REVIEW ARTICLE

Rapidly induced changes in neuromagnetic fields following repetitive hand movements

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Sensory feedback plays a major role in movement execution and motor learning, particularly in motor rehabilitation. Whilst elaborating therapeutic strategies, it is of interest to visualize the effect of a therapeutic intervention at the moment of its application. We analyzed the effect of repeated execution of a simple extension and flexion movement of the wrist on the sensorimotor cortex of seven healthy subjects using magnetoencephalography. Spatial filtering based on current dipoles was used to quantify the strength of cortical activation. Our results showed an increase of cortical activation reflecting activity of efferent neurons, whereas the activity of proprioceptive afferent neurons was not affected. Since only efferent activity increased, it is suggested that this reflects phenomena of long-term potentiation.

Introduction

The input–output coupling within the human sensorimotor system is poorly understood, although it appears to be crucial for motor learning. On the basis of their observations in monkeys, Asanuma and co-workers emphasize the major role of sensory feedback to motor centers of the brain for movement execution and motor learning [1,2]. Human motor behavior is very precise, even though the properties of our body and the objects we interact with change over time. In order to achieve and to maintain this remarkable precision, the motor system has to match its estimation of the actual properties of objects within the environmental context with its prior knowledge by comparing actual and predicted sensory feedback [3,4].

According to Asanuma and Keller [5] and Asanuma and Pavlides [6], proprioceptive and cutaneous impulses arising during repeated execution of a movement induce long-term potentiation (LTP) phenomena in particular neuronal populations of the motor cortex that activate the corresponding muscles involved in the movement. LTP, as one basis of motor learning, is supposed to facilitate synaptic transmission and, in turn, motor initiation and execution. This hypothesis put forward by Asanuma and Keller [5] led to several prospective studies in stroke patients that demonstrated the functional benefit resulting from repetitive movement execution [7–9].

Whilst elaborating novel therapeutic strategies, it is of special interest to visualize the influence of a therapeutic intervention at the moment of its application. Furthermore, a method documenting its influence – when applied over a defined period of time – on neuronal plasticity is needed. Magnetoencephalography (MEG) with its high-temporal resolution and its power to localize event-related brain activity appears to be a promising approach. Movement-related neuromagnetic fields in self-initiated movements consist of a slow pre-movement readiness field (RF, 1–0.5 s prior to movement onset), a motor field (MF, approximately at the time of onset of EMG activity) and several motor evoked fields (MEF), of which the MEF I (about 100 ms after EMG onset) is the largest and most robust signal [10,11].

There is an extensive amount of literature dealing with the 'Bereitschaftspotential'. However, its probably generators, whether it has several components, and if so whether these reflect the concurrent or sequential activity of different brain regions are still unanswered questions. MEG studies have led to the proposal that the RF reflects the degree of effort associated with movements. There is some evidence that activation of the supplementary motor area (SMA) preceding primary motor cortex (M1) activation during the Bereitschaftspotential recorded prior to self-paced movements (for review see [12]). In an EEG-study, Knösche *et al.* [13] could clearly distinguish separate contributions of midline sources (including presumably SMA) and motor cortex to the Bereitschaftspotential.

The MEF I is thought to be generated mainly by proprioceptive input arising from the moving limb [11,14]. In a comparison of the dipole location of MEF I with a dipole detected after electrical stimulation of

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the index finger, Kristeva-Feige *et al.* [11] could demonstrate that the dipole of MEF I is located deeper, probably reflecting an activation of Brodmann's area (BA) 3a.

Functional brain imaging studies using positron emission tomography (PET) indicate that activation within the primary motor cortex (M1) increases with movement repetition [15,16].

The aim of the present study was to analyze the effect of repeated execution of a simple hand movement on the sensorimotor cortex of healthy subjects using MEG as a direct measure of neuronal activity. A method capable of monitoring the effect of therapeutic intervention at the moment of application would be of great value in both basic research and neurological rehabilitation practice.

Methods

Subjects and tasks

Neuromagnetic data were recorded from seven healthy right-handed persons. The four females and three males, aged 23–32 years, mean 27, had neither actual symptoms nor any history of neurological disorders. Written informed consent of the subjects and approval of the ethical committee are present. Subjects were positioned in a comfortable seat in a magnetically shielded room (Fa. Vakuumschmelze GmbH; Hanau, Germany). Eyes were open and the right distal arm and hand were fixed in a splint with a joint leaving full range of flexion and extension at the wrist. In order to realize an isotonic contraction without gravitational influence, the hand was positioned in a middle position between pronation and supination, i.e. with the thumb upwards. The hand movement was mechanically transmitted to a digital goniometer recording the angle at the wrist. The electromyogram (EMG) was recorded by means of surface electrodes over the extensor carpi radialis and flexor carpi radialis muscles.

Subjects executed voluntary self-paced fast right-hand extensions and flexions with an interval between movements of about 6 s. Between movements, the hand did not rest in a middle position, i.e. the flexion movement started with the hand extended and *vice versa*. The measurement session was divided into four blocks of 15 min each separated by breaks of 2–3 min. Subjects were asked to perform the movements as constant as possible (cf. Fig. 1).

Data acquisition and processing

The MEG was continuously recorded using a 148-channel 4D-NeuroImaging Magnes WHS 2500 (4D-NeuroImaging, San Diego, CA, USA) whole head system. Signals were digitized with a bandwidth of 0.1–100 Hz and a sampling rate of 508.63 Hz. Environmental magnetic field distortions were suppressed online by transforming magnetometer signals into software gradiometer signals. This method is part of the usual measurement scheme and described elsewhere [17]. Horizontal and vertical electro-oculograms (EOG) were recorded in order to control for ocular artifacts. Four surface EMG channels were used (left and right extensor and flexor carpi ulnaris muscles) for two purposes: to exclude voluntary contractions between movements and control for mirror movements. Ag/AgCl-electrodes were mounted in a bipolar fashion over the muscle bellies with a mutual distance of 2 cm. The subjects' head positions were measured before and after each experimental block by the sensor positioning system of the MEG device. The head surface was digitized once per session.

The data were averaged with respect to movement onset. To ensure maximal MEF the averaging was based on those epochs which started with an angular hand speed of at least 75°/s within the first 100 ms. Seven hundred milliseconds prior to the movement no other movements were allowed and no plateau phase within the movement was accepted. Prior to analysis the epochs were controlled by visual inspection of the goniometer data.

The data acquisition process yielded a matrix of averaged MEG data with one row for each of the 148 channels and one column for each of the 1273 time steps, spanning the interval from 1500 ms before to 1000 ms after movement onset. This spatiotemporal block of data represented a superposition of MF and MEF I as well as other brain activity and noise. In order to achieve a sufficient separation of these components that would allow judging their correlation to the experimental variables, two measures were taken. First, we selected for each of the relevant components a time point, most probably dominating the entire brain activity. These time points were extracted by inspection of the wave patterns of the data and by comparison with the literature (see below). The second step was to relate the MEG to the activity of the underlying generators in the brain. Straightforward dipole localization on the single subject data did not yield consistent results because of low signal-to-noise ratio and probably also temporal overlap between the different motor related activities. However, since the purpose of this study was not to establish the precise location of the MF and MEF I sources, but rather to reveal any training induced changes in their activity level, we could exploit that for each of the components (MF, MEF I) a hypothesis on the location of the generator is established (see below). This way, it was
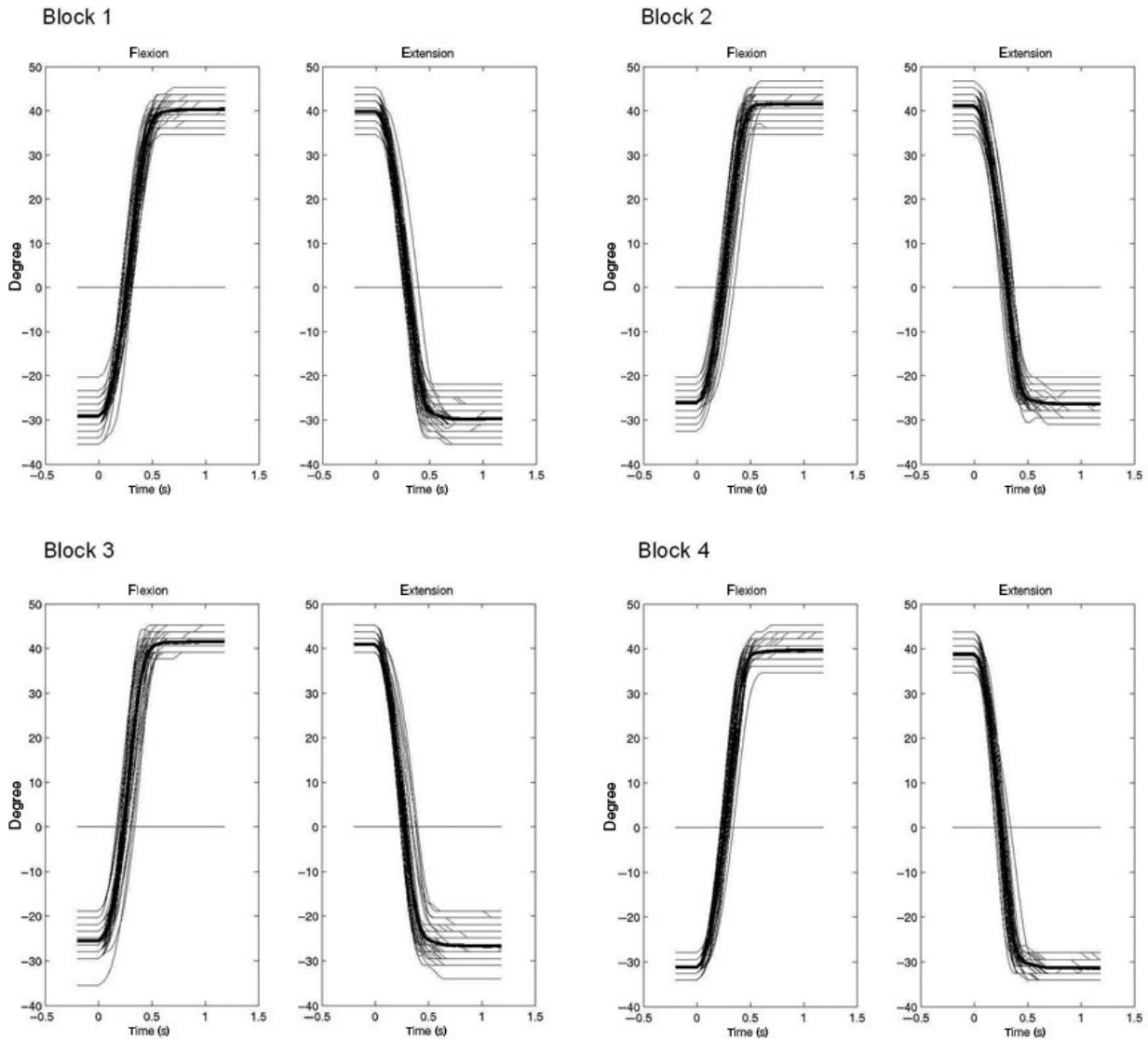
Figure 1 Typical example of goniometer data of wrist movements divided into four acquisition blocks lasting 15 min each. The thick black line represents the mean value. Note the precision of the movements over the entire session.

possible to build a spatial filter that reduces influences from brain regions other than the target region and thus yields stable results. The most straightforward way to establish such a filter is the linear projection of the MEG data onto the lead fields of a current dipole in the target region. As a result, only that portion of the MEG data passes the filter, which can be explained by a source in the respective region. This approach is similar to the source space projection method [18] with the difference that the signal space is derived from a priori knowledge on the source position rather than from the signal itself. Note that the spatial resolution of this method is limited (the separation limit is about 2–3 cm, for a detailed study see Fujimaki *et al.* [19]), which causes only an incomplete separation of the

different brain regions and noise, but makes the method tolerant towards interindividual anatomical differences.

The lead fields of a dipole of a target region consisted of three components[1] corresponding to three orthogonal dipole directions. Each of the components was computed as the forward solution of the respective dipole using a single-shell spherical volume conductor.

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[1]In principle, one could try to reduce the degrees of freedom of the model by assuming only one dipole perpendicular to the cortical sheet. However, in our case there are at least two reasons against this option: (1) the individual curvature of the subjects is quite different (we did not have individual MRI data); (2) the target positions taken from literature have to be considered approximate, hence the spatial filter has to focus on a whole region rather than a very focal spot.

This was sufficient, because our candidate sources lie in the parietal pericentral and precentral area of the brain, where the local curvature of the inner boundary of the skull is fairly spherical. Realistic head modeling using the boundary element method was, therefore, not necessary. Analysis was carried out with the ASA software (A.N.T. Software B.V., Enschede, The Netherlands).

For determining the time point for source reconstruction of MF and MEF I in each block, the following strategy was employed. For the MEF I, the maximum peak between 100 ms before and 100 ms after the movement onset was taken, whilst for the MF the first major peak prior to that was employed, with a minimum latency difference between MF and MEF I of 50 ms. This broad time window for MEF I was chosen on the basis of data from a previous study [20]. In this study, we found an electromechanical delay between EMG onset and movement onset of 97.6 ± 6.2 ms for the wrist extensors and 55.7 ± 20.5 ms for the flexors. The MF is related to the EMG onset and, therefore, we had to expect MF at least about 100 ms before movement onset. Using the described strategy, we now found

mean latencies of −132 ms for the MF and −10 ms for the MEF I for wrist flexion and for wrist extension −154 ms for MF and −13 ms for MEF I.

As target locations, we chose (in nose–ear–coordinate system; x, y, z) for MF (17, 30, 93) mm according to Cheyne and Weinberg [14] and Mima *et al.* [21], and for MEF I (3, 19, 85) mm according to Cheyne and Weinberg [14].

The statistical analysis was carried out by means of repeated measure ANOVA between dipole magnitudes of each block, which was in case of significant differences followed by a *post-hoc* Holm–Sidak analysis. Alpha-risk was set to $P \leq 0.05$.

Results

The analysis of movement related neuromagnetic fields over time requires well-controlled, constant movement parameters. As described in methods, controlling was done by an automatic procedure and a visual inspection. This way, only movements within a very small range of parameters (especially velocity and acceleration) were used for further analysis (Fig. 1).
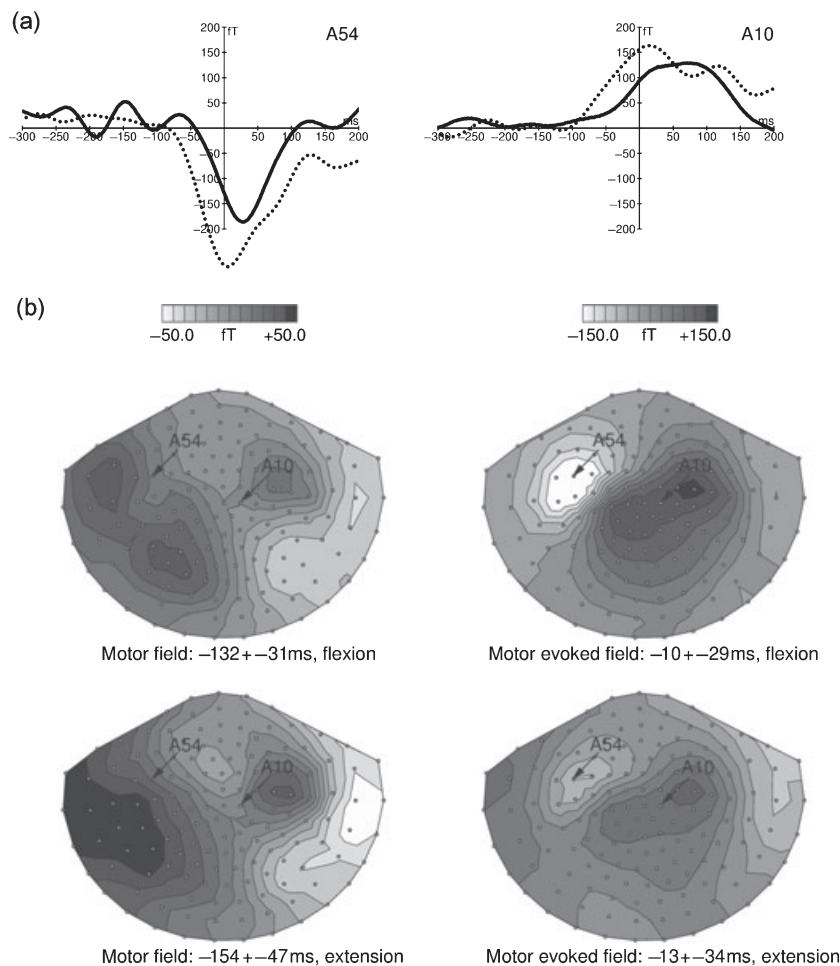

Figure 2 Grand averages of motor-related magnetic fields in femto Tesla (fT). Averaging was done with respect to movement onset. (a) Time courses of two selected channels. Dotted line: flexion, solid line: extension. (b) Topographic maps represent the flattened helmet-shaped sensor array. Averaging window was set to the mean latency ± SD of the motor field and the motor evoked field, respectively.

In Fig. 2, the grand average waveforms for two selected channels (Fig. 2a) as well as the topographic maps (Fig. 2b) for two characteristic time intervals are depicted. The topographic patterns for flexion and extension are very similar (cf. [22]), whilst the time courses show some differences in that the MEF I for flexion shows a slightly earlier and larger peak. Obviously, there is a second magnetic field on the ipsilateral hemisphere, visible in the time window of the MF (left
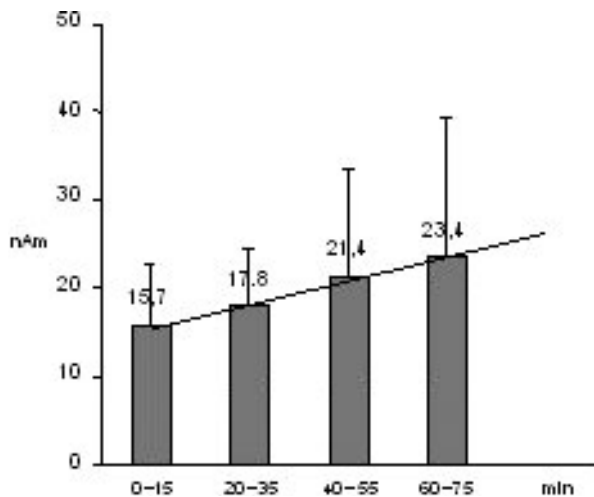
in Fig. 2b). This magnetic field is located more inferior and, therefore, not in the motor cortex. The dipole magnitudes for the different blocks are depicted in Figs 3 and 4. The results clearly showed a significant increase of dipole magnitude for MF (Fig. 3). In detail, the differences of dipole magnitude between the first and the third measurement block (40–55 min, $P = 0.037$), the first and the last (fourth) block (60–75 min, $P = 0.006$) and the second (20–35 min) and the fourth block ($P = 0.04$) were statistical significant.

On the contrary, the dipole magnitude of MEF I was not affected by the intervention. The repetitive voluntary execution of a simple hand movement therefore, exclusively enhances the neuromagnetic activity of efferent neuronal structures.

Figure 3 Motor field mean power in dipole position 17, 30, 93 in mm in the nose–ear–coordinate-system corresponding to the region of the primary motor area about four blocks in one session of repetitive sensorimotor training. The line indicates the increasing trend of the dipole power.
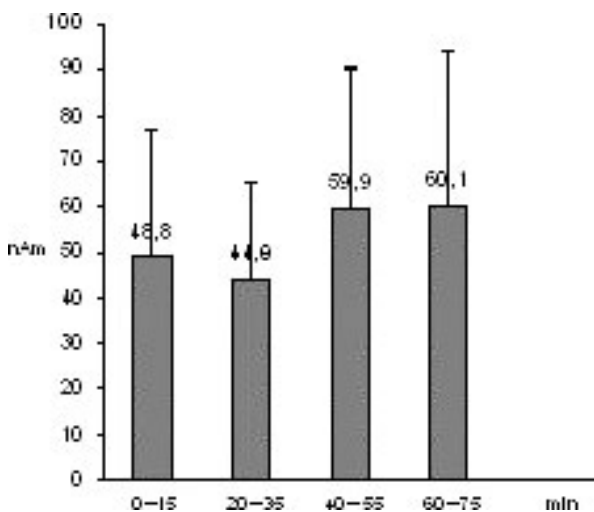

Figure 4 Motor evoked field I mean power in dipole position 3, 19, 85 in mm in the nose–ear–coordinate-system corresponding to the region of proprioceptive input, Brodmann area 3a, about four blocks in one session of repetitive sensorimotor training. Between dipole power in block 1 and block 4 no statistically significant difference was observed ($P > 0.5$).

Discussion

The repetitive sensorimotor training of simple movements (RST) of the hand has proved to be effective in the rehabilitation after stroke [7–9]. In order to learn more about the physiological basis of RST, we designed the paradigm of the present MEG study similar to the RST.

Already after the first block, i.e. after 15 min RST the dipole magnitude of the motor field started to increase, even though this increase reached significance from the third block on. Classen *et al.* [23] could show that after 15–30 min practice of a thumb movement in a direction opposite to the direction evoked by focal transcranial magnetic stimulation (TMS), the TMS came to evoke movements in or near the practiced direction for several minutes before returning to the original direction. These data suggest that repetitive voluntary movements can induce a rapid functional reweighting within the cortical neuronal network representing the moved body part.

Tetanic stimulation of motor cortical neurons induces a twofold increase of excitatory post-synaptic potential (EPSP) amplitudes, known as LTP. LTP phenomena were shown for pyramidal and non-pyramidal neurons having somata in layer II and III of the motor cortex. These layers are mainly formed by corticocortical and intracortical neurons participating in intracortical information processing. Projections from the sensory cortex to the motor cortex are highly specific. Proprioceptive and cutaneous impulses arising during repetitive execution of a movement are supposed to induce LTP phenomena, in particular, neuronal populations of the motor cortex that activate the muscles involved in the movement. It can be hypothesized that repeated practice of a particular movement increases the excitability of selected efferent zones in M1 [5,6]. This corresponds to the results of the present MEG study: dipole magnitude of MF representing

activity of efferent neurons increases whereas the dipole magnitude of MEF I which is thought to be generated by proprioceptive input to BA 3a [11,14] remains unchanged.

The present data are in accordance with other studies using brain imaging techniques visualizing brain activities by detecting changes of glucose metabolism (PET) [15,16,24]. These studies, dealing with motor learning tasks in healthy volunteers, found a practice related increase of the regional cerebral blood flow in the primary motor cortex. The main advantage of MEG is the direct measurement of neuronal activity. EPSP are the major generator of magnetic fields detected by MEG. As LTP phenomena enhance EPSP, it is supposed that the increase of the dipole magnitude could reflect LTP phenomena. Besides LTP it cannot ruled out that spatial and temporal summation effects may contribute to the dipole increase.

The described method appears to be appropriate to visualize the influence of motor practice on neuronal plasticity. Future investigations dealing with the effect of RST on task-related neuromagnetic fields in stroke patients are warranted. Based on these results, novel therapeutic strategies could be developed and evaluated.

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