NeuroImage 55 (2011) 616–621

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Relating MEG measured motor cortical oscillations to resting γ-Aminobutyric acid (GABA) concentration☆

W. Gaetz *, J.C. Edgar, D.J. Wang, T.P.L. Roberts

Lurie Family Foundations' MEG Imaging Center, Dept. of Radiology, Children's Hospital of Philadelphia, Philadelphia, PA, USA

ARTICLE INFO

Article history:
Received 4 October 2010
Revised 8 December 2010
Accepted 29 December 2010
Available online 6 January 2011

Keywords:
Magnetic resonance spectroscopy (MRS)
γ-Aminobutyric acid (GABA)
Event-related desynchrony/synchrony (ERD/ERS)

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) remains 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.

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

Abbreviations: MRGS, Movement-related gamma synchrony; PMBR, Post-movement beta rebound.

☆ Disclaimer: No author declares a conflict of interest.

* Corresponding author. Department of Radiology, Children's Hospital of Philadelphia, 34th St. and Civic Center Boulevard, Philadelphia, PA 19104, USA. Fax: +1 215 590 1345.
E-mail address: gaetzw@email.chop.edu (W. Gaetz).

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doi:10.1016/j.neuroimage.2010.12.077

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.

Materials 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 years). 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 1 mm isotropic voxel resolution (TR/TE = 1900/2.87 ms; Inversion time = 1100 ms; Flip angle = 9°). Single voxel (30×30×30 mm) 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. (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 Fig. 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 Fig. 1). Comparison of the PMBR and MRGS motor locations showed that PMBR localized to a more superior