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Hyperarousal during sleep in untreated, major depressed subjects with prodromal insomnia: A polysomnographic study

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ABSTRACT

In primary insomnia, specific dynamics of hyperarousal are evident during the night. Similarly, in major depression, many elements also favor of the presence of hyperarousal. Thus, it would be interesting to investigate if hyperarousal presents the same dynamic in major depression. Polysomnographic data from 30 healthy controls, 66 patients with major depression and prodromal insomnia, and 86 primary insomnia sufferers recruited from the sleep laboratory database were studied for whole night and thirds of the night. Insomnia sufferers and patients with depression exhibit a similar polysomnographic pattern both for whole night (increased sleep latency and WASO and reduced SWS and REM) and thirds of night (increased WASO at first and last thirds, reduced SWS in first third, and reduced in REM in first and last third). No alterations were detected during the second third of the night. Just as in primary insomnia, the hyperarousal phenomenon is found mainly in major depression with prodromal insomnia during the sleep-onset period and the first and last thirds of the night, but lesser during the second third of the night. These specific dynamics of hyperarousal may aid in the understanding of the particular relationship between insomnia and depression.

1. Introduction

In Western countries, the annual prevalence of major depression varies from 3.9% to 6.6%; whereas the life-time prevalence ranges from 9.9% to 16.2% (Alonso et al., 2004; Kessler et al., 2003; Patten et al., 2015). The average duration of a major depressive episode is three months (Spijker et al., 2002). Half of patients with major depression (PMD) have a remission of their disorder during these three months; whereas depression becomes chronic for 20% of individuals (Spijker et al., 2002). However, for PMD in remission, the risk of recurrence is high, ranging from 21% to 37%, and this increases to 85% after 15 years (Kanai et al., 2003; Maj et al., 1992; Mueller et al., 1999). In addition, major depression has a negative impact on the quality of life (Rapaport et al., 2005) and causes higher absenteeism and inefficiency at work (Sanderson et al., 2007).

Sleep disorders are common with major depression, and 90% of depressed subjects have complaints related to their sleep, such as insomnia (Mendelson et al., 1977). Insomnia sufferers present a significantly higher risk of developing depression (Baglioni et al., 2011; Riemann and Voderholzer, 2003) or committing suicide (Bjørngaard et al., 2011) than those without insomnia. The hyperarousal model (Riemann et al., 2010) is one of the theories currently proposed to explain the pathophysiology of insomnia sufferers, and it also seems to play a role in major depression (van den Burg and van den Hoofdakker, 1975; Zung et al., 1964). In major depression, as in primary insomnia, hyperarousal can be divided into three categories (Hein et al., 2016; Leistedt et al., 2007a), which are highly interrelated and occur in the model of chronic insomnia (Morin, 1993): somatic hyperarousal (characterised by increased activity of autonomic activity (van der Kooy et al., 2006; Volkers et al., 2003) and hypothalamic-pituitary-adrenal [HPA] systems (Linkowski et al., 1985; Steiger and Holsboer, 1997)); cognitive hyperarousal (characterised by greater ruminations while falling asleep (Pillai et al., 2014)); and cortical hyperarousal (characterised by an increase in PET scan nocturnal brain activity (Ho et al., 1996) and alterations in low frequency (Borbély et al., 1984) and high frequency bands (Kupfer et al., 1989)). This helps to explain the tendency of PMD with insomnia to have difficulty falling asleep, nocturnal awakenings, and early morning awakenings. Therefore, there

Abbreviations: BDI, Beck Depression Inventory; DSM IV-TR, Diagnostic and Statistical Manual of Mental Disorders fourth edition - Text Revision; HPA, hypothalamic-pituitary-adrenal; ISI, Insomnia Severity Index; PMD, Patient with Major Depression; REM, rapid eye movement; SE, sleep efficiency; SL, sleep latency; SOP, sleep-onset period; SPT, sleep period time; SSRI, selective serotonin reuptake inhibitors; SNRI, Serotonin–norepinephrine reuptake inhibitor; SWS, slow-wave sleep; TST, total sleep time; WASO, wake after sleep onset

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seems to be a depressive subtype with a pathophysiology that is identical to that of insomnia hyperarousal, and it can manifest itself as prodromal insomnia.

This phenomenon of hyperarousal is present only in some PMD, especially those with insomnia complaints, in whom there are alterations of the HPA axis resulting in cortisol secretion not suppressed after dexamethasone administration. In these non-responding subjects, the post-dexamethasone administration cortisol levels are positively correlated with the amount of wake after sleep onset (WASO) and the duration of stage 1 sleep, but negatively correlated with the amount of slow-wave sleep (SWS) and rapid eye movement (REM) sleep (Hubain et al., 1998). Staner et al. (2003a) also identified a subtype of depression characterised by the presence of cortisol in a dexamethasone suppression test and by significant alterations of sleep (excessive WASO and stage 1 sleep and reduced SWS). In these subjects, there are therefore polysomnographic alterations consistent with the hyperarousal model, including an increase in sleep latency (SL) and the number and duration of WASO episodes, a decrease in sleep efficiency (SE), stage 2, and SWS (Hudson et al., 1992; Pillai et al., 2011), and reduced REM, which was highlighted by Hubain et al. (2006) (in which PMD presented greater polysomnographic alterations) and by Smagula et al. (2015) (in which PMD were older). However, similar changes are also found in primary insomnia sufferers (Baglioni et al., 2014). These polysomnographic alterations related to hyperarousal may be considered indirect markers of this phenomenon (Spiegelhalder and Riemann, 2013) and used to indirectly highlight its presence during sleep in primary insomnia and major depression. (Baglioni et al., 2014; Hubain et al., 2006). In addition, the nocturnal alterations of the HPA axis in major depression are located mainly at the beginning and end of night (Steiger et al., 1989; Wong et al., 2000). This element suggests that it would be interesting to study sleep in thirds of the night in major depression with prodromal insomnia to see if there are specific polysomnographic alterations in the first and last third of the night where biological alterations are the most important.

The study aims to empirically verify the presence of specific dynamics of polysomnographic alterations related to hyperarousal during the night in PMD with prodromal and current insomnia as well as to investigate their dynamics over time by breaking the night into thirds. The hypothesis of our study was that the polysomnographic pattern in major depression with prodromal and current insomnia would be similar to that highlighted in our preliminary on primary insomnia (Hein et al., 2017a) for both the whole night and thirds of the night. The highlighting of these specific dynamics of hyperarousal in these patients may help to understand the particular relationship between insomnia and depression. This is the first study to investigate the sleep of PMD during thirds of the night, rather than during the whole night or in terms of sleep cycles (Kempenaers et al., 1988; Leistedt et al., 2007b; Rotenberg et al., 2002).

2. Materials and methods

2.1. Population

Participants aged 18–68 years were allocated to a control group of 30 healthy controls (17 men and 13 women), a group of 66 PMD with prodromal insomnia (26 men and 40 women), and a group of 86 primary insomnia sufferers (49 men, 37 women). These participants were recruited from the database of the sleep laboratory of Erasme Hospital, where 3511 individuals completed sleep laboratory monitoring during the years 2002–2014. The healthy controls present in our database were recruited from prospective studies of our sleep laboratory on major depression, and only those meeting the inclusion criteria of this study were included in the control group. All primary insomnia sufferers come from our preliminary study on primary insomnia (Hein et al., 2017a) and have been included to provide a better understanding of the results of this study.

For healthy controls, the inclusion criteria were male or female, 18–65 years old, lack of sleep pathology, no psychiatric disorders, absence of a somatic pathology that is severe or may affect sleep, lack of addiction or history of substance abuse, lack of psychotropic or somatic treatment that may affect sleep and no significant daytime sleepiness (Epworth scale score of < 10) (Johns, 1991).

The inclusion criteria for the PMD with prodromal insomnia were male or female, age ≥ 18 years, presence of a major depressive episode meeting the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition-Text Revision (DSM IV-TR) (American Psychiatric Association, 2000), presence of secondary insomnia meeting the diagnostic criteria of the DSM IV-TR at the time of the sleep laboratory study, presence of prodromal insomnia complaint for at least three months before the onset of major depression, and an Insomnia Severity Index (ISI) score ≥ 8 (indicating a subjective complaint of insomnia) (Morin, 1993).

The inclusion criteria for primary insomnia sufferers were male or female, aged 18–65 years, the presence of primary insomnia meeting the diagnostic criteria of the DSM IV-TR (American Psychiatric Association, 2000), a score ≥ 15 on a scale of insomnia severity (Morin, 1993) (indicating moderate to severe insomnia), and sleep efficiency from polysomnography $< 85\%$ (indicating objective insomnia).

The common exclusion criteria for primary insomnia sufferers and PMD with prodromal insomnia were presence of a sleep disorder other than insomnia, presence of a severe somatic pathology that may affect sleep, use of a psychotropic drug or somatic treatment that may affect sleep, and past or present substance abuse. The specific exclusion criterion for primary insomnia sufferers was the presence of a comorbid psychiatric disorder, whereas for PMD with prodromal insomnia, it was the presence of a psychiatric disorder other than major depression.

The PMD with prodromal insomnia and primary insomnia sufferers have an insomnia that was not due to an iatrogenic cause or somatic/psychiatric condition (other than major depression for PMD with prodromal insomnia). Moreover, they were never undergoing treatment; therefore, they did not have to be weaned off medication before polysomnography. The duration of the current episode of major depression is at least two weeks, meeting the diagnostic criteria of DSM IV-TR.

2.2. Medical and psychiatric evaluation of participants

All subjects upon admission to the sleep laboratory of Erasme Hospital had their medical records reviewed and a complete somatic check-up performed, including a blood test, electrocardiogram, a daytime electroencephalogram, urinalysis and a chest X-ray (only for those over age 45). These steps allowed for a systematic diagnosis of potential somatic pathologies present in people admitted to our unit and the exclusion of subjects from our study who had somatic diseases that could affect sleep.

Patients were seen on the day of admission by a unit psychiatrist who potentially assigned psychiatric diagnoses per the DSM IV-TR criteria to exclude from our study subjects with psychiatric disorders other than major depression.

On admission, patients completed a series of self-questionnaires for an initial general assessment of their complaints, as follows:

- The presence of depressive symptoms was investigated using the Beck Depression Inventory (BDI). This scale consists of 13 items that can be scored from 1 to 3. The final score can vary from 0 to 39. A final score of 0–4 indicates an absence of depression, 5–7 a slight depression, 8–15 a moderate depression, and > 16 a severe depression (Beck et al., 1996).
- The presence of anxiety symptoms was investigated using the Spielberger questionnaire. The state section evaluates anxiety at the laboratory itself while the trait section assesses anxiety in daily life. These two sections each consist of 20 questions scored from 1 to 4. For each section, the score can vary from 20 to 80. The lower the