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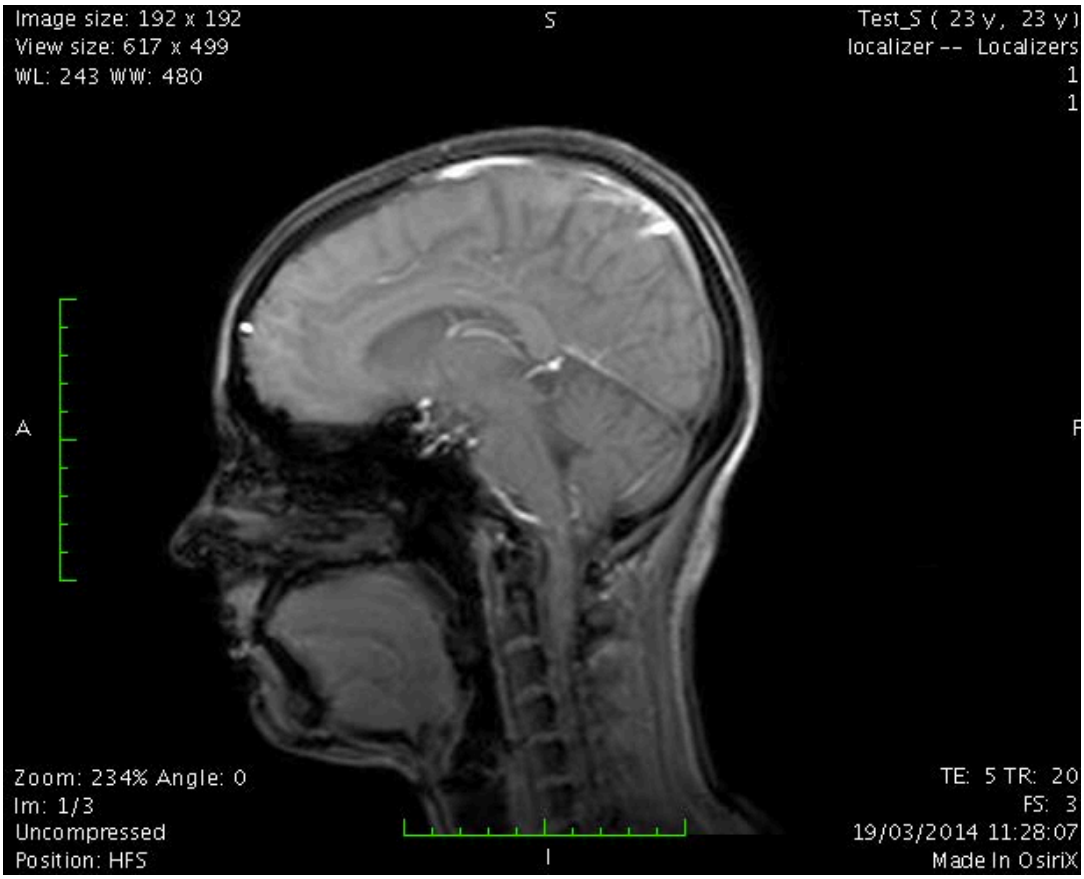
Effects of aging on interhemispheric cross-talk during unimanual motor learning – an fMRI/EEG study



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Abstract

Objectives: To investigate how and where neural changes alter the symmetry of activity patterns during unimanual motor learning in elderly.

Design: Subjects learn a polyrhythmic task, which requires an integration of perceptual and motor components, while being monitored with fMRI/EEG recordings.

Subjects: Two groups participated: 16 healthy young subjects (20-25 yrs) and 16 healthy older subjects (60-70 yrs). All subjects were right-handed non-musicians without neurological history.

Methods: Subjects performed rhythmic unimanual forces that are known to induce behavioral left/right interference. Subjects were asked to squeeze an air-filled rubber bulb with their right hand in a 4:3 frequency ratio to a visual cue (cuing tempo 1.8 Hz, squeeze tempo 1.35 Hz). If performed properly, the visual feedback displayed an iso-frequency outcome at 1.8 Hz. During this learning task (20 min) and during resting state periods pre and post learning (2×5 min) both EEG and fMRI were recorded. This was supplemented by structural MRI and DTI recordings (~15 min).

Analysis: Performance was measured through the strength of frequency locking between the visual cue and the performed force. The EEG-based time course of beta-activity during learning served as regressor for the BOLD signal per voxel.

Statistics: The data were modeled to make interferences about effects of interests. A t-test was performed to test whether the beta-regressor significantly explains the measured BOLD data. Based on the single-subject contrast a group-level random-effect analysis was calculated.

Results: Both groups showed a significantly improved performance when comparing the start with the final learning. The elderly group showed more active brain regions compared to the younger group while performing the same task.

Conclusions: Performing a unimanual motor task appears more challenging for elderly and they compensate for this by activating more brain regions, which is more difficult to orchestrate and, hence, comes with an increase in learning time.

Key words

Aging; Interhemispheric inhibition; Learning; Simultaneous EEG-fMRI

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1 Introduction

With age our body undergoes various neurophysiological changes. This includes the central nervous system – in general – and the motor network – in particular. It has been suggested that it is because of these systemic, or say 'structural', changes that older people have more problems with motor control, especially with the coordination between limbs. In the current research I investigated how and where these structural neural changes alter the symmetry of activity patterns during unimanual movements. Here, unimanual movements are considered a special case of bimanual ones, i.e. both entail activity in bilateral primary motor cortices (M1s) (Kim et al., 1993; Ghacibeh et al., 2007; Rao et al., 1993). Under normal circumstances contralateral M1 is far more active during unimanual movements than its ipsilateral counterpart. Because of this lateralization, contralateral M1 is considered the main controller of hand and finger movements. In view of the bilateral activity, however, one may argue that unimanual movements are realized by inhibiting ipsilateral motor areas (Daffertshofer et al., 2005). By this inhibition, activation of the homologous limb is suppressed.

Elderly often encounter more problems with deactivating ipsilateral primary motor areas during unimanual movements (Van Impe et al., 2009; Coxon et al., 2010; Goble et al., 2010), which may lead to over-activation in the according end-effectors (Hutchinson et al., 2002; Ward and Frackowiak 2003; Newton et al., 2005). Ward and co-workers (2003) reported that activity in the contralateral M1 did not show a correlation with age, whereas activity in ipsilateral M1 during precision grip is increased in the elderly in comparison to younger subjects. This may be indicative for a decreased inter-hemispheric inhibition (Van Impe et al., 2009). Van Impe et al.'s research aimed to investigate the idea that this decrease stems from an age-related degeneration of the corpus callosum (CC) integrity (see also Sullivan and Pfefferbaum, 2006). Trans-callosal pathways can be inhibitory, implying that a decline in CC integrity may readily come with a decline in inter-hemispheric inhibition. However, trans-callosal pathways are believed to be primarily excitatory (see Daffertshofer et al., 2005, and references therein), which is the reason for inter-hemispheric crosstalk. The excitation via the CC must hence be inhibited intra-hemispherically (Stinear & Byblow 2002). Daffertshofer and co-workers (2005) submitted that this intra-hemispheric inhibition is mediated through pre-motor areas: contralateral M1 projects through the CC to ipsilateral M1 (yielding cross talk, i.e. unwanted left/right interference); the same contralateral M1 also projects to ipsilateral pre-motor area (PM1) that is likewise excited; cortico-cortical connections from PM1 to M1 are considered inhibitory so that, whenever PM1 is active, M1 is inhibited – this is referred to as 'effective' inter-hemispheric inhibition. Dis-balance in the inter-hemispheric cross talk and the intra-hemispheric inhibition may cause an improper, *effective inter-hemispheric inhibition*, which may underlie age-related increases in left/right interference and age-related diffi-

culties in left/right coordination. Interestingly, when unimanual movements become more complex, the amplitude of ipsilateral motor-related fields increases profoundly (Hoshiyama et al., 1997; Babiloni et al., 1999; Salinas 2001).

As a function of age, linear decreases in performance have been shown in motor tasks, such as repetitive finger tapping (Shimoyama et al., 1990). Although, more complex effects are seen in more demanding time tasks and visually guided hand movements (Ward et al., 2003; Houx and Jolles, 1993; Kauranen and Vanharata, 1996; Smith et al., 1999). To investigate the age-related differences in the process of learning, a motor learning paradigm is employed in which subjects have to learn a polyrhythmic motor task, which requires an integration of perceptual and motor components (Houweling et al., 2008), while being monitored with fMRI/EEG. The integration was expected to facilitate the learning when the perceptual outcome is properly chosen (i.e. simple) (Mechsner et al., 2001). The goal of my research was answering the following questions:

1. *Which changes in M1 and PM1 activity correlate with age during unimanual movements?*
2. *What are the age-related differences in the process of learning a polyrhythm?*

To answer these questions I combined two different modalities: electroencephalography (EEG) and functional magnetic resonance imaging (fMRI). The combination of EEG and fMRI overcomes the spatial limitations of EEG and the temporal limitations of fMRI. Therefore it provides a proper monitoring tool for the analysis of brain state fluctuations (Ritter and Villringer 2006). Based on the findings of Houweling et al. (2008) the investigation focused on beta-band activity (13-30 Hz) stressing the motor network (which is primarily M1 and possibly PM1). The beta-activity patterns as recorded using EEG served as regressor for the fMRI to specify the Blood Oxygen Level Dependent (BOLD) changes that in consequence are considered relevant for motor performance. This type of analysis has been previously successfully employed for sensori-motor alpha and beta rhythms (Ritter et al., 2009) and visual alpha rhythm (Moosmann et al., 2003; Becker et al., 2011). The expected primary Regions of Interest (ROIs) were, as said, bilateral M1 and PM1.

Learning time was expected not to exceed 15 minutes in both groups and to increase with age (Mechsner et al.; 2001, Houweling et al., 2008). Bilateral M1 were expected to be the most dominant ROIs. Beta-modulation in the ipsilateral M1 was expected to be stronger in the elderly, indicating less effective inter-hemispheric inhibition in that group compared to young participants. Most probably this age-related difference in ipsilateral activity correlates with CC integrity (CC thickness and fractional anisotropy (FA)).

2 Methods & Procedures

2.1 Subjects

Two different groups were measured: 16 healthy young subjects (20-25 yrs) and 16 healthy elderly subjects (60-70 yrs). The age-range in the second group was larger to facilitate the recruitment of elderly subjects. Since I was interested in learning, subjects should not be able to perform the task at start of the experiment. To higher this probability subjects were excluded if they had a musical background, or followed non-professional music lessons. All subjects were right handed according to the Edinburgh Handedness Inventory test (Oldfield et al., 1971). Based on a systematic literature search (Appendix A) a cognitive assessment was performed to examine the mental state of the elderly that perform the task, the Montreal Cognitive Assessment (MoCA, Appendix B). All participants had no history of neurological, psychiatric, or chronic somatic diseases and were physically fit, since they could come at their own to the Berlin Center of Advanced Neuroimaging (BCAN). General exclusion criteria for participating in an MRI study can be found in Appendix C. All subjects were extensively informed about the procedure and acquisition of EEG and fMRI data (Appendix D). All subjects gave their written informed consent. The Medical Ethical Committee of the Charité – Universitätsmedizin Berlin approved the study protocol prior to conductance. Note that in the current thesis not all EEG and fMRI data of the subjects will be reported, because this is beyond the scope of this thesis: 5 subjects of every experimental group will be included in the analysis. By contrast, the behavioral data of all subjects was analyzed. All data will be analyzed during a PhD project covering this master's thesis.

2.2 Procedures

Every subject performed rhythmic unimanual movements, which, as said, were expected to induce left/right interference. A learning task was implemented to prompt neural changes over time and to define the age-related differences in the process of learning a polyrhythm. For this sake, a protocol introduced by Houweling et al. (2008) was adapted to a unimanual task. Subjects were asked to squeeze in an air-filled rubber bulb with their right hand in a 4:3 frequency ratio to a visual cue (Peper et al., 1995). Several pilots showed that a 3:2 polyrhythm was too easy. The 4:3 performance was mapped non-linearly to a 1:1 visual feedback which was easy to accomplish and known to ease motor performance (Mechsner et al., 2001). The produced forces were aligned to a computer display with Labview (see figure 1).

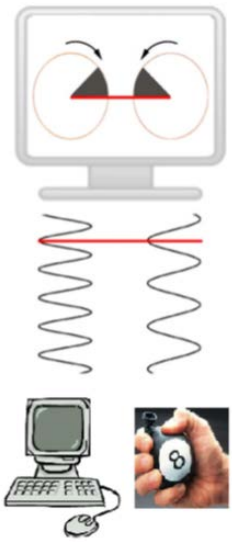

Figure 1. Setup

The left force, simulated by the computer, and the right force, performed by the subject, were displayed as two rotating disks. In the case of proper performance, the disks counter rotated with a 1:1 frequency ratio, i.e. in synchrony and in-phase. The rhythm of the produced force was 'phase twisted', i.e. the computer displays a disk that rotates at a 1.33 time faster frequency than the one produced by the subject. Subjects had to perform the slower rhythm (1.35 Hz) and match this to the faster rhythm/cuing tempo (1.8 Hz) of the computer in order to get the two displayed disks rotating at a 1:1 ratio. Subjects had to learn this task, but were expected to do so within about 20 min (Houweling et al., 2008).

To facilitate keeping the subjects motivated and to improve their performance, next to the online feedback, offline feedback about the performance was provided, i.e. they received knowledge of results (KR). Every trial of 2 minutes was followed by a break of 15 seconds, where the KR appeared. The KR was based on estimating the peak in the power spectra, and telling the subjects if they squeeze too slow, too fast or were doing well during the previous trial. Subjects performed a total of 10 trials, i.e. the total task time (15 sec breaks included) was 22 minutes and 30 seconds. Before the experiment started a baseline measurement was done to correct for the offset that was created by just holding the balloon in their hand. This baseline measurement was followed by 90 seconds of practice a 1:1 frequency ratio to familiarize subjects with the task procedures.

During the experiment, subjects lay in a supine position inside the scanner. They were repeatedly informed to relax, lie still, and minimize head movements. To support the subjects in minimizing head movements, their head was immobilized with removable vacuum cushions (Siemens equipment). Earplugs served to prevent adverse effects due to scanner noise. Because eye movements may cause gross artifacts in the EEG data, subjects were asked to focus their gaze on a cross between the two disks. See Appendix E for the full description subjects had to read before the experiment started including instructions to reduce head movements.

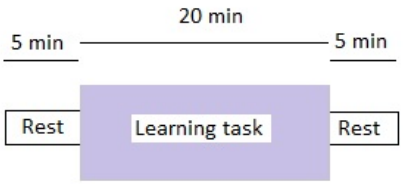

Figure 2. Experimental design

Motor learning was supplemented by two blocks of 5 minutes resting state recordings yielding baseline measurements (figure 2). During these 5 minutes subjects were asked to close their eyes, stay awake and not move their head.

Each session started with the recording of the localizer, to localize the head in the scanner, followed by an anatomic T1- weighted MRI (MP-Rage, duration 4:26 min), an anatomic T2-weighted scan (2.16 min), Diffusion-Tensor-Imaging (8:23 min), which together took around 15 minutes. After the anatomical scan session, subjects came out the MR scanner to get the EEG-cap prepared.

The next day, a retention test was performed identical to the learning task of the previous day performed in the scanner. A behavioral re-assessment was mandatory to identifying learning. Learning is a significant difference between training and retention. Given the brevity of the training (less than 30 minutes) a retention test a day later was considered to be most appropriate.

2.3 EEG data acquisition

EEG recordings were conducted with a 64-channel MR compatible EEG system (Brain Products, Gilching, Germany; 0.1-250 Hz hardware band-pass filter, 0.5 µV resolution, 5kHz sampling rate) and an EEG cap (Easycap, Herrsching, Germany), using ring-type sintered silver chloride electrodes with iron-free copper leads. The cap was used to place the 61 scalp electrodes arranged based on the International 10-20 System (figure 3), two electrocardiogram (ECG) electrodes and one vertical electro-oculogram under the subjects left eye. The reference was located at electrode position FCz and the ground was located at electrode position AFz.

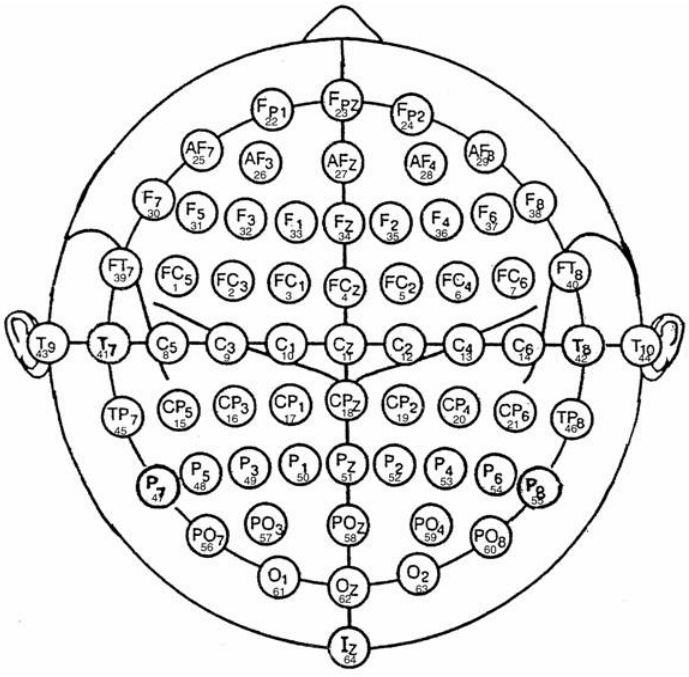

Figure 3. International 10-20 System used to arrange scalp electrodes

First, the skin under each electrode was cleaned with alcohol. Second, an abrasive electrolyte gel (Abralyt 2000, Easycap, Herrsching, Germany) was used to keep the impedances of all electrodes below 5 kΩ. The EEG-sampling was synchronized to the gradient-switching clock of the MR scanner, to ensure time-invariant sampling of the image acquisition artifact (IAA) during simultaneous EEG-fMRI recordings (SyncBos, Brain Products, Gilching, Germany; scanner frequency 10 MHz, update interval set to 2 sec) (Anami et al., 2003; Freyer et al., 2009). Also start- and end-triggers of every trial were recorded.

2.4 fMRI data acquisition

For fMRI recordings a 3T Siemens Trim Trio MR scanner with a 12-channel Siemens head coil was used. For each participant the scan session started with a localizer sequence (TR 20 ms, TE 5 ms, 3 slices (8 mm), voxel size 1.9×1.5×8.0 mm, FA 40°, FoV 280 mm, 192 matrix), followed by an anatomical T1-weighted scan (TR/TE 1900/2.52 ms, FA 9°, 192 sagittal slices (1.0 mm), voxel size 1×1×1 mm, FoV 256 mm, 256 matrix), an anatomical T2-weighted scan (TR 2640 ms, TE1 11 ms, TE2 89 ms, 48 slices (3.0 mm), voxel size 0.9×0.9×3 mm, FoV 220 mm, 256 matrix) and Diffusion-Tensor-Imaging (TR/TE 7500/86 ms, 61 transversal slices (2.0 mm), voxel size 2.3×2.3×2.3 mm, FoV 220 mm, 96 matrix). Afterwards the EEG-setup was prepared and functional MRI (BOLD-sensitive, T2*-weighted, TR/TE 1940/30 ms, FA 78°, 32 transversal slices (3 mm), voxel size 3×3×3 mm, FoV 192 mm, 64 matrix) was recorded simultaneously to the EEG recording. The DTI measurements will not be discussed in the current report, due to a lack of time.

2.5 Behavioral data acquisition

Subjects pressed a balloon that was connected to an 8-meter long tube (figure 4). The software Labview analyzed the incoming data, in accordance to Houweling et al. (2008). See Appendix F for details about the used settings. Via a Parallel Port from the computer to the EEG software a trigger was given for every start and end of a trial.

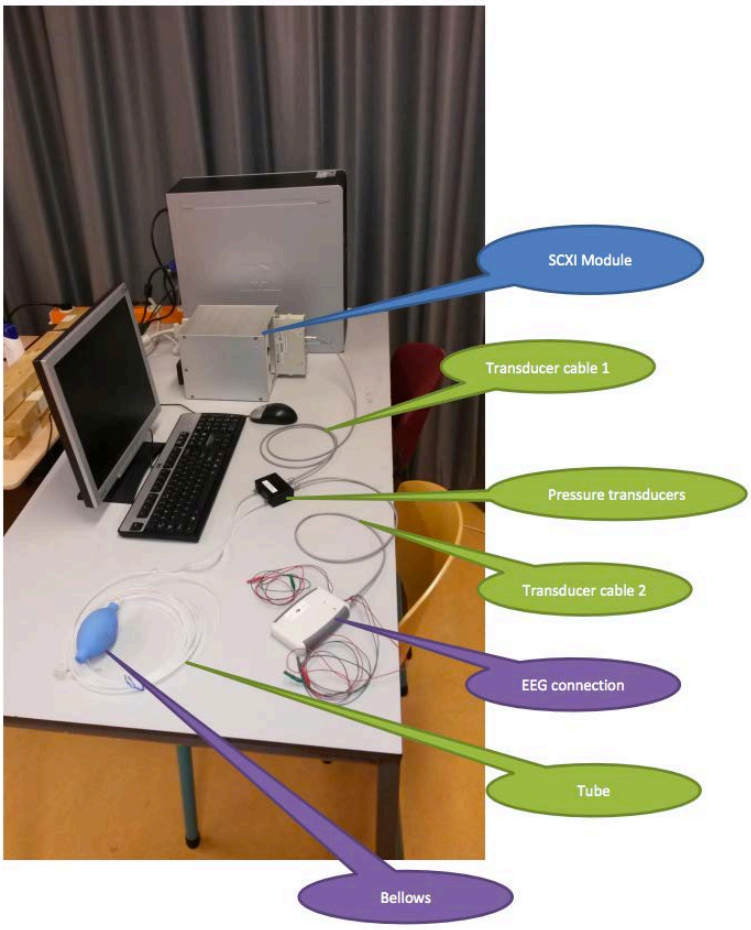

Figure 4. Behavioral setup. The EEG connection and second transducer cable are not used. The air pressure produced by the subjects squeezing the balloon reaches the pressure transducer. This transducer converts the physical quantity to an electrical signal, and is connected to a SCXI module (National Instruments) that amplifies the signal from 100 mV to 10V. The SCXI is connected to a computer that measures the amplified signal and saves them.

2.6 Data pre-processing

2.6.1 EEG data

The first steps in the EEG data analysis were made with the BrainVision Analyzer software (Brain Products). The EEG data were segmented in 3 parts: first rest, task and second rest. Every segment was corrected for the MR gradient artifact by detecting the scanner gradient artifacts with the software. The gradient trigger (µV/ms) was set manually, based on the peak values in a histogram (x-axis µV/ms, y-axis %). Since there was a set number of scans during rest or task segments, the markers were considered correct if the amount of detected markers matched with the number of scans. Otherwise, a manual view through the data would have been required to control where the wrong marker was placed. The performance of a baseline correction was used to prevent jumps in the corrected EEG. Otherwise there would be a constant offset in the correction template. For averaging, the 'Sliding Average Calculation' was used. This allowed to address the problem of combined EEG-fMRI measurements, namely that the scanner artifacts may sometimes be greatly modified by even slight movements of the test subjects' head in the scanner. The total number of intervals for the sliding average was 11. After the data were corrected the ballistocardiogram (BCG) was identified and saved. The data were down-sampled to 200 Hz.

Further analysis of the EEG data was performed using Matlab (Mathworks Inc., Natwick, MA), supported by the toolboxes FieldTrip (http:// fieldtrip.fcdonders.nl) and EEGlab (http://sccn.ucsd.edu/eeglab/). With fieldtrip the precise start and end of every trial was calculated and the EEG data were synchronized to the start of the fMRI measurements. The main aim for using these toolboxes in this study is the performance of the Independent Component Analysis (ICA), a computational method for separating a multivariate signal into independent components (Hyvärinen et al., 2001). In this study, EEGlab was used to perform the ICA. It is assumed that the independent components are non-Gaussian and statistically independent. By using ICA, artifacts can be identified and removed from the EEG data. EEG artifacts can be divided into one of the two categories: physiological artifacts and non-physiological artifacts. Artifacts of the first category arise from a variety of body activities, due to either movements of the head, body or scalp that affect the electrode scalp interface, bioelectrical potentials that are generated within the body from moving sources as the eye or muscle twitches, or stationary sources such as scalp muscles or the heartbeat. A third source of physiological artifacts is altered volume conduction due to changes in the conductance of tissues and fluids between the cortex and recording electrodes. Artifacts of the second category, non-physiological artifacts, arise from two main sources, external electrical interference from other power sources and internal electrical malfunction of the recording system (cables, amplifiers etc.) (Fisch and Spehlmann, 1999). The use of ICA artifact removal required a visual as-

sessment of every component. Before ICA, the data were 0.3 Hz high-pass filtered and 60 Hz low-pass filtered. More detailed information about component acceptation or rejection can be found in appendix G.

2.6.2 fMRI data

fMRI data were processed using Matlab toolbox 'Statistical Parametric Mapping' (SPM) (version 8 and 12) (www.fil.ion.ucl.ac.uk/spm). The first step of the preprocessing was the spatial realignment of all volumes to the first scan to correct for inter-scan movement to primarily remove movement artifacts (Ward et al., 2003). For proper correction, subjects cannot move more than 2mm in any direction. Since even smaller movements cause larger artifacts in the EEG, subject should not even move more than 0.5mm. A set of six translational and rotational realignment parameters and constant offsets was determined for every session. Next, normalization of the resulting images was performed using a standardized EPI template based on the Montreal Neurological Institute reference brain in Talairach space (Talairach & Tournaux, 1988) provided by SPM. Last, smoothing the image volumes with a Gaussian kernel with a full-width, half-maximum (FWHM) of double the voxel size was performed to suppress noise and effects due to residual differences in functional and gyral anatomy during inter-subject averaging (SPM12 manual, The FIL Methods Group, 2014).

2.7 Data analysis

2.7.1 Behavioral data

Performance was measured through the strength of frequency-locking between the visual cue and the force performed by the subject (Daffertshofer et al., 2000). The normalized spectral overlap provides the similarity ψ_x^y between two power spectra P_x and P_y after rescaling the frequency axis by a factor $\rho = p{:}\,q$:

$$\psi_x^y(\rho) = \frac{2\int P_x(\omega)P_y(\rho\omega)d\omega}{\int\left[P_x^2(\omega)+P_y^2(\rho\omega)\right]d\omega}$$

2.7.2 EEG data

Beta-activity patterns, measured with EEG, served as regressors for the fMRI, to specify the BOLD changes that can thus be considered relevant for motor performance. The approach taken for the time-frequency analysis of the EEG data is the Hilbert transformation, a transform that is used to determine the analytic signal and, by this, the instantaneous amplitude and phase of a given band-pass signal (Bruns, 2004). Here, the chosen frequency band is 15–30 Hz to acquire beta-activity over one time course. The rele-

vant outcome of the Hilbert transformation for this study is the Hilbert amplitude on a frequency-time plane, the Hilbert spectrum.

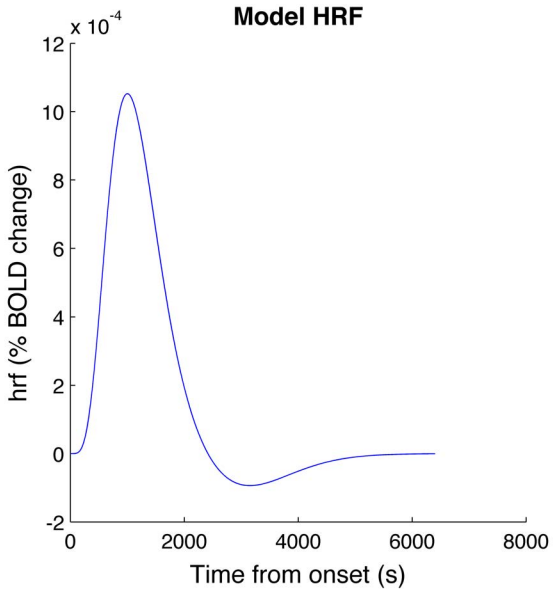

Figure 5 Haemodynamic response function using the standard parameters with repetition time (RT) being 1/200 seconds.

BOLD-responses have a delayed and dispersed form. Therefore, for every channel a regressor is calculated by convolving the beta-power (obtained with the Hilbert transformation) with the haemodynamic response function. This function is produced with SPM (figure 5).

For every subject a beta-activity regressor was calculated of the complete task period of 22.30 minutes. These regressors were down sampled to 700 samples, the same length as the fMRI volumes. Since the beta-activity regressors were likely to be quite correlated and a high amount of regressors (statistically parameters) had the effect of decreasing the degrees of freedom (DOF), Principal Component Analysis (PCA) was performed to reduce the amount of regressors (Daffertshofer et al., 2004). PCA uses an orthogonal transformation that converts the regressors into a set of linearly uncorrelated variables, such that the greatest variance is explained in the first principal component. A vector that consisted of only positive values accompanied the first component. This indicates an overall brain wave, independent from the motor task. A beta brain state that associated is with waking consciousness (Yanagawa et al., 2014). Therefore, the second component was used for further analysis.

2.8 Statistics

The mass-univariate toolbox with a voxel-based approach, SPM, test hypotheses about regionally specific effects (Penny et al., 2011). A combination of the general linear model (GLM) and Gaussian random field (GRF) theory makes classical inferences about spatially extended data through statistical parametric maps. The GRF theory was used to resolve the multiple comparison problem that arises when making inferences over a volume of the brain (Friston et al., 2003). The data were modeled with the GLM to make interferences about effects of interests. This was done by decomposing the data into effects and error and forming statistics using the estimates of these effects and error.

The GLM was given by

$$Y = \beta_k X_k + e$$

with Y as the voxel-wise time series of the BOLD data. This is a data vector with the length of the number of scans and for every scan all the independent voxels. A design matrix (model) was created to explain the BOLD data ($\beta_k X_k + e$). This design matrix embodies all available knowledge about experimentally controlled factors and potential confounds. By adding regressors (X), additional columns are included in the design matrix. Here, the experimental design, i.e. task function, the EEG-based beta-activity regressors and the set of six translational and rotational realignment parameters and constant session offset were included in the design matrix (figure 11 and 12 show examples of this design matrix). These were all vectors with the same length as the number of scans in the BOLD data. For every regressor a voxel-wise parameter β was estimated by minimizing the residual variance (e) by using the Ordinary Least Squares estimation (OLS). Assumed is that the smallest errors are found when e is orthogonal to X (Phillips, 2011). This leads to:

$$X^T e = 0$$
$$X^T\left(Y - X\hat{\beta}\right) = 0$$
$$X^T Y = X^T X\hat{\beta}$$
$$\hat{\beta} = (X^T X)^{-1} X^T Y$$

Defining a contrast through selecting a combination of parameters processed the results. As Poline showed in his presentation, T-tests are simple combinations of the parameters; they are either positive or negative. While F-tests test for the additional variance explained by a larger model with respect to a simpler model. Here, we want to test, performing a T-test, whether the parameter β estimated based on the beta-activity regressor differs from zero (null-hypothesis; β = 0), with:

$$T = \frac{contrast\ of\ estimated\ parameters}{\sqrt{variance\ estimate}}$$

SPM calculated T values for every voxel by assessing the ratio of explained variance (the contrasted parameter β) and unexplained variance (the amount of variance that could not be fitted in your model). If a region in the brain reaches a p-value smaller than 0.01 indicates this that the parameter β differs significantly from zero and is greater than only being noise. The regressor coupled to this parameter significantly explains the BOLD data

at these voxels. Next to this test, we tested the effect of the experimental design. Where do we find significant differences when movement (2 min trials) is compared to rest (15 sec break), without taking the beta-activity into account? Based on the single-subject contrast a group-level-random effect analysis was calculated.

3 Results

3.1 Behavioral task

In total, 23 young subjects completed the 10 trials of the behavioral task. As explained before, for every subject the performance was measured through the strength of frequency locking between the visual cue and the force performed by the subject. Subjects that performed the first 3 trials a frequency locking of 0.8 or higher were excluded from the study. As a result, the mean performance of 18 young subjects is shown in figure 6a. One elderly subject used both hands during the unimanual task. This subject is discarded from further analyses. The behavioral data of 13 elderlies were included in the analyses shown in figure 6b. Both groups showed a significant improved performance at trial 10 compared to trial 1 *(young; trial 1: 0.34 (mean) ± 0.05 (standard error), trial 10: 0.66 ± 0.04 (p = 0.005), elderly; trial 1: 0.35 ± 0.06, trial 10: 0.57 ± 0.08 (p = 0.003))*.

The behavioral re-assessment, necessary to differentiate between training and learning, showed an improvement of the task performed the next day. Figure 7 shows the mean retention test for the young (a) and elderly (b) subjects.

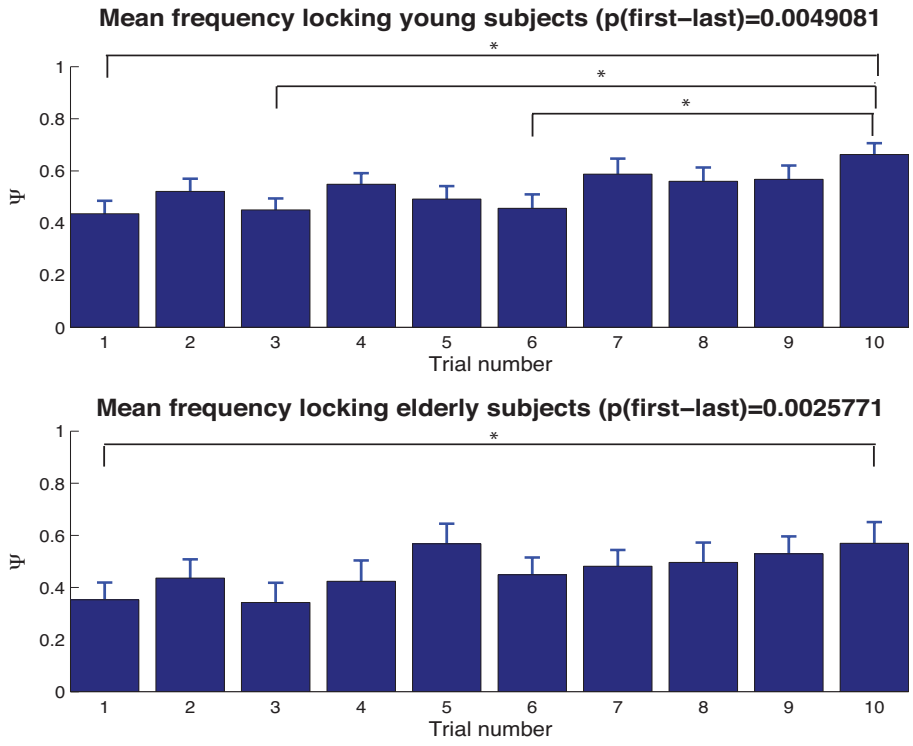

Figure 6 Mean performance and standard error per trial of a) 18 healthy young subjects and b) 13 healthy elderly subjects (* = p < 0.01).

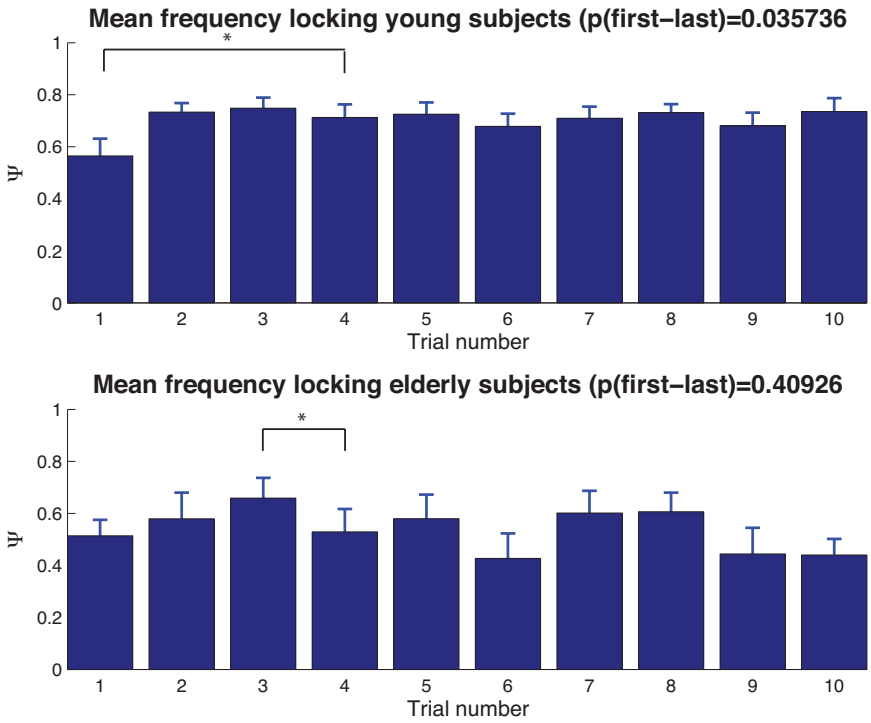

Figure 7 Retention test: mean performance and standard error per trial of a) 18 healthy young subjects and b) 13 healthy elderly subjects (* = p < 0.01).

3.2 Bilateral interference

In the current report the EEG and fMRI data of 5 elderly subjects and 5 young subjects were analyzed. During the final step of group analysis, the data of one elderly did not match the dimensions of the others, so the group analysis is performed with the data of only 4 elderly. Figure 8 shows the regions in the brain that are significantly active as a result of the experimental design, movement activity versus the 15 seconds break, of one younger and one elderly subject.

Figure 9 shows the group results of the young and elderly subjects. The glass brain images show a significant inverse relationship between the EEG-based beta-activity parameter and the BOLD signal for the complete brain. Only activation that exceeds the threshold is shown. The darker the grey dots in the plots, the larger the T-value, the more significant the EEG-based beta-activity regressor explains the BOLD-data. The analysis did not show any significant correlations at the applied threshold of P < 0.001 (uncorrected for multiple comparisons). A lower threshold yielded positive correlations (P < 0.01).

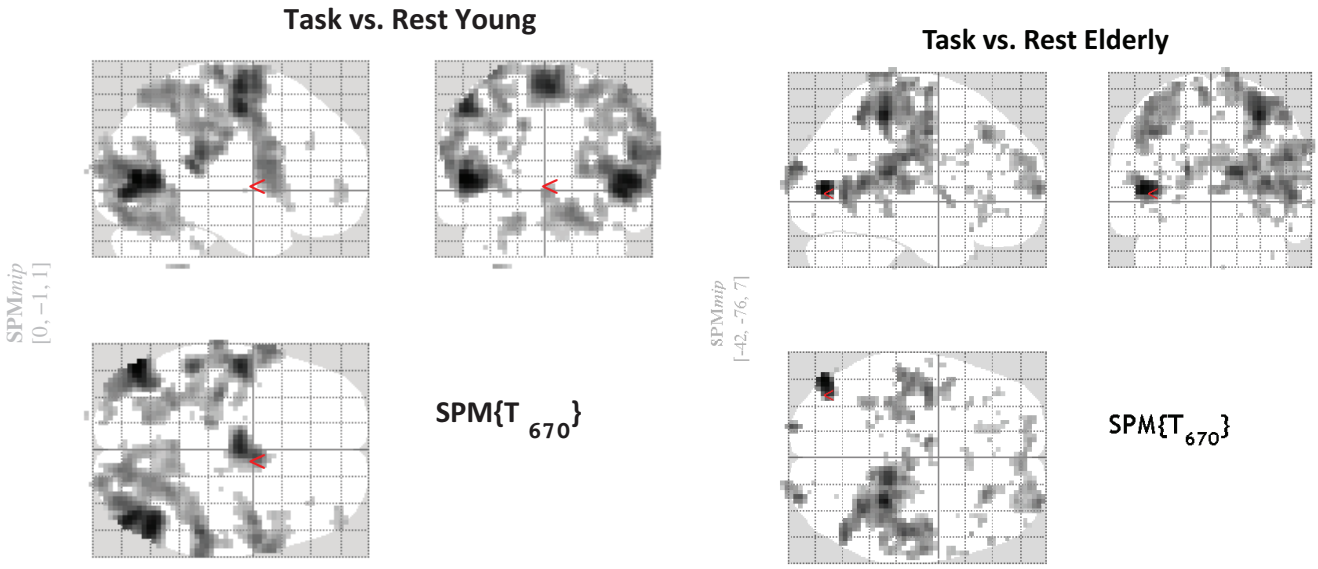

Figure 8 Glass-brain images of one younger individual show the significant activity related to the experimental design (task-related activity and the 15 seconds rest) (p<0.0001 {uncorr.}). The top-right image is coronal with the top (superior) of the head displayed at the top and the left shown on the left, as if the subject is viewed from behind. The top-left image is sagittal with the front of the head (anterior) of the head at the right and the top of the head shown at the top, as if the subject is viewed from the left. The bottom-left image is axial with the front (anterior) of the head at the left and the left at the bottom, as if the subject is shown from behind.

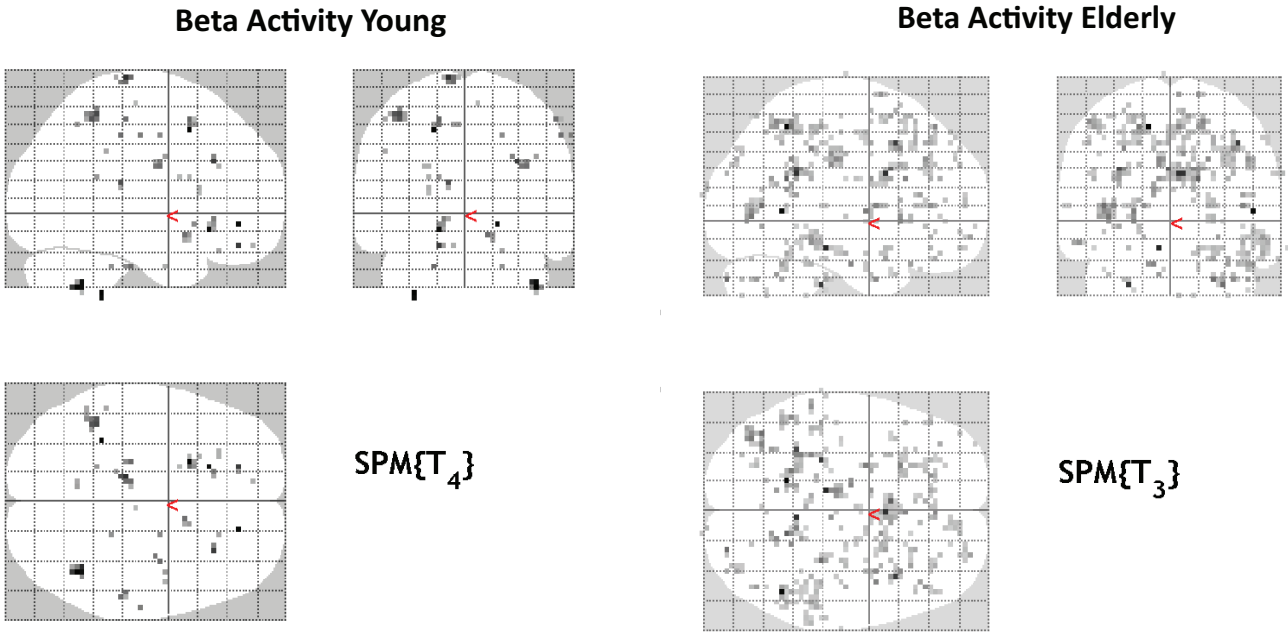

Figure 9 Group results young (left) and elderly (right) subjects. Glass-brain images show the significant relationships between the EEG-based beta-activity regressors and the BOLD signal for the respectively complete brain (p<0.01 {uncorr.}).

The individual results of two subjects are shown in figure 11 and 12. Again the significant inverse relationship between the EEG-based beta-activity parameter and the BOLD signal for the complete brain is visible. In the elderly subject (figure 12), more activation was found over the whole brain compared to the younger subject. The results of the other 8 analyzed subjects can be found in Appendix H.

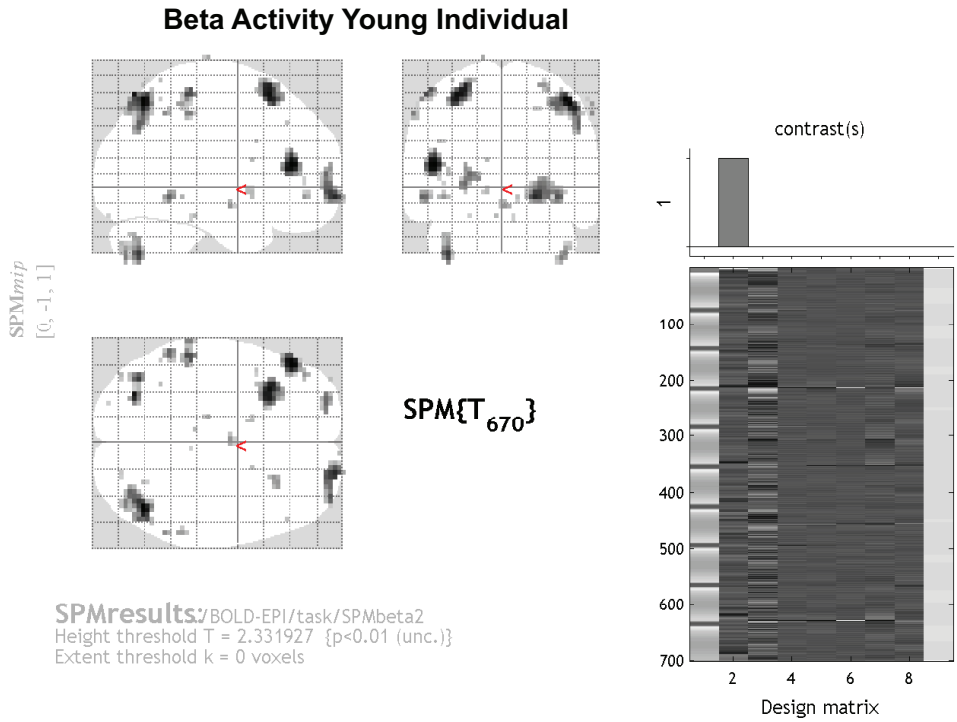

Figure 11 Individual single level result young subject. Glass-brain images show the significant relationship between the EEG-based beta-activity regressors and the BOLD signal for the complete brain (p<0.01 {uncorr.}). On the right is shown that the contrast that is chosen of the design matrix is the beta-activity parameter. Not the paradigm or the set of six translational and rotational realignment parameters.

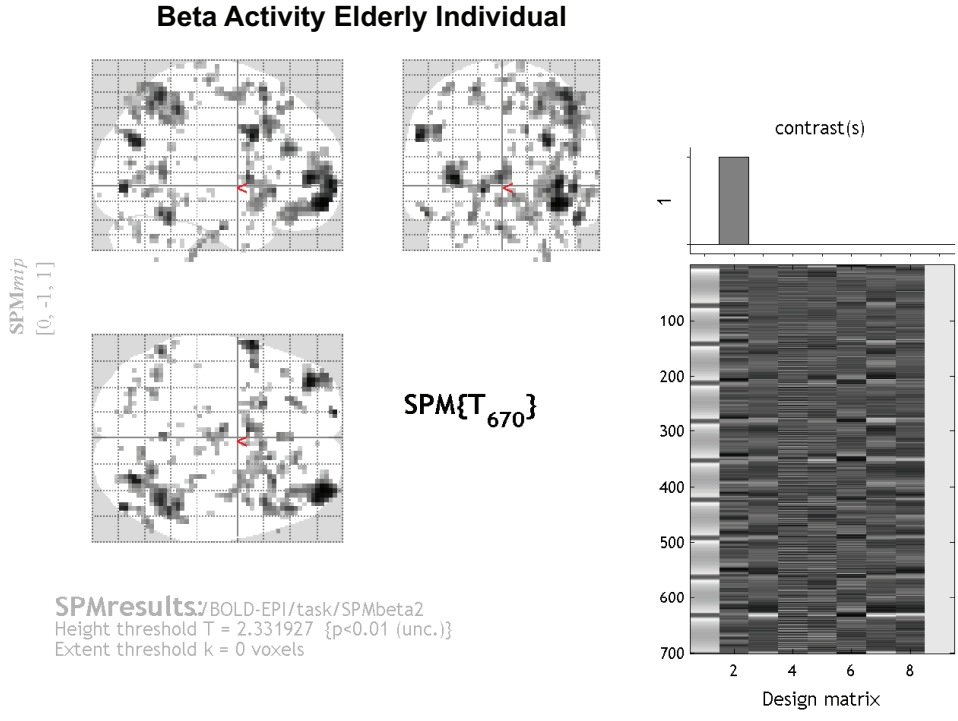

Figure 12 Individual single level result elderly subject. Glass-brain images show the significant relationship between the EEG-based beta regressors and the BOLD signal for the complete brain (p<0.01 {uncorr.}). On the right is shown that the contrast that is chosen of the design matrix is the beta-activity parameter. Not the paradigm or the set of six translational and rotational realignment parameters.

4 Discussion

4.1 Behavioral task

Learning was expected to not exceed 15 minutes in both groups and to be increased with age. Both groups significantly improved performing the unimanual motor task and the retention test shows that we can consider this as learning, since one day later subjects performed from the start of the experiment on better than the day before. Most likely the integration of perception and motor components made this possible (Mechsner et al., 2001). In both groups, there was no learning plateau visible after 15 minutes. From the start, young subjects performed better than the elderly subjects. This is probably due to their experience with controlling devices. The elderly people experienced already difficulties by just properly squeezing the balloon. Interestingly however, overall the elderly group had a more significant learning effect, in line with previous findings (Shimoyama et al., 1990; Ward et al., 2003; Houx and Jolles, 1993; Kauranen and Vanharata, 1996; Smith et al., 1999)

During the experiments we encountered many difficulties with the balloon as recording device. Performing a correct baseline without drift or flipping was difficult, rendering informing participants to not squeeze too hard more important than expected. An alternative for assessing unimanual force production, like the isometric force sensors used in the experiments of Houweling et al. (2008), might be easier to handle, in particularly for the elderly. One may also expect that these sensors result in a smaller between-subjects variability because they involve fewer degrees of freedom in producing the force as compared to pressing a balloon. However, one has take into account that the device has to be MR-compatible.

4.2 Bilaterale interference

Bilateral M1 were expected to be the most dominant ROIs during the task. Beta-modulation in the ipsilateral M1 was expected to be stronger in the elderly, indicating less effective inter-hemispheric inhibition compared to young participants. As expected, when comparing the task-related activity with the resting breaks of 15 seconds, the bilateral M1 are the most dominant active regions. The main finding of the group analysis was the greater overall brain activity in the elderly group compared to the younger group while performing the same task. Suggested is that because of a degeneration of the elderly brain (mainly of the corpus callosum), a dis-balance in the inter-hemispheric cross-talk and inhibition is caused (Daffertshofer et al., 2005). Further research should – and will – investigate the anatomical part by analyzing DTI data. Notable activity found in the younger subjects was activity in the cerebellum. The cerebellum plays an important role in motor control and coordination. Due to its capability of long-term depression of parallel fibers, the cerebellum stands out as primary site of adaptive changes. During motor con-

trol, the cerebellum is a main contributor to the communication between PM1 and M1 (Houweling et al., 2008). However, Houweling et al. (2008) found alpha-activity instead of beta-activity. Further research could investigate this frequency band.

A group analysis appears beyond the scope of the current internship. A group analysis cannot be reliable when performed with 5 young, vis-à-vis 4 older subjects; after all there are only 4 (or 3) degrees of freedom. More subjects need to be analyzed to draw conclusions. For this reason, the focus is on the individual results of two subjects. The younger subject (figure 11) showed a strong activation in a part of the parietal lobe. Fogassi and Luppino (2005) state that the posterior partial lobe can be considered as part of the motor system. One of its roles is to integrate sensory and motor signals necessary for motor planning and sensory guidance of movement. There is also activity visible anterior to the M1-S1 compounds in the young subject, which is absent in the left hemisphere. This part of the frontal lobe includes executive functions, thinking, planning and organizing.

The elderly subject (figure 12) showed, like most elderly subjects (appendix H), a strong activity all over the brain. Although it was a right-handed motor task, most activity was visible in the right hemisphere for this subject. The largest activation was found in the prefrontal cortex (figure 12). This area is involved in cognitive and emotional functions and participates in the cognitive aspects of behavior (Fuster, 1988). The task seemed more demanding for the elderly subjects, which explains why they used a region that is engaged in the organization of goal-directed behavior. Whether these age-related differences in brain activity, in particular ipsilateral activity, correlate with CC integrity cannot be concluded from this study. The DTI data that were obtained will be analyzed in the future.

As of today simultaneous EEG-fMRI measurements appear one of the most proper ways to localize neuronal activity noninvasively (Moosman et al., 2003). Both modalities have already been used separately for a long time; the combination is a state-of-the art way to investigate brain function. Although, combing the two modalities brings several technical challenges. The major problem is the electromagnetic induction, i.e. the emergence of an electromotive force in a conductor enclosed by a change (Ritter & Villringer, 2006). Another well-known problem of EEG is volume conduction, the effect of recording electrical potentials at a distance from their source generator (Rutkove et al., 2007). Also volume conduction has major influences on source strength estimation and causes difficulties with source localization (Haueisen et al., 2002). To improve the current results, the influence of volume conduction needs to be reduced. However, since invasively methods are mostly not appreciated, analyzing techniques like the Laplace transform or using EEG networks as regressors are needed to minimize the effects of volume conduction.

To get rid of the multiple comparison problem, which would be present with 61 regressors (from 61 channels), a method for dimension reduction had to be used. The partial least squares (PLS) and principle component analysis (PCA) are the two most common used methodologies (Maitra & Yan, 2008). The difference between the two, also stated by Maitra and Yan (2008), is that PCA is applied without the consideration of the correlation between the dependent variable and the independent variable, while PLS is applied based on the correlation. Since the dependent variable was unknown and needed, the PCA method was used. At the same time, this is also a drawback of the PCA technique, because no importance was given to the predictability of each variable.

SPM12 offers different ways and options for analyzing imaging data. When the model is fitted, each regressor receives a beta that determines the amount of variance explained by that regressor. Several combinations are possible when defining contrasts. Here, a simple contrast, a T-contrast is used, to test whether the beta determined by the beta-activity regressor differs from zero. Another option would be to take into account both the beta-activity regressor and the paradigm. If any of the regressors, regardless of directions, explains a significant amount of variance, conducting a F-test is more accurate. Also interesting for further research would be to focus more specific on smaller time frames and compare for example the first two minutes with the last two minutes.
The Hilbert transform provides two different outcome variables: amplitude (power) and phase. To create the regressor, the beta power was used in the current analysis. Another option would have been to use the beta phase output as a regressor, expressing the frequency as a rate of change in phase.

5 Conclusions

Aim of the current study was to investigate how and where structural neural changes alter the symmetry of activity patterns during unimanual movements and the age-related differences in the process of learning. Elderly subjects activated more brain areas compared to young subjects while performing the same task. Next, elderly subjects needed more time to learn a unimanual polyrhythmic motor task. This suggests that performing a unimanual motor task is more demanding for elderly, which results in a compensation by activating more brain regions – the more regions are involved the longer it takes to orchestrate them to produce (coordinated) motor behavior. Final conclusions can only be draw when more subjects are analyzed, which will be done during a PhD project covering this master's report.

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7 Appendix

7.1 Appendix A

Systematic literature search assessments/tests for elderly subjects

Authors + Year	**Journal**	**Age (y) participants**	**Edinburgh Handedness Inventory**	**CERAD-PLUS*1**	**Mini-Mental State Examination**	**Montreal Cognitive Assessment**
Salimpour and Shadmehr (2014)	Journal of Neuroscience	59.2 ± 8	X			
Lindenberg et al. (2013) *2	Journal of Neuroscience	68.2 ± 5	X	X		
Heise at al. (2013) *3	Journal of Neuroscience	20-88	X			
Goble et al. (2011)*4	Journal of Neuroscience	62.3 – 81.3	X		X	
Berchicci et al. (2014) *5	Frontiers Aging Neuroscience	65 – 86	X		X	
Zimerman et al. (2014) *6	Cerebral cortex	58 - 85	X		X	
Fling at al. (2012)	Cerebral Cortex	67.2 ± 5.2	X			X
Stewart et al. (2014) *7	NeuroImage	48-77	X		X	
Coxon et al. (2010)	Cerebral Cortex	60 – 74	X		X	
Goble et al. (2010) *8	Human Brain Mapping	61.1 – 78.7	X		X	
Huang et al. (2014) *9	Journal of Neurophysiology	73.8 ± 5.6				
Plow et al. (2013) *10	Journal of Neurophysiology	74.79 ± 1.37	X		X	
Fujiyama et al. (2013) *11	Journal of Neurophysiology	70.6 ± 6.4			X	

*1: Neuropsychological test battery oft he Consortium to Establish a Registry for Alzheimer's Disease

*2: None of the subjects reported use of psychoactive medication or recreational drugs, and none of them had neurological or psychiatric disorders

*3: All subjects were screened regarding neurological of psychiatric illness, other medical conditions, and medication intake interfering with the experimental procedures or outcome (Rossi et al., 2009)
*4: No neuromuscular impairment or use of psychoactive or vasoactive medications. Elderly were generally physically fit.
*5: All of the participants were healthy and without history of neurological, psychiatric, or chronic somatic problems. They were not taking psychoactive or vasoactive medication.
*6: None reported a history of serious medical, neurological, or psychiatric diseases or any contraindications for tDCS or TMS, as probed by a standardized questionnaire, none of them were taking any CNS-active medication
*7: Excluded if they had a history of any neurological diagnosis that affected movement of the arms.
*8: Subjects were free of neuromuscular impairment at the time of testing and were not under psychoactive or vasoactive medication
*9: Subjects had no physical injuries, known pathologies, or factors that affected their neurological, musculoskeletal, and cardiorespiratory health. With respect to neurological medications, none of the subjects was taking antidepressants, medications to prevent seizures, antipsychotics, sedatives, hypnotics, or pain medications.
*10: Exclusion criteria included any confounding neurological disorder or musculoskeletal condition affecting the upper limbs.
*11: All participants were free of any neurological or symptomatic cardiovascular disease, diabetes, or hypertension.

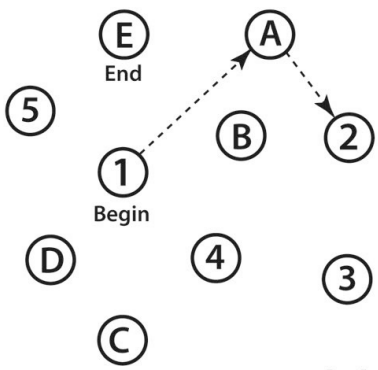
7.2 Appendix B

Montreal Cognitive Assessment (MoCA)

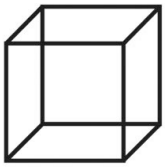
MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.1 Original Version

NAME :
Education : Date of birth :
Sex : DATE :

VISUOSPATIAL / EXECUTIVE — POINTS



Copy cube



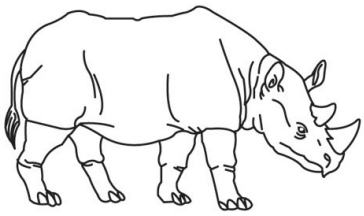
[ ] [ ]

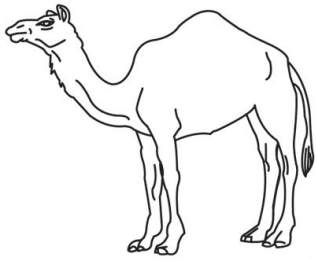
Draw CLOCK (Ten past eleven)
(3 points)

[ ] Contour [ ] Numbers [ ] Hands

___/5

NAMING





[ ] [ ] [ ]

___/3

MEMORY Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION Read list of digits (1 digit/ sec.).

Subject has to repeat them in the forward order [ ] 2 1 8 5 4

Subject has to repeat them in the backward order [ ] 7 4 2

___/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

___/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**

___/3

LANGUAGE Repeat : I only know that John is the one to help today. [ ]

The cat always hid under the couch when dogs were in the room. [ ]

___/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words)

___/1

ABSTRACTION Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler

___/2

DELAYED RECALL

	Has to recall words **WITH NO CUE**	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only
Optional	Category cue						
	Multiple choice cue						

___/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

___/6

© Z.Nasreddine MD **www.mocatest.org** Normal ≥ 26 / 30

TOTAL ___/30

Add 1 point if ≤ 12 yr edu

Administered by: _____

7.3 Appendix C

Exclusion criteria MRI study

	Yes	No
Pregnancy or lactation		
Chronic-degenerative or inflammatory CNS-disease		
Severe cognitive or/and neuropsychological impairment		
Severe pain syndrome or other severe somatic diseases		
Known epilepsy		
Severe psychiatric disease		
Severe neurological disease		
Severe diabetic polyneuropathy		
Malignancy		
Heart failure		
Heart attack / stroke		
Severe chronic liver- or kidney failure		
Severe diseases of the hematopoietic system		
Alcohol addiction or drug abuse		
A history with severe allergic or toxic reactions		
Participation to an other clinical medical/drug study less than 4 months for inclusion		
Doubts about the business- or capacity for insight		
Custody in an institution of judicial or administrative arrangement		
Treatment with centrally acting medications (Anti-psychotics, Anti-epileptics, Anti-depressives etc.)		
Non-removable metals (aneurysm clips, artificial joints, clips etc.) or implanted electronic devices (pacemakers, pumps etc.)		
Tattoos		
Claustrophobia		
Acute infection/discomfort		

If one of the points is answered with "yes", will this be used as exclusion criteria

7.4 Appendix D

Information participation study

CHARITÉ

CharitéCentrum für Neurologie, Neurochirurgie und Psychiatrie

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Information zur Teilnahme an der Studie:

" Bilaterale Interferenz –
Warum wird die Koordination schwieriger im Alter?"

Sehr geehrte/r Proband/in,

Bevor Sie sich entscheiden, an dieser Untersuchung teilzunehmen, möchten wir Sie kurz über das Ziel der Studie, den Ablauf und ihre Untersuchungsmethoden unterrichten. Bitte lesen Sie die folgenden Informationen sorgfältig durch. Sie können jederzeit nachfragen, wenn Ihnen etwas unklar ist.

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Aufbau des Versuches
Ziel des Versuches ist es zu untersuchen, inwiefern die veränderte Symmetrie funktioneller Aktivierungsmuster im Großhirn (Cortex) auf altersbedingte neuroanatomische Veränderungen im Balken (Corpus Callosum) – der Verbindung beider Hirnhälften – zurückzuführen ist. Dafür benötigen wir sowohl anatomische als auch funktionelle Messungen Ihres Gehirns, die wir mittels Elektroenzephalografie (EEG) und Magnetresonanztomografie (MRT) gewinnen.

Ablauf:

1. Anatomische Messungen
   - reine Magnetresonanztomografie (MRT), Dauer etwa 19 Minuten
   - Aufgabe: ruhig liegen, Bewegungen (besonders des Kopfes) vermeiden
2. Messung der Ruheaktivität
   - zunächst reine Elektroenzephalografie (EEG), Dauer etwa 1 Minute
   - anschließend simultane EEG-MRT-Messung, Dauer etwa 5 Minuten
   - Aufgabe: ruhig liegen, Augen geschlossen halten, Bewegungen (besonders des Kopfes) vermeiden, **nicht einschlafen!**

3. Test- und Lernphase

- simultane EEG-MRT-Messung, Dauer etwa 20 Minuten
- Aufgabe: **mittels rhythmischer Bewegen der rechten Hand die visuelle Rückmeldung auf dem Computerdisplay kontrollieren**; dabei ruhig liegen, sonstige Bewegungen (besonders des Kopfes) vermeiden

4. Messung der Ruheaktivität

- simultane EEG-MRT-Messung, Dauer etwa 5 Minuten
- Aufgabe: ruhig liegen, Augen geschlossen halten, Bewegungen (besonders des Kopfes) vermeiden, **nicht einschlafen!**

Die Untersuchungen dauern inklusive Vor- und Nachbereitung etwa 2,5 Stunden, unterbrochen von Ruheperioden. Die reine Zeit im MRT wird 45 Minuten nicht überschreiten. Die Messungen können von ihnen jederzeit abgebrochen werden.

Untersuchungen und ihre Risiken
Bei allen Untersuchungen werden Sie von uns begleitet und genau angeleitet. Liegen keine Bedenken vor, können Sie sich entscheiden, ob sie an der Studie freiwillig teilnehmen möchten. Ihre Einwilligung können Sie jederzeit widerrufen.

Elektroenzephalografie
Mit Hilfe der Elektroenzephalografie – kurz EEG – wird ihre Hirnaktivität gemessen. Unser Gehirn generiert elektrische Signale, die von außen registriert werden können. Dazu wird Ihnen eine spezielle Haube aufgesetzt an der Messaufnehmer (Elektroden) angebracht sind. Diese Haube müssen Sie während der gesamten Untersuchung tragen, damit wir die Hirnaktivität erfassen können. Für die Messung muss ein Kontakt mit ihrer Kopfhaut hergestellt werden. Das wird erreicht, indem die Elektroden mit einem hypoallergenen Gel, welches im Wesentlichen aus Wasser, Kochsalz und Verdickungsmittel besteht, gefüllt werden. Um die Signale aufzuzeichnen und auszuwerten ist die Haube mit einem Messsystem verbunden. Die Messung erfolgt aber rein passiv, d.h. es wird dabei kein Strom an Ihren Körper angelegt. Um das Gel nach der Messung von der Kopfoberfläche wieder zu entfernen, müssen Sie sich die Haare waschen. Dazu stehen in unserem Labor ein Waschbecken und Shampoo zu Verfügung. Wir sind Ihnen gerne beim Waschen und Trocknen der Haare behilflich.

Mögliche Risiken der Elektroenzephalografie
Die Messung der Hirnaktivität (EEG-Messung) ist für den Körper völlig unschädlich. Bei der EEG-Messung kommen nur solche Geräte zum Einsatz, die den einschlägigen Sicherheits-bestimmungen genügen. Sie werden in gleicher Form auch in klinischen Routineuntersuchungen in vielen Krankenhäusern weltweit eingesetzt.

Magnetresonanztomographie
Die Magnetresonanztomographie – kurz MRT – ist ein modernes Verfahren, das zur Abbildung der Hirnanatomie (strukturelle Bildgebung) und der Hirntätigkeit (funktionelle Bildgebung) eingesetzt werden kann.
Die strukturelle Bildgebung kann z.B. Veränderungen in der Dichte der grauen Substanz oder in der Faserdichte der weißen Substanz des Gehirns aufzeigen. Dazu werden bestimmte magnetische Eigenschaften der Gewebe ausgenutzt, z.B. verhält sich Wasser anders als Fett. So können am Computer anatomische Bilder des Gehirns erstellt werden.
Die „funktionellen Untersuchungen“ erlauben demgegenüber eine „Markierung“ der Hirnareale, die während einer Aufgabenstellung „aktiv“ sind und miteinander arbeiten. Die Nervenzellen des Gehirns verbrauchen bei ihrer „Arbeit“ Sauerstoff. Sauerstoffarmes und sauerstoffreiches Blut besitzen unterschiedliche magnetische Eigenschaften. Daher lässt sich neben der Anatomie auch die Gehirntätigkeit mit MRT darstellen. Das MRT-Gerät arbeitet zur Bildherstellung mit Radiofrequenzen im UKW-Bereich in einem starken Magnetfeld, also nicht mit Röntgenstrahlen oder radioaktiven Stoffen. Die Signale aus Ihrem Körper werden von einer sehr empfindlichen

Spule („Antenne“) aufgefangen und über Computerprogramme in Bilder umgewandelt.
Die MRT-Untersuchung wird in einem speziellen Raum durchgeführt. Während der Untersuchung liegen Sie mit dem Oberkörper in einer speziellen Röhre (starker Magnet). Diese ist vorn und hinten offen und hat einen Durchmesser von ca. 60 cm. Manche Menschen empfinden das als etwas ungewohnt, gewöhnen sich aber in der Regel nach wenigen Minuten daran. Sie werden gebeten, sich auf eine bewegliche Liege zu legen, die etwa 1 m in die Öffnung der Röhre gefahren wird. Unser MRT-Personal hilft Ihnen bei der Lagerung.
Das MRT-Gerät wird aus einem Nebenraum heraus bedient. Die Untersuchungsleiter können Sie während der Untersuchung durch ein Fenster und durch ein Kamerasystem sehen. Über eine eingebaute Gegensprechanlage können wir Sie hören und mit Ihnen reden. Auf diesem Wege geben wir Ihnen während der Untersuchung Informationen und fragen Sie nach Ihrem Befinden.

Zusätzlich erhalten Sie eine Alarmklingel (Druckball), mit der Sie sich jederzeit bemerkbar machen können, z.B. wenn sie die Untersuchung aus irgendeinem Grund abbrechen möchten.
Während der eigentlichen Messung werden Sie unterschiedlich laute Klopfgeräusche hören, die auf elektromagnetischen Schaltvorgängen im Magneten beruhen und Ihnen signalisieren, dass jetzt Daten aufgenommen werden. Um die Lärmbelastung zu verringern, erhalten Sie schalldämpfende Ohrenstöpsel, die Sie während der gesamten Untersuchung tragen.
Die Gesamtdauer der MRT-Untersuchung beträgt etwa 45 Minuten. Es ist außerordentlich wichtig, dass Sie die gesamte Zeit über sehr ruhig liegen und insbesondere den Kopf nicht bewegen, denn leider führen bereits Kopfbewegungen von weniger als einem Zentimeter zu unbrauchbaren Bildern (ähnlich dem Verwackeln beim Fotografieren).

Mögliche Risiken der Magnetresonanztomographie
Metallteile, die in das Magnetfeld gelangen, können zu Verletzungen und Bildstörungen führen!
Deshalb müssen sämtliche metallische, magnetische und elektronische Gegenstände vor Betreten des Untersuchungsraums abgelegt werden. Beispielsweise betrifft dies Prothesen, herausnehmbaren Zahnersatz, Brille, Hörgeräte, Geldbörsen und Kreditkarten, Uhren, Mobiltelefone, Haarspangen, Schmuck, Piercings, Kugelschreiber, Schlüssel, Taschenmesser, etc. Ihre Wertgegenstände können Sie für die Zeit der Untersuchung in einem Schrank verschließen. Auch in Make-ups bzw. Lidschatten können metallische Anteile sein, die die Bildqualität beeinträchtigen. Zu Ihrer eigenen Sicherheit bitten wir Sie, sich an die Anweisungen des MRT-Personals zu halten.
Die Anwendung von Magnetfeldern bei der MRT-Untersuchung schließt die Teilnahme von Personen aus, die elektrische Geräte (z.B. Herzschrittmacher, Medikamentenpumpen usw.) im oder am Körper haben. Wenn Sie Träger eines medizinischen Implantats sind (z. B. künstliche Herzklappe, Shunt, Portsystem, künstliche Gelenke, Schrauben nach Knochenbrüchen), muss vor der Untersuchung überprüft werden, ob das Implantat für eine MRT-Untersuchung geeignet ist. Die räumlichen Verhältnisse im MRT-Magneten lassen es nicht zu, Personen mit starken Rückenbeschwerden oder übermäßigem Übergewicht zu untersuchen. Auch sollten starke, schnelle Bewegungen im MR-Magneten unterbleiben.
Der Magnetresonanztomograph verursacht während der Untersuchung sehr laute Klopfgeräusche. Dies hat, wie erwähnt, technische Gründe und ist völlig normal. Um Gehörschädigungen auszuschließen, werden Sie während des Experiments Ohrenstöpsel tragen.
In der verhältnismäßig engen Röhre des MR-Tomographen kann es zu Empfindungen von Platzangst kommen. Sobald Sie sich unwohl fühlen, können Sie den Versuch, ohne Angabe von Gründen, jederzeit beenden und sich von uns aus dem MR-Tomographen helfen lassen.

Umgang mit Zufallsbefunden
Die Untersuchung wird zu rein wissenschaftlichen Zwecken durchgeführt und dient nicht der klinischen Diagnostik. Die MRT-Aufnahmen werden aber durch einen Arzt beurteilt, wobei manchmal Auffälligkeiten festgestellt werden. Die Häufigkeit solcher Zufallsbefunde liegt unter 10%. In seltenen Fällen führen Zufallsbefunde auch zur Feststellung behandlungsbedürftiger Erkrankungen (z.B. Tumoren, Gefäßmissbildungen, Multiple Sklerose). In einem solchen Fall werden wir Sie umgehend informieren und mit Ihnen weitere erforderliche Diagnoseschritte besprechen. Aus diesem Grund können Sie nur an der Untersuchung teilnehmen, wenn Sie krankenversichert sind. Bitte beachten Sie auch, dass sich die Feststellung von Zufallsbefunden

ungünstig auf die Aufnahme in eine private Krankenversicherung auswirken kann. Außerdem können Zufallsbefunde negative psychologische Folgen wie depressive Verstimmung haben.

Aufwandsentschädigung der Studienteilnehmer
Für die Teilnahme wird nach Beendigung der Studie eine Aufwandsentschädigung in Höhe von 10 Euro pro Stunde gezahlt. Durch ihre Teilnahme an der Studie entstehen Ihnen keine Kosten.

Ein- und Ausschlusskriterien
An der Untersuchung teilnehmen können gesunde Probanden im Alter zwischen 20-25 Jahren bzw. zwischen 60-70 Jahren.
Eine Teilnahme kann bei Hinweisen auf neurologische Erkrankung, Einnahme von Medikamenten, die auf das zentrale Nervensystem wirken, Vorliegen einer gravierenden internistischen oder psychiatrischen Vorerkrankung, Demenz, Drogen- oder Alkoholabhängigkeit nicht erfolgen. Um Personen mit möglichem Risiko von der Untersuchung auszuschließen, möchten wir Sie bitten, den beiliegenden **Fragebogen** sorgfältig auszufüllen.

Datenschutz
Durch Ihre Unterschrift auf der Einwilligungserklärung erklären Sie sich damit einverstanden, dass die Studienleiterin und das Studienteam Ihre personenbezogenen Daten zum Zweck der o.g. Studie erheben und verarbeiten dürfen. Personenbezogene Daten sind z.B. Ihr Name, Geburtsdatum, Ihre Adresse und Daten zu Ihrer Gesundheit oder Erkrankung oder andere persönliche Daten, die während Ihrer Teilnahme an der Studie zweckgebunden erhoben wurden.
Der Studienleiter und das Studienteam werden Ihre personenbezogenen Daten für Zwecke der Verwaltung und Durchführung der Studie verwenden und diese, mit einer Codenummer (Pseudonym) versehen, so dass eine spätere Zuordnung der Daten zu Ihrer Person nur noch der Studienleiterin und ihrem Studienteam, nicht jedoch Dritten, möglich ist.
Die pseudonymisierten Daten dienen ausschließlich dem Zwecke der Forschung und statistischen Auswertung und werden zu ausschließlich diesem den Arbeitsgruppen von Prof. Andreas Daffertshofer, der Universität Amsterdam und Prof. Xie Song-yun, der Polytechnischen Universität, Xi'an, China, zur Verfügung gestellt und im Zuge des Projektes: „The Virtual Brain" (http://www.thevirtualbrain.org) auf einen Server in Toronto, Kanada, geladen und damit anderen Forschungsgruppen zugänglich gemacht. Der übermittelte, pseudonymisierte Datensatz enthält neben den gemessenen Daten lediglich Alter, Geschlecht und Händigkeit. Auf den Codeschlüssel, der es erlaubt, die studienbezogenen Daten mit Ihnen in Verbindung zu bringen, hat nur die Studienleiterin und ihr Studienteam Zugriff. Eine Zuordnung der auf den Servern hinterlegten Daten durch andere Arbeitsgruppen ist damit nicht möglich und Ihre Identität bleibt anonym.
Bitte beachten Sie, dass der Zweck der Forschung auch die Veröffentlichung der Ergebnisse in Fachzeitschriften umfasst. Dabei werden aber keine Ergebnisse einzelner Personen, sondern nur von Personengruppen berichtet. Ihre Identität bleibt in jedem Fall anonym.
Sie haben das Recht auf Auskunft über alle beim Studienarzt oder dem Auftraggeber der Studie vorhandenen personenbezogenen Daten über Sie. Ferner haben Sie das Recht auf Berichtigung unrichtiger personenbezogener Daten. Die vorhandenen Daten werden für den Zeitraum von 10 Jahren gespeichert und danach vernichtet. Sie können jederzeit der Weiterverarbeitung Ihrer im Rahmen der o.g. Studie erhobenen Daten widersprechen und deren Löschung verlangen.
In diesen Fällen wenden Sie sich bitte an die Studienleiter/-in (die Kontaktdaten der Studien-verantwortlichen finden sie am Anfang dieser Information).

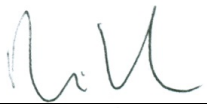
Freiwilligkeit der Teilnahme / Vorzeitiger Abbruch der Untersuchung
Die Untersuchungen dürfen erst beginnen, wenn Sie das Informationsblatt für Teilnehmer gelesen und die Einverständniserklärung ausgefüllt und unterschrieben haben. Ihre Teilnahme an der Studie ist freiwillig!
Wichtig ist für Sie zu wissen, dass Sie Ihr Einverständnis jederzeit ohne Angabe von Gründen widerrufen können, ohne dass hieraus Nachteile für Sie entstehen.

Versicherungsschutz
Für diese Studie wurde keine gesonderte Versicherung abgeschlossen. Die Studienarztin und wissenschaftlichen Mitarbeiter der Studie sind durch die Betriebshaftpflichtversicherung der Charité gegen Haftungsansprüche, welche aus ihrem schuldhaften Verhalten resultieren könnten, versichert.

Rechte und Pflichten der Probandinnen/Probanden
Ihre Teilnahme an dem Versuch ist freiwillig. Ihr Einschluss in diesen Versuch beruht auf der Annahme, dass Sie Mitglied in einer Krankenversicherung sind und Anspruch auf medizinische Behandlung haben.
Während der Dauer der Studienteilnahme sind die Anweisungen des/der Studienarztes/-ärztin zu befolgen. Veränderungen Ihres gesundheitlichen Wohlbefindens sind der Studienleitung unverzüglich mitzuteilen.

An wen können Sie sich wenden, wenn Sie Fragen zum Ablauf der Studie haben?
Falls Sie Fragen haben, wenden Sie sich bitte vor Beginn der Untersuchung an die Untersuchungsleiterin, Frau Dr. Petra Ritter. Für eventuell später auftretende Fragen oder Probleme bezüglich der Studie kontaktieren Sie Frau Ritter unter der oben angegebenen Telefonnummer. Sie können uns auch jederzeit eine E-mail schicken.

Vielen Dank für Ihr Interesse und Ihre freundliche Mitarbeit!



PD Dr. Petra Ritter

7.5 Appendix E

Information experimental design subject and tips for reducing head movements

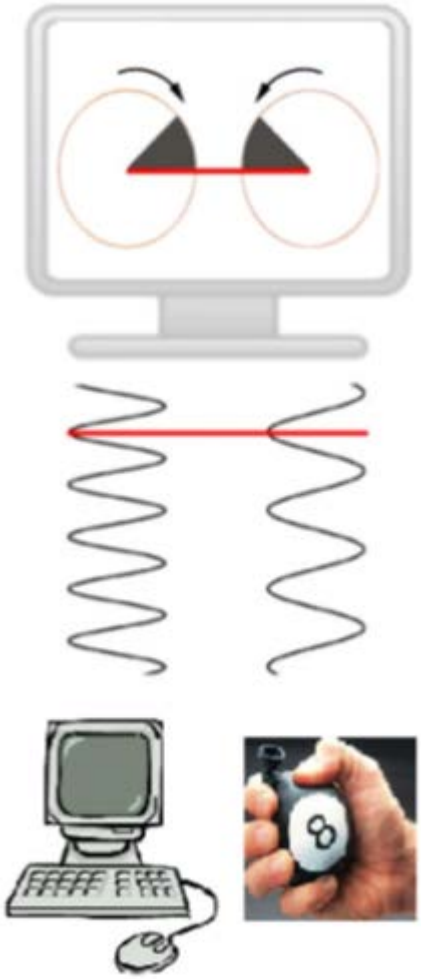
Sehr geehrte/r Proband/in,

bitte lesen Sie sich vor Beginn des Experiments diese Anleitung und Hinweise sorgfältig durch und scheuen Sie sich nicht, aufkommende Fragen umgehend an die/den Studienleiter/in zu richten.

Der Versuch ist in 3 Phasen unterteilt:

Teil 1: Ruhe-Messungen, Dauer: 5:00 min

Aufgabe: Bitte liegen Sie ruhig und entspannen Sie sich. Bitte ***schließen Sie die Augen*** und schlafen Sie nicht ein! ***Versuchen Sie Kopfbewegungen zu vermeiden*** und insbesondere Augenbewegungen auf ein Minimum zu reduzieren.



Teil 2: Bearbeitung der Aufgabe, Dauer: 22:30 min

Ablauf: 10 Durchgänge à 2 min mit je 15 sec Ruhe zwischen den Durchgängen.

Aufgabe: Auf dem Bildschirm vor Ihnen werden 2 entgegengesetzt rotierende Scheiben erscheinen. Die linke wird vom Computer gesteuert und rotiert mit konstanter Geschwindigkeit/Frequenz.

Die Kontrolle über die rechte Scheibe übernehmen Sie mit Hilfe des Druckballs. Der Druckball soll nun in einem solchen Rhythmus gedrückt werden, dass beide auf dem Bildschirm sichtbaren Scheiben mit der gleichen Geschwindigkeit synchron rotieren.

Die Geschwindigkeit, mit der Sie den Druckball drücken müssen, weicht jedoch von der wahrgenommenen Geschwindigkeit der Rotation ab.

Versuchen Sie die richtige Frequenz zu finden, mit der der Druckball gepresst werden muss, damit beide Scheiben synchron rotieren. Sobald Sie diese erreicht haben, rotieren die Scheiben synchron. Nach jedem Durchgang erhalten Sie eine Rückmeldung über Ihre Leistung.

Bitte versuchen Sie die Kraft des Drückens über die Dauer des Experiments möglichst konstant zu halten. Zur Bedienung des Druckballs und damit der rechten Scheibe reicht dabei schon leichter Druck. Die Stärke des Drückens hat keinen Einfluss auf die Geschwindigkeit der Rotation.

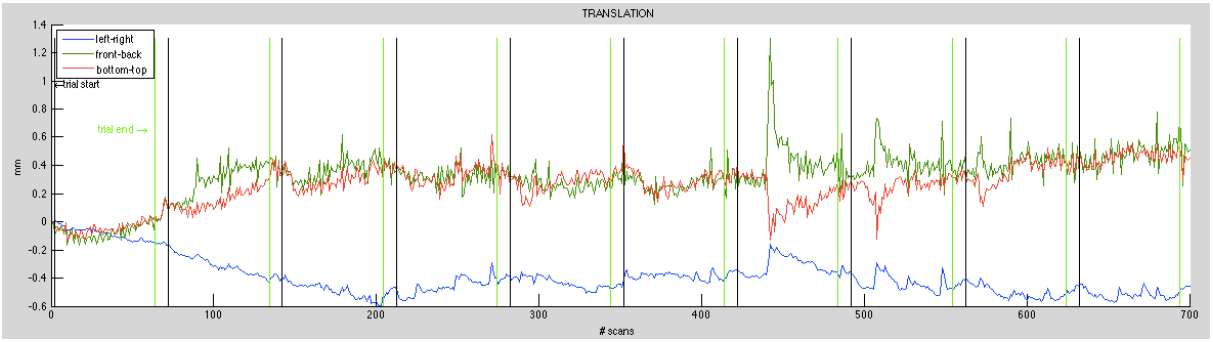
Bitte geben Sie Ihr Bestes und versuchen Sie so gut wie möglich zu werden.

Teil 3: Ruhe-Messungen, Dauer: 5:00 min

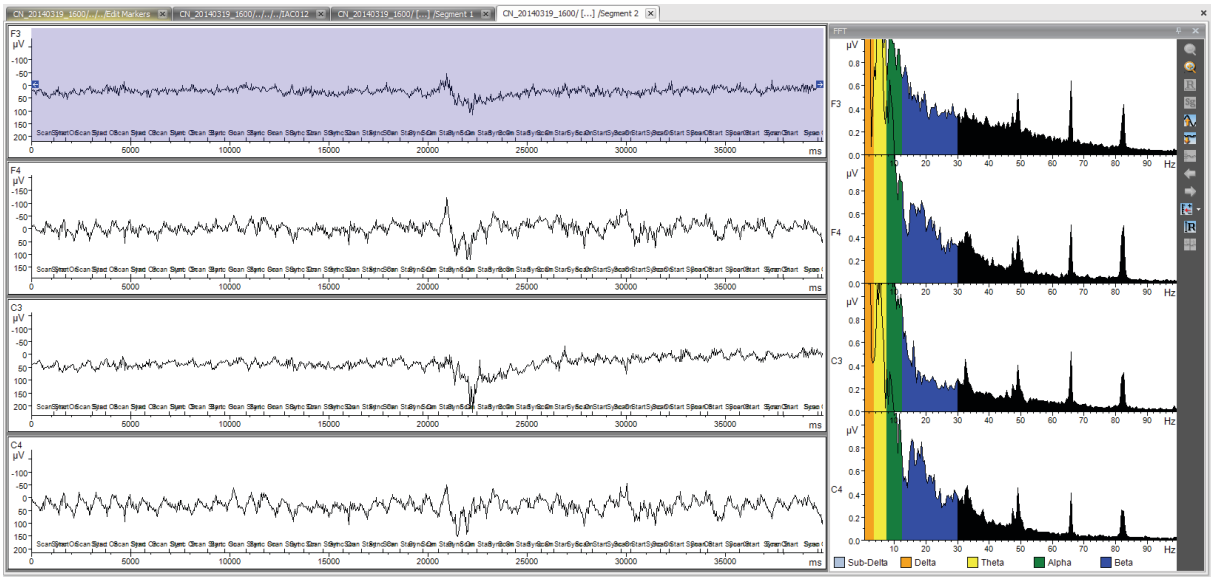
Aufgabe: Bitte liegen Sie ruhig und entspannen Sie sich. Bitte ***schließen Sie die Augen*** und schlafen Sie nicht ein! ***Versuchen Sie Kopfbewegungen zu vermeiden*** und insbesondere Augenbewegungen auf ein Minimum zu reduzieren.

Bitte lesen Sie auch die folgenden Hinweise sorgfältig durch! Bei aufkommenden Fragen stehen wir jeder Zeit zu Ihrer Verfügung.

Bei der kombinierten Messung von EEG und fMRT führen schon kleinste Bewegungen – insbesondere des Kopfes – zu diversen Artefakten (unerwünschte Signale) in den Aufnahmen der Elektroenzephalographie.



Exemplarischer Verlauf der Bewegung eines Probanden während des Experiments (in allen Raumrichtungen). Abrupte Bewegungen – insbesondere wie in der letzten Hälfte dieses Beispiels – führen zu problematischen Störsignalen (Artefakte) in den Aufnahmen der Elektroenzephalographie.



Folgen derartiger Bewegungen sind deutliche Artefakte in den Aufnahmen der Elektroenzephalographie. Daten, die durch Bewegungen in diesem Maße verändert werden, sind für weiterführende Analysen unbrauchbar.

Um diese Artefakte zu vermeiden, sind wir auf Ihre Hilfe angewiesen! Wir bitten Sie Bewegungen – insbesondere Ihres Kopfes – zu vermeiden!

Über die komplette Dauer des Versuches (≈ 30 min) ist es – zugegebener Maßen – nicht einfach, Bewegungen auszuschließen. Um Ihnen dabei behilflich zu sein, haben wir im Folgenden Hinweise zur Minimierung von Kopfbewegungen zusammengefasst.
Das Vermeiden von Kopfbewegungen ist während des gesamten Experiments von Bedeutung. Dazu zählen auch die Ruhemessungen vor und nach Bearbeitung der Aufgabe, sowie die Pausen nach den einzelnen Durchgängen.

- Stellen Sie vor Beginn des Experiments sicher, dass Sie bequem und entspannt liegen. Anfangs erträglich scheinende Unbequemlichkeiten können sich im Verlauf der Messungen verstärken und letztlich Positionsänderungen und damit Bewegungen nötig machen. Je bequemer Sie liegen, desto leichter wird es Ihnen fallen, Bewegungen zu vermeiden. Scheuen Sie sich daher bitte nicht uns wissen zu lassen, falls Sie unbequem liegen.
- Im Fokus steht die Minimierung von Kopfbewegungen. Kleinere Bewegungen der Arme und Beine, die keine Bewegung des Kopfes mit sich bringen, sind daher weniger problematisch.
- Bewegungen der Gesichtsmuskulatur, beispielsweise beim Kauen, Schlucken und Gähnen haben Bewegungen des Kopfes zur Folge, auch wenn diese für Sie kaum wahrnehmbar sein sollten. Wir bitten Sie daher diese auf ein für Sie erträgliches Minimum zu reduzieren!
- Um heftige Augenbewegungen und die daraus resultierenden Artefakte zu vermeiden, bitten wir Sie während der Bearbeitung der Aufgabe Ihren Blick stets auf das mittig platzierte Kreuz (Fixationskreuz) zu fokussieren und nicht abschweifen zu lassen. Auch starkes Zwinkern führt zu Artefakten!

Bitte geben Sie für die komplette Dauer der Messungen Ihr Bestes, um eine hohe Qualität und damit letztlich den Erfolg der Studie zu gewährleisten.

Danke für Ihre Teilnahme und Bemühungen!

7.6 Appendix F

Settings Labview aquistition behavioral data

Sample frequency	100 Hz
Data Source	ForceTransducer
Task	SensorSlowhand_simulationFasthand
Frequency1	1.8 Hz
Frequency2	1.35 Hz
BandCutoffLow	0.5 Hz
BandCuroffHigh	2.5 Hz
LowPassCutoff	2.5 Hz
NrSD	3.0

7.7 Appendix G

Independent Component Analysis (accept or reject?)

A comprehensive thesis can be written about the choices that are made during acceptation and rejection of independent components during ICA decomposition. Here, a brief summary of the decisions that are made during this study are given and explained.

Given that we feed the ICA with 64 channels, EEGlab provides us 64 independent components plotted on a scalp map (figure 1 appendix).

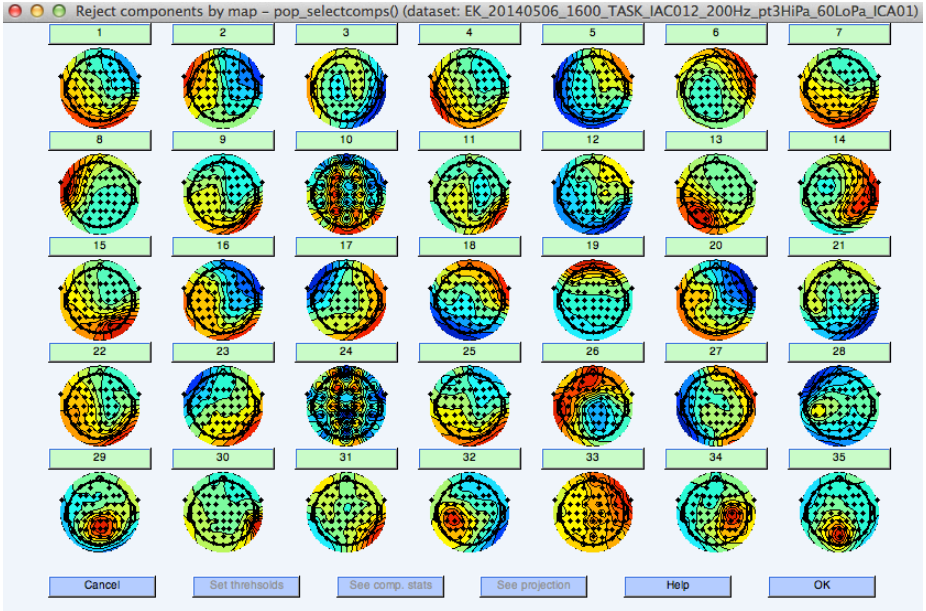


Figure 1 Appendix Scalp map of first 35 components

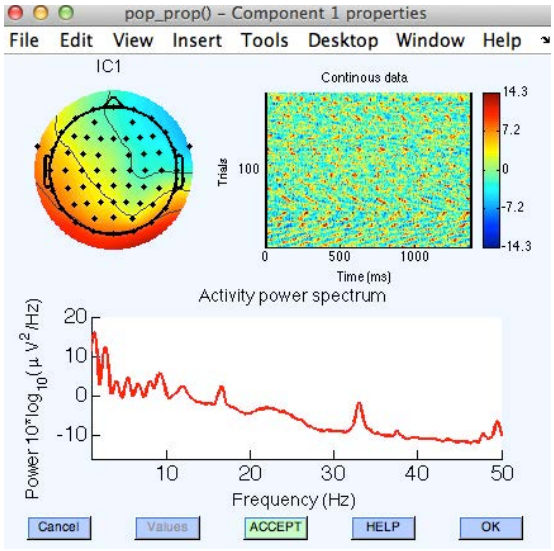


Figure 2 Appendix. Example of component properties

By clicking on the rectangular button above the scalp map of the components, the properties of each component are provided (figure 2 appendix).

Again, a clear map of the activity projected on the scalp is visible. The color bar shows how strong the activity is (pay attention to the scale of the color bar).

Next to the scalp map the continuous activity data are visible. Here, you can see the activity levels over time. As last, an activity power spectrum is plotted which shows the power of every frequency. For this figure, attention needs to be paid to the logarithmic scale of the y-axis.

During this analysis, the main causes of rejecting components were: eye artifacts, muscle artifacts, BCG and scanner artifacts. Below, an example is given of every artifact.

Eye artifact

An eye artifact can be identified for several reasons, but the clearest one is a strong frontal activation on the scalp map. Next, regular very strong bursts of activations are visible in the continuous data and the power of the lower frequencies is very large. An example is given in figure 3 of this appendix.

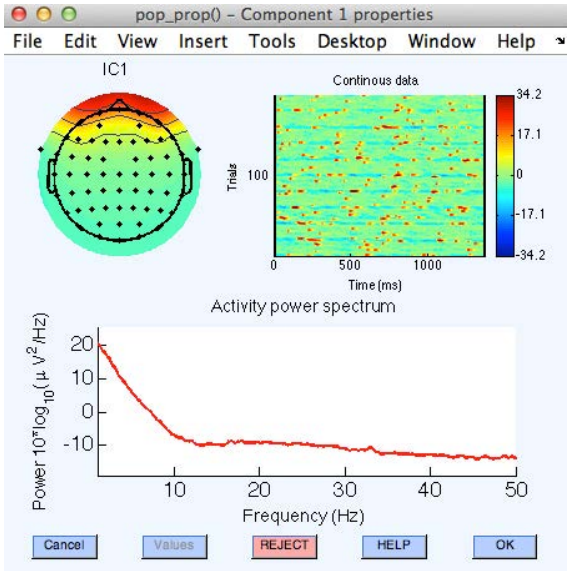


Figure 3 Appendix. Example eye artifact component

Muscle artifact

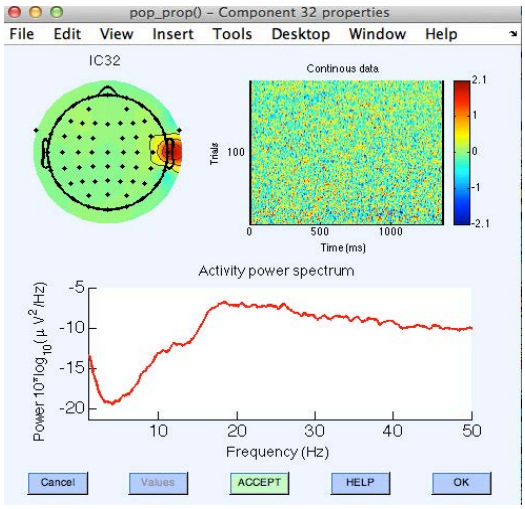


Figure 4 Appendix. Example muscle artifact component

As shown in figure 4 of this appendix, a muscle artifact is typically spatially localized and shows a high power at high frequencies (20-30 Hz).

BCG

In these data, artifacts that are caused by the beating of the heart give the highest values in the power spectrum. Therefore, it is very important to get rid of these artifacts, otherwise any other neuronal activity will completely fade away. The power spectrum shows at the low frequencies a noisy activity that goes up and down. Next, the scalp map shows mostly a dipole composition (figure 2).

Scanner artifacts

Luckily, most scanner artifacts consist of a low power, much lower than most neuronal activity. For this reason, scanner artifacts affect the neuronal data barely. When some components consist of scanner artifact and perhaps some neuronal activity, the choice is made to maintain these components. Although, when one component consists solely of a scanner artifact, it will be rejected. The constant harmonic peaks in the activity power spectrum can identify this artifact. Also, in the scalp map, the activity is concentrated around a single channel.

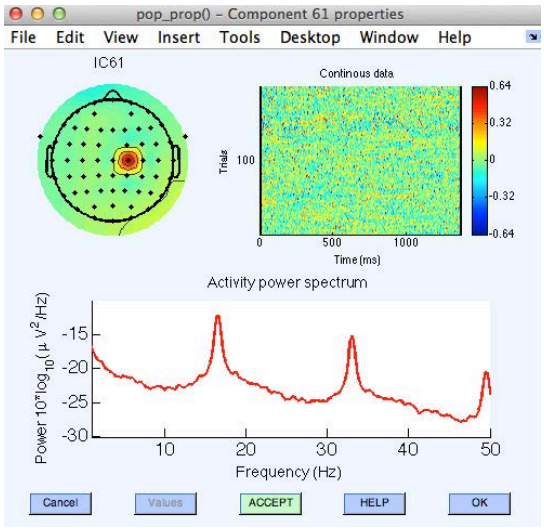


Figure 5 Appendix. Example scanner artifact component

Figure 6 of this appendix shows a component that with very clear neuronal activity of our interest. High power activity is visible around M1 and PM1 with a peak in the power spectrum around the beta frequency band.

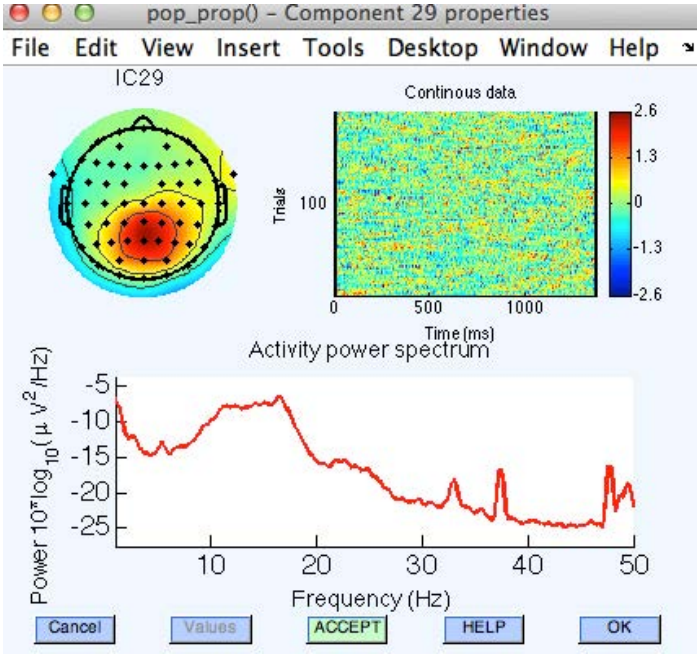


Figure 6 Appendix. Example of beta component

7.8 Appendix H

Individual single level results

Young subjects:

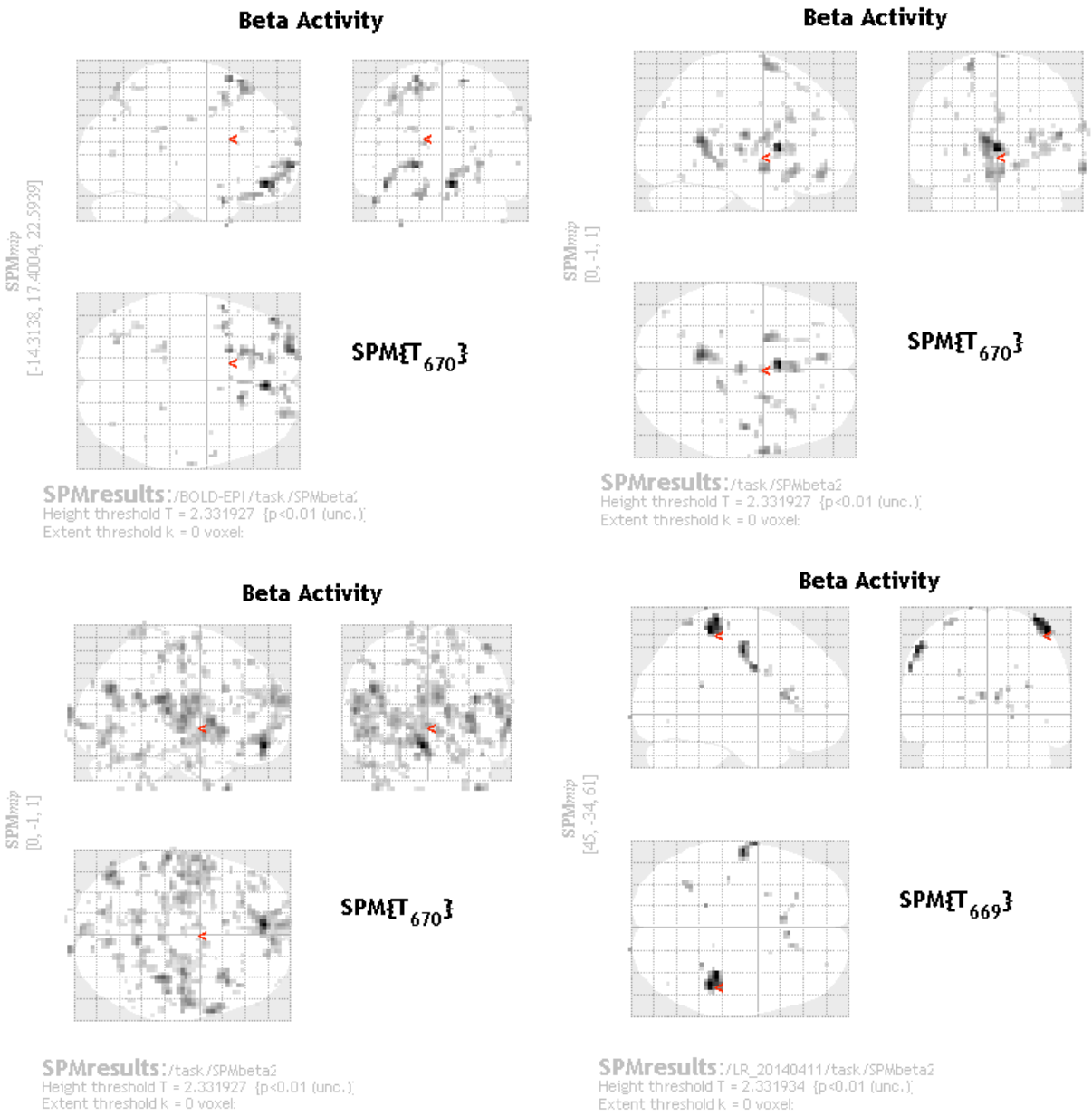


Figure 7 Appendix. Individual single level results young subjects. Glass-brain images show the significant relationships between the EEG-based beta regressors and the BOLD signal for the complete brain (p<0.01 {unc}).

Elderly subjects:

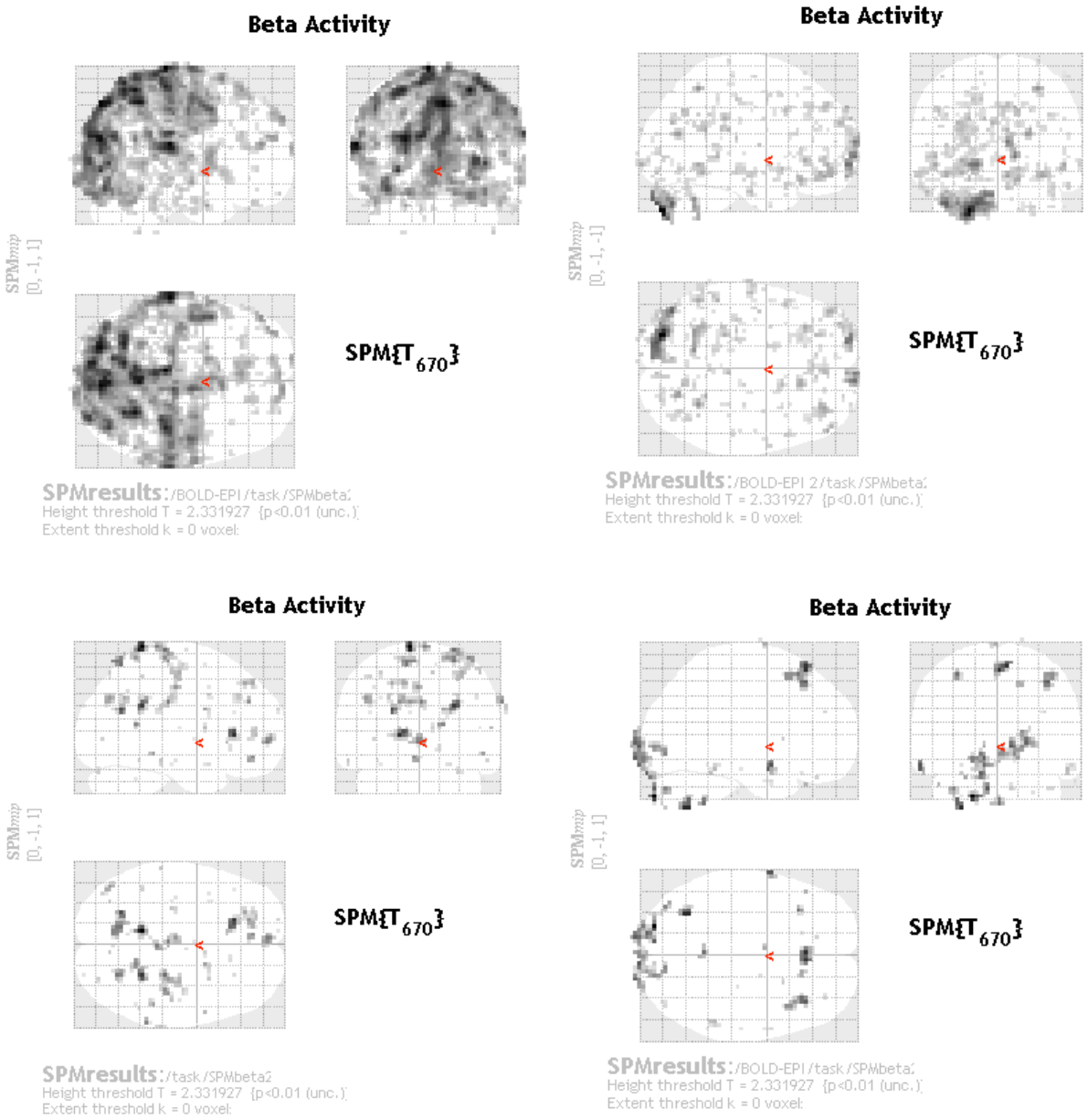


Figure 8 Appendix. Individual single level results elderly subjects. Glass-brain images show the significant relationships between the EEG-based beta regressors and the BOLD signal for the complete brain (p<0.01 {unc}).