Zolpidem: a magical drug?

An essay on *"Awakening after a sleeping pill: Restoring functional brain networks after severe brain injury" (Arnts et al.)*

The phrase, "Awakening after a sleeping pill" in the title of the paper by Arnts et al. is itself a paradox. This study is an attempt to understand the paradoxical behaviour of a sleeping pill "*Zolpidem*" that helps patients with severe brain injury regain to some extent, critical brain functions such as motor control, speech, and consciousness for a short time interval. The goal of this research was to study how functional connectivity in the brain is affected by the use of zolpidem and propose a hypothesis of its working mechanism. Functional connectivity is the correlation of functionally similar but distant regions in the brain when the brain is at rest [1]. The authors particularly focus on the role of beta-band functional connectivity on neurological defects. The motivation for this study is well placed as the authors in my view, correctly state that the internal working mechanism for this drug is largely unknown. This may be in part because the results from different studies for the same drug are inconsistent. For example, in a study by Du et al. [2], they found that the neurological improvements due to zolpidem are not dependent on the time or frequency of the medication when given a single dose per day. Whereas, in this paper, the authors have reported a decrease in the remedial effects of the drug when administered multiple times a day for several consecutive days. They have stated that to observe the optimal effects of a single dose of zolpidem, a cool-down period of two to three weeks is required between doses, and the maximum consecutive dosage period to observe optimal restoration effect is five days on a single dose per day.

For data collection, the authors used two popular neuroimaging techniques EEG (Electroencephalography) and MEG (Magnetoencephalography). For EEG data, the authors recorded two 30 minute sessions for both pre and post-zolpidem states out of which they selected the highest quality 4.8 mins for pre-zolpidem and 4.4 mins of post-zolpidem data. For MEG data, they identified roughly 9.5 minutes of the highest quality data for both pre and post-zolpidem administration. The authors performed a primary analysis for spectral power and functional connectivity for EEG and MEG using the following slices.

EEG spectral power analysis: 9.2 mins total [4.8 mins (pre)+4.4 mins (post)]

EEG functional analysis: 4 mins total (30 epochs of 4 seconds each) [2 mins (pre) + 2 mins (post)]

MEG spectral power analysis: 3 mins total (90 epochs of 1 second each) [1.5 min (pre) + 1.5 min (post)]

MEG functional analysis: 3.3 mins total (60 epochs of 3.3 seconds each)

The data collection for MEG is not very clear as there are some discrepancies between the paper and the supplementary material. Both EEG and MEG data is passed through a robustness check where the results for all the analysis are tested 10 times using random sampling of epochs from the highest quality dataset. Montreal Cognitive Assessment (MoCA) and Coma Recovery Scale-Revised (CRS-R) tests are used to analyze results. Before the medication, the patient was at a minimally conscious state which is why the utility of CRS-R is very little [3]. The MoCA score was 0/30 and he was not able to perform cognitive tasks. After the medication, the patient showed a high level of awareness. He was able to speak, use objects and even walk with assistance. The

MoCA score increased to 13/30. However, this effect was temporary and lasted for about 60 mins. The results of the spatial-spectral analysis showed a general trend of increase in beta and gamma power in the cortical regions of the brain. While there was a lack of clear differentiation in the power of the frontal vs backward region of the brain in the EEG analysis, MEG analysis seemed to have pretty clear results in this regard. The authors highlight the results of the functional connectivity study and state that the beta band functional connectivity reduced post-zolpidem medication. These results passed the robust checking method of random sampling as well. The resting-state beta-band functional connectivity was higher pre-zolpidem as compared to healthy individuals but dropped to comparable levels to the healthy subjects post-zolpidem medication. A study has shown that resting-state beta-band functional connectivity is both positively and negatively correlated with motor learning [4]. Taking the positive correlation into account, motor learning increases with an increase in beta-band rs-FC. Can this result be applied to the context of this study? If so, it would suggest that the patient in a pre-medication state that has higher beta-band rs-FC should be able to perform motor tasks better than the post-medication state. Another study states that zolpidem can increase functional connectivity in resting-state networks which contradicts the results of this study [5]. Du et al. [2] showed that patients with non-brain-stem type injury respond to zolpidem with higher efficacy while patients with brain-stem injury do not show any clear results of the medication which the authors did not discuss. It would have been good to see some more discussion theorizing about the working mechanism of zolpidem as a GABA agonist. Again, Du et al [2] suggested that brain damage can cause either irreversible neuronal damage or the nerve cells can survive but enter a dormant state due to GABA. The dormant state can induce abnormality in the metabolism of the neurotransmitters. Since zolpidem is a highly selective GABA receptor, it could potentially bind with the dormant cells and terminate the abnormal cell metabolism which is why the patients can regain some cognitive functionalities for a short interval. Lastly, while the authors cited Whyte et al. (2009) [6] in which, 1 out of 15 subjects (6.66%) responded to the medication, they did not cite an updated study where Whyte et al. (2014) [7] measured CRS-R scores for zolpidem response with placebo control for a larger group and observed similar results to their previous study where only 4.76% (4 out of 84) patients responded to the medication. In conclusion, the increase in power of beta and gamma waves during pre and post-zolpidem state agrees with the literature while the definite role of beta-band rs-FC in predicting cognitive behaviour is inconsistent. The supplementary data was helpful as a summary of the study but there are some discrepancies with the paper. This study is beneficial as it can inspire further research to discern the inconsistent results of beta-band functional connectivity.

References

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