Neurobiological correlates of psychological treatments for insomnia – A review

Daniel Ruivo Marques and Ana Allen Gomes

Department of Education, University of Aveiro, Portugal and IBILI (FCT Research Unit),

Faculty of Medicine of University of Coimbra, Portugal

Vanda Clemente and José Moutinho dos Santos

Coimbra University Hospital Centre (CHUC), Sleep Medicine Centre, Portugal

Gina Caetano and Miguel Castelo-Branco

IBILI (FCT Research Unit), Faculty of Medicine of University of Coimbra, Portugal

Author Note

Corresponding author: Daniel Ruivo Marques, Department of Education, University of Aveiro, Campus Universitário de Santiago, 3810 Aveiro, Portugal. Phone: +351 234 372 428 E-mail: drmarques@ua.pt

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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.

INSERT TABLE 1 ABOUT HERE

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).

INSERT FIGURE 1 ABOUT HERE

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. One of the most interesting subjects to further examine in future researches is the connection of cognitive schemas and neurobiology of insomnia. Specifically, to explore in what extent the experience of cognitive modification during CBT-I is linked to specific changes in activity in key brain regions or networks. 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).

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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.

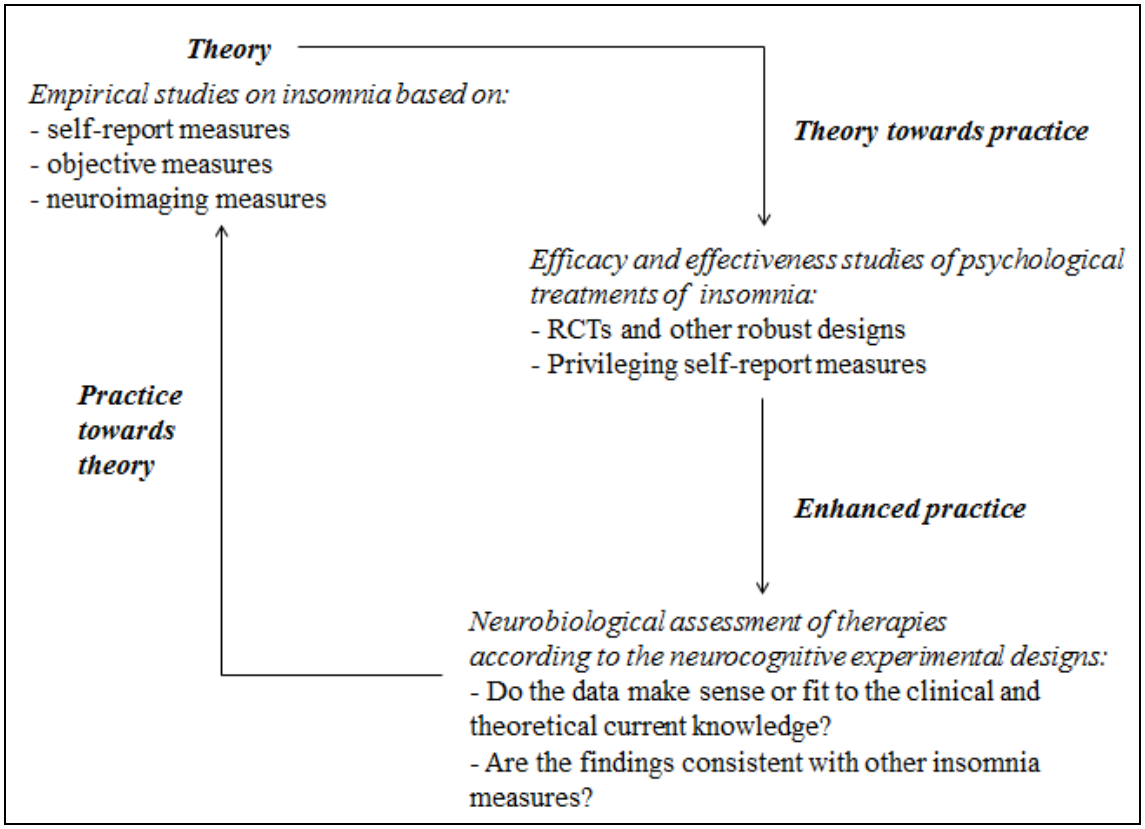

Figure 1. A conceptual framework displaying the relevance of studying the neural changes induced by psychological treatment for insomnia.