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Abnormal gamma and beta MEG activity during finger movements in early onset psychosis

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Abstract

Patients with psychosis often exhibit abnormalities in basic motor control, but little is known about the neural basis of these deficits. This study examines the neuro-dynamics of movement using magnetoencephalography (MEG) in adolescents with early-onset psychosis and typically-developing controls. MEG data were imaged using beamforming then evaluated for task and group effects before, during, and after movement onsets. Primary findings included weaker activation in patients during movement execution in cerebellar cortices. Such aberrations likely contribute to the decreased motor control exhibited by patients with psychosis, and may reflect GABAergic-based inhibitory deficits comparable to those seen in cellular and system-level studies.

Keywords

bipolar; schizophrenia; adolescent; magnetoencephalography; GABA; cerebellum

1.1 Introduction

Aberrations in basic motor control are well accepted in adults with schizophreniform and affective psychoses. The most commonly described abnormalities include involuntary movements and many of the motor-related neurological soft signs, such as motor integration, motor coordination, complex motor sequencing, primitive reflexes, disinhibition, and sensory integration (e.g., Bombin et al., 2005; Whitty et al., 2009). The brain basis of these impairments and their relationship to the overall syndromes are less

understood, but such impairments are apparently not a product of antipsychotic medications or disease duration as multiple studies have demonstrated motor anomalies in medication naïve patients, prodromal populations, and unaffected relatives (Whitty et al., 2009; Wobrock et al., 2009). Furthermore, delayed achievement of motor milestones during infancy and neuromotor aberrations during childhood and adolescence appear to be some of the most reliable predictive factors of schizophrenia, bipolar disorder with psychosis, or other psychotic disease onset later in life (Isohanni et al., 2001; Sorensen et al., 2010).

Literature concerning the neural basis of these sensorimotor abnormalities is substantially limited, although several functional magnetic resonance imaging (fMRI) and transcranial magnetic stimulation (TMS) studies have provided important insights. Most of the fMRI data has suggested reduced activation in primary sensorimotor cortices and/or the supplementary motor area (SMA) in patients during finger tapping and other basic hand/upper limb movement tasks (Muller et al., 2002; Rogowska et al., 2004). However, at least for left finger tapping, there have been reports of negative findings as well (Braus et al., 2000; for review, see Rogowska et al., 2004). In regards to the TMS literature, a substantial number of studies have utilized stimulation paradigms to focus on cortical-cortical and/or cortical-cerebellar-thalamic-cortical circuitry in the motor system of healthy adults and patients with psychosis (for methodological reviews, see Ziemann and Hallett, 2000). Several studies have used a TMS paired-pulse paradigm to demonstrate reduced inhibitory function in the motor cortex of adults with schizophreniform psychoses (Daskalakis et al., 2002; Fitzgerald et al., 2002a; Pascual-Leone et al., 2002; Wobrock et al., 2008, 2009). Another method of assessing cortical inhibition is through electromyography (EMG) measurements of voluntary tonic motor activity suppression after a TMS pulse to the contralateral primary motor cortex, and this method has also revealed deficits in patients with psychosis (Daskalakis et al., 2002; Fitzgerald et al., 2002a; Wobrock et al., 2009). Although only indirectly related to the motor cortices, TMS paradigms that putatively gauge transcallosal inhibition have also suggested aberrant inhibitory function in subjects with psychotic symptoms (Daskalakis et al., 2002; Fitzgerald et al., 2002b), and a preliminary study by Daskalakis et al. (2005) has indicated that cerebellar inhibition is also reduced in patients with schizophreniform psychoses. The paradigm for assessing cerebellar inhibition putatively activates Purkinje cells, leading to a decrease of the excitatory drive from the dentate and interpositus nuclei to the motor cortex via the thalamus (Ugawa et al., 1995). Thus, an abnormality in either cerebellar-cortical connectivity or Purkinje cell function could underlie such a deficiency in cerebellar inhibition to the motor cortices. Thus, overall, TMS studies have offered solid evidence for dysfunctional inhibitory circuits within the motor system of adult patients with psychosis. These inhibition deficits may underlie the reduced activation and/or lateralization (White et al., 2010) seen in fMRI studies, but fundamental disparities between these neuroscientific tools (TMS and fMRI) prevent straightforward comparison.

Relatively few electrophysiological investigations have been conducted in this area, which is disappointing given the exquisite temporal resolution of these techniques and the central role that neuronal timing is thought to play in the overall syndrome (Andreasen et al., 1999). However, a large number of normative studies have characterized the oscillatory dynamics of neural responses culminating in the sensorimotor cortices. Such responses begin several hundred milliseconds before movement onset with a strong decrease in oscillatory power, which “rebounds” with an abrupt increase in rhythmic power shortly after movement termination (Pfurtscheller and Lopes da Silva, 1999). The most robust and commonly studied oscillatory motor rhythm is the ~14-30 Hz beta-frequency band. An array of sensorimotor events have been shown to modulate beta activity, including passive movements (Cassim et al. 2001), voluntary movements (Cassim et al., 2001; Jurkiewicz et al., 2006; Parkes et al., 2006), imagined movements (Pfurtscheller et al., 2005), and even

observing another agent's movements (Hari et al., 1998). The pre-movement decrease in power is typically termed an event-related desynchronization or pre-movement beta ERD, and the post-movement increase is an event-related synchronization (ERS) or in this literature, the post-movement beta rebound (PMBR). These oscillatory changes are normally gauged relative to a baseline period that occurred 3-5 seconds from the most recent movement (i.e., before and after movement). Although the ERD reflects a decrease in power, the underlying mechanism is believed to be activation of a small patch(es) of cortex near the peak of the frequency-specific ERD, which serves some aspect of the motor output (Pfurtscheller and Lopes da Silva, 1999). In contrast, the PMBR may indicate the return of these cortices to their highly synchronous resting state following completion of the motor task (i.e., the idling hypothesis; Pfurtscheller and Lopes da Silva, 1999); albeit, other models suggest the PMBR results from active inhibition and/or somatosensory reafferent input to motor cortices (Cassim et al., 2001; Gaetz et al., 2010). Finally, most studies have found the pre-movement beta ERD to be generated in the postcentral gyrus and extending into the precentral gyrus, and that the neural correlates of the PMBR are slightly anterior in the precentral gyrus and/or premotor cortices (Gaetz et al., 2010; Jurkiewicz et al., 2006; Wilson et al., 2010), with contralateral dominance and motorotopic mapping being a property of both responses.

Although some have speculated that the PMBR reflects inhibitory processes (e.g., Gaetz et al., 2010), the frequency range of another motor rhythm suggests there are other, potentially more direct, candidates of cortical inhibition. Several studies using invasive methods have described high-frequency gamma activity in the 65-100 Hz range near motor cortices during sustained muscle contractions, continuous movements, and a few other motor tasks in epilepsy patients (Miller et al., 2007; Szurhaj et al., 2006). In addition, a few recent MEG studies have described similar gamma activity in sensors near motor cortex, or precisely in the hand region of primary motor cortex (Cheyne et al., 2008; Wilson et al., 2010). Cheyne et al. (2008) showed that these high-frequency gamma responses coincide with the movement onset, are strongly lateralized to the contralateral hemisphere, and largely follow the somatotopic organization of the primary motor cortex with respect to the foot, biceps and index finger. These findings, at least for the hand, have been partially replicated in typically-developing children and adolescents (Gaetz et al., 2010; Wilson et al., 2010) although several additional brain areas, including the SMA and cerebellum, also showed significant gamma activation during hand movement. The spatiotemporal dynamics of this motor-related gamma activation are intriguing as the response could reflect the initial activation of primary motor neurons serving movement, a form of feedback allowing advanced control of discrete movements (see Cheyne et al., 2008), and/or local inhibitory processes. The latter view arises from the widely supported notion that local interneuronal networks are central to the generation and maintenance of gamma-band discharges, as they function as GABA-gated pacemakers for cortical oscillatory activity (Bartos et al., 2007; Fries et al., 2007; Singer, 1999; Traub et al., 1996). This intricate link between gamma activity and inhibitory interneuronal networks is not unique to the motor system, but more a fundamental property of the neocortex (Bartos et al., 2007; Fries et al., 2007; Uhlhaas et al., 2009).

In the current study, we examine the full gamut of motor-related oscillatory dynamics by recording high-density magnetoencephalography (MEG) data during unilateral flexion-extension movements of each index finger, and subjecting these data to a frequency-domain beamforming approach to image the beta- and gamma-frequency responses that were temporally linked to movement-onset. Our main comparisons were between a larger psychotic group, including both schizophreniform and mood related psychoses, and a matched-sample of typically-developing adolescents. Comparing across specific diagnoses is justified in the sense that there are likely biological markers shared in common across particular manifestations of psychosis, which relate more directly to psychosis (e.g., positive

symptoms) than to other phenotypes (e.g., negative symptoms, mood instability). For instance, evidence has shown that the age of achievement of early developmental milestones such as standing, walking, and potty training is predictive of both schizophreniform and non-schizophreniform psychosis later in life (Isohanni et al., 2001). Additionally, data has shown that early-onset psychotic, but not non-psychotic, mood disorders are associated with delays in language, social, and/or motor development (Sigurdsson et al, 1999). Our primary hypothesis was that patients with psychosis would show decreased inhibition in motor circuitry, as indexed by a reduction of gamma activity in the ipsilateral (to limb moved) cerebellum and contralateral SMA and precentral gyrus.

2. Experimental Methods

2.1. Subject Selection

We studied 12 children and adolescents diagnosed with early-onset psychosis (5 females) and 10 of their typically-developing peers (6 females). The two groups were statistically equivalent in handedness, sex, education, ethnicity, and age (mean age: patients = 12.7 years, controls = 11.4 years; range: patients = 8.8 - 17.8 years, controls = 8 - 16.3 years). All subjects were right-handed as determined by the Annett Handedness Scale (mean: patients = 0.9, controls = 0.85). In the early-onset psychosis group, 10 patients were Caucasian and two were African American. Seven of the healthy comparison participants were Caucasian, two were African American, and one was Hispanic. In the patient group, four participants were diagnosed with schizoaffective disorder, four with bipolar I disorder with psychotic features, and the remaining four had schizophrenia. All patients were in outpatient treatment and medicated during the study. No patients were medicated with typical antipsychotic medications, nine were being treated with atypical antipsychotic drugs (chlorpromazine-equivalencies: mean = 412.8; range = 37.5 – 933.3), and three patients were not taking any antipsychotic medication during the study. Upon enrollment, all participants in the psychosis group were re-diagnosed using the Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime Version (K-SADS-PL; Kaufman et al., 1997), and a review of medical records. Since no patients were medicated with typical antipsychotic drugs, extrapyramidal symptoms were not assessed. Exclusionary criteria included any medical illness affecting CNS function, confounding-dual diagnoses, neurological disorder, history of head trauma, and current substance abuse. Comparison subjects met the same exclusionary criteria, but had no history of Axis I disorder or first-degree relatives with an Axis I diagnosis; all were recruited from the local community. Informed consent was obtained in accord with guidelines of the Colorado Multiple Institutional Review Board.

2.2. Experimental Paradigm

Throughout the experiment, participants were seated in a custom-made child booster-seat below a PVC stand designed specifically for this task. The stand was comprised of two plastic rods attached at 90 degrees to plastic arm braces that allowed elbow to hand to be fully extended. The arm braces were attached to two plastic pipes for hand grips and, near the elbow, two additional pipes connected to the MEG chair to provide stability. Participants rested both arms on the stands and wrapped their hands around the hand grips. Accelerometer chips were attached to each index fingertip, using Delrin rings, to precisely quantify the movement onsets. Participants were instructed to fixate on a crosshair presented centrally and to perform a single knuckle flexion-extension using the index finger each time a dot reached the 12 o'clock position. This dot completed one full revolution, around a clock-like circle without tick marks or numbers, every 6 s. Each participant performed two blocks (left/right) of ~105 trials, with the order of finger block randomized across participants.

2.3. Data Acquisition

With an acquisition bandwidth of 0.1–200 Hz, neuromagnetic responses were sampled continuously at 508 Hz using a Magnes 3600 WH equipped with 248 first-order axial-gradiometer sensors (4-D Neuroimaging, San Diego, CA, USA). MEG data were subjected to a global noise filter subtracting the external, non-biological noise obtained through the MEG reference channels.

Prior to MEG measurement, five coils were attached to the head and the locations of these coils, together with the three fiducial points and scalp surface, were determined with a 3-D digitizer (Fastrak 3SF0002, Polhemus Navigator Sciences, Colchester, VT, USA). With this coordinate system (including the scalp surface points), each participant's MEG data were coregistered with structural T1-weighted MRI data (3T G.E. Signa, quadrature head coil, TR/TE/TI = 9/2/500 ms, NEX = 1, FOV = 220 mm, Matrix = 256^2 , 124 coronal, 1.7-mm thick slices) prior to source imaging. BrainVoyager 2000 software (Version 4.9; Brain Innovations, Netherlands) was used for MRI-MEG co-registration.

2.4. MEG Pre-Processing

All MEG processing was conducted in BESA 5.1 (MEGIS Software GmbH, Grafelfing, Germany). Artifact rejection was based on a fixed threshold method (MEG level exceeding ± 1.2 pT), augmented with visual inspection. Epochs were of 6 s duration, with 0 ms defined as the movement onset and the baseline being the -3000 to -2200 ms window. Artifact-free epochs were transformed to the time-frequency domain using complex demodulation, and the resulting spectral density power estimations per sensor were averaged over trials. These data were normalized by dividing the power of each time-frequency bin by the respective frequency's baseline power, calculated as the mean power during the 800 ms baseline period (-3.0 to -2.2 s). This normalization procedure allowed task-related power fluctuations to be readily visualized in sensor space as event-related synchronizations (ERS; power increases) or desynchronizations (ERD; power decreases). In Figure 1, a representative example of a normalized time-frequency representation is shown with the time-domain average waveform that corresponds to the same MEG data set.

For beta ERS/ERD, the 16–28 Hz band was defined within a -0.3 to 0.4 s time window (pre-movement ERD) and a 1.7 to 2.4 s time window (post-movement ERS). Note that our so-called pre-movement ERD period persists into the post-movement period, which is consistent with other similar electrophysiological studies (e.g., Gaetz et al., 2010; Jurkiewicz et al., 2006). We chose to maintain the pre-movement ERD nomenclature for consistency with the published literature. High-gamma ERS responses were defined between 74–86 Hz and the -0.05 to 0.2 s time window. All passbands and time bins were chosen to focus on maximum responses (i.e., MEG ERD/ERS) across the sample, thus sacrificing some precision on the single-subject level to achieve a consistent analytical approach across participants. Nonetheless, it is worth noting that similar time-frequency windows have been used in the majority of comparable MEG studies involving the motor system (e.g., Cheyne et al., 2008; Gaetz et al., 2010; Jurkiewicz et al., 2006).

2.5. MEG Source Imaging

Cortical networks were imaged through an extension of the minimum variance vector beamformer (Gross et al., 2001), which employs spatial filters in the frequency domain to calculate source power for the entire brain volume. The single images are derived from the cross spectral densities of all combinations of MEG sensors within the time-frequency range of interest, and the solution of the forward problem for each location on a grid specified by input voxel space. Following convention, source power in these images was normalized per condition and subject using a pre-stimulus noise period of equal duration and bandwidth. In

principle, the beamformer operator generates a spatial filter for each voxel (i.e., grid point), which passes signals without attenuation from the given neural region while minimizing interference from activity in all other brain areas.

Normalized power was computed for the selected frequency bands over the entire brain volume. Each participant's images were imported to SPM2 (Statistical Parametric Mapping; Wellcome Department of Cognitive Neurology, London, UK), where the structural volume was transformed into standardized space (MNI; Montreal Neurological Institute, Montreal, Canada). This transformation was then applied to all functional images, which were co-registered to the structural volume prior to source imaging. These spatially normalized functional images were resampled to $4.5 \times 4.5 \times 4.5$ mm resolution.

The effect of group was examined separately using a random effects analysis for each of the three time-frequency components (TFC) of interest per condition. In addition, one-sample *t*-tests were conducted to probe activation patterns per TFC across groups. To reduce the risk of false positive results while increasing sensitivity, a masking procedure was used. This mask included only cortical regions directly involved in motor behavior or programming, plus cerebellar areas, with the primary goal being to ensure statistical tests were performed only on neural regions of a priori interest. This mask included bilateral cerebellum, pre- and post-central gyri, and SMA as defined with the automated anatomical labeling template (AAL; Tzourio-Mazoyer et al., 2002) implemented in the WFU Pickatlas (Maldjian et al., 2003).

3. Results

3.1. Sensor Space Analyses

In agreement with previous studies, finger movements generated beta rhythm ERDs several hundred milliseconds preceding movement onset, which also extended into the movement period in all participants (Jurkiewicz et al., 2006; Pfurtscheller and Lopes da Silva, 1999). Likewise, after movement termination, a beta frequency ERS was observed and the duration of this response was typically 500-900ms. Unlike beta, mu rhythms were not significantly reactive to impending movements and did not show any rebound effect after the movement terminated, instead transforming into low amplitude ERD that was only faintly distinguishable from mu power during the baseline period. Relative to the strong beta ERD and ERS components, the lack of mu reactivity is consistent with other studies (e.g., Gaetz et al., 2010; Jurkiewicz et al., 2006; Wilson et al., 2010). Given this lack of rhythmic power, mu-frequency activity was not evaluated in the source analyses (see below). Lastly, we observed a gamma-band ERS component coinciding with the movement onset, and this response dissipated substantially before movement termination.

3.2. Source Space Analyses

3.2.1 Activation by Task—All resulting statistical parametric maps were thresholded at a family-wise error (FWE) rate of $p < 0.05$ and inspected for regions of significant ERS or ERD. Table 1 shows the brain regions and coordinates for the cluster maxima for each of the TFCs per condition. We observed considerable similarity in the activation maxima contralateral to movement across the two conditions, along with more bilateral activation for beta ERD responses. We describe results for the pre-movement ERD, the high-frequency movement ERS, and the post-movement ERS for each index finger in turn.

Left Index-Finger Movements: The FWE-corrected pre-movement ERD maps showed strong activation in the right SMA, right post-central gyrus extending into the pre-central gyrus, left postcentral gyrus, and multiple areas of the right cerebellum (i.e., crus I and II,

lobule VI, and lobule VIIb; see Table 1). Likewise, the high-frequency gamma synchronization was significant in the right SMA, right pre-central gyrus, bilateral post-central gyri, and the right cerebellar lobule VI. For the PMBR activation, clusters were found in the right pre- and post-central gyri, and the left post-central gyrus.

Right Index-Finger Movements: The pre-movement ERD associated with right index-finger movement was strongest in the left post-central gyrus, stretching anterior to the left pre-central gyrus. Additional areas with significant ERD activity included the right post-central gyrus, right cerebellar crus II, and left cerebellum (crus II and lobule VI). Analogous to that of the left, the high-frequency ERS associated with right finger movement was centered on the hand “knob” region of the contralateral primary motor cortex and extended medially into the left SMA and posterior into the post-central gyrus (see Figure 2). This gamma ERS and the PMBR (discussed below) were strongly lateralized to the contralateral cerebral hemisphere. The PMBR for right finger movements involved the anterior and lateral left pre-central gyrus (near pre-motor cortices), the left post-central gyrus, the right cerebellar lobule VI and crus I, and the left cerebellar lobule VI and crus I (see Figure 3).

3.2.2 Group-wise Comparisons—Group-wise comparisons for each TFC per condition are shown in Table 2, with coordinates for each cluster maxima. Functional maps were initially thresholded at $p < 0.01$ (uncorrected) and suprathreshold clusters were further scrutinized using the small volume correction (6 mm) tool implemented in SPM2. This section will focus on clusters surviving correction.

Beta ERD/ERS Results: There were no group differences in the beta-frequency ERD or PMBR response during left index-finger movements. During right index-finger movements, patients showed stronger pre-movement beta ERD activation in several areas including the left pre- and post-central gyrus, left cerebellar crus I and lobule VI, and a small cluster in the right pre-central gyrus (see Figure 4). In contrast, the TD group showed greater PMBR activity in the right SMA, right superior parietal, and right cerebellar lobule VI during right finger movements.

Gamma ERS Results: During left index-finger movements, the TD group had stronger gamma ERS activation in the left post-central gyrus and right cerebellar lobule VI compared with the patient group (see Figure 5). The TD group also exhibited stronger gamma ERS activation in the right cerebellar crus I and lobule VI relative to patients in the right index-finger condition (see Figure 5).

3.2.3 Effect of Antipsychotic Medications—To evaluate whether group differences were modulated by the presence of antipsychotic medications in the patient group, a series of Pearson Correlation coefficients were computed using the chlorpromazine equivalencies. Briefly, the amplitude of each peak group difference voxel (i.e., all coordinates listed in Table 2) was extracted for each patient. These values and the chlorpromazine-equivalency values were subjected to exploratory Pearson correlation analyses. The results indicated that the patients' chlorpromazine-equivalencies were not significantly correlated ($p > 0.10$, two-tailed test) with the amplitude of the peak group difference voxels.

4. Discussion

We examined the oscillatory dynamics serving knuckle flexion-extension movements in a group of adolescents with early-onset psychosis and their typically-developing peers. Consistent with previous normative studies, we observed a beta-frequency ERD response that predominated before and slightly after movement onset, as well as a beta ERS response (i.e., PMBR) that began shortly after movement termination and continued for about 700

milliseconds. The neural correlates of these beta-band responses closely resembled adult findings in rolandic regions (pre- and post-central gyri), but with additional areas of activation in cerebellar cortices and the SMA. Likewise, we observed high-frequency gamma oscillations in the contralateral pre-central gyrus that coincided with the movement onset; although again, these children exhibited additional nodes in the cerebellum and SMA where gamma synchrony increased in temporal unison. Such beta- and gamma-frequency activations outside of the classic rolandic regions may indicate that additional nodes are involved in each aspect of basic motor control in the developing motor system. In regards to the study's primary focus, the adolescents with psychosis exhibited reduced gamma-band activation in lobule VI of the right cerebellum, during movement of either index finger, compared with the TD group. Reduced gamma ERS was also found in the left post-central gyrus of the psychosis group during movements of the left index-finger. In addition, patients exhibited significantly weaker PMBR activity during right index-finger movements in lobule VI of the right cerebellum, as well as the right SMA and superior parietal lobule. Finally, the patient group exhibited significantly stronger beta ERD responses prior to movements of the right index finger in the right pre-central gyrus, left pre- and post-central gyri, and the left cerebellum lobule VI and crus I. These results are discussed in-depth below with a particular focus on the reduced high-frequency gamma response in patients with psychosis, and how this reduction may relate to the ubiquitous evidence for a basic cortical inhibition deficit in schizophrenia and affective psychoses.

The reduced high-frequency gamma response in patients with psychosis is likely the most interesting finding of the current study, especially in light of recent TMS data. To gain a further understanding of the cortical inhibition deficits, several TMS studies have developed interleaved stimulation methods which allow EEG data to be collected in conjunction with the standard experimental outcome measures (e.g., EMG). These EEG/TMS studies have shown that cortical inhibition is associated with the selective suppression of gamma oscillations in normal adult participants (Farzan et al., 2009, 2010; Fitzgerald et al., 2009), and that such gamma suppression is absent in adults with chronic schizophrenia (Farzan et al., 2010). Several lines of evidence indicate that this suppression of gamma oscillations, and the concomitant peripheral EMG measures, is mediated by cortical GABAergic interneuronal networks (Bartos et al., 2007; Fries et al., 2007; McDonnell et al., 2006). Furthermore, beyond the motor system, there is abundant evidence that GABAergic networks and the gamma oscillations they serve are disturbed in patients with psychosis. For example, investigations of the 40 Hz steady-state response have demonstrated abnormally diminished power in adolescents (Wilson et al., 2008) and adults with mood-related or schizophreniform psychoses (Krishnan et al., 2009; O'Donnell et al., 2004; Spencer et al., 2008). As for cellular evidence, post-mortem studies of subjects with psychosis have indicated a 40% selective decrease, which was statistically unrelated to medication, in the axonal terminal density of GABAergic interneurons that synapse exclusively with pyramidal cells (Pierri et al., 1999). Similar post-mortem studies have shown that the dendritic projections of GABAergic interneurons are reduced in several cortical areas of the schizophrenic brain (Selemon and Goldman-Rakic, 1999), and there is also evidence for impaired GABA synthesis and reuptake in the interneurons of patients with psychosis (Akbarian et al., 1995; Volk et al., 2001). These deficits in reuptake and synthesis of GABA were especially prominent in parvalbumin-positive interneurons (Hashimoto et al., 2003), which is intriguing given recent data that such fast spiking, parvalbumin-expressing interneurons are causal players in the generation of gamma oscillations (Sohal et al., 2009). Thus, the evidence supporting GABAergic interneuronal deficits, aberrant gamma oscillations, and the link between the two is very substantial in the literature (for reviews, see Lewis et al., 2005; Uhlhaas and Singer, 2010).

An interesting feature of the gamma abnormalities observed in the current study was their condition-invariant focus. Essentially, group differences were strongest in lobule VI of the right cerebellum regardless of index finger moved (left or right). This finding is consistent with a recent somatosensory study of adolescents with psychosis, where abnormal right cerebellar activity was present in the patient group regardless of which hand was pneumatically stimulated (Wilson et al., 2009). In this somatosensory study, the most robust group differences were in the gamma-frequency range, although 8-16 Hz oscillations also differed between groups in the right cerebellum (Wilson et al., 2009). Thus, both mechanoreceptive stimulation and the execution of movement, using the right or left hand, are associated with abnormal gamma activity in the right cerebellar cortices of adolescents with psychosis. These data likely indicate greater aberration in the right cerebellum relative to left hemispheric homologue areas in these patients. This is in agreement with a prior study of persons at high risk for schizophrenia which showed significant gray matter density reductions were limited to right cerebellar brain areas and the left temporal lobe 2-3 years preceding disease onset (Job et al., 2005). Likewise, several studies have shown bilateral decreases in cerebellar volume of psychotic adults, but attempts to link the clinical-behavioral and neural indices have been more successful for the right cerebellum (Bottmer et al., 2005; Thomann et al., 2009). In particular, one study showed that total neurological soft sign scores were inversely correlated with the volume of the right cerebellar hemisphere, with the strongest effect being for the motor coordination subscale measure (Thomann et al., 2009; see also, Bottmer et al., 2005). Abnormal right cerebellar activity was also detected during the PMBR response for right index-finger movements, which is discussed below. Finally, it is worth noting that some of the TMS/EEG studies discussed above have shown that the normal gamma suppression associated with cortical inhibition, and its absence in adult schizophrenia, occurs strongest in left prefrontal cortex and not in the motor cortex (Farzan et al., 2009; 2010). The current study found strong gamma activation in the contralateral pre-central gyrus across groups (i.e., main effect), but also found no evidence for between group gamma-band differences in these motor regions. Thus, although speculative, it is unfortunate that these TMS/EEG studies were not able to directly monitor neuronal activity (i.e., gamma-band) in the cerebellar cortices.

Beyond gamma activity, we also found group differences in the beta rhythm, but only for the right finger condition. These included stronger pre-movement beta ERD responses in the left pre- and post-central gyri, right pre-central gyrus, and the left cerebellum of patients relative to the TD group. Several normative studies have shown that the beta ERD response peaks in the contralateral post-central gyrus, with weaker activation in the ipsilateral homologue cortices (Gaetz et al., 2010; Jurkiewicz et al., 2006; Wilson et al., 2010). Thus, activation in these rolandic areas is largely similar to what is generally reported, which may indicate that the group differences simply reflect increased movement programming or activation of larger motor representations in patients with psychosis. Such an increase in motor programming could serve to compensate decreased specialization for controlling movements of the dominant hand (e.g., Crow et al., 1996), whereas anomalous functional representations (e.g., larger or redundant maps) could be a mere feature of the disease as it is reported in other cortical areas (Rojas et al., 2002; Wilson et al., 2007). The increased ipsilateral beta ERD to right finger movements might be consistent with TMS literature suggestive of transcallosal inhibitory deficits (Daskalakis et al., 2002; Fitzgerald et al., 2002b). In regards to the left cerebellum, the greater beta ERD in patients likely reflects disturbed circuitry in these adolescents as, from a motor network perspective, the left cerebellum should not be activated during movement programming of the right hand. In contrast to the beta ERD, the PMBR was stronger in the right SMA, parietal lobule, and the right cerebellum (lobule VI) of the TD group. Recent work has shown that the PMBR exhibits robust developmental trends in rolandic regions (Gaetz et al., 2010) and higher order areas such as the SMA and right cerebellum (Wilson et al., 2010). Thus, these

differences may reflect abnormal cortical inhibition in patients with psychosis, reduced motor network resetting (via an unknown mechanism), the disease process itself, and/or the aberrant brain maturational patterns (Wilson et al., 2007) that are known to accompany the disease process. The current data cannot discriminate among these alternatives, but there is some evidence that the integrity of beta rhythms may also depend on GABAergic circuitry (Uhlhaas and Singer, 2010).

In conclusion, we have described the spatiotemporal dynamics of oscillatory motor responses in a group of adolescents with early-onset psychosis and their TD peers. Our most interesting findings are likely the reduced high-frequency gamma responses during movement execution in the right cerebellar cortices of patients with psychosis. We believe these data indicate that GABAergic interneurons, functional GABAergic synapses, or some other inhibitory mechanism is deficient in patients with early-onset psychosis. Our findings of abnormal PMBR responses after right finger movements may also reflect anomalous inhibition in the patient group. Future studies will need to ascertain the degree to which cerebellar gamma abnormalities are maintained throughout the disease course. In this regard, data acquired using TMS/EEG methods would be especially informative. Likewise, continued exploration and testing of the value of motor signs in the early identification of psychotic illness in pediatric samples will be important to further develop the biomarker application. Finally, it is important to recognize the limitations of this work including the relatively smaller sample sizes, inherent difficulty of diagnostic specificity in cases of early-onset psychosis, and the relatively unknown effects of medication on neuronal indices, all of which limit the generalizability of these findings. Of course, given the rareness, studies of early-onset psychosis will always have to rely on smaller sample sizes than investigators would generally prefer. Future studies of patients with early-onset psychoses that are medication-naïve will be important to corroborate the current findings, as our correlational analyses cannot rule out the presence of medication effects. In addition, the current study was not designed to test potential differences in persons with different DSM-IV psychotic disorders (e.g., schizophrenia versus bipolar disorder with psychotic features). While the literature on motor risk factors suggests a similar, if not identical, risk profile for motor dysfunction and delay for bipolar disorder and schizophrenia (Isohanni et al. 2001), a future study could examine the expression of that risk within the brain using similar methods to those described here. A final caveat to this and related work is that GABAergic aberrations cannot be considered specific to psychosis as they have been reported in other conditions such as autism (Casanova et al., 2003), which may indicate these anomalies are better understood as nonspecific risk factors for a variety of neurodevelopmental disorders.

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Figure 1.

Time-domain and time-frequency domain representations of data from the same MEG sensor. Representative example of an unfiltered time-domain average waveform is shown above the normalized time-frequency representation that corresponds to the same MEG data from a sensor near sensorimotor cortices. In both plots, time is shown on the abscissa in seconds with 0 s indicating movement onset as determined with an accelerometer chip. On the ordinate, amplitude in femto Tesla (fT) is shown in the time-domain plot (top) whereas frequency (in Hz) appears in the time-frequency domain representation (bottom). As shown, the beta ERD (blue) response begins before movement onset and stretches well into the movement period. The beta ERD activity is followed by a strong beta ERS (red) that continues well after the movement. The color scale appears across the top of the time-frequency representation. The time-domain plot (top) shows a strong evoked motor response that peaks 100 - 150 ms after movement onset, which likely corresponds to the low-frequency (< 10 Hz) ERS response that can be seen in the bottom plot.

Figure 2.

High-Frequency Gamma Activation during Right Finger Movements. During the execution of right index finger movements, robust gamma activity was observed across groups in the left pre-central gyrus and extended medially into the left SMA and posterior into the left post-central gyrus. As shown, gamma activity was strongly lateralized to the contralateral hemisphere across groups. Images are shown in neurological (right = right) convention and arranged from the most inferior slice to the most superior, which is next to the sagittal image (bottom right) indicating the placement of all shown axial slices in the volume (threshold: $p < 0.05$, FWE-corrected).

Figure 3.

Post-Movement Beta Rebound (PMBR) after Right Finger Movements. Across groups significant PMBR activation following right index finger movement termination was strongest in the left pre-central gyrus. Activation was strongly lateralized to the left hemisphere and extended into premotor cortices and the post-central gyrus. Significant PMBR responses were also observed in bilateral cerebellar cortices (not shown). Lines in the sagittal image (far right) indicate the placement of shown axial slices. Images are in neurological convention (threshold: $p < 0.05$, FWE-corrected).

Figure 4.

Group Effect for the Right Finger Pre-Movement Beta ERD. During the right index finger condition, the adolescents with early-onset psychosis exhibited greater pre-movement beta ERD responses compared with their typically-developing peers in the left cerebellum (lobule VI and crus I), left post-central gyrus, and the pre-central gyrus bilaterally. Images are shown in neurological (right = right) convention and arranged from inferior to superior, with the most superior slice being next to the sagittal image (bottom right) indicating the placement of shown axial slices in the volume (threshold: $p < 0.01$, uncorrected).

Figure 5A-C.

Group Effect for High-Frequency Gamma Activation. Typically-developing participants exhibited greater gamma activation during movement execution compared with patients, regardless of which index-finger was being moved. During left finger movements, adolescents with psychosis exhibited reduced gamma activity in the left post-central gyrus (A) and lobule VI of the right cerebellum (B). During the right finger movement condition, these patients also showed significantly decreased gamma in lobule VI of the right cerebellum (C). As displayed, the peak group difference for right finger movements (C) was slightly inferior to that of the left index finger condition (B), although both were clearly centered within lobule VI. For each row (A-C), the lines in the sagittal image (far right) indicate the placement of axial slices for the given row. Images are in neurological convention (threshold: $p < 0.01$, uncorrected).

Table 1

Task Effects: Peak Activation Coordinates per TFC

	Anatomical Label	MNI Coordinates (x,y,z)	T Score
Left Finger			
Pre-movement beta ERD	R sup motor area	5 -23 59	10.56
	R postcentral gyrus	54 -18 54	9.54
	L postcentral gyrus	-50 -18 18	8.82
	R cerebellum VI	41 -36 -32	5.46
	R cerebellum crus I	50 -45 -32	5.44
	R cerebellum crus II	41 -81 -41	5.24
	R cerebellum VII-b	45 -54 -50	5.22
High-frequency ERS			
R sup motor area	9 -18 52	7.75	
R precentral gyrus	45 -9 50	7.74	
R postcentral gyrus	45 -18 41	7.71	
L postcentral gyrus	-27 -41 68	6.96	
R cerebellum VI	18 -59 -14	5.25	
Post-movement beta ERS			
R precentral gyrus	36 -9 63	7.93	
R postcentral gyrus	27 -36 68	6.94	
L postcentral gyrus	-63 -14 32	6.36	
Right Finger			
Pre-movement beta ERD			
L postcentral gyrus	-36 -27 45	8.13	
R postcentral gyrus	54 -27 59	7.70	
R cerebellum crus II	45 -72 -45	7.55	
R postcentral gyrus	63 -9 27	7.29	
L cerebellum crus II	-36 -81 -41	6.36	
L cerebellum VI	-29 -45 -32	6.33	
High-frequency ERS			
L precentral gyrus	-32 -9 45	8.68	
L postcentral gyrus	-50 -18 50	7.11	

Anatomical Label	MINI Coordinates (x,y,z)	T Score
Post-movement beta ERS		
L precentral gyrus	-59 5 41	6.95
L postcentral gyrus	-45 -23 63	6.60
R cerebellum VI	40 -50 -27	6.60
R cerebellum crus I	59 -63 -27	6.17
L cerebellum crus I	-45 -77 -27	5.74
L cerebellum VI	-27 -63 -18	5.46

Note: all maxima (T values) are significant at $p < 0.05$ (FWE-corrected), roman numerals indicate the cerebellar lobule involved

Table 2

Group Effects: Peak Activation Coordinates per TFC & Condition

	Direction of Significant Effect	Anatomical Label	MNI Coordinates (x,y,z)	T Score
Left Finger				
High-frequency ERS	Controls > Patients	R cerebellum VI	23 -54 -23	3.43
		L postcentral gyrus	-54 -27 54	3.00
Right Finger				
Pre-movement beta ERD	Patients > Controls	L precentral gyrus	-59 9 40	5.16
		L postcentral gyrus	-63 -5 32	4.53
		R precentral gyrus	63 5 23	2.65
		L cerebellum crus I	-41 -81 -23	2.57
		L cerebellum VI	-23 -54 -23	2.45
High-frequency ERS	Controls > Patients	R cerebellum VI, crus I	36 -41 -36	3.35
Post-movement beta ERS	Controls > Patients	R sup motor area	9 0 48	2.87
		R sup parietal lobule	14 -54 77	2.77
		R cerebellum VI	41 -32 -32	2.42

Note: all maxima (T values) are significant at $p < 0.05$ (SVC-corrected), roman numerals indicate the cerebellar lobule involved