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DOI
10.1016/j.cortex.2020.08.011

Publication date
2020

Document Version
Final published version

Published in
Cortex

License
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Link to publication

Citation for published version (APA):
Arnts, H., van Erp, W. S., Boon, L. I., Bosman, C. A., Admiraal, M. M., Schrantee, A., Pennartz, C. M. A., Schuurman, R., Stam, C. J., van Rootselaar, A.-F., Hillebrand, A., & van den Munckhof, P. (2020). Awakening after a sleeping pill: Restoring functional brain networks after severe brain injury. *Cortex*, *132*, 135-146. https://doi.org/10.1016/j.cortex.2020.08.011

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Download date:09 Nov 2026

CORTEX 132 (2020) 135–146

Available online at www.sciencedirect.com

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Exploratory Report

Awakening after a sleeping pill: Restoring functional brain networks after severe brain injury

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ARTICLE INFO

Article history:
Received 23 September 2019
Reviewed 26 November 2019
Revised 9 February 2020
Accepted 11 August 2020
Action editor Robert McIntosh
Published online 3 September 2020

Keywords:
Awakening
Beta band
Electroencephalography

ABSTRACT

Some patients with severe brain injury show short-term neurological improvements, such as recovery of consciousness, motor function, or speech after administering zolpidem, a GABA receptor agonist. The working mechanism of this paradoxical phenomenon remains unknown. In this study, we used electroencephalography and magnetoencephalography to investigate a spectacular zolpidem-induced awakening, including the recovery of functional communication and the ability to walk in a patient with severe hypoxic-ischemic brain injury. We show that cognitive deficits, speech loss, and motor impairments after severe brain injury are associated with stronger beta band connectivity throughout the brain and suggest that neurological recovery after zolpidem occurs with the restoration of beta band connectivity. This exploratory work proposes an essential role for beta rhythms in goal-directed behavior and cognition. It advocates further fundamental and clinical

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https://doi.org/10.1016/j.cortex.2020.08.011
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Functional connectivity
Magnetoencephalography
Oscillations
Severe brain injury
Zolpidem

research on the role of increased beta band connectivity in the development of neurological deficits after severe brain injury.

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1. Introduction

Paradoxical signs of temporary neurological recovery have previously been described in a subgroup of patients with severe brain injury after administering zolpidem, a GABA receptor agonist (Bomalaski, Claflin, Townsend, & Peterson, 2017). This phenomenon is primarily known in patients with disorders of consciousness, but also occurs in patients with degenerative disorders, such as Parkinson's disease, or those with neurological deficits after stroke (Daniele, Panza, Greco, Logroscino, & Seripa, 2016; Sutton & Clauss, 2017). However, a paradoxical response to zolpidem remains rare. For instance, in a study of a small group of patients with a disorder of consciousness, only 6.7% experienced signs of neurological recovery after zolpidem (Whyte & Myers, 2009). Nonetheless, zolpidem has gained considerable research interest in recent years, as its action mechanism may represent a new treatment for patients with a variety of neurological disorders. Nevertheless, this action mechanism and the reason for zolpidem's selective activity remain largely unknown.

Previous studies on the restorative effects of zolpidem have suggested that the drug can restore abnormalities in GABAergic signaling that arise after brain injury (Hall et al., 2010, 2014; Prokic et al., 2015). Furthermore, zolpidem is thought to temporarily suppress pathologically increased levels of slow–wave activity after brain damage that is known to result in cognitive and motor deficits (Hall et al., 2010; Williams et al., 2013). However, little is known about the effects of zolpidem on the mechanisms supporting large-scale integration throughout the brain. Large-scale integration from spatially distinct brain regions is crucial for several cognitive functions, such as selective attention, short- and long-term memory, and flexible routing of information (Bosman, Lansink, & Pennartz, 2014; Fries, 2015; Varela, Lachaux, Rodriguez, & Martinerie, 2001). Not surprisingly, a wide variety of neurological disorders have already been associated with dysfunctions in neuronal synchronization (Schnitzler & Gross, 2005; Stam, 2014).

In this open-ended exploration, we set out to study the effects of zolpidem on functional connectivity: a measure used to characterize functional integration. We used both EEG and MEG to study a zolpidem-induced awakening, including the recovery of functional communication and motor behavior in a patient with severe hypoxic-ischemic brain injury. We report the pharmacologically-induced neurophysiological changes paralleling this recovery and use this evidence to propose novel hypotheses that explain zolpidem-induced awakenings in patients with severe brain injury.

2. Materials and methods

2.1. Ethical approval

Family members gave written informed consent to the research protocol, which was approved by the medical ethical committee of the Amsterdam University Medical Center (location Academic Medical Center), The Netherlands. Ethics review criteria conformed to the Declaration of Helsinki. Moreover, consent was obtained for publishing video material. No part of the study procedures or analysis plans was preregistered in an institutional registry prior to the research being conducted. In the following section, we report how we determined our sample size in the control group, all data exclusions, all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study.

2.2. Clinical case

A man, 29-year old, with a history of alcohol abuse suffered from hypoxic-ischemic brain injury after choking on a piece of meat. After an initial, though slow neurological recovery, spontaneous movement and speech disappeared. The patient developed such a severe impairment of arousal that he required intensive auditory and tactile stimulation to maintain a wakeful state. No structural lesions were found using a computerized tomography (CT) scan to explain this secondary deterioration, and conventional EEG-recordings showed no evidence of epilepsy. After a stay in the ICU and neurology department, the patient was transferred to a nursing home without a formal diagnosis explaining his hyporesponsive state. A structural MRI at follow-up showed signs of diffuse atrophy without hydrocephalus.

Eight years passed without any further improvement and neurological follow-up. Eventually, a new nursing home physician with experience in hyporesponsive disorders took over the patient's treatment and performed a new neurological examination to find directions to improve his care. Upon clinical assessment, the now 37-year old patient seemed awake, but showed a complete lack of voluntary movement (akinesia) and absence of speech (mutism). More specifically, the patient showed no affective reactions, initiation of eating or drinking, and remained incontinent. Although the patient showed no signs of spontaneous speech or vocalization on request, he was able to respond to questions or commands with movements with a significant delay (usually a couple of seconds) and with evident ataxia and muscle rigidity. Despite his intact awareness, the patient's initiative was so severely impaired that he remained wheelchair-bound and entirely dependent on

nursing care for all daily activities, including the need for enteral tube feeding. His behavioral condition was classified as akinetic mutism (AM): a severe disorder of diminished motivation (Arnts et al., 2020; Marin & Wilkosz, 2005).

After consultation with his family, a single dose of zolpidem (10 mg) was administered by the nursing home physician. This dose is frequently used for patients with persistent hyporesponsive disorders (Bomalaski et al., 2017). Within 20 min, the patient started communicating spontaneously, asking the nurse how his wheelchair was to be operated, and requesting fast food. He managed to walk while being supported by the staff and phoned his father, who had not heard his son's voice for years. Despite evident retrograde amnesia, going back three years before the brain injury, and an apparent hearing deficit, he was cheerful, alert, and showing interest in the people and objects surrounding him. Two hours after zolpidem administration, he gradually fell back into his diminished motivational state. Following this observation, the nursing home physician gave him a drug-regimen of three daily doses of zolpidem (10 mg) around mealtimes.

However, a severe reduction in effectiveness became noticeable after administering zolpidem for several consecutive days. The time windows during which the patient was able to talk and move got narrower, and his abilities to move and speak during these time windows decreased. Usually, the restorative effects of a single dose of zolpidem could be reproduced once a day for about five consecutive days. After this period, drug administration did not result in observable clinical effects. The use of multiple doses of zolpidem during a single day showed no improvement in his clinical condition and sometimes even caused sedation.

On average, it would require two to three medication-free weeks to notice the effects of a single dose of zolpidem again. Consequently, zolpidem administration was restricted to special occasions, such as family visits or dental appointments. With this amended pharmacological regime, a single zolpidem dose could again lead to the effects observed after the first administration of the drug. Under these conditions, the effects of zolpidem became noticeable after approximately 30 min from oral administration and lasted for 30–60 min. Hereafter, a wearing-off phase followed of about 30–60 min.

At the start of the current study, the patient was 38 years old, weighed 65 kg, and was 60 days-off of zolpidem. During this period, the patient received no other drugs or neurostimulants that could have affected his neurological condition.

2.3. Clinical assessment

Clinical tests were performed once before and once after zolpidem administration using the Montreal Cognitive Assessment tool (MoCA) and Coma Recovery Scale-Revised (CRS-R). The MoCA is a brief screening tool used for patients with mild cognitive impairment (Nasreddine et al., 2005), while the CRS-R is a screening tool for patients with disorders of consciousness (Schnakers et al., 2009). These clinical tests were performed on the same day as the EEG. Since the maximum effects of zolpidem lasted for a relatively short time (approximately 30–60 min), the clinical tests were performed only once after administration, enabling a full 30-minute resting-state EEG recording.

2.4. EEG/MEG

2.4.1. EEG data-acquisition and pre-processing

The EEG-data were recorded in a resting-state condition with the patient lying in bed and using a sampling frequency of 1024 Hz (Micromed, Mogliano Veneto, TV, Italy). 21 Ag–Cl electrodes (19 scalp electrodes + 2 electrodes positioned at both ear lobes serving as recording reference) were placed according to the international 10–20 system. Two recordings with a duration of 30 min each were performed. The patient was first recorded pre-zolpidem, following which zolpidem (10 mg) was administered. Then, 30 min after the administration of zolpidem, the patient started talking and spontaneously moving (became 'awake'), after which another EEG was recorded. From these two recording sessions, we split the continuous EEG recording into epochs of 1-second duration. Epochs with eyes closed were selected for both conditions. These epochs were visually inspected to discard potential sleep periods, and ocular and motor artifacts. Power line artifacts were eliminated using a digital notch filter (Bosman et al., 2012). The 1-second epoching allowed us to eliminate poor EEG segments, yet still provided an adequate frequency resolution to accurately study low-frequency power dynamics. Since a relatively large number of subtle and more substantial movement artifacts were identified, the primary analyses of EEG (and MEG, see below) were therefore based on selected data segments of higher quality (for an overview of data selection, see Supplementary Figure 1). In total, we obtained 286 epochs of 1-second duration (4.8 min) for the condition before the administration of zolpidem and 263 epochs of 1-second duration (4.4 min) for the condition after administration of zolpidem. For the spectral power analysis, we used all (549 in total) artifact-free epochs of 1-second duration. Clean epochs were digitally filtered between .5 and 100 Hz and subsequently average referenced.

To check if our results were robust and if we would find the same results in subsets of our data, we performed the same power analysis using 60 randomly selected epochs from the total recording set for each condition. We repeated this procedure 10 times. From these 10 sets of subsampled epochs, we obtained the power spectrum across frequencies. We report the average and 95% CI across repetitions.

For the functional connectivity analysis, 98 and 76 artifact-free epochs (digitally filtered between .5 and 100 Hz and subsequently average referenced) were available from the pre- and post-administration of zolpidem conditions, respectively. The epochs were 4 s of length to be able to calculate amplitude envelopes reliably. First, we restricted the analysis to the 30 highest-quality epochs per condition. Next, as for the power analysis, we performed the functional connectivity analysis for 30 randomly chosen 4-seconds epochs per condition as a robustness-check. We repeated this procedure 10 times, also reporting the average and 95% CI across repetitions.

2.4.2. MEG data-acquisition and pre-processing

MEG recordings were obtained in a magnetically shielded room in a supine resting-state condition. The MEG recordings

were performed on a separate occasion, three months after the EEG. Two datasets of 5-minute duration each were recorded pre-zolpidem. Next, the patient was administered zolpidem (10 mg) outside of the magnetically shielded room. Once again, after 30 min, the patient became awake, and two more datasets of 5-minute duration were obtained. Data were recorded using a 306-channel whole-head system (Elekta Neuromag Oy, Helsinki, Finland) with a sampling frequency of 1250 Hz and online anti-aliasing (410 Hz) and high-pass filtering (.1 Hz). The head position relative to the MEG sensors was recorded continuously using the signals from five head position indicator (HPI) coils. The HPI positions and the outline of the patient's scalp (around 500 points) were digitized before the recording using a 3D digitizer (Fastrak, Polhemus, Colchester, VT, USA). The patient's MEG data were co-registered to his structural MRI using a surface-matching procedure with an estimated resulting accuracy of 4 mm (Whalen, Maclin, Fabiani, & Gratton, 2008). This structural MRI of the head had been obtained two months before the MEG session as part of clinical care, using a 3T Philips MRI scanner (Philips Medical Systems, Best, The Netherlands).

For MEG source-level analysis, the following extra processing steps were undertaken. First, bad channels were removed after visual inspection of the data (mean number of excluded channels 11; range 10–12). Thereafter, the temporal extension of Signal Space Separation (tSSS) in MaxFilter software (Elekta Neuromag Oy, version 2.2.15) was applied using standard settings, a correlation limit of .9, and a sliding window of 10 s (Hillebrand, Fazio, de Munck, & van Dijk, 2013; Taulu & Simola, 2006). The automated anatomical labeling (AAL) atlas was used to label the voxels in 78 cortical and 12 subcortical regions of interest (ROIs) (Gong et al., 2009; Tzourio-Mazoyer et al., 2002). We used each ROI's centroid voxel as representative for that ROI (Hillebrand et al., 2016). Subsequently, an atlas-based scalar beamforming approach (beamformer, version 2.1.28; Elekta Neuromag Oy), similar to Synthetic Aperture Magnetometry (Robinson & Vrba, 1999), projected the sensor signals to these (source-space) centroid voxels, resulting in a broadband (.5–48 Hz) time series for each centroid of the 90 ROIs (Hillebrand et al., 2016). The source-space data were visually checked for significant artifacts, and these parts of the recording were discarded, leaving 560 s of data pre-zolpidem administration and 550 s of data post-zolpidem administration. Next, we visually selected the highest-quality epochs based on the absence of small artifacts and drowsiness (e.g., slow waves and slow eye movements on electrooculography).

For the power analysis, we selected 90 high-quality epochs (1 s per epoch) per condition. As described for the EEG dataset, we checked if our results were robust by selecting 10 sets of 60 epochs of 1-second length per condition, and reporting the average and 95% CI across repetitions. For the functional connectivity analysis, time-series were split into longer epochs of 4096 samples (3.28 s). The sixty best-quality epochs per condition (30 epochs per recording) were selected for further analysis. Again, we performed a robustness-check by obtaining 10 sets of 60 randomly chosen epochs (per condition) and repeating the functional connectivity analysis and reporting the average and 95% CI across repetitions.

MEG-based functional connectivity for the patient (in both conditions) was visually compared with the average functional connectivity obtained from three healthy male volunteers. Three healthy volunteers were considered enough to make an adequate comparison with our patient. The healthy male volunteers were 38, 40, and 41 and had all undergone one five-minute, eyes-closed, resting-state MEG recording without medication. Data acquisition, pre-processing, and analysis were performed in the same way as for the patient dataset.

2.4.3. *Video-recordings*

Since the CRS-R has a ceiling effect in patients with disorders of motivation, and the MoCA a floor effect, video-recordings were performed to capture the full spectrum of behavioral changes in our patient qualitatively. The video-recordings were made in the nursing home of the patient in the time-frame between the separately performed EEG and MEG recording session.

2.5. *Data analysis*

For both EEG and source-space MEG data, the spectral power was obtained using a Fast Fourier Transform (FFT) algorithm after multitapering with 3 tapers (Mitra & Pesaran, 1999). Given an epoch length of 1 s for the spectral analysis, this resulted in a spectral smoothing of 8 Hz (~4 Hz from the frequency center) for both datasets. Relative power values were expressed as a percentage of the total power by dividing the power in every frequency bin by the total power (.5–48 Hz for MEG and 2–50 Hz for EEG) per channel/ROI. The relative band power in each canonical frequency band was averaged over all channels/ROIs and over each brain lobe (frontal, parietal, temporal, and occipital; for MEG only). The frequency bands were defined as theta (4–8 Hz), alpha (8–12 Hz), beta (15–30 Hz), and gamma (30–48 Hz for MEG and 30–50 Hz for EEG analysis).

Also, frequency band-specific functional connectivity analyses were performed for both EEG (epoch length 4 s) and MEG data (epoch length 3.2 s). Functional connectivity was estimated using the corrected amplitude envelope correlation (cAEC). The cAEC is a measure of functional connectivity between brain regions that corrects for the effects of volume conduction/field spread, using a symmetric orthogonalization procedure (Brookes, Woolrich, & Barnes, 2012; Hipp, Hawellek, Corbetta, Siegel, & Engel, 2012). To adjust for any negative correlations, 1 was added to all values, and the successive numbers were divided by 2. The cAEC therefore ranges from 0 to 1, with a value of .5 indicating no connectivity. The cAEC was calculated for all possible pairs of channels/ROIs, leading to a 19 × 19 (EEG) or 90 × 90 (MEG) adjacency matrix that contained the functional connectivity values between all pairs. cAEC values were subsequently averaged per channel/ROI (hence, indicating the functional connectivity between one channel/ROI and all other channels/ROIs).

The observed power and cAEC between pre- and post-zolpidem states are reported as average across epochs and the 95% CI. The effect size of the differences in power and cAEC between pre- and post-zolpidem states is reported using Cohen's d.

The spectral and functional connectivity analyses were performed using FieldTrip (http://www.fieldtriptoolbox.org) (Oostenveld, Fries, Maris, & Schoffelen, 2011) in MATLAB 2016b (Mathworks; 9.1.0.441655) and in-house software (BrainWave, version 0.9.152.12.26; CJS, available from https://home.kpn.nl/stam7883/brainwave.html), respectively. Raw data and source-space data with analysis code, together with clinical assessment data and the data from the control participants, is available online using the following weblink: https://data.mendeley.com/datasets/d8jncnwjx7/2.

3. Results

3.1. Clinical changes

Consistent with the previously established diagnosis of akinetic mutism, the patient showed (inconsistent) functional object use of more than two objects before zolpidem administration, and therefore a ceiling score on the CRS-R, indicating an intact level of consciousness. 30 min after zolpidem administration, the patient showed remarkable signs of awakening, including the return of functional speech, spontaneous intentional object use, and awareness of his surroundings (see Video in Supplementary Materials). Moreover, he was able to walk several steps with some assistance. The MoCA score improved from 0/30 to 13/30. These effects lasted for 60 min. Hereafter, the patient gradually returned back to his original akinetic and mute state within a period of 30–60 min.

3.2. EEG and MEG

Qualitatively, the pre-zolpidem resting-state EEG in our patient is of average voltage and shows a generalized abundance of fast (alpha/beta) and slow (delta) activity, though without a normal anterior-posterior differentiation (see Mendeley dataset link for EEG's). As in healthy individuals, drowsiness and sleep are characterized by further slowing and K-complexes, and increases of fast (alpha/beta) activity after short verbal stimuli to arouse the patient. Post-zolpidem, the patient is much more awake. The background pattern is more or less the same, with a presence of generalized fast activity (beta) and some (frontal) theta/delta, though the EEG still lacks a clear anterior-posterior differentiation, which is different than in healthy persons. However, it is much faster than one would generally expect in, for instance, a patient with encephalopathy (Ebersole & Pedley, 2003).

Quantitatively, the EEG sensor-space spectral analysis of the pre-zolpidem condition revealed a peak in relative theta and alpha power over the frontal, and parietal cortices, which decreased after zolpidem administration (Cohen's d for the contrast between conditions: theta = .51, alpha = 1.13). Besides, a small increase in relative beta and gamma power was observed after zolpidem administration (Cohen's d for beta = .29, and gamma band = .32), most notably over frontal, temporal, and central/parietal regions (Fig. 1c). These differences are highlighted for the two central electrodes (Fz - Cz, Fig. 1a), but were observed for five different groups of electrodes (Supplementary Fig. 2a-e). Fig. 1b shows the average relative power and 95% CI for the four different frequency bands for both conditions. We subsequently performed a robustness-check on the selected epochs, repeating (n = 10) the above analysis using 60 randomly chosen epochs across the recording session for both conditions. The results remained the same (Supplementary Fig. 2f-j).

The MEG source-space spectral analysis confirmed these observations, but showed a larger effect size for the increase in beta and gamma power (Cohen's d for the contrast between conditions: theta = .7, alpha = .5, beta = .63, and gamma = 1.11; see Fig. 2 for relative power for both conditions, and Supplementary Fig. 3 and Supplementary Table 1 for the contrast between the two conditions). After zolpidem administration, we observed an increase in beta and gamma power for all cortical brain regions. Interestingly, the topographical analysis revealed that this beta power increase was most pronounced for frontal and parietal regions, while temporo-occipital regions showed higher levels of theta power pre-zolpidem, which is followed by a shift in power towards the alpha frequency range after the administration of zolpidem (Fig. 2c–f and Supplementary Figure 3). The robustness-check confirmed these results (Supplementary Fig. 4).

Furthermore, we studied the functional connectivity across different brain areas before and after the administration of zolpidem. We observed a reduction in beta band functional connectivity throughout the brain in both the EEG and MEG analyses (Fig. 3 and Supplementary Fig. 5). We did not find large effect sizes for the contrast between conditions for the other frequency bands. Therefore, we focused the rest of our analyses on beta band functional connectivity. Interestingly, the EEG analysis revealed a decrease with a medium effect size in functional connectivity in the beta band after administering zolpidem for most electrodes (Cohen's d = .65; Fig. 3a). The MEG source-space cAEC analysis confirmed these results, but showed an even larger effect size for beta (Cohen's d = .83; Fig. 3b). We observed a decrease of beta band functional connectivity across all cortical and subcortical AAL brain regions (Fig. 3b) after zolpidem administration. These effects were also observed in randomly chosen data segments across the entire recording (Supplementary Fig. 5).

Finally, we compared the MEG source-space pre- and post-zolpidem functional connectivity values with those observed in three healthy subjects (see Fig. 3b for average cAEC and Supplementary Fig. 6 for comparison with individual controls). In the pre-zolpidem condition, we observed higher resting-state functional connectivity throughout the patient's brain compared to the healthy controls. After zolpidem administration, this level of beta band functional connectivity in the patient decreased to levels that were comparable to those observed in the three healthy subjects (Fig. 3b). This decrease was observed for all cortical and subcortical brain regions.

4. Discussion

4.1. General discussion

4.1.1. Power changes

First, we observed that zolpidem administration in our patient was associated with a decrease in theta/alpha power and an

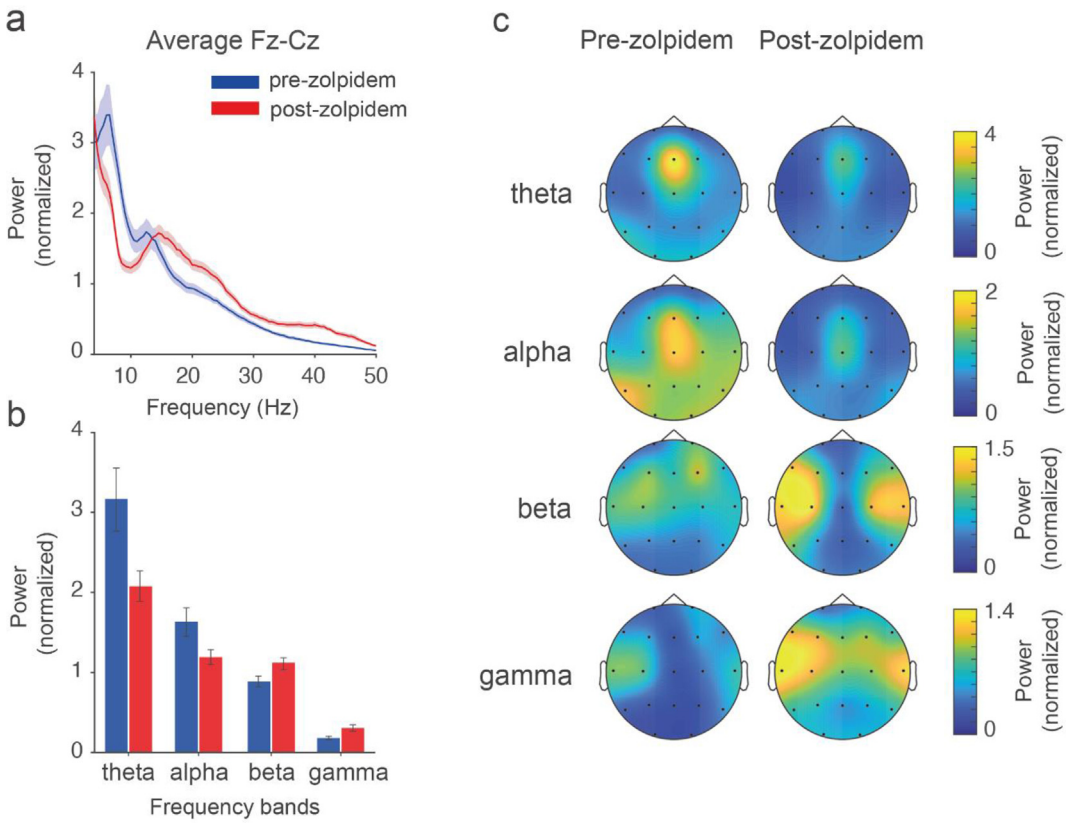

Fig. 1 – Effect of zolpidem on spectral power (EEG). A. Local normalized spectral power (percentage of each frequency bin relative to the total power) from the midline (average and 95% CI, Fz and Cz electrodes) for pre- and post-zolpidem conditions. B. Global normalized spectral power presented as bar chart per frequency band (average and 95% CI) for both conditions. C. Head plots of the topography of normalized spectral power per frequency band, viewed from the top: theta band, 4–8 Hz; alpha band, 8–12 Hz; beta band, 15–30 Hz; gamma band, 30–50 Hz. CI = confidence interval.

increase in beta/gamma power (see result section for effect sizes). This power shift from low to high-frequency rhythms corresponds with previous neurophysiological studies in zolpidem-responsive patients with other neurological deficits (Hall et al., 2010; Williams et al., 2013). For instance, Hall and colleagues were the first to report that zolpidem decreases elevated levels of low-frequency rhythms after brain injury (Hall et al., 2010). They suggested that these specific changes result in cognitive and motor improvements, especially after a stroke. Subsequently, Williams and colleagues also described similar results in three patients with severe brain injury. They described both a zolpidem-induced decrease of abnormal levels of theta/alpha power, and an increase in beta power, which is in line with the changes observed in our patient (Figs. 1 and 2). They further hypothesized that increased low-frequency power might be a pathognomonic signature in some patients with brain injury and considered these patients more prone to the paradoxical effects of zolpidem. They also proposed that a shift towards higher frequencies might be a consequence of the restoration of inhibitory GABAergic signaling within specific (mesocortical) neurocircuits that are known to be involved in the regulation of arousal and behavior (Schiff, 2010). Although we cannot mark the EEG baseline spectral power in our patient as high or low without a control group, this mechanism might also play a role in the restorative effects of zolpidem in akinetic mutism.

In addition to an overall shift towards higher frequencies of the spectrum, our source-space MEG results also suggest a peak frequency shift from theta to alpha in temporal and occipital regions (see Fig. 2d–f). Peak frequency shifts are considered to reflect changes in a behavioral state (Haegens, Cousijn, Wallis, Harrison, & Nobre, 2014; Mierau, Klimesch, & Lefebvre, 2017). In specific, alpha power increases with increasing cognitive demands (Handel, Haarmeier, & Jensen, 2011) and temporo-occipital alpha power fluctuations have been associated with a flow of information in visual areas (Jokisch & Jensen, 2007; Mazaheri, Nieuwenhuis, van Dijk, & Jensen, 2009). The observed peak frequency shift in our patient might, therefore, reflect the transition from the akinetic mute state to a state of increased attention and arousal (see the video in supplementary materials for clinical overview of attention and arousal changes).

If we specifically look at beta power, previous studies have reported different effects of zolpidem. While some authors report increases in beta power (Williams et al., 2013), others report the opposite (Hall et al., 2010). Previous studies have shown that zolpidem is capable of a bidirectional modulation of neuronal network activity, restoring disease-specific

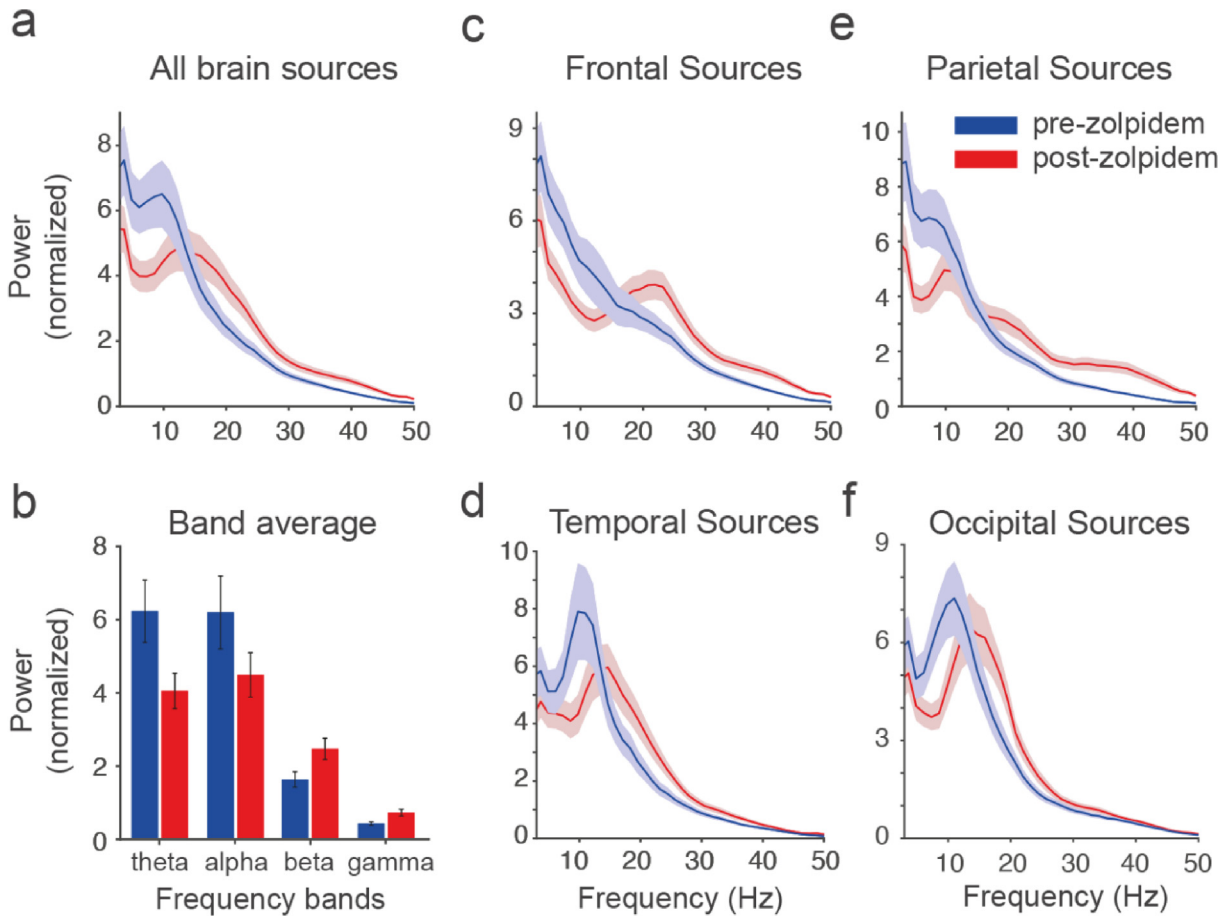

Fig. 2 – Effect of zolpidem on source-space spectral power (MEG). A: Normalized spectral power (average and 95% CI) across all brain regions. B: Global normalized spectral power, presented as bar chart per frequency band (average and 95% CI). C–F: As in A., but for Frontal (C), Temporal (D), Parietal (E), and Occipital (F) brain regions. CI = confidence interval. For regional spectral power in theta, alpha, beta, and gamma bands see Supplementary Material Fig. 4.

oscillatory imbalances through simultaneous augmentation and depression of beta band activity (Hall et al., 2014). Importantly, the actual direction of the effects of zolpidem on oscillatory beta band activity seems to be dose-dependent (Prokic et al., 2015). As such, zolpidem reduces beta power at sub-sedative doses, while it increases beta-power at higher dosages. Our patient only showed behavioral effects after administering 10 mg of zolpidem, which is considered a sedative dose for healthy subjects. Since our patient's weight was limited (65 kg), 10 mg may be a relatively high dose, which may account for the fact that we see an overall increase in beta power.

4.1.2. *Changes in functional connectivity*

The neurophysiological recordings in our patient showed a decrease in functional connectivity in the beta band throughout the brain after zolpidem administration (see Fig. 3 and Supplementary Figs. 5-6). These changes were observed in both the EEG (medium effect size) and MEG recordings (large effect size), which were made with a three-month interval. The contrast between the increase in relative beta power and decrease in functional connectivity supports the assumption that the band power changes do not entirely drive the functional connectivity changes. Pathological changes in functional connectivity have been associated with various clinical deficits in a wide variety of brain disorders (Schnitzler & Gross, 2005; Stam, 2014; Uhlhaas & Singer, 2006). More specifically, a pathological increase in beta band functional connectivity is thought to be associated with deterioration of flexible behavioral and cognitive control (Engel & Fries, 2010). For instance, higher beta band functional connectivity has been observed in patients with Parkinson's disease (Bosboom et al., 2006; McCarthy, Ching, Whittington, & Kopell, 2012). In these patients, symptom relief correlates with lowering of beta band functional connectivity trough drug (dopamine agonist) administration (Bosboom et al., 2006; Engel & Fries, 2010; Silberstein et al., 2005). We suggest that the widespread hypoxic-ischemic injury in our patient might have resulted in a similar pathological enhancement of beta band functional connectivity throughout the brain, causing abnormally strong inhibition of behavioral and cognitive functions. Administering zolpidem seems to temporarily reverse abnormally high levels of beta band connectivity, thereby restoring functional brain networks and improving large-scale brain functioning.

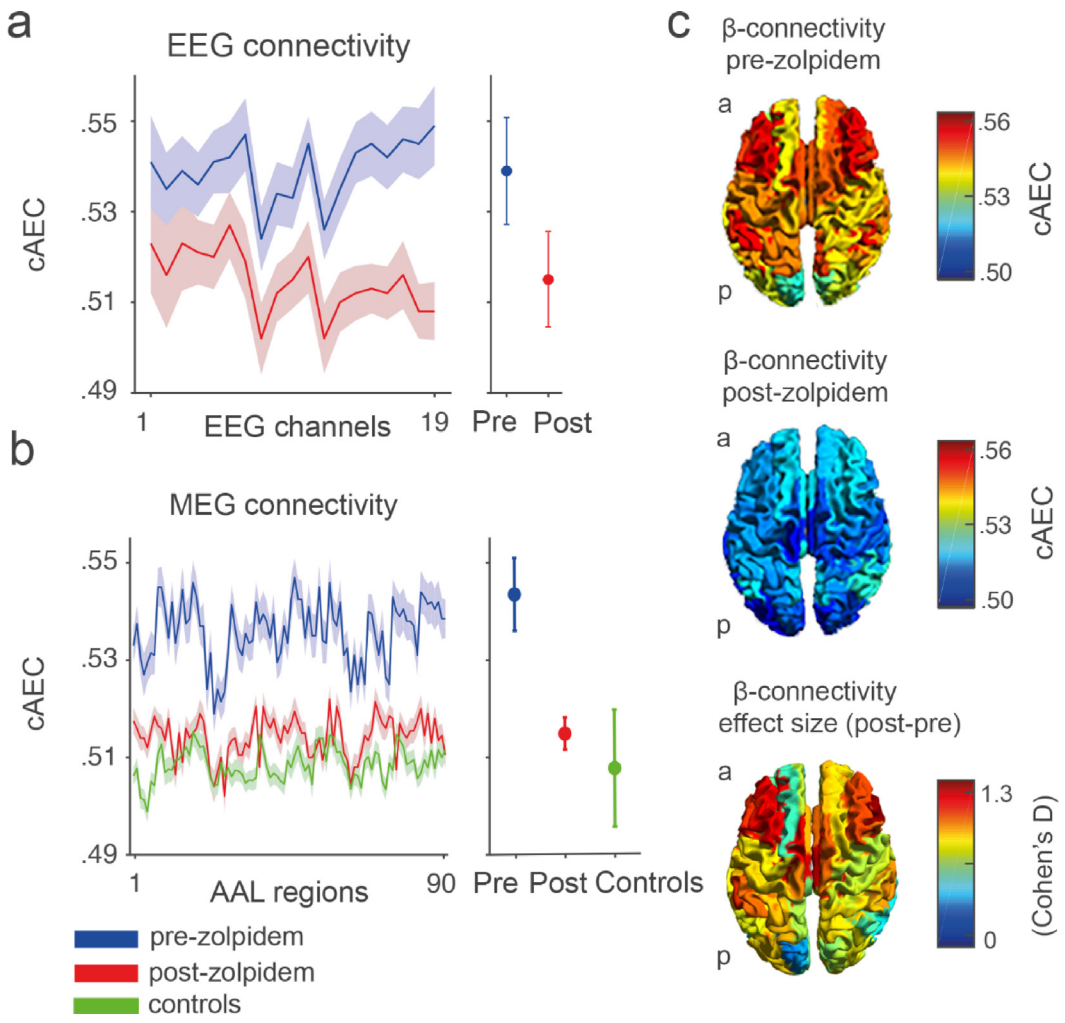

Fig. 3 – Effect of zolpidem on EEG/MEG beta band functional connectivity. A. EEG functional connectivity (cAEC) per condition for each channel (left: average and SEM) and averaged over all channels (right: average and 95% CI). B. Source-space MEG functional connectivity (cAEC) per condition for each brain region (left: average and SEM) and averaged over all brain regions (right: average and 95% CI). C. Beta band MEG functional connectivity for both conditions, and the contrast between conditions, displayed on a parcellated template brain, viewed from above. For visualization purposes, only cortical brain regions are displayed. From top to bottom: average beta band cAEC per region in the pre- and post-zolpidem condition and effect size of beta band functional connectivity differences between pre/post-zolpidem, expressed as Cohen's d. SEM = standard error of the mean. CI = confidence interval. a = anterior, p = posterior. For AAL atlas regions, see Supplementary Materials Table 2.

Recent evidence from animal studies suggests a possible mechanism for this reversal. Brain injury, such as stroke, might cause a shift in $GABA_A$ receptor-mediated communication as a result of injury-induced impairments of specific GABA transporters and dysfunction in $GABA_A$ receptor subunits (Clarkson, Huang, Macisaac, Mody, & Carmichael, 2010; Guerriero, Giza, & Rotenberg, 2015; Hiu et al., 2016). These impairments eventually lead to a shift in $GABA_A$ receptor-mediated inhibition, changing the dynamics of GABA signaling from phasic to predominantly tonic, thereby altering network excitability (Farrant & Nusser, 2005; Prokic et al., 2015). Zolpidem is thought to act on GABAergic fast-spiking interneurons that generally act to synchronize neuronal signals across large networks, and are a crucial component for both spectral power and functional connectivity (Cardin, 2018; Chen et al., 2017; Manseau et al., 2010). After brain injury, zolpidem seems to be able to reverse the excessive tonic conductance in GABA interneurons, restoring normal phasic GABA signaling and promoting functional recovery (Clarkson et al., 2010; Hiu et al., 2016; Prokic et al., 2015). This reversal is associated with a change in rhythmic activities in different neuronal networks and the

regulation of synchronous population activity throughout the brain, which may account for the changes in functional connectivity (and spectral power) we observed in our patient.

4.2. Limitations

The above-described findings of power changes should be interpreted cautiously. First of all, our study is subject to performance confound, meaning that if the behavioral performance is substantially different in two experimental conditions (as is the case for the pre- and post-zolpidem conditions), some measures of brain physiology might also differ between those conditions, thereby representing an epiphenomenon (Morales, Chiang, & Lau, 2015; Williams et al., 2013). Neurophysiological activity is well-known to change in different behavioral conditions. For instance, increasing arousal is associated with clear decreases in delta, theta, and (lower) alpha activity, which might explain the reduction seen in these frequency bands in our patient (Foucher, Otzenberger, & Gounot, 2004; Niedermeyer & Lopes da Silva, 1999). Experiments in which EEG's were used as means to measure cortical arousal previously even relied on the inverse correlation of arousal with the power of low EEG frequencies during awakening (Danos, Guich, Abel, & Buchsbaum, 2001; Foucher et al., 2004). However, behavioral changes are usually associated with a decrease in beta power, which is opposite of the effects seen in our patient (Engel & Fries, 2010). Moreover, behavioral improvements are usually accompanied by an increase rather than a decrease in functional connectivity, which suggests that the observed changes were directly related to the observed behavioral changes (Ohara et al., 2001; Rissman, Gazzaley, & D'Esposito, 2004). Also, it is opposite to what is seen in other neurological disorders, such as mild cognitive impairment and Alzheimer's disease, where cognitive and behavioral decline is associated with loss of beta band synchronization (Stam, van der Made, Pijnenburg, & Scheltens, 2003).

Furthermore, the effects observed might be similar in healthy patients receiving zolpidem, since we lack a placebo control in this study. For instance, it is well-known that GABA-agonists can cause decreases in low-frequency power and increases in beta-activity (Patat et al., 1994; Williams et al., 2013). However, these effects on spectral power are of short-term and variously reported in healthy patients (Perez, Machado, Rodriguez, Estevez, & Chinchilla, 2016). Also, behavioral improvements are usually accompanied by an increase in functional connectivity, which is in contrast with the results of our study (Ohara et al., 2001; Rissman et al., 2004).

Although we present the neurophysiological results of a single patient, similar effects were seen in both the EEG as MEG recordings, which were made on two different occasions under similar conditions. The observed behavioral improvements (as seen in the video), in combination with the changes in beta functional connectivity (medium effect size for EEG and large effect size for MEG) is quite remarkable to observe in a single patient. However, the relative differences in effect size between the power and functional connectivity changes in the EEG and MEG suggests the necessity of larger sample sizes. In contrast to the changes in beta functional connectivity, the changes in beta power were smaller. Future studies should re-examine our results in a confirmatory design (see section 4.3) with larger samples, with a placebo control group, and ideally controlling for performance capacity confounds known for patients with severe brain injury (Morales et al., 2015). Furthermore, future studies need to include a larger group of healthy subjects to compare baseline spectral power and functional connectivity and compare neurophysiological findings after zolpidem administration.

4.3. Hypothesis generation

Our study suggests that patients with neurological deficits after hypoxic-ischemic brain injury, especially those with akinetic mutism, may maintain higher levels of beta band functional connectivity. As mentioned above, a study with a larger sample of patients is necessary to confirm this hypothesis. This study must preferably contain patients with similar clinical presentations and an equivalent response to zolpidem to prevent bias, though this may be challenging since zolpidem awakenings remain rare (Arnts et al., 2020; Whyte & Myers, 2009). Therefore, international collaboration and the clustering of cases in specialized centers will be necessary actions for further research.

Our study also suggests that zolpidem can temporarily reduce and restore beta band functional connectivity to a level that allows functionality to return. Interestingly, Williams and colleagues demonstrated a subtle increase in frontal interhemispheric coherence within the 20–30 Hz range in two of their three patients. More recently, Sripad and co-workers also described similar results in another case-study (Sripad et al., 2020). An explanation for the difference with our case (i.e., increased versus decrease beta band connectivity) may be found in the fact that all of these patients experienced brain injury from traumatic origin. Therefore, additional studies, including patients with different types of brain injury, both from traumatic and hypoxic-ischemic origins, are necessary to clarify these contradicting results. These studies should also include a treatment schedule with low- and high-dose zolpidem to reveal what the real dose-dependent effects are of zolpidem in human subjects (Prokic et al., 2015).

Further insights into the action mechanisms of zolpidem might eventually lead to new treatment strategies for patients with severe brain injury. For instance, if a reduction in beta band functional connectivity also relates to functional improvement in other patients with brain injury, it is conceivable to think that therapies that reduce beta band connectivity might be beneficial for a larger group of patients. These therapies may include a variety of dopamine agonists, or invasive treatments that are known to more permanently affect beta band functional connectivity, such as deep brain stimulation (Boon et al., 2020).

Beta rhythms are traditionally associated with sensorimotor functions. However, they have recently become more broadly implicated in top-down processing, long-range communication, and other cognitive functions (Bastos et al., 2015). Our findings contribute to an increasing corpus of evidence that demonstrates a complex role for beta oscillations in the coordination of the flow of information across brain areas (Spitzer & Haegens, 2017). Future animal and human studies should elucidate how brain injuries could

affect the functionality of beta oscillations in cortical microcircuit regulation, top-down processing, and long-range communication.

5. Conclusion

Overall, our findings suggest an essential role of the beta band in goal-directed behavior and cognition. Our results also advocate further fundamental and clinical research on the role of beta band functional connectivity in the development of neurological deficits after severe brain injury, as this may lead to new therapeutic strategies.

CRediT authorship contribution statement

Hisse Arnts: Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Visualization, Writing – original draft; Willemijn S. van Erp: Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Writing – Review & Editing; Lennard I. Boon: Conceptualization, Formal analysis, Software, Visualization, Writing – Review & Editing; Conrado A. Bosman: Conceptualization, Formal analysis, Software, Visualization, Writing – Review & Editing; Marjolein M. Admiraal: Investigation, Methodology, Writing – Review & Editing; Anouk Schrantee: Investigation, Methodology, Writing – Review & Editing; Cyriel M.A. Pennartz: Conceptualization, Supervision, Writing – Review & Editing; Rick Schuurman: Conceptualization, Funding acquisition, Supervision, Writing – Review & Editing; Cornelis J. Stam: Conceptualization, Supervision, Writing – Review & Editing; Anne-Fleur van Rootselaar: Conceptualization, Supervision, Writing – Review & Editing; Arjan Hillebrand: Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Supervision, Writing – Review & Editing; Pepijn van den Munckhof: Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Supervision, Writing – Review & Editing.

Open practices

The study in this article earned an Open Data badge for transparent practices. Materials and data for the study are available at https://data.mendeley.com/datasets/d8jncnwjx7/2.

Declaration of Competing Interest

None.

Acknowledgments

This work was supported by a grant of Amsterdam Neuroscience (HA and PvdM) and by the FLAG-ERA (JTC) 2015 project Canon (co-funded to CAB by NWO).

Supplementary data

Supplementary data to this article and video can be found online at https://doi.org/10.1016/j.cortex.2020.08.011.

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