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S.D. Hall, I.M. Stanford, N. Yamawaki, C.J. McAllister, K.C. Rönnqvist, G.L. Woodhall, P.L. Furlong

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The role of GABAergic modulation in motor function related neuronal network activity.

Hall SD, Stanford IM, Yamawaki N, McAllister CJ, Rönnqvist KC, Woodhall GL and Furlong PL.

Affiliation for all authors: Neurophysiology and Clinical Neuroimaging Research Group
School of Life and Health Sciences
Aston University
Birmingham
UK

Corresponding Author: Dr Stephen D. Hall
RCUK Fellow: Translational Neuroscience,
Neurophysiology and Clinical Neuroimaging Research Group
School of Life and Health Sciences
Aston University
Birmingham
UK
hallsd@aston.ac.uk

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Abstract

At rest, the primary motor cortex (M1) exhibits spontaneous neuronal network oscillations in the beta (15-30Hz) frequency range, mediated by inhibitory interneuron drive via GABA-A receptors. However, questions remain regarding the neuropharmacological basis of movement related oscillatory phenomena, such as movement related beta desynchronisation (MRBD), post-movement beta rebound (PMBR) and movement related gamma synchronisation (MRGS). To address this, we used magnetoencephalography (MEG) to study the movement related oscillatory changes in M1 cortex of eight healthy participants, following administration of the GABA-A modulator diazepam. Results demonstrate that, contrary to initial hypotheses, neither MRGS nor PMBR appear to be GABA-A dependent, whilst the MRBD is facilitated by increased GABAergic drive. These data demonstrate that while movement-related beta changes appear to be dependent upon spontaneous beta oscillations, they occur independently of one other. Crucially, MRBD is a GABA-A mediated process, offering a possible mechanism by which motor function may be modulated. However, in contrast, the transient increase in synchronous power observed in PMBR and MRGS appears to be generated by a non-GABA-A receptor mediated process; the elucidation of which may offer important insights into motor processes.

Introduction

At rest, the primary motor cortex (M1) exhibits ongoing neuronal network oscillations in the beta (15-30Hz) frequency range (Baker et al., 1997; Murthy and Fetz, 1996). Studies in both animal (Yamawaki et al., 2008) and humans (Hall et al., 2010a; Jensen et al., 2005) have demonstrated that these oscillations appear to be under the direct control of GABAergic modulation. Specifically, these previous works have demonstrated that beta frequency oscillations are elevated in amplitude and reduced in frequency following the administration of GABAergic modulators such as diazepam.

The GABAergic mechanism by which these oscillations are generated and modulated is well described in neuronal network models (Traub et al., 1996) and confirmed using *in-vitro* animal recordings from cortex (Whittington et al., 1995). Although first described as a mechanism for the generation of gamma (30-80Hz) frequency activity, subsequent studies have described this same mechanism underlying beta frequency oscillations in M1 (Yamawaki et al., 2008). Simply put, these oscillations are facilitated by increasing the inhibitory drive of GABAergic interneurons via GABA-A receptors, whereby the inhibitory post synaptic potential (IPSP) decay-time is lengthened, thereby reducing the frequency of the locally oscillating neuronal network population. Consequently, this serves to facilitate the recruitment of principal cells to the oscillating population, giving rise to an increase in the amplitude of the oscillatory power, as the participating neuronal pool is increased. Increases in GABA-A receptor driven beta frequency oscillatory power occurs in M1 layers III and V (Yamawaki et al., 2008), the predominant generators of signals measured using EEG and MEG approaches (Murakami and Okada, 2006).

Whilst the model of beta oscillatory generation works well to explain the generation and modulation of ongoing beta activity in the motor cortex, it is unknown to what

extent it serves to modulate the functionally related neuronal network activity. Understanding the neuropharmacological basis of these functional oscillatory changes is of fundamental importance in identifying potential therapeutic targets for the treatment of neurological disorders in which motor impairments are associated with oscillatory abnormalities. Motor function, such as finger movement, is accompanied by several discrete neuronal network features, which can be measured in humans using non-invasive methods such as electroencephalography (EEG) and magnetoencephalography (MEG). Prior to finger movement, the ongoing beta oscillation in primary motor cortex (M1) decreases in amplitude (Pfurtscheller and Berghold, 1989), a feature referred to here as movement related beta desychronisation (MRBD). Following the termination of movement, an increase in beta oscillatory power above the pre-movement oscillatory amplitude is observed (Pfurtscheller et al., 1996). It is postulated that this feature, commonly referred to as post-movement beta rebound (PMBR) (Jurkiewicz et al., 2006), reflects a sensory re-afference to motor cortex following movement (Cassim et al., 2000). In addition to the changes in beta frequency activity in motor cortex, and the well-characterised movement-related-potential, there is a transient increase in power in the gamma frequency range; specifically in the 60-90Hz frequency, temporally coincident with movement onset (Cheyne et al., 2008).

Here we investigated the impact of the benzodiazepine diazepam, a non-specific GABA-A receptor modulator, on the functional neuronal network activity in M1. Diazepam is known to modulate resting-state beta activity in the motor cortex with a characteristic pharmacodynamic profile (Hall et al., 2010a). In the present study, we used motor function to localise to peak regions of interest (ROIs) in M1 and to obtain frequency specific measures of functional oscillatory power. The dependence of these

motor related features upon GABAergic modulation was then determined by comparison of their pharmacodynamic profiles with respect to non-drug baseline and ongoing activity. We predicted that increases in both beta and gamma frequency activity would be modulated by GABAergic modulation, consistent with a GABAergic interneuron-based mechanism underlying their generation.

Methods

MEG Recordings

Eight right-handed male participants (mean age 36, range 26-48yrs), with normal or corrected to normal vision, were positioned in a supine posture in a 275-channel magnetoencephalography (MEG) system (VSM Medtech, BC, Canada) for a period of 60 minutes. During this time participants were required to perform a visual reaction time task, in which they responded as quickly as possible to a change in fixation cross colour, with a button press using the right index finger. Response stimuli were presented in two-minute blocks, interspersed by 3-minute rest periods. Stimuli were presented with a mean inter-stimulus duration of 4-seconds, with randomised jitter of <1-second (± 500ms), providing a total of 300 stimuli over the 60-minute duration. Immediately prior to the start of recording, diazepam (5mg) was administered in a polysaccharide casing in order to allow drug delivery after approximately 10 minutes (Hall et al., 2010a). MEG data were co-registered with the individual participant's anatomical MRI, obtained using a 3-Tesla MRI system (Siemens Erlangen, Germany), by surface matching a 3-dimensional digitisation of the participants scalp created using a Polhemus Isotrak system (Kaiser Aerospace Inc.). Head position was monitored throughout by matching the digitised position of three surface-mounted electromagnetic positioning coils (left and right pre-auricular and nasion), which were

then monitored throughout the recording process. MEG data were acquired at a sampling rate of 600Hz using a 3rd order gradiometer configuration with a 50Hz notch filter and a 1-300 Hz low/high pass filter.

Data Analysis

The movement related oscillatory changes were localised using the synthetic aperture magnetometry (SAM) beamforming method (Hillebrand et al., 2005; Vrba and Robinson, 2001). Specifically, with time-zero defined as the onset of the button press, the post-movement-beta-rebound (PMBR) was localised by comparing the change in beta (15-30Hz) frequency power following movement termination (0.5 to 1.0 sec) with the pre-movement beta power (-2.0 to -1.5 sec); comparable to the methods described by Jurkiewicz *et al*. (2006). Similarly, the peak of movement related gamma synchronisation (MRGS) was localised by comparing the movement period (0 to 0.3 sec) with the pre-movement period (-2.0 to -1.7 sec); comparable to the methods described by Cheyne et al. (2008).

Morlet-wavelet time-frequency analysis was used to identify the time profile of the beta desynchronisation and rebound and gamma synchronisation in each participant. The latency of maximal PMBR and MRGS power and minima of MRBD power were used to centre the windows (300ms) for further analysis; for example with a MRGS peak at 150ms, the MRGS time window was set to 0-300ms. The power in the beta (15-30Hz) and gamma (60-90Hz) frequency range was computed for each trial over the period of drug uptake. From this, the MRBD, PMBR and MRGS amplitude measures were obtained and plotted alongside the spontaneous beta and gamma power.

These measures demonstrated that, consistent with our previous observations (Hall et al., 2010a), spontaneous beta power is increased in M1 following the administration

of diazepam, whilst spontaneous gamma power remains unchanged. Similarly, MRGS in the focal 60-90Hz range remained unchanged following diazepam, whilst both MRBD and PMBR in the 15-30Hz range show a similar overall pharmaco-dynamic profile to that of spontaneous beta.

Figure 1 Here

In order to investigate the specific dependence of these features on GABAergic modulation, as opposed to change as a consequence of spontaneous beta modulation, it is necessary to use a specific measure of beta power change that accounts for the shift in frequency that occurs as a consequence of GABAergic modulation (see Jensen et al. (2005) for a description and explanation of this phenomenon). In order to do this, we used a custom-made Matlab programme (Mathworks Inc., Natick, USA) to compute the power at the maximal beta frequency point for each trial, thereby removing the influence of frequency change on the entropy of a fixed bandwidth (e.g. 15-30Hz) measure. These data were then normalised with respect to the spontaneous beta power in the non-drug period, in order to determine the change in power and frequency as a consequence of drug uptake. Subsequently, to determine the independent effect of GABAergic modulation on MRBD and PMBR, the increase in spontaneous beta power during diazepam uptake was subtracted from both measures to reveal the differential change in power not due to a relative effect of spontaneous beta modulation. Finally, to confirm the underlying basis of GABA mediated oscillatory change, we determined the rate of synchronous change. Thereby, establishing the independence of feature specific GABAergic modulation, whilst accounting for changes in temporal profile of oscillatory change.

Results

As previously observed, spontaneous beta in the 15-30Hz range is increased dramatically by the administration of diazepam (fig. 1a), whereas gamma power remains unchanged (fig. 1b). The measures of MRBD and PMBR were taken from the minima and maxima of beta (15-30Hz) power (fig. 1c) taken from virtual electrodes reconstructed at the location of the SAM peaks for the PMBR (fig. 1d) and MRGS (fig. 1e). The beta frequency power in the MRBD and PMBR periods both display a significant ($F_{(5,294)}$= 40.74, $p<0.001$ and $F_{(5,294)}$= 53.72, $p<0.001$ respectively) increase over the period of diazepam uptake, consistent with the increase in spontaneous beta power (fig. 2a). Conversely, the MRGS gamma power showed no significant increase ($F_{(5,294)}$=1.56, p=0.173) consistent with spontaneous gamma power (fig. 2b). Analysis of peak beta power and frequency demonstrates that in each condition, the increase in beta power is accompanied by a reduction in frequency and that MRBD and PMBR remain, respectively, lower and higher than the spontaneous beta baseline throughout (fig. 2c). Analysis of peak-frequency-specific power confirmed that in the non-drug (0-10min) period the beta power in the PMBR is 18.4% ± 3.12% higher than the spontaneous control power, whilst MRBD power is 19.2 % ± 2.51% lower.

Figure 2 Here

Analysis of the residual change in MRBD and PMBR power over the period of drug uptake (fig. 3) revealed that the depth of MRBD, with respect to spontaneous beta power, is significantly increased over the period of drug uptake by a maximum of 10.87% ($F_{(5,294)}$=5.74, $p<0.001$). However, PMBR appears to show no significant change in residual power, with respect to spontaneous beta power, following

diazepam administration ($F_{(5,294)}$=2.21, p=0.054). Analyses of the rate of desynchronisation revealed that the mean MRBD desynchronisation rate (DR) increased from 1.01^{-10}nAm/s before diazepam, to 1.92^{-10}nAm/s at peak diazepam, whilst the mean PMBR synchronisation rate (SR) increased from $4.21n^{-10}$Am/s to 5.4^{-10}nAm/s. Furthermore, no change was observed following drug administration in either the onset latency of MRBD and PMBR ($F_{(5,294)}$=1.62, p=0.156 and $F_{(5,294)}$=1.25, p=0.284 respectively) or peak duration of MRBD and PMBR ($F_{(5,294)}$=1.81, p=0.11 and $F_{(5,294)}$=2.051, p=0.072 respectively). Perhaps correspondingly, no change was observed in either the reaction time ($F_{(5,294)}$=1.63, p=0.152) or response duration $F_{(5,294)}$=2.11, p=0.064) following drug administration.

Figure 3 Here

Discussion

The results demonstrate a direct relationship between the amplitude of spontaneous oscillatory activity and motor-function-related oscillatory changes in motor cortex. Specifically, as the spontaneous beta rhythm generated in the motor cortex is elevated by an increase GABAergic drive, this appears to have a direct influence on the functionally modulated changes at beta frequency by increasing both the MRBD and PMBR power. Similarly, and consistent with a lack of change to the spontaneous gamma power, the amplitude of the MRGS remains unchanged by an increase in GABAergic drive.

We predicted that both MRGS and PMBR would be directly influenced by an increased GABAergic drive, based upon previous studies in both animal (Yamawaki et al., 2008) and humans (Hall et al., 2010a) that demonstrate a dependence of M1

beta-frequency oscillations on GABAergic tone and mechanistic neuronal-network models used to explain the mechanisms by which these oscillations are generated (Jensen et al., 2005; Traub et al., 1996). However, these results demonstrate that neither MRGS nor PMBR are specifically GABAergically modulated beyond that inferred by spontaneous oscillatory changes, whilst the depth of MRBD is increase in a manner directly dependent upon the GABAergic drive (fig. 3b) and consistent with the pharmacokinetic profile of diazepam administration (Moolenaar et al., 1980). These results demonstrate several points: firstly, that MRBD and PMBR are to some extent independent phenomena, whilst both are to varying degrees related to the spontaneous activity in the local network. Secondly, that the amplitude of PMBR is not directly under the influence of GABAergic drive, whilst MRBD is directly driven by GABAergic modulation. Thirdly, the MRGS is not, directly or indirectly, influenced by a diazepam-mediated increase in GABAergic drive. However, recent works by Muthukumaraswamy (2010), providing a comprehensive characterisation of MRGS, shows that it appears stronger in earlier trials in a sequence; likely a consequence of sensorimotor interaction. It is possible that this fluctuation is influential when observing changes in MRGS over extended trials, as is the case here.

These results are surprising, as they appear inconsistent with pyramidal-interneuron-generated (PING) beta and gamma mechanisms (Whittington et al., 1995), typically under the direct influence of GABA tone, although spontaneous oscillatory activity in this region is consistent with this model. However, *in vitro* models demonstrate that beta power in primary motor cortex is also directly related to glutamatergic and cholinergic drive. This is demonstrated by a requirement for kainic acid and carbachol in the artificial cerebrospinal fluid of *in vitro* preparations of M1 in order to elicit beta frequency activity (Yamawaki et al., 2008); with cholinergic activation known to be a

driver of these oscillations in various cortical regions (Buhl et al., 1998; Fisahn et al., 1998). In addition, experiments in adjacent regions of somatosensory cortex have demonstrated the presence of beta frequency oscillations that are not GABAergically dependent (Roopun et al., 2006). Furthermore, given that PMBR is postulated to reflect somatosensory re-afference (Cassim et al., 2000), the observation of GABA-A independent beta in these regions is of potential importance in explaining the basis of this feature. Specifically, that somatosensory re-afference is a non-GABAergically mediated process. Similarly, it is important to discuss the alternate possibility that the PMBR signal is merely an epiphenomenon of re-synchronisation following the reduction in synchronous power. The independence of MRBD and PMBR demonstrated here argues against this postulate, as do previous observations of modulation by changing movement duration and motor load (Stancak, et al., 1997; Stancak, and Pfurtscheller, 1995). The influence of diazepam on the MRBD, specifically increasing the level of desynchronisation, provides an important focus for investigating the role of GABAergic modulation in motor function. Particularly, as recent studies have demonstrated that abnormally elevated beta oscillations in M1 appear to be directly related to impaired motor function in stroke (Hall et al., 2010b). Moreover, exaggerated beta oscillations are a central feature of movement disorders such as Parkinson's disease (Brown and Marsden, 1998), the symptoms of which are alleviated during stimulation induced reduction of beta in the motor network (Brown et al., 2004) and can be mimicked in control participants using stimulation at beta frequency (Pogosyan et al., 2009). The mechanism by which GABAergic drive would facilitate desynchronisation is unclear, particularly as it is best characterised through enhancing oscillatory activity. It is entirely possible that this phenomenon is not a

reflection of direct GABA mediated desynchronisation in M1, but rather a facilitation of a remote network resulting in desynchronisation in M1.

The functional implications of these results remain unclear as, although both spontaneous beta power and MRBD appear to be modulated by increased GABAergic drive, no significant difference in reaction time of duration of movement was observed. It is possible that the sub-therapeutic dose used was insufficient to elicit a functional change or that participant compensation obscures subtle effects. However, it is also possible that the observed changes in synchrony are associated with features not measured here, such as force modulation. Previous studies have observed that GABAergic modulation using diazepam reduces the corticomuscular coherence between motor cortex EEG and EMG during an auxotonic grip task (Baker and Baker, 2003). The observation here of reduced MRBD power, may offer an explanation for this by virtue of the relationship between coherence and power in these measures. Furthermore, that these features are involved in maintenance of motor output force may explain why no modulation of reaction time or duration was observed here. Similarly, as MRBD is observed in cued imaginary movement (Pfurtscheller and Neuper, 1997), it is possible that the manipulation of this feature has no actual function related to motor movement, a distinction not made in the current study.

In conclusion, this study demonstrates that although the various oscillatory features related to motor function share a degree of dependence upon the ongoing oscillatory state of the spontaneous network, they fundamentally differ in their mechanisms of generation. It is clear from this study that further investigation of the mechanisms underlying the generation of these features is central to understanding their role in movement in healthy and disease states. This work demonstrates the central role for

translational approaches in elucidating the pharmacological basis of neuronal networks in motor function.

Acknowledgments

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Legends

Figure 1. Oscillatory activity in primary motor cortex (M1).

(a) Spontaneous beta (15-30Hz) oscillations in M1 demonstrate a characteristic increase in power(see Hall *et al*., (, 2010a) for details) over the 60minute period of diazepam uptake. **(b)** Gamma (30-80Hz) activity, shows no modulation in power as a result of drug uptake**. (c)** Movement-related oscillatory change in motor cortex associated with an externally paced button press (time-zero), demonstrates the spontaneous activity (termed 'control'), a reduction in the synchronous power immediately prior to and during movement (termed 'MRBD'), an increase in beta power following movement termination (termed 'PMBR) and a transient burst of gamma frequency power at the point of movement (termed 'MRGS'). **(d/e)** Source location of PMBR and MRGS using SAM beamformer analysis, showing typical bi-lateral localisation of PMBR sources and unilateral (contralateral) MRGS source in M1 (see Jurkiewicz *et al*., (2006) and Cheyne *et al.,* (2008) for details).

Figure 2. **GABAergic modulation of motor related oscillatory activity.**

(a) Oscillatory power (nA-m/T) of M1 virtual electrode output in the beta (15-30Hz) range for the control, MRBD and PMBR intervals in the 60-minute period following diazepam administration. **(b)** Oscillatory power (nA-m/T) of M1 virtual electrode output in the gamma (60-90Hz) range for the control and MRGS intervals in the 60-minute period following diazepam administration. **(c)** Power-spectral-density (PSD) in the PMBR, control and MRBD intervals for each 10-minute period following diazepam administration. All PSD traces are normalised with respect to the peak of control beta power in the non-drug (0-10min) period. Therefore, images show both the relative difference in MRBD or PMBR and control and the change in power and frequency during diazepam uptake.

Figure 3. **Differential change in PMBR and MRBD power following diazepam administration**.

(a) Schematic representation the how differential beta power is computed. **(top left)** for each trial the power at peak beta frequency (see fig. 2c) are taken for control interval (A) and event interval (B), then (**middle left)** the difference between the control and event power are calculated for each trial and finally **(bottom left)**, the mean of this difference (A-B) is plotted over the period of drug uptake. This provides a measure of the change in residual beta power, not explained by the increase in spontaneous power. **(b)** The change in residual beta power (Δ beta power) over 60 minutes following diazepam administration, with respect to control beta power (0). This shows the mean difference in PMBR power (circles) and how this varies from the non-drug (0-10min) period over the period of drug uptake. Also the mean difference in MRBD power (triangles), in the non-drug (0-10min) period and the change in this power over the drug uptake period. **(c)** The influence of diazepam on the motor-related changes in beta power (movement onset=0). This shows the desynchronisation rate (DR) during MRBD and synchronisation rate (SR) during PMBR in the control (non-drug) and diazepam (maximal beta power) periods.

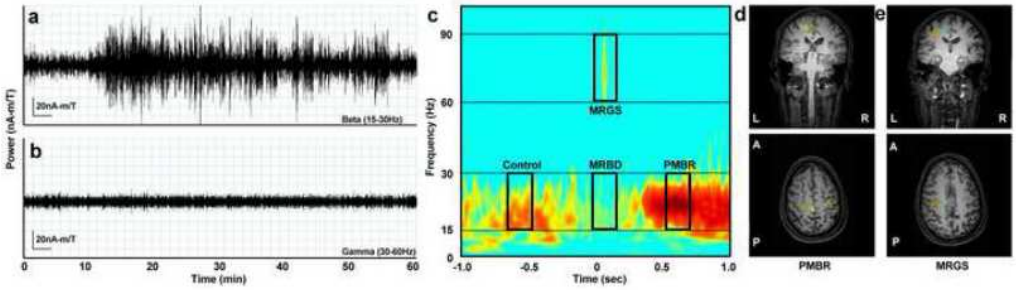

Figure 1

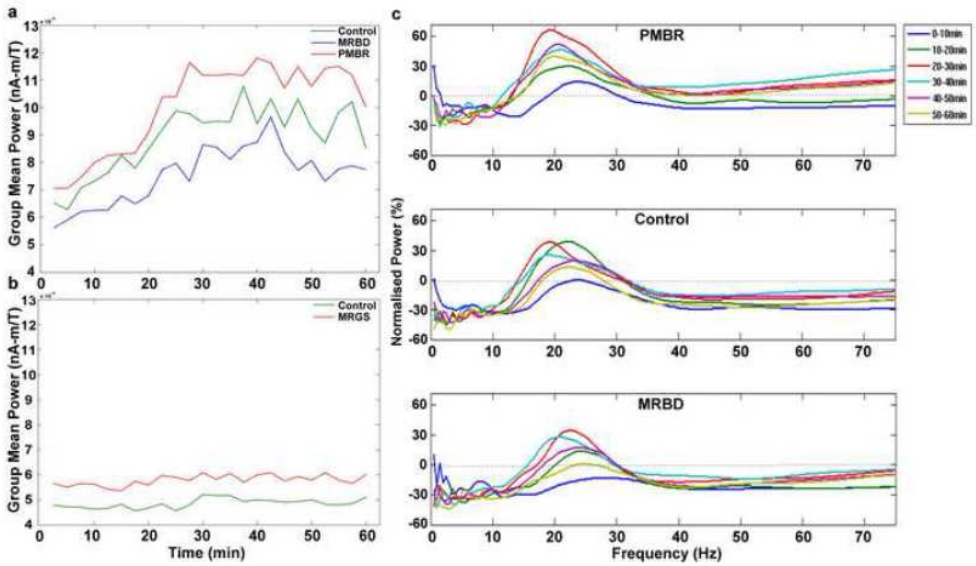

Figure 2

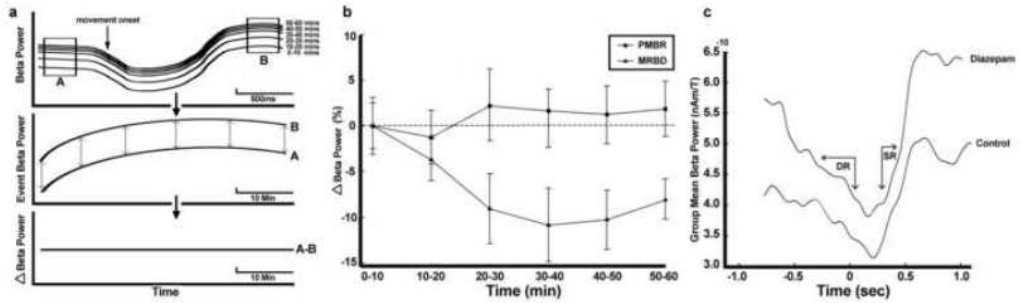

Figure 3

Research Highlights

Pharmaco-MEG can be used a tool to determine the neuropharmacological mechanisms underlying functionally related oscillations.

Movement-related-beta desynchronisation (MRBD) in primary motor cortex (M1) is specifically enhanced by increased GABA-A receptor drive.

Post-movement beta rebound (PMBR) and movement related gamma synchronisation (MRGS) in M1 are non-GABA-A receptor mediated.

MRBD and PMBR are both directly dependent upon the spontaneous beta activity, but are modulated independently of one another.