Targeted reinforcement of neural oscillatory activity with real-time neuroimaging feedback

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Biofeedback and brain–computer interfacing using EEG has been receiving continuous and increasing interest. However, the limited spatial resolution of low-density scalp recordings is a roadblock to the unequivocal monitoring and targeting of neuroanatomical regions and physiological signaling. This latter aspect is pivotal to the actual efficiency of neurofeedback procedures, which are expected to engage the modulation of well-identified components of neural activity within and between predetermined brain regions. Our group has previously contributed to demonstrate the principles of real time magnetoencephalography (MEG) source imaging. Here we show how the technique was further developed to provide healthy subjects with region-specific neurofeedback to modulate successfully predetermined components of their brain activity in targeted brain regions. Overall, our results positively indicate that neurofeedback based on time-resolved MEG imaging has the potential to become an innovative therapeutic approach in neurology and neuropsychiatry.

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Introduction

Brain-computer interface (BCI) techniques are currently gaining interest as therapeutic and assisted-living devices (Kaiser et al., 2011; Manyakov et al., 2011; Shindo et al., 2011; Tam et al., 2011). In a nutshell, BCI technology consists in establishing a form of communication between brain activity and an external device. Traditionally, most of the interest has been focused on using this connection in a unidirectional way to steer and control external objects such as motorized wheelchairs, computer interfaces or game consoles (Vallabhaneni et al., 2005). More recently, there has been a new focus on using BCI to provide feedback based on the subject’s own brain activity. For example, commercial providers now offer basic BCI solutions to assist people in practicing meditation or in promoting concentration and vigilance (Lutz et al., 2009). Preliminary research studies have also argued in favor of BCI with feedback as a potential therapeutic approach to multiple neurological and psychiatric conditions (Dayan and Cohen, 2011; Lubar et al., 1995; Sanes and Donoghue, 2000; Sterman, 1981; Sterman and Egner, 2006). A possible approach consists in providing biofeedback indexed on the participant’s own brain activity, thereby enabling a form of neurofeedback. BCI and neurofeedback commonly make use of scalp electroencephalography (EEG) electrodes to access brain activity. In the case of interfacing users with ambulatory machines or personal applications, the portability and cost-efficiency of the EEG are essential. However, when considering potential therapeutic applications, the highest priority is in the ability to provide feedback indexed on predetermined components of the patient’s brain activity generated within targeted brain regions. Unfortunately, the spatial smearing caused by the skull bone in particular impedes the spatial resolution of scalp EEG across a wide spectrum of oscillatory components (Schaul, 1998; Varela et al., 2001). Consequently, EEG scalp signals are of poor spatial specificity and sensitivity to the local neural processes that need to be monitored and quantified during neurofeedback.

Recently, it has been shown that magnetoencephalography (MEG) can be used as a real time neurofeedback device, enabling subjects to modulate ongoing or task-related brain rhythms associated with awareness, attention, and motor performance (Birbaumer and Cohen, 2007; Meller et al., 2007; Wang et al., 2010). However so far, MEG-based neurofeedback has been only indexed on MEG sensor time series (Egner et al., 2004; Vernon et al., 2003). As such, the existing MEG approaches are akin to EEG’s because extra-cranial MEG sensor data is also impeded — although to a lesser extent than EEG — to the spatial smearing of contributions from multiple brain areas (Baillet et al., 2001; Gross and Schoeffelen, 2009).

In the present contribution, we demonstrate how real-time MEG source imaging can be used to access ongoing neural activity within predefined brain regions. Our group had previously demonstrated the technical feasibility of real-time MEG source imaging with an engineering perspective (Sudre et al., 2011). This previous study, however, did not investigate the possible effects of longitudinal neurofeedback training with this technique. In essence, we present here a proof of concept and feasibility that may yield new avenues of future therapeutic brain-computer interfacing.
research in a multiplicity of neurological and neuropsychiatric disorders. The technique of real-time MEG source imaging makes it possible to provide subjects with feedback on the time-resolved activity of targeted brain regions. In the context of multiple-session neurofeedback training, advancing the signal-capture technique from the scalp to the scale of the brain regions may improve the specificity and therefore, the efficiency of the approach. We therefore demonstrate in the present study that 1) it is possible to provide subjects with region-specific real time neurofeedback and 2) subjects can be successfully trained to modulate components of oscillatory neural activity within the targeted brain regions.

Methods

Anatomical data and targeted neurofeedback regions

One healthy female and one male volunteer (age 25 and 41 years) participated in a longitudinal MEG neurofeedback training protocol. To enable cortically-constrained MEG source imaging, a T1-weighted MRI scan of the participant’s brain was obtained (General Electric Signa 1.5-T, IR FSPGR, 240 × 240 mm field of view, 124 1.3-mm axial slices). The individual cortical surfaces were extracted from the MRI volume data using the automatic segmentation pipeline available in Brainvisa (http://brainvisa.info), with default parameter settings. The scalp and cortical surface envelopes were imported into Brainstorm, the open-source software environment we used for offline MEG data analysis (Tadel et al., 2011). The high-resolution triangulated cortical surfaces (~75,000 vertices) were down-sampled with Brainstorm to about 15,000 vertices, to serve as image supports for MEG source imaging (Baillet et al., 2001).

The individual MRI volumes and cortical surfaces were also used for defining the anatomical regions of interest (ROIs) targeted by the neurofeedback training (Fig. 1): We selected the bilateral dorsal aspect of the superior parietal lobule, anterior and posterior aspects of the central sulcus, and aspects of the dorsomedial frontal cortex (pre-supplementary motor area; preSMA). In terms of functional relevance, these brain regions were previously identified to be involved in motor imagery, a possible strategy for subjects to modulate online neurofeedback indices (Buch et al., 2008; Dechent et al., 2004; Ehrsson et al., 2003; Lotze and Halsband, 2006; Munzert et al., 2009). Overall the definition of the ROIs was empirical in both subjects. The goal was to test whether the activity in roughly defined brain regions could be arbitrarily modulated by neurofeedback training. In that respect, and because this is a longitudinal study, results should be considered individually. At the extreme, we could have selected anatomically different sets of regions in both subjects.

Neurofeedback training protocol

The two subjects participated in a multi-day training protocol consisting of 9 (1 baseline reference and 8 with neurofeedback) sessions in the MEG, scheduled over 14 days. The timeline of the training paradigm is illustrated in Fig. 2.

The MEG recording parameters were for an Elekta/Neuromag Vectorview system (204 planar gradiometers, 102 magnetometers), with data sampling rate set at 2000 Hz. Electro-oculogram (EOG) and -cardiogram (ECG) leads were applied to capture eye blinks and heartbeat artifacts, following guidelines of good MEG practice (Gross et al., 2013). Visual presentations were displayed on a back-projection screen.

All 9 sessions began with a 2-minute empty-room MEG recording, to capture daily environmental noise statistics (sample data covariance across MEG channels) that were used for MEG source modeling (see below).

The baseline reference session (Session 1) consisted of 2 runs, each with 10 trials, interspersed with 5 to 10 s of rest (eyes open). Each trial entailed 30 s of a pre-recorded movie presentation of a color-changing disk (as later used to provide actual neurofeedback). The disk’s color was updated every 500 ms, ranging from dark red to bright yellow. To maintain vigilance, subjects were instructed to silently count the number of color changes during each trial.

At the beginning of each of the 8 neurofeedback training sessions (Session 2–9), subjects were instructed that they would need to find a strategy to change the color of the presented disk to the brightest levels of yellow color, and to maintain these levels as long as possible. They were indicated that the color of the disk was indexed on their ongoing brain activity. After the last training session was completed (Session 9), subjects were asked to report on the nature of the strategy that they had developed.

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Fig. 1. Targeted regions of interest for MEG neurofeedback (in red): The bilateral dorsal aspect of the superior parietal lobule, anterior and posterior aspects of the central sulcus, and the dorsomedial frontal cortex (pre-supplementary motor area; preSMA) were manually delineated onto the cortical surface of the two participants: S1 and S2. The dark grey areas indicate sulcal folds; light grey areas represent gyral crowns. The cortical surfaces are shown with spatial smoothing applied to facilitate 3D visualization of the cortical manifold.

Fig. 2. Neurofeedback training protocol: On Session 1, subjects were only presented with movie clips showing colored disks changing colors, interspersed with short resting-state segments. The collected data was later used to derive reference levels in actual training sessions 2–9. In the following 8 training sessions real-time feedback and movie segments were presented alternated and interspersed with short sections of resting-state.
The training sessions began with a 2-minute MEG recording of the subject at rest (eyes open). We then recorded 30 more seconds of rest and a 30 second feedback segment, which was used for standardizing subsequent feedback levels (see below). The rest of the training consisted of 12 trials interspersed with 5 to 10 s of rest (eyes open). The trials entailed two conditions: 1) the actual neurofeedback task, with presentation of the color-changing disk (feedback condition) and 2) the passive presentation of a silent movie clip of an athletic performance (Movie condition). The duration of the Feedback and Movie segments was randomized uniformly between 20 and 30 s.

The main purpose of the Movie condition was for subjects to relax between feedback segments. A secondary objective was that the presentation of a clip engaging observation of motor actions would promote activity in the brain regions targeted by neurofeedback.

Overall, the session duration of MEG acquisition for each training run was 12–18 min.

**Real-time imaging and visual feedback**

At the beginning of each training session, one short reference recording was obtained (20 second resting-state, eyes open). This run was used to locate the subject's head within the MEG helmet. Head localization was measured by energizing 4 head-positioning coils, following standard procedures. This information was then used to complete the registration of the MEG channel array with the subject's head surface envelopes obtained from MRI, thereby defining a subject-centered coordinate system (SCS). MEG forward and inverse modeling steps were subsequently completed using Brainstorm (Tadel et al., 2011): multi-sphere analytical approximation (Huang et al., 1999) and weighted-minimum norm estimate (wMNE) (Mosher et al., 2003), respectively, all using Brainstorm's default parameter settings.

The subjects were instructed to remain still during the training session. Head movements were controlled by evaluating the displacement of SCS head center between the beginning and the end of the recording run. The maximum displacement observed across subjects and runs within one training session was 12.5 mm.

During the training runs within a training session, the MEG data flow was intercepted using the rtMEG software (Sudre et al., 2011). Real-time source imaging of ongoing activity extracted from ROIs was performed over a MEG data segment of 500 ms duration. We reported elsewhere that the data buffering process was completed in less than 45 ms (Sudre et al., 2011). The online preprocessing of the MEG data buffer followed by the application of the wMNE linear source imaging kernel took less than 50 ms, using a basic Windows XP PC (Intel Core2 Duo, 2.40 GHz; 1.98 GB RAM). Running Matlab 7.4 (The Mathworks, MA). Therefore, the total processing time was at most 95 ms. The delay due to the projector was 36 ms on average, which are both very short durations with respect to visual conscious perception and integration in the context of neurofeedback.

The use of noise reduction techniques during the feedback sessions was limited due to the computational time limitations imposed by the real-time condition. However, the data were preprocessed using an in-house implementation of the signal-space-separation (SSS) technique (Taulu et al., 2004), which was reduced to the projection of online MEG traces away from a predefined noise subspace. The default SSS settings for the recording site were used: orders of spherical harmonic expansions for the inner and outer source models were 8 and 3, respectively. The SSS orthogonal projectors were applied to the online MEG traces, at each 500-ms buffer, taking less than 50 ms per buffer.

The visual display during Feedback was updated every 500 ms and was indexed by the ratio of theta (4–8 Hz) to alpha (8–12 Hz) power (T2A) over the selected anatomical ROIs. The T2A ratio has been used previously as target index in biofeedback studies based on scalp EEG (Gruzelier, 2009; Ros et al., 2009). In the present context of neurofeedback encouraged by motor imagery, the rationale for choosing T2A was that alpha activity has been shown to be decreased during motor imagery (van Wijk et al., 2013), while higher theta activity is involved in higher cognitive processes (Enriquez-Geppert et al., 2013; Mitchell et al., 2008). Note that our choice of T2A was not to demonstrate that its modulation may be functionally beneficial: the objective was to demonstrate that a relatively arbitrary index of brain activity can be increased in predetermined brain regions using neurofeedback based on MEG imaging.

The T2A index was computed for each 500-ms MEG data buffer M(t) indexed with t = 0,...,T, where T = 1200 corresponds to the last 500-ms data segment over a 10-minute session. At each running buffer t, the short-term fast Fourier transform (FFT) was obtained for each MEG sensor trace. The linear wMNE imaging kernel K restricted to the target ROIs was applied to the resulting array of FFT coefficients M(f):

\[ \hat{S}(f) = K \cdot M(f), \]

where \( f \) represents a running FFT frequency bin and \( \hat{S}(f) \) is the array of FFT coefficients of each source time series in the ROI model. This resulted in the direct mapping of cortically-distributed FFT coefficients of MEG source time series within the targeted ROIs. The frequency bins corresponding to the alpha and theta frequency bands were previously identified and the respective FFT modulus at each elementary source location was obtained. In each ROI, indexed with \( i \), the T2A ratio was computed as the average of each elementary source’s T2A ratio across the ROI. The global T2A level was defined as the median T2A ratio across all ROIs.

For each running buffer \( t \), the online T2A levels were standardized (using z-score, \( zT2A_{online} \)) with respect to the T2A scores measured over the 30-second baseline segment at the beginning of each neurofeedback session. The baseline segment was decomposed into 60 contiguous 500-ms epochs. The mean and standard deviation of all 60 baseline T2A scores were obtained across epochs and used for z-score standardization of the online T2A levels measured during the Feedback condition. After the 30 second rest, there was a 30 second reference feedback period where the subject was to perform the real time feedback task (Fig. 2).

Finally, the ongoing standardized \( zT2A_{online} \) level was passed through a median filter of length 10 (5 s), comprising the 9 previous and current \( zT2A_{online} \) levels \( t-10 \) to \( t \), to achieve a smoothed running presentation of Feedback disk color updates. The color map used was the default autumn Matlab colormap, with 128 color levels. The brightest yellow color was set to 1.5 times the maximum value observed over the 30-s reference feedback segment at the beginning of each training session. The darkest red color was adjusted to correspond to 128th of this maximum value.

All raw MEG traces and real-time imaging levels (T2A) were saved to disk for subsequent offline analysis.

**Offline data analysis**

The MEG data from all sessions were further analyzed offline after they were cleaned from environmental noise, eye blinks and cardiac artifacts: offline SSS using Elekta/Neuromag Maxfilter commercial software was applied (same default setting as for online SSS processing). Eye blinks and cardiac events were detected automatically using Brainstorm’s dedicated process, with default parameters. One dimensional signal-space projectors (SSP) were used for each type of artifact (Nolte and Curio, 1999).

For each training session, the 30-s trials of both the Feedback and Movie conditions were extracted from the cleaned recordings and concatenated by condition. The T2A ratio at each elementary cortical source (≈15,000) was calculated offline from 1-s time windows with 50% overlap, following the same procedure as above. We used 1-s time windows rather than the 500-ms windows used during online processing, to obtain more robust estimates of FFT coefficients. The T2A score from each 1-s buffer was standardized with respect to mean.
and standard deviation of the T2A levels measured from the baseline recording at Day 1 (zT2A).

The hypothesized positive effect of the 8-session training program on increased T2A levels in targeted brain regions was tested with linear regression. At each cortical location i, the following model was adjusted over the 8 local zT2A scores (Day 2–9, indexed with j = 1,...,8): 

\[ zT2A_{ij}^{\text{train}} = c_i + a_i j + e_{ij} \]  

(2)

where \( zT2A_{ij}^{\text{train}} \) is the local, standardized offline T2A score observed at cortical location i during feedback training session j; \( c_i \) is a constant term, \( a_i \) is the slope coefficient and \( e_{ij} \) is an error variable.

To compare the obtained set of slopes \( a_i \) against baseline, the same linear regression procedure was applied over \( zT2A_{ij}^{\text{rest}} \), the local, standardized T2A scores measured during the 2-minute recordings of spontaneous activity that started every training session: \( zT2A_{ij}^{\text{rest}} \) was substituted to \( zT2A_{ij}^{\text{train}} \) as dependent variable in Eq. (2).

Results

Both subjects reported on resorting to distinct strategies to improve their performance during neurofeedback training. While Subject 1 did settle on a self-centered motor imagery strategy, Subject 2 reported trying to reproduce a more abstract form of mental imagery as the “sensation” experienced by this participant during the passive Movie condition.

Fig. 3 shows the average zT2A ratio per session, for all 8 training sessions (Session 2–9). In both subjects, several brain regions demonstrated a positive response to training with increased levels of T2A score with respect to Session-1 baseline reference. Within subjects, the anatomy of zT2A increases was remarkably consistent across training sessions. Between subjects, the maps covered distinct subsets of targeted ROIs. In Subject 1, the zT2A increases were particularly strong over frontal ROIs, whereas Subject 2 increases were more posterior (superior parietal, essentially). Overall, both subjects demonstrated longitudinal increases in T2A scores across training sessions. Comparing the global (across ROIs) median zT2A score between the first (Session 2), intermediate (Session 6), and last training sessions (Session 9), both subjects reached the highest global T2A scores with respect to Day 1 baseline levels towards the end of the training program as shown in Fig. 4.

Discussion

The present study demonstrates the feasibility and basic response to neurofeedback training enabled by high-temporal resolution MEG source imaging. The visual feedback provided was indexed on the instantaneous combination of oscillatory signal power in targeted frequency bands of interest within pre-selected, anatomically-specific brain regions. When compared with fMRI, the main benefit of using MEG as a neurofeedback instrument is to access directly the large palette of fast dynamics of oscillatory signal components that are emerging spontaneously or with task modulations, from neural population (Buzsaki, 2006).

Our study demonstrates that subjects can train with MEG-imaging neurofeedback to modulate specific components of fast neural activity, within specific anatomical regions. We had preselected fairly broad regions of interest based on their known involvement in mental imagery, a process which we and others thought would facilitate training effects in the proposed paradigm (Kaiser et al., in press; Ono et al., in press). Both subjects reported in being engaged in different forms of motor imagery: Subject 1 adopted a self-centered strategy, imagining being him/herself performing motor actions. Subject 2 adopted an observer position, internally visualizing actions performed by someone else. Whether the differences in brain regions responding more to the training can be accounted for by the respective individual strategies, it cannot be concluded. Still, the subjective reports are compatible with our findings indicating that Subject 1 strongly engaged the motor and premotor cortices, while Subject 2 showed stronger responses from...
the dorsal attentional and central cortices. Overall, the stronger, positive effects from training mapped to subsets of pre-determined ROIs in both subjects. These results suggest that future studies should consider including an index reporting on the anatomical specificity of the brain’s response, in the feedback score of the subject.

We anticipate single and/or smaller brain regions could possibly be defined as targets, with no behavioral priming from the paradigm (here, motor imagery and Movie condition). With this level of anatomical and functional specificity, and its ability to target a large palette of electrophysiological manifestations of neural plasticity and compensatory mechanisms, it might now be conceivable that MEG may become a therapeutic tool for rehabilitation and recuperation in response to a variety of neurological and psychiatric conditions. While MEG neurofeedback based on source imaging allows to target specific, predefined brain regions more robustly than with EEG, this comes at a cost. EEG has the advantage of being technically less involved and hence less expensive, portable, and more widely available. For instance, with today’s technology, EEG can enable convenient home-based training programs. MEG occupies the other end of the specificity-cost tradeoff. Hence we expect MEG-imaging training to be most relevant for cases where a very anatomically-specific training effect is necessary to ensure therapeutic success. This would justify the higher cost, to the benefit of unique performances.

Previous neurofeedback studies using scalp EEG training have reported possible side effects (Hammond and Kirk, 2008). So far the main expertise in EEG feedback stems from epilepsy and ADHD patients. For those patients negative effects from neurofeedback with EEG included seizures, manic behavior, anger and irritability, anxiety and agitation, fatigue, sleep disturbance, and headaches. 12 months after data acquisition, the subjects in our study did not report any side-effects. Because source-MEG training is more anatomically and physiologically specific than scalp EEG or fMRI, it is conceivable that it

Fig. 4. Within-session global zT2A levels on training sessions 1, 5, and 8. The time courses of global zT2A levels (median value across targeted ROIs) were obtained from the offline analysis of MEG data. For each session, the global zT2A levels were computed over 1-s time windows (with 50% overlap) and averaged across the 12 trials of the feedback condition, reduced to their minimal duration (20 s) (see Methods). The curves indicated that higher levels of zT2A are reached more rapidly later as the training program unfolded (from Session 6 in Subject 1 by Session 9 in Subject 2).

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might facilitate subject adaptation to training, and eventually yield fewer adverse effects. However, while our study proves the concept of MEG-imaging neurofeedback and outlines promising potential uses, further studies evaluating the benefits and side-effects in particular applications are needed. A rigorous evaluation with a larger sample and appropriate control conditions is needed. Future studies should also aim at confirming our finding of region-specific T2A modulation – or any other index of neural dynamics obtained from MEG source time series – for a larger sample or with specific hypotheses regarding the target mechanisms to be engaged with this technique. However, given that controlled EEG studies previously showed that subjects are able to control particular aspects of their brain activity (Kotchoubey et al., 2001; Kuhlman, 1978), and that the neural current flows generating MEG and EEG measures are similar, our longitudinal results shall be considered as reproducible, despite the small sample size. The aim of this study was not to demonstrate that T2A is functionally beneficial, but to demonstrate the feasibility of region-specific training using MEG-imaging neurofeedback.

Finally, our study focused on providing the first report on the effectiveness of MEG-imaging neurofeedback in modulating oscillatory neural components within brain regions of interest. The selection of theta-to-alpha power ratio was not to demonstrate this latter is functionally beneficial, but rather that any brain region and any arbitrary measure of time-resolved, ongoing brain activity can be targeted in principle. We also anticipate that neurofeedback metrics of interest can extend to statistics of functional connectivity between distant brain regions, provided that their extraction from ongoing data is compatible with real time computation contingencies.

Conclusion

The targeting of pre-selected brain regions and the training of specific fast components of time-resolved brain activity within these regions is possible with real-time MEG-imaging neurofeedback. We found that the modulation of these predefined components of brain dynamics was reinforced by real-time visual feedback to subjects and is specific of targeted brain regions. Overall, this study opens new perspectives in the development of new therapeutic strategies based on real-time neurofeedback training, with direct access to the broadest range of neural dynamics, known to be affected by most neurological and neuropsychiatric conditions (Bragin et al., 2010; Laaksonen et al., 2013; Wilson et al., 2007).

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Fig. 5. Anatomically-specific effects of neurofeedback training: The offline analysis of the MEG data collected over the 8 feedback training sessions was conducted to estimate the slope of a linear regression model to the changes in T2A levels detected across sessions, at each cortical location. The colored regions indicate where a slope of positive, linear increase was found to be significant (p < 0.01) when compared with pre-training baseline fluctuations in T2A levels. Although different between subjects, the regions engaged strongly overlap with the targeted ROIs. The graph plot inserts indicate the global T2A ratio across all 8 training sessions and the linear regression model for the brain region indicating the steepest response to training (Subject 1: dorsal preSMA; Subject 2: superior parietal lobule).
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