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Relating MEG Measured Motor Cortical Oscillations to resting γ -Aminobutyric acid (GABA) Concentration

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Abstract

The human motor cortex exhibits characteristic beta (15-30 Hz) and gamma oscillations (60-90 Hz), typically observed in the context of transient finger movement tasks. The functional significance of these oscillations, such as post-movement beta rebound (PMBR) and movement-related gamma synchrony (MRGS) remain unclear. Considerable animal and human non-invasive studies, however, suggest that the networks supporting these motor cortex oscillations depend critically on the inhibitory neurotransmitter γ -Aminobutyric acid (GABA). Despite such speculation, a direct relation between MEG measured motor cortex oscillatory power and frequency with resting GABA concentrations has not been demonstrated.

In the present study, motor cortical responses were measured from 9 healthy adults while they performed a cued button-press task using their right index finger. In each participant, PMBR and MRGS measures were obtained from time-frequency plots obtained from primary motor (MI) sources, localized using beamformer differential source localization. For each participant, complimentary magnetic resonance spectroscopy (MRS) GABA measures aligned to the motor hand knob of the left central sulcus were also obtained. GABA concentration was estimated as the ratio of the motor cortex GABA integral to a cortical reference NAA resonance at 2 ppm.

A significant linear relation was observed between MI GABA concentration and MRGS frequency ($R^2 = 0.46$, $p < 0.05$), with no association observed between GABA concentration and MRGS power. Conversely, a significant linear relation was observed between MI GABA concentration and PMBR power ($R^2 = 0.34$, $p < 0.05$), with no relation observed for GABA concentration and PMBR frequency. Finally, a significant negative linear relation between the participant's age and MI gamma frequency was observed, such that older participants had a lower gamma frequency ($R^2 = 0.40$, $p < 0.05$).

Present findings support a role for GABA in the generation and modulation of endogenous motor cortex rhythmic beta and gamma activity.

Keywords

Magnetic Resonance Spectroscopy (MRS); γ -Aminobutyric acid (GABA); Event-related desynchrony / synchrony (ERD/ERS)

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Introduction

Animal (Roopun et al., 2006; Yamawaki et al., 2008) and non-invasive human studies (Hall et al., 2010; Jensen et al., 2005; Wanquier, 1998) have demonstrated a strong relationship between cortical electrical oscillations and the inhibitory neurotransmitter γ -aminobutyric acid (GABA). Magnetoencephalographic (MEG) observations have recently shown that primary visual cortex (VI) gamma activity (~40 Hz) is associated with magnetic resonance spectroscopy (MRS)-derived visual cortex GABA concentrations in adults (Muthukumaraswamy et al., 2009). It is currently unknown whether a similar relationship exists between gamma oscillations and GABA concentration at other cortical locations.

Motor cortex gamma oscillations are observed at movement onset (~300 ms in duration) in children (Gaetz et al., 2010) and adults (Cheyne et al., 2008), here termed movement-related gamma synchrony (*MRGS*). In addition to motor gamma activity, beta amplitude is known to decrease at movement onset and then “rebound” approximately 0.5 s following movement termination (Pfurtscheller and Neuper, 1997; Pfurtscheller et al., 1996). This motor cortical post-movement beta rebound (PMBR) period is associated with an increased state of transient motor cortical inhibition or a process of active immobilization of the motor network (Cassim et al., 2001; Pfurtscheller et al., 1996; Salmelin et al., 1995). Resting motor cortical beta oscillations have been shown to be sensitive to administration of GABAergic compounds (Hall et al., 2010; Jensen et al., 2005; Wanquier, 1998). For example, the GABAergic antagonist benzodiazepine has been shown in numerous studies to increase beta band power over Rolandic areas in resting MEG (Hall et al., 2010; Jensen et al., 2005). Given that beta cortical oscillations are reactive (i.e. exhibit greater beta synchrony) to GABAergic compounds, the influence of intrinsic GABA mediated inhibition accompanying beta synchrony (such as PMBR) is plausible. A direct association between oscillatory motor activity (amplitude and frequency) with resting GABA, however, has yet to be demonstrated.

The present study compared motor cortex (MI) gamma activity (~60 to 90 Hz), detected with magnetoencephalography (MEG), with each subject's GABA concentration in MI areas, detected with magnetic resonance spectroscopy (MRS). Based on a similar study relating visual cortex (VI) GABA concentration with VI gamma band activity (Muthukumaraswamy et al., 2009), a linear association between MI GABA concentration and MRGS frequency was predicted. Associations between motor cortex PMBR with GABA concentration in MI was also examined, with the hypothesis that PMBR amplitude would vary with GABA concentration.

Material and methods

MEG methods—Recordings were performed at the Lurie Family Foundations' MEG Imaging Center of the Department of Radiology in a magnetically shielded room using a whole-cortex 275-channel MEG system (VSM MedTech Inc., Coquitlam, BC). Nine healthy adult subjects (4F) participated (mean age = 31.9, range 22.7 to 42.7 yrs). At the beginning of each session, participants were fitted with three electromagnetic head coils (nasion and pre-auriculars), used for monitoring within-session head movement and for subsequent co-registration. Following each MEG session, MRI contrast markers were placed at MEG fiducial coil locations and were used to co-register the MEG data to the subject's structural MRI (MRI / MRS methods follow below). The study was approved by the CHOP Institutional Review Board and all participants' gave written informed consent.

Motor Paradigm: Participants made button press responses using their right-index finger in response to a change in the color of a visually presented fixation cross. Data were

continuously recorded for 400 s (600 Hz sample rate), with 1 button press every 4 s on average (3.5 to 4.5 s ISI), and later epoched into 100 trials of 4 s duration (−2 s to +2 s) with the button press at time zero.

Source localization (synthetic aperture magnetometry, SAM)

MRGS: Movement-related gamma synchrony occurs in close temporal relation to movement onset (Cheyne et al., 2008). Differential beamformer (SAM) (Robinson and Vrba, 1999) images of the 60-90 Hz frequency band were created at 0.4 cm resolution using an active time window of −0.1 to 0.2 s and a control window of −1.8 to −1.5 s. A previous report using these parameters demonstrated successful localization of MRGS sources in adult as well as pediatric populations (in children as young as 4 years old) (Gaetz et al., 2010). Time-frequency percent-change plots from the individually-determined MI gamma peak locations were then analyzed for frequency and amplitude using in-house Matlab software (The MathWorks, Inc. Natick, MA). MRGS measures were reported as the frequency corresponding to the largest mean percent-change amplitude observed within the −0.1 to 0.2 s active time window (collapsing over time) for the 60-90 Hz frequency range.

PMBR: Post-movement beta rebound activity was also similarly localized using the differential SAM beamformer. To measure PMBR, beta band amplitude was localized for the 15-30 Hz frequency band using an active time window of 0.5 to 1.0 s and a control window of −2.0 to −1.5 s, with the button press defining time zero. Time-frequency plots obtained from the peak MI PMBR source waveforms were then used to obtain PMBR frequency and amplitude measures in units of percent change. PMBR measures were reported as the frequency corresponding to the largest mean percent change amplitude observed within the 0.5 to 1.5 s active time window (collapsing over time) for the 15-30 Hz frequency range.

Time-frequency plots for both PMBR and MRGS sources were visually inspected to ensure that the peak frequencies reported occurred within the frequency bands of interest.

Structural MRI and MRS Methods: MRI data were acquired on a 3T Siemens Verio™ scanner using a 12-channel receive only head RF coil. For each participant, a 3D MP-RAGE anatomic scan was obtained in an axial orientation, with field of view = 256×256×192 and matrix = 256×256×192 to yield 1mm isotropic voxel resolution (TR/TE = 1900/2.87 ms; Inversion time = 1100 ms; Flip angle = 9°). Single voxel (30×30×30mm) GABA MRS was obtained using the MEGAPRESS spectral editing sequence (Mescher et al., 1998), with TE=68 ms at 3T (acquisition time < 13'). Following recently published methods (Evans et al., 2010), MRS voxels were placed based on anatomic considerations, with ROIs centered on the “hand-knob” of the left central sulcus (Yousry et al., 1997). In the coronal plane, ROI voxels were then rotated to best match adjacent scalp surface (avoiding CSF/bone/fat contamination). Local high-order shimming allowed FWHM line-widths <10 Hz for the unsuppressed water peak. After Fourier transformation, phase correction was applied to the unsubtracted Cr resonance. The integral under the GABA resonance (at 3 ppm) was obtained by spectral peak-fitting using a Gaussian resonance (the expected doublet structure was not resolved). GABA levels were estimated with respect to the NAA resonance at 2 ppm and reported as GABA/NAA. Following procedures outlined in Harada et al. (Harada et al., 2010) the NAA reference was obtained from the subtraction to allow for any potential subtraction errors that might have contaminated the GABA resonance. Associations between GABA concentration and PMBR and MRGS power and frequency, as well as between GABA concentration and the participant's age, were examined using linear regression in SPSS 16.0.

Results

MRGS

Beamformer differential images of MRGS 60-90 Hz activity consistently localized sources to the contralateral MI (see Figure 1). MRGS sources strongly lateralized to contralateral MI and, unlike PMBR sources, did not include ipsilateral MI activity. Time-frequency plots of source waveform activity obtained from the peak locations showed that MRGS duration was approximately 300 ms, arising with the button press at time zero.

PMBR

Beamformer differential PMBR peak locations were observed from bilateral MI in all participants (typically stronger contralaterally). Time-frequency plots obtained from the contralateral PMBR MI peak location showed the expected beta-band ERD, typically arising ~0.3 s prior to the button press and continuing ~0.4 s after button press. PMBR typically reached maximum amplitude within 0.5 to 0.8 s, and remained elevated (relative to pre-movement levels) throughout the 2 s post-movement epoch (see Figure 1). Comparison of the PMBR and MRGS motor locations showed that PMBR localized to a more superior aspect of primary motor cortex than MRGS peak locations (paired t-test (corrected); $p < 0.01$).

MI MRS GABA

An example of MI ROI placement and the corresponding GABA spectra is shown in Figure 2, and subtracted spectra from all 9 subjects are shown in Figure 3. Although the GABA level varies across subjects, GABA and the subtracted NAA peaks are clearly and consistently resolved in all subjects and appear to be relatively free of artifact.

As anticipated, MI GABA was positively correlated with MRGS frequency ($R^2 = 0.46$, $p = 0.02$; see Figure 4). No such relation was observed for GABA and MRGS amplitude.

As anticipated, a significant association was observed between MI GABA concentration and PMBR amplitude ($R^2 = 0.34$, $p = 0.049$; See Figure 5). No such association was observed for PMBR frequency.

A negative association between age and MI MRGS frequency was observed ($R^2 = 0.40$, $p = 0.03$; see Figure 6), as was a marginally significant negative association between GABA and age ($R^2 = 0.32$, $p = 0.06$).

Discussion

Results demonstrate that GABA concentration can be successfully resolved from cortical motor areas and, as hypothesized, that motor cortex GABA is associated with specific aspects of motor cortex beta and gamma oscillations. More specifically, recent studies have shown that MEG measures of VI gamma activity are associated with GABA concentration (Muthukumaraswamy et al., 2009), and based on these previous findings, we hypothesized that motor cortex GABA levels would correlate positively with motor cortex gamma frequency. Although MI cortical gamma responses differ from VI gamma responses in many respects (e.g., method of activation, duration, bandwidth, etc.), -like VI gamma oscillations, present findings show that the *frequency* of MI gamma varies with *in vivo* MI GABA concentration. Present results thus suggest a common GABA-related mechanism governing VI and MI gamma networks.

The literature provides some information about the properties of these networks. Neural network models based on hippocampus CA1 field-potential recordings suggest that the

synaptic release of GABA generates inhibitory postsynaptic potentials (IPSPs) that briefly and rhythmically attenuate random axonal activity. This attenuation modulates excitatory inputs and thus promotes the gamma field oscillation (Traub et al., 2003). In the case of MI gamma, these modulating signals may arise briefly in relation to movement initiated proprioceptive signals (Muthukumaraswamy, 2010), or possibly from sub-cortical structures such as the sub-thalamic nucleus, also known to exhibit coherent gamma bursts in relation to transient movement (Lalo et al., 2008).

As shown in Figure 6, the peak MRGS frequency was inversely correlated with age. A previous developmental MEG study (Gaetz et al., 2010) compared MRGS across healthy controls from three age groups (4-6 yrs, 11-13 yrs, and Adults), and observed no group MRGS frequency differences. Given the Gaetz et al. (2010) finding, the present observation of a significant relation between age and MRGS frequency ($p = 0.03$) is somewhat surprising. Post hoc analysis of the previously published findings (Gaetz et al., 2010), however, did show the same pattern of decreased MRGS with increasing age, but only in the adult group. The above argues for the possibility of a non-linear relation of MRGS frequency and age over the lifespan. Overall, larger N studies are needed to assess the degree to which age predicts MI GABA concentration and MRGS frequency over the lifespan.

A marginally significant negative correlation of GABA/NAA decrease with increasing age was also observed. A small number of studies have noted similar relationships. For example, a plastic down-regulation of normal adult inhibitory GABA neurotransmission has long been reported in the rat auditory system (Caspary et al., 1999; Ling et al., 2005), and in humans, region specific *in vivo* GABA decreases as a function of age have also been reported (Grachev and Apkarian, 2001). A weakness of the present study is that GABA measures were obtained from only a single MRS voxel. Future studies examining associations between GABA concentration and gamma cortical oscillations from additional ROI locations are needed to determine whether the age associations observed in the present study are system specific or a ubiquitous feature of the aging brain.

With regard to beta activity, present results provide support for the theory that post-movement “beta rebound” represents a period of GABAergic inhibition. Numerous studies have observed a transient increase in MI beta amplitude following transient motor movements (Jurkiewicz et al., 2006) and transient tactile stimulation (Gaetz and Cheyne, 2006). This post-movement/stimulus rebound in beta amplitude has been associated with a state of *reduced* motor cortex excitability. For example, Chen et al. (Chen et al., 1999) reported decreased Motor Evoked Potential (MEPs) amplitudes from an intrinsic hand muscle when stimulating the contralateral MI with transcranial magnetic stimulation (TMS) during a period of post-stimulus beta synchrony. Although this inferred period of beta synchrony was not due to movement per se, the report of decreased MI excitability during a period known to be associated with increased beta synchrony is important – especially as GABA is the leading candidate signal for MI inhibition and known through pharmacology studies to directly augment beta power (Hall et al., 2010; Jensen et al., 2005; Wanquier, 1998). Early reports of PMBR in the MEG literature (Pfurtscheller and Neuper, 1997; Salmelin et al., 1995) have speculated that this rebound period represents a time of increased motor inhibition. Findings from the present study, the first to show associations between *in vivo* GABA concentration with beta rebound amplitude, support the hypothesis that PMBR is associated with GABAergic inhibition. Additional studies are needed to replicate these novel findings. In addition, the current study compared *resting* GABA concentration with beta and gamma band measures obtained using a simple motor task. The relationship between GABA and *resting-state* cortical oscillations (from MI and other cortical locations) is also an interesting topic for future studies.

Present findings suggest a common GABAergic mechanism underlying gamma and beta oscillations. The blockade of motor cortical beta oscillations by the gap-junction inhibitor carbenoxolone has been observed (Yamawaki et al., 2008). These data suggest that the mechanism underlying beta oscillations in layer V of MI is similar to that mediating gamma oscillations via GABAergic output at the level of gap-junction connections at the axonal plexus (Traub et al., 2003). Although similar in this respect, Yamawaki et al., (2008) has shown that, unlike gamma cortical oscillations, excitatory synaptic drive is not needed for MI beta oscillatory activity to occur (Yamawaki et al., 2008). The present study has also shown that proximal but spatially distinct regions of MI cortex can exhibit different oscillatory frequencies. Whether these rhythms arise from different interneuronal groups or whether a single interneuron can participate in the generation of multiple rhythms simultaneously remains an interesting question for future research.

In the current study, PMBR was observed to be highest (greatest % change) in participants with relatively high MI GABA levels (see Figure 5). This finding is supported indirectly by recent observations where Autistic adult participants were shown to exhibit significantly reduced PMBR in an action observation task (Honaga et al., 2010). Moreover, children with Autism have been shown to exhibit less GABA from motor / frontal lobe ROIs than age matched controls (Harada et al., 2010). Together, these findings help strengthen the inferred relation between GABA and PMBR and provide a clear prediction for GABA/PMBR studies involving clinical populations where GABA downregulation may be implicated (such as Autism, Schizophrenia and Epilepsy).

In conclusion, present findings show that non-invasive multimodal imaging can assess associations between brain oscillations and brain chemistry. It is hoped that continued work in this area will lead to a better understanding of the mechanisms influencing the generation and modulation of endogenous and exogenous rhythmic brain activity. Such insights may help explain the underlying functional mechanisms as they relate to normal development of the motor system. It is also likely that work in this area will provide insight to the neural mechanisms underlying the abnormal oscillatory activity frequently observed patient populations (e.g., schizophrenia and autism), with work in this area helping to create treatments that target very specific neurotransmitters and, by extension, specific cortical network abnormalities in these patient populations.

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Abbreviations

MRGS	Movement-related gamma synchrony
PMBR	Post-movement beta rebound

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Research highlights

- We observed a significant linear relation between MI GABA concentration and PMBR power.
- We observed a significant linear relation between MI GABA concentration and MRGS frequency.
- We observed a significant negative linear relation between the participant's Age and MI Gamma frequency.
- Present findings support a role for GABA in the generation and modulation of endogenous motor cortex rhythmic activity.

Fig.1.

Movement-related gamma synchrony (MRGS), and post-movement beta rebound (PMBR) locations are shown for a representative subject. The time-frequency total power plot from the PMBR peak location (lower left) is shown on the right. Time-frequency colors indicate increases (red) and decreases (blue) in source power with respect to a pre-stimulus baseline (–2 to –1.5 sec), plotted in units of percent change. Given the proximity of PMBR and MRGS locations, only a single TFR result is shown.

Fig. 2. Edited (subtraction) spectrum showing GABA and NAA resonance obtained from radiological left-hemisphere motor cortex. MRI images to the right show the MRS voxel in relation to the motor “hand knob”. GABA reference phantoms can be observed in the coronal MRI (top right).

Fig. 3. Subtracted MRS spectra from all 9 subjects. Although GABA (dashed line at 3 ppm) and NAA levels (2 ppm) vary across subjects, both peaks are clearly and consistently resolved in each subject. Note the anticipated GABA doublet structure is rarely resolved.

Fig. 4.

Scatterplot showing linear association between MI GABA concentration (x axis) and peak MRGS (y axis). As GABA levels increased, the peak MRGS increased ($R^2 = 0.46$, $p < 0.05$). For every 0.1 increase in GABA concentration, an increase of 3.9 Hz MRGS frequency was observed.

Fig. 5. Scatterplot showing linear association between MI GABA concentration (x axis) and peak PMBR power (y axis). Increases in GABA concentration were associated with increased PMBR power ($R^2 = 0.34$, $p < 0.05$). For every 0.1 increase in GABA concentration, an increase in PMBR amplitude of 10.5% was observed.

Fig. 6. Scatterplot showing a negative linear association between the participant's Age and MI Gamma frequency. Older participants show a lower gamma frequency ($R^2 = 0.40$, $p < 0.05$). For every 10 year increase in age, a decrease of 4.8 Hz in MRGS frequency was observed.