Author’s response to reviews

Title: Similar polysomnographic pattern in primary insomnia and major depression with objective insomnia: A sign of common pathophysiology?

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Author’s response to reviews:

Reviewer 1

I thank the reviewer for this excellent and pertinent review.

The answers to the questions are as follows.

Jennifer Goldschmied (Reviewer 1): The authors provide a well-conducted and interesting study investigating the relationship between polysomnographically derived variables and insomnia in major depression and primary insomnia. The study is novel in its methodology and its conclusions are fairly interesting, however the writing should be revised substantially to improve readability (several areas of repetitive statements, preposition confusion, overall wordiness). I am including several concerns that limit my overall enthusiasm for this paper, but feel that addressing these concerns may allow this to be an interesting, albeit incremental addition to the literature:

We were able to include 29 additional major depressed patients with objective insomnia in our study. These additional patients were obtained because we found in our paper archives some missing questionnaires and we were able to solve the compatibility problem present on some sleep records for the calculation of thirds of the night.

1. The rationale of the present study seems to rest on a reference to Hubain et al that contradicts most commonly found PSG measures in MDD. However, the summary of these
findings and their clinical relevance, as it is currently written, is not particularly compelling, which results in the overall aim of the present study being left on shaky ground.

The text has been amended to take account of this remark: “Further, Hubain et al.16 highlighted in some patients with major depression a sleep reduction affecting both REMS and NREMS in comparable percentages. This difference from the literature can be explained by the fact that in this study, one of the main markers of depression was in fact the absence of sleep, whether observed as long delays prior to entering sleep, or excessive intermittent awakenings that are also characteristics of primary insomnia. Consequently, these patients with major depression presented polysomnographic alterations of objective insomnia type. It is therefore possible that some major depressed patients with objective insomnia (MDOI) show a similar polysomnographic pattern to that of primary insomnia even at REM level.” (See Introduction)

2. Sleep efficiency was used as an inclusion criterion for both the insomnia and MDOI groups, however the authors did not discuss how SE was obtained. My assumption is that PSG defined SE from night 2 was used, however this should be clarified. Additionally, it is difficult to interpret conclusions based on differences in SE (as compared to HC) when SE was used as an inclusion criterion.

The text has been amended to take account of this remark: “The polysomnographic data collected were as follows: SL; SPT; TST; SE (defined as TST/time in bed); number of cycles; number of awakenings; duration of each third of the night; the percentages SPT of stage 1, stage 2, stage 3 (SWS), REM, and WASO for the entire night; and the percentages of stage1, stage2, SWS, REM, and WASO for each third of the night.” (See Sleep evaluation and study)

As indicated in the "Sleep evaluation and study" section, the polysomnographic data used for the analyses were collected during the second night of the sleep laboratory. => “Participants stayed in a sleep laboratory for two nights, including a first night of habituation and a second night of polysomnography from which the data were collected for analysis.” (See Sleep evaluation and study)

Data related to SE were presented in order to be as complete as possible in terms of results.

3. Relatedly, the authors suggest that due to the limited differences in PSG measures between insomnia and MDOI, the two disorders must share a common pathophysiology. However, since the MDOI group was selected based on their similarity in symptomatology to primary insomnia, this renders this kind of interpretation questionable (I believe the authors may hint at this concern, although the language in the paragraph at the top of page 17 is somewhat hard to follow). Instead, I would suggest changing the aims of this study to ask if an
additional diagnosis of MDD adds incremental PSG disturbance to a diagnosis of insomnia, as this seems to be a more parsimonious question.

Indeed, MDOI subjects were recruited specifically for symptomatology similar to insomnia sufferers. Of course, by recruiting subjects with similar symptoms, it was very likely that the polysomnographic pattern was similar to the level of the whole night. If one limits oneself to this approach, it is of course impossible to affirm the presence of a common pathophysiology. However, the use of the thirds of the night avoids this limitation. Indeed, if there is no common pathophysiology, the distribution of alterations during the thirds of the night should be different. On the other hand, if this distribution is similar, it would reinforce the theory of a common pathophysiology that could be hyperarousal.

The paragraph concerned was amended as requested: “In PI and MDOI, we have shown that hyperarousal is associated with an increase in brain activity during NREM and REM, causing a tendency to awaken and greater instability at these sleep stages with consequent an increased WASO, and reduced NREM and REM for the whole night. Indeed, in primary insomnia, at the NREM level, Nofzinger et al.72 have shown that WASO (subjective and objective) were positively correlated with increased brain activity in a PET scan. In addition, it has been demonstrated that PI showed increased brain activity in the β band during NREM,61 and more precisely during stage 262 and SWS.63 At the REM level, Merica et al.73 and Perlis et al.74 also highlighted more significant β activity during this stage of sleep. On the other hand, patients with major depression have an increased Ω power band at the REM and NREM levels.56 Furthermore, Nofzinger et al.75,76 showed an increase in nocturnal cerebral metabolism during REM and NREM in the PET scan. Moreover, among major depression patients, the activity of the β power band is positively correlated with brain metabolism in the PET scan and negatively to the subjective quality of sleep.77 Thus, these alterations induced by hyperarousal make it possible to better understand the similar polysomnographic pattern of objective insomnia type between PI and MDOI for the whole night.” (See Discussion)

4. The results section (and corresponding tables) reads like a laundry list of findings with no cohesive narrative - I had a very hard time identifying the most important results. I would suggest narrowing the results down to key areas and discussing how certain findings complement (or do not) one another. Additionally, representing some data graphically, instead of in a table, would also help to highlight the most important findings. Furthermore, the addition of tables 3 and 5 seem to be redundant - this information can also be represented in tables 2 and 4. As a note, I actually suggest highlighting the analysis of PI vs MDOI, than HC vs PI and MDOI, as it stands currently.

The text has been amended to take account of this remark (See Results):

Polysomnographic data
Sleep onset period and whole night

Polysomnographic results for the sleep onset period and the whole night are shown in Table 2. MDOI and PI had a similar polysomnographic pattern both at the level of the whole night (increased SL and reduced SE, SPT, duration of each third of the night, and TST) and at the level of the sleep architecture (increased WASO, and reduced REM and SWS). There was no significant difference for REM latency. There is a stage 2 deficiency evident only for PI. These differences persist after adjusting results for age and gender (Table 3).

Thirds of the night

Polysomnographic results for thirds of the night and the analysis of REM, stage1, stage 2, SWS, and WASO are shown in Table 4. At the level of thirds of the night, MDOI and PI had a similar polysomnographic pattern (a REM deficit in the first and last third of the night, a SWS deficit in the first third of the night, a stage 2 deficit in the first and second third of the night, and a WASO excess in the first, second, and last third of the night). These differences persist after adjusting the results for age, gender, and the number of cycles where necessary, except in the second third of the night when excess WASO becomes non-significant in PI and MDOI (Table 5).

Effect of the thirds of night on the percentage of different stages of sleep and WASO

The effect of thirds of the night on the percentage of REM, stage 1, stage 2, SWS, or WASO is shown in Table 4. The interaction between the third’s and the group’s factors were significant for SWS (p < 0.001) and WASO (p = 0.020), but non-significant for stage 1 (p = 0.828), stage 2 (p = 0.318), and REM (p = 0.563). For the whole sample as well in each group, the comparison of the means across the thirds were significant for REM, stage 1, stage 2, SWS, and WASO, except for stage 1 in MDOI.

Correlations between different stages of sleep and WASO

Correlations between different stages of sleep and WASO are shown in Table 6. For the whole night as well as the first and last third of the night, the percentage of WASO was significantly negatively correlated with the percentage of REM, SWS, and stage 2. There was a higher correlation between WASO and stage 2 than between WASO and REM or SWS. In addition, REML was significantly negatively correlated in PI and MDOI with the percentage of REM in the first third of the night.
In order not to overload Tables 2 and 4, we have not included the data from Tables 3 and 5. The analysis of PI vs MDOI were added as requested.

5. The discussion of increased hyperarousal in insomnia and MDD in the discussion section is an important one, however, as it is currently written, it is neither clear nor compelling. Similar to my suggestion for the results section, I would encourage the authors to identify the main, key points and highlight these with regard to the present data and past research findings to allow for a more cohesive narrative.

The text has been amended to take account of this remark:

- “We further demonstrated an elongated SL, decreased SE, and increased WASO in primary insomnia and MDOI. These polysomnographic alterations can be considered as indirect markers of hyperarousal,45 which is one of the currently proposed theories to explain the physiopathology of primary insomnia and major depression.46,47,48,49 Hyperarousal can be defined as increased emotional, cognitive, and physiological activity that interferes with natural disengagement from the environment and reduces the likelihood of sleep.50 In major depression, as in primary insomnia, hyperarousal can be divided into three categories51,52 that are highly interrelated and occur in the model of chronic insomnia30: somatic hyperarousal (characterized by increased activity of autonomic activity and HPA systems),19,53,54,55,56,57,58 cognitive hyperarousal (characterized by greater ruminations while falling asleep),59,60 and cortical hyperarousal (characterized by an increase in PET scan nocturnal brain activity and high frequency bands).61,62,63,64,65,66 These elements indicate a state of hypervigilance, and this tendency for hyperarousal is present throughout the 24-hour cycle.67,68 Thus, hyperarousal provides a reasonable explanation for the tendency to have nighttime awakenings, early morning awakenings, and difficulties with falling asleep, all of which characterize primary and secondary insomnia. However, although there are also elements in favor of hyperarousal in major depression, it would seem that hyperarousal is present only in some patients with major depression, especially those with marked sleep alterations of objective insomnia type. Indeed, some patients with major depression, like those with primary insomnia, show hyperactivity of the HPA axis resulting in failure to suppress cortisol secretion after administration of dexamethasone.69 In these non-responders, there are polysomnography elements in favor of objective insomnia consistent with hyperarousal: reduced TST, SE, SWS, and increased WASO.70 Furthermore, alterations in the HPA axis in such individuals are positively correlated with percentages of WASO and stage 1, as they are negatively correlated with percentages of stage 2, SWS, and REM.71 Since we recruited only MDOI, we showed polysomnographic abnormalities of objective insomnia type consistent with hyperarousal that could be common
pathophysiology explaining the existence of a polysomnographic pattern similar to primary insomnia.” (See Discussion)

- “In PI and MDOI, we have shown that hyperarousal is associated with an increase in brain activity during NREM and REM, causing a tendency to awaken and greater instability at these sleep stages with consequent an increased WASO, and reduced NREM and REM for the whole night. Indeed, in primary insomnia, at the NREM level, Nofzinger et al.72 have shown that WASO (subjective and objective) were positively correlated with increased brain activity in a PET scan. In addition, it has been demonstrated that PI showed increased brain activity in the β band during NREM,61 and more precisely during stage 262 and SWS.63 At the REM level, Merica et al.73 and Perlis et al.74 also highlighted more significant β activity during this stage of sleep. On the other hand, patients with major depression have an increased Ω power band at the REM and NREM levels.56 Furthermore, Nofzinger et al.75,76 showed an increase in nocturnal cerebral metabolism during REM and NREM in the PET scan. Moreover, among major depression patients, the activity of the β power band is positively correlated with brain metabolism in the PET scan and negatively to the subjective quality of sleep.77 Thus, these alterations induced by hyperarousal make it possible to better understand the similar polysomnographic pattern of objective insomnia type between PI and MDOI for the whole night.” (See Discussion)

- “At the level of thirds of the night, we have demonstrated that excess WASO occurs during the first and last third of the night, which corresponds to the location of the main biological changes associated with hyperarousal highlighted in PI and MDOI (e.g., in alterations of the HPA axis).18,19,20,21 The highlighting of this specific dynamics of the polysomnographic alterations related to hyperarousal as well as the particular distribution of the sleep stages during the night (SWS in the first third and REM in the last third of the night) provide a better understanding of the location of deficits in SWS (the first third of the night) and REM (the first and last third of the night). The presence of a similar distribution of polysomnographic alterations during thirds of the night reinforces the theory of hyperarousal as a common pathophysiology in PI and MDOI.” (See Discussion)

6. The rationale for the inclusion of analysis of the 'thirds' of the night in the introduction was not particularly compelling since it has limited support (Sventnik et al). Additionally, since there didn't seem to be many significant results regarding the split by thirds, I would suggest to discuss these findings sparingly, and not to include it as a primary aim.

We added additional references to highlight the value of using analysis by thirds of the night in our study.

On the contrary, the use of analysis by thirds of the night is essential for the main objective of our study. Indeed, the demonstration of a similar polysomnographic pattern between primary
insomnia and MDOI only at the level of the whole night is not sufficient to envisage a common pathophysiology. On the other hand, if in addition to this similar polysomnographic pattern, there is a similar dynamics of alterations consistent with the hyperarousal during the thirds of the night. This will reinforce the theory of a common pathophysiology that would be the hyperarousal.

As a note, the discussion regarding the distribution of the night as the reason behind the SWS deficit being limited to the first third while the REM deficit is present in the first and last third being does not seem to fit, however the discussion of the WASO changes in the 'thirds' of the night does seem to have some potential - I would suggest exploring and expanding this piece.

The text has been amended to take account of this remark: “At the level of thirds of the night, we have demonstrated that excess WASO occurs during the first and last third of the night, which corresponds to the location of the main biological changes associated with hyperarousal highlighted in PI and MDOI (e.g., in alterations of the HPA axis).18,19,20,21 The highlighting of this specific dynamics of the polysomnographic alterations related to hyperarousal as well as the particular distribution of the sleep stages during the night (SWS in the first third and REM in the last third of the night) provide a better understanding of the location of deficits in SWS (the first third of the night) and REM (the first and last third of the night). The presence of a similar distribution of polysomnographic alterations during thirds of the night reinforces the theory of hyperarousal as a common pathophysiology in PI and MDOI.” (See Discussion)

Reviewer 2

I thank the reviewer for this excellent and pertinent review.

The answers to the questions are as follows.

Xiangdong Tang (Reviewer 2): The authors demonstrated that major depressed patients with objective insomnia (MDOI) showed a similar polysomnographic pattern to that of primary insomnia. Then they speculated that there was a potential common pathophysiology between MDOI and primary insomnia. This is a novel study with a good methodological design and clear results. However, I have two questions which should be addressed by the authors in the revised version of the manuscript.

We were able to include 29 additional major depressed patients with objective insomnia in our study. These additional patients were obtained because we found in our paper archives some missing questionnaires and we were able to solve the compatibility problem present on some sleep records for the calculation of thirds of the night.

1. The authors measured the subjective daytime sleepiness using the Epworth Sleepiness Scale. Unfortunately, I couldn't find the value of ESS in the Results section. It is well known that
patients with major depression usually present significant daytime sleepiness. As the authors emphasized the possible pathophysiology of hyperarousal in patients with MDOI, I am interested in the result of ESS in these subjects.

As requested, the ESS data was added. (See Table 1)

2. In the discussion section, the authors explained some variables of PSG were the indirect marker of hyperarousal. Actually, the Multiple Sleep Latency Test (MSLT) is a valid measure of physiological arousal. They should refer some related study in the discussion and point this is a valid marker of hyperarousal which should be conducted in the future study.

The text has been amended to take account of this remark: “Another research approach could relate the polysomnographic alterations highlighted in our study and the daytime consequences of hyperarousal using the multiple sleep latency tests, which is a valid measure of physiological arousal.78,79.” (See Discussion)