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Differences between magnetoencephalographic (MEG) spectral profiles of drugs acting on GABA at synaptic and extrasynaptic sites: A study in healthy volunteers

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ABSTRACT

A range of medications target different aspects of the GABA system; understanding their effects is important to inform further drug development. Effects on the waking EEG comparing these mechanisms have not been reported; in this study we compare the effects on resting MEG spectra of the benzodiazepine receptor agonist zolpidem, the delta sub-unit selective agonist gaboxadol (also known as THIP) and the GABA reuptake inhibitor tiagabine. These were two randomised, single-blind, placebo-controlled, crossover studies in healthy volunteers, one using zolpidem 10 mg, gaboxadol 15 mg and placebo, and the other tiagabine 15 mg and placebo. Whole head MEG recordings and individual MEG spectra were divided into frequency bands. Baseline spectra were subtracted from each post-intervention spectra and then differences between intervention and placebo compared. After zolpidem there were significant increases in beta frequencies and reduction in alpha frequency power; after gaboxadol and tiagabine there were significant increases in power at all frequencies up to beta. Enhancement of tonic inhibition via extrasynaptic receptors by gaboxadol gives rise to a very different MEG signature from the synaptic action of zolpidem. Tiagabine theoretically can affect both types of receptor; from these MEG results it is likely that the latter is the more prominent effect here.

This article is part of the Special Issue entitled 'GABAergic Signaling in Health and Disease'.

1. Introduction and rationale

The GABA system is the key inhibitory system in the brain and many neuropsychiatric disorders result from its dysregulation including insomnia, epilepsy, anxiety disorders, some aspects of substance abuse and possibly psychosis. There are a range of medications that target different aspects of this system and understanding their effects is important to inform further drug development. One approach has been to examine the effects of medication on EEG-measured sleep architecture in humans. These studies have shown marked differences between the drugs which promote GABA function by effects on extrasynaptic receptors [e.g. gaboxadol], or by inhibition of reuptake [e.g. tiagabine], compared with the positive allosteric modulators (PAMs) such as the benzodiazepines. Therefore it would be interesting to look at the effects of these different classes of drugs on the waking state to compare brain mechanisms.

In this paper we report on the use of human MEG to examine the actions of 3 drugs acting on this system – specifically the intrasynaptic benzodiazepine alpha-1 selective receptor site PAM zolpidem, the extra-synaptic alpha-4 delta receptor PAM gaboxadol and a presumed synaptic GAT1 GABA reuptake blocker tiagabine, all of which have been used for the treatment of human brain disorders.

GABA-A benzodiazepine receptor PAMs such as benzodiazepines and zolpidem enhance synaptic phasic inhibitory currents. Their effects on EEG have been studied extensively in man. During waking, and persisting into sleep, they give rise to a dose-dependent and plasma-concentration-dependent appearance of a regular, smoothly formed beta rhythm over the whole of the

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cortical region, beginning at the frontal area (Greenblatt et al., 2006; Malizia et al., 1996). This rhythmic beta activity has no correlation with state of awareness but is correlated with brain benzodiazepine receptor occupation (Malizia et al., 1996). It is seen in the EEG healthy participants receiving acute doses of these drugs for research studies, but also in patients who are taking the drugs long-term and are tolerant to their sedative effects. Barbiturates also produce this beta activity, and both they and benzodiazepines have been used clinically for many years to identify areas of damaged cortex in epilepsy and other disorders: the so-called 'beta gap' where damaged tissue does not produce this drug-induced rhythm (Claus et al., 2012, 2009; Pampiglione, 1952). A MEG study of diazepam described increased power and decreased frequency of beta oscillations over rolandic areas and attributed this to an increase in IPSCs onto inhibitory neurons rather than an increase in IPSCs onto excitatory pyramidal cells (Jensen et al., 2005). These drugs also reduce alpha-frequency activity over the whole cortical area (Connemann et al., 2005) during wakefulness. During sleep, there are the usual EEG signs of reduced awareness with increases in slower activity as in normal drowsiness and sleep, but these PAM drugs increase the amount of spindle activity, and in higher doses reduce delta activity (Brunner et al., 1991; Hindmarch et al., 2005; Karacan et al., 1981).

Gaboxadol also known as THIP (4,5,6,7-tetrahydroisoxazolopyridin-3-ol) is the first extra-synaptic GABA-A agonist to have been used in humans (Faulhaber et al., 1997). It enhances tonic GABA-A-mediated current (Drasbek et al., 2007) and has sleep promoting properties (Lancel et al., 2001) but can cause undesirable mental effects at higher doses. There are no published studies of the effect of gaboxadol on EEG or subjective ratings during wakefulness in man. In mice, both waking and sleeping EEG show a dramatic increase in slower EEG frequencies (<6 Hz) after gaboxadol, and this effect is not seen in mice deficient in the GABA-A delta-subunit gene (Winsky-Sommerer et al., 2007). Human sleep studies have described gaboxadol's effects in detail, with reports of marked increases in power in frequencies below 10 Hz delta and high theta activity and reduction of sleep spindles (Dijk et al., 2010; Walsh et al., 2007). There are no reported studies of MEG and gaboxadol.

Tiagabine is a GAT1 reuptake blocker originally developed as a treatment for epilepsy, whose effects are largely thought to be on intra-synaptic GABA (Madsen et al., 2009). The extent of GABA spillover into peri- and extra-synaptic space after GAT1 blockade is not well understood, but may contribute to tiagabine's effects. Extra-synaptic and pre-synaptic GABA mechanisms such as tonic inhibition and feedback autoinhibition may be activated by reuptake blockade (Axmacher and Draguhn, 2004). The effect of tiagabine on waking EEG in man has not been reported, although there are MEG studies of stimulus-related responses after tiagabine (Muthukumaraswamy et al., 2012, 2013b). In the rat in the awake state there was a small increase in beta band power in one study (Cleton et al., 1999) and no significant change in any spectral band in another (Lancel et al., 1998). Its effect on the human EEG has been studied during sleep (Mathias et al., 2001; Walsh et al., 2006); in

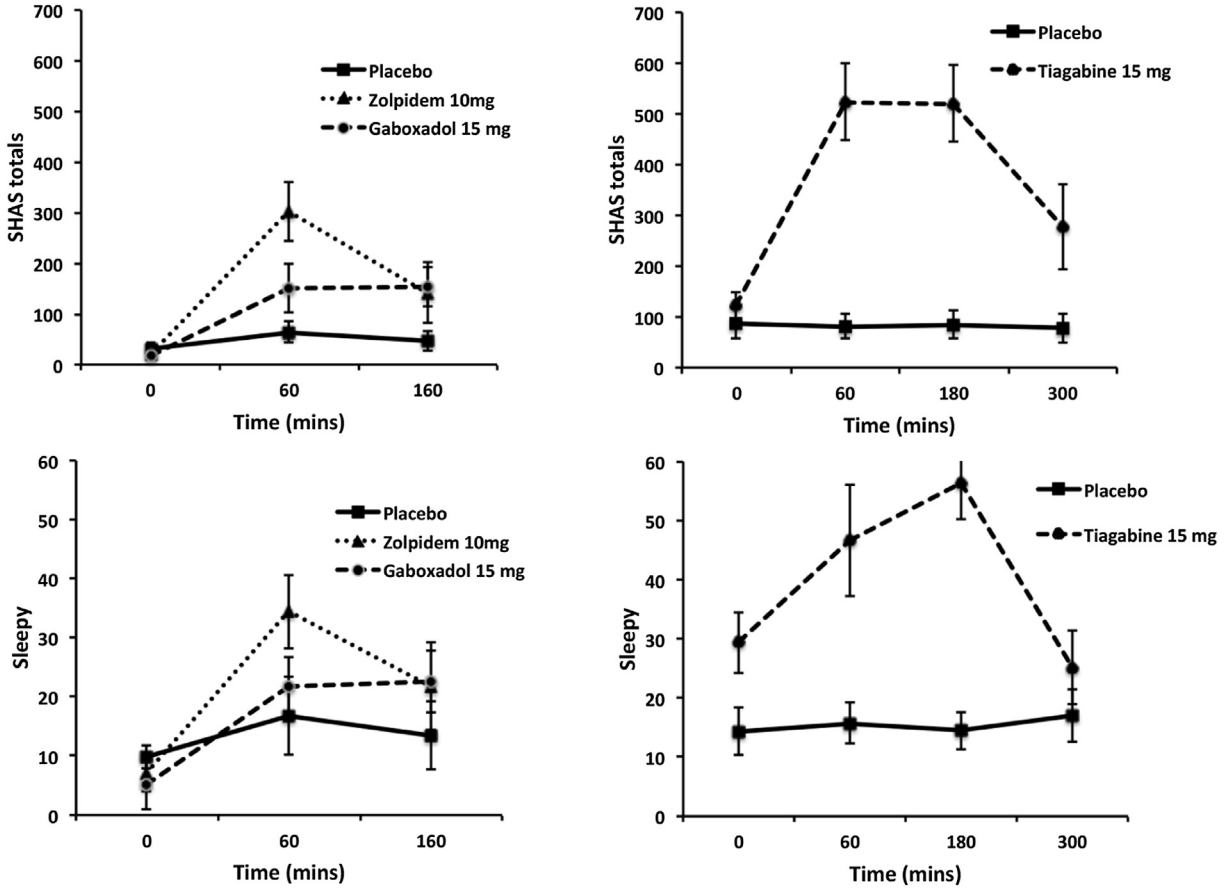

Fig. 1. Summary of total scores (upper panels) for participants on the subjective high assessment scale for gaboxadol/zolpidem (left) and tiagabine (right) with a single sub-scale item (sleepy) displayed on the lower charts. The SHAS consists of 13 items scored 0–100. These items are "uncomfortable", "high", "clumsy", "muddled", "slurred speech", "dizzy", "nauseated", "drunk", "sleepy", "distorted sense of time", "effects of alcohol", "difficulty concentrating" and "feeling of floating".

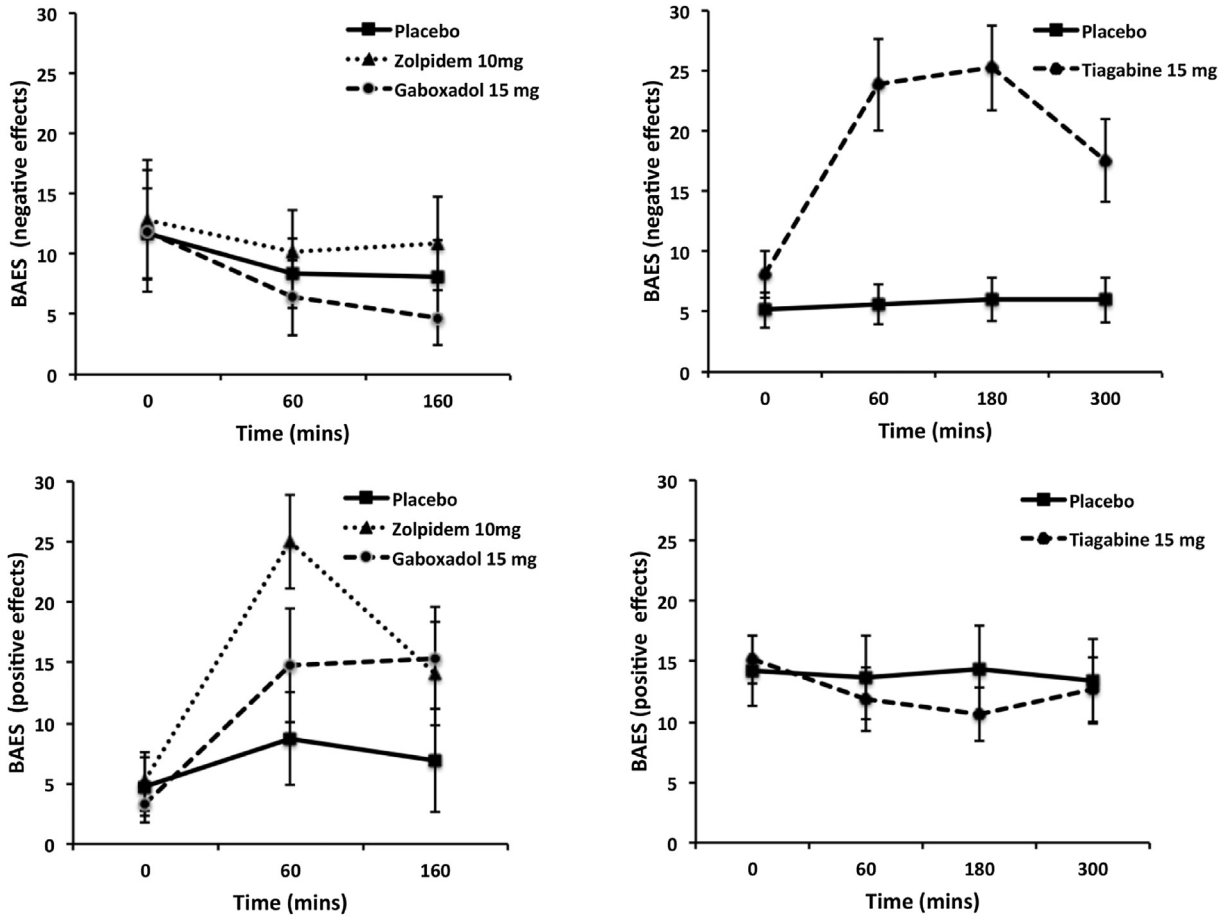

Fig. 2. Summary of scores for participants on the biphasic alcohol effects scale for gaboxadol/zolpidem (left) and tiagabine (right). The upper panels represent summed negative effects whereas the lower panels represent positive effects. Scale-items contributing to the negative effects include "difficulty in concentrating", "down", "heavy head", "inactive", "sedated", "slow thoughts" and "sluggish". Scale-items contributing to the positive effects include "elated", "energised", "excited" "stimulated" "talkative", "up" and "vigorous". Items are scored between 0 and 8.

non-REM sleep it gave rise to a marked increase in power in all frequencies below 10 Hz and in REM sleep this increase was more prominent for frequencies between 5 and 10 Hz.

Magnetoencephalography (MEG) is a neuroimaging technique with high temporal resolution and moderately good spatial resolution that allows direct measurement of the magnetic fields generated by synchronised ionic neural currents in the brain. When combined with pharmacological interventions, MEG (pharmaco-MEG) is a powerful tool for measuring the effects of experimental modulations of neurotransmission in the living human brain, in both patient and healthy control groups (Muthukumaraswamy, 2014). Compared with EEG, it provides superior spatial resolution, and reduced contamination of the brain signals by physiological artefacts such as blinks and muscle potentials.

In this study we examined resting MEG spectra to investigate the impact of three GABAergic drugs with highly specific and distinct mechanisms of action. We studied the effect of zolpidem and gaboxadol on resting MEG and compared with previously collected but not reported resting data from a previous study of tiagabine, using a similar protocol (Muthukumaraswamy et al., 2012).

2. Methods

2.1. Design and participants

These were two randomised, single-blind, placebo-controlled, crossover studies in healthy volunteers. One was a comparison of single doses of zolpidem, gaboxadol and placebo, and the other a comparison of tiagabine with placebo. We chose doses of 15 mg gaboxadol and 10 mg zolpidem which were well-tolerated and approximately equipotent with regard to sleep parameters in a study of insomnia (Hajak et al., 2009). The elimination half-lives of these two drugs is similar at approximately 1.5–2.0 h in fasting subjects. The 15 mg dose of tiagabine study was chosen because it could be administered as standard tablet doses, is very similar to the 16 mg used in a PET study by Frankle et al. (2012) and is identical with that used in several ongoing imaging studies by our group (Muthukumaraswamy et al., 2013b; Stokes et al., 2014) which have shown that GABA levels are increased.

Both studies were conducted at Cardiff University Brain Research Imaging Centre with similar protocols, and were approved by the UK National Research Ethics Service and local NHS Trust research authorities.

Twelve healthy male participants (mean age 27.7, range 21–35) took part in the zolpidem/gaboxadol experiment. We were unable to collect gaboxadol data from 2 of these. (Participants for the tiagabine experiment were the same as those for which we have previously published task-related data (Muthukumaraswamy et al., 2013b)). These included fourteen healthy males and one healthy female participant (mean age 25.5, range 20–32). In this experiment we had originally intended to use a mixed sex cohort, however early in data collection we found that all but one females became too heavily sedated to complete the protocol; therefore females were subsequently excluded during data collection (see Hamandi et al., 2014 for further elaboration). All participants were medically screened and excluded for significant medical, psychiatric or neurological condition and current recreational or prescription drug use. They were tested before each session for drugs of abuse (urine screen) and breath alcohol.

For each session, participants were scanned on separate days, after at least a seven day washout period, at approximately the same time-of-day. On each day, an initial baseline MEG recording was obtained. Participants then orally ingested a capsule containing either placebo/15 mg of tiagabine (tiagabine experiment) or placebo/15 mg of gaboxadol/10 mg of zolpidem (zolpidem/gaboxadol experiment). Participants were blinded to the contents of the capsules and placebo/control session order was counterbalanced across both experiments. For the

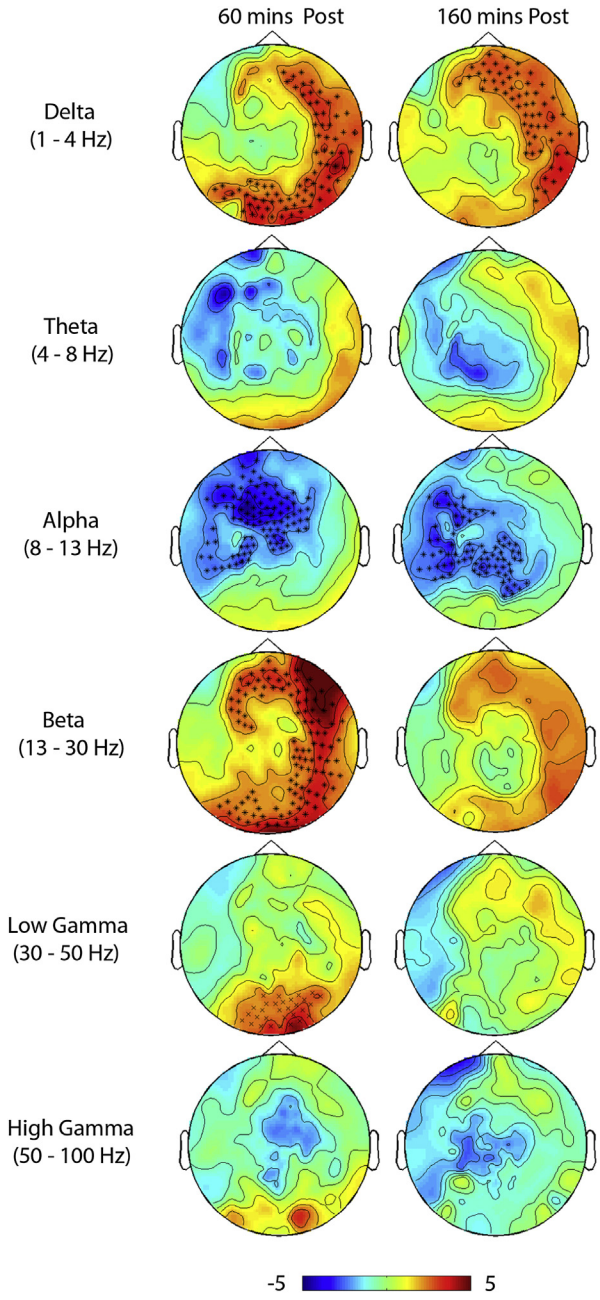

Fig. 3. Statistical analysis of planar gradiometer configured MEG data for the zolpidem experiment ($n = 12$). "Pre" recordings were subtracted from each time-point and then a contrast performed between zolpidem and placebo. Red indicates relatively more power following the drug and blue indicates relatively less. Units are t statistics. Significant sensor clusters are marked such that dark circles correspond to $p \leq 01$, and crosses to $p < 0.05$. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

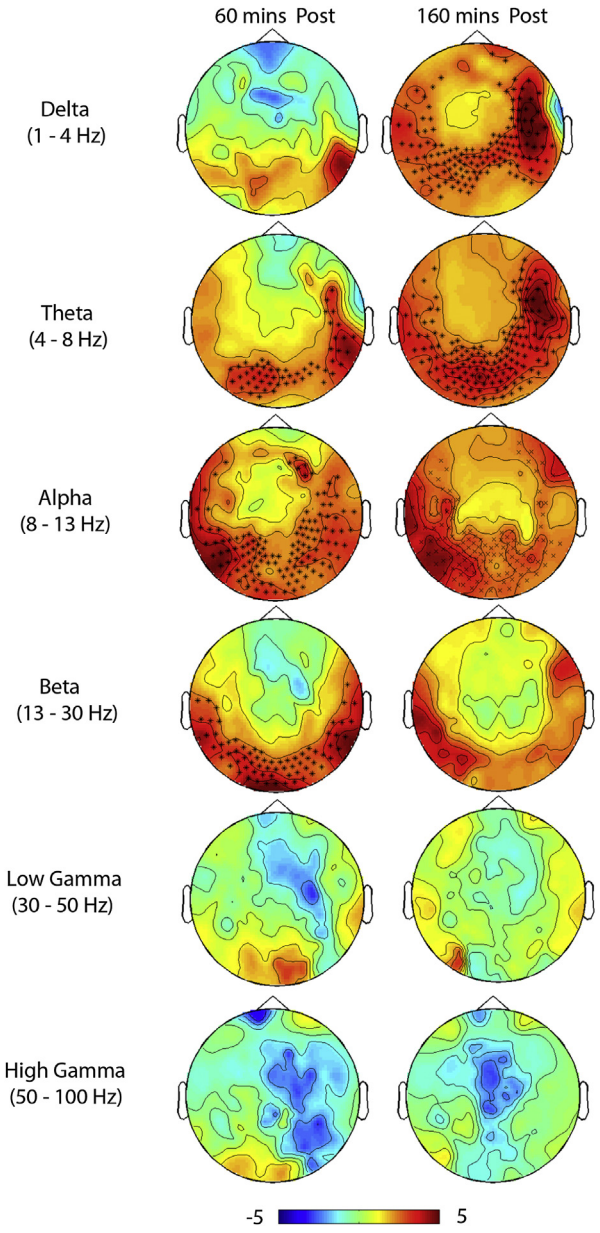

Fig. 4. Statistical analysis of planar gradiometer configured MEG data for the gaboxadol experiment ($n = 10$). "Pre" recordings were subtracted from each time-point and then a contrast performed between gaboxadol and placebo. See Fig. 3 for further details.

tiagabine experiment, following drug administration, MEG recordings were obtained from the participants at 60, 180 and 300 min time-points. For the gaboxadol/zolpidem experiment MEG recordings were obtained at 60 and 160 min time-points. At the conclusion of every MEG recording, the participants completed subjective questionnaires focussing on the expected effects of GABAergic drugs. These were the Subjective High Assessment Scale (Schuckit, 1980) which presents 13 items (see Fig 1 and legend) and asks subjects to mark a visual analogue line anywhere from 0 to 10 cm, and the Biphasic Alcohol Effects Scale (Martin et al., 1993), which presents 7 items related to sedation and 7 related to stimulation effects (see Fig 2 and legend) and asks the subject to rate each of these effects on a 9 point scale. They were also asked to qualitatively report their psychological state.

During each MEG session, 5 min resting recordings were obtained. In the tiagabine experiment participants sat with their eyes closed while in the gaboxadol/zolpidem experiment participants had their eyes open.

Zolpidem and tiagabine were sourced from an NHS hospital pharmacy, and gaboxadol was donated by Lundbeck as part of the ECNP Medicines Chest Initiative (Nutt et al., 2014).

2.2. MEG acquisition and analysis

Whole head MEG recordings were made using a CTF 275-channel radial gradiometer system sampled at 1200 Hz (0–300 Hz bandpass). An additional 29 reference channels were recorded for noise cancellation purposes and the primary sensors were analysed as synthetic third-order gradiometers (Vrba and Robinson, 2001). Three of the 275 channels were turned off due to excessive sensor noise.

For analysis, the 5 min of resting data were high-pass filtered at 1 Hz, and segmented into epochs of 2 s in length. Hence, there were 150 epochs available for analysis. Each epoch was first visually inspected, and those with gross artefacts (e.g., head movements, jaw clenches) were removed from the analysis. Of the 222 MEG

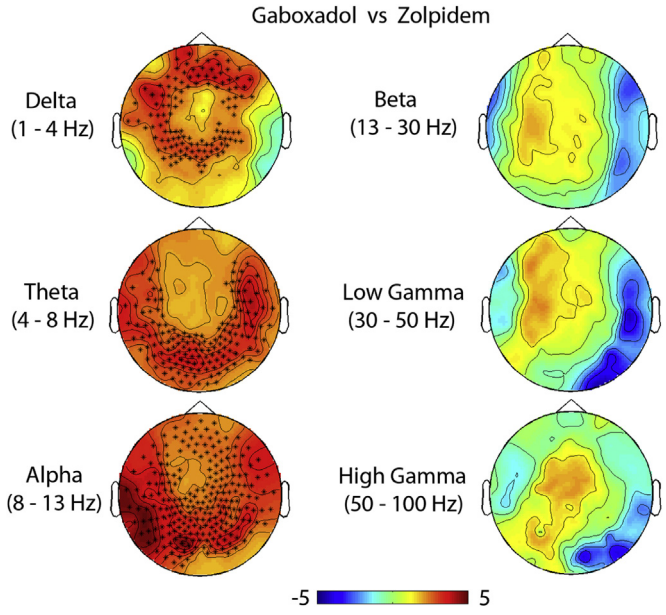

Fig. 5. Statistical comparison of zolpidem data at 60 min with gaboxadol data at 160 min ($n = 10$) for planar gradiometer configured MEG data. See Fig. 3 for further details.

datasets analysed in this report on average 4.89% of the 150 epochs were removed (std 5.77; range 0–41%). For the gaboxadol/zolpidem experiment we applied independent components analysis, as implemented in EEGLAB (Delorme and Makeig, 2004), to the data, to identify and remove low-frequency artefact components related to eye-blinks and eye-movements. Using the FieldTrip toolbox (Oostenveld et al., 2011), we converted our MEG data to planar gradient configuration and then conducted a frequency analysis of the individual vector directions. Frequency analysis was conducted using Hanning windowed fast Fourier transforms between 1 and 100 Hz at 0.5 Hz frequency steps and then the planar directions combined to give local maximal under the sensors. Analysis of sensor-level MEG data in a planar gradient (spatial-derivative) configuration has the advantage of easy interpretability as field maps can be interpreted as having a source directly underneath field maxima (Bastiaansen and Knosche, 2000).

For statistical analysis we divided individual spectra into the following frequency bands, delta (1–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz), low gamma (30–50 Hz) and high gamma (50–100 Hz) (Muthukumaraswamy et al., 2013a). The pre-intervention baseline spectra were subtracted from each post-intervention spectra and then differences between intervention and placebo tested using permutation testing of t statistics at each post intervention time-point (Nichols and Holmes, 2002; Maris and Oostenveld, 2007). The type 1 error rate was controlled using cluster randomization analysis with an initial cluster forming threshold of $p = 0.05$ repeated over 500 permutations. To perform correlations with psychometric measures a similar approach was used where we correlated the sensor-level power on each recording with various psychometric measures using the same randomisation approach.

3. Results

The SHAS total scores for zolpidem were significantly elevated at the 60 ($t = 4.39$, $p = 0.0011$) but not at the 160 min time points ($t = 1.33$ $p = 0.2$; see Fig. 1). SHAS scores were significantly elevated for gaboxadol at both the 65 ($t = 3.17$ $p = 0.201$) and 160 ($t = 2.50$ $p = 0.034$) minute time-points. For tiagabine, SHAS scores were significantly elevated at the 60 ($t = 6.00$ $p = 3.2e\text{-}05$), 180 ($t = 6.48$ $p = 1.4e\text{-}05$) and 300 ($t = 2.4$ $p = 0.028$) minute time-points. For the item "sleepy", neither zolpidem nor gaboxadol were significantly different to placebo at either time-point, but as can be seen from Fig 1, the highest mean score for sleepiness was at 60 min for zolpidem and 160 min for gaboxadol. All subjective ratings returned to baseline levels in the assessment at 240 min (data not shown). However, for tiagabine this item was elevated at the 60 ($t = 3.0$ $p = 0.01$) and 180 ($t = 8.6$ $p = 5.7e\text{-}07$) minute time-points but not at 300 min ($t = 1.3$ $p = 0.21$).

In Fig. 2 the results of BAES scores are plotted, sub-divided into total sedating and stimulating effects. Neither gaboxadol nor zolpidem showed significantly different sedating effects at the 60 or 160 min time-points. Conversely, tiagabine showed elevated sedation effects at 60 ($t = 5.02$ $p = 1.9e\text{-}04$), 120 ($t = 5.6$ $p = 1.1e\text{-}05$) and 180 ($t = 4.1$ $p = 0.001$) minute time-points. For stimulatory effects, zolpidem showed enhanced effects at 60 ($t = 6.67$ $p = 5.6e\text{-}05$) minutes but not at 160 min while gaboxadol showed enhanced effects at 60 ($t = 2.68$ $p = 0.02$) and 165 ($t = 2.68$ $p = 0.03$) minutes. Tiagabine showed no stimulatory effects.

Zolpidem showed significantly enhanced delta power (1–4 Hz) at both time-points, but reduced alpha power (8–13 Hz; see Fig. 3). Additionally, at 60 min there was significantly enhanced beta and low gamma. For gaboxadol, there was a general enhancement of low frequency power from the delta through beta range (1–30 Hz; see Fig. 4). Direct comparison of the peak effects of gaboxadol and zolpidem at peak (60 min for zolpidem and 160 min for gaboxadol) revealed that gaboxadol showed significantly enhanced delta, theta and alpha activity, with the increases in delta power having a more anterior focus. Similar to gaboxadol, for tiagabine there was enhancement of low frequency power through the delta through beta range. This enhancement was spatially widespread in the delta and theta frequency ranges while in the alpha and beta bands posterior occipital/parietal increases were absent and slightly (although non-significantly) reversed. Additionally for tiagabine, at the 180 min time-point there was a decrease in both low (30–50 Hz) and high frequency (50–100 Hz) gamma power centred over parietal sensors (see Fig. 5). Since our cohort included only one female we performed a subsidiary analysis with this participant excluded(see Supplementary materials) with nearly identical results seen. The peak time points of drug effect for each drug are plotted side-by side, to facilitate qualitative comparison of the spectral effects of the three drugs (See Fig. 7).

Finally, the exploratory correlational analysis of the four psychometric variables shown in Figs. 1 and 2 with the unsubtracted MEG time-point data analysed in Fig. 6 revealed no meaningful patterns of correlations.

4. Discussion

In this study we qualitatively evaluated the effects of three GABAergic modulators, with very different sites of action; gaboxadol, an extra-synaptic GABA-A PAM, zolpidem, an intra-synaptic GABA-A PAM and tiagabine, a reuptake inhibitor on whole-head MEG spectra. Gaboxadol and tiagabine were most similar in increasing low frequency rhythms from delta through to beta whereas zolpidem increased delta and beta but decreased theta and alpha. All three drugs tended to reduce parietal high frequency gamma rhythms, most notably tiagabine. We expected both gaboxadol and zolpidem to produce sedation as a result of their mechanism to enhance GABA action, and this was indeed the case. However although the absorption characteristics and elimination half-lives of zolpidem and gaboxadol are reported to be similar, we noted from both MEG and subjective measurement of sleepiness that effects of zolpidem were earlier to appear and diminish than those of gaboxadol. Correlations between subjective and objective results did not reveal any meaningful associations, but it is notoriously difficult to derive significant results from these – the way each individual assesses themselves on subjective scales differs widely.

The impact of zolpidem on MEG in our study is consistent with those previously reported in EEG studies, with increase in beta frequencies and reduction in alpha frequency power. In addition, we can now report from the current MEG study that it also increases low gamma power, a frequency that is not possible to assess

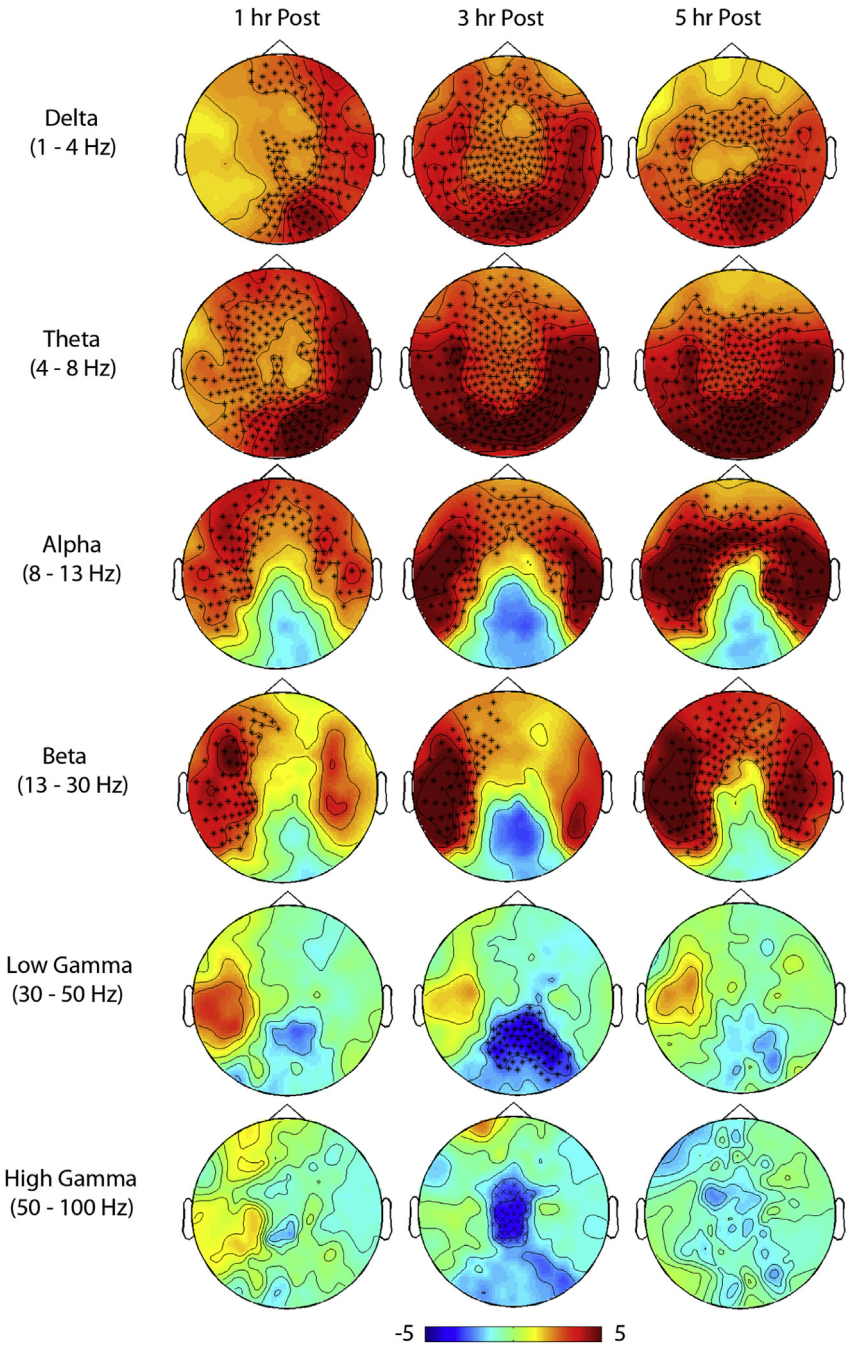

Fig. 6. Statistical analysis of planar gradiometer configured MEG data for the tiagabine experiment ($n = 10$). "Pre" recordings were subtracted from each time-point and then a contrast performed between tiagabine and placebo. See Fig. 3 for further details.

in EEG. Delta power was increased, but this was not marked as with the other 2 drugs.

We report here for the first time the impact of gaboxadol and tiagabine on resting MEG. Importantly, there was very little similarity to zolpidem, with increases in power at all frequencies up to beta. During previous EEG sleep studies, power in delta and theta frequencies was increased by both drugs. The increases in low frequency MEG power produced by gaboxadol and tiagabine were associated with pronounced subjective effects particularly sedation, and confusion with tiagabine [this is a major element in the elevated SHAS score for this drug]. Early in our analyses, in fact on inspection of raw data, we noticed that these there were highly synchronous bursts of low frequency activity after the 2 drugs, particularly tiagabine, took effect (see Fig. 6 and Supplementary Materials for waveform examples from three individuals and also Hamandi et al., 2014; Azar et al., 2013). This suggested that relatively widespread cortical areas were being synchronised but importantly it also directly impacts on the choice of methods used to analyse the current data. It has been the approach not of only our own group (Muthukumaraswamy et al., 2013a, 2013b; Saxena et al., 2013) but also of others (Hall et al., 2010, 2011; Bauer et al., 2012; Ronnqvist et al., 2013) to pharmaco-MEG data, to perform source localisations, and this has been done primarily with beamformers (Van Veen et al., 1997). While beamformers have excellent abilities

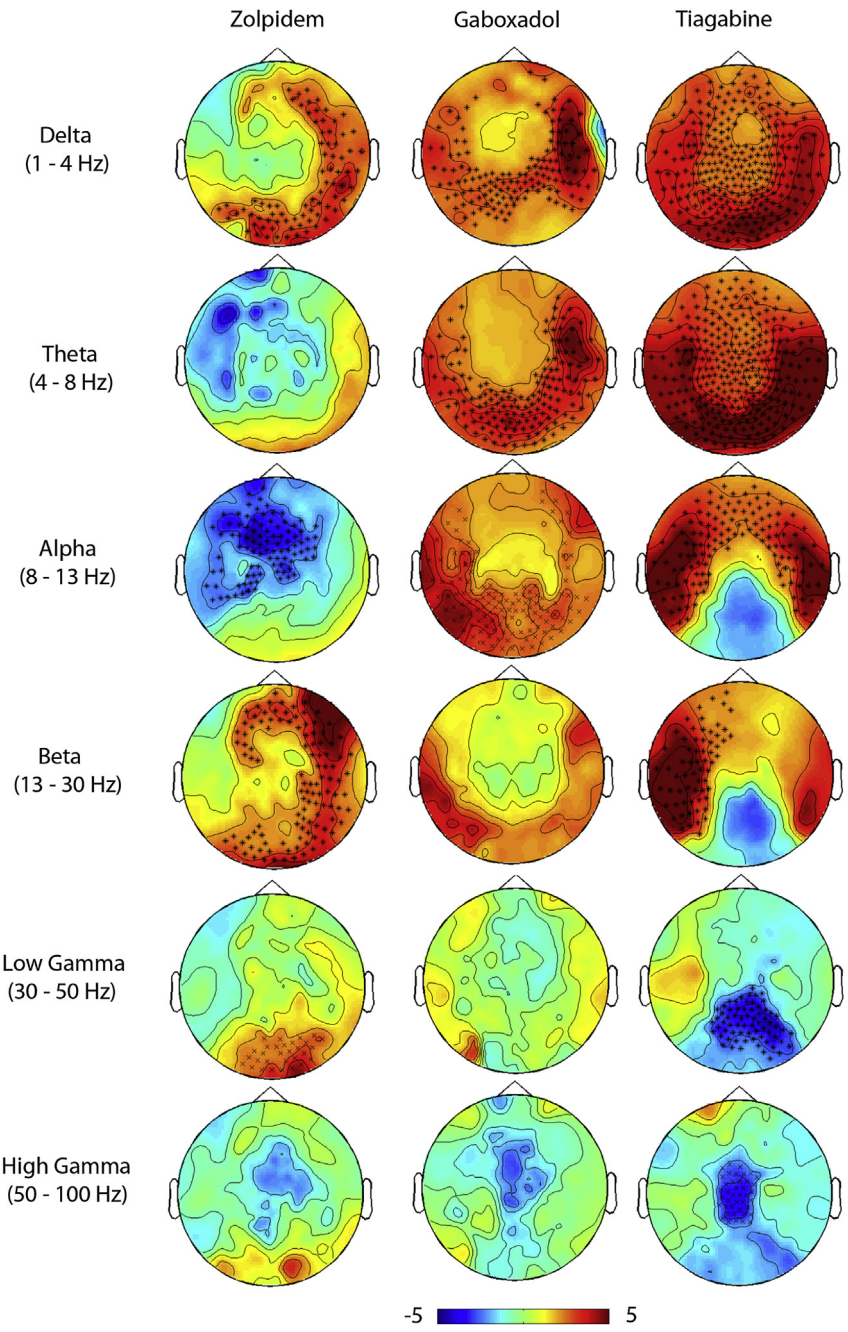

Fig. 7. Summary figure combining selected panels from Figs. 3–5. The time-points for each drugs showing the maximal effect has been selected (zolpidem = 60 min, gaboxadol = 160 min, tiagabine = 180 min).

to both localise distributed source activity and reject physiological and environmental artefacts, they have the disadvantage that highly correlated source activity can potentially be absent in beamformer images. The best known example of such correlated sources are the symmetrical sources that occur following auditory stimulation and are difficult to detect with beamfomer approaches (Dalal et al., 2006; Brookes et al., 2007). It has been suggested that there may well be relatively few distributed highly correlated sources with regard to spontaneous activity (Hillebrand et al., 2005), but this is less likely in the pathological or pharmacologically altered brain. As such, there is a need for a thorough quantitative evaluation of MEG source localization techniques for these types of data and would include not only beamformer approaches but other common techniques such as the minimum norm approaches. Such an evaluation is beyond the scope of this work but would be a valuable addition to the advancement of pharmaco-MEG.

There are several limitations to the study that prevent a more direct quantitative comparison of the different drugs being evaluated. Specifically there is no way a priori to know the dose required to generate a functional effect, and indeed all drugs evaluated here have different pharmacodynamic time-courses. Each drug at multiple doses would need to be investigated to fully explore the pharmacokinetic–pharmacodynamic relationship which was beyond the scope of this study. The data for tiagabine was recorded under slightly different experimental conditions (eyes-closed).

However, we attempted to reduce this as confound by first subtracting the pre-drug baseline spectra prior to comparing the active dose with placebo to remove main effects of state (i.e. eyes open or closed). As such any confounding differences would need to confound the interaction effects (state × drug) rather than the baseline power levels. Nevertheless Fig. 7 should be interpreted qualitatively and with caution.

In conclusion this work shows that MEG is sensitive to the actions of three distinct types of positive GABA-A modulators and that there are distinctive differences in the patterns of MEG effects produced. In particular the enhancement of tonic inhibition by via extrasynaptic receptors by gaboxadol gives rise to a very different MEG signature from that produced by the intrasynaptic PAM zolpidem. The GABA reuptake blocker tiagabine theoretically can lead to effects on both types of receptor, the first by blocking uptake in the synapse and thus enhancing post-synaptic effects, and the second by overspill of increased GABA to extrasynaptic areas. From these MEG results it is likely that the latter is the more prominent effect here, or at least this action obscures any intra-synaptic MEG signal. Overall this research shows that MEG could play an important role in determining the cortical effects of GABAergic medications and how their effects may relate to clinical efficacy and possibly unwanted actions. MEG could also be of use in exploring the actions of new drugs designed to act at the GABA-A receptor.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.neuropharm.2014.08.017

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