxiety and depressive disorders) (cf. Implications for treatment section);

(v)Strengthens the link between methodological approaches in cognitive neuroscience and psychological science knowledge.

Limitations:

(i) It cannot be a model or theory that explains insomnia disorder per se;

(ii) It is a new research topic. Thus, there is scarce evidence (few studies yet) of the DMN dysfunction in insomnia;

(iii) As the most used tool to study DMN is fMRI, the development in this field might be delayed because of cumbersome costs and resistance of some patients in voluntarily collaborating in a lengthy study.

5. Implications for treatment

If future research validates the hypotheses that (a) there is a significant correlation between activity of DMN´s regions and the cognitive experiences that patients often report, and (b) that this association is significantly different from control samples (i.e., individuals without sleep disorders), psychotherapeutic techniques derived from cognitive therapies may be strategies to favor in the management of insomnia, giving strength to the idea that all insomnia treatment packages must contain explicitly cognitive techniques. Current recommendations regarding insomnia´s treatment suggest that cognitive strategies are effective only when they are included in a multimodal approach (i.e., along with behavioral techniques such as stimulus control therapy, sleep restriction therapy, and relaxation training (Morgenthaler et al., 2006). Therefore, there is no evidence to recommend cognitive therapy as the only methodology for insomnia´s treatment. However, recent studies have begun to pinpoint to the effectiveness of this therapy by itself (Morin, Harvey, & Bélanger, 2011). Moreover, this research may help to validate strategies based on mindfulness and acceptance approaches, which will surely contribute to the debate about the integration of third generation CBT with traditional CBT-I.

Still, if CBT-I induces significant objective changes in activity of these brain areas involved in the DMN, the relevance of so-called empirically validated psychotherapies will gain a new role (Linden, 2006). We believe this will help to validate, from another perspective (i.e., neurobiological), the psychological interventions that have been proven effective in treatment of many neuropsychiatric disorders, including insomnia (Bastien, 2012).

6. Concluding remarks

We think that the model of impaired DMN function and the raised provisional hypotheses we propose in this paper, can be integrated in other comprehensive models of insomnia that already exist (e.g., Espie´s psychobiological inhibition model). In clinical

practice, it is common to observe that different explanatory models can be used successfully to different patients with PI diagnosis.

It will be helpful to foster future research on the putative role of different functional clusters within DMN in PI patients with respect to the temporal orientation of cognitive processes (i.e., past, present, and future) since there is evidence suggesting that these are functionally segregated within the DMN (Andrews-Hanna et al., 2010; Schacter, Addis, & Buckner, 2007).

We posit that the study of DMN in the field of sleep medicine (particularly in insomnia) will bring new translational research challenges to the field of sleep neuroscience, in particular, concerning to the conceptual link with clinical practice (Wamsley & Stickgold, 2011).

Ultimately, perhaps the results obtained with the resting-state paradigm may help improve the understanding of PI etiological models and reconcile key concepts that seem to underlie its clinical expression: hyperarousal and failure to inhibit wakefulness processes (Perlis, Shaw, Cano, & Espie, 2011).

Snyder and Raichle (2012) refer that resting-state neuroimaging studies have been motivated essentially by neurobiological questions and much less by clinically oriented cognitive science. It is our expectation that research regarding DMN in PI can bridge this gap.

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PART II

METHODS

CHAPTER 5: General considerations on methodology

Chapter 5

General considerations on methodology*

"There is no «ideal» research design, since researchers need to match their aims to their methods, and the design of trials often represents a compromise reflecting the intents, interests, and resources of investigators"
[Roth & Fonagy, 2005, p.18]

***** This chapter aims to briefly describe the overall methodological steps regarding the studies presented in Part III. Other details and specificities may be consulted in methods/methodology sections in Chapters 6, 7, and 8.

General aims

1 - To study in what extent do a group of PI patients and a sex- and age- matched healthy group differ in terms of cortical activation upon the appraisal of visualized negative affective laden-words (cf. chapter 6);

2 - To explore if DMN and other brain resting-state networks are compromised in PI compared to a healthy group of individuals (cf. chapter 7);

3 - To examine if tailored CBT-I has some kind of beneficial effect in neural activation pertaining to self-referential ruminations and worries and in resting-state networks´ integrity (cf. chapter 8);

Participant´s recruitment

Concerning PI patients´ selection we adopted the following inclusion/exclusion criteria:

Inclusion criteria:

- Diagnosis of PI according to ICSD-2 (2005);
- Age > 18 and < 60 yrs;
- Insomnia Severity Index (ISI) > 8 points;
- Motivation to collaborate in the study.

Exclusion criteria:

- Having other non-treated sleep disorder such as sleep apnea;
- Having a severe diagnosed psychiatric disorder (e.g., schizophrenia);
- Having a chronic medical disorder that could interfere with sleep behavior.

On the other hand, control subjects were recruited according to contact lists of the researchers and using a wide institutional database containing people who would be responsive to collaborate in scientific researches.

Ethical Procedures

All the empirical studies contained in this dissertation were carried out in accordance with the ethical tenets posited by the Order of Portuguese Psychologists (OPP, 2012) and the ethical statements contained in the Declaration of Helsinki (Almeida & Freire, 2003; Field, 2005; Pais-Ribeiro, 1999). All participants had more than 18 yrs. and gave their written informed consent in order to collaborate in the studies. These studies were approved by the Institutional Review Board of "Centro Hospitalar e Universitário de Coimbra".

Notes on CBT-I idiosyncratic approach

Although it was important to ideally follow a treatment manual to ensure uniformity or standardization of therapeutic procedures, in this investigation, we chose to follow the suggestion made by some researchers in the field who posited that the fact that be the same therapist / experienced clinical team to perform psychological intervention can compensate for the fact that the treatment was not manualized (Bower & Gilbody, 2010). It is a scheme defined by some authors as "successive sieves" (Lacks, 1999). The strategy of using adapted and idiosyncratic CBT-I to each patient is something already discussed by Espie and Brooks (1989). The therapeutic strategies followed closely the international recommendations for chronic insomnia´s treatment, being applied in a consistent manner, yet flexible, and according to idiosyncratic formulation of each clinical case (Carney & Edinger, 2008; Espie & Brooks, 1989; Morin, 1993; Morin & Espie, 2003; Morgenthaler et al, 2006). The average duration of each therapy session is presented in Tables 1 and 2; however, for some patients, the sessions lasted more or less time, depending on the features of the case (Gellis, 2012).

Table 1. Flexible organization of CBT-I sessions (Assessment Phase)

Session	Phase	Aims / techniques	Duration (approx.)	Periodicity (average)
1	A S S E S S M E N T	*Clinical Evaluation I* - Clinical interview; - Self-report measures (i.e., **ISI**, Epworth Sleepiness Scale, BDI-II).	90 min.	Monthly
2		*Clinical Evaluation II* - Clinical interview (cont.); - Self-report measures (cont.) (i.e., **DBAS-30**, **WHOQOL-Bref**, Activation scale (sleep), EC-I, BSI, MPS); - Planning for **Sleep Diary** (7 days); - Planning for Actigraphy (7 days).	50 min.	

Note. The self-report instruments used in our research are highlighted in boldface.

The clinical team was constituted by a senior clinical psychologist expert in CBT-I and a Ph.D. student in clinical psychology/sleep psychology.

In the pre-test phase, the first patients´ fMRI studies were carried out between the second and third session. In some cases, given the logistical and / or availability constraints of equipment and patients themselves, the fMRI study was performed after the third session (i.e., in this specific case the study would have to be carried out in the same day as the third session). We assured that this fact would not cause any contamination of the data since the first session mainly dedicated to the intervention is nonspecific for insomnia (third session); thereby, patients would not have time to begin applying some of the general requirements for sleep hygiene. Until post-test, the patients could have up to 12 sessions, including the ones devoted to psychological assessment.[8] For an overview over the whole treatment plan see Tables 1 and 2.

[8] Note that the usual duration of cognitive-behavioral treatment round the 6-8 sessions (Troxel, Germain, & Buysse, 2012). Note also that in a recent study, published in the journal "Behavior Therapy", it is highlighted the need to make psychological interventions quicker and more parsimonious (Cougle, 2012).

Table 2. Flexible organization of CBT-I sessions (Intervention Phase)

Session	Phase	Aims / techniques	Duration (approx.)	Periodicity (average)
3	I N T E R V E N T I O N	*Group Session* - Education about sleep behavior and sleep hygiene rules.	120 min.	Monthly
4		*Intervention I* - Discussion about modifications of sleep habits and their impact in patients´ life; - Confrontation between subjective sleep data and objective sleep data (behavioral experiment) and Socratic debate regarding it.	50 min.	
5		*Intervention II* - Sessions dedicated to the application and training of several particular cognitive and behavioral techniques for insomnia, according to the specific case of the patients. Within the package of techniques we outline: - Stimulus control technique; - Time in bed restriction; - Relaxation training; - Cognitive therapy [Cognitive Restructuring method];	50 min.	
6			50 min.	
7			50 min.	
8			50 min.	
9			50 min.	
10			50 min.	
11			50 min.	
12			50 min.	

Note. It was not mandatory to complete all the 12 sessions.

It must, however, stand out a fundamental idea: the purpose of this investigation was not to proceed to the validation of CBT as a treatment for PI since this is, as mentioned in the theoretical chapters of this dissertation, an effective intervention supported by numerous rigorous controlled and randomized studies. The strategy of tailoring the psychological techniques regarding the idiosyncratic characteristics of patients was therefore a conscious decision in order to foster clinical applicability and realism, thereby decreasing the internal validity but maximizing the external validity (Matthews, Arnedt, McCarthy, Cuddihy, & Aloia, 2013). The idea with this kind of studies is to approach fundamental research to the clinical practice of "real context" (Goldfried, 2013). Moul et

al. (2007) state that "the composite cognitive-behavioral philosophical approach to treatment is probably best when used flexibly and creatively with each patient in a prospective way, over time, in follow-up" (p. 619). Besides, in the words of Alferes (1997) the validity issue is not an all-or-none question, being the intuition of the researcher the best decision maker.

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PART III

RESULTS / EMPIRICAL STUDIES

CHAPTER 6: Self-referential dysfunction and default mode hyperactivation in insomnia patients: A case-control fMRI study

CHAPTER 7: Unbalanced default-mode network activity in psychophysiological insomnia

CHAPTER 8: The effect of tailored cognitive-behavioral therapy on neurobiological function in insomnia patients: an fMRI study

Chapter 6

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

* Marques, D., Gomes, A., Clemente, V., Santos, J., Duarte, I., Caetano, G., & Castelo-Branco, M. (2016, June). *Self-referential dysfunction and default mode hyperactivation in insomnia patients: A case-control fMRI study*. Poster presented at the 3rd International Conference of the European Society for Cognitive and Affective Neuroscience (ESCAN), Porto, Portugal.

***** Marques, D., Gomes, A., Clemente, V., Santos, J., Duarte, I., Caetano, G., & Castelo-Branco, M. (2016). *Self-referential dysfunction and default mode hyperactivation in insomnia patients: A case-control fMRI study*. Manuscript submitted for publication

Highlights:

- We examined self-referential neural correlates in insomnia
- Insomnia patients are hyper-responsive to worries-related words
- Brain regions related with default network appear to be dysfunctional in insomnia

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 PI patients group and a healthy-control group while they are exposed to idiosyncratic ruminations and worries evoked visually by words and 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 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 overrecruitment of brain areas related to DMN and self-referential processing when they were compared to healthy volunteers. The differences between the clinical and control groups were also evident in self-report measures. In sum, despite the relatively small sample size, due to the stringent inclusion criteria, 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, neuroimaging

Introduction

Psychophysiological insomnia (PI) is one of the most common sleep disorders (AASM, 2005, 2014; APA, 2014; Drake & Roth, 2006), with a prevalence ranging from 3 to 5% in the general population (Riemann, Kloepfer, & Berger, 2009). 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 (AASM, 2005, 2014; Riemann et al., 2010). Cognitive hyperarousal seems to be the most compromised mechanism (Spiegelhalder et al., 2012). According to some authors, insomnia patients are ten times more likely to report their perceived pattern of cognitive arousal as more disturbed than the physiological one (Lichstein & Rosenthal, 1980). Additionally, there is evidence suggesting that insomnia patients are more vulnerable to evaluate stressing/threatening stimuli as more negative compared to healthy individuals (Morin, Rodrigue, & Ivers, 2003). Even so, both do not diverge in terms of the reported frequency of these same negative events. However, a recent neuroimaging study found that although there were no noticeable differences between a group of insomnia patients and a control group when passively viewing negative pictures, the clinical group did show increased amygdala activation during cognitive reappraisal of the negative stimuli (Franzen, Siegle, Jones, & Buysse, 2013). According to several models on the understanding of insomnia and the current clinical practice, it seems evident that dysfunctional cognitive-affective patterns related to rumination and worry foster the maintenance of insomnia (Carney, Harris, Moss, & Edinger, 2010; Mitchell, Mogg, & Bradley, 2012). In the psychological literature it is usual to distinguish the concept of rumination from worry (Fresco, Frankel, Mennin, Turk, & Heimberg, 2002). Although both concern to a kind of repetitive and persistent cognitive activity related to the self and characterized by a negative focus (Behar et al., 2012), 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 (Takano, Lijima, & Tanno, 2012). Further, rumination is more related with depressive states whereas worry is more associated with anxiety states (Fresco et al., 2002). This is relevant to insomnia research as depression and anxiety disorders are

the most prevailing clinical comorbid conditions (AASM, 2005; Takano et al., 2012; Taylor, Lichstein, Durrence, Reidel, & Bush, 2005). Insomnia patients are characterized by an excessive focus on their preoccupations over own sleep. However, preoccupations pertaining to other life themes emerge in cognitive activity as well, and are likely to cause sleep disruption (Franzen et al., 2013; Kales & Kales, 1894; O´Kearney, & Pech, 2014). In this sense, Watts, Coyle, and East (1994) 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 would be the ones predominantly anxious with 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 technology such as positron emission tomography (PET) and thereafter functional magnetic resonance imaging (fMRI) (Damasio, 2010). There is some evidence suggesting 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 (Johnson et al., 2002; Johnson et al., 2006; Lou et al., 2004; Yoshimura et al., 2009). For example, these brain regions are particularly activated during the visualization of self-related stimuli (Moran, Macrae, Heatherton, Wyland, & Kelley, 2006).

Nevertheless, neuroimaging studies on insomnia using fMRI technology in particular, are scarce in the literature (Chuah & Chee, 2008; Nofzinger, 2004). Research concerning neuroimaging and disrupted self-related information processing in neuropsychiatric disorders has known some advances recently (Broyd et al., 2009). 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 (Basta, Chrousos, Vela-Bueno, & Vgontzas, 2007). In a study by Paulesu et al. (2010), it was shown that the same network of brain regions was similarly recruited, in both generalized anxiety disorder (GAD) patients and healthy subjects, 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 (medial prefrontal cortex) - remained

significantly activated in GAD individuals. Zhao et al. (2007) 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 (posterior cingulate gyrus) 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 control group. In an fMRI study on major depressive disorder (MDD), it was found that pertaining to ruminative stimuli, 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 (Cooney, Joormann, Eugène, Dennis, & Gotlib, 2010). 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. This finding was observed in an experiment using a self-referential task recurring to emotional trait words as stimuli (Yoshimura et al., 2013).

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 future, relevant decision-making, and theory of mind (Greicius, Krasnow, Reiss, & Menon, 2003; Gusnard, Akbudak, Shulman, & Raichle, 2001; Spreng & Grady, 2009). 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 (Buckner, Andrews-Hanna, & Schacter, 2008; Whitfield-Gabrieli, & Ford, 2012). 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 DMN, Andrews-Hanna, Reidler, Sepulcre, Poulin and Buckner (2010) found that this network may be divided in two main components, taking into account the self-reference and temporal orientation variables. These authors reported

that one of the components is the *medial prefrontal cortex subsystem* - encompassing 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 *temporal lobe subsystem* which includes the medial prefrontal cortex ventral medial, the posterior inferior parietal lobe, the retrosplenial cortex, the parahippocampal cortex and the hippocampal formation, and 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 (Addis, Wong, & Schacter, 2007; Andrews-Hanna, Saxe, & Yarkoni, 2014; Botzung, Denkova, & Manning, 2008; Szpunar, Watson, & McDermott, 2007; Viard et al., 2011). However, there are specificities regarding each one. Whitfield-Gabrieli et al. (2011) 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 examine 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, 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 DMN between both groups. We hypothesized that more pronounced activity in self-related brain regions would be present in insomnia patients when they are exposed both 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 including a clinical psychologist/somnologist and a pneumologist/somnologist. At this Sleep Medicine Centre, first, all cases are evaluated in a general sleep consultation; 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 insomnia diagnosis. Besides, all the patients underwent polyssonographic examination to discard other sleep disorders. 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 symptom duration of 55 months approximately. One of the insomnia patients was taking psychiatric drugs for other health problems (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 (Bastien, Vallières, & Morin, 2001; Clemente, 2007/2013), the Dysfunctional Beliefs and Attitudes About Sleep – DBAS-30 (Morin, 1993, Clemente, 2007/2013), and the World Health Organization Quality of Life measure – WHOQOL–Bref (Vaz-Serra et al., 2006), respectively. Finally, it was requested

to all participants to complete a sleep diary during 1 week (7 nights) (Morin, 1993; Clemente, 2006).

Table 1 – Demographic and psychological characteristics of the sample

	PI patients (n=5) Mean ± SD	Healthy controls (n=5) Mean ± SD
Age (years)	41.6 ± 8.7	38.6 ± 7.1
Education (years)	13.6 ± 3.0	18.0 ± 1.5
Sex	3 F / 2 M	3 F / 2 M

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

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 words were generated by own participants, and guided by the first author. 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 - i.e., reading mechanisms (Buckner, 2012). Our experimental design was based on previous published studies performed by Hoehn-Saric, Schlund and Wong (2004) and Zhao and Wang (2007).

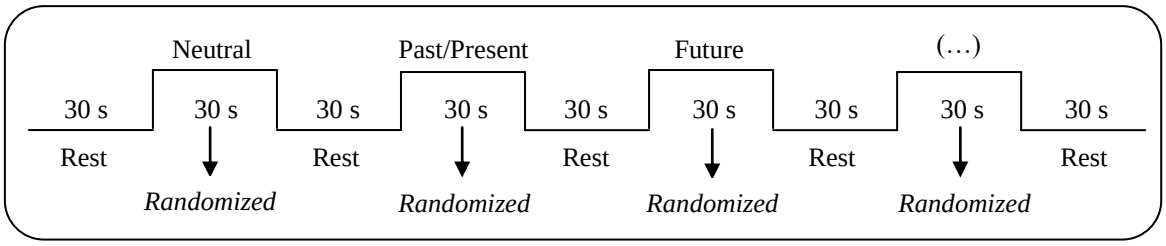


Figure 1 – Experimental fMRI block-design of the study

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 mm3; 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) (Goebel, 2012). Structural volumes were corrected for intensity inhomogeneities, the brain was segregated from head tissue, and transformed into Talairach stereotaxic space (Talairach, & Tournoux, 1988). 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 used corresponds to a cortex inflation of a control participant whose brain was the most identical to the average brain of the whole sample.

To compute descriptive statistics (medians and percentiles) and inferential statistics (Mann-Whitney tests) 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 insomnia group (See Table 2). However, not all variables were significantly different between groups, probably related to the small sample size.

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; 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.

fMRI results

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

Several cortical brain regions showed 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.

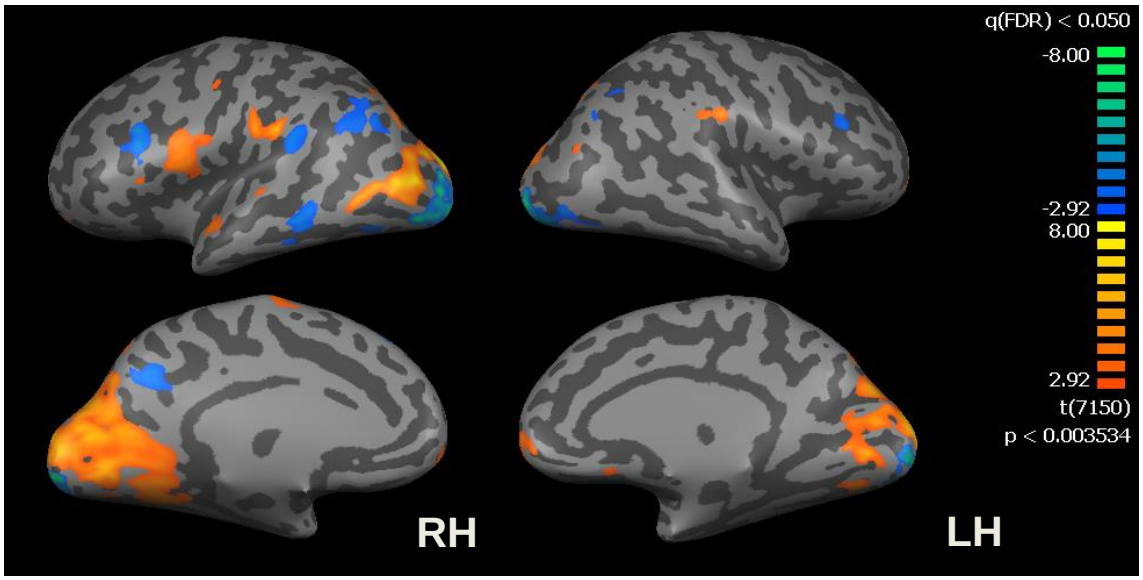


Figure 2 – Brain regions more activated in PI patients (warm colors) than in control participants when it is analyzed the contrast pertaining to neural activation of past/present activating self-related words. Brain regions more activated in control participants are presented in cool colors. On the top panel are depicted the lateral views of both hemispheres; on the bottom panel are shown the medial views of both hemispheres. RH=right hemisphere; LH=left hemisphere. Radiological display convention was used.

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							
Insomnia > 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 > Insomnia							
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.

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.

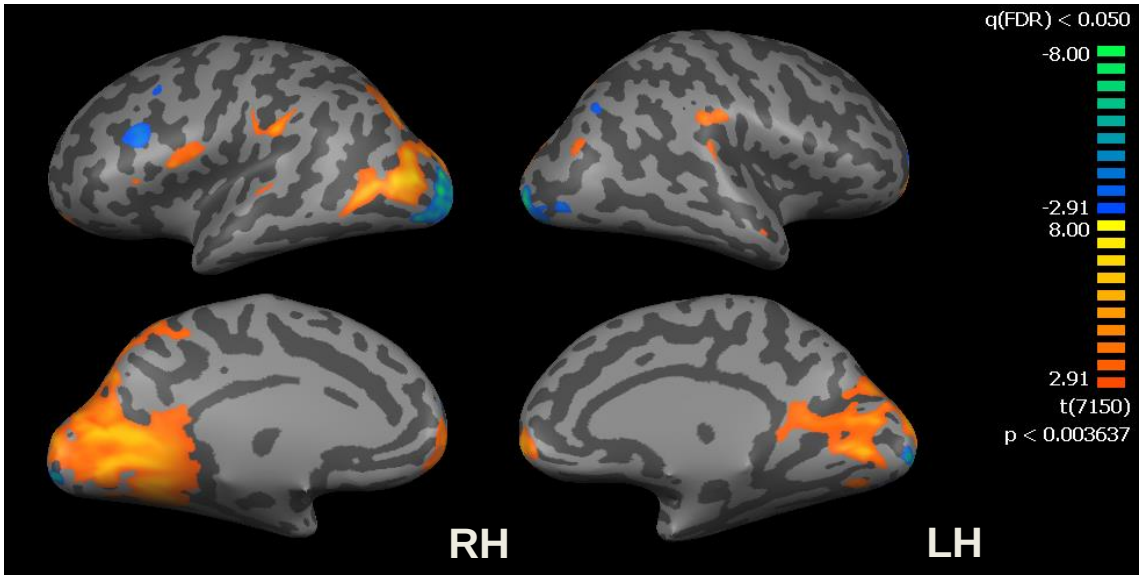


Figure 3 – Brain regions more activated in PI patients (warm colors) than in control participants when it is analyzed the contrast pertaining to neural activation of future activating self-related words. Brain regions more activated in control participants are presented in cool colors. On the top panel are depicted the lateral views of both hemispheres; on the bottom panel are shown the medial views of both hemispheres. RH=right hemisphere; LH=left hemisphere. Radiological display convention was used.

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

			Talairach coordinates				
Region	Hemisphere	BA	x	y	z	Cluster size (k)	*t*-value
Future words							
Insomnia > 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 > Insomnia							
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.

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

Several cortical brain regions showed 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.

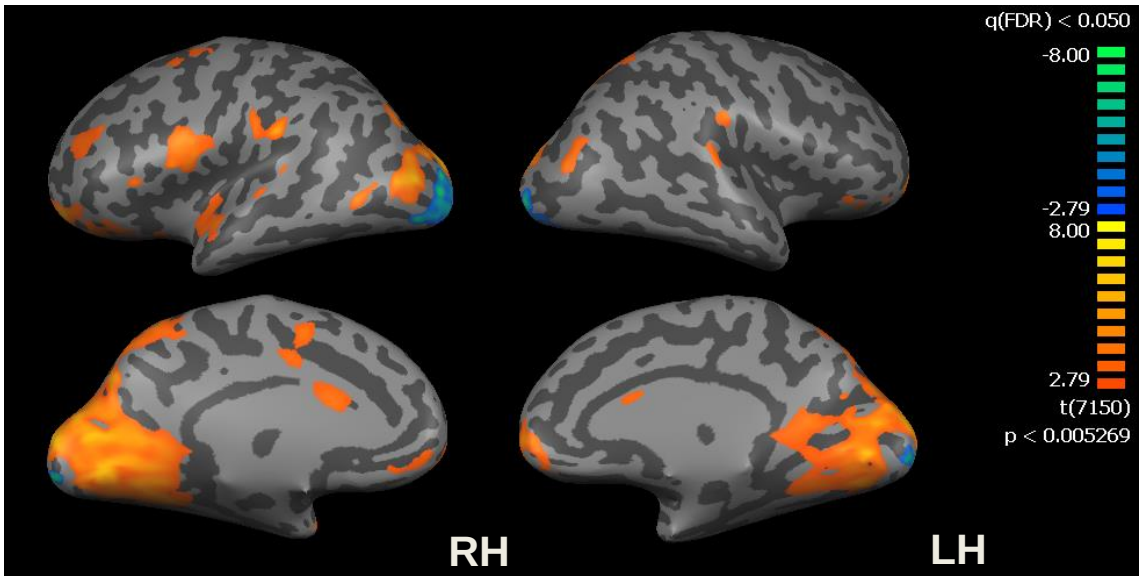


Figure 4 – Brain regions more activated in PI patients (warm colors) than in control participants when it is analyzed the contrast pertaining to neural activation of neutral words. Brain regions more activated in control participants are presented in cool colors. On the top panel are depicted the lateral views of both hemispheres; on the bottom panel are shown the medial views of both hemispheres. RH=right hemisphere; LH=left hemisphere. Radiological display convention was used.

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

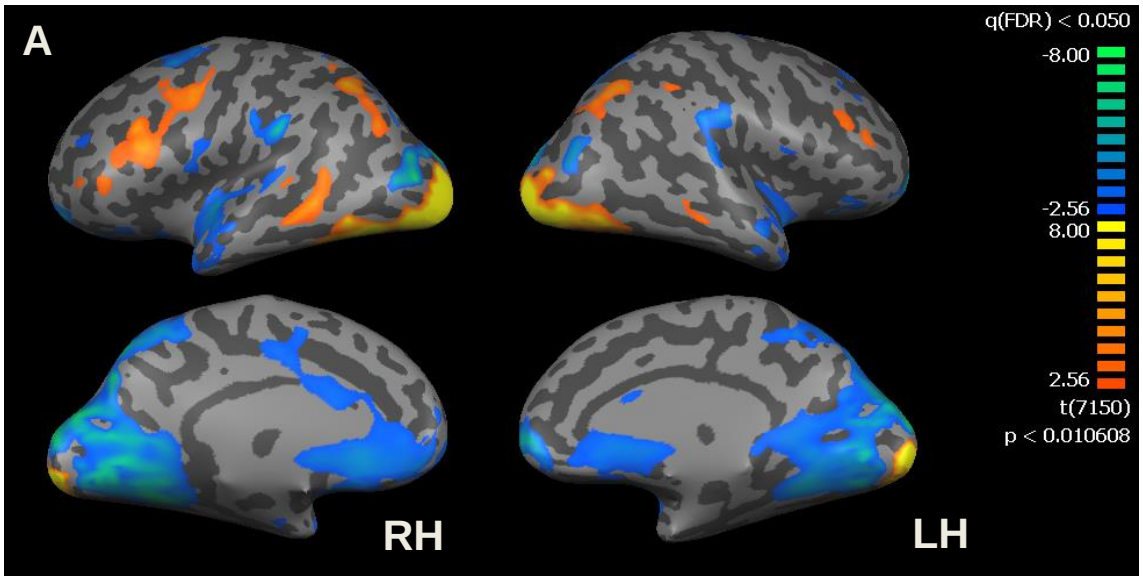
		Talairach coordinates					
Region	Hemisphere	BA	x	y	z	Cluster size (k)	*t*-value
Neutral words							
Insomnia > Healthy controls							
Middle Occipital Gyrus	L	19	-24	-97	19	3745	7.514253
Middle Occipital Gyrus	L	19	-24	-97	19		7.514253
Middle Occipital Gyrus	L	19	-24	-97	19		7.514253
Cuneus	L	18	0	-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 > Insomnia							
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.

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).



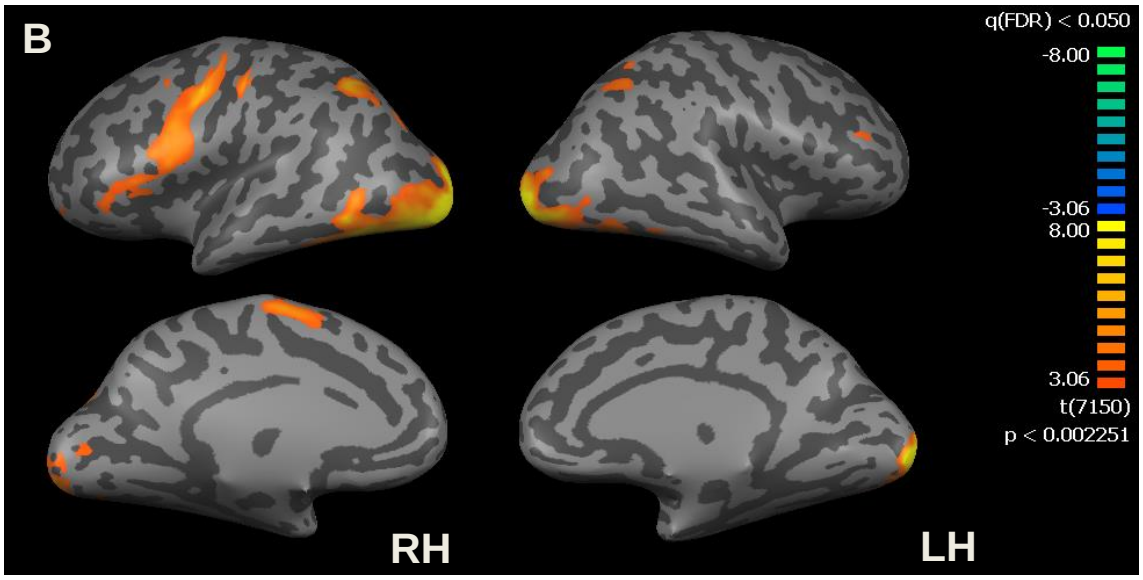


Figure 5 – Activated (warm colors) and deactivated (cool colors) brain regions for the contrast neutral words (+) vs. baseline (-) for healthy-controls group (A) and PI patients (B). On the top panel of each of the figures are depicted the lateral views of both hemispheres; on the bottom panel are shown the medial views of both hemispheres. RH=right hemisphere; LH=left hemisphere. Radiological display convention was used.

Table 6 - Talairach coordinates of activation regions regarding the contrast between neutral words and resting-state conditions

	Talairach coordinates						
Region	Hemisphere	BA	x	y	z	Cluster size (k)	*t*-value
Neutral words > Baseline							
Insomnia							
Lingual Gyrus	L	18	18	-97	-2	2690	12.676134
Cuneus	R	17	15	-97	4		11.990587
Fusiform Gyrus	R	37	48	-58	-11		4.822765
Inferior Occipital Gyrus	L	18	-30	-85	-8		9.584706
Fusiform Gyrus	L	37	-42	-61	-11		7.823190
Precentral Gyrus	L	6	-51	-1	46	667	6.428001
Precentral Gyrus	L	6	-45	2	28		4.821782
Inferior Frontal Gyrus	L	9	-54	11	31		4.518545
Precentral Gyrus	L	44	-57	11	31		4.434950
Inferior Frontal Gyrus	L	45	-54	11	4		4.409202
Superior Parietal Lobule	L	7	-27	-55	13	215	6.339924
Medial Frontal Gyrus	L	6	-3	-4	61	124	5.389038
Superior Parietal Lobule	R	7	27	-52	46	74	4.131346

Cuneus	L	19	-27	-73	28	45	4.130363
Middle Frontal Gyrus	R	46	45	26	25	37	3.710981
Healthy controls							
Cuneus	R	17	18	-94	-2	2214	22.487026
Lingual Gyrus	L	18	-18	-97	-2		21.012764
Inferior Occipital Gyrus	L	18	-33	-88	-5		17.712637
Declive	L	-	-36	-73	-20		12.366952
Fusiform Gyrus	L	19	-45	-67	-11		11.670420
Fusiform Gyrus	R	19	45	-70	-11		7.877334
Angular Gyrus	L	39	-30	-55	37	252	5.831431
Middle Temporal Gyrus	L	22	-63	-46	4	197	5.011939
Superior Parietal Lobule	R	7	30	-55	43	151	5.006845
Middle Frontal Gyrus	R	46	54	32	22	84	4.364421
Middle Temporal Gyrus	R	21	63	-37	-11	44	4.320076
Inferior Parietal Lobule	R	40	45	-34	40	20	3.629347
Middle Frontal Gyrus	R	37	36	29	22	37	3.611630
Baseline > Neutral words							
Healthy controls							
Middle Occipital Gyrus	R	18	9	-97	16	4259	-8.445270
Middle Occipital Gyrus	L	19	-45	-82	16		-7.905782
Cuneus	L	19	-6	-79	31		-7.341609
Cuneus	L	18	-9	-94	19		-6.954923
Precuneus	L	7	-6	-70	55		-6.305066
Posterior Cingulate	L	31	-18	-61	16		-4.893944
Declive	L	-	-9	-73	-8		-6.961752
Fusiform Gyrus	L	37	-24	-49	-8		-6.533489
Precuneus	R	19	12	-82	40		-6.409410
Precuneus	R	7	12	-61	58		-4.719768
Precuneus	R	7	15	-73	49		-4.138207
Lingual Gyrus	L	18	-12	-61	4		-6.238555
Parahippocampal Gyrus	R	19	27	-46	-2		-5.100996
Culmen of Vermis	R	-	6	-61	1		-5.089694
Precuneus	L	7	-6	-55	52		-4.685173
Medial Frontal Gyrus	R	10	18	59	1	1909	-7.089081
Anterior Cingulate	L	-	-12	41	-2		-3.571726
Superior Frontal Gyrus	L	10	-12	53	-2		-4.014193

Lentiform Nucleus (Putamen)	L	-	-18	11	-2		-5.361804
Caudate (Caudate Head)	R	-	12	14	-2		-4.551436
Anterior Cingulate	L	25	0	20	-5		-4.271658
Medial Frontal Gyrus	L	11	-6	47	-11		-3.871681
Inferior Parietal Lobule	L	40	-66	-28	28	200	-6.298433
Superior Occipital Gyrus	R	19	42	-76	25	115	-4.950890
Claustrum	L	-	-39	-10	-2	711	-4.874508
Insula	L	13	-42	-76	25		-4.258756
Middle Temporal Gyrus	L	38	-39	11	-38		-3.963431
Superior Temporal Gyrus	L	38	-51	14	-23		-3.679601
Inferior Frontal Gyrus	L	47	-33	17	-17		-3.568850
Inferior Parietal Lobule	R	40	57	-25	31	163	-4.535203
Superior Frontal Gyrus	L	6	-21	8	55	82	-4.483413
Middle Frontal Gyrus	R	46	54	32	22	84	4.364421
Superior Temporal Gyrus	R	38	36	5	-14	182	-4.285243
Middle Frontal Gyrus	R	8	27	35	43	60	-4.171256
Middle Temporal Gyrus	R	21	51	-7	-14	101	-4.134885
Superior Temporal Gyrus	R	38	36	14	-38	76	-3.789847

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

Discussion

PI is a sleep disorder characterized by conditioned bedtime arousal and disturbing thoughts about the self (Harvey, 2005). 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 (Riemann e al., 2010). Our main goal in this study was to observe in what extent a hypothetical correlation between cognitive arousal and neurobiological indicators differs between PI patients and healthy individuals. 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 (Riemann et al., 2010).

It is consensual in the 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, there are other important brain areas with implications for the "self" which 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 show also 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 (Cavanna, & Trimble, 2006; Utevsky, Smith, & Huettel, 2014). There is some evidence associating superior frontal gyri with self-referential processing (Goldberg, Harel, & Malach, 2006). The superior and medial temporal cortices are intimately linked to retrieval of autobiographical memories (Squire, Stark, & Clark, 2004). 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 (Hoehn-Saric et al., 2004). Many of the regions we discussed have also 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) (Ochsner et al., 2004).

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 both related with their past and their future (Botzung et al., 2008). Insomnia 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 insomnia 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 (Marques, Gomes, Clemente, Santos, & Castelo-Branco, 2015).

Finally, when neutral words contrast are performed between the clinical and control groups, it is visible that PI patients show a generalized pattern of activation in brain areas very similar to those found in past/present and futures concern conditions. Besides, even more regions associated with DMN and self processing emerged. 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. 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 (Gusnard et al., 2001). 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 (Paulesu et al., 2009; Zhao et al., 2007). This finding is in line with the hypothetical state of arousal and hypervigilance typical of insomnia disorder. This finding might 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 occipital lobes (e.g., cuneus, lingual gyrus, occipital medial cortex) were systematically more activated in control individuals than in PI patients (Sreenivas, Boehm, Linden, 2012; Gonçalves, Marques, Lori, Sampaio, & Castelo-Branco, 2010). This finding might relate to the easiest detachment from introspective mode by healthy individuals. One should note that a study by Schlochtermeier et al. (2013) 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 (Whitfield-Gabrieli et al., 2011). 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 (2011) posit that it is expected that brain regions involved in self-awareness such as the precuneus are over-activated both during bedtime and NREM sleep in PI patients. Our results suggest that perhaps this arousal might be extensive 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 (Harvey, 2002; Ong, Ulmer, & Manber (2012). It seems that the manner in which PI patients cope with their negative cognitions might be more relevant than the content of own thoughts. When the participants of both groups filled out the list of words for fMRI, it was notorious that the core concerns were not significantly different.

Our study has some strengths, of which we highlight: we used a novel way to collect evoked responses at the fMRI scanner; the participants visualized idiosyncratic words, not a standardized list of predefined traits or words that they would have to decide whether applied to themselves or not; the total time the individuals were inside the fMRI machine

accounted for the robustness of the data; and before we carried out the study, we performed a pilot study to check whether the experiment was well adjusted to our aims and to confirm whether the paradigm containing the lists of words was being discriminative.

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 machine 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. Furthermore, 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 (Kazdin, 2010).

The continuity of this research line appears to be important. As such, for future studies we suggest replicating 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 it would also be interesting to assess effects on brain rhythms. Finally, one other point to be studied could be the administration of more psychological assessment measures to correlate further with activity in key regions-of-interest such as MPFC or precuneus. However, if this is carried out, one must have a large sample size to assure careful interpretation of the data to avoiding overinterpretation of correlational data (Vul, Harris, Winkielman, & Pashler, 2009); 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 hypothetical underlying DMN brain dysfunction and hyperactivity (Buysse et al., 2011).

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Conflict of Interest Statement

The authors declare that there are no conflicts of interest.

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Chapter 7

Unbalanced resting-state networks activity in psychophysiological insomnia*

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Highlights:

- Insomnia patients present impairments in some resting-states of the brain.
- These dysfunctions may aid to understand the insomnia´s phenomenology.

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 (van den Heuvel & Pol, 2010).

Within these resting-state networks, the brain "default mode network" (DMN) has been of particular interest (Buckner, Krienen, & Yeo 2013; Poldrack, Mumford, & Nichols, 2011). The DMN is characterized by a set of brain regions that increase their activity when an individual is not performing any attention or cognitive demanding task (Raichle et al., 2001). 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 (Whitfield-Gabrieli & Ford, 2012). 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 (Buckner, Andrews-Hanna, & Schacter, 2008). 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 (Buckner, 2012; Buckner et al., 2008).

The DMN is therefore well suited as a subject of investigation both in healthy and clinical populations (Anticevic et al., 2013; Broyd et al., 2009; Buckner et al., 2008; Greicius et al., 2003; Whitfield-Gabrieli & Ford, 2012). 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 (Anticevic et al., 2013; Broyd et al., 2009).

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 (AASM, 2005, 2014; APA, 2013) whose key feature is hyperarousal (Riemann et al., 2010). 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 mode network in PI given the clinical phenomenology of the disorder (Marques, Gomes, Clemente, Santos, & Castelo-Branco, 2015).

In general, neuroimaging studies on insomnia are lacking (Nofzinger, 2010, 2013; Nofzinger et al., 2004). Although there are some studies on DMN activity across sleep stages and sleep-wakefulness transitions (Koike, Kan, Misaki, & Miyauchi, 2011; Sämann et al., 2011; Wamsley, & Stickgold, 2011), only a few published studies consider the DMN or resting-state neural activity in insomnia. The investigation led by Hasler and colleagues (2013) 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 (Drummond et al., 2013). 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 (Huang et al., 2012). 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 (Buysse, Germain, Hall, Monk, & Nofzinger, 2011; Marques et al., 2015).

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 (Coutinho et al., 2014). 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 (Killgore, Schwab, Kipman, DelDonno, & Weber, 2013)

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. 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 (Riemann et al., 2010) and the resting-state might be an excellent simulator of what happens whenever the individual goes to bed every night in order to sleep (Marques et al., 2015). 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 and 5 sex- and age-matched healthy controls. 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

(AASM, 2005), 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 (cf. Table 1). The clinical features of the insomnia participants are shown in Table 2.

Table 1. Demographic characteristics of the total sample (N=10)

	Insomnia group (n=5)	Healthy controls (n=5)
	M (SD)	M (SD)
Age (years)	41.6 (8.7)	38.6 (7.1)
Education (years)	13.6 (3.0)	18.0 (1.5)
	n (%)	n (%)
Gender		
Male	2 (40)	2 (40)
Female	3 (60)	3 (60)

Note. M=Mean; SD=Standard Deviation

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).

Table 2. Clinical characteristics of the insomnia group

Insomnia subtype* (n /%)	
Initial	3/60%
Intermediate	5/100%
Terminal	3/60%
Non-refreshing sleep	3/60%
Frequency of complaints [nr of insomnia nights per week] (M ± SD)	4.20 ± 1.79
Duration of complaints [months] (M ± SD)	55.2 ± 39.2

* This is not mutually exclusive. The patients may be classified in more than one of these categories. *Note.* M = Mean; SD = Standard deviation

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 (Clemente, 2007/2013; Morin, 1993);

- *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 (Bastien, Vallières, & Morin, 2001; Clemente, 2007/2013);

- *Sleep Diary* – The sleep diary enables to obtain important indicators of subjective sleep perception (Clemente, 2006; Morin, 1993). 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., 2006) – 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 (Vaz-Serra et al., 2006). 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 (Long et al., 2008; van den Heuvel & Pol, 2010; Whitfield-Gabrieli & Ford, 2012). ICA is a model-free or data-driven method unlike the seed-based analysis which is a hypothesis-driven approach (van den Heuvel & Pol, 2010).

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 (2010). 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 (Formisano,

Esposito, Di Salle, & Goebel, 2004). 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 (van den Heuvel, M. & Pol, H. (2010), 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 (De Martino et al., 2007; Esposito et al., 2013; Goebel, Esposito, & Formisano, 2006). At group-level analyses we extracted 38 ICs components from each individual data set without loss of the dimensionality of the data (Kornelsen et al., 2013). The resulting ICs from the SogICA group level analysis, which showed high spatial similarity to RSNs (Jann, Kottlow, Dierks, Boesch, & Koenig, 2010; van den Heuvel, M. & Pol, H. (2010), 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 3).

Table 3. 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.

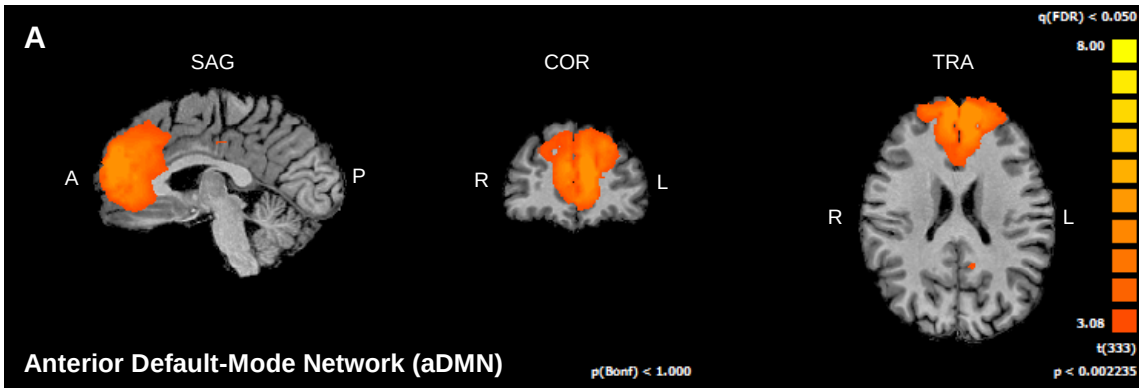
Note. M = Mean; SD = Standard deviation; SL = Sleep latency; WASO = Waking after sleep-onset; TST = Total sleep time; TIB = Time in bed; SE = Sleep efficiency; ISI = Insomnia Severity Index; DBAS-30 = Dysfunctional Beliefs and Attitudes About Sleep; DBAS-30[F1] = Beliefs about the effects of insomnia; 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.

Neuroimaging measures

In participants of both groups, using ICA analysis, we identified the most known sub-networks during rest (Jann, et al., 2010): 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.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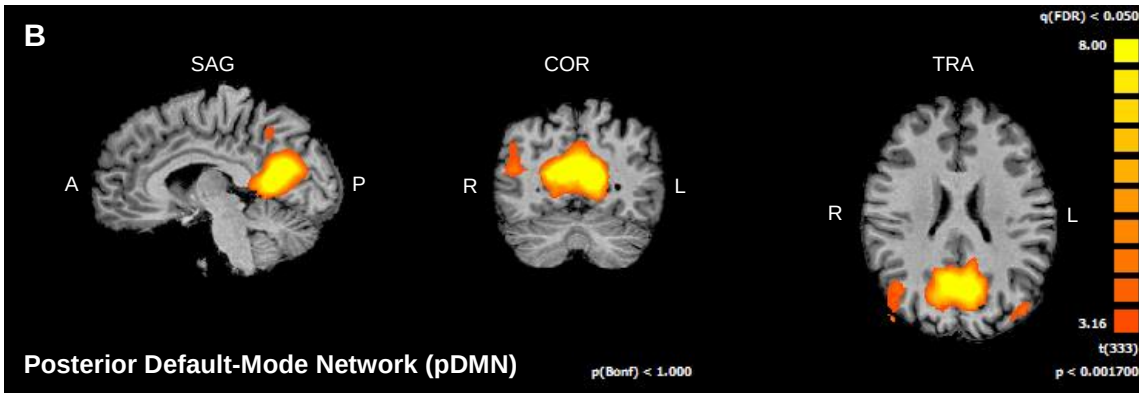
p < 0.002235
Anterior Default-Mode Network (aDMN)
p(Bonf) < 1.000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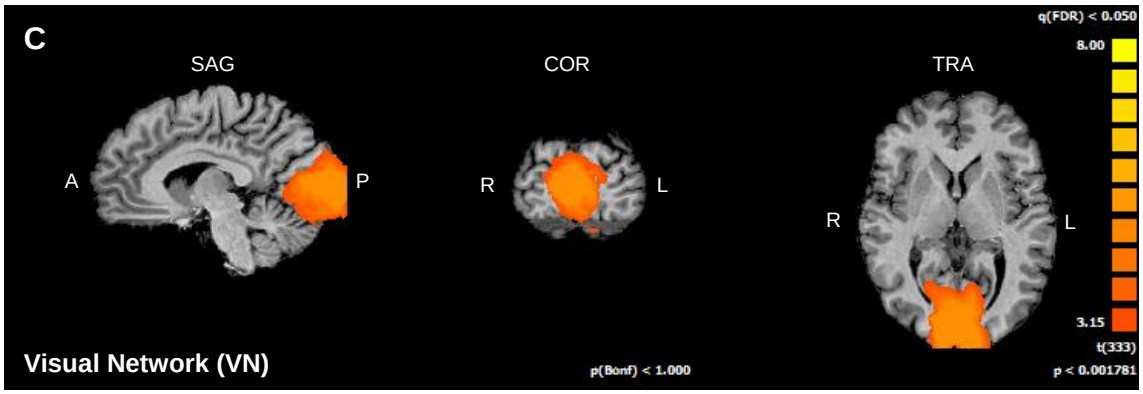
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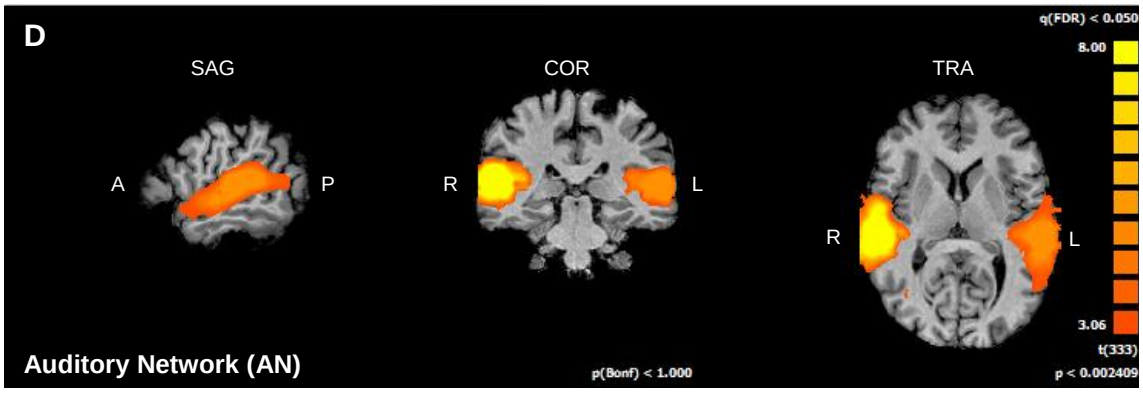
Visual Network (VN)
p(Bonf) < 1.000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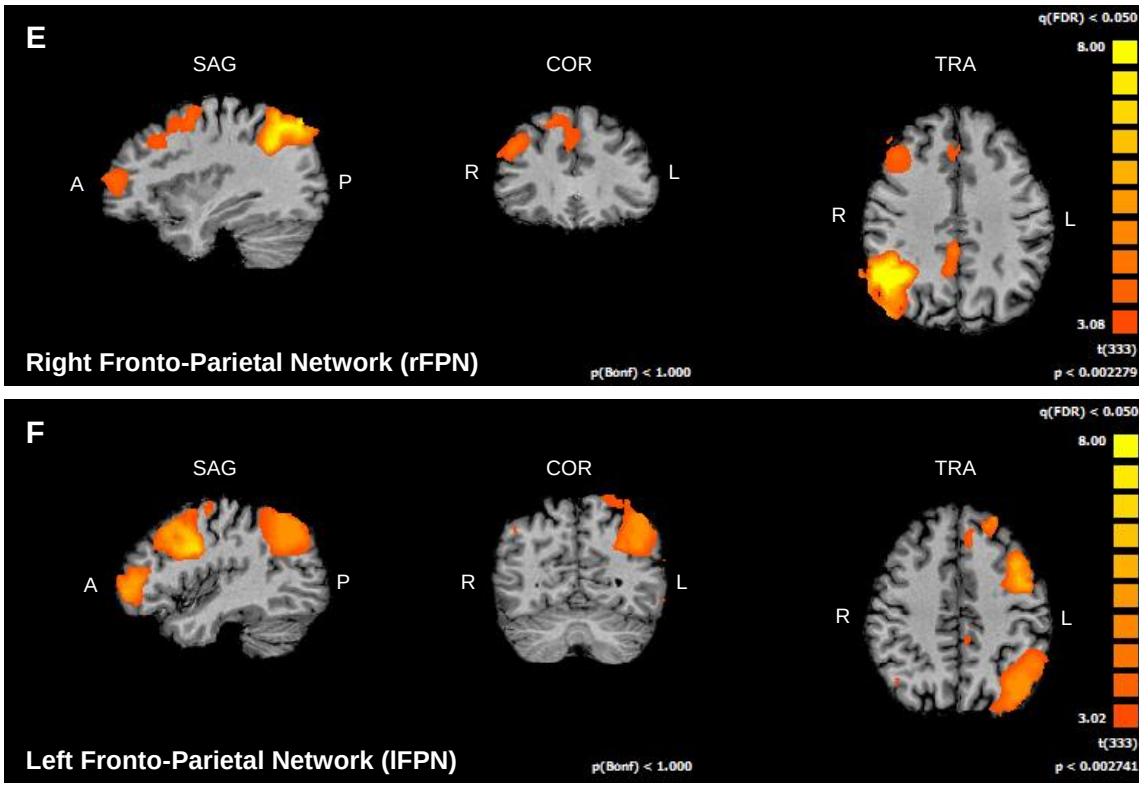
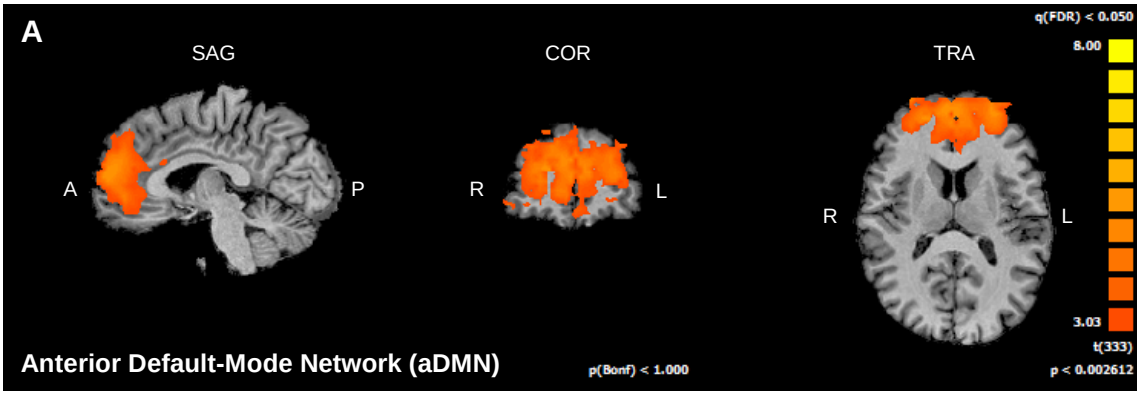


Figure 1. Resting-state networks activation in PI patients. A=aDMN, B=pDMN, C=VN, D=AN, E=rFPN, F=lFPN. Radiological display convention was used.

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.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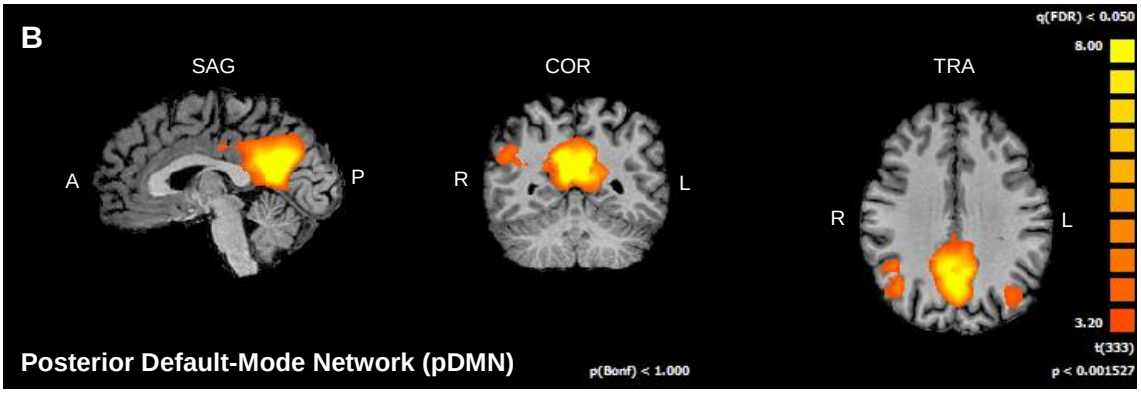
Anterior Default-Mode Network (aDMN)
p(Bonf) < 1.000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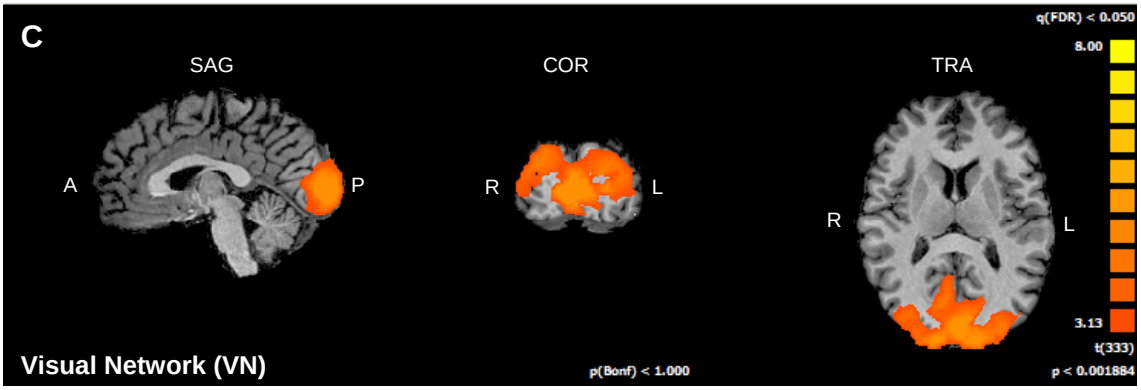
Posterior Default-Mode Network (pDMN)
p(Bonf) < 1.000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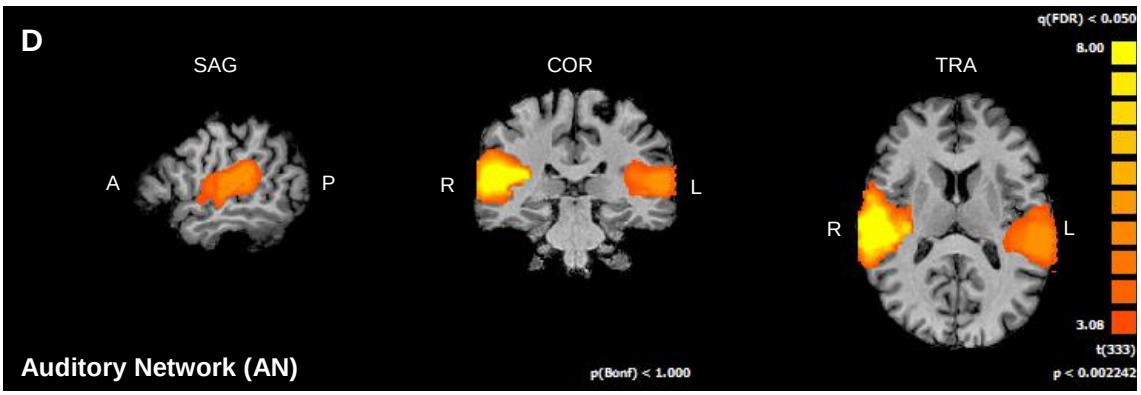
Visual Network (VN)
p(Bonf) < 1.000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Auditory Network (AN)
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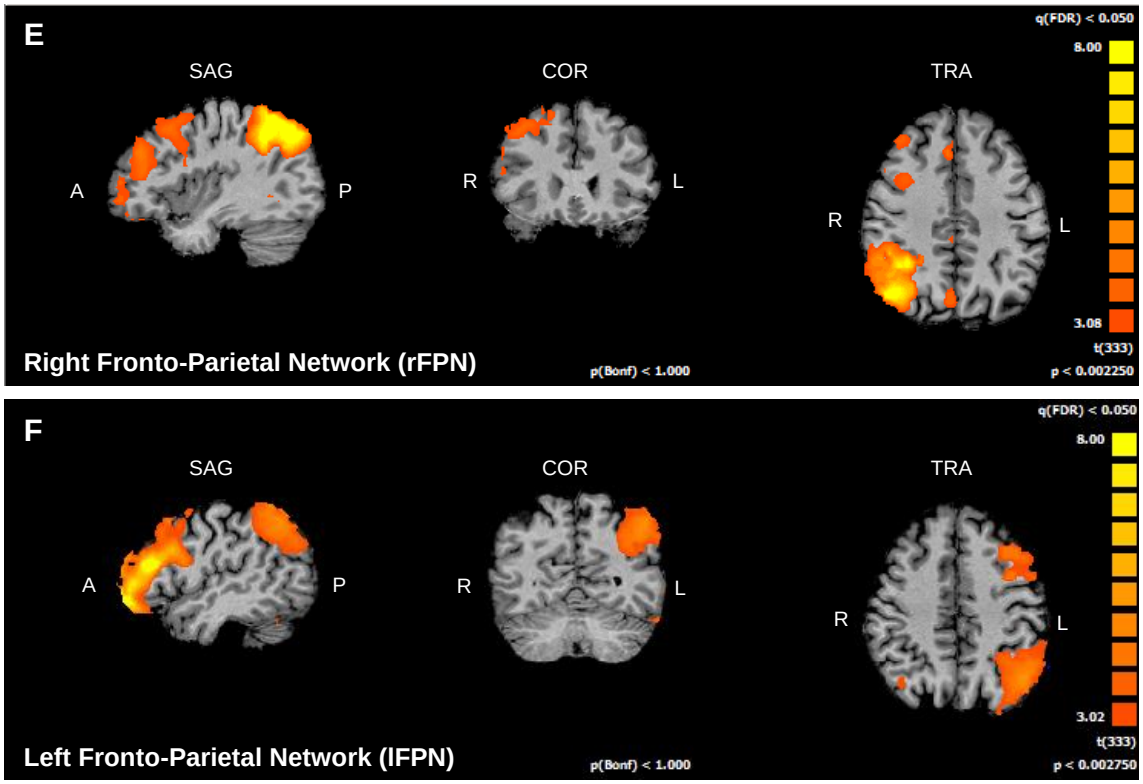
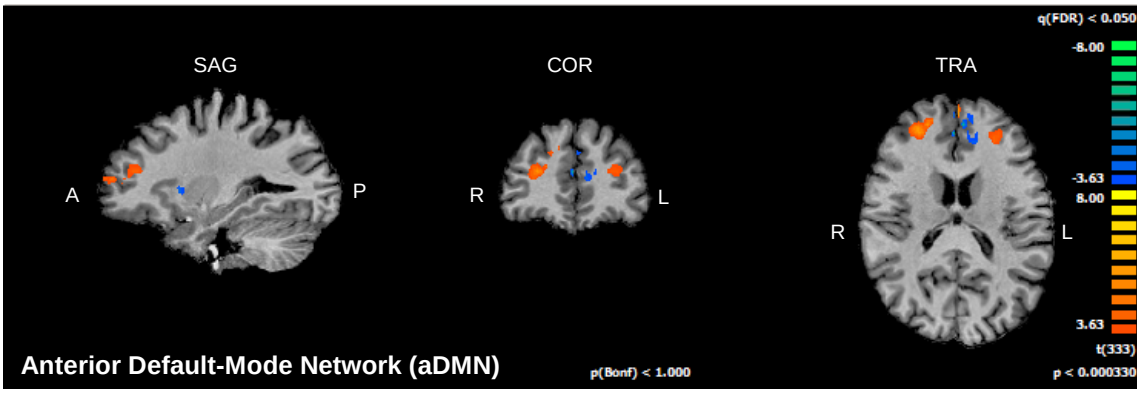
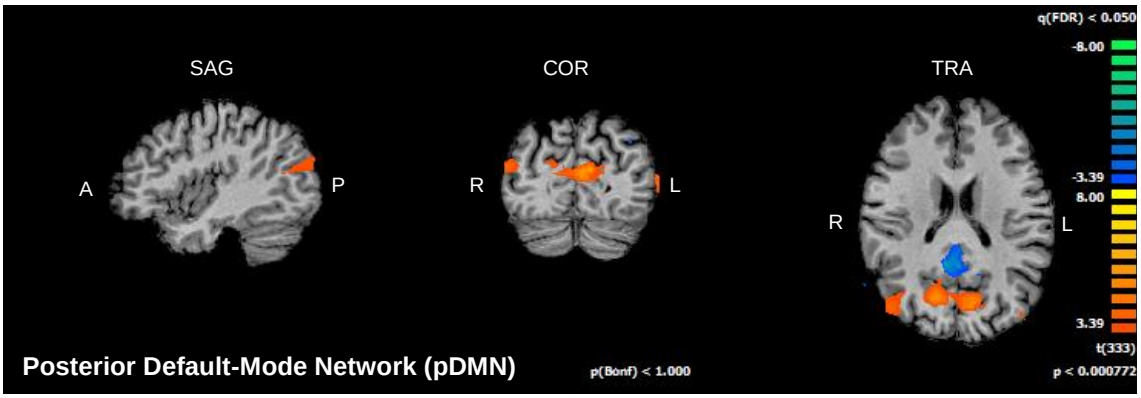


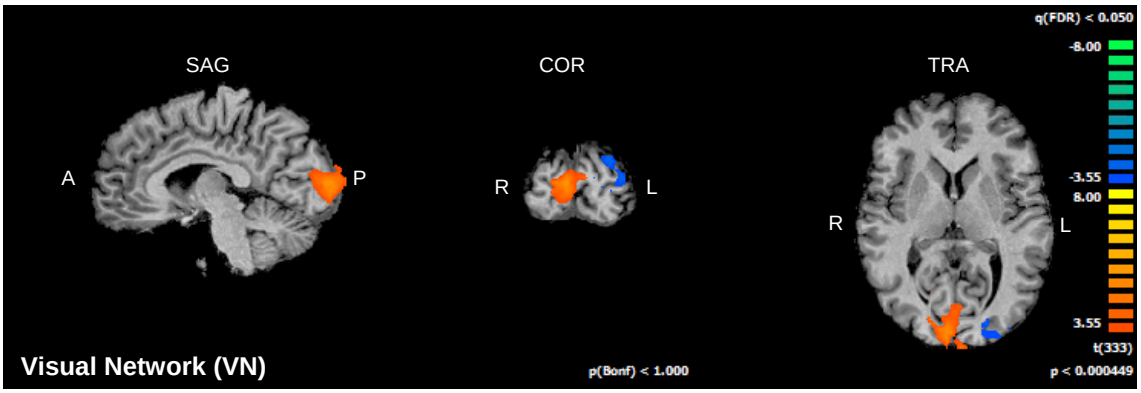
Figure 2. Resting-state networks activation in healthy-controls. A=aDMN, B=pDMN, C=VN, D=AN, E=rFPN, F=lFPN. Radiological display convention was used.

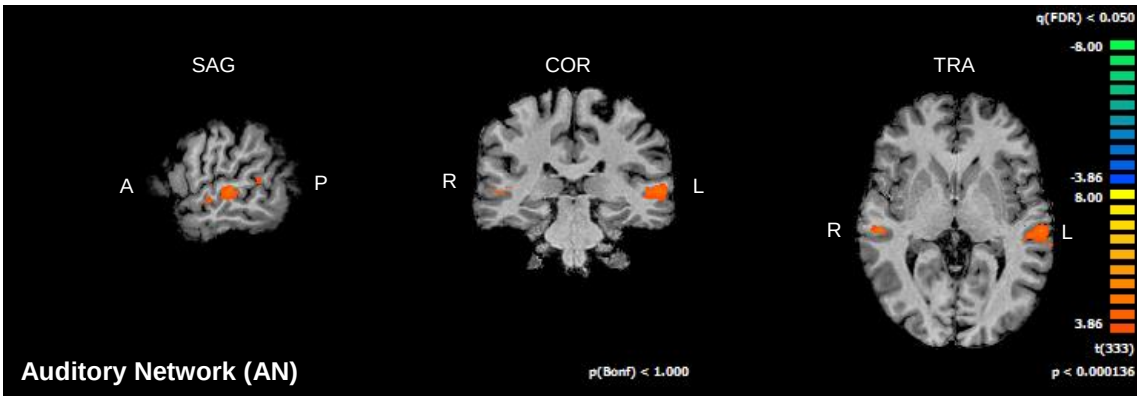
Contrasts between the patients group and the control group

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 4.


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
-8.00
-3.86
8.00
3.86
t(333)
p < 0.000136
Auditory Network (AN)
p(Bonf) < 1.000

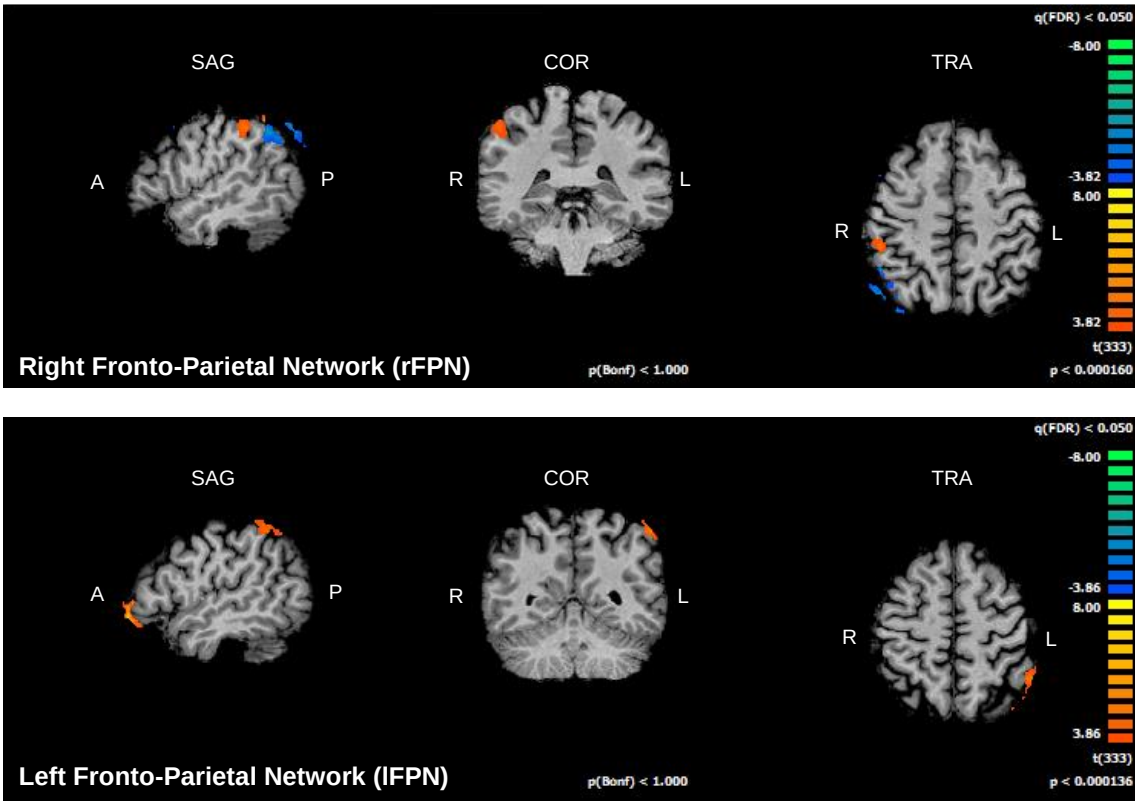


Figure 3. Contrast maps of different resting-state networks´ activation between PI patients and healthy-control participants. In warm colors are displayed the brain networks that are functionally more recruited in PI patients compared to healthy participants; in cool colors are displayed the brain networks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

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.

Table 4. 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.

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 (e.g., Lois, Linke, & Wessa, 2014). 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. This pattern of overactivity in both superior and medial prefrontal cortices may relate to an eventual cognitive maladaptive strategy to cope with disturbing thoughts. 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 (Franzen, Siegle, Jones, & Buysse, 2013). 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 (Ansfield, Wegner, & Bowser, 1996). 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 (Ong, Ulmer, & Manber, 2012) 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 (Buckner et al., 2008; van den Heuvel & Pol, 2010). This hyper-activity might be related with an increase in the episodic memory contents, in order to simulate future events (Schacter & Addis, 2009). 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. (2008) 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. (2003), 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. (2003); 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 (Lois et al., 2014). This finding is in line with the overall hypothesis of hyperarousal in insomnia (Riemann et al., 2010). The cognitive performance of PI patients and healthy individuals is identical; however, the neural underlying mechanisms appear to be altered (Drummond et al., 2003).

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. 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" (Marques et al., 2015). 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 (Killgore et al., 2003; Riemann et al., 2010). Similar to other clinical conditions, PI might be conceptualized also as a disorder that disrupts brain networks rather than single brain regions (van den Heuvel & Pol, 2010).

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Conflicts of interest statement

None of the authors declares conflicts of interest.

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Chapter 8

The effect of tailored cognitive-behavioral therapy on neurobiological function in insomnia patients: an fMRI study *

***** Marques, D., Gomes, A., Clemente, V., Santos, J., Duarte, I., Caetano, G., & Castelo-Branco, M. (2016). *The effect of tailored cognitive-behavioral therapy on neurobiological function in insomnia patients: an fMRI study*. Manuscript submitted for publication.

Highlights:

- Cognitive-behavioral therapy normalizes brain impaired activity in insomnia
- Default network is reestablished after non-pharmacological intervention for insomnia

Abstract

Background: Chronic Insomnia Disorder (CID) is one of the most prevalent sleep disorders. One of the main features of CID is the striking dysfunctional cognitive activity which interferes with duration, depth, and overall quality of sleep. CID patients are often disturbed by thoughts related to the self (i.e., ruminations and worries) both during daytime and nighttime. **Methods:** Two repeated-measure experiments were performed, in this two-case study report: in Experiment 1, we investigated to what extent successful tailored cognitive-behavioral therapy for insomnia (CBT-I) modified the neural activity pattern observed before the intervention, when two patients (free of psychiatric drugs) were exposed to idiosyncratic stimuli pertaining to past/present and future concerns; in Experiment 2, comprising the same participants, we aimed at investigating whether CBT-I would reflect in activation changes of the main resting-state brain networks, in particular, the default-mode network (DMN). **Results:** Regarding Experiment 1, our findings suggest that successful CBT-I seems to normalize brain overactivity. This finding is enhanced by the visible attenuation of activity in brain regions implicated in self-referential processing (such as the precunei and prefrontal cortex) and also by the pattern of enhanced activation within visual areas across all experimental conditions. Concerning the resting-state experiment (Experiment 2), modifications were found in the anterior component of the DMN, in the visual network, and in the auditory network, after successful CBT-I. The most notable result was a decreased activity in the medial prefrontal cortex from pre- to post-intervention. This finding suggests that cognitive overactivity, associated with increased prefrontal activity before treatment, might be attenuated, at least partially, by CBT-I. **Conclusion:** In sum, the promising results from these two longitudinal experiments support the idea that successful psychological interventions for insomnia may translate into modifications of neural activity: in particular, DMN deactivation, expected in healthy individuals, was observed after the psychological intervention.

Keywords: Chronic insomnia; cognitive-behavioral therapy for insomnia (CBT-I); default-mode network; resting-state; self; fMRI.

Introduction

Chronic insomnia disorder (CID) is one of the most prevalent sleep disorders which may develop solely or in association with other clinical disorders such as psychiatric ones (AASM, 2005, 2014; APA, 2013; Drake & Roth, 2006; Taylor, Lichstein, Durrence, Reidel, & Bush, 2005). It is well known that CID patients have a widespread pattern of cognitive activation—inferred by clinical interviews, self-report measures, and reported associations with various brain regions´ activation assessed through different neuroimaging techniques—that consequently disrupts the amount and the quality of sleep (Harvey, 2005; Mitchell, Mogg, & Bradley, 2012). Likewise, the sleeping time and the remaining in bed may constitute aversive stimuli for the patients, maintaining the insomnia complaints and consequently the vicious circle of chronic insomnia (Marques, Gomes, Clemente, Santos, & Castelo-Branco, 2015a; Morin, 1993; Riemann et al., 2010). There is compelling evidence suggesting that this cognitive arousal is closely related to rumination and worrying that, albeit idiosyncratic for each individual, share two common features: (1) the negative emotional valence, and (2) the central role of the self (Takano, Lijima, & Tanno, 2012). In the psychological sciences it is posited the distinction between rumination and worry as different psychological constructs, albeit related (Carney, Harris, Moss, & Edinger, 2010; O´Kearney & Pech, 2014; Watts, Coyle, & East, 1994). Also, affective and cognitive neurosciences have been interested in studying the brain regions associated with the self. Several cortical areas have been implicated, such as the prefrontal medial cortex, the anterior and posterior cingulate cortices, the precuneus, the medial temporal cortex, the bilateral inferior parietal lobules, among other regions (Buckner, Andrews-Hanna, & Schacter, 2008; Gusnard, Akbudak, Shulman, & Raichle, 2001; Johnson et al., 2002; Moran, Macrae, Heatherton, Wyland, & Kelley, 2006; Raichle et al., 2001; Whitfield-Gabrieli & Ford, 2012; Whitfield-Gabrieli et al., 2009; Yoshimura et al. 2009).

Over the last decades there has also been an interest in studying neurobiological correlates of psychological interventions targeted at distinct neuropsychiatric disorders (Roffman, Marci, Glick, Dougherty, & Rauch, 2005)—in particular depressive and anxiety disorders (Linden, 2006). According to some authors, CID appears to be a suitable clinical condition to be investigated with the aid of neuroimaging both in terms of assessment and treatment purposes (Marques, Gomes, Clemente, Santos, & Castelo-Branco, 2014; Riemann, Kloepfer, & Berger, 2009; Spiegelhalder, Regen, Baglioni, Riemann, &

Winkelman, 2013). Similarly, there has been a growing interest in studying the fundamental neurobiological basis of insomnia, particularly through functional magnetic resonance imaging (fMRI; see e.g., Marques et al., 2014; Nofzinger, 2013; Spiegelhalder, Regen, Baglioni, Riemann & Winkelman, 2013). A recent case-series study has shown that CID patients exhibited an increased activation in self-referential processing areas when they visualized personal concerns, compared with a group of healthy individuals. In addition, it was observed that these patients showed altered functioning in brain regions related to the default-mode network (DMN) (Marques et al., 2015c). In a similar study, with visual emotional stimuli (i.e., self-reference traits), but including depressive patients, decreased activation in the medial prefrontal cortex and the ventral anterior cingulate cortex were observed after successful completion of cognitive-behavior therapy for depression (Yoshimura et al. 2013). Another study with generalized anxiety disorder patients, which used a pre-posttest fMRI paradigm, observed decreased activations in prefrontal areas, in the striatum, insula and paralimbic regions after patients underwent psychopharmacology treatment (i.e., citalopram). The study used an fMRI paradigm comprising worry-related words displayed visually (Hoehn-Saric, Schlund & Wong, 2004), albeit the stimuli content was the same for each of the participants and therefore not individually tailored (the stimuli were not idiosyncratic).

Over the last decades, cognitive neuroscience has also devoted attention to a specific type of experimental paradigm widely used in fMRI studies—the resting-state experiment (RS-fMRI). Unlike traditional neuroimaging, RS-fMRI studies aim at observing the functional connectivity of brain networks when individuals are not performing any specific task. This seems a very suitable approach to study insomnia patients, as it simulates what is likely to happen when they are in bed trying to fall asleep every night (Marques, Gomes, Clemente, Santos, & Castelo-Branco, 2015b). One of the most studied resting-state networks is the DMN, whose principal functions relate to self-reflection comprising recollection of episodic memories, prospective memory, emotion processing, decision-making, and theory of mind (Raichle et al., 2001). The anterior and posterior medial and lateral cortices—in particular, ventral and dorsal medial prefrontal cortices (MPFC), posterior cingulate cortex (PCC), precuneus, and parietal inferior lobes—are suggested to be the core areas. Resting-state and chiefly DMN dysfunctions have been studied in several clinical disorders (Broyd et al., 2009; Whitfield-Gabrieli & Ford, 2012). As far as we

know, there is only a single empirical study whose principal findings directly suggest that there might be an abnormal DMN activity in insomnia patients (Marques et al., 2015d).

Cognitive-behavioral therapy for insomnia (CBT-I) is a solid non-pharmacological treatment comprising several evidence-based intervention techniques (Espie & Kyle, 2012). Despite its proven efficacy and effectiveness, some limitations exist concerning its dissemination to applied settings (Espie, 2009; Vitiello, McCurry, & Rybarczyk, 2013). Moreover, the conditions in which the standard treatments are tested in randomized controlled trials are difficult to transfer to daily clinical practice. In this sense, the standard treatments are often adapted and tailored taking into account the diverse clinical constraints and comorbidity among patients (Haynes & Bootzin, 2010). As CBT-I influences biological, circadian, cognitive and affective variables in order to decrease insomnia symptoms, it may be considered a psychobiologic therapy (Espie & Kyle, 2012). Thus, it is useful to explore eventual neurobiological modifications induced (at least partially) by CBT-I (Marques et al., 2014).

In the current paper we present two fMRI longitudinal experiments: In Experiment 1, we tested the general hypothesis that CBT-I might attenuate the overall pattern of hyperarousal observed in CID patients when they visualized diverse stimuli (words regarding to past/present and future worries and neutral words); additionally, we hypothesized that some brain regions such as visual areas would be more activated in the post-CBT-I, resembling the neural patterns observed in healthy-controls as in the study by Marques et al. (2015c). In Experiment 2, we explored the hypothesis that a tailored CBT-I might revert the altered functioning of brain networks previously identified in these patients, when at rest (Marques et al., 2015d), as related to decreased insomnia symptomatology and concomitant improvement of overall quality of life.

Methods

Participants

Two right-handed male patients (ages: 43 and 53 yrs; years of education: 9 and 16) diagnosed with psychophysiological insomnia according to ICSD-2 (AASM, 2005) — currently named chronic insomnia disorder (ICSD-3, AASM, 2014) —and who did not meet criteria for another untreated sleep or psychiatric disorder, accepted voluntarily to take part in the study. The two patients reported in average 5±1.4 insomnia episodes/nights

per week and a mean duration of complaints of 30.0±16.9 months. Both participants gave their informed written consent to participate in the study. The study was approved by the medical ethical committee of the Coimbra University Hospital Center (CHUC), where our patients were recruited, and in accordance to the Declaration of Helsinki.

Materials

In this study we used the following self-report measures:

- Insomnia Severity Index – ISI (Bastien, Vallières, & Morin, 2001; European Portuguese Version by Clemente, 2007, 2013);
- Dysfunctional Beliefs and Attitudes About Sleep – DBAS-30 (Morin, 1993; European Portuguese Version by Clemente, 2007, 2013);
- World Health Organization Quality of Life measure – WHOQOL–Bref (The WHOQOL Group, 1998; European Portuguese Version by Vaz-Serra et al., 2006), respectively.
- Sleep Diary (Morin, 1993; European Portuguese Version by Clemente, 2006) during 1 week (7 nights).

Procedure

Patients were recruited at the Sleep Medicine Center of Coimbra University Hospital Center (CHUC), Portugal. Both participants met the following inclusion 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 Centre, first, all cases are evaluated in a general sleep consultation; after this process, the patient is forwarded to a specific specialty; (2) age ranging from 18 to 60 years; and (3) exclusion of untreated psychiatric or other sleep disorders that could explain fully the insomnia diagnosis. Moreover, for this study, we selected patients who were not taking medication at the beginning of the treatment and never took medication during the course of the CBT-I treatment. Patients were assessed two times: at the pre-treatment and at the post-treatment phases. The moment of the post-treatment phase was variable, depending on the patient progression along the treatment. The maximum number of therapy sessions that patients assisted in order to be evaluated in the post-treatment phase was 12 (including the two sessions aimed

to psychological assessment and case formulation). Notwithstanding, the patients could maintain the sessions beyond the 12th session. The CBT-I sessions occurred on a monthly basis. We assumed that for re-evaluation purposes, 12 monthly sessions would be enough to see results (≈1 year of treatment). Even counting with missing sessions and other eventualities, the quantity of the sessions is appropriate: according to the literature, the mean number of CBT-I sessions is around 6-8 (excluding follow-up), albeit on a weekly or fortnightly basis (Troxel, Germain, & Buysse, 2012).

Psychological intervention

The psychological intervention was partially structured, even so being idiosyncratic to the patients` insomnia problems (Espie & Brooks, 1989). The selection of the used therapeutic interventions was performed in accordance to the best scientific evidence for insomnia´s treatment. The privileged clinical strategies were the stimulus control procedure, the relaxation training, the cognitive restructuring techniques, the sleep restriction technique and sleep hygiene psychoeducation (Morgenthaler et al., 2006). On average, 10 psychotherapy sessions were performed, accounting for the first two sessions that were dedicated to structured psychological and clinical assessment.

fMRI stimuli and task

The experimental design of Experiment 1 was based on the research by Marques et al. (2015c). 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 words were generated by own participants, and guided by the first author. 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) (Marques et al., 2015c).

Pertaining to experiment 2, we carried out a resting-state study. 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 (Marques et al., 2015d).

Image data acquisition

Anatomical and functional images were acquired with a Siemens MAGNETON Trio 3.0 Tesla at the ICNAS (Institute of Nuclear Sciences Applied to Health, Portugal), with a standard 12 channel head coil. The participants underwent structural imaging (MPRAGE – magnetization prepared rapid gradient echo) and fMRI, after completion of a priori safety questionnaire to assess whether they met the requirements to undergo MR imaging. 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. The visual stimuli (i.e., words) were programmed using the software MatLab© (MathWorks, 2012a).

For both experiments, functional images were acquired within the same scanning session, and one structural scan was performed. The structural scan (MPRAGE) had the following parameters: 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.

Blood Oxygenation Level Dependent images were collected. In Experiment 1, 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. Regarding Experiment 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

Neuroimaging data were pre-processed and analyzed using BrainVoyager QX 2.6™ [Brain Innovation BV, Maastricht, The Netherlands] (Goebel, 2012). Structural volumes were corrected for intensity inhomogeneities and the brain was segregated from head tissue and transformed into Talairach stereotaxic space. The preprocessing of fMRI data included: 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 Experiment 1, concerning the whole-brain analysis, we ran a fixed effects general linear model (FFX-GLM) analysis (see Marques et al. 2015c): 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 FFX 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 ($q < 0.01$). The Talairach coordinates and the information about the brain clusters were extracted with NeuroElf (http://neuroelf.net), and labeling of brain peak activation clusters

was performed with 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 used corresponds to a cortex inflation of one of the insomnia patients.

For Experiment 2, the data preprocessing step included slice-scan-time corrections, temporal filtering and motion-correction. We applied also spatial smoothing (8mm) and transformed the data into Talairach space. When the data were clean and adjusted we performed a cortex-based independent component analysis (ICA) to extract 48 independent components for each subject (see Marques et al. 2015d, for full details). We used the fast ICA algorithm for the single-subject level (first-level) analysis and the self-organizing group ICA (SogICA) algorithm for the two-subject-level (second-level) analysis (Esposito et al., 2005; Goebel, Esposito, & Formisano, 2006). Individual ICs were inspected to identify the presence, within each subject, of components with higher spatial correlation with known and validated RSN templates (van den Heuvel, M. & Pol, H. (2010), with an emphasis on the DMN, whilst ensuring these ICs derived from BOLD signal through the ICA fingerprint method, as implemented in BrainVoyager QX. For the two-subjects' analysis we chose to extract only 38 components, discarding the ten most Gaussian-like components. Correction for multiple comparisons was performed with a False Discovery Rate (FDR) correction ($q < 0.05$). To identify and label the Talairach coordinates of the brain´s peak activation, we used the Talairach Client - Version 2.4.3.

The IBM SPSS Statistics™ Version 22 (IBM, SPSS, Chicago, IL) was used to calculate descriptive statistics.

Results

Sleep and self-report measures

According to the self-report measures we used, we observed that after CBT-I the insomnia severity, the endorsement of dysfunctional beliefs about sleep, and the subjective quality of life indicators improved compared with the moment before the psychological therapy. The same was observed with the subjective sleep indicators obtained from sleep

diaries; the SL, the WASO, the TST, the TIB, and SE showed a clear improvement at post-treatment evaluation (cf. Table 1).

Table 1. Sleep log and self-report measures

	Before CBT-I (n=2)	After CBT-I (n=2)
	Mean ± SD	Mean ± SD
SL (min.)	37.0 ± 41.0	9.5 ± 0.7
WASO (min.)	77.0 ± 11.3	2.0 ± 2.8
TST (min.)	356.0 ± 105.6	383.5 ± 51.6
TIB (min.)	271.5 ± 38.8	428.5 ± 37.4
SE (%)	0.54 ± 0.35	0.90 ± 5.6
ISI	19.5 ± 6.36	3.0 ± 4.2
DBAS-30	5.26 ± 0.04	2.65 ± 0.4
WHOQOL-Bref overall	68.7 ± 8.8	81.2 ± 8.8
WHOQOL-Bref [D1]	44.6 ± 2.5	89.2 ± 15.1
WHOQOL-Bref [D2]	72.9 ± 8.8	85.4 ± 14.7
WHOQOL-Bref [D3]	70.8 ± 41.2	87.5 ± 17.6
WHOQOL-Bref [D4]	75.0 ± 13.2	76.5 ± 6.6

Note. CBT-I = Cognitive-behavioral therapy for insomnia; SD = Standard deviation; SL = Sleep latency; WASO = Waking after sleep onset; TST = Total sleep time; TIB = Time in bed; SE = Sleep efficiency; 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.

Neuroimaging measures

Experiment 1

Brain areas recruited for past/present condition before CBT-I > past/present condition after CBT-I

Concerning the *past/present* condition, we observed that "before CBT-I" the bilateral cunei and the left uncus were significantly more activated comparatively to the "after CBT-I" condition. On the other hand, after CBT-I, several brain regions exhibited

pronounced activation, in particular, the bilateral fusiform gyri, the bilateral precunei, the left angular gyrus, the right middle occipital gyrus, the left middle temporal gyrus, and the right precentral gyrus. (cf. Figure 1). For details see Table 2.

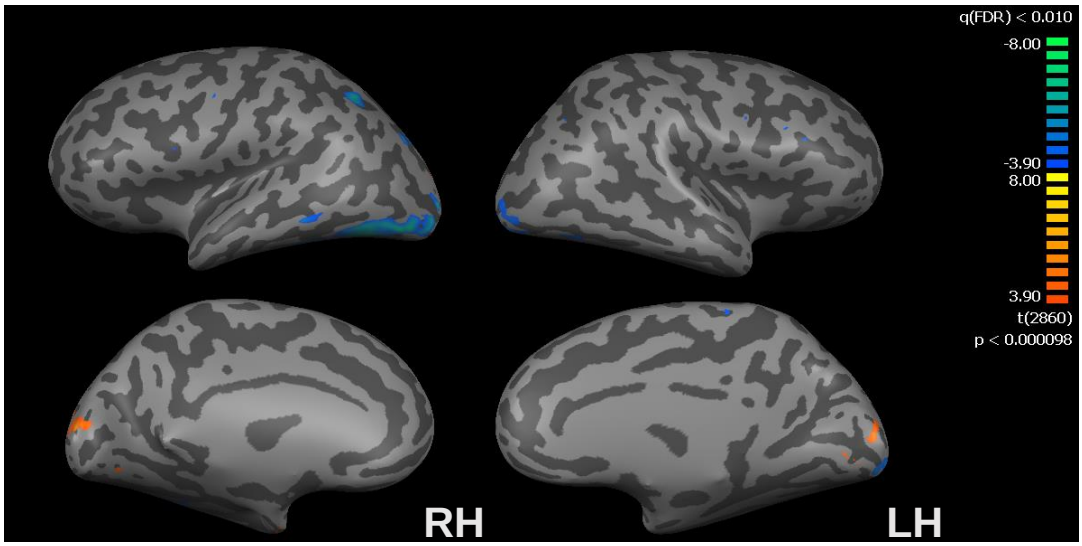

Figure 1 – Brain regions more activated before CBT-I (warm colors) than after CBT-I when it is analyzed the contrast pertaining to neural activation of past/present activating self-related words. Brain regions more activated after CBT-I are presented in cool colors. RH=right hemisphere; LH=left hemisphere. Radiological display convention was used.

Table 2. Talairach coordinates of activated clusters regarding past/present words

		Talairach coordinates					
Region	Hemisphere	BA	x	y	z	Cluster size (k)	*t*-value
Past/present words							
*Before CBT-I > After CBT-I**							
Cuneus	L	17	-9	-94	7	134	6.681372
Cuneus	R	18	9	-88	13		5.189012
Uncus	L	38	-21	5	-35	24	5.213591
After CBT-I > Before CBT-I							
Fusiform Gyrus	L	19	-33	-79	-11	464	-7.320926
Angular Gyrus	L	39	-27	-58	34	46	-6.509027
Precuneus	L	31	-24	-73	22	24	-6.184945
Middle Occipital Gyrus	R	18	27	-91	4	149	-6.079915
Middle Temporal Gyrus	L	21	-63	-40	-2	25	-5.608497
Fusiform Gyrus	R	19	39	-67	-11	24	-4.780194
Precuneus	R	7	24	-61	31	28	-4.444017
Precentral Gyrus	R	6	48	-1	34	20	-4.428421

Note. R=Right hemisphere; L=Left hemisphere; BA=Brodmann Area. Minimum size of clusters=20.
*In order to identify the cunei in both hemispheres as shown in Figure 1, the following parameters in NeuroElf were used: ('minsize'=20, 'localmax'=100 and 'localmin'=90).

Brain areas recruited for future condition before CBT-I > future condition after CBT-I

Concerning the *future* condition, we observed that using a FDR correction of q(0.01) there were no brain regions more activated comparatively to "after CBT-I" condition. On the other hand, after CBT-I, several brain regions exhibited pronounced activation, in particular, the left inferior occipital gyrus, the bilateral fusiform gyri, the right middle occipital gyrus, and the left inferior frontal gyrus (cf. Figure 2). For details see Table 3.

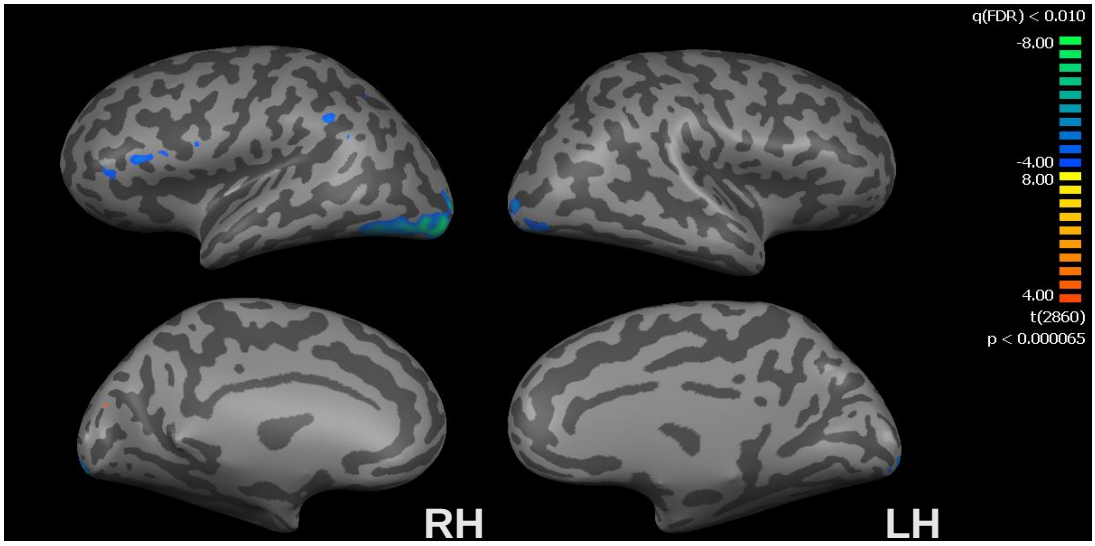

Figure 2 – Brain regions more activated before CBT-I (warm colors) than after CBT-I when it is analyzed the contrast pertaining to neural activation of future self-related words. Brain regions more activated after CBT-I are presented in cool colors. RH=right hemisphere; LH=left hemisphere. Radiological display convention was used.

Table 3. Talairach coordinates of activated clusters regarding future words

		Talairach coordinates					
						Cluster size	
Region	Hemisphere	BA	x	y	z	(k)	*t*-value
Future words							
After CBT-I > Before CBT-I							
Inferior Occipital Gyrus	L	18	-30	-91	14	546	-8.931306
Fusiform Gyrus	L	19	-33	-79	-14		-7.409595
Declive	L	-	-15	-91	-17		-6.502111
Fusiform Gyrus	R	37	-45	-61	-11		-5.629869
Middle Occipital Gyrus	R	18	24	-88	4	136	-5.741570
Inferior Frontal Gyrus	L	45	-57	14	19	41	-4.936071

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

Brain areas recruited for neutral condition before CBT-I > neutral condition after CBT-I

Concerning the *neutral* condition, we verified that "before CBT-I" several brain areas such as the bilateral middle frontal gyri, the bilateral precuneus, and the left superior frontal gyrus were significantly more activated comparatively to the "after CBT-I" condition. On the other hand, after CBT-I, several brain regions exhibited pronounced activation, in particular, the left inferior occipital gyrus, the right middle occipital gyrus,

the left fusiform gyrus, and the left inferior frontal gyrus. (cf. Figure 3). For a detailed list of brain regions see Table 4.

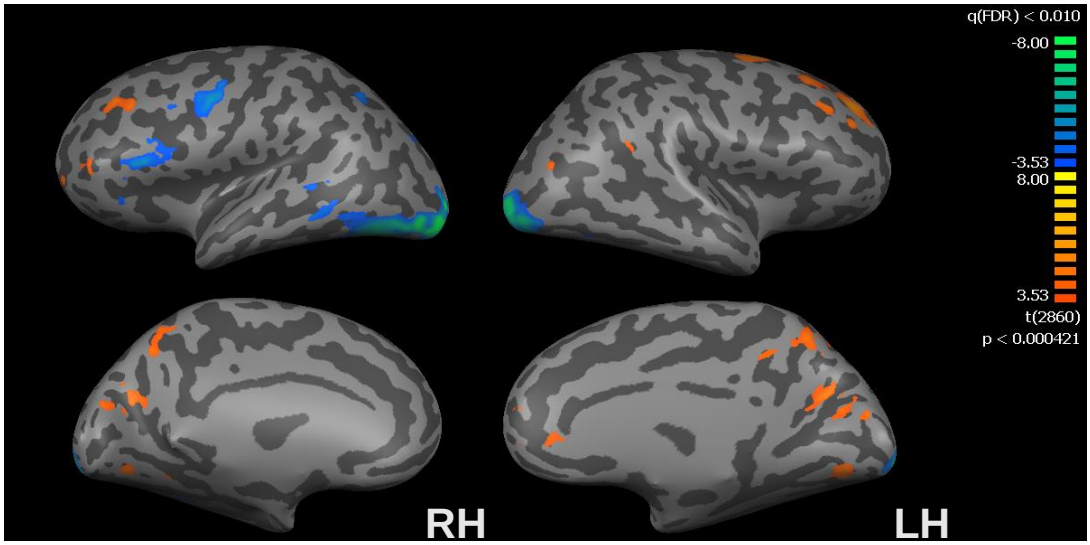

Figure 3 – Brain regions more activated before CBT-I (warm colors) than after CBT-I when it is analyzed the contrast pertaining to neural activation of neutral words. Brain regions more activated after CBT-I are presented in cool colors. RH=right hemisphere; LH=left hemisphere. Radiological display convention was used.

Table 4. Talairach coordinates of activated clusters regarding neutral words

			Talairach coordinates				
Region	Hemisphere	BA	x	y	z	Cluster size (k)	*t*-value
Neutral words							
Before CBT-I > After CBT-I							
Middle Frontal Gyrus	R	9	30	35	34	278	6.270286
Superior Frontal Gyrus	L	10	-21	50	4	40	5.542151
Precuneus	R	31	18	-61	25	104	5.259617
Cerebellar Tonsil	L	-	-42	-52	-35	48	5.228975
Precuneus	L	7	-3	-61	49	125	5.088202
Middle Frontal Gyrus	L	9	-30	32	40	35	5.081700
Precuneus	L	31	-15	-61	22	29	4.725729
Culmen	R	-	12	-67	-5	47	4.668866
Lingual Gyrus	L	19	-18	-67	-8	25	4.589840
After CBT-I > Before CBT-I							
Inferior Occipital Gyrus	L	37	-21	-97	-8	871	-10.771976
Inferior Occipital Gyrus	L	18	-33	-85	-11		-8.780780
Fusiform Gyrus	L	37	-39	-61	-11		-7.445870
Fusiform Gyrus	L	19	-36	-73	-11		-7.359221
Middle Occipital Gyrus	R	18	21	-94	4	366	-8.425616
Precentral Gyrus	L	4	-48	-7	46		-6.434310
Inferior Frontal Gyrus	L	46	-51	26	16		-5.433775

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

For data regarding the contrast [neutral vs. baseline] before and after CBT-I separately consult Supplementary Material (i.e., Figure 1 and Table 1).

Experiment 2

In both conditions, before CBT-I and after CBT-I, it was possible to identify the best known sub-networks during rest (Jann, Kottlow, Dierks, Boesch, & Koenig, 2010): aDMN (anterior default-mode network), pDMN (posterior default-mode network), VN (visual network), and AN (auditory network).

Resting-state activity before CBT-I

Figure 2 (cf. Supplementary Material) displays the resting-state networks before both CID patients begin psychological treatment—the aDMN is represented by a cluster activation in the medial prefrontal cortex, the pDMN is represented by activation in the precuneus and posterior cingulate, the VN is represented by the activation in the occipital lobe, and the AN is represented by the activation in the bilateral superior temporal lobes.

Resting-state activity after CBT-I

In Figure 3 (cf. Supplementary Material) the same resting-state networks are now displayed for the "after CBT-I" condition. The major clusters of neural activation are highly similar to those in Figure 1 pertaining to the "before CBT-I".

Pre-CBT-I vs. post-CBT-I contrasts

When we proceeded to the contrasts between both conditions, that is *Pre-CBT-I* > *Post-CBT-I* and *Pre-CBT-I* < *Post-CBT-I*, we found differences within three resting-state networks: aDMN, VN, and AN (cf. Figure 4 and Table 5). With regard to the aDMN, we observed an increase of activity in the left medial frontal gyrus for the pre-CBT-I condition. Concerning the VN, we found that the right lingual gyrus was more activated in the pre-CBT-I condition; on the other hand, at the post-CBT-I moment, patients presented more activation in the left lingual gyrus. Finally, regarding AN, we observed that the right superior temporal gyrus and the left inferior parietal lobule were more activated at the pre-CBT-I condition. For the remaining resting networks (i.e., pDMN) we did not find significant differences from pre- to post-psychological intervention.

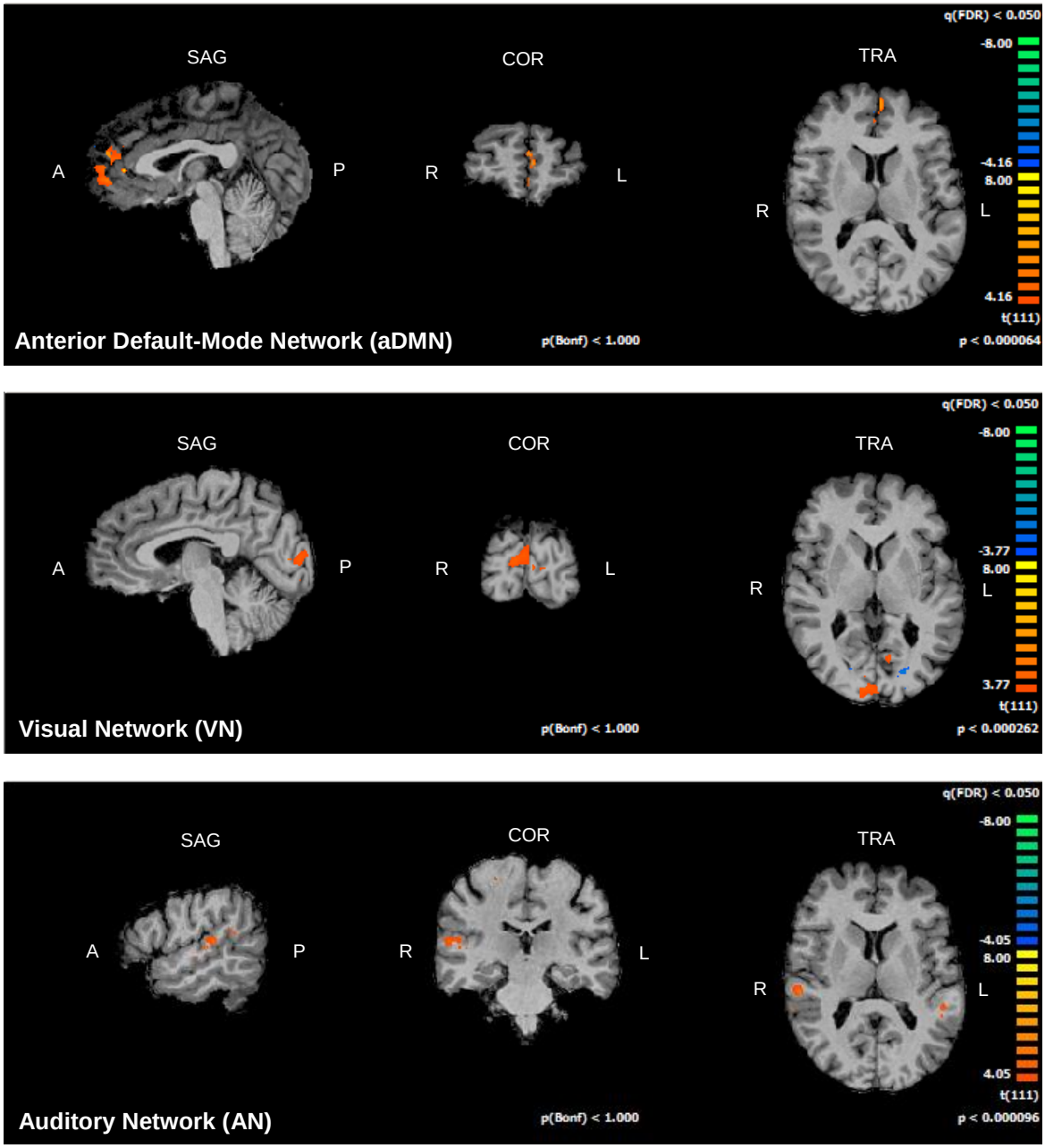

Figure 4. Contrast maps of different resting-state networks` functional activity which showed significant differences. In warm colors are displayed the brain regions that are functionally more connected in "before CBT-I" condition compared to "after CBT-I" condition; in cool colors are displayed the brain regions that are functionally more connected in "after CBT-I" condition. Radiological display convention was used.

Table 5. Resting-state contrast maps between "before CBT-I" and "after CBT-I" conditions

Region	Hemisphere	BA	x	y	z	*t*-value	*p*-value
Before CBT-I > After CBT-I							
aDMN							
Medial frontal gyrus	L	9	-1	53	18	13.837806	0.000000
VN							
Lingual Gyrus	R	17	8	-89	6	5.674643	0.000000
AN							
Superior Temporal Gyrus	R	41	56	-20	6	8.188150	0.000000
Inferior Parietal Lobule	L	40	-52	-32	42	4.956768	0.000003
After CBT-I > Before CBT-I							
VN							
Lingual Gyrus	L	18	-19	-71	-6	-5.931457	0.000000
Lingual Gyrus	L	17	-22	-80	3	-5.754686	0.000000
Culmen	L	-	-37	-53	-18	-4.970579	0.000002

Note. aDMN = anterior default-mode network; VN = visual network; AN = auditory network; R = Right hemisphere; L = Left hemisphere; BA = Brodmann Area.

Discussion

Although recognized that CID is characterized by abnormal levels of arousal in several domains (Riemann et al., 2010) no study had so far, to our knowledge, addressed how therapy influences the underlying neural systems. This study demonstrates that successful psychological interventions may translate into modifications of neural activity.

Our major aim in Experiment 1 was to investigate whether CBT-I could modify the dysfunctional levels of neural activation as observed when patients were exposed to idiosyncratic words related with ruminations (past/present) and worries (future). Our central hypothesis was that CBT-I would at least contribute partially to a decrease of activation in cortical brain areas related to self-processing; besides, we also expected that this decrease might be accompanied by an improvement in sleep logs indicators and subjective measures.

When participants were exposed to past/present idiosyncratic words, we observed that some brain areas such as the bilateral cunei and the left uncus were significantly more

activated “before CBT-I” comparatively to “after CBT-I”. Additionally, we observed that after CBT-I, a relatively well-defined spot of activation in the occipital and visual areas emerges. Interestingly, this finding might be probably explained by a new allocation process to the stimuli and related as well to endogenous attentional processes. It seems plausible that the activating stimuli (i.e., words related with the past/present) might have lost affective load and the patient focused more on the properties of the stimulus (i.e., color, reading). Among other brain regions more activated during the “after CBT-I” condition, we identified for example the precuneus which is a major brain implicated in self-related processing. As such, it is expected to be activated in normal individuals when they are confronted with stimuli related with episodic memory, for example (Buckner et al., 2008; Raichle et al., 2001). In our study, this might be eventually accounted through the process of reinterpretation of the stimuli. In this vein, it is important to outline that CBT-I has cognitive restructuring methods as relevant techniques, where reinterpretation and consequently loss of the excessive affective load related to the stimuli/situation is an intended aim.

Regarding the words about future worries, we do not observe differences when looking for brain areas which are significantly more activated “before CBT-I” compared with “after CBT-I” condition. After CBT-I, we observed that the fusiform gyri exhibited pronounced activation compared with the moment before CBT-I. Fusiform gyri are brain regions linked with face processing. Nonetheless, it is also known they are engaged during visual processing in general, including reading, in healthy populations (Cohen et al., 2002). In the scope of the current study, we posit the participants directed their attention to the visual stimuli. Besides, the left inferior occipital gyrus, the right middle occipital gyrus, and the left inferior frontal gyrus were also more activated after clinical intervention. Similar to the “past/present” condition, after CBT-I, the generalized pattern of occipital activation is visible.

In Experiment 2 we aimed to explore whether CBT-I might contribute to the stabilization or normalization of the dysfunctional recruitment of brain resting-state networks in insomnia patients. Our study, devoted preferentially to the neuroimaging of DMN´s activation, revealed a hyperarousal pattern within those areas. Perhaps the disengagement of default-brain activity is harder for insomnia patients as the self-related

cognitions are more stressful, attentional resources are not disengaged, and coping strategies are less effective.

Our findings support the idea that resting-state networks activity changes after CBT-I – this was observed in three out of four networks. The DMN is the most studied resting-state network of the brain. Given the functions attributed to this network and the clinical phenomenology of insomnia, we expected the DMN activity to be positively affected by psychological therapy. According to some studies, there is now some evidence (albeit scant) that DMN is dysfunctional in CID (Buysse, Germain, Hall, Monk, & Nofzinger, 2011; Marques et al., 2015c; Marques, et al., 2015d). In the current study, we observed that only the aDMN is significantly modified after CBT-I. Interestingly, a major component in CBT-I is the cognitive restructuring method, which is intended to identify and dispute irrational beliefs and cognitive schemes about sleep and insomnia. This process of cognitive restructuring is correlated with prefrontal cortex activation (including moral reasoning, decision making and executive functions). These results suggest that after psychological therapy the significant activity in the medial prefrontal cortex which was observed at the pre-treatment moment is attenuated after successful CBT-I enabling therefore the normalization of the putative cognitive hyperarousal. Moreover, it is well known that medial prefrontal cortex has an important role in self-referential tasks, decision making, memory and theory of mind, being one of the major hubs in the DMN (D´Argembeau et al., 2007; Euston, Gruber, & McNaughton, 2012; Gusnard, Akbudak, Shulman, & Raichle, 2001).

Finally, concerning to the AN, the greater activity in the superior temporal gyrus at the pre-CBT-I moment is somehow congruent with the general hyperarousal theory of insomnia (Riemann, 2010) outlining the emotional and sensory-motor reactivity typical of insomnia patients. More studies will now be needed to understand deeply, replicate or extend this finding.

We might infer that our results possibly reflect the consolidation of the therapeutic gains (Lilienfeld, Ritschel, Lynn, Cautin, & Latzman, 2014). Despite this, one should note that there was no between group comparison and the repeated measure design suffers form this intrinsic limitation.

One must note that our study (comprising both experiments) has additional important limitations. First, the reduced sample size (N=2) restricts the generalization of the findings,

and might increase the possibility of type I errors, albeit our aim was to test an exploratory and novel hypothesis. Because of the small number of patients, we could only perform a fixed-effects analysis (FFX), and not proceed with a random-effects analysis which would enable the generalization of the conclusions to the population. For instance, the obtained results in experiment 2 suggest that resting-state networks might be successfully modulated by CBT-I—we found evidence in three of the four networks identified. Increasing the sample size, it is expected that changes in remaining networks might be observed. Second, it was not possible to carry out this study recurring to a wait-list or a placebo control group, thus, we do not know for sure whether the obtained results reveal "real" modifications induced by CBT-I. Third, we did not use a manualized CBT-I but instead we adapted the clinical strategies to the specificities of each patient, thus fostering ecological validity.

For the future, it would relevant and interesting to replicate this study with a large sample of participants from different sleep medicine centers or, in its absence, from specialized sleep medicine consultations. Furthermore, it would be important to infer whether the results obtained from idiosyncratic CBT-I could be compared against the outcomes obtained from manualized CBT-I (typical of randomized controlled trials). Also, it would be very useful to assess several follow-up moments, even if doing so within a controlled case-study design. Finally, we emphasize that follow-up of case failures in CBT-I might open new avenues of research and deepen our understanding of neural correlates of insomnia, its psychological treatment, and its neural change mechanisms (Marques et al., 2014).

Cognitive and behavioral techniques applied to insomnia seem to modify the information processing related to the self. In this study, we found that the hyperarousal typically involved in CID decreased significantly after CBT-I, and consequently, several brain areas appears to normalize after successful intervention.

In summary, it is important to reinforce that our aim in this study was to approximate research and clinical practice. Thus, it is a study concerned with effectiveness rather than efficacy.

Conflicts of interest statement

None of the authors declares conflicts of interest.

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Supplementary Material

Title of the manuscript: The effect of tailored cognitive-behavioral therapy on neurobiological function in insomnia patients: an fMRI study

Contrast [neutral vs. baseline] before and after CBT-I separately

For the *contrast neutral words* > *baseline* in the "before CBT-I" condition, we observed significant activations regarding neutral words in several brain areas, such as the left fusiform gyrus, the left cuneus, the bilateral inferior occipital gyri, the bilateral inferior frontal gyri, the right precuneus, and the superior temporal gyri comparatively to baseline. No significant brain activation was observed for the inverse contrast, that is *baseline* > *neutral words*.

For the contrast between *neutral words* > *baseline* for "after CBT-I" condition, we observed activations regarding neutral words in several brain areas comparatively to baseline; we outline the bilateral inferior occipital gyrus, the left middle temporal gyrus, the left inferior frontal gyrus, the bilateral middle frontal gyrus, the right fusiform gyrus, and the supramarginal gyrus (cf. Figure 4). For a detailed list of brain regions see Table 5.

Regarding "after CBT-I" condition for the inverse contrast (i.e., baseline > neutral words) several brain regions exhibited pronounced activation, in particular, the bilateral precunei, the bilateral middle frontal gyri, the right middle temporal gyrus, the right inferior parietal lobule, and the right lingual gyrus and left cuneus (cf. Figure 1). For a detailed list of brain regions see Table 1.

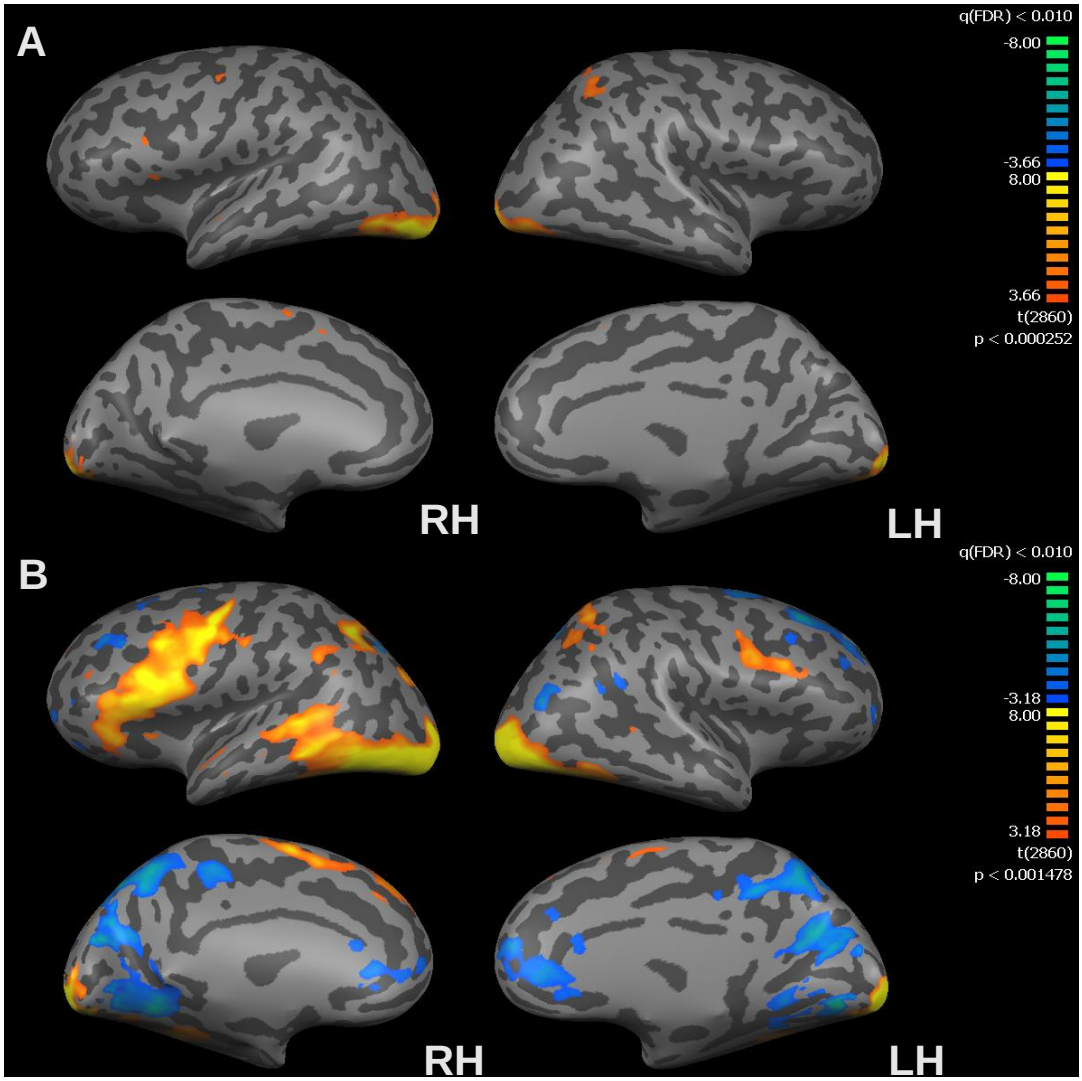

Figure 1 – Activated (warm colors) and deactivated (cool colors) brain regions for the contrast neutral words (+) vs. baseline (-) for before CBT-I (A) and after CBT-I (B). On the top panel of each of the figures are depicted the lateral views of both hemispheres; on the bottom panel are shown the medial views of both hemispheres. RH=right hemisphere; LH=left hemisphere. Radiological display convention was used.

Table 1. Talairach coordinates of activated regions regarding neutral words > baseline

			Talairach coordinates				
Region	Hemisphere	BA	x	y	z	Cluster size (k)	*t*-value
Neutral words > Baseline							
Before CBT-I							
Fusiform Gyrus	L	19	-33	-79	-14	2123	11.071474
Cuneus	L	18	-27	-94	-2		6.058881
Inferior Occipital Gyrus	L	18	-36	100	-14		6.927111
Pyramis (Cerebellum)	L	-	-30	-64	-29		6.820507
Inferior Occipital Gyrus	R	17	21	-91	-8		9.821012
Lingual Gyrus	L	17	-15	-94	-14		9.457373
Tuber (Cerebellum)	L	-	-39	-61	-26		7.351311
Tuber (Cerebellum)	R	-	36	-61	-26		6.255591
Inferior Frontal Gyrus	R	45	66	17	4	150	6.241836
Inferior Frontal Gyrus	R	11	27	32	-29	24	6.022314
Precuneus	R	7	30	-52	49	106	5.426612
Superior Frontal Gyrus	R	6	3	8	55	43	4.425189
Inferior Frontal Gyrus	L	4	-42	17	10	25	4.284132
Superior Temporal Gyrus	L	22	-60	5	-2	28	4.223474
After CBT-I							
Declive (Cerebellum)	L	-	-33	-82	-14	3995	22.375380
Pyramis (Cerebellum)	R	-	6	-74	-23		5.679691
Middle Temporal Gyrus	L	37	-51	-52	4		6.559645
Inferior Occipital Gyrus	L	17	-21	-97	-8		21.685678
Lingual Gyrus	R	18	15	-97	-5		18.961294
Inferior Occipital Gyrus	R	18	30	-85	-8		16.233810
Culmen (Cerebellum)	L	-	-39	-40	-20		11.216290
Fusiform Gyrus	R	19	39	-73	-11		9.434289
Middle Temporal Gyrus	L	21	-63	-40	-2		8.527771
Precentral Gyrus	L	4	-48	-7	43	1632	12.291205
Inferior Frontal Gyrus	L	9	-51	14	28		9.223313
Inferior Frontal Gyrus	L	46	-51	26	16		8.046140
Middle Frontal Gyrus	L	11	-33	41	-20		7.604753
Inferior Frontal Gyrus	L	9	-39	8	25		7.088065
Angular Gyrus	L	39	-27	-55	34	255	9.150126

Precuneus	L	31	-24	-73	22	48	7.917247
Medial Frontal Gyrus	L	6	-6	2	58	149	7.618069
Superior Parietal Lobule	R	7	33	-55	52	212	6.592761
Middle Frontal Gyrus	R	9	5	34	1	144	6.484832
Middle Frontal Gyrus	R	11	33	38	-23	33	6.231543
Supramarginal Gyrus	L	40	-51	-46	34	75	5.397113
Superior Frontal Gyrus	L	8	-6	47	46	206	5.382336
Baseline > Neutral words							
After CBT-I							
Lingual Gyrus	R	18	12	-70	-5	1717	-6.648008
Precuneus	L	7	-12	-70	40		-6.503504
Parahippocampal Gyrus	L	37	-24	-46	-8		-6.470300
Precuneus	R	31	18	-61	25		-6.417082
Precuneus	R	7	9	-67	46		-6.212846
Precuneus	L	7	-3	-61	49		-6.024446
Cuneus	L	18	-6	-76	22		-6.021926
Precuneus	R	7	12	-58	46		-5.523343
Middle Frontal Gyrus	R	8	27	17	43	392	-6.172289
Middle Temporal Gyrus	R	19	39	-76	22	39	-5.335163
Superior Frontal Gyrus	L	10	-21	50	4	295	-5.271086
Middle Frontal Gyrus	L	9	-27	35	37	51	-4.624573
Superior Frontal Gyrus	R	10	30	53	13	26	-4.525782
Cerebellar Tonsil	L	-	-42	-52	-35	36	-4.363134
Inferior Parietal Lobule	R	40	48	-46	28	31	-4.363134

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

Discussion

We performed contrast between both moments of intervention concerning neutral words. We observed that the bilateral middle frontal gyri, the bilateral precunei, and the left superior frontal gyrus were significantly more activated “before CBT-I” comparatively to “after CBT-I”. Likewise as in previous analyzed contrasts, areas comprising the DMN such as the prefrontal and temporal cortices and precunei are more activated at the pre-test moment (Buckner et al., 2008; Raichle et al., 2001). This finding is interesting, suggesting that even when the patients are confronted with affect-free stimuli, the general pattern of hyperactivation is present and thus it can influence the processing of the stimuli or

information processing within a top-down framework. Put it simply, the neutral words condition is working as another affective condition alike the past/present and future worries. This is consistent with the notion of an absent absolutely neutral condition. This interpretation seems plausible as after CBT-I a decreased activity within those areas was concomitant to a significantly higher recruitment of visual areas.

Similarly to the data analysis performed in Marques et al. (2015c), we explored the contrast *neutral words* > *baseline* in both "before CBT-I" and "after CBT-I" conditions. Some areas comprising DMN (e.g., precuneus) exhibited higher levels of activation before the psychological intervention when participants were exposed to visual presentation of neutral words, whereas no areas were unveiled as significant for *baseline* > *neutral words*. This finding is in line with the study by Marques et al. (2015c), suggesting that CID patients experience problems in DMN deactivation. On the other hand, it is evident that several DMN areas deactivate significantly after CBT-I. That is, after the psychological intervention, the expected DMN deactivation is visible (Buckner et al., 2008; Raichle et al., 2001). Similar to other studies (cf. Soares et al., 2003), in our study some visual areas such as the cunei and lingual gyri also show decreased activity simultaneously with the traditional areas of DMN (i.e., precuneus, frontal gyri, temporal cortex).

As demonstrated in a recent study, there is a dysfunction concerning DMN functioning in insomnia (Marques et al., 2015c). That is, the CID patients do not deactivate DMN brain regions when there is an attentional-demanding task, even when this task is very simple, such as visualizing neutral words or seeing neutral emotional images. In our study, we aimed to compare the eventual modification in brain activity incited by psychological intervention. We found that after CBT-I, insomnia patients exhibited brain activation patterns, namely those comprising the DMN, similar to what is observed in healthy individuals.

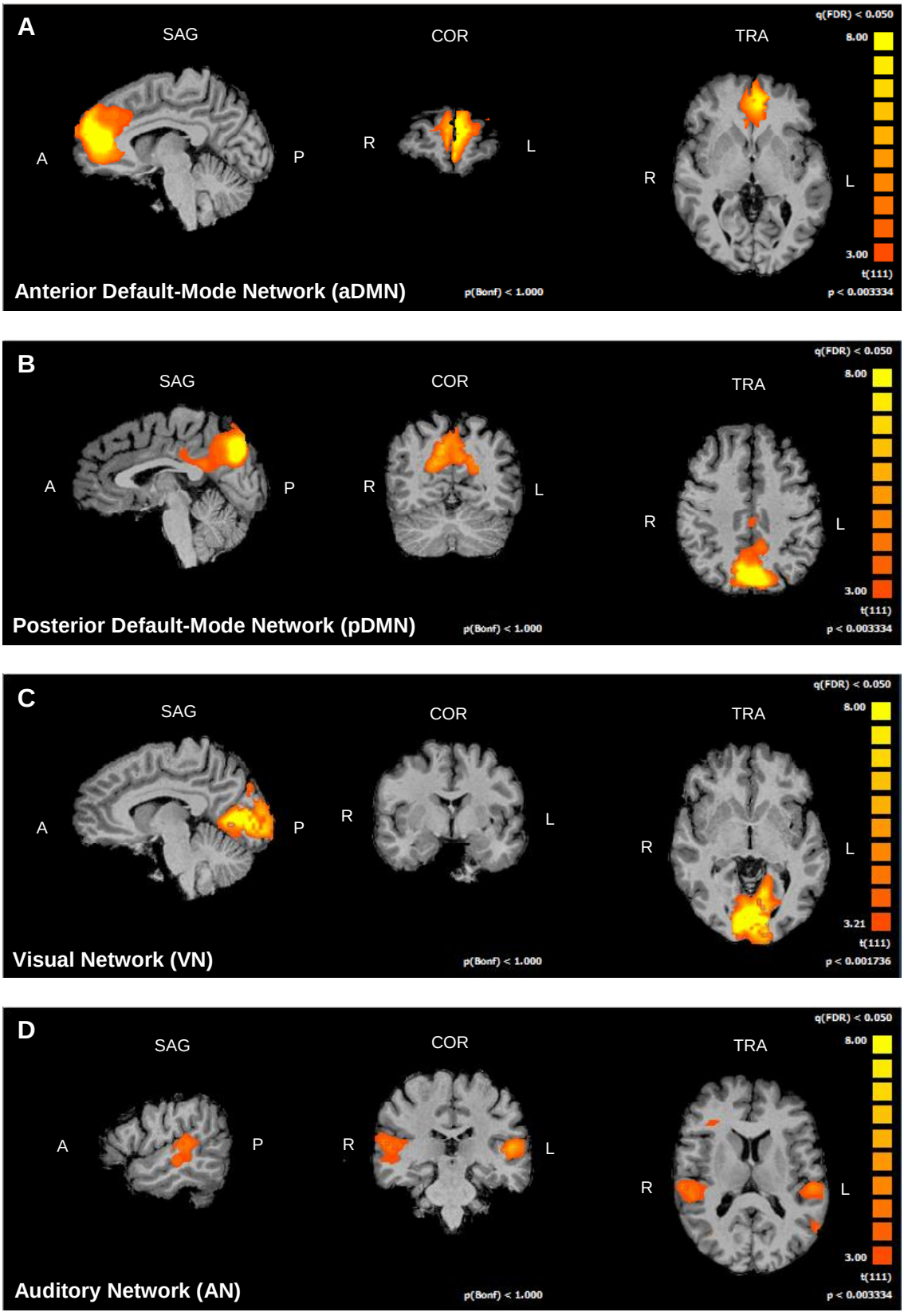

Figure 2. Resting-state networks activation before CBT-I. A=aDMN, B=pDMN, C=VN, D=AN. Radiological display convention was used.

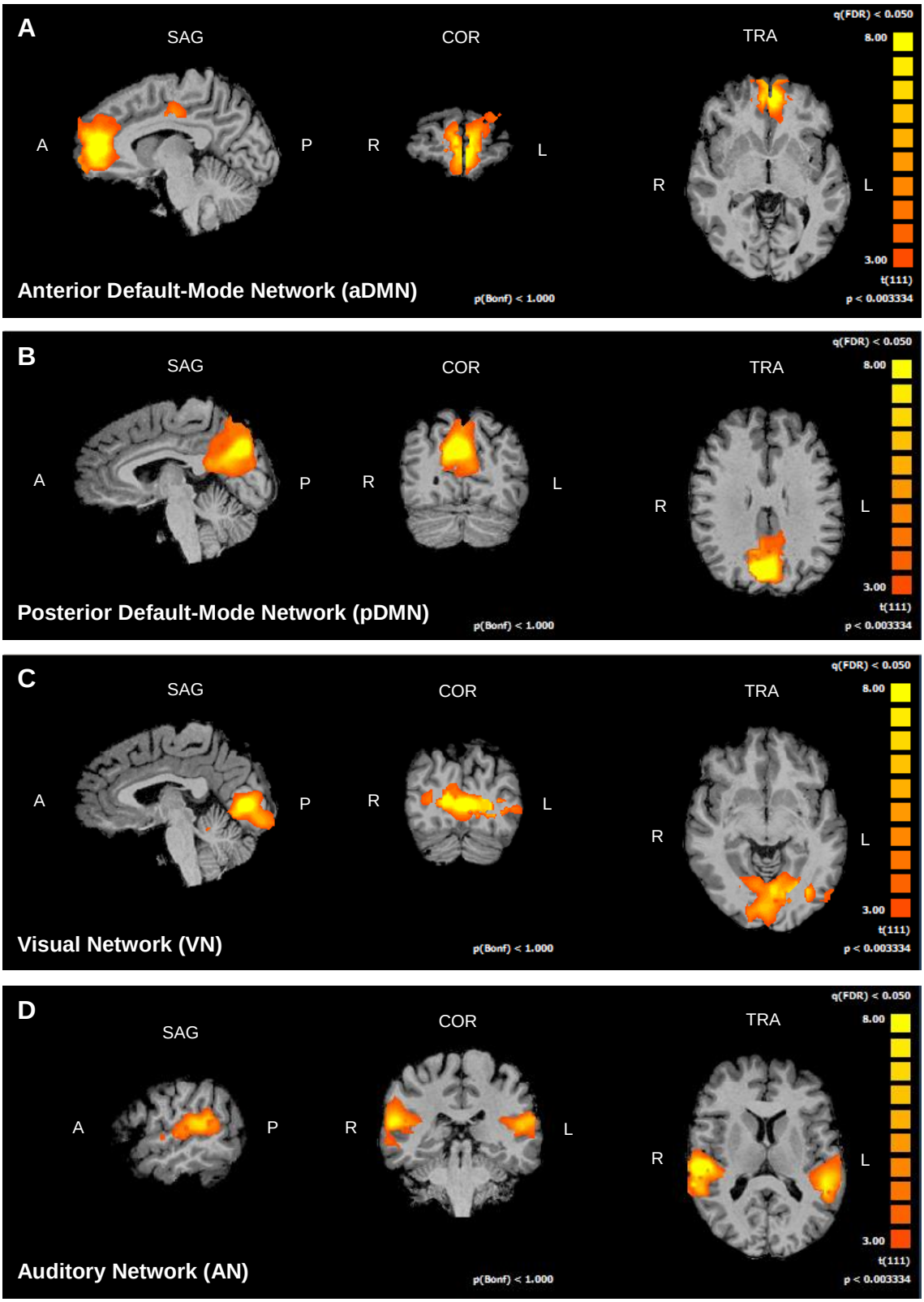

Figure 3. Resting-state networks functional activity after CBT-I. A=aDMN, B=pDMN, C=VN, D=AN. Radiological display convention was used.

PART IV

CONCLUDING REMARKS

CHAPTER 9: General discussion and conclusions

Chapter 9

General discussion and conclusions

"Resting state is not truly a resting state at all"
[Snyder & Raichle, 2012, p.904]

"Ainda que o cérebro esteja geneticamente
programado para funcionar de uma certa forma,
este não age isoladamente das experiências do indivíduo"
[Dattilio, 2009, p.308]

General Discussion

Throughout this thesis, we had the opportunity to verify that insomnia may be conceptualized both as an important symptom and an independent sleep disorder classified in the main medical manuals of diagnostic such as ICSD-3, DSM-5 and CID-10 (cf. Chapter 1). Moreover, we observed that several comprehensive models exist to account for insomnia. It was concluded that all of the models have, in overall, its importance in explaining this disorder (cf. Chapter 2). As psychological therapies are the best evidence for insomnia´s treatment and there is scanty evidence on neurobiological correlates of insomnia, we reflected upon the link between neurobiological dysfunction that may underlie CBT-I (cf. Chapter 3). Finally, ending the theoretical framework, we presented some novel ideas concerning the research on neurobiology of insomnia disorder and we discussed the need to study the brain resting-state networks, in particular DMN, in insomnia (cf. Chapter 4). These chapters/papers enabled us to constitute the main hypotheses to test in our empirical studies.

In this final chapter of the thesis we try to summarize the main findings regarding our empirical works, integrate them with the relevant literature reviewed in the first part of this thesis. Further, we propose a proto or preliminary model that might account to the role of the DMN in insomnia, in line with other insomnia models such as the one investigated by Espie et al. (2006).

Finally, we discuss some limitations, practical implications, suggestions for future research and we put forward some conclusions or "take-home" messages.

1. Hyperarousal and emotional reactivity in insomnia

In Chapter 6, we conducted an fMRI study which intended to explore eventual differential patterns of neural activation of insomnia patients compared to healthy-controls. Our principal hypothesis was that insomnia patients would exhibit more generalized neural activation compared to healthy individuals when they were confronted visually (through written words) with idiosyncratic concerns regarding past/present and future time orientations (ruminations and worries, respectively). Moreover, we would expect that when

the patients were confronted with neutral words they presented this overactivity pattern as well. In fact, our results supported this hypothesis; despite the small sample size, we found robust patterns of brain activity suggesting that insomnia patients present a general activation, particularly in brain regions regarding DMN. This is expected as the words that individuals saw at the fMRI screen were self-related and, consequently, they should mobilize brain regions pertaining to episodic memory and self-referential processing. These findings are in accordance with some studies which report that there is an altered emotional reactivity in insomnia disorder (Baglioni et al., 2010).

2. Insomnia patients disturbed at rest

In Chapter 7, we explored the brain´s resting-state networks in a sample of insomnia patients and healthy-controls (the same sample enrolled in the study of Chapter 6) in a different run. There was no study about the topic to date, at least to our knowledge. Our focus was on DMN, however, we decided to study other resting-networks as well. Interestingly, we found alteration in activity within brain regions comprising aDMN and pDMN and some additional networks as well (i.e., visual network, auditory network, right fronto-parietal network and left fronto-parietal network).

3. The contribute of psychological interventions and their role in brain neuroplasticity

Our aim in Chapter 8 was to replicate both previous studies (Chapters 6 and 7) after some patients have completed successfully an evidence-based psychological treatment for insomnia (i.e., CBT-I). As we discussed in Chapter 3, there seems to be relevance in studying neurobiological correlates of CBT-I; in this sense, we wanted to perform a repeated measures design pilot study (N=2) to attempt to clarify which could be the impact of a non-pharmacological intervention for insomnia in brain´s neuroplasticity. We are aware that these studies have a limited power because of the reduced sample size; notwithstanding, these studies have some strong points: they concern to patients (1) who completed successfully CBT-I and (2) never took medication for their sleep problems.

Therefore, concerning the repetition of the block-design fMRI after psychological intervention, we found that insomnia patients decreased their generalized cortical activation - more related with the self-referential processing - from pre to post-test. Interestingly, after CBT-I, we found a similar pattern (predominantly visual activation) as observed in healthy individuals (cf. Chapter 6).

With respect to fMRI resting-state experiment after psychological therapy, we found modification in four of the brain resting networks; it is possible that differences / modifications in other networks were not identified because of the limited sample size.

4. Connecting empirical findings with theoretical framework: A proto-model of DMN dysfunction in chronic insomnia disorder

This thesis focused on neurobiological correlates of insomnia. It is well-established that CID is an important sleep disorder with a significant prevalence among general population. In chapter 2, we presented the principal theoretical models on insomnia. The majority of those models have overlapping features and, in general, all of them follow a cognitive-behavioral orientation. According to the findings obtained in our studies which were analyzed in this thesis, we think that A-I-E insomnia´s pathway from Espie et al. (2006) could give an important input for our integration of DMN in insomnia´s formal conceptualization. Notwithstanding, it is important to outline that a pathophysiological role for DMN in insomnia is yet proposed also by Buysse, Germain, Hall, Monk and Nofzinger (2011). In Figure 1 we display a proto-model of DMN dysfunction in insomnia.

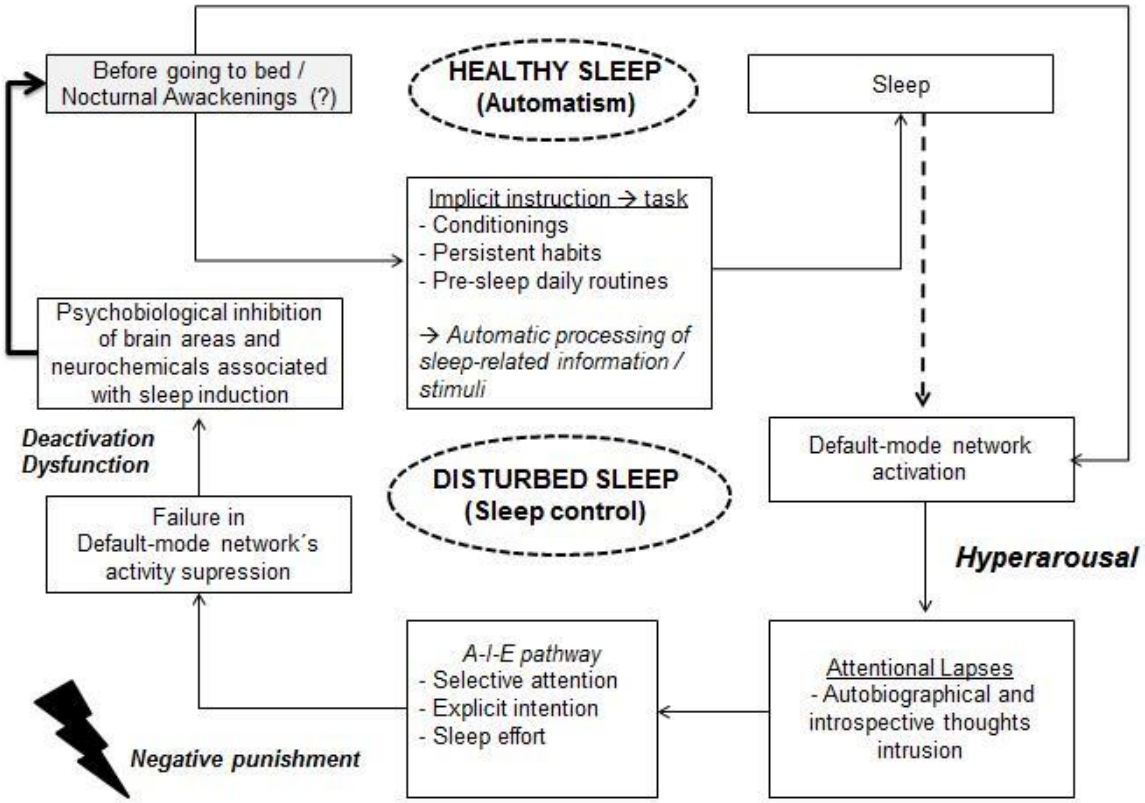

Figure 1. A hypothetical model on the role of default-mode network in insomnia

The proto-model of DMN dysfunction in insomnia is embedded in the psychobiological inhibition model proposed by Espie et al. (2006). Our aim was to integrate DMN dysfunction hypothesis within a well-established theory of insomnia and not to propose a new one. It is intended to account for initial and (eventually) intermediate insomnia sub-types (cf. question mark in Figure 1). In the normal process of falling asleep / before going to sleep, the information processing regarding sleep cues or stimuli related to sleep is intensified, albeit in an automatic or involuntary way. To this end, are important the learning repertoire, the established conditionings, the pre-sleep automatic routines and a whole set of activities that do not mobilize conscious processing of information at that time. In this sense, this is in line with the idea of Espie et al. (2006) when they suggest that in the normal sleep process, the individual has a passive role; as there is no intention or explicit planning for sleeping behavior, the individual finds no significant difficulties in falling asleep. One might hypothesize that there is an implicit task (i.e., preparing the sleep behavior) being processed. On the other hand, in the case of individuals prone to develop

sleep problems, particularly insomnia, what is suggested is that there may be a DMN dysfunctional or impaired activity which interferes with this implicit "sleeping task". The persistent activity of DMN, in its fluctuation, reaches a certain threshold that will provoke an intense cognitive activity, particularly in the form of ruminations and worries with a strong self-referential valence; this is visible in the reports of patients, and is consistent with clinical practice and the results of several studies. These attentional lapses will disrupt the automated task of sleeping and, consequently, the attentional resources of the individual are mobilized to dysfunctional autobiographical or episodic cognitive contents. The automaticity, being disturbed or inhibited, will generate the explicit intention to sleep and consequently several deliberate attempts to fall asleep. This is, therefore, the A-I-E pathway of insomnia (Espie et al., 2006). In this line, this behavior will not enable the decrease of DMN given the attention that the individual maintains on sleep. This overall hyperarousal implicating the DMN, leads to a delay in the activation of neural structures implicated in the relaxation response and sleep induction. From this perspective, this impaired behavior tends to persist in time, being perpetuated by selective attention mechanisms and anxiogenic expectations. It thus creates a vicious circle. The association between cognitive processes involved in the A-I-E pathway and the failure in the suppression of DMN activity may be maintained due to a negative punishment mechanism. This perspective integrating the DMN in the conceptualization of insomnia has the virtue of combining the process of hyperarousal hypothesis and the failure to inhibit wakefulness in primary insomnia. Both appear to be relevant and complementary to the understanding of insomnia (Marques, Gomes, Clemente, Santos & Castelo-Branco (2015). One should note, however, that this perspective is preliminary and exploratory and further studies are required.

5. Limitations

As in all scientific research projects, our studies have major limitations that should be underlined. In this respect one should note (1) the fact that the samples were not randomly extracted from the populations (patients and controls), although this is a minor limitation given that no randomized clinical trial was planned, but instead prospective case-control

investigations; we must note that the reduced sample size was mainly due to the following reasons: the participants were recruited at a single Sleep Medicine Centre, some patients had no compatible agenda to participate, some patients did not participated because their fMRI machine fears, and in the most cases, and the patients were from other cities of the country which consequently make their participation inviable; (2) the reduced sample size which is insufficient to generalize the results obtained (FFX analyses); (3) the use of some self-report instruments that are not studied psychometrically in Portuguese samples, although this was not one of the major aims of our studies; (4) regarding the control group, due to our goals for this study, it interest us studying healthy controls (i.e., individuals without insomnia), therefore, a control group of insomnia patients was not constituted; it would have been important to find out treatment effects in terms of neural activity in a more specific manner; (5) another obstacle relates to the inclusion of one medicated patient at the pretest moment who was medicated for other problems than insomnia (however, one should note that the data of this patient were not different from the remaining patients), which turned out to be a limitation for our research; at the same time, it brought the possibility of increasing the sample size and to consider "real-life" patients, concomitantly; (6) as in other studies, the "context" may have contributed to some of the results obtained in this study, constituting a threat to internal validity – over the time, may be occurred significant changes in the life of the participants which may have influenced the data collected and that the patients did not report; and (7) it should be emphasized that the total duration of the tests (especially neuroimaging ones – about 1 hour) were likewise a limitation mainly because the participants might have felt restrained in terms of movements (i.e., as they were within the fMRI machine); notwithstanding, after the execution of movement correction algorythm of the software, no problematic cases were detected. Finally, (8) one must note also that the noise present at the time of the scans might attenuate the DMN activity (Gaab, Gabrieli, & Glover, 2008).

6. Practical implications

Since the conceptualization of this study we assumed and privileged an eminently clinical perspective. According to a biopsychossocial framework, it was our intention that

this study had strong practical impact and could change the way how we think about psychological interventions for insomnia and psychotherapy in general. We think that the results arising from this work brings, among others, two important practical implications, namely:

1 - Contribution to give projection to a new field of psychology (i.e., sleep psychology) at both national and international level (APA, 2013);

2 - Incentive to give empirical consistency to the clinical notion that there are significant and solid changes at neurobiological point of view in insomnia patients which are associated with psychotherapeutic interventions - in this case based on the cognitive-behavioral model (Folensbee, 2007).

Despite the encouraging results that were obtained with this research, mainly the role of CBT-I in modification of neural activity, we agree with Jokic-Begic (2010) when he argues that "the question remains if the observed changes represent neurobiological correlates of therapeutic interventions or just changes accompanying improvements in the condition" (p. 249). On the other hand, and similar to what is reported by Buckner et al. (2008) for the autistic spectrum disorders, it should be borne in mind that changes in the DMN associated with various clinical conditions may not be connected or related to developmental events that cause the disease but rather represent a consequence. That is, the eventual dysfunction associated DMN may emerge as an indirect consequence of developmental events that begin "outside" of this brain network.

7. Notes for future research

Pertaining to future studies we present a list of suggestions that deserve attention: *a*) it would be useful to assess the results of a group of CID patients treated with psychiatric drugs compared to a group of patients without being subjected to any kind of psychotropic prescription (i.e., "free" of medications); *b*) comparing clinical sub-types of insomnia (e.g., early vs. intermediate insomniacs) as well as compare PI with other types of insomnia,

such as paradoxical insomnia; *c*) it would be useful to replicate this study using other sleep samples of patients without insomnia (e.g., parasomnias, circadian rhythm disorders) and verify whether the pattern of activation of the DMN is distinct among various sleep disorders; *d*) another point is the possibility of performing new neuroimaging and psychological assessment after a follow-up period (e.g., after 6 months); *e*) it would also be useful to compare two groups with CID but submitted to different treatment processes, i.e., a group subject to CBT-I idiosyncratic treatment, as established in our research, and another group undergoing CBT-I manualized treatment; *f*) study the tailored cognitive-behavioral strategies for each patient (respondent and non-respondent) (Laar, Verbeek, Pevernage, Aldenkamp, & Overeem, 2010); *g*) the possibility or feasibility of conducting a randomized controlled clinical trial (RCT) would undoubtedly bring another level of evidence and experimental rigor to this study; *h*) according to Edinger and Wohlgemuth (1999) it would be fruitful to understand if insomnia subtypes respond differently to CBT-I (Riemann et al., 2011); *i*) what is the minimum effective "dose" of psychotherapy and even *j*) taking into account the results that were obtained with this exploratory study using the more traditional cognitive-behavioral intervention for insomnia, we think that given the characteristics of the models of new models of CBT (third generation) we should study them in the same way and, if possible, compared them with more conventional psychological interventions. In addition to the replication of the research we carried out, it would be very helpful if we could *k*) investigate brain areas that proved to be most significant in our study through the use of molecular imaging techniques, complementary to fMRI studies (Linden, 2006).

Conclusions

The study of structure and functions of the DMN is a promising field of research. This is a position bolstered by contemporary neuroscientists (Damasio, 2010; Raichle, 2009).

The DMN study is important to study as is easy to assess, comfortable for the participants – that is, there are no demanding tasks to performed, and the inherent functions attributed to DMN are related to fundamental aspects of human experience (Whitfield-Gabrieli & Ford, 2012). Besides, there is cumulative evidence suggesting that DMN is

impaired in several neuropsychiatric disorders (for a comprehensive review cf. Broyd et al., 2009 and Whitfield-Gabrieli & Ford, 2012).

It is worth noting that neuroimaging methods have relevant limitations and, consequently, one should be aware of these in the data analyses and publication processes (APA, 2007; Beck, 2010; Satel & Lilienfeld, 2013; Weisberg, Keil, Goodstein, Rawson, & Gray, 2008). In the field of psychotherapy and its relationship with neuroscience we agree with the position of Bishop (2012, March 5) when she argues that:

"(…) if an intervention is effective, [neuro]imaging may help throw light on its mechanism of action. However, I do not think it is worthwhile to do poorly-designed studies of small numbers of participants to test the mode of action of an intervention that has not been shown to be effective in properly-controlled trials. It would make more sense to spend the research funds on properly controlled trials that would allow us to evaluate which interventions actually work".

At the end of this work, we would like to underline the need to make psychosocial interventions for insomnia more accessible and more timely, available to a larger portion of the population (Barlow, 2004); besides, it is worthy to outline the importance that the proper management of sleep complaints and sleep disorders have on health prevention and promotion, in particular, in the context of primary health care (Pais-Ribeiro, 2007). In this regard, we totally agree with Espie (2009): "the challenge for CBT is no longer to prove its credentials, but to punch its weight. For at least a decade, CBT should have been a contender as the treatment of first choice for insomnia. In reality, however, it has had very little impact on the high volume of insomnia patient care. Indeed, it has amounted to little more than a cottage industry patchy" (p.1549).

To finish, we believe, as emphasized by Espie and Morin (2012), that the field of behavioral sleep medicine is an increasingly and eminent area, contributing to the recognition of psychologists as a professional class. It was our intention with this work to have contributed to this major goal.

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APPENDICES

Appendix 1. Request for permission to collect data at the CHUC

Daniel Ruivo Marques
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Sra. Dra. Rosa Reis Marques
Presidente do Conselho de Administração do CHC
Centro Hospitalar de Coimbra
Quinta dos Vales, S. Martinho do Bispo
3041-853 Coimbra

Aveiro, 6 de Janeiro de 2012

Assunto: Pedido de autorização para recolha de dados no Centro de Medicina do Sono

Exmos. Srs.

Chamo-me Daniel Ruivo Marques, sou aluno do Programa Doutoral em Psicologia do Departamento de Educação da Universidade de Aveiro (DE-UA) e Bolseiro de Doutoramento da Fundação para a Ciência e Tecnologia (FCT) com a referência SFRH/BD/77557/2011 e propus-me desenvolver uma investigação sobre insónia intitulada *"A hipótese da hiperativação na insónia psicofisiológica: Estudo da default-mode network e sua modificação após terapia cognitivo-comportamental"*, sob orientação da Prof. Doutora Ana Cardoso Allen Gomes (Professora Auxiliar do Departamento de Educação da Universidade de Aveiro (DE-UA) e do Prof. Doutor Miguel de Sá e Sousa de Castelo-Branco (Professor Auxiliar da Faculdade de Medicina da Universidade de Coimbra (FMed-UC) e Diretor do Instituto Biomédico de Investigação da Luz e da Imagem (IBILI) da mesma Universidade.

No âmbito deste doutoramento, prevemos desenvolver um estudo que incidirá sobre a avaliação de aspectos neuroimagiológicos (avaliados por ressonância magnética funcional – sem utilização de substâncias de contraste – que será efetuada no Instituto Biomédico de Investigação da Luz e da Imagem, instituição colaboradora nesta investigação), medidas objetivas (dados de actigrafia) e subjetivos (questionários de auto-resposta) – sendo que à exceção de um questionário, todas as outras medidas fazem já parte do protocolo de avaliação utilizado no vosso Centro de Medicina do Sono – em doentes com insónia psicofisiológica antes e após se submeteram a terapia cognitivo-comportamental (TCC), comparando-os com um grupo sem perturbações de sono (grupo de controlo).

Neste sentido, solicitamos a V. Ex.as a autorização para recolher a amostra clínica do nosso estudo (De 01 de Março de 2012 até 31 Outubro de 2014) no vosso Centro de Medicina do Sono. Estas são datas previstas que, poderão estar sujeitas a algumas alterações que, caso seja necessário, oportunamente informaremos V. Ex.as (nomeadamente se houver uma renovação de um ano adicional de bolsa de Doutoramento) Desejamos obter um efetivo amostral de cerca de 20 doentes. De referir que o Diretor do referido Centro (Dr. José Moutinho dos Santos) e a psicóloga clínica especialista (Dr.ª Vanda Clemente) já nos demonstraram toda a sua disponibilidade para nos auxiliar nesta tarefa, estando também eles integrados na nossa equipa de investigação.

1/2

Appendix 1. Request for permission to collect data at the CHUC (continued)

Informa-se ainda que toda a informação recolhida será confidencial e anónima e que será ainda solicitado o preenchimento de um documento de consentimento informado a cada um dos participantes nesta investigação.

O processo de investigação obedecerá a todas as exigências respeitantes ao código de ética da investigação científica.

Mais se informa que não existirá qualquer custo quer para o referido Centro quer para o próprio Centro Hospitalar de Coimbra (CHC).

Após a defesa da tese de Doutoramento que está relacionada com este trabalho, comprometo-me a enviar um exemplar do trabalho, em ficheiro pdf, ao Serviço de Gestão da Formação e Documentação.

Encontro-me disponível para todo e qualquer esclarecimento adicionais que possam achar relevantes.

Em anexo, encontrarão uma cópia do meu CV, o projeto de investigação detalhado e cronogramas provisórios e ainda um exemplar do termo de consentimento informado que será entregue a cada doente.

Fico então a aguardar, com expectativa, pelo vosso parecer.

Com os meus melhores cumprimentos,

Daniel Ruivo Marques

Daniel Ruivo Marques
Aluno do Programa Doutoral em Psicologia da Universidade de Aveiro (UA)
Bolseiro de Doutoramento da Fundação para a Ciência e Tecnologia (FCT) – SFRH/BD/77557/2011

Appendix 1. Request for permission to collect data at the CHUC (continued)

Daniel Ruivo Marques
R. Luís de Camões, 155
3830-696 Gafanha da Nazaré
Tlm: 916 719 651
E-mail: drmarques@iol.pt

Exmo. Sr.
Presidente do Conselho de Administração
Dr. José Martins Nunes
Centro Hospitalar e Universitário de Coimbra - CHUC, E.P.E.
Av. Bissaya Barreto / Praceta Prof. Mota Pinto
3000-075 Coimbra

Aveiro, 30 de Abril de 2012

Assunto: Pedido de autorização para recolha de dados "A hipótese de hiperativação na insónia psicofisiológica: Estudo da default-mode network e sua modificação após terapia cognitivo-comportamental".

Exmo. Sr. Presidente do Conselho de Administração do CHUC, E.P.E.,

Em resposta à carta enviada por V.Exª datada de 12/04/2012 (Ofício n.º 501/12) em relação ao pedido que efetuei para a realização da minha investigação de doutoramento intitulada *"A hipótese da hiperativação na insónia psicofisiológica: Estudo da default-mode network e sua modificação após terapia cognitivo-comportamental"* (Registo n.º 283/12), sob orientação da Prof. Doutora Ana Cardoso Allen Gomes (Professora Auxiliar do Departamento de Educação da Universidade de Aveiro (DE-UA) e do Prof. Doutor Miguel de Sá e Sousa de Castelo-Branco (Professor Auxiliar da Faculdade de Medicina da Universidade de Coimbra (FMed-UC) e Diretor do Instituto Biomédico de Investigação da Luz e da Imagem (IBILI) da mesma Universidade e de forma a satisfazer todos os requisitos necessários para levar a cabo a investigação no vosso Centro de Medicina do Sono (HG-CHUC) envio, em anexo, um documento com a metodologia prevista para a recolha e estudo do grupo de controlo assim como o respetivo documento de consentimento informado para o referido grupo, conforme me solicitaram.

Fico então a aguardar, com expectativa, pelo vosso parecer.

Com os meus melhores cumprimentos,

Daniel Ruivo Marques

Daniel Ruivo Marques
Aluno do Programa Doutoral em Psicologia da Universidade de Aveiro (UA)
Bolseiro de Doutoramento da Fundação para a Ciência e Tecnologia (FCT) – SFRH/BD/77557/2011

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Appendix 2. Permission to enroll insomniac patients at the CHUC

Centro Hospitalar e Universitário de Coimbra, E.P.E.

CONSELHO DE ADMINISTRAÇÃO

Exmo. Senhor
Daniel Ruivo Marques
Rua Luís de Camões, 155
3830-696 Gafanha da Nazaré

S/Ref.ª	S/Comunicação	N/Ref. – Ofício n.º	Data
		PC 902/12	16.07.2012

Assunto: Pedido de autorização para recolha de dados "A hipótese de hiperativação na insónia psicofisiológica: Estudo de default-mode network e sua modificação após Terapia cognitiva-comportamental"

Na sequência do pedido de autorização para a realização do estudo acima referenciado, a realizar no Hospital Geral – CHUC, no âmbito do seu Doutoramento em Psicologia, informo que, de acordo com o parecer favorável da Comissão de Ética do Centro Hospitalar e Universitário de Coimbra, de que se junta cópia, se autoriza a sua realização.

Com os melhores cumprimentos,

O Presidente do Conselho de Administração do
Centro Hospitalar e Universitário de Coimbra, EPE

(Dr. José Martins Nunes)

JMN/FD

Av. Bissaya Barreto / Pct.ª Prof. Mota Pinto
3000-075 Coimbra
e-mail: casec@huc.min-saude.pt Tel.: 239 400 407 / 607 Fax: 239 822 291

Appendix 2. Permission to enroll insomniac patients at the CHUC (continued)

Centro Hospitalar e Universitário de Coimbra, E.P.E.

COMISSÃO DE ÉTICA PARA A SAÚDE

Exmo. Senhor:
Presidente do Conselho de Administração
Dr. José Martins Nunes
CHUC, E.P.E.

N/Refª	Ofício Nº	Data
CES	0122	29.06.2012

ASSUNTO: Pedido de autorização para recolha de dados *"A hipótese de hiperativação na insónia psicofisiológica: Estudo da default-mode network e sua modificação após terapia cognitiva-comportamental"* - Daniel Ruivo Marques - Aluno do Programa Doutoral em Psicologia do Departamento de Educação da Universidade de Aveiro - (estudo a ser realizado no Centro de Medicina do Sono - HG-CHUC) - (registo 283/2012).

Cumpre-me informar Vossa Ex.ª que a Comissão de Ética para a Saúde do CHUC, EPE, reunida em 29 de Junho de 2012, com a presença da maioria dos seus membros, após análise dos esclarecimentos adicionais prestados pelo investigador e a inclusão dos elementos em falta e ouvido o relator, emitiu ***parecer favorável*** à sua realização. Deliberação aprovada por unanimidade.

Mais se informa que a CES do CHUC deve ser semestralmente actualizada em relação ao desenvolvimento dos estudos favoravelmente analisados e informada da data da conclusão dos mesmos, que deverá ser acompanhada de relatório final.

Com os melhores cumprimentos,

C.H.L.U.C., E.P.E.
CONSELHO DE ADMINISTRAÇÃO
Reg. Nº 283 PCA
Origem
Data 13/7/2012

P/ A COMISSÃO DE ÉTICA PARA A SAÚDE
C.H.U.C., E.P.E.
Comissão de Ética para a Saúde
DO CHUC, E.P.E.

Prof. Doutor José Joaquim Sousa Barros
Presidente da CES do HUC - CHUC

A CES do HUC-CHUC: Prof. Doutor José Joaquim Sousa Barros; Prof.ª Doutora Maria Fátima Pinto Saraiva Martins; Dr. Mário Rui Almeida Branco Enf.º Adélio Tinoco Mendes; Prof. Doutor Carlos Alberto Fontes Ribeiro; Dra. Alexandra Vilela; Padre José António Afonso Pais.
A CES do HSC-CHUC: Dra. Cláudia Santos; Dra. Conceição Pascoal; Dra. Ana Maria Martins, Dr. Paulo Figueiredo; Enf.ª Fernanda Pereira.
A CES do HG-CHUC: Dra. Maria Alice Torcato; Dr. José Alves Grilo Gonçalves; Enf.º Fernando Mateus; Dra. Maria Helena Gomes; Dr. José António Pinheiro; Dra. Margarida Cunha Martins

Av. Bissaya Barreto / Pct.ª Prof. Mota Pinto
3000-075 Coimbra
E-mail: dirclinica@huc.min-saude.pt Tel.: 239 400 408 Fax: 239 405 646

Appendix 3. Informed consent document for insomnia sample

NI: □□□□-□

INVESTIGAÇÃO

A hipótese da hiperativação na insónia psicofisiológica: Estudo da default-mode network e sua modificação após terapia cognitivo-comportamental

Caro(a) participante:

No âmbito de um projeto de doutoramento a decorrer na Universidade de Aveiro (UA) estamos interessados em realizar um estudo que avalie pessoas com insónia antes e depois de se submeterem ao respetivo tratamento psicológico (terapia cognitivo-comportamental). É neste âmbito que vimos solicitar a sua colaboração.

Qual é o seu papel?

Na sua segunda consulta no CMS-CHUC, iremos pedir-lhe que preencha alguns questionários breves de auto-resposta, que durante cerca de 1 semana utilize um atígrafo e que realize um exame neuroimagiológico (ressonância magnética funcional) no Instituto de Imagem Biomédica e Ciências da Vida (IBILI), em Coimbra, em data a acordar com o responsável da investigação. Após o término do seu tratamento para a insónia, iremos pedir-lhe que repita o mesmo procedimento de avaliação inicial. O investigador responsável pelo projeto vai acompanhá-lo(a) sempre neste processo.

Tenha em atenção que os seus dados serão confidenciais, sendo somente identificados por um código e tratados coletivamente, isto é, junto com os dados dos outros participantes. Note que, em qualquer momento, poderá desistir de participar na investigação, sem que isso acarrete qualquer tipo de prejuízo ou consequência para si e para o tratamento que lhe é prestado.

A sua colaboração é fundamental pois estará a ajudar-nos a compreender melhor a insónia e a melhorar os tratamentos disponibilizados às pessoas com este problema de sono.

Desde já, muito obrigado pela sua colaboração!

Consentimento informado

Eu, _____ declaro ter tomado conhecimento dos objetivos do estudo e do meu papel neste. Fui esclarecido(a) em relação às questões que coloquei e fui informado(a) de que posso recusar participar no estudo a qualquer momento sem que isso traga quaisquer consequências para mim e para o meu tratamento.

Ass: _____ , Coimbra, __ de _____ de 20__.

Responsável pelo projeto:
Dr. Daniel Ruivo Marques (E-mail: drmarques@ua.pt)
Doutorando em Psicologia pela Universidade de Aveiro (UA)
Instituto de Imagem Biomédica e Ciências da Vida (IBILI)
Bolseiro de Doutoramento da FCT – SFRH/BD/77557/2011

Appendix 4. Informed consent document for healthy controls´ sample

FOLHA DE INFORMAÇÃO AO PARTICIPANTE/ CONSENTIMENTO INFORMADO

TÍTULO DO ESTUDO: Novos Avanços metodológicos no estudo do IRM do Espectro de Difusão e as suas implicações para o imageamento no cérebro da correlação entre funcionamento e estrutura

PROTOCOLO: CE-002/2013

PROMOTOR	IBILI (Prof. Doutor Miguel Castelo Branco – diretor)
INVESTIGADOR COORDENADOR	Não aplicável
CENTRO DE ESTUDO	IBILI – Instituto Biomédico de em Luz e Imagem
INVESTIGADOR PRINCIPAL	Prof. Doutor Nicolás Francisco Lori
MORADA	IBILI, Faculdade de Medicina da Universidade de Coimbra Azinhaga Santa Comba, Celas - 3000-548 Coimbra
CONTACTO TELEFÓNICO	239 480 248
NOME DO DOENTE (IMPRESSO)	_____

É convidado(a) a participar voluntariamente neste estudo porque é um adulto saudável. Este procedimento é chamado consentimento informado e descreve a finalidade do estudo, os procedimentos, os possíveis benefícios e riscos. A sua participação poderá contribuir para melhorar o conhecimento e o tratamento das doenças do cérebro.

Receberá uma cópia deste Consentimento Informado para rever e solicitar aconselhamento de familiares e amigos. O investigador do estudo irá esclarecer qualquer dúvida que tenha sobre o termo de consentimento e também alguma palavra ou informação que possa não entender.

Deve tomar a decisão de participar ou não no estudo depois de entender o estudo e de não ter qualquer dúvida acerca do mesmo. Caso queira participar, ser-lhe-á solicitado que assine e date este formulário. Após a sua assinatura e a do investigador, ser-lhe-á entregue uma cópia. Caso não

Appendix 4. Informed consent document for healthy controls´ sample (continued)

queira participar, não haverá qualquer penalização nos cuidados que irá receber.

1. INFORMAÇÃO GERAL E OBJECTIVOS DO ESTUDO

Este estudo irá decorrer no IBILI, FMUC em colaboração com o ICNAS e tem como objectivo conhecer as causas e os mecanismos que provocam doenças no cérebro. De forma mais específica, pretender determinar se há alterações em mecanismos neuronais da matéria branca.

Trata-se de um estudo observacional, pelo que não será feita nenhuma alteração nas suas rotinas diárias ou tratamentos habituais. Este estudo foi aprovado pela Comissão de Ética Independente da FMUC de modo a garantir a protecção dos direitos, segurança e bem-estar de todos os pacientes e garantir prova pública dessa protecção.

Como participante neste estudo, beneficiará da vigilância institucional e encaminhamento adequado garantindo assim a sua segurança.

Este estudo é constituído por 2 visitas independentes que se podem realizar em dias diferentes. Cada visita terá a duração aproximada de 90 minutos. Serão incluídos cerca de 30 participantes controlo.

2. PROCEDIMENTOS E CONDUÇÃO DO ESTUDO

2.1. Procedimentos

Avaliação neuropsicológica

Um investigador do estudo realizar-lhe-á uma avaliação neuropsicológica que compreende uma grande variedade de tarefas entre as quais resposta a perguntas de cultura geral, tarefas de memória e cálculo matemático, visualização de imagens de objectos ou realização de puzzles.

Exame de Ressonância Magnética

A ressonância magnética é uma técnica não invasiva e que não comporta nenhum risco para o participante. Será colocado/a numa mesa que deslizará para o interior de uma câmara onde será realizado o exame, tendo apenas que ser assegurado que o participante não é portador de implantes metálicos. Note-se que a ressonância magnética só será feita em condições que permitam a colaboração do participante, não sendo necessária anestesia geral nem injecção de agentes de contraste. Serão efectuados estudos de ressonância magnética de difusão, e ressonância magnética funcional:

Estudo de ressonância magnética de difusão - Este exame utiliza um aparelho de ressonância

Appendix 4. Informed consent document for healthy controls´ sample (continued)

magnética, para obter informação sobre a anatomia da matéria branca e não é invasivo.

Estudo de ressonância magnética funcional (fMRI) - Este exame será realizado em simultâneo com a execução das tarefas escolhidas para estudar as propriedades dos neurónios visuais e permitirá obter informação relativa a activação de regiões do cérebro envolvidas no desempenho da tarefa.

Caracterização do processamento cerebral de informação visual

Iremos utilizar tarefas no computador que permitirão estudar a forma como processa informação.

2.2. Calendário das visitas/ Duração

Este estudo é constituído por 2 visitas independentes que se podem realizar em dias diferentes. Cada visita terá a duração aproximada de 90 minutos. Seguidamente encontrar-se uma descrição do estudo:

Procedimento:

Serão realizados os seguintes procedimentos/exames:

- Exame de Ressonância Magnética, composto por ressonância magnética de difusão (não invasivo) e ressonância magnética funcional (não invasivo);
- Testes psicofísicos computorizados (não invasivo);

Serão feitas perguntas a respeito da sua história médica e da medicação que toma.

2.3. Tratamento/ Randomização

Não serão realizados quaisquer tratamentos no âmbito deste estudo.

3. RISCOS E POTENCIAIS INCONVENIENTES PARA O DOENTE

Todos os equipamentos têm marcação UE e são utilizados para o uso em seres humanos. Os riscos e inconvenientes deste estudo são mínimos.

Ressonância Magnética

Exame não invasivo. Apesar de não causar qualquer desconforto ao paciente, é necessário que permaneça imóvel durante o exame. Não apresenta contra indicações, excepto a portadores de materiais metálicos.

Appendix 4. Informed consent document for healthy controls´ sample (continued)

4. POTENCIAIS BENEFÍCIOS

Este estudo tem a vantagem de estudar com detalhe a sua doença e permitir um melhor conhecimento dos mecanismos que podem estar associados a défices cognitivos. Além disso, a informação que será recolhida irá contribuir para uma melhor informação dos investigadores e dos médicos de forma a melhorar os cuidados clínicos a prestar aos doentes com doenças do neurodesenvolvimento.

5. NOVAS INFORMAÇÕES

Será informado de qualquer informação que possa ser relevante para a sua condição ou que possa influenciar a sua vontade de continuar a participar no Estudo.

6. TRATAMENTOS ALTERNATIVOS

Não receberá qualquer tratamento no contexto do estudo em que irá participar.

7. SEGURANÇA

Embora não se espere que devido à sua participação venha a sofrer problemas de saúde, se sofrer alguma lesão física como resultado de quaisquer procedimentos do estudo, realizados de acordo com o protocolo, será reembolsado pelas despesas médicas necessárias para as tratar.

8. PARTICIPAÇÃO/ ABANDONO VOLUNTÁRIO

É inteiramente livre de aceitar ou recusar participar neste estudo. Pode retirar o seu consentimento em qualquer altura sem qualquer consequência para si, sem precisar de explicar as razões, sem qualquer penalidade ou perda de benefícios e sem comprometer a sua relação com o investigador que lhe propõe a participação neste estudo. Ser-lhe-á pedido para informar o seu investigador se decidir retirar o seu consentimento.

O investigador do estudo pode decidir terminar a sua participação neste estudo se entenderem que não é do melhor interesse para o seu bem-estar (ou para a sua saúde) continuar nele. A sua participação pode ser também terminada se não estiver a seguir o plano do estudo, por decisão administrativa ou decisão da Comissão de Ética. O investigador do estudo notificá-lo-á se surgir uma dessas circunstâncias, e falará consigo a respeito da mesma.

Appendix 4. Informed consent document for healthy controls´ sample (continued)

9. CONFIDENCIALIDADE

Sem violar as normas de Confidencialidade, serão atribuídos a Auditores e Autoridades Reguladoras acesso aos registos médicos para verificação dos procedimentos realizados e informação obtida no Estudo, de acordo com as leis e regulamentos aplicáveis. Os seus registos manter-se-ão confidenciais e anonimizados de acordo com os regulamentos e leis aplicáveis. Se os resultados deste estudo forem publicados a sua identidade manter-se-á confidencial.

Ao assinar este consentimento informado autoriza este acesso condicionado e restrito.

Pode ainda em qualquer altura exercer o seu direito de acesso à informação. Pode ter também acesso à sua informação médica/biomédica/resultados dos testes através do investigador deste estudo. Tem também o direito de se opor à transmissão de dados que sejam cobertos pela confidencialidade profissional.

Os registos médicos que o identificarem e o formulário de consentimento informado que assina serão verificados para fins do estudo pelo Promotor e/ou por representantes do Promotor, e para fins regulamentares pelo promotor e/ou pelos representantes do promotor e agências reguladoras noutros países. A Comissão de Ética responsável pelo estudo pode solicitar o acesso aos seus registos médicos para assegurar-se que o estudo está a ser realizado de acordo com o protocolo. Não pode ser garantida confidencialidade absoluta devido à necessidade de passar a informação a essas partes.

Ao assinar este termo de consentimento informado, permite que as suas informações médicas neste estudo sejam verificadas, processadas e relatadas conforme for necessário para finalidades científicas legítimas.

Confidencialidade e tratamento de dados pessoais

Os dados pessoais dos participantes no estudo, incluindo a informação médica ou de saúde recolhida ou criada como parte do estudo, (tais como registos médicos ou resultados de testes), serão utilizados para condução do estudo, designadamente para fins de investigação científica e farmacológica relacionados com o medicamento ou com a patologia em estudo.

Ao dar o seu consentimento à participação no estudo, a informação a si respeitante, designadamente a informação experimental/clínica, será utilizada da seguinte forma:

Appendix 4. Informed consent document for healthy controls´ sample (continued)

1. O Promotor, os investigadores e outras pessoas envolvidas no estudo recolherão e utilizarão os seus dados pessoais para as finalidades acima descritas.
2. Os dados do estudo, associados às suas iniciais ou a outro código que não o identifica directamente (e não ao seu nome) serão comunicados pelos investigadores ou outras pessoas envolvidas no estudo ao Promotor do estudo, que os utilizará para as finalidades acima descritas.
3. Os dados do estudo, associados às suas iniciais ou a outro código que não permita identificá-lo directamente, poderão ser comunicados às autoridades de saúde americanas (FDA), à autoridade de saúde europeia (EMA), às autoridades de saúde portuguesas (INFARMED) ou às autoridades de saúde de outros países.
4. A sua identidade não será revelada em quaisquer relatórios ou publicações resultantes deste estudo.
5. Todas as pessoas ou entidades com acesso aos seus dados pessoais estão sujeitas a sigilo profissional.
6. Ao dar o seu consentimento para participar no estudo autoriza o Promotor ou empresas de monitorização de estudos especificamente contratadas para o efeito e seus colaboradores e/ou autoridades de saúde, a aceder aos dados constantes do seu processo clínico, para conferir a informação recolhida e registada pelos investigadores, designadamente para assegurar o rigor dos dados que lhe dizem respeito e para garantir que o estudo se encontra a ser desenvolvido correctamente e que os dados obtidos são fiáveis.
7. Nos termos da lei, tem o direito de, através de um dos médicos envolvidos no estudo, solicitar o acesso aos dados que lhe digam respeito, bem como de solicitar a rectificação dos seus dados de identificação.
8. Tem ainda o direito de retirar este consentimento em qualquer altura através da notificação ao investigador, o que implicará que deixe de participar no estudo. No entanto, os dados recolhidos ou criados como parte do estudo até essa altura que não o(a) identifiquem poderão continuar a ser utilizados para o propósito de estudo, nomeadamente para manter a integridade científica do estudo, e a sua informação médica não será removida do arquivo do estudo.
9. Se não der o seu consentimento, assinando este documento, não poderá participar neste estudo. Se o consentimento agora prestado não for retirado e até que o faça, este será válido e manter-se-á em vigor.

Appendix 4. Informed consent document for healthy controls´ sample (continued)

10. COMPENSAÇÃO

Este é um estudo da iniciativa do investigador e, por isso, não haverá lugar a qualquer compensação financeira para a elaboração e execução deste estudo para os investigadores, o centro de estudo e os participantes. No entanto, se além das visitas previstas neste estudo, planeadas de acordo com a actual prática clínica, lhe forem solicitadas visitas suplementares no âmbito deste estudo, as despesas decorrentes dessas visitas deverão ser-lhe reembolsadas.

11. CONTACTOS

Se tiver perguntas relativas aos seus direitos como participante deste estudo, deve contactar:
Presidente da Comissão de Ética da FMUC,
Azinhaga de Santa Comba, Celas – 3000-548 Coimbra
Telefone: 239 857 707
e-mail: comissaoetica@fmed.uc.pt

Se tiver questões sobre este estudo deve contactar:
Direcção do IBILI/FMUC e
Investigador Principal: Prof. Miguel Castelo-Branco
Contacto Telefónico: 239 480 261

NÃO ASSINE ESTE FORMULÁRIO DE CONSENTIMENTO INFORMADO A MENOS QUE TENHA TIDO A OPORTUNIDADE DE PERGUNTAR E TER RECEBIDO RESPOSTAS SATISFATÓRIAS A TODAS AS SUAS PERGUNTAS.

Appendix 4. Informed consent document for healthy controls´ sample (continued)

CONSENTIMENTO INFORMADO

De acordo com a Declaração de Helsínquia da Associação Médica Mundial:

1. Declaro ter lido este formulário e aceito de forma voluntária participar neste estudo.
2. Fui devidamente informado(a) da natureza, objectivos, riscos, duração provável do estudo, bem como do que é esperado da minha parte.
3. Tive a oportunidade de fazer perguntas sobre o estudo e percebi as respostas e as informações que me foram dadas.

   A qualquer momento posso fazer mais perguntas ao investigador(a). Durante o estudo e sempre que quiser, posso receber informação sobre o desenvolvimento do estudo. O investigador(a) dará toda a informação importante que surja durante o estudo que possa alterar a minha vontade de continuar a participar no estudo.
4. Aceito que utilizem a informação relativa à minha história médica e os meus tratamentos no estrito respeito do segredo médico e anonimato. Os meus dados serão mantidos estritamente confidenciais. Eu autorizo a consulta dos meus dados apenas por pessoas designadas pelo Promotor e por representantes das Autoridades Reguladoras.
5. Aceito seguir todas as instruções que me forem dadas durante o estudo. Aceito em colaborar com o investigador(a) e informá-lo(a) imediatamente das alterações do meu estado de saúde e bem-estar e de todos os sintomas inesperados e não usuais que ocorram.
6. Autorizo o uso dos resultados do estudo e, em particular, aceito que esses resultados sejam divulgados às autoridades de saúde de todos os países.
7. Aceito que os dados gerados durante o Estudo sejam informatizados pelo Promotor ou outrem por si designado. Eu posso exercer o meu direito de rectificação e/ ou oposição.
8. Tenho conhecimento que sou livre de desistir do Estudo a qualquer momento, sem ter de justificar a minha decisão e sem comprometer a qualidade dos meus cuidados médicos. Eu tenho conhecimento que o investigador(a) tem o direito de decidir sobre a minha saída prematura do estudo e que me informará da causa da mesma.
9. Fui informado que o estudo pode ser interrompido por decisão do Investigador, do Promotor ou das Autoridades Reguladoras.

Appendix 4. Informed consent document for healthy controls´ sample (continued)

Nome do Participante ou Representante Legal

_____

Assinatura : _____ ***Data:***_____/____/____

Eu confirmo que expliquei ao participante acima mencionado e ao seu representante legal a natureza, os objectivos e os potenciais riscos do estudo acima mencionado.

Nome do Investigador:_____

Assinatura: _____ ***Data:***_____/____/____

Appendix 5. Case Report Form

DATA: __/__/_____ **NI:** □□□□-□

INVESTIGAÇÃO

A hipótese da hiperativação na insónia psicofisiológica: Estudo da default-mode network e sua modificação após terapia cognitivo-comportamental

CASE REPORT FORM

– A preencher pelo Investigador / Clínico –

PARTE A (Pré-Teste)

– Ambos os grupos –

A1. Data de nascimento
__/__/_____

A2. Sexo:
- □ Masculino
- □ Feminino

A3. Lateralidade manual:
- □ Direita
- □ Esquerda
- □ Ambas

A4. Estado civil:
- □ Solteiro(a)
- □ Casado(a) / União de facto
- □ Separado(a) / Divorciado(a)
- □ Viúvo(a)

A5. Escolaridade:
- □ Não sabe ler nem escrever
- □ 1.º ciclo (1.º até 4.º ano)
- □ 2.º ciclo (5.º e 6.º anos)
- □ 3.º ciclo (7.º até 9.º ano)
- □ Secundário (10.º até 12.º ano)
- □ Ensino Superior

A5.1. N.º de anos de escolaridade concluídos: ____ anos.

A6. Situação profissional:
- □ Ativo/a
- □ Desempregado/a
- □ Reformado/a
- □ Estudante
- □ Outra (trab-estud., doméstica)

*Especificar qual:*_____.

A6.1. Especificar consoante os casos: Profissão exercida atualmente, profissão anteriormente exercida ou área de estudo.

_____

1/10

Appendix 5. Case Report Form (continued)

DATA: __/__/_____ **NI:** □□□□-□

A7. Distúrbios do sono (de acordo com a ICSD, AASM, 2005)

A.7.1. Existe historial de problemas de sono? Sim □ Não □

A.7.2. Se sim, assinalar e especificar qual(ais)?

□ Insónias: _____
□ Perturbações do sono relacionadas com a respiração: _____
□ Hiperssónias de origem central: _____
□ Perturbações do ritmo circadiano: _____
□ Parassónias: _____
□ Perturbações do sono relacionadas com o movimento: _____
□ Sintomas isolados e variantes normais: _____
□ Outras perturbações de sono: _____

A8. Psicopatologia (de acordo com o DSM-IV-TR, 2002)

A.8.1. Existe historial de problemas psiquiátricos / saúde mental? Sim □ Não □

A.8.2. Se sim, assinalar e especificar qual(ais)?

□ Perturbações do humor: _____
□ Perturbações da ansiedade: _____
□ Perturbações psicóticas:_____
□ Perturbações da personalidade: _____
□ Perturbações habituais na infância / adolescência: _____
□ Perturbações sexuais:_____
□ Perturbações relacionadas com o uso de substâncias:_____
□ Outras perturbações psiquiátricas: _____

A9. Distúrbios neurológicos

A.9.1. Existe historial de problemas neurológicos? Sim □ Não □

A.9.2. Se sim, assinalar e especificar qual(ais)?

□ Demências:_____
□ Doença de Parkinson:_____
□ Cefaleias / Enxaquecas:_____
□ Epilepsia: _____
□ AVC: _____
□ Traumatismos crânio-encefálicos: _____
□ Outras perturbações neurológicas: _____

A10. Outros problemas médicos

A.10.1. Existe historial de outros problemas médicos? Sim □ Não □

A.10.2. Se sim, assinalar e especificar qual(ais)?

□ Fibromialgia: _____
□ Diabetes: _____
□ Doenças reumáticas:_____
□ Dor crónica: _____
□ Doenças cardiovasculares: _____
□ Outras perturbações médicas: _____

2/10

Appendix 5. Case Report Form (continued)

DATA: __/__/_____ **NI:** □□□□-□

A11. Medicação

A.11.1. O participante toma algum tipo de medicação regularmente? Sim □ Não □

A.11.2. Se sim, especificar:

Medicação	*Dosagem*	*Problema de saúde*
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____

A12. Escalas de auto-avaliação aplicadas e resultados:

□ WHOQOL-Bref

WHOQOL-Bref_Geral: ____
WHOQOL-Bref_Físico: ____
WHOQOL-Bref_Psicológico: ____
WHOQOL-Bref_Relações sociais: ____
WHOQOL-Bref_Ambiente: ____

□ DBAS-30

DBAS-30_Total: ____
DBAS-30 (F1) crenças erradas acerca das causas da insónia: ____
DBAS-30 (F2) perceção diminuída de controlo e previsibilidade do sono: ____
DBAS-30 (F3) expectativas irrealistas de sono: ____
DBAS-30 (F4) atribuição errada ou amplificação das consequências da insónia: ____
DBAS-30 (F5) crenças erradas acerca dos hábitos de promoção do sono____

□ ISI

ISI_Total: ____

A13. Dados objetivos do comportamento de sono:

□ Atigrafia (total)

Média-TIB: ____ (minutos) Mín.____ Máx. ____
Média-TST: ____ (minutos) Mín.____ Máx. ____
Média-SOL: ____ (minutos) Mín.____ Máx. ____
Média-WASO: ____ (minutos) Mín.____ Máx. ____
Hora média de deitar: __:__ [hh:mm] :: Hora média de adormecer __:__ [hh:mm]
Hora média de acordar: __:__ [hh:mm] :: Hora média de levantar __:__ [hh:mm]
Eficiência de Sono: ____ %

3/10

Appendix 5. Case Report Form (continued)

DATA: __/__/_____ **NI:** □□□□-□

□ Atigrafia (semana)
Média-TIB: ____ (minutos) Mín.____ Máx. ____
Média-TST: ____ (minutos) Mín.____ Máx. ____
Média-SOL: ____ (minutos) Mín.____ Máx. ____
Média-WASO: ____ (minutos) Mín.____ Máx. ____
Hora média de deitar: __:__ [hh:mm] :: Hora média de adormecer __:__ [hh:mm]
Hora média de acordar: __:__ [hh:mm] :: Hora média de levantar __:__ [hh:mm]
Eficiência de Sono: ____ %

□ Atigrafia (fim de semana)
Média-TIB: ____ (minutos) Mín.____ Máx. ____
Média-TST: ____ (minutos) Mín.____ Máx. ____
Média-SOL: ____ (minutos) Mín.____ Máx. ____
Média-WASO: ____ (minutos) Mín.____ Máx. ____
Hora média de deitar: __:__ [hh:mm] :: Hora média de adormecer __:__ [hh:mm]
Hora média de acordar: __:__ [hh:mm] :: Hora média de levantar __:__ [hh:mm]
Eficiência de Sono: ____ %

A14. Dados subjetivos do comportamento de sono:

□ Diário de sono (total)
Média-TIB: ____ (minutos) Mín.____ Máx. ____
Média-TST: ____ (minutos) Mín.____ Máx. ____
Média-SOL: ____ (minutos) Mín.____ Máx. ____
Média-WASO: ____ (minutos) Mín.____ Máx. ____
Hora média de deitar: __:__ [hh:mm] :: Hora média de adormecer __:__ [hh:mm]
Hora média de acordar: __:__ [hh:mm] :: Hora média de levantar __:__ [hh:mm]
Eficiência de Sono: ____ %

□ Diário de sono (semana)
Média-TIB: ____ (minutos) Mín.____ Máx. ____
Média-TST: ____ (minutos) Mín.____ Máx. ____
Média-SOL: ____ (minutos) Mín.____ Máx. ____
Média-WASO: ____ (minutos) Mín.____ Máx. ____
Hora média de deitar: __:__ [hh:mm] :: Hora média de adormecer __:__ [hh:mm]
Hora média de acordar: __:__ [hh:mm] :: Hora média de levantar __:__ [hh:mm]
Eficiência de Sono: ____ %

□ Diário de sono (fim de semana)
Média-TIB: ____ (minutos) Mín.____ Máx. ____
Média-TST: ____ (minutos) Mín.____ Máx. ____
Média-SOL: ____ (minutos) Mín.____ Máx. ____
Média-WASO: ____ (minutos) Mín.____ Máx. ____
Hora média de deitar: __:__ [hh:mm] :: Hora média de adormecer __:__ [hh:mm]
Hora média de acordar: __:__ [hh:mm] :: Hora média de levantar __:__ [hh:mm]
Eficiência de Sono: ____ %

4/10

Appendix 5. Case Report Form (continued)

DATA: __/__/_____ **NI:** □□□□-□

A15. O participante realizou o estudo neuroimagiológico pré-teste?

□ Sim. Indicar data: __/ __/ 20__
□ Não.

Questionar o participante diretamente:

A16. Tendo em conta as listas de palavras que lhe foram apresentadas na sessão de ressonância magnética funcional, avalie em que medida…

A16.1. As palavras referentes ao passado/presente lhe fizeram recordar os acontecimentos aos quais faziam referência:

☐Nada

☐Um pouco

☐Muito

☐Muitíssimo

A16.2. As palavras referentes ao futuro lhe fizeram recordar os acontecimentos aos quais faziam referência:

☐ Nada

☐ Um pouco

☐ Muito

☐ Muitíssimo

A17. Tendo em conta a última instrução que lhe foi dada enquanto estava na máquina de ressonância magnética funcional: "*Abra os olhos e procure relaxar. Se sentir necessidade de dormir pode fechar os olhos*", refira em que medida sentiu sonolência durante esse período:

☐ Nenhuma sonolência

☐ Pouca sonolência

☐ Bastante sonolência, mas não chegando a dormir

☐ Muita sonolência, chegando mesmo a dormir

5/10

Appendix 5. Case Report Form (continued)

DATA: __/__/_____ **NI:** □□□□-□

PARTE B
– Grupo Clínico –

B1. Tipo de insónia psicofisiológica (Assinalar, se necessário, mais do que uma opção):
- □ Inicial
- □ Intermédia
- □ Terminal
- □ Sono não reparador

B2. Frequência da sintomatologia:
N.º de noites por semana (em média): ____.

B3. Duração média das queixas de insónia: ____ (meses).

B4. N.º de sessões de psicoterapia concluídas: ____.

B5. Mudanças significativas no plano terapêutico (e.g., medicação) suscetíveis de interferir com o processo de tratamento.

B6. Mudanças significativas na vida do doente suscetíveis de interferir com o processo de tratamento.

6/10

Appendix 5. Case Report Form (continued)

DATA: __/__/_____ **NI:** □□□□-□

PARTE C (Pós-Teste)
– Ambos os grupos –

C1. Escalas de auto-avaliação aplicadas e resultados

□ WHOQOL
WHOQOL_Geral: ____
WHOQOL_Físico: ____
WHOQOL_Psicológico: ____
WHOQOL_Relações sociais: ____
WHOQOL_Ambiente: ____

□ DBAS-30
DBAS-30_Total: ____
DBAS-30_ (F1) crenças erradas acerca das causas da insónia: ____
DBAS-30_ (F2) perceção diminuída de controlo e previsibilidade do sono: ____
DBAS-30_ (F3) expectativas irrealistas de sono: ____
DBAS-30_ (F4) atribuição errada ou amplificação das consequências da insónia: ____
DBAS-30_ (F5) crenças erradas acerca dos hábitos de promoção do sono____

□ ISI
ISI_Total: ____

C2. Dados objetivos do comportamento de sono

□ Atigrafia (total)
Média-TIB: ____ (minutos) Mín.____ Máx. ____
Média-TST: ____ (minutos) Mín.____ Máx. ____
Média-SOL: ____ (minutos) Mín.____ Máx. ____
Média-WASO: ____ (minutos) Mín.____ Máx. ____
Hora média de deitar: __:__ [hh:mm] :: Hora média de adormecer __:__ [hh:mm]
Hora média de acordar: __:__ [hh:mm] :: Hora média de levantar __:__ [hh:mm]
Eficiência de Sono: ____ %

□ Atigrafia (semana)
Média-TIB: ____ (minutos) Mín.____ Máx. ____
Média-TST: ____ (minutos) Mín.____ Máx. ____
Média-SOL: ____ (minutos) Mín.____ Máx. ____
Média-WASO: ____ (minutos) Mín.____ Máx. ____
Hora média de deitar: __:__ [hh:mm] :: Hora média de adormecer __:__ [hh:mm]
Hora média de acordar: __:__ [hh:mm] :: Hora média de levantar __:__ [hh:mm]
Eficiência de Sono: ____ %

7/10

Appendix 5. Case Report Form (continued)

DATA: __/__/_____ **NI:** □□□□-□

□ Atigrafia (fim de semana)
Média-TIB: ____ (minutos) Mín.____ Máx. ____
Média-TST: ____ (minutos) Mín.____ Máx. ____
Média-SOL: ____ (minutos) Mín.____ Máx. ____
Média-WASO: ____ (minutos) Mín.____ Máx. ____
Hora média de deitar: __:__ [hh:mm] :: Hora média de adormecer __:__ [hh:mm]
Hora média de acordar: __:__ [hh:mm] :: Hora média de levantar __:__ [hh:mm]
Eficiência de Sono: ____ %

C3. Dados subjetivos do comportamento de sono:

□ Diário de sono (total)
Média-TIB: ____ (minutos) Mín.____ Máx. ____
Média-TST: ____ (minutos) Mín.____ Máx. ____
Média-SOL: ____ (minutos) Mín.____ Máx. ____
Média-WASO: ____ (minutos) Mín.____ Máx. ____
Hora média de deitar: __:__ [hh:mm] :: Hora média de adormecer __:__ [hh:mm]
Hora média de acordar: __:__ [hh:mm] :: Hora média de levantar __:__ [hh:mm]
Eficiência de Sono: ____ %

□ Diário de sono (semana)
Média-TIB: ____ (minutos) Mín.____ Máx. ____
Média-TST: ____ (minutos) Mín.____ Máx. ____
Média-SOL: ____ (minutos) Mín.____ Máx. ____
Média-WASO: ____ (minutos) Mín.____ Máx. ____
Hora média de deitar: __:__ [hh:mm] :: Hora média de adormecer __:__ [hh:mm]
Hora média de acordar: __:__ [hh:mm] :: Hora média de levantar __:__ [hh:mm]
Eficiência de Sono: ____ %

□ Diário de sono (fim de semana)
Média-TIB: ____ (minutos) Mín.____ Máx. ____
Média-TST: ____ (minutos) Mín.____ Máx. ____
Média-SOL: ____ (minutos) Mín.____ Máx. ____
Média-WASO: ____ (minutos) Mín.____ Máx. ____
Hora média de deitar: __:__ [hh:mm] :: Hora média de adormecer __:__ [hh:mm]
Hora média de acordar: __:__ [hh:mm] :: Hora média de levantar __:__ [hh:mm]
Eficiência de Sono: ____ %

C4. O participante realizou o estudo neuroimagiológico pós-teste?

□ Sim. Indicar data: __/ __/ 20__
□ Não.

8/10

Appendix 5. Case Report Form (continued)

DATA: __/__/_____ **NI:** □□□□-□

Questionar o participante diretamente:

C5. Tendo em conta as listas de palavras que lhe foram apresentadas na sessão de ressonância magnética funcional, avalie em que medida…

C5.1. As palavras referentes ao passado/presente lhe fizeram recordar os acontecimentos aos quais faziam referência:

☐Nada

☐Um pouco

☐ Muito

☐Muitíssimo

C5.2. As palavras referentes ao futuro lhe fizeram recordar os acontecimentos aos quais faziam referência:

☐ Nada

☐ Um pouco

☐ Muito

☐ Muitíssimo

C6. Tendo em conta a última instrução que lhe foi dada enquanto estava na máquina de ressonância magnética funcional "*Abra os olhos e procure relaxar. Se sentir necessidade de dormir pode fechar os olhos*", refira em que medida sentiu sonolência durante esse período:

☐ Nenhuma sonolência

☐ Pouca sonolência

☐ Bastante sonolência, mas não chegando a dormir

☐ Muita sonolência, chegando mesmo a dormir

C7. O participante colaborou na investigação até ao final?

☐ Sim.
☐ Não. Indicar motivo(s): _____
_____
_____
_____

9/10

Appendix 5. Case Report Form (continued)

DATA: __/__/_____ **NI:** □□□□-□

SÓ PARA A AMOSTRA CLÍNICA

C8. Como é que o doente classifica, subjetivamente, a sua evolução clínica após a intervenção psicológica?

- □ Está muito melhor
- □ Está melhor
- □ Nem melhor nem pior
- □ Está pior
- □ Está muito pior

C9. Como é que o clínico classifica a evolução clínica do doente após a intervenção psicológica?

- □ Está muito melhor
- □ Está melhor
- □ Nem melhor nem pior
- □ Está pior
- □ Está muito pior

Notas:

10/10

Appendix 6. Document on constitution of list of words for fMRI

NI: □□□□-□

INVESTIGAÇÃO

A hipótese da hiperativação na insónia psicofisiológica: Estudo da default-mode network e sua modificação após terapia cognitivo-comportamental

Instruções:

Caro(a) participante,

Nesta tarefa iremos pedir-lhe para gerar 15 conjuntos de palavras para compor 3 listas (uma lista composta por 15 conjuntos de palavras que constituíram preocupações que teve no *passado* ou que tem no momento *presente*, uma lista que conterá 15 conjuntos de palavras que para si constituem preocupações relativas ao *futuro* e uma outra lista que deverá ser composta por 15 conjuntos de palavras *neutras*, ou seja, que não lhe fazem recordar nada de emocionalmente significativo).

Antes de realizar esta tarefa analise com atenção as próximas folhas; elas constituem um exemplo já preenchido que o(a) poderão ajudar a perceber melhor o objetivo da tarefa que lhe pedimos.

Qualquer dúvida que tenha poderá esclarecê-la junto do investigador responsável.

Muito obrigado pela sua colaboração!

Investigador responsável
Dr. Daniel Ruivo Marques
E-mail: drmarques@ua.pt

Appendix 6. Document on constitution of list of words for fMRI (continued)

NI: □□□□-□

EXEMPLO

FOLHA DE REGISTO DO PROTOCOLO DE ESTIMULAÇÃO PARA IRMf

BLOCO DE PALAVRAS ACERCA DE PREOCUPAÇÕES SOBRE O PASSADO/PRESENTE

As mesmas palavras podem ter significados emocionais diferentes para pessoas diferentes e como tal fazer evocar memórias distintas. Por exemplo, para uma pessoa no momento atual que vive, as palavras "desemprego do filho", podem causar ativação emocional relembrando-a da situação de desemprego atual do filho. Por outro lado, para outra pessoa, essas palavras podem não significar nada em particular que seja emocionalmente significativo ou ativador no momento presente.

Abaixo irá encontrar 15 espaços para completar com palavras que para si representam ou lhe fazem lembrar preocupações que tem relativamente ao presente ou a situações que vivenciou no passado. Deve utilizar no mínimo 2 e no máximo 3 palavras por espaço, desde que, neste último caso, uma palavra seja de ligação, como por exemplo, "de", "com", "na", etc.

Por favor, tente ser o(a) mais objetivo possível e utilize letras maiúsculas para facilitar a compreensão (Exemplo: DESEMPREGO DO FILHO).

1. DOENÇA JOANA
2. COMUNICAÇÃO OPP
3. CIRURGIA JOELHO
4. MORTE DE AVÔ
5. RELAÇÃO COM GRAÇA
6. ESCOLHA DO CURSO
7. RELAÇÃO COM SOFIA
8. DEFESA MESTRADO
9. NOTA ESTÁGIO
10. EXAMES NACIONAIS
11. DESEMPREGO IRMÃO
12. RELAÇÃO COM JULIANA
13. CONSULTAS REUMATOLOGIA
14. AULAS UNIVERSIDADE
15. ACIDENTE DE CARRO

Appendix 6. Document on constitution of list of words for fMRI (continued)

NI: □□□□-□

EXEMPLO

FOLHA DE REGISTO DO PROTOCOLO DE ESTIMULAÇÃO PARA IRMf

BLOCO DE PALAVRAS ACERCA DE PREOCUPAÇÕES SOBRE O FUTURO

As mesmas palavras podem ter significados emocionais diferentes para pessoas diferentes e como tal fazer evocar memórias distintas.

Abaixo irá encontrar 15 espaços para completar com palavras que para si representam ou lhe lembram preocupações que tem relativamente ao futuro. Deve utilizar no mínimo 2 e no máximo 3 palavras por espaço, desde que, neste último caso, uma palavra seja de ligação, como por exemplo, "de", "com", "na", etc.

Por favor, tente ser o(a) mais objetivo possível e utilize letras maiúsculas para facilitar a compreensão (Exemplo: CRÉDITO 2012).

1. VIAGENS DE TRABALHO
2. SAÚDE AVÓ
3. RELAÇÃO COM NAMORADA
4. CRISE ECONÓMICA
5. SAÚDE DOS PAIS
6. EMPREGO FUTURO
7. FICAR SOZINHO
8. FINALIZAR TESE
9. LECIONAR NA UNIVERSIDADE
10. FUTURO DO PAÍS
11. TER FILHOS
12. DOENÇAS FUTURAS
13. RELAÇÃO COM AMIGOS
14. ESTÁGIO OPP
15. CONTRATO FCT

Appendix 6. Document on constitution of list of words for fMRI (continued)

NI: □□□□-□

EXEMPLO

FOLHA DE REGISTO DO PROTOCOLO DE ESTIMULAÇÃO PARA IRMf

BLOCO DE PALAVRAS NEUTRAS

As mesmas palavras podem ter significados emocionais diferentes para pessoas diferentes e como tal fazer evocar memórias distintas.

Abaixo irá encontrar 15 espaços para completar com palavras que para si não têm nenhum significado emocional, em especial, no momento atual.

Deve utilizar no mínimo 2 e no máximo 3 palavras por espaço, desde que, neste último caso, uma palavra seja de ligação, como por exemplo, "de", "com", "na", etc.

Por favor, tente ser o(a) mais objetivo possível e utilize letras maiúsculas para facilitar a compreensão (Exemplo: PORTA DA GARAGEM).

1. MAÇÃ VERMELHA
2. RIO VOUGA
3. JORNAL DE NOTÍCIAS
4. TOALHA DE MESA
5. GUARDA-CHUVA
6. LÂMPADA ACESSA
7. COPO DE ÁGUA
8. CAIXA DE CARTÃO
9. RODA DE BICICLETA
10. RATO DE COMPUTADOR
11. PAREDE BRANCA
12. LIVRO DE RECEITAS
13. LÁPIS DE COR
14. MOLA DA ROUPA
15. VASO DO JARDIM

Appendix 6. Document on constitution of list of words for fMRI (continued)

NI: □□□□-□

INVESTIGAÇÃO

A hipótese da hiperativação na insónia psicofisiológica: Estudo da default-mode network e sua modificação após terapia cognitivo-comportamental

FOLHA DE REGISTO DO PROTOCOLO DE ESTIMULAÇÃO PARA IRMf

BLOCO DE PALAVRAS ACERCA DE PREOCUPAÇÕES SOBRE O PASSADO/PRESENTE

As mesmas palavras podem ter significados emocionais diferentes para pessoas diferentes e como tal fazer evocar memórias distintas. Por exemplo, para uma pessoa no momento atual que vive, as palavras "desemprego do filho", pode causar ativação emocional negativa relembrando-a da situação de desemprego atual do filho. Por outro lado, para outra pessoa essas palavras podem não significar nada em particular que seja emocionalmente significativo ou ativador no momento presente.

Abaixo irá encontrar 15 espaços para completar com palavras que para si representam ou lhe fazem lembrar preocupações que tem relativamente ao presente ou situações que vivenciou no passado. Pode utilizar no máximo 3 palavras por espaço, desde que uma seja de ligação, como por exemplo, "de", "com", "na", etc.

Por favor, tente ser o(a) mais objetivo possível e utilize letras maiúsculas para facilitar a compreensão (Exemplo: DESEMPREGO DO FILHO).

1._____

2._____

3._____

4._____

5._____

6._____

7._____

8._____

9._____

10._____

11._____

12._____

13._____

14._____

15._____

Appendix 6. Document on constitution of list of words for fMRI (continued)

NI: □□□□-□

INVESTIGAÇÃO

A hipótese da hiperativação na insónia psicofisiológica: Estudo da default-mode network e sua modificação após terapia cognitivo-comportamental

FOLHA DE REGISTO DO PROTOCOLO DE ESTIMULAÇÃO PARA IRMf

BLOCO DE PALAVRAS ACERCA DE PREOCUPAÇÕES SOBRE O FUTURO

As mesmas palavras podem ter significados emocionais diferentes para pessoas diferentes e como tal fazer evocar memórias distintas.

Abaixo irá encontrar 15 espaços para completar com palavras que para si representam ou lhe lembram preocupações que tem relativamente ao futuro. Pode utilizar no máximo 3 palavras por espaço, desde que uma seja de ligação, como por exemplo, "de", "com", "na", etc.

Por favor, tente ser o(a) mais objetivo possível e utilize letras maiúsculas para facilitar a compreensão (Exemplo: CRÉDITO 2012).

1._____

2._____

3._____

4._____

5._____

6._____

7._____

8._____

9._____

10._____

11._____

12._____

13._____

14._____

15._____

Appendix 6. Document on constitution of list of words for fMRI (continued)

NI: □□□□-□

INVESTIGAÇÃO

A hipótese da hiperativação na insónia psicofisiológica: Estudo da default-mode network e sua modificação após terapia cognitivo-comportamental

FOLHA DE REGISTO DO PROTOCOLO DE ESTIMULAÇÃO PARA IRMf

BLOCO DE PALAVRAS NEUTRAS

As mesmas palavras podem ter significados emocionais diferentes para pessoas diferentes e como tal fazer evocar memórias distintas.

Abaixo irá encontrar 15 espaços para completar com palavras que para si não têm nenhum significado emocional, em especial, no momento atual.

Por favor, tente ser o(a) mais objetivo possível e utilize letras maiúsculas para facilitar a compreensão (Exemplo: PORTA DA GARAGEM).

1._____
2._____
3._____
4._____
5._____
6._____
7._____
8._____
9._____
10._____
11._____
12._____
13._____
14._____
15._____

Appendix 7. Request for WHOQOL-Bref´s using

FORMULÁRIO WHOQOL *

Centro Português da Organização Mundial de Saúde (OMS) para Avaliação da Qualidade de Vida

1. Instrumento

☐ WHOQOL – 100 ■ WHOQOL - bref

2. Identificação do Estudo/Projecto

A hipótese da hiperativação na insónia psicofisiológica: Estudo da *default-mode network* e sua modificação após terapia cognitivo-comportamental (Tese de Doutoramento)

3. Identificação do Investigador Responsável ou [para alunos] Orientador/supervisor de projecto/tese

Nome: Daniel Ruivo Marques

Morada: R. Luís de Camões, n.º 155
3830-696 Gafanha da Nazaré

Telefone: 916 719 651

E-mail: drmarques@iol.pt

4. Identificação dos elementos da equipa do projecto

Mestre Daniel Ruivo Marques – Aluno do Programa Doutoral em Psicologia da Universidade de Aveiro e Bolseiro de Doutoramento da Fundação para a Ciência e Tecnologia (FCT).

Prof. Doutora Ana Allen Gomes (Orientadora) – Professora Auxiliar do Departamento de Educação da Universidade de Aveiro.

Prof. Doutor Miguel Castelo-Branco (Co-Orientador) – Professor Auxiliar da Faculdade de Medicina da Universidade de Coimbra. Diretor do Instituto Biomédico de Investigação da Luz e da Imagem (IBILI).

Mestre Vanda Clemente – Psicóloga Clínica especialista do Centro Hospitalar de Coimbra.

Dr. José Moutinho dos Santos – Médico Pneumologista. Diretor do Centro de Medicina de Sono do Centro Hospitalar de Coimbra (CMS-CHC).

5. Objectivos do Projecto

Esta investigação tem como **objetivo principal** estudar as componentes da *default-mode network* (DMN) envolvidas em processos auto-referenciais e temporais (i.e., passado/presente e futuro) e suas eventuais alterações numa amostra clínica de indivíduos diagnosticados com insónia comparativamente com uma amostra controlo. Posteriormente, no grupo clínico, pretende-se verificar se esses indicadores são modificados após uma intervenção psicológica empiricamente validada (i.e., terapia cognitivo-comportamental). Pretende-se explorar eventuais alterações relacionadas com a DMN em indivíduos diagnosticados com insónia, durante o dia e em estado de vigília, recorrendo ao paradigma da provocação de sintomas em estado de vigília e da *resting state network* (RSN) e utilizando a ressonância magnética funcional (fMRI). Prevê-se relacionar estes indicadores com outras medidas objectivas (actígrafo) e subjectivas (questionários) de sono assim como com uma medida de auto-relato referente à qualidade de vida.

6. Dados Metodológicos

5.1. Tipo de população

Grupo clínico constituído por doentes com diagnóstico primário de insónia psicofisiológica;

Grupo de controlo constituído por pessoas sem qualquer tipo de perturbações de sono / psiquiátricas.

Appendix 7. Request for WHOQOL-Bref´s using (continued)

5.2. Tamanho da amostra

Grupo clínico: Espera-se, pelo menos, obter um n=20

Grupo de controlo: Espera-se, pelo menos, obter um n=20

5.3. Bateria de avaliação (outros instrumentos)

Escala de Atitudes e Crenças sobre o Sono [DBAS-30; Dysfunctional Beliefs and Attitudes about Sleep] (Morin, 1993; Tradução Portuguesa: Clemente, 2007).

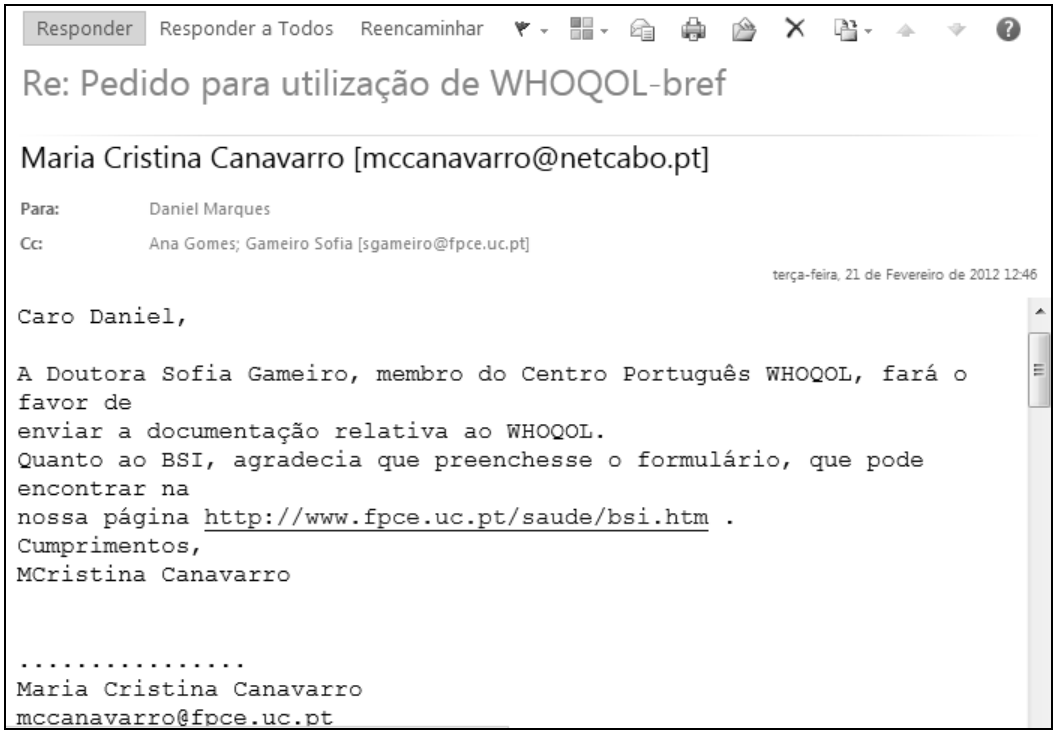
Escala de Gravidade de Insónia [ISS; Insomnia Severity Scale] (Morin, 1993; Bastien, Vallières & Morin, 2001; Tradução Portuguesa: Clemente, 2010).

Eventualmente, outras provas a definir.

Data: Aveiro, 20 de Fevereiro de 2012 **Assinatura:** Daniel Ruivo Marques

- **Enviar para**: mccanavarro@fpce.uc.pt
  Ou Professora Doutora Maria Cristina Sousa Canavarro
  Faculdade de Psicologia e de Ciências da Educação da Universidade de Coimbra
  Rua do Colégio Novo – Apartado 6153
  3001-802 Coimbra

Appendix 8. Permission to use the WHOQOL-Bref



Responder | Responder a Todos | Reencaminhar

Re: Pedido para utilização de WHOQOL-bref

Maria Cristina Canavarro [mccanavarro@netcabo.pt]

Para: Daniel Marques

Cc: Ana Gomes; Gameiro Sofia [sgameiro@fpce.uc.pt]

terça-feira, 21 de Fevereiro de 2012 12:46

Caro Daniel,

A Doutora Sofia Gameiro, membro do Centro Português WHOQOL, fará o favor de
enviar a documentação relativa ao WHOQOL.
Quanto ao BSI, agradecia que preenchesse o formulário, que pode encontrar na
nossa página http://www.fpce.uc.pt/saude/bsi.htm .
Cumprimentos,
MCristina Canavarro

.....
Maria Cristina Canavarro
mccanavarro@fpce.uc.pt

Appendix 9. WHOQOL-Bref questionnaire

Instruções

Este questionário procura conhecer a sua qualidade de vida, saúde, e outras áreas da sua vida.

Por favor, responda a todas as perguntas. Se não tiver a certeza da resposta a dar a uma pergunta, escolha a que lhe parecer mais apropriada. Esta pode muitas vezes ser a resposta que lhe vier primeiro à cabeça.

Por favor, tenha presente os seus padrões, expectativas, alegrias e preocupações. Pedimos-lhe que tenha em conta a sua vida nas **duas últimas semanas**.

Por exemplo, se pensar nestas duas últimas semanas, pode ter que responder à seguinte pergunta:

	Nada	Pouco	Moderadamente	Bastante	Completamente
Recebe das outras pessoas o tipo de apoio que necessita?	1	2	3	4	5

Deve pôr um círculo à volta do número que melhor descreve o apoio que recebeu das outras pessoas nas duas últimas semanas. Assim, marcaria o número 4 se tivesse recebido bastante apoio, ou o número 1 se não tivesse tido nenhum apoio dos outros nas duas últimas semanas.

Por favor leia cada pergunta, veja como se sente a respeito dela, e ponha um círculo à volta do número da escala para cada pergunta que lhe parece que dá a melhor resposta.

		Muito Má	Má	Nem Boa Nem Má	Boa	Muito Boa
1 (G1)	Como avalia a sua qualidade de vida?	1	2	3	4	5

		Muito Insatisfeito	Insatisfeito	Nem satisfeito nem insatisfeito	Satisfeito	Muito Satisfeito
2 (G4)	Até que ponto está satisfeito(a) com a sua saúde?	1	2	3	4	5

As perguntas seguintes são para ver até que ponto sentiu certas coisas nas duas últimas semanas.

		Nada	Pouco	Nem muito nem pouco	Muito	Muitíssimo
3 (F1.4)	Em que medida as suas dores (físicas) o(a) impedem de fazer o que precisa de fazer?	1	2	3	4	5
4 (F11.3)	Em que medida precisa de cuidados médicos para fazer a sua vida diária?	1	2	3	4	5
5 (F4.1)	Até que ponto gosta da vida?	1	2	3	4	5
6 (F24.2)	Em que medida sente que a sua vida tem sentido?	1	2	3	4	5
7 (F5.3)	Até que ponto se consegue concentrar?	1	2	3	4	5
8 (F16.1)	Em que medida se sente em segurança no seu dia-a-dia?	1	2	3	4	5
9 (F22.1)	Em que medida é saudável o seu ambiente físico?	1	2	3	4	5

WHOQOL-BREF 3

Appendix 9. WHOQOL-Bref questionnaire (continued)

As seguintes perguntas são para ver **até que ponto** experimentou ou foi capaz de fazer certas coisas nas duas últimas semanas.

		Nada	Pouco	Moderadamente	Bastante	Completamente
10 (F2.1)	Tem energia suficiente para a sua vida diária?	1	2	3	4	5
11 (F7.1)	É capaz de aceitar a sua aparência física?	1	2	3	4	5
12 (F18.1)	Tem dinheiro suficiente para satisfazer as suas necessidades?	1	2	3	4	5
13 (F20.1)	Até que ponto tem fácil acesso às informações necessárias para organizar a sua vida diária?	1	2	3	4	5
14 (F21.1)	Em que medida tem oportunidade para realizar actividades de lazer?	1	2	3	4	5

		Muito Má	Má	Nem boa nem má	Boa	Muito Boa
15 (F9.1)	Como avaliaria a sua mobilidade [capacidade para se movimentar e deslocar por si próprio(a)]?	1	2	3	4	5

As perguntas que se seguem destinam-se a avaliar se se sentiu **bem ou satisfeito(a)** em relação a vários aspectos da sua vida nas duas últimas semanas.

		Muito Insatisfeito	Insatisfeito	Nem satisfeito nem insatisfeito	Satisfeito	Muito Satisfeito
16 (F3.3)	Até que ponto está satisfeito(a) com o seu sono?	1	2	3	4	5
17 (F10.3)	Até que ponto está satisfeito(a) com a sua capacidade para desempenhar as actividades do seu dia-a-dia?	1	2	3	4	5
18 (F12.4)	Até que ponto está satisfeito(a) com a sua capacidade de trabalho?	1	2	3	4	5
19 (F6.3)	Até que ponto está satisfeito(a) consigo próprio(a)?	1	2	3	4	5
20 (F13.3)	Até que ponto está satisfeito(a) com as suas relações pessoais?	1	2	3	4	5
21 (F15.3)	Até que ponto está satisfeito(a) com a sua vida sexual?	1	2	3	4	5
22 (F14.4)	Até que ponto está satisfeito(a) com o apoio que recebe dos seus amigos?	1	2	3	4	5
23 (F17.3)	Até que ponto está satisfeito(a) com as condições do lugar em que vive?	1	2	3	4	5
24 (F19.3)	Até que ponto está satisfeito(a) com o acesso que tem aos serviços de saúde?	1	2	3	4	5
25 (F23.3)	Até que ponto está satisfeito(a) com os transportes que utiliza?	1	2	3	4	5

As perguntas que se seguem referem-se à **frequência** com que sentiu ou experimentou certas coisas nas duas últimas semanas.

		Nunca	Poucas vezes	Algumas vezes	Frequentemente	Sempre
26 (F8.1)	Com que frequência tem sentimentos negativos, tais como tristeza, desespero, ansiedade ou depressão?	1	2	3	4	5

DIÁRIO DO SONO (Morin, 1993; Adapt. Clemente, V., 2006)

Nome: _____ **Data:** _____ **a** _____

INSTRUÇÕES

Para melhor compreender o seu problema do sono e para registar os progressos durante o tratamento, deve registar os dados importantes sobre o seu padrão do sono. Após levantar-se, responda às 10 questões do diário do sono. É importante que complete este diário todas as manhãs. Por exemplo, quando se levanta numa 4ª feira, deve completar a coluna correspondente à 3ª feira. É difícil calcular quando tempo leva a adormecer ou quanto tempo está acordado durante a noite. Lembre-se que deve registar apenas a melhor estimativa. Se acontecer algo pouco habitual numa determinada noite, faça um breve apontamento.

	2ª feira	3ª feira	4ª feira	5ª feira	6ª feira	sábado	domingo
1. Fiz sesta das ____ horas às ____ horas (registe os horários de todas as sestas).							
2. Tomei ____ mg do medicamento ____ e/ou ____ cl de alcóol como ajuda para dormir.							
3. Fui para a cama às ____ horas e deliguei a luz às ____ horas.							
4. Após ter deligado a luz, adormeci em ____ minutos.							
5. O meu sono foi interrompido ____ vezes (especifique o número de acordares nocturnos.							
6. O meu sono foi interrompido ____ minutos (especifique a duração de cada acordar nocturno).							
7. Acordei às ____ horas (registe o horário do último acordar).							
8. Levantei-me da cama às ____ horas (especifique o horário).							
9. Quando me levantei, esta manhã, senti-me ____ . 1 = exausto,; 2 = cansado; 3 = médio; 4 = quase repousado; 5 = muito repousado							
10. Globalmente, o meu sono durante a noite passada foi ____ . 1 = muito agitado; 2 = agitado; 3 = médio; 4 = sossegado; 5 = muito sossegado							

Appendix 11. DBAS-30 scale

DBAS – 30

(Morin, C., 1993; Clemente, V., 2013)

Apresentamos diversas afirmações que reflectem crenças e atitudes das pessoas acerca do sono. Por favor, indique em que medida concorda ou discorda com cada uma das afirmações. Não existe uma resposta certa ou errada.

Para cada uma das afirmações, coloque um círculo no número que corresponde à sua opinião pessoal. Por favor, responda a todos os itens, mesmo que algum deles não se aplique directamente à sua situação.

1) Preciso de dormir 8 horas para me sentir revigorado e funcionar bem durante o dia.

Discordo Totalmente — Concordo Totalmente

0 1 2 3 4 5 6 7 8 9 10

2) Quando não durmo o suficiente numa determinada noite, preciso de recuperar no dia seguinte, fazendo uma sesta ou dormindo mais na noite a seguir.

Discordo Totalmente — Concordo Totalmente

0 1 2 3 4 5 6 7 8 9 10

3) Como estou a ficar mais velho, preciso de dormir menos.

Discordo Totalmente — Concordo Totalmente

0 1 2 3 4 5 6 7 8 9 10

4) Receio que, se passar 1 ou 2 noites sem dormir, venha a ter um esgotamento nervoso.

Discordo Totalmente — Concordo Totalmente

0 1 2 3 4 5 6 7 8 9 10

5) Preocupa-me que a insónia crónica possa ter graves consequências na minha saúde física.

Discordo Totalmente — Concordo Totalmente

0 1 2 3 4 5 6 7 8 9 10

6) Se passar mais tempo na cama, geralmente durmo mais e no dia seguinte sinto-me melhor.

Discordo Totalmente — Concordo Totalmente

0 1 2 3 4 5 6 7 8 9 10

7) Quando tenho dificuldade em dormir, devo ficar na cama e esforçar-me mais para dormir.

Discordo Totalmente — Concordo Totalmente

0 1 2 3 4 5 6 7 8 9 10

8) Preocupa-me poder perder o controlo sobre a minha capacidade em dormir.

Discordo Totalmente — Concordo Totalmente

0 1 2 3 4 5 6 7 8 9 10

9) Como estou a ficar mais velho, à noite devo ir para a cama mais cedo.

Discordo Totalmente — Concordo Totalmente

0 1 2 3 4 5 6 7 8 9 10

Appendix 11. DBAS-30 scale (continued)

10) Depois de uma má noite de sono, já sei que isso vai interferir com as minhas actividades diárias no dia seguinte.

Discordo Totalmente — Concordo Totalmente

0___1___2___3___4___5___6___7___8___9___10

11) Para estar alerta e funcionar bem durante o dia, fico melhor se tomar um comprimido para dormir do que se dormir mal uma noite.

Discordo Totalmente — Concordo Totalmente

0___1___2___3___4___5___6___7___8___9___10

12) Quando me sinto irritável, deprimido ou ansioso durante o dia, é sobretudo porque não dormi bem na noite anterior.

Discordo Totalmente — Concordo Totalmente

0___1___2___3___4___5___6___7___8___9___10

13) Como a pessoa que dorme comigo adormece logo que se deita na cama e dorme durante a noite, eu também deveria ser capaz de fazer o mesmo.

Discordo Totalmente — Concordo Totalmente

0___1___2___3___4___5___6___7___8___9___10

14) Sinto que a insónia é, basicamente, o resultado do envelhecimento e não há muito a fazer por este problema.

Discordo Totalmente — Concordo Totalmente

0___1___2___3___4___5___6___7___8___9___10

15) Às vezes, tenho medo de morrer durante o sono.

Discordo Totalmente — Concordo Totalmente

0___1___2___3___4___5___6___7___8___9___10

16) Quando tenho uma boa noite de sono, já sei que terei de pagar isso na noite seguinte.

Discordo Totalmente — Concordo Totalmente

0___1___2___3___4___5___6___7___8___9___10

17) Quando durmo mal uma noite, já sei que isso irá perturbar os meus horários de sono durante toda a semana.

Discordo Totalmente — Concordo Totalmente

0___1___2___3___4___5___6___7___8___9___10

18) Sem uma boa noite de sono, dificilmente consigo funcionar no dia seguinte.

Discordo Totalmente — Concordo Totalmente

0___1___2___3___4___5___6___7___8___9___10

19) Nunca consigo prever se vou ter uma boa ou má noite de sono.

Discordo Totalmente — Concordo Totalmente

0___1___2___3___4___5___6___7___8___9___10

20) Tenho pouca capacidade para lidar com as consequências negativas de um sono perturbado.

Discordo Totalmente — Concordo Totalmente

0___1___2___3___4___5___6___7___8___9___10

Appendix 11. DBAS-30 scale (continued)

21) Quando me sinto cansado, sem energia ou quando parece que não consigo funcionar bem durante o dia é, geralmente, porque não dormi bem na noite anterior.

Discordo Totalmente — Concordo Totalmente

0___1___2___3___4___5___6___7___8___9___10

22) À noite, fico dominado pelos meus pensamentos e, frequentemente, sinto que não consigo controlar esses pensamentos, que não param de correr na minha cabeça.

Discordo Totalmente — Concordo Totalmente

0___1___2___3___4___5___6___7___8___9___10

23) Sinto que consigo levar uma vida satisfatória, apesar das minhas dificuldades em dormir.

Discordo Totalmente — Concordo Totalmente

0___1___2___3___4___5___6___7___8___9___10

24) Acredito que a insónia é, essencialmente, o resultado de um desequilíbrio químico.

Discordo Totalmente — Concordo Totalmente

0___1___2___3___4___5___6___7___8___9___10

25) Sinto que a insónia está a arruinar a minha capacidade de apreciar a vida e que me impede de fazer o que quero.

Discordo Totalmente — Concordo Totalmente

0___1___2___3___4___5___6___7___8___9___10

26) Evito ou desmarco compromissos (sociais, familiares, ocupacionais) após uma má noite de sono.

Discordo Totalmente — Concordo Totalmente

0___1___2___3___4___5___6___7___8___9___10

27) Tomar uma bebida alcoólica antes de ir para a cama é uma boa solução para os problemas de sono.

Discordo Totalmente — Concordo Totalmente

0___1___2___3___4___5___6___7___8___9___10

28) A medicação é, provavelmente, a única solução para a falta de sono.

Discordo Totalmente — Concordo Totalmente

0___1___2___3___4___5___6___7___8___9___10

29) O meu sono está cada vez pior e não acredito que alguém me possa ajudar.

Discordo Totalmente — Concordo Totalmente

0___1___2___3___4___5___6___7___8___9___10

30) Habitualmente, nota-se na minha aparência física quando não dormi bem.

Discordo Totalmente — Concordo Totalmente

0___1___2___3___4___5___6___7___8___9___10

Appendix 12. ISI scale

ÍNDICE DE GRAVIDADE DE INSÓNIA (ISI)

Nome: _____ **Data:** _____

Para cada questão apresentada, por favor, coloque um círculo no número que corresponde à sua resposta.

1. Qual a **GRAVIDADE** actual (últimas 2 semanas) do(s) seu(s) problema(s) de insónia?

	Nenhuma	Ligeira	Moderada	Grave	Muito Grave
Dificuldade em adormecer	0	1	2	3	4
Dificuldade em manter-se a dormir	0	1	2	3	4
Acordo demasiado cedo, antes da hora habitual	0	1	2	3	4

2. Está satisfeito/insatisfeito com o seu padrão actual do sono?

Muito Satisfeito	Satisfeito	Neutro	Insatisfeito	Muito Insatisfeito
0	1	2	3	4

3. Acha que o seu problema do sono interfere com o seu funcionamento diário (ex: fadiga diurna, capacidade para trabalhar, concentração, memória, humor, etc.)?

Não Interfere Nada	Pouco	Interfere Moderadamente	Muito	Interfere Muitissimo
0	1	2	3	4

4. Acha que as outras pessoas notam o impacto que o seu problema do sono tem na sua qualidade de vida?

Não Notam Nada	Pouco	Notam Moderadamente	Muito	Notam Muitissimo
0	1	2	3	4

5. Está preocupado com o seu actual problema do sono?

Nada Preocupado	Pouco	Moderadamente	Muito	Muitissimo Preocupado
0	1	2	3	4