

Imaging the Neural Control of Voluntary Movement using MEG

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1 Introduction

Throughout the history of behavioral neuroscience there has been a great interest in how the human brain processes sensory information and the neural mechanisms that underlie our perception of the outside world. Indeed, much of experimental psychology has its roots in the study of sensation and perception. Similarly, the study of human perceptual-motor skills has largely focused on our ability to perform a variety of tasks that involve the processing of sensory input and the mapping of that input onto motor responses. The development of neuroimaging techniques such as PET, functional MRI, high-resolution EEG, and magnetoencephalography (MEG) has contributed greatly to our understanding of the neural processes that perform such sensory-motor transformations. However, the neural mechanisms underlying internally generated movements – movements that are performed in the absence of a sensory cue – are less well understood, due in part to the difficulty in measuring those processes that guide our spontaneous actions and even the simplest of motor skills that we use on a daily basis. In 1965, Kornhuber and Deecke published their observation of electrical brain activity preceding a self-initiated movement after striking upon the idea of backwards averaging of brain potentials recorded during voluntary finger movements [49]. This pioneering discovery of the so-called *Bereitschaftspotential* (readiness potential) led to an increased interest in using electrophysiological techniques to study not only the brain's response to external events as reflected in the processing of sensory stimuli, but also to gain insights into neural activity that precedes the generation of voluntary movements, perhaps even elucidating the organizational principles by which spontaneous, self-willed actions arise. In this regard, neuroimaging of human brain activity during self-paced movements offers the unique opportunity to study those neural mechanisms that govern the planning, initiation, and control of volitional behavior.

Modern neuroimaging techniques such as functional MRI provide us with powerful methods with which to localize brain areas involved in various

aspects of motor control. However, methods based on brain hemodynamics lack the temporal resolution required to investigate the precise sequence of neural events as they unfold over the course of a few hundred milliseconds during the execution of a single voluntary movement. High-resolution EEG and MEG studies utilizing state-of-the-art source modeling techniques, on the other hand, may hold the greatest promise to determine the time-dependent neural processes underlying motor control in humans. The following chapter provides a brief overview of the use of MEG to study the cortical control of voluntary movements and also describes the development of new MEG source reconstruction techniques that offer the ability to non-invasively image human brain activity during motor tasks with unparalleled spatial and temporal resolution.

2 Movement-Related Magnetic Fields

The first recordings of magnetic fields accompanying simple finger movements were reported by Deecke and colleagues [26] who observed slow magnetic field changes in recordings over sensorimotor areas of the brain preceding voluntary movements of the digits using a single channel magnetometer. These early recordings revealed that slow magnetic field shifts began several hundred milliseconds prior to movement and appeared to be the magnetic counterpart of the electrically recorded readiness potential. Subsequent studies using more extensive spatial sampling showed that these movement-related magnetic fields (MRMFs) were widely distributed over the scalp and indicated that pre-movement MEG activity could not be explained by a single generator in the contralateral primary motor area [21]. In addition, a number of transient field reversals were observed following the onset of electromyographic activity in the involved muscles, presumably reflecting cortical activity involved in movement execution and the processing of proprioceptive feedback, and were termed movement-evoked fields [21, 51]. Early attempts to model the generators of movement-related fields as equivalent current dipoles showed that at least two sources were necessary to account for pre-movement magnetic field patterns, even during unilateral movements, due to consistently observed activity in the ipsilateral hemisphere [21, 51]. The observation of bilateral motor cortex activation for unilateral movements was somewhat contrary to conventional models of motor control at the time; however, this finding is consistent with recent evidence of bilateral cortical activity during unilateral motor tasks.

The introduction of whole-head MEG systems in the early 1990s and recent advances in source reconstruction methods now offer the possibility of constructing more detailed models of distributed brain activity accompanying movement. Initial whole-head MEG studies of voluntary finger movements combined with dipole modeling have confirmed earlier findings regarding primary motor area activation, including the presence of ipsilateral MI activation [22, 63]. Fig. 1 shows the time course and magnetic field patterns accompanying

Movement-related magnetic fields (right index finger)

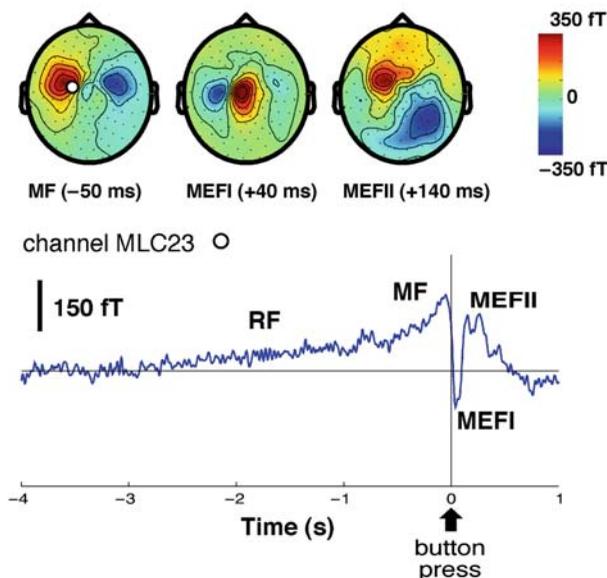


Fig. 1. Movement-related magnetic fields accompanying a self-paced movement of the right index finger, recorded from 151 first-order axial gradiometers covering the whole-head (VSM Medtech Ltd, Coquitlam, BC, Canada) and averaged over 80 trials. Color maps of magnetic field amplitude (red = ingoing, blue = outgoing) show the topography of the three main peaks in the time trace (below) for a sensor located over the contralateral hemisphere (white dot). RF = readiness field, MF = motor field, MEF = movement-evoked fields. fT = femtoTesla. Modified from [17]

a self-paced movement of the right index finger in a right-handed subject using a 151-channel whole-head magnetometer system. The averaged waveform from a sensor overlying the contralateral motor cortex shows a typical slow pre-movement readiness field (RF) with a rapid increase in amplitude beginning approximately 600 ms prior to movement onset and reaching peak amplitude (motor field – MF) about 50 ms prior to movement onset, roughly coincident with onset of EMG activity in the active muscles [21]. Movement-evoked fields can be seen during the execution phase of the movement, with the largest component (MEFI) reaching maximum amplitude at a latency of 40 ms (approximately 100 ms following the onset of EMG activity) followed by a second field reversal at about 140 ms (MEFII). One can also observe in the example shown in Fig. 1, the typical bilateral topography of the MF for a unilateral movement, with larger amplitude over the hemisphere contralateral to the side of movement [51]. Although this pattern has the appearance of a single midline source, it can be shown to reflect bilateral activation of the sensorimotor areas (bimanual movements produce an almost identical pattern)

with cancellation of oppositely oriented magnetic fields over the central scalp, thus complicating reconstruction of the underlying sources. The degree of hemispheric asymmetry of the MF tends to vary across subjects and with side of movement, with greater degree of asymmetry for movements of the dominant hand in comparison to the non-dominant hand in right-handed subjects [51]. This functional asymmetry of motor cortex activation was confirmed in a whole-head MEG study [93] and additionally found that left-handed subjects showed a mixed pattern of asymmetry compared to right handers.

In contrast to the complex patterns of pre-movement brain activity, the first movement-evoked field (MEFI) at a latency of 30 or 40 ms following the button press (Fig. 1, middle map) shows a much more lateralized pattern of activity that can be modeled as a single source in the contralateral hemisphere [51]. This MEFI occurs about 100 ms after onset of EMG activity in the agonist muscle, around the same latency as single unit activity recorded from primary somatosensory cortex [6, 64]. Sources for the MEFI have been localized to the postcentral gyrus and show a homuncular distribution for movements of different body parts [55] suggesting that this component reflects somatotopically organized activation of neuronal populations in SI. Studies have shown evidence that the MEFI is produced by muscle activity in the periphery since it is delayed by cooling of the peripheral nerves [18], modulated by transient deafferentation [53] and localizes to portions of the postcentral gyrus that receive tactile and proprioceptive afferents [54, 69].

The exact role of peripheral feedback in the generation of the MEFI is not clear. The above studies suggest that such feedback may involve both afferent input from muscle spindle receptors monitoring changes in muscle length as well as sensory organs in joints and tendons, although a recent study found that MEFI latency was more time-locked to onset of muscle stretch than physical movement of the finger joint [70]. The hypothesis that the MEFI may reflect encoding of kinematic variables associated with muscle stretch is also consistent with the findings of Kelso and colleagues [43] who showed that MEG activity overlying the contralateral sensorimotor cortex during a continuous motor task correlated most highly with movement velocity, independently of explicit task requirements (flexion version extension). Interestingly, in a recent EEG study, the electrical counterpart to the MEFI was shown to be absent in a deafferented patient who could still perform flexions of their index finger without any sensation of movement [50]. The authors speculated that the MEFI might therefore reflect feedback from the periphery to the sensorimotor cortex necessary for the “perceptual awareness” of movement. Movement-evoked fields at latencies greater than 100 ms (e.g., MEFII and MEFIII) have rather complex topographies and are not amenable to modeling as simple configurations of dipole sources. The MEFIII component, occurring at latencies of up to 300 ms after EMG onset, may be associated with movement termination or subsequent muscular contractions during complex movements as it is more strongly detected during flexion–extension movements than for flexion only [39].

2.1 Rhythmic Brain Activity Accompanying Voluntary Movements

Recently there has been renewed interest amongst neuroscientists in the role of synchronized rhythmic activity in the brain, particularly as it pertains to the coupling or phase-locking of different neuronal networks that may underlie cognitive processes such as object recognition or perceptual ‘binding’ of multiple sensory inputs [91, 96]. Similarly, there has been an increased interest in the role of neural oscillations in motor control [7, 60]. It has long been known that movements elicit frequency-specific changes in the EEG, particularly within the β (15–30 Hz) and μ (8–14 Hz) frequency bands. These changes in ongoing or *induced* oscillations are similar to those observed during cognitive tasks in that they tend to be only coarsely time-locked to specific components of the movement. Within the EEG literature, these increases and decreases in spectral power have been traditionally termed event-related synchronization (ERS) and desynchronization (ERD), respectively, and have been shown to be elicited during and following preparation and performance of voluntary movements [72, 73, 80], passive movements [11], and even during imagined movements [74, 83]. Using MEG, Jensen and colleagues [40] have demonstrated that augmentation of β -band activity by benzodiazepines was localized to regions of the sensorimotor cortex with a concomitant shift in peak frequency. The authors compared their findings with a neural network model showing that the frequency specificity of cortical β -rhythms may reflect the inherent time-constant of neural networks involving both long-range thalamocortical connections, as well as local intracortical connectivity between inhibitory interneurons and excitatory pyramidal cells. Higher frequency (>30 Hz) γ -band oscillations have also been reported in motor cortical areas during a variety of visuomotor tasks and appear to be more related to aspects of motor planning, such as movement trajectory [15, 71] or attentional aspects of the motor task [8] and likely arise from premotor and parietal regions.

The functional role of μ and β rhythmic activity in the sensorimotor cortex is not well understood. One interpretation is that they simply reflect background or ‘idling’ rhythms that are disrupted during movement and are enhanced (rebound) during periods of cortical inhibition following movement onset [14]. The observation that β -band rebound exhibits frequency specificity related to the body part being moved has led to speculation that the frequency of oscillation reflects the extent of the cortical area activated, and in turn the dynamics of a local cortical oscillatory network [73]. Others have speculated that these oscillations may reflect perceptual “binding” in the motor system analogous to that found for gamma band oscillations in the visual system [9]. Alternatively, sensorimotor oscillations have been suggested to reflect a type of *sensorimotor sampling* [60] in which sensory input necessary for the guidance of movements can be more efficiently combined with synchronously firing neuronal populations involved in motor output.

2.2 Corticomuscular Coherence

Using a single channel magnetometer, Conway and colleagues [25] made the interesting observation of increased coherence (correlation in the frequency domain) between the surface electromyogram activity in a contracting muscle and MEG recordings made over the contralateral motor areas. This has led to a large number of studies on MEG–EMG or *corticomuscular* coherence (CMC) and speculation on the functional relationship between spontaneous cortical rhythms and EMG activity during movement [4, 9]. Changes in the frequency of coherence varies with the strength of muscular contraction [10] and MEG studies have shown changes in CMC frequency in patients with Parkinson’s disease [79] leading to hypotheses regarding the role of CMC in maintaining efficient cortical ‘drive’ to the peripheral motor neurons during normal muscular contraction. The observed constant phase lag between cortex and muscle during CMC suggests that it is produced by fast corticomotoneuronal pathways, although reduction of CMC in a deafferented patient indicates some dependence on sensory afferents [46]. Patterns of corticomuscular coherence are best observed during extended periods of isometric force, as relatively long sampling periods are required to compute reliable estimates of coherence. Hence the relationship of CMC to specific phases of discrete voluntary movements is not clearly understood. However, recent MEG studies have shown CMC was related to task-specific aspects of movement [44] and was reduced during the phasic part of a movement relative to a hold phase [45]. In addition, there are periods of increased CMC following voluntary movements [29] that have been shown to correlate with the level of attention to motor performance [52] and CMC has been correlated with readiness to respond in a reaction time task [84]. This suggests that corticomuscular coherence may not only function as a mechanism for stabilizing corticospinal output to the muscles during periods of sustained muscular force but may also subserve a higher-order role in motor control.

3 Methodological Issues

In order to use MEG to model the rather complex patterns of cortical activity observed during even simple motor tasks, as well as concomitant changes in cortical oscillatory activity, we require more sophisticated approaches to magnetic source reconstruction than provided by the dipole modeling approach. Fortunately, more advanced MEG source reconstruction methods have been recently developed, capable of localizing both time-locked and induced oscillatory activity from multiple brain regions, thereby allowing us to take full advantage of the temporal information in the MEG signal. As described in the following section, these new approaches offer the promise of a true *spatiotemporal* brain imaging method that can disentangle the complex nature of ongoing and evoked neural activity during motor control.

3.1 Beamforming: A New Approach to Neuromagnetic Source Reconstruction

Neuromagnetic inverse solutions involve determining the distribution of electrical activity within the brain that contributes to the magnetic field recorded by sensors outside of the head. Such inverse solutions are non-unique (i.e., there are many possible combinations of sources that may produce a given pattern at the sensors) and often highly underdetermined (i.e., there may be many more sources than sensors). Simple dipole fitting or scanning methods are limited by the fact that the existence of unknown sources can result in erroneous solutions due to the superposition of signals across the sensor array. General linear inverse methods, such as those based on the minimum-norm solution [36], are thus preferred, as they can model distributed activity without assuming a fixed number of active sources. However, these methods must account for an arbitrary number of distributed sources by incorporating the magnetic field patterns (*lead fields*) of all possible sources in the solution. This requires minimizing the dimensions of the resulting inverse operator, usually by restricting solutions to the cortical surface and using regularization techniques to stabilize the solutions. An alternative source reconstruction approach involves a signal processing technique known as beamforming – a method introduced in the 1950s in the field of radio communications using multiple antenna arrays. These algorithms were developed to optimally reduce interference (cross-talk) between signals arriving from multiple directions at the antenna array. Signal processing based on beamforming has been adapted to the neuromagnetic inverse problem only in the last few years, as it relies on correlations across multiple detectors and is thus suited to modern MEG systems that consist of arrays of 100 or more sensors.

Various types of beamforming algorithms have been recently adapted to neuromagnetic measurements [34, 77, 87], the most common of which is the minimum-variance beamformer [95]. Beamforming methods are also described as *spatial filters*, since source activity at any brain location is derived by passing the measured data through a set of coefficients or weights that suppress signals coming from other sources. Compared to model-based linear inverse methods, the beamformer approach is a data-based or adaptive inverse solution, where the forward model for all possible sources is replaced by the estimated data covariance. Thus beamforming methods work best when the data (i.e., source) covariance is well estimated by including a sufficient amount of sample data. Beamformer solutions also have the added advantage of inherently attenuating artifacts, even those of non-brain origin (e.g., environmental noise, eye movements) as these signals are included in the data covariance, whereas minimum-norm-based solutions only model brain sources, and thus require relatively artifact-free data. In addition, since beamformer solutions are constructed volumetrically throughout the brain they are readily amenable to averaging across groups of subjects using spatial normalization techniques [12, 88].

3.2 Imaging Cortical Oscillations Using the SAM Beamformer

A beamforming technique known as *synthetic aperture magnetometry* (SAM) was introduced by Robinson and colleagues [77] that derived a single optimal current orientation at each voxel, based on the assumption that MEG signals are dominated by intracellular pyramidal cell currents flowing perpendicular to the cortical surface. This method is computationally simpler, and also produces slightly higher spatial resolution than multidimensional or vector beamformers [86] that model current flow in multiple orthogonal directions. Most importantly, however, the SAM beamformer was designed to work with single trial data and provided a single time series of source activity at each brain location, making the method ideal for time–frequency analysis of source activity. As a result, this method has been used primarily as a frequency-based imaging technique to measure induced changes in oscillatory neural activity. This is achieved by integrating the output from a lattice of SAM spatial filters constructed throughout the brain volume within specific frequency bands and measuring the changes in source power for selected time windows, relative to a pre-stimulus or pre-movement baseline. This approach has been successfully used to localize induced cortical oscillatory activity associated with visual [28], auditory [38] and somatosensory [33, 85] stimulation as well as oscillatory changes accompanying self-paced movements [19, 92].

In a recent study [42] we used the SAM algorithm to localize changes in the μ and β frequency bands during self-paced finger movements. As shown in Fig. 2, using this method one can construct robust images of frequency-specific source activity in the sensorimotor cortex, even within single subjects. When averaging images across subjects, we found that suppression of μ -band (8–15 Hz) activity preceded movement onset and was localized mainly to regions of the postcentral gyrus. In contrast, power in the β -band (15–30 Hz) also decreased prior to movement onset but showed a marked sudden increase beginning approximately 300 ms after termination of EMG activity in the active muscle (first dorsal interosseus) and lasting for over 500 ms. This *post-movement β rebound* (PMBR) localizes to bilateral regions of the precentral gyrus, with larger amplitude changes in the contralateral hemisphere, confirming previous reports that PMBR is generated by neural populations in the primary motor cortex [81]. Interestingly, PMBR is coincident with a period of decreased cortical excitability in MI as shown by transcranial magnetic stimulation [13]. We also found that PMBR was time-locked to the cessation, rather than the onset of movement [42] and other MEG studies have shown similar patterns of β rebound in motor cortex following median nerve [80] and tactile stimulation [33]. Thus, augmentation of β -band oscillatory activity appears to constitute an *off-response* to the termination of sustained afferent or refferent input to the primary motor cortex.

Beamforming methods have also been adapted to model coherence between different brain sources or even corticomuscular coherence. A frequency domain beamforming method termed *dynamic imaging of coherence sources* developed

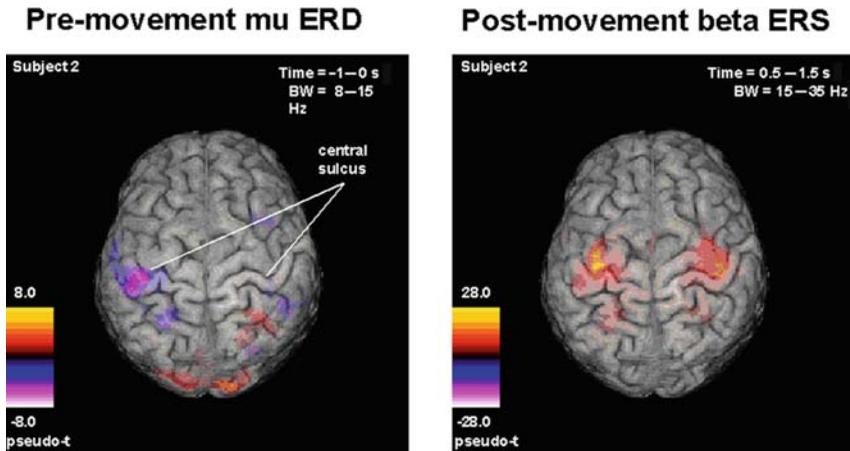


Fig. 2. Localization of induced cortical oscillations during a voluntary right finger movement in a single subject using the SAM beamformer source reconstruction algorithm. Differential source power (pseudo-t) decreases (blue) and increases (red) are superimposed on the subject’s MRI. Left: Decreased power in the μ (8–15 Hz) frequency band during the pre-movement period is seen in the contralateral post-central gyrus and parietal areas (left). Right: Increases in the β (15–30 Hz) band begin approximately 0.5 s after movement onset and are localized to bilaterally to the primary motor cortex

by Gross and colleagues [34] has been recently used to image task-dependent oscillations during continuous motor tasks [35] localizing the generators of corticomuscular coherence in the β and γ frequency bands to regions of the primary motor cortex and supplementary motor area. This method has also been used to image coherence between multiple cortical regions during Parkinsonian tremor [94].

3.3 Spatiotemporal Imaging of Movement-Related Brain Activity

Beamformer localization methods based on coherence or band-limited power differences have provided a powerful new method for the localization of oscillatory brain activity, however, this approach sacrifices temporal resolution by integrating power over relatively long (e.g., 200 ms) time windows and is therefore not applicable to imaging transient motor and movement-evoked fields. We recently introduced the use of an “event-related” beamformer (ERB) algorithm adapted for the localization of instantaneous or evoked brain responses [17]. Similar to the SAM method, a beamformer filter is derived from the single trial MEG data with a single optimal current direction at each voxel. The output of the spatial filter for each voxel is then averaged with respect to stimulus or movement onset to measure the event-related source activity. Three-dimensional ERB images are constructed by mapping the spatial distribution

of the averaged response at selected latencies, to produce millisecond-by-millisecond three-dimensional images of brain activity.

We used the ERB algorithm to localize the generators of movement-related fields in a study of self-paced movements (button press with right or left index finger) in eight right-handed adults. Selected time frames from the resulting spatiotemporal ‘movie’ of source activity are shown in Fig. 3 for one subject (left-sided movements) revealing a rapid sequential activation of regions of the contralateral precentral and postcentral cortices. Three peaks of maximal source activity are observed, the first occurring in the hand region of the precentral gyrus, reaching peak magnitude at the latency of the MF (-50 ms before button press). This is followed by a brief activation of the postcentral gyrus at around 40 ms and a second activation of the precentral gyrus at approximately 140 ms, corresponding to the latencies of the MEFI and MEFII,

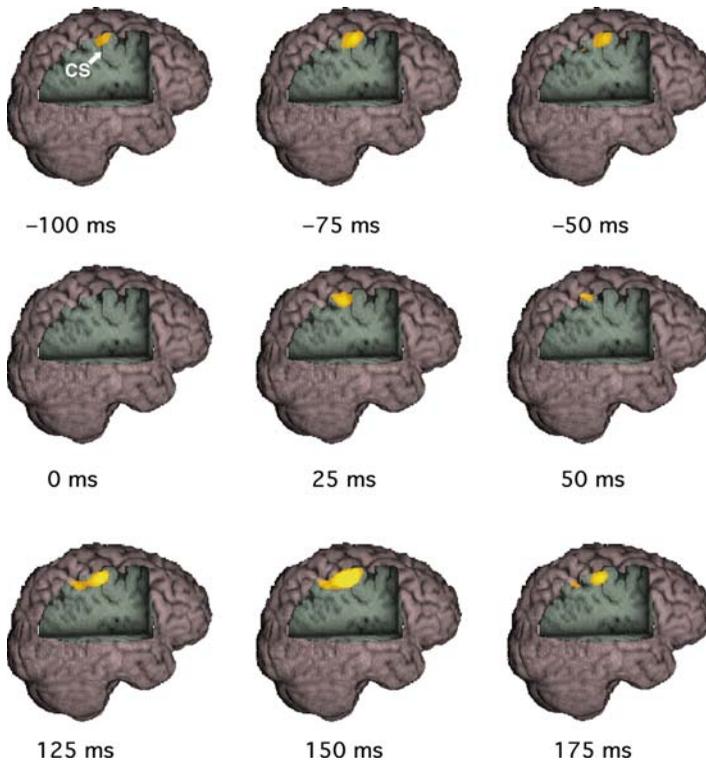


Fig. 3. Snapshots from a spatiotemporal “movie” of activity in the contralateral sensorimotor cortex of a subject performing self-paced movements of their left index finger. Images of instantaneous source power were computed using the event-related beamformer algorithm. Latencies are relative to the time of the button press, and show sequential activation of the pre- and postcentral gyrus during movement onset. The central sulcus (CS) is indicated by the white arrow

respectively. This sequence was observed for both left and right finger movements across subjects, and demonstrated the ability of the ERB algorithm to image movement-related brain activity with sufficient spatial and temporal resolution to resolve multiple generators within regions of the sensorimotor cortex only several millimeters apart.

We proposed a model of the putative generators of the MF, MEFI and MEFII [17] based on a sequential activation of MI and SI around the period of movement onset, as revealed by the event-related beamformer analysis. As shown in Fig. 4, this involves an initial activation of an anterior portion of the precentral gyrus that gives rise to the motor field (MF). The involvement of both the anterior bank of the central sulcus and the crown of the precentral gyrus may account for the somewhat variable amplitude of the MF (since MEG is less sensitive to radially oriented currents) as has been suggested in EEG modeling studies [63]. This also implies activation of neurons in Brodmann's area 6, rather than the somatotopically organized corticospinal output from area 4. This is followed by the MEFI component occurring about 100 ms later, representing a brief and highly time-locked activation of the postcentral gyrus due to reafferent feedback, involving both proprioceptive and tactile input to areas 3a and 3b, respectively. Finally, during the MEFII, activity shifts back to regions of the precentral gyrus. This activity was observed to be typically greater in strength, and slightly inferior in location to MF activity, suggesting the activation of a functionally different region of MI.

Prior to these new findings, the generator of the MEFII component was unknown, and assumed to be primarily sensory in nature since it occurs shortly after movement onset. However, these new results suggest that the MEFII reflects activity of neural populations in MI, possibly related to ongoing motor control such as onset of the antagonist burst (braking function)

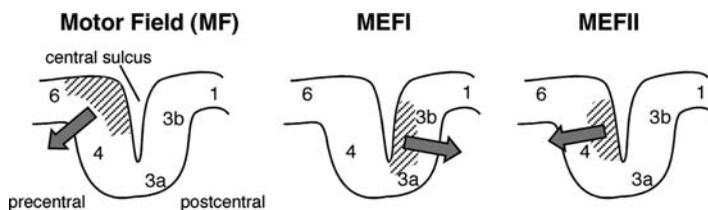


Fig. 4. A model of the generators of movement-related magnetic fields during voluntary finger movement. The pre-movement motor field (MF) reaches maximal amplitude at the time of movement onset and reflects activation of anterior portions of primary motor cortex in the anterior bank of the central sulcus and/or the crown of the precentral gyrus (shaded area). The movement-evoked field I (MEFI) is generated by activity in the posterior wall of the central sulcus due to feedback to regions of SI in the postcentral gyrus. The MEFII appears as a second activation of the precentral gyrus, slightly posterior and inferior to the location of the MF. Approximate location of Brodmann areas are shown relative to the central sulcus. Arrows indicate the direction of net intracellular current flow. Modified from [17]

or proprioceptive feedback to MI from the periphery via other cortical areas [57]. Interestingly, TMS studies have shown that latency of the MEFII corresponds to a transient period of increased excitability of motor cortex [13]. We also found that MEFII latency was remarkably consistent across subjects who showed variable patterns of EMG activity suggesting that the MEFII reflects neural activity in MI involved in the feed-forward control of the movement once it has been initiated [82] and is likely independent of movement duration or the precise timing of sensory feedback.

3.4 Ipsilateral Motor Fields

In addition to the robust source activations in the contralateral sensorimotor area during movement onset, significant activity was also observed in the ipsilateral precentral gyrus during both right and left finger movements in almost all subjects. Figure 5 shows MF activity superimposed on the MRI in one subject, demonstrating bilateral activation in the hand region of the precentral gyrus for both right and left index finger movements. The averaged time course of source activity at these locations is shown below. Bilateral MI activity can be seen beginning as early as 1 s prior to movement that returns to baseline shortly after movement onset. A sharp deflection corresponding to the MEFI just after movement onset is seen only in the contralateral MI source waveform (due to pick-up of source activity in the adjacent postcentral gyrus). These results provide further evidence that movement-related brain activity preceding voluntary movements involves very early activation of the primary

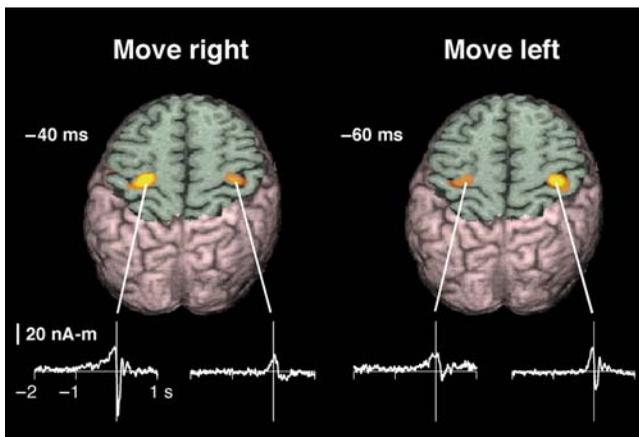


Fig. 5. Bilateral activation of the primary motor cortex during unilateral movements. Averaged source activity at the peak latencies of the motor field (MF) is shown for a subject performing right and left index finger movements. Time traces show the averaged output of the spatial filter in units of source strength (nanoAmpere-meters) at the location of the MF source. Modified from [17]

motor cortex of both hemispheres. In the example shown in Fig. 5, one can also observe an earlier onset of the pre-movement activity in the left MI in comparison to the right MI for both contralateral and ipsilateral movements. Interestingly, this earlier onset of the motor field in the right hemisphere motor cortex, independent of the side of movement, was consistent across the group of subjects. This may be related to handedness (all subjects were right handed) or may reflect a left hemisphere specialization for movement preparation.

3.5 Localization of Non-primary Motor Areas Using MEG

Neuroimaging studies of voluntary movement tasks using functional magnetic resonance imaging (fMRI) or positron emission tomography (PET) typically show activation of multiple secondary motor areas, including premotor areas of the frontal lobes thought to be critical in the initiation of movements [32, 41]. In addition, EEG studies have successfully modeled activation of the supplementary motor area (SMA) during the pre-movement period [3, 5]. MEG studies to date have only reported weak activation of the frontal midline [27] presumably due to cancellation of tangential currents in the opposing hemispheres [21, 56]. However, in the above study we were able to detect source activity in both left and right dorsal premotor regions and parietal cortex, as well as weak activation in the SMA when averaging ERB source images across subjects [17]. This suggests that MEG combined with beamformer source reconstruction methods can be used to localize activity in non-primary motor areas not previously reported by MEG studies of voluntary movements.

4 Theoretical Considerations

4.1 What is the Significance of Ipsilateral MI Activity?

The neural sources contributing to movement-related magnetic fields have been debated in the literature, particularly with respect to the role of the ipsilateral motor cortex. Based on our initial observations of ipsilateral MEG activity during unilateral movement, we speculated that this was evidence of an intrinsically bilateral organization of movement control within the motor system, demonstrated by the occasional presence of associated or mirror movements that must be somehow suppressed during precise independent and unilateral movements of the digits [16, 21]. Evidence of the existence of inhibitory transcallosal pathways between the primary motor cortices has been provided by a number of transcranial magnetic stimulation (TMS) studies, implying the need for inhibitory control over the ipsilateral motor cortex during movement [30, 48, 66]. While some fMRI studies have reported ipsilateral activation of the sensorimotor cortex during motor tasks [47], other studies have shown only weak or inconsistent activation of the ipsilateral precentral

gyrus for simple movements [1], with dependence on complexity of the motor task [68] or handedness [48, 59]. Interestingly, fMRI studies have also reported *decreased* BOLD responses in MI during ipsilateral movements that appear to reflect neuronal deactivation [2, 89]. Based on their observation of BOLD co-activation of homologous regions of MI, Stippich and colleagues [90] suggested that unilateral movements were accompanied by a “global” activation of MI prior to movement, with an increasing ratio of excitation to inhibition in the area of MI contralateral to the generated movement.

MEG measures of pre-movement brain activity, taken together with results from fMRI and TMS studies, support the hypothesis that the ipsilateral motor cortex is actively inhibited during unilateral movements, most likely through transcallosal excitatory projections from the contralateral motor cortex onto local inhibitory interneurons [68, 89]. This mechanism alone would predict a net decrease or inhibitory pattern of neural activity in the ipsilateral motor cortex during movement; however, MEG source analysis shows that pre-movement activity in MI is similar in both location and direction of intracellular current flow for both ipsilateral and contralateral movements – indeed, pre-movement field patterns during non-dominant finger movements may be almost indistinguishable from those for bilateral movements [51]. This suggests that during the preparation of both bilateral and unilateral finger movements MI receives bilateral input from premotor brain structures (e.g., supplementary motor areas and dorsal premotor areas). During unilateral movements, MI of the non-moving hand also receives inhibitory input via transcallosal projections from the contralateral MI, presumably to suppress the occurrence of mirror movements, resulting in reduction of activity in the ipsilateral MI. TMS studies have shown that this contra- to ipsilateral MI inhibition is asymmetric [65] with stronger inhibitory connections from the dominant to non-dominant hemisphere. This would predict greater reduction of ipsilateral MI activity for movements of the dominant hand and is consistent with our observation of greater asymmetry of the MF for dominant hand movements [51, 93]. Recently it has been proposed that this interhemispheric inhibition may even play a role in motor deficits and subsequent recovery in unilateral stroke due to abnormal inhibition of the lesioned primary motor cortex by the intact (contralesional) motor cortex [62].

Bilateral preparation of unilateral movements may provide a mechanism by which the motor system can rapidly switch between different outputs during skilled motor tasks. Alternatively, this may reflect the ontogeny of the human motor system and the transition from bilateral control of the proximal musculature to the relative independent control of movements of the distal musculature [58]. TMS studies have shown that inhibitory transcallosal pathways between motor areas develop with age as demonstrated by the presence of ipsilateral motor evoked potentials prior to the age of 10 that are presumably suppressed in adults once these inhibitory pathways are fully developed [67]. This may underlie similar age-related changes in the development of fine motor skills, along with the disappearance of mirror movements at around the

same age [61]. ERP studies [24] have shown changes in the topography and polarity of the readiness potential with age, with early pre-movement activity emerging after the age of 6 years as positive potential, and developing into the negative slow shift observed in adults only after 9 or 10 years of age [23]. Although MEG measurements in younger children, particularly during voluntary movement tasks, are technically challenging, studies of motor cortex function during development may provide an ideal avenue for the investigation of these issues.

4.2 What is the Functional Role of the Sensorimotor Cortex?

The activation of the sensorimotor cortex in the absence of overt movement raises questions regarding the neuronal populations involved in the generation of the motor field and their functional role in the production of movement. The presence of activity in both the contralateral and ipsilateral primary motor cortex during the pre-movement period, prior to any detectable increases in EMG activity, precludes the activation of direct monosynaptic excitatory inputs to spinal motoneurons, even though these *corticomotoneuronal* pathways are well developed in humans and thought to play a relatively important role in the independent control of the digits [58]. However, much of the output of the descending corticospinal tract converges indirectly on spinal motoneurons through polysynaptic pathways. Thus, although the primary motor cortex has a direct role in the efferent control of movement, it exerts both excitatory and inhibitory effects on the segmental spinal motoneurons via both direct and indirect connections, indicative of a complex and diverse role in movement control [58]. This is supported by the observation of activity of the primary motor cortex during a variety of tasks that appear to engage the sensorimotor system but do not involve motor output, such as motor imagery [83] or action observation [37]. Similarly, we observed highly similar patterns of oscillatory activity in the primary motor cortex during both tactile stimulation of the index finger and while the subject observed another individual's finger being stimulated [20]. This suggests a close interrelationship between neuronal networks in the same cortical area activated by both somatosensory stimulation and visual monitoring of events in the environment associated with either sensory input or movement. Thus, it is clear that activity of neural populations in MI can be modulated in a variety of situations that do not necessarily involve movement production or control, and reflect their role in more general aspects of sensorimotor coordination, or even motor learning [75].

Interestingly, cortical oscillations preceding and following unilateral voluntary movements are also bilaterally distributed. This might at first suggest that they simply mirror the activation of the sensorimotor cortex as described above for movement-related fields. However, the transition from desynchrony to synchrony does not appear to correspond to onset or offset of electromyographic activity in the involved muscles, or specific components of movement-related fields. This is demonstrated in Fig. 6, which shows the

relationship between induced oscillatory changes (spectral power integrated over single trials) and event-related activity (source activity averaged over trials) in the contralateral precentral gyrus during a self-paced button press. The results, averaged over a group of eight subjects, show the very different time course of oscillatory activity in comparison to the movement-evoked field activity in the same cortical area, with onset of suppression in the μ and β frequency bands appearing more than 1 s prior to movement and continuing after EMG activity has terminated. In contrast, the averaged event-related responses show highly time-locked changes immediately around the period of the button press with no concomitant change in oscillatory power in these higher frequency bands, but rather appears as a transient increase in power at lower (<10 Hz) frequencies. Fetz and colleagues [31] also noted the lack of a direct correspondence between oscillatory activity in the sensorimotor cortex and EMG activity during intracellular recordings in awake monkeys and suggested that oscillatory activity may be an indication of global facilitation of synaptic interactions related to changes in levels of attention or arousal.

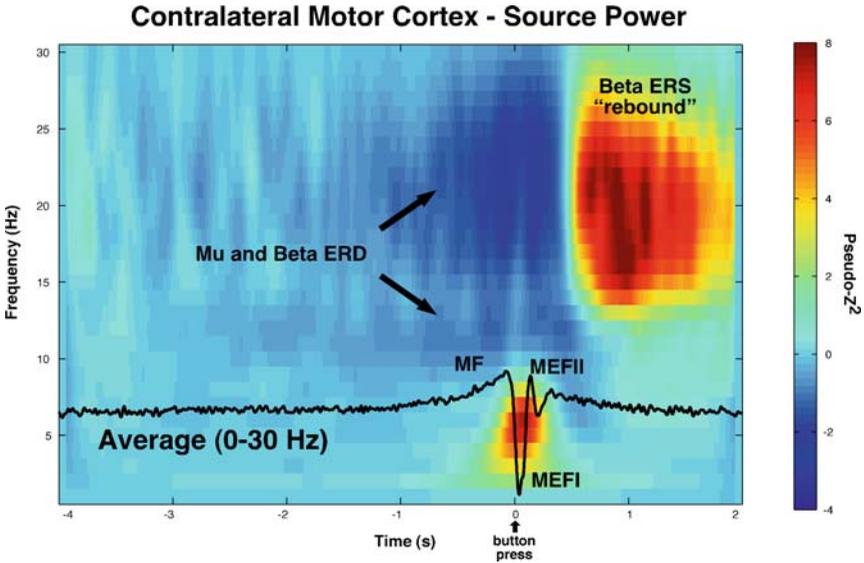


Fig. 6. Comparison of oscillatory and event-related activities in the contralateral motor cortex for a right index finger movement, averaged over eight subjects. Increases (red) and decreases (blue) in source power relative to pre-movement baseline (-4 to -3 s) are shown as a time–frequency plot using a Morlet wavelet transform of the beamformer output, integrated over 80 movements. The same data filtered between 0 and 30 Hz and averaged over all trials is superimposed on the same plot (black trace). MF = motor field, MEFI and MEFII = movement-evoked field I and II. ERD = event-related desynchronization, ERS = event-related synchronization

Taken together, these results suggest that induced rhythms and motor-evoked fields reflect the activation of different functional systems.

The fact that pre-movement μ -band activity arises from regions of the postcentral gyrus is also of interest, indicating that the primary somatosensory cortex (SI) is active during movement preparation in the absence of sensory input. However, a significant portion of the corticospinal tract originates from regions of the postcentral gyrus [78]. Moreover, these neurons project largely to the dorsal horn of the spinal cord and are thought to be involved in the descending control of sensory inputs or even ‘gating’ of proprioceptive input during movement [58]. Riddle and Baker [76] recently emphasized the role of sensorimotor integration in the generation of motor cortex oscillations and speculated that they may reflect a type of *recalibration* or interrogation of the ‘system-state’ after each movement. This favors the sensorimotor sampling theory of cortical oscillations [60] and the idea that oscillatory activity in the sensorimotor cortex reflects the monitoring of various parameters of the motor system (hand position, muscle length), even prior to feed-forward control of simple ballistic movements. In addition, in many studies of self-paced movements, including our own MEG experiments, movement tasks often require orientation of the hand to a button or similar triggering device and likely involves, to some degree, the integration of haptic information needed to perform the movement accurately from trial to trial.

Converging evidence from MEG studies of voluntary movement and other imaging and electrophysiological techniques points to the role of the sensorimotor cortex as a system for sensorimotor integration. However, this brain region has also evolved in humans to exert fast, feed-forward control of fractionated movements of the digits, as reflected by greater direct connectivity to the segmental neuronal pool. For example, the severe motor deficits resulting from damage to the primary motor cortex in humans in comparison to modest deficits in other species including non-human primates is thought to be due, in part, to increased direct monosynaptic terminations onto motoneurons in the ventral horn of the spinal cord, which also provides a possible mechanism for more dexterous control of the digits [58]. Superimposed on this lower level of input–output control of movement, however, are oscillatory changes in the same cortical areas that appear to have a more variable and indirect relationship to specific motor parameters. In their recent review, Bressler and Kelso [7] emphasized the need for flexibility (*metastability*) within distributed cortical networks that would allow rapid transitions from one functional coupling between networks to another, thereby allowing information to be combined across different neural networks in real time. It has been proposed that synchronization between cortical networks may underlie such large-scale integration in the brain [96]. Thus, the complex patterns of cortical oscillations that we observe during self-paced voluntary movements likely reflect the recruitment of additional cortical and subcortical networks involved in integration of interoceptive and exteroceptive information needed to rapidly adapt our movements to changes in the environment. The apparent tendency of these

systems to become engaged, even when performing relatively simple self-paced finger movements, perhaps demonstrates the self-organizing nature of the human motor system in which the control of individual movements is embedded within larger scale neural networks that govern the cognitive control of our actions, plans and goals.

5 Conclusions

MEG studies of voluntary movement have contributed greatly to our knowledge of the function of cortical motor areas in humans. The results from studies carried out to date, taken together with results from animal studies and other imaging modalities, support the concept of distributed activation of the sensorimotor cortex during the preparation and performance of skilled voluntary finger movements. This activity reflects not only preparation for, and the subsequent efferent control of movement, but also the integration of sensory inputs needed to adjust parameters within the context of ongoing behavior, as well as the processing of proprioceptive feedback that may be important in motor learning. As shown in this review, the introduction of MEG instruments capable of recording magnetic fields simultaneously from many brain regions using large arrays of sensors covering the head, combined with recent advances in neuromagnetic source reconstruction techniques offers the possibility of using MEG to study both evoked and induced cortical activity during voluntary movement tasks with exquisite spatial and temporal resolution. These techniques can thus provide unique insights into the spatiotemporal organization of brain activity controlling the preparation and performance of both volitional movements and the dynamics of sensorimotor coordination.

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References

1. Alkadhi H, Crelier GR, Boendermaker SH, Hepp-Reymond MC, Kollias SS (2002) Somatotopy in the ipsilateral primary motor cortex. *Neuroreport* 13:2065–2070
2. Allison JD, Meador KJ, Loring DW, Figueroa RE, Wright JC (2000) Functional MRI cerebral activation and deactivation during finger movement. *Neurology* 54:135–142

3. Babiloni F, Carducci F, Cincotti F, Del Gratta C, Pizzella V, Romani GL, Rossini PM, Tecchio F, Babiloni C (2001) Linear inverse source estimate of combined EEG and MEG data related to voluntary movements. *Hum Brain Mapp* 14:197–209
4. Baker SN, Kilner JM, Pinches EM, and Lemon RN (1999) The role of synchrony and oscillations in the motor output. *Exp Brain Res* 128:109–117
5. Ball T, Schreiber A, Feige B, Wagner M, Lucking CH, Kristeva-Feige R (1999) The role of higher-order motor areas in voluntary movement as revealed by high-resolution EEG and fMRI. *Neuroimage* 10:682–694
6. Bioulac B, Lamarre Y (1979) Activity of postcentral cortical neurons of the monkey during conditioned movements of a deafferented limb. *Brain Res* 172:427–437
7. Bressler SL, Kelso JA (2001) Cortical coordination dynamics and cognition. *Trends Cogn Sci* 5:26–36
8. Brovelli A, Lachaux JP, Kahane P, Boussaoud D (2005) High gamma frequency oscillatory activity dissociates attention from intention in the human premotor cortex. *Neuroimage* 28:154–164
9. Brown P (2000) Cortical drives to human muscle: the Piper and related rhythms. *Prog Neurobiol* 60:97–108
10. Brown P, Salenius S, Rothwell JC, Hari R (1998) Cortical correlate of the Piper rhythm in humans. *J Neurophysiol* 80:2911–2917
11. Cassim F, Monica C, Szurhaj W, Bourriez JL, Defebvre L, Derambure P, Guieu J-D (2001) Does post-movement beta synchronization reflect an idling motor cortex? *NeuroReport* 17:3859–3863
12. Chau W, McIntosh AR, Robinson SE, Schulz M, Pantev C (2004) Improving permutation test power for group analysis of spatially filtered MEG data. *Neuroimage* 23:983–996
13. Chen R, Hallett M (1999) The time course of changes in motor cortex excitability associated with voluntary movement. *Can J Neurol Sci* 26:163–169
14. Chen R, Yaseen Z, Cohen LG, Hallett M (1998) Time course of corticospinal excitability in reaction time and self-paced movements. *Ann Neurol* 44:317–325
15. Chen Y, Ding M, Kelso JAS (2003) Task-related power and coherence changes in neuromagnetic activity during visuomotor coordination. *Exp Brain Res* 148:105–116
16. Cheyne D (1988) Magnetic and electric field measurements of brain activity preceding voluntary movements: implications for supplementary motor area function. PhD Thesis: Simon Fraser University: Burnaby, BC, Canada.
17. Cheyne D, Bakhtazad L, Gaetz W (2006) Spatiotemporal mapping of cortical activity accompanying voluntary movements using an event-related beamforming approach. *Hum Brain Mapp* 27:213–229
18. Cheyne D, Endo H, Takeda T, Weinberg H (1997) Sensory feedback contributes to early movement-evoked fields during voluntary finger movements in humans. *Brain Res* 771:196–202
19. Cheyne D, Gaetz W (2003) Neuromagnetic localization of oscillatory brain activity associated with voluntary finger and toe movements. *NeuroImage* 19 (Suppl):1061
20. Cheyne D, Gaetz W, Garnero L, Lachaux JP, Ducorps A, Schwartz D, Varela FJ (2003) Neuromagnetic imaging of cortical oscillations accompanying tactile stimulation. *Brain Res Cogn Brain Res* 17:599–611

21. Cheyne D, Weinberg H (1989) Neuromagnetic fields accompanying unilateral finger movements: pre-movement and movement-evoked fields. *Exp Brain Res* 78:604–612
22. Cheyne D, Weinberg H, Gaetz W, Jantzen KJ (1995) Motor cortex activity and predicting side of movement: neural network and dipole analysis of pre-movement magnetic fields. *Neurosci Lett* 188:81–84
23. Chiarenza GA, Villa M, Vasile G (1995) Developmental aspects of Bereitschaftspotential in children during goal-directed behaviour. *Int J Psychophysiol* 19:149–176
24. Chisholm RC, Karrer R (1988) Movement-related potentials and control of associated movements. *Int J Neurosci* 42:131–148
25. Conway BA, Halliday DM, Farmer SF, Shahani U, Maas P, Weir AI, Rosenberg JR (1995) Synchronization between motor cortex and spinal motoneuronal pool during the performance of a maintained motor task in man. *J Physiol* 489 (Pt 3):917–924
26. Deecke L, Weinberg H, Brickett P (1982) Magnetic fields of the human brain accompanying voluntary movement: Bereitschaftsmagnetfeld. *Exp Brain Res* 48:144–148
27. Erdler M, Beisteiner R, Mayer D, Kaindl T, Edward V, Windischberger C, Lindinger G, Deecke L (2000) Supplementary motor area activation preceding voluntary movement is detectable with a whole-scalp magnetoencephalography system. *Neuroimage* 11:697–707
28. Fawcett IP, Barnes GR, Hillebrand A, Singh KD (2004) The temporal frequency tuning of human visual cortex investigated using synthetic aperture magnetometry. *Neuroimage* 21:1542–1553
29. Feige B, Aertsen A, Kristeva-Feige R (2000) Dynamic synchronization between multiple cortical motor areas and muscle activity in phasic voluntary movements. *J Neurophysiol* 84:2622–2629
30. Ferbert A, Priori A, Rothwell JC, Day BL, Colebatch JG, Marsden CD (1992) Interhemispheric inhibition of the human motor cortex. *J Physiol* 453:525–546
31. Fetz EE, Chen D, Murthy VN, Matsumura M (2000) Synaptic interactions mediating synchrony and oscillations in primate sensorimotor cortex. *J Physiol Paris* 94:323–331
32. Fink GR, Frackowiak RS, Pietrzyk U, Passingham RE (1997) Multiple nonprimary motor areas in the human cortex. *J Neurophysiol* 77:2164–2174
33. Gaetz W, Cheyne D (2006) Localization of sensorimotor cortical rhythms induced by tactile stimulation using spatially filtered MEG. *Neuroimage* 30: 899–908
34. Gross J, Kujala J, Hamalainen M, Timmermann L, Schnitzler A, Salmelin R (2001) Dynamic imaging of coherent sources: studying neural interactions in the human brain. *Proc Natl Acad Sci USA* 98:694–699
35. Gross J, Pollok B, Dirks M, Timmermann L, Butz M, Schnitzler A (2005) Task-dependent oscillations during unimanual and bimanual movements in the human primary motor cortex and SMA studied with magnetoencephalography. *Neuroimage* 26:91–98
36. Hamalainen MS, Ilmoniemi RJ (1998) Interpreting measured magnetic fields of the brain: Estimates of current distribution. Report TKK-F-A559. Helsinki University of Technology: Espoo, Finland

37. Hari R, Forss N, Avikainen S, Kirveskari E, Salenius S, Rizzolatti G (1998) Activation of human primary motor cortex during action observation: a neuro-magnetic study. *Proc Natl Acad Sci USA* 95:15061–15065
38. Herdman AT, Wollbrink A, Chau W, Ishii R, Pantev C (2004) Localization of transient and steady-state auditory evoked responses using synthetic aperture magnetometry. *Brain Cogn* 54:149–151
39. Holroyd T, Endo H, Kelso JAS, Takeda T (1999) Dynamics of the MEG recorded during rhythmic index-finger extension and flexion, in *Recent Advances in Biomagnetism: Proceedings of the 11th International Conference on Biomagnetism*, Yoshimoto T, Kotani M, Kuriki S, Nakasato N, and Karibe H, Editors. Tohoku University Press, pp. 446–449
40. Jensen O, Goel P, Kopell N, Pohja M, Hari R, Ermentrout B (2005) On the human sensorimotor-cortex beta rhythm: sources and modeling. *Neuroimage* 26:347–355
41. Joliot M, Papathanassiou D, Mellet E, Quinton O, Mazoyer N, Courtheoux P, Mazoyer B (1999) FMRI and PET of self-paced finger movement: comparison of intersubject stereotaxic averaged data. *Neuroimage* 10:430–447
42. Jurkiewicz MT, Gaetz WC, Bostan AC, Cheyne D (2006) Post-movement beta rebound is generated in motor cortex: evidence from neuromagnetic recordings. *Neuroimage* 32:1281–1289
43. Kelso JAS, Fuchs A, Lancaster R, Holroyd T, Cheyne D, Weinberg H (1998) Dynamic cortical activity in the human brain reveals motor equivalence. *Nature* 392:814–818
44. Kilner JM, Baker SN, Salenius S, Hari R, Lemon RN (2000) Human cortical muscle coherence is directly related to specific motor parameters. *J Neurosci* 20:8838–8845
45. Kilner JM, Baker SN, Salenius S, Jousmaki V, Hari R, Lemon RN (1999) Task-dependent modulation of 15–30 Hz coherence between rectified EMGs from human hand and forearm muscles. *J Physiol* 516(Pt 2):559–570
46. Kilner JM, Fisher RJ, Lemon RN (2004) Coupling of oscillatory activity between muscles is strikingly reduced in a deafferented subject compared with normal controls. *J Neurophysiol* 92:790–796
47. Kim SG, Ashe J, Georgopoulos AP, Merkle H, Ellermann JM, Menon RS, Ogawa S, Ugurbil K (1993) Functional imaging of human motor cortex at high magnetic field. *J Neurophysiol* 69:297–302
48. Kobayashi M, Hutchinson S, Schlaug G, Pascual-Leone A (2003) Ipsilateral motor cortex activation on functional magnetic resonance imaging during unilateral hand movements is related to interhemispheric interactions. *Neuroimage* 20:2259–2270
49. Kornhuber HH, Deecke L (1965) Changes in the brain potential in voluntary movements and passive movements in Man: Readiness Potential and Reafferent Potentials. *Pflugers Arch Gesamte Physiol Menschen Tiere* 284:1–17
50. Kristeva R, Chakarov V, Wagner M, Schulte-Monting J, Hepp-Reymond MC (2006) Is the movement-evoked potential mandatory for movement execution? A high-resolution EEG study in a deafferented patient. *Neuroimage* 31:677–685
51. Kristeva R, Cheyne D, Deecke L (1991) Neuromagnetic fields accompanying unilateral and bilateral voluntary movements: topography and analysis of cortical sources. *Electroencephalogr Clin Neurophysiol* 81:284–298

52. Kristeva-Feige R, Fritsch C, Timmer J, Lucking CH (2002) Effects of attention and precision of exerted force on beta range EEG-EMG synchronization during a maintained motor contraction task. *Clinical Neurophysiology* 113:124–131
53. Kristeva-Feige R, Rossi S, Pizzella V, Sabato A, Tecchio F, Feige B, Romani GL, Edrich J, Rossini PM (1996) Changes in movement-related brain activity during transient deafferentation: a neuromagnetic study. *Brain Res* 714:201–208
54. Kristeva-Feige R, Rossi S, Pizzella V, Tecchio F, Romani GL, Erne S, Edrich J, Orlacchio A, Rossini PM (1995) Neuromagnetic fields of the brain evoked by voluntary movement and electrical stimulation of the index finger. *Brain Res* 682:22–28
55. Kristeva-Feige R, Walter H, Lutkenhoner B, Hampson S, Ross B, Knorr U, Steinmetz H, Cheyne D (1994) A neuromagnetic study of the functional organization of the sensorimotor cortex. *Eur J Neurosci* 6:632–639
56. Lang W, Cheyne D, Kristeva R, Beisteiner R, Lindinger G, Deecke L (1991) Three-dimensional localization of SMA activity preceding voluntary movement. A study of electric and magnetic fields in a patient with infarction of the right supplementary motor area. *Exp Brain Res* 87:688–695
57. Lemon RN (1979) Short-latency peripheral inputs to the motor cortex in conscious monkeys. *Brain Res* 161:150–155
58. Lemon RN, Griffiths J (2005) Comparing the function of the corticospinal system in different species: organizational differences for motor specialization. *Muscle Nerve* 32:261–279
59. Li A, Yetkin FZ, Cox R, Haughton VM (1996) Ipsilateral hemisphere activation during motor and sensory tasks. *AJNR Am J Neuroradiol* 17:651–655
60. MacKay WA (1997) Synchronized neuronal oscillations and their role in motor processes. *Trends Cogn Sci* 1:176–181
61. Mayston MJ, Harrison LM, Stephens JA (1999) A neurophysiological study of mirror movements in adults and children. *Ann Neurol* 45:583–594
62. Murase N, Duque J, Mazzocchio R, Cohen LG (2004) Influence of interhemispheric interactions on motor function in chronic stroke. *Ann Neurol* 55:400–409
63. Nagamine T, Kajola M, Salmelin R, Shibasaki H, Hari R (1996) Movement-related slow cortical magnetic fields and changes of spontaneous MEG- and EEG-brain rhythms. *Electroencephalogr Clin Neurophysiol* 99:274–286
64. Neshige R, Luders H, Shibasaki H (1988) Recording of movement-related potentials from scalp and cortex in man. *Brain* 111(Pt 3):719–736
65. Netz J (1999) Asymmetry in transcallosal inhibition. *Electroencephalogr Clin Neurophysiol Suppl* 51:137–144
66. Netz J, Ziemann U, Homberg V (1995) Hemispheric asymmetry of transcallosal inhibition in man. *Exp Brain Res* 104:527–533
67. Nezu A, Kimura S, Uehara S, Kobayashi T, Tanaka M, Saito K (1997) Magnetic stimulation of motor cortex in children: maturity of corticospinal pathway and problem of clinical application. *Brain Dev* 19:176–180
68. NirKKo AC, Ozdoba C, Redmond SM, Burki M, Schroth G, Hess CW, Wiesendanger M (2001) Different ipsilateral representations for distal and proximal movements in the sensorimotor cortex: activation and deactivation patterns. *Neuroimage* 13:825–835
69. Oishi M, Kameyama S, Fukuda M, Tsuchiya K, Kondo T (2004) Cortical activation in area 3b related to finger movement: an MEG study. *NeuroReport* 15:57–62

70. Onishi H, Soma T, Kameyama S, Oishi M, Fujimoto A, Oyama M, Furusawa AA, Kurokawa Y (2006) Cortical neuromagnetic activation accompanying two types of voluntary finger extension. *Brain Res* 1123:112–118
71. Pesaran B, Pezaris JS, Sahani M, Mitra PP, Andersen RA (2002) Temporal structure in neuronal activity during working memory in macaque parietal cortex. *Nat Neurosci* 5:805–811
72. Pfurtscheller G, Aranibar A (1977) Event-related cortical desynchronization detected by power measurements of scalp EEG. *Electroencephalogr Clin Neurophysiol* 42:817–826
73. Pfurtscheller G, Lopes da Silva FH (1999) Event-related EEG/MEG synchronization and desynchronization: basic principles. *Clin Neurophysiol* 110:1842–1857
74. Pfurtscheller G, Neuper C, Brunner C, da Silva FL (2005) Beta rebound after different types of motor imagery in man. *Neurosci Lett* 378:156–159
75. Richardson AG, Overduin SA, Valero-Cabre A, Padoa-Schioppa C, Pascual-Leone A, Bizzi E, Press DZ (2006) Disruption of primary motor cortex before learning impairs memory of movement dynamics. *J Neurosci* 26:12466–12470
76. Riddle CN, Baker SN (2006) Digit displacement, not object compliance, underlies task dependent modulations in human corticomuscular coherence. *Neuroimage* 33:618–627
77. Robinson SE, Vrba J (1999) Functional neuroimaging by synthetic aperture magnetometry, in *Recent Advances in Biomagnetism*, T. Y. Kotani M, Kuriki S, H. K, Nakasato N, Editors. Tohoku University Press, Sendai, pp. 302–305
78. Rothwell JC (1994) *Control of human voluntary movement*, 2nd edn. Chapman and Hall, London
79. Salenius S, Avikainen S, Kaakkola S, Hari R, Brown P (2002) Defective cortical drive to muscle in Parkinson's disease and its improvement with levodopa. *Brain* 125:491–500
80. Salenius S, Schnitzler A, Salmelin R, Jousmaki V, Hari R (1997) Modulation of human cortical rolandic rhythms during natural sensorimotor tasks. *Neuroimage* 5:221–228
81. Salmelin R, Hari R (1994) Spatiotemporal characteristics of sensorimotor neuromagnetic rhythms related to thumb movement. *Neuroscience* 60:537–550
82. Sanes JN, Jennings VA (1984) Centrally programmed patterns of muscle activity in voluntary motor behavior of humans. *Exp Brain Res* 54:23–32
83. Schnitzler A, Salenius S, Salmelin R, Jousmaki V, Hari R (1997) Involvement of primary motor cortex in motor imagery: a neuromagnetic study. *Neuroimage* 6:201–208
84. Schoffelen JM, Oostenveld R, Fries P (2005) Neuronal coherence as a mechanism of effective corticospinal interaction. *Science* 308:111–113
85. Schulz M, Chau W, Graham SJ, McIntosh AR, Ross B, Ishii R, Pantev C (2004) An integrative MEG-fMRI study of the primary somatosensory cortex using cross-modal correspondence analysis. *Neuroimage* 22:120–133
86. Sekihara K, Nagarajan SS, Poeppel D, Marantz A (2004) Asymptotic SNR of scalar and vector minimum-variance beamformers for neuromagnetic source reconstruction. *IEEE Trans Biomed Eng* 51:1726–1734
87. Sekihara K, Nagarajan SS, Poeppel D, Marantz A, Miyashita Y (2001) Reconstructing spatio-temporal activities of neural sources using an MEG vector beamformer technique. *IEEE Trans Biomed Eng* 48:760–771

88. Singh KD, Barnes GR, Hillebrand A (2003) Group imaging of task-related changes in cortical synchronisation using nonparametric permutation testing. *Neuroimage* 19:1589–1601
89. Stefanovic B, Warnking JM, Pike GB (2004) Hemodynamic and metabolic responses to neuronal inhibition. *Neuroimage* 22:771–778
90. Stippich C, Blatow M, Durst A, Dreyhaupt J, Sartor K (2006) Global activation of primary motor cortex during voluntary movements in man. *Neuroimage* 34: 1227–1237
91. Tallon-Baudry C, Bertrand O (1999) Oscillatory gamma activity in humans and its role in object representation. *Trends Cogn Sci* 3:151–162
92. Taniguchi M, Kato A, Fujita N, Hirata M, Tanaka H, Kihara T, Ninomiya H, Hirabuki N, Nakamura H, Robinson SE, Cheyne D, Yoshimine T (2000) Movement-related desynchronization of the cerebral cortex studied with spatially filtered magnetoencephalography. *NeuroImage* 12:298–306
93. Taniguchi M, Yoshimine T, Cheyne D, Kato A, Kihara T, Ninomiya H, Hirata M, Hirabuki N, Nakamura H, Hayakawa T (1998) Neuromagnetic fields preceding unilateral movements in dextrals and sinistrals. *NeuroReport* 9:1497–1502
94. Timmermann L, Gross J, Dirks M, Volkmann J, Freund HJ, Schnitzler A (2003) The cerebral oscillatory network of parkinsonian resting tremor. *Brain* 126: 199–212
95. Van Veen BD, van Drongelen W, Yuchtman M, Suzuki A (1997) Localization of brain electrical activity via linearly constrained minimum variance spatial filtering. *IEEE Transactions on Biomedical Engineering* 44:867–880
96. Varela F, Lachaux JP, Rodriguez E, and Martinerie J (2001) The brainweb: phase synchronization and large-scale integration. *Nat Rev Neurosci* 2:229–239