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Title: Motor neuroplasticity: A MEG-fMRI study of motor imagery and execution in healthy ageing

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Abstract

Age-related decline in motor function is associated with over-activation of the sensorimotor circuitry. Using a multimodal MEG-fMRI paradigm, we investigated whether this neural over-recruitment in old age would be related to changes in movement-related beta desynchronization (MRBD), a correlate of the inhibitory neurotransmitter γ-aminobutyric acid (GABA), and whether it would characterize compensatory recruitment or a reduction in neural specialization (dedifferentiation). We used MEG to assess age-related changes in beta band oscillations in primary motor cortices, fMRI to localize age-related changes in brain activity, and the Finger Configuration Task to measure task performance during overt and covert motor processing: motor execution (ME) and motor imagery (MI). The results are threefold: first, showing age-related neuroplasticity during ME of older adults, compared to young adults, as evidenced by increased MRBD in motor cortices and over-recruitment of sensorimotor areas; second, showing similar age-related neuroplastic changes during MI; and finally, showing signs of dedifferentiation during ME in older adults whose performance negatively correlated with connectivity to bilateral primary motor cortex. Together, these findings demonstrate that elevated MRBD levels, reflecting greater GABAergic inhibitory activity, and over-activation of the sensorimotor network during ME may not be compensatory, but rather might reflect an age-related decline of the quality of the underlying neural signal.

Keywords: Ageing; Compensation; Dedifferentiation; Motor Execution; Motor Imagery

Motor neuroplasticity: A MEG-fMRI study of motor imagery and execution in healthy ageing

Motor function is known to decline with age and older adults exhibit age-related reductions in motor control and accuracy, as well as a general slowing of movements (Hoogendam *et al*., 2014; Seidler *et al*., 2010). A multitude of factors have been suggested to account for the age-related decline of motor function, including changes in musculoskeletal function and structure (Dutta *et al*., 1997; Lexell, 1997), and decreases of white matter integrity in corticospinal networks (Madden *et al*., 2004). Recent evidence further suggests that age-related decline of motor function may be mediated by neurochemical changes, specifically increased levels of the inhibitory neurotransmitter γ-aminobutyric acid (GABA), which result in increased motor inhibition (Muthukumaraswamy *et al.*, 2013; Opie & Semmler, 2014; Rossiter *et al*., 2014). Previous studies, using electroencephalography and magnetoencephalography (MEG) to study movement-related brain oscillations, have demonstrated that increases in movement-related beta desynchronization (MRBD), *i.e.*, power reduction in beta band oscillations during preparatory movement phases, is related to GABA-A receptor binding in motor cortices (Baker & Baker, 2003; Hall *et al*., 2011; Rossiter *et al*., 2014). Therefore, the first aim of this study was to investigate whether the amplitude of MRBD in primary motor cortices during movement changes with age.

Functional magnetic resonance imaging (fMRI) studies show increased and more widespread brain activations in older adults during motor execution (ME) tasks (Heuninckx *et al*., 2005; Wu & Hallett, 2005), suggesting that, in order to maintain performance at a level similar to young adults, older adults need to engage a more

distributed network. However, whether these changes reflect dedifferentiation, *i.e.*, a reduction in neural specialization of domain-specific regions (Li & Lindenberger, 1999), or compensatory neuroplasticity, *i.e.*, over-recruitment of existing or alternate brain circuits to support declining motor function (Cabeza *et al*., 2002; Grady, 2012; Reuter-Lorenz & Cappell, 2008; Reuter-Lorenz & Park, 2014), is still a matter of debate (Heuninckx *et al*., 2008; Ward, 2006). Whilst it is unlikely that dedifferentiation mediates good task performance, the strongest evidence for age-related compensation is the recruitment of additional neural resources to support *better* behavioural performance (Cabeza and Dennis, 2013; Grady 2008). Additionally, although distinct mechanisms, our recent studies demonstrate that dedifferentiation and compensation may not be mutually exclusive, but rather may co-occur (Burianová *et al*., 2013b; Burianová *et al*., 2015). In two previous studies, we found age-related reductions in efficiency in the primary network subserving face-processing (Burianová *et al*., 2013b) and working memory (Burianová *et al*., 2015) associated with compensatory activity outside the network. This compensatory activity correlated positively with accuracy, but also with reaction time, suggesting that over-recruitment of brain regions outside of the primary network aids performance but reduces processing speed. These findings align with the partial compensation hypothesis, the idea that neural over-recruitment might be the consequence of overburdened neural resources and/or less efficient processing. In other words, whilst over-recruitment of brain regions outside of the network that subserves a specific cognitive task might help old adults' performance, it might not compensate for the reduced efficiency within the primary network (Burianová *et al*., 2015; de Chastelaine *et al*., 2011; Grady, 2012). As such, the second aim of the study was to use fMRI to

investigate whether age-related neuroplasticity during ME would be associated with reduced neural selectivity and compensatory recruitment.

The neural correlates of ME overlap greatly with those of motor imagery (MI; Burianová *et al*., 2013a; Jeannerod, 2001; Lotze & Halsband, 2006) - the internal reproduction of motor movements in the absence of overt physical action (Annett, 1995; Jeannerod, 1995). Because MI shares the sensorimotor circuitry with ME, motor imagery has been proposed as a viable rehabilitative technique to optimize motor function after stroke or injury, and to counteract age-related decline in motor control (Saimpont *et al*., 2013; for a review, see Bamidis *et al*., 2014). However, several studies have documented changes in MI performance associated with older age, such as a decline in covert motor prediction or slowing of the speed of covert motor execution (Personnier *et al*., 2008; Personnier *et al*., 2010; Skoura *et al*., 2005; Skoura *et al*., 2008), suggesting that ageing affects the efficiency of MI. The underlying neural changes are still unclear and neuroimaging studies investigating MI of gait (Allali *et al*., 2014; Zwergal *et al*., 2012) and finger movement (Sharma & Baron, 2014; Zapparoli *et al*., 2013) in older age diverge in their results. While some studies report age-related changes in the primary sensory-motor network (Sharma & Baron, 2014; Zwergal *et al*., 2012), others locate changes in medial and lateral frontal regions (Allali *et al*., 2014; Zapparoli *et al*., 2013). An important question for the effectiveness of therapeutic MI training is whether it would impact neurofunctional changes in older adults due to dedifferentiation and/or compensatory neuroplasticity (Zapparoli *et al*., 2016). As a consequence, the value of therapeutic applications of MI in ageing is unclear. Recently, we demonstrated rapid and lateralized post-immobilization neuroplasticity in the sensorimotor circuitry of ME and

MI (Burianová *et al*., 2016), establishing that a sudden reduction in motor output significantly affects *both* motor execution and motor imagery. Based on this evidence, the third aim of the study was to investigate whether MI exhibits age-related neuroplasticity similar to that of ME.

To address the three aims of the study, we combined MEG to assess age-related changes in MRBD in primary motor cortex, fMRI to localize age-related changes in brain blood oxygenation level dependent (BOLD) activity, and the Finger Configuration Task (FCT; Burianová *et al*., 2013a) to measure task performance during ME and MI. Based on recent evidence showing that age-related motor neuroplasticity is associated with GABA increases (Rossiter *et al*., 2014), we thus expected that during ME older adults would show stronger MRBD, an established correlate of GABA (Baker & Baker, 2003; Hall *et al*., 2011), compared to young adults. Thus, age-related increases in MRBD during motor activity would indicate increases in GABA, which would imply that the effectiveness of neural communication within the motor system might be compromised due to higher levels of noise (Faisal, Selen, & Wolpert, 2008; Heise *et al*., 2013; Aumann & Prut, 2015). In addition, given that older adults reliably show over-activation of the sensorimotor circuitry (Heuninckx *et al*., 2005; Wu & Hallett, 2005), we predicted that older adults would show stronger and more widespread BOLD activity during ME compared to young adults. Furthermore, we hypothesized that if MI undergoes similar neuroplasticity changes as ME, in contrast to young adults, older adults would show stronger MRBD and increased BOLD responses indicative of over-activation of sensorimotor areas during MI. Finally, we hypothesized that if age-related neuroplasticity changes within the sensorimotor network were compensatory, increases in MRBD and

BOLD activation would positively correlate with accuracy on the FCT, in contrast to dedifferentiation, which would not be associated with good task performance (Grady, 2012; Heuninckx *et al*., 2008; Li & Lindenberger, 1999).

Materials & Methods

Participants

Sixteen young adults (mean age = 26 years; SD = 4.3; 8 females) and 16 older adults (mean age = 64 years; SD = 4.5; 8 females) participated in the study. All participants were strongly right-handed (Oldfield, 1971), had normal or corrected-to-normal vision, and had no history of neurological impairment, psychotropic substance use, or psychiatric illness. All participants provided written informed consent approved by the Macquarie University Human Research Ethics Committee. To confirm that participants were able to form mental images with sufficient vividness, they completed the Vividness of Visual Imagery Questionnaire (Marks, 1973). The range of the vividness scores for young participants was 51-73 (out of 80); mean score = 63.8; SD = 6.9, and for older participants it was 52-80; mean score = 69.3; SD = 9.3. Older adults reported no cognitive difficulties and scored in the normal range on the Mini-Mental State Examination (MMSE; Folstein *et al*., 1975; M = 28.9; SD = 1.1; range 28-30).

Experimental Design

Prior to the experimental session, the Finger Configuration Task was verbally and visually explained to the participants. They then completed a practice session, which ensured a proper familiarization with the task's instructions and timing, as well as a comparable behavioural performance between the two groups of participants. Special

emphasis was placed on the vividness of sustained imagery, as well as inhibition of any movement during the imagery trials. In each of the four practice blocks, the participants completed 10 trials, equal in length and layout to those in the actual experiment. The training started with the execution conditions (first right, then left hand), followed by imagery conditions (first right, then left hand), so that the participants could imagine the movement of their own fingers as it was just executed in the preceding conditions. Specific instructions given to the participants were: "We would like you to imagine your own hand and fingers in your mind and focus on slowly curling in or extending your fingers according to the given auditory cues. In your mind, move your fingers deliberately slowly." Participants' performance was monitored by the experimenter who, when necessary, paused the practice and reiterated the task requirements. All participants gave verbal feedback on their motor imagery experience.

The Finger Configuration Task is a paradigm that reliably invokes motor execution and motor imagery and is transferable across imaging techniques in an identical protocol. The details of this experimental paradigm are described elsewhere (Burianová *et al*., 2013a), but, in brief, starting from a default position in which the arms rested alongside the body, with all fingers of the hand extended, at each trial, participants heard a random sequence of 4 or 5 auditory cues (numbers 1 to 5 representing the fingers of the hand) and either (i) *executed* the movement – *i.e*., curled in or extended a specific finger of the left or right hand (LE = left-hand execution; RE = right-hand execution), or (ii) *imagined executing* the movement (LI = left-hand imagery; RI = right-hand imagery). Auditory cues were presented for 1 s and followed by a response period of either 2.6 or 3.5 s, depending on whether five or four cues were presented, respectively. At the end of

each cue sequence, participants saw a picture of a hand configuration and matched their own hand configuration to it by moving their right foot for "match" or left foot for "no match" (**Fig 1**). We used a blocked design, with four trials of each condition presented in sequence, followed by a 21-second block of rest/baseline (during which participants viewed a fixation cross and were not required to respond), followed by the next condition. The order of conditions was randomized and counterbalanced across participants, but identical for MEG and fMRI. Across four imaging runs, a total of 72 data points per condition and participant were collected.

Electromyographic (EMG) measurements were acquired during the MEG session to ensure that there was no muscle contraction during imagery trials. Two MEG compatible surface electrodes were attached to the *extensor digitorum* of each arm following the procedure described in Burgar, Valero-Cuevas, and Hentz (1997) and muscle contraction was recorded using a BrainProducts MEG-compatible polygraphic system (BrainProducts GmbH, Gilching, Germany). EMG data were acquired at a sampling rate of 1000 Hz and a bandpass filter of 20-500 Hz. We were unable to collect EMG data during the fMRI session; instead, an experimenter observed participants' hands closely via a scanner camera throughout the scanning session to ensure that participants did not move their fingers during MI conditions. Although ultimately measuring EMGs during both imaging sessions would have been optimal, we believe that we controlled immobility sufficiently by an extensive task practice, a careful positioning of the scanner camera, and EMG monitoring of finger movement during the preceding MEG session. We can confirm that, during MEG, EMG traces for each hand were examined for every trial to ensure that there was no overt activation during the imagery

conditions.

[Insert Figure 1 here]

MEG & fMRI Data Acquisition

Prior to MEG recordings, marker coil positions and head shape were measured with a pen digitizer (Polhemus Fastrack, Colchester, VT). MEG recordings were obtained from participants in a supine position in a magnetically shielded room (Fujihara Co. Ltd., Tokyo, Japan) using the KIT-Macquarie MEG160 (Model PQ1160R-N2, KIT, Kanazawa, Japan). Data were recorded using 160 coaxial first-order gradiometers with a 50 mm baseline (Kado *et al*., 1999; Uehara *et al*., 2003). MEG data were acquired at a sampling rate of 1000 Hz and a bandpass filter of 0.03–200 Hz.

Following the MEG session, participants took part in a fMRI session on the same day. Anatomical and functional magnetic resonance images were acquired at Macquarie University Hospital, Sydney, using a 3 Tesla Siemens Magnetom Verio scanner with a 12-channel head coil. T1-weighted volumetric structural images were acquired using a 3D MP-RAGE sequence (208 axial slices, TR = 2000 ms, TE = 3.94 s, FOV = 240 mm, voxel size = 0.9 mm^3, TI = 900, flip angle = 9º). Brain activation was assessed using the BOLD effect (Ogawa *et al.*, 1990) with optimal contrast. Functional images were obtained using a whole head T2*-weighted echo-planar image (EPI) sequence (40 axial slices with interleaved acquisition, 0.5 mm gap, TR = 3000 ms, TE = 30 ms, flip angle = 90º, FOV = 260 mm, voxel size = 2.5 mm^3).

MEG Preprocessing & Data Analysis

MEG data preprocessing and analysis were conducted with Statistical Parametric Mapping software for M/EEG (SPM8; http://www.fil.ion.ucl.ac.uk/spm). Data were

downsampled to 250 Hz prior to analysis. To eliminate low frequency and electrical line noise, a bandpass filter with a cut-off of 0.1 and 100 Hz and a stop band filter ranging from 49 to 51 Hz were applied. Data were epoched from -1600 to 2100 ms relative to the onset of the auditory cue. Trials containing artifacts due to eye blinks and jaw or eye-movements, identified by Fieldtrip visual artifact rejection implemented in SPM8 (Oostenveld *et al*., 2011), were removed from the analysis. The average number of rejected trials were comparable between young/older adults across all conditions: LI *M* = 16/15; LE *M* = 21/22; RI *M* = 16/16; and RE *M* = 22/22. Overall, an average of 54 data points per condition and participant survived the artefact rejection. To calculate source lead fields, a canonical cortical mesh derived from the MNI template was warped, in a nonlinear manner, to match the participant's individual structural MRI, and a forward model was computed using a single shell model.

Source reconstruction

For the analysis, separate regions-of-interests (ROIs) were defined for left and right sensorimotor cortices. The time courses of source intensities for the 2 ROIs (radius 10 mm) were reconstructed using adaptive beamforming. Beamforming uses spatial filters to block out the contribution of any sources other than each pre-specified ROI to the lead field and thereby creates virtual sensors. Virtual sensors were placed at MNI coordinates [-30 -18 58] and [28 -14 58], based on the results from our previous fMRI study and defined as group average coordinates of the peak intensity voxel that showed an overlap between ME and MI (see Table 1 in Burianová *et al*., 2013a). For each participant, time courses for each of the 2 virtual sensors were computed using a linearly constrained minimum variance (LCMV) spatial filter (0.1% regularization) for each of

the 4 trial types (Condition × Hand; van Veen *et al.*, 1997). The resulting data were then subjected to time-frequency analysis in order to examine MRBD.

Time-Frequency Analysis

Time-frequency analysis was conducted on the source-reconstructed signal in the frequency range between 15 and 30 Hz (beta band). Power was analyzed in 0.1 Hz steps using Morlet wavelets with a seven-cycle width (Tallon-Baudry *et al*., 1996). Epochs were averaged within conditions and the resulting average epoch was cropped from -1500 to 2000 ms to remove edge effects. The resulting spectra were then rescaled to a baseline time-window, which was defined as the epoch from -1500 to -500 ms. MRBD was investigated in a time-window from 250 ms to 500 ms post-stimulus onset. The time-windows were chosen based on previously published time-frequency analyses of the same task (Burianová *et al*., 2013a, 2016; Hall *et al.*, 2011, 2014; Muthukumaraswamy *et al.*, 2013).

To assess statistically significant differences in the spectral profiles, the individual spectrograms were converted to statistical parametric images and entered into a 2 x 2 x 2 mixed design analysis of variance with the random effects factor group (young and older adults), and fixed effects factors hand (left and right), and condition (imagery and execution) for each ROI separately. To correct for multiple comparisons, a family-wise error (FWE) correction using Gaussian random field theory was employed (Worsley *et al*., 1996) and resulting statistical parametric maps were thresholded at $p < 0.05$. The source of main effects and interactions was followed up by posthoc comparisons thresholded at $p < 0.05$.

fMRI Preprocessing & Data Analysis

The acquired fMRI images were preprocessed using the Statistical Parametric Mapping software (SPM8; http://www.fil.ion.ucl.ac.uk/spm). The functional images were realigned to a mean image for head-motion correction, the anatomical image was segmented and spatially normalized to the T1-weighted Montreal Neurological Institute (MNI) template, and the normalization parameters were applied to the functional data. Finally, the data were spatially smoothed by convolving each volume with an isotropic Gaussian kernel (FWHM = 6 mm).

The procedure of the fMRI analysis was twofold, each addressing a specific hypothesis. We conducted (1) a whole-brain analysis to examine age-related changes in sensorimotor areas during all experimental conditions *vs.* baseline; and (2) a functional connectivity, brain-behaviour analysis to examine whether brain activity within the sensorimotor network significantly correlated with accuracy on the FCT. As ME and MI are the result of integrated and coordinated activity of groups of brain regions (*i.e.*, distributed brain networks) rather than the independent activity of any single brain region, we utilized a multivariate analytical technique called Partial Least Squares (PLS; McIntosh *et al.*, 1996; for a detailed tutorial and review of PLS, see Krishnan *et al.*, 2011). An advantage of the PLS method is that all variables (task conditions, seed values, and indices of behavioural performance) can be entered simultaneously into the analysis, thus facilitating identification of groups of brain regions distributed over the entire brain whose activity changes as a function of task demands or is correlated with behavioural performance. In the current study, we examined modulation of brain activity during the experimental conditions and further examined the relation of sensorimotor network activity and accuracy on the FCT, using the coordinates [-30 -18 58] and [28 -14 58] as

seed regions for delineating the sensorimotor network. These coordinates were attained from the results of our previous fMRI study and defined as group average coordinates of the peak intensity voxel that showed an overlap between ME and MI (see Table 1 in Burianová *et al*., 2013a). Specifically, here we delineated a large-scale network that was active during ME and MI by determining those areas of the brain whose activity was correlated with that of the two seed regions, *i.e*., its functional connectivity (Friston *et al*., 1993; Horwitz, 1994; McIntosh, 1999) and with accuracy on the FCT.

PLS analysis uses singular value decomposition (SVD) of a single matrix that contains all participants' data to find a set of latent variables (LVs), which are mutually orthogonal dimensions that reduce the complexity of the data set. In other words, PLS decomposes the data to maximize the amount of covariance of an LV with respect to the experimental conditions. Thus, akin to Principal Component Analysis (PCA; *e.g*., Friston, Frith, & Frackowiak, 1993), PLS enables us to differentiate the degree of contribution of different brain regions associated with task or performance. Each LV consists of a singular image of voxel saliences (*i.e*., a spatiotemporal pattern of brain activity that reflects task-related changes or brain-behaviour correlations seen across conditions), a singular profile of task saliences (*i.e*., a set of weights that indicate how brain activity in the singular image is expressed in each of the experimental conditions), and a singular value (*i.e*., the amount of covariance accounted for by the LV). The first LV always accounts for the largest amount of covariance (*i.e*., has the largest singular value), with subsequent LVs accounting for progressively smaller amounts. For each condition in each LV, we calculated summary measures of how strongly each participant expresses the particular pattern of activity seen on the LV. These measures, called brain scores, are the

products of the weighted salience of each voxel and BOLD signals summed across the entire brain for each participant in each condition on a given LV. Salience indicates the degree to which a voxel is related to the LV and can be positive or negative, depending on the voxel's relation to the pattern of task-dependent differences identified by the LV.

The significance for each LV is determined by permutation tests (here we used 500 permutations) and the reliability of each brain voxel's salience included in the pattern identified by the LVs is estimated by bootstrap resampling, using 100 bootstrapping steps (Efron, 1985). Peak voxels with a bootstrap ratio (BSR; *i.e.*, salience/standard error) > 3.3 were considered to be reliable, as these approximate $p < 0.001$ (Sampson *et al.*, 1989). No correction for multiple comparisons was necessary, as each analysis is conducted in single analytical step.

Results

Behavioural Results

To assess performance on the Finger Configuration Task, 2 (Condition) x 2 (Hand) x 2 (Group) repeated-measures ANOVAs were conducted on the accuracy of responses during the MEG and fMRI sessions, respectively. The analyses did not reveal any significant main effects or interactions (*p*s > 0.1; see **Fig 2** and **Table 1**), demonstrating consistency in performance across conditions and age groups. Equating between-group performance in neuroimaging studies of healthy ageing is critical because otherwise evaluation of differential neural activation may be confounded with differences in task performance between the groups, potentially reflecting different cognitive strategies (Snyder *et al.*, 2011).

[Insert Table 1 & Figure 2 here]

MEG Results

Movement-Related Beta Desynchronization (MRBD).

For both hemispheres, the ANOVA of the time-frequency responses showed a significant main effect for the factor group in the 20-25 Hz band between 340 and 500 ms as well as a significant main effect for the factor condition across the entire beta band (15-30 Hz) between 360 and 500 ms post-stimulus onset (both $F_{1,112} > 9.6$, $p < 0.05$ FWE; see **Fig 3** and **Table 2**). In both hemispheres, the group comparison revealed a stronger MRBD for older than young adults as well as for the execution than the imagery conditions (both $t_{112} > 2.8$, $p < 0.05$ FWE).

[Insert Table 2 & Figure 3 here]

MRBD-Behaviour Analysis.

Correlations between MRBD scores in left and right hemispheres and accuracy on the FCT for each group and each ROI were not significant after Bonferroni correction for multiple comparisons (all *p*s > 0.1), suggesting that age-related increases in MRBD may not be compensatory, but rather might reflect an overall age-related decline of motor functioning.

fMRI Results

Whole-Brain Analysis.

The whole-brain analysis of the 4 experimental conditions and 2 age groups yielded one significant LV ($p < 0.001$), which accounted for 59.45% of covariance in the data and delineated a pattern of activity related to all experimental conditions, in contrast to the baseline (**Fig 4**). This pattern included bilateral activations in primary motor

cortex, premotor cortex, primary sensory cortex, basal ganglia, thalamus, insula, cerebellum, inferior and middle frontal gyrus, posterior parietal cortex, and middle temporal gyrus, reflecting the primary nodes of the sensorimotor network. Areas whose activity negatively correlated with the task conditions included medial frontal gyrus, fusiform gyrus, inferior and middle occipital gyrus, inferior parietal lobule, and posterior cingulate gyrus, reflecting the primary nodes of the default mode network (*e.g.*, Buckner, Andrews-Hanna & Schacter, 2008).

To test the hypothesis that older adults would exhibit significantly stronger activations of sensorimotor regions compared to young adults, we additionally compared the magnitude of brain activity between the two groups using a 2 (Condition) x 2 (Hand) x 2 (Group) repeated-measures ANOVA of mean brain scores (the summary measures that indicate the extent to which each participant expressed the whole-brain pattern seen in **Fig 4**). The main effect of Condition was significant ($F_{1,30} = 13.95$, $p < 0.01$; $\eta_p^2 = .317$), as was the effect of Group ($F_{1,30} = 8.99$, $p < 0.01$; $\eta_p^2 = .231$). The interaction was not significant. These results indicate that both groups activated the sensorimotor regions more during ME than during MI conditions, and, more importantly, that older adults engaged the sensorimotor regions more strongly than young adults during both motor execution and motor imagery.

[Insert Figure 4 here]

Brain-Behaviour Analysis.

To investigate whether age-related over-activation of the sensorimotor network during ME and MI reflects dedifferentiation or compensation, we conducted a brain-behaviour analysis in which we correlated accuracy on the FCT with activity in the

sensorimotor network. No data were removed due being an outlier (defined as > 2.5 SD from the mean). In young adults, accuracy did not correlate significantly with activity in the sensorimotor network or in the seed regions (left and right M1) during either ME or MI (*i.e.*, error bars, which denote 95% confidence intervals for the correlations calculated from the bootstrap procedure, cross zero, see **Fig 5**). In older adults, accuracy did not correlate significantly with activity in the sensorimotor network or in the seed regions (left and right M1) during MI. During ME, however, older adults showed a significant *negative* correlation between accuracy and activity in the sensorimotor network and in both seed regions (left and right M1; $p < 0.001$; **Table 3**). In other words, poorer performance in older adults was associated with increased activation in the sensorimotor network during hand movement. In addition, poorer performance was associated with greater connectivity to bilateral primary motor cortex during either hand movement (**Fig 5**), in contrast to young adults who recruited primary motor cortex contralateral to the specific hand movement. The results suggest that age-related over-recruitment of sensorimotor areas is associated with the engagement of bilateral primary motor cortex and poorer performance, possibly reflecting an age-related decline of motor functioning due to reduced neural selectivity (dedifferentiation).

[Insert Table 3 & Figure 5 here]

Discussion

With old age, motor control, accuracy, and speed decline (Hoogendam *et al*., 2014; Seidler *et al*., 2010), yet it is unclear whether this decline is mediated by increased noise in the motor system as a result of changes in neurotransmitter levels, which lead to increased motor inhibition (Opie & Semmler, 2014; Rossiter *et al*., 2014). Thus, the first

aim of the study was to investigate whether motor functioning in old age is associated with increased MRBD, an established correlate of GABA (Baker & Baker, 2003; Hall *et al*., 2011). The results confirmed significantly stronger MRBD for older than young adults during both ME and MI, suggesting that age-related increases in MRBD reflect a general age-related decline of motor functioning that is possibly due to elevated GABA levels. Older adults also commonly show more widespread neural activity during ME tasks (Heuninckx *et al*., 2005; Wu & Hallett, 2005), indicating the possibility of compensatory recruitment (Cabeza *et al*., 2002; Grady, 2012). The second aim of this study was to investigate whether age-related over-recruitment of sensorimotor areas during the execution of motor tasks reflects a reduction in neural specialization (dedifferentiation) or compensatory neuroplasticity. The results were not consistent with the compensatory hypothesis, showing instead that stronger connectivity to bilateral M1 in the older group is negatively correlated with performance on the ME, but not MI, task. Finally, given that MI has been proposed as a viable therapeutic tool to maintain motor functioning in old age, it was important to examine whether the widespread neural activity found during ME tasks is also found during MI. Thus, the third aim of the study was to investigate whether MI, a process that engages overlapping sensorimotor correlates related to motor planning (Jeannerod, 2001; Lotze & Halsband, 2006), exhibits age-related neuroplasticity similar to that of ME. The results provide strong evidence of similar age-related over-activation of the sensorimotor network and stronger MRBD during MI, reflecting comparable impact of ageing on both ME and MI. In summary, the findings indicate that increased MRBD levels and over-activation of the sensorimotor network during hand movement may not compensatory, but rather might reflect an

overall age-related decline of motor ability as the quality of the underlying neural signal decreases.

Previous MEG studies have demonstrated that the degree of MRBD is associated with the amount of GABA-A receptor binding and GABA levels (Baker & Baker, 2003; Hall *et al*., 2011; Muthukumaraswamy *et al.*, 2013; Rossiter *et al*., 2014). Age-related increases in MRBD during motor activity might, therefore, indicate a neurotransmitter imbalance. Such an increase in GABA levels due to ageing could significantly impact the effectiveness of neural communication within the motor system, leading to higher levels of noise (Faisal, Selen, & Wolpert, 2008; Heise *et al*., 2013; Aumann & Prut, 2015). Age-related alterations in GABAergic synthesis and receptor subunit composition impact postsynaptic-response amplitude, which, in turn, is subject to considerable noise (Caspary *et al*., 1999; Ling *et al*., 2005). Other age-related sources of noise in the system include an increased number of neurotransmitter molecules per vesicle (Sulzer & Edwards, 2000) and the variability in the number and density of receptor proteins at a synapse (Paulsson, 2004). While a certain level of noise is tolerable and even desirable (McDonnell & Ward, *et al*., 2011), too much noise can have wide-reaching detrimental effects for neural functioning (Harris & Wolpert, 1998). For instance, some researchers propose that age-related increase in noise may lead to the generation of additional control signals from the cortex to the basal ganglia during voluntary movement and increased motor cortical activity, which would be stronger for those individuals with higher levels of noise (Albin, Young & Penney, 1989; Alexander & Crutcher, 1990).

This argument is supported by our finding that worse performance on the motor task is associated with greater over-activation of the sensorimotor network, and

recruitment of bilateral primary motor cortex for a typically left- or right-lateralized function of a hand movement. Although age-related increases in activity in existing functional networks have been interpreted as compensatory (Cabeza *et al*., 2002; Persson *et al*., 2004), the absence of positively correlated behavioural performance in our data does not support this interpretation. Rather, the findings are consistent with the idea of dedifferentiation and show that the neural signature of the hand-specific motor processes becomes less distinct (Li & Lindenberger, 1999). Previous studies have reported age-related reductions in neural sensitivity in visual processing (Burianová *et al*., 2013b; Carp *et al*., 2010; Schiavetto *et al*., 2002), memory processing (St-Laurent *et al*., 2011), and auditory processing (Grady *et al*., 2011). It is argued that this age-related reduction in functional segregation could be due to dysregulation of executive control (Dirnberger *et al*., 2010) and expending of available resources more quickly and ineffectively (Reuter-Lorenz and Cappell, 2008). We suggest that the age-related dedifferentiation in motor processing, concomitant with decreased intracortical and interhemispheric GABAergic inhibition, may underlie increased levels of noise in the sensorimotor neural circuitry (Faisal, Selen & Wolpert, 2008).

The results of this study also reveal similar age-related over-activation and stronger MRBD for motor imagery. Since MI shows considerable overlap with the motor planning stages of ME (Jeannerod, 2001; Lotze & Halsband, 2006), this finding demonstrates that the increased noise levels in older adults affect not only the sensorimotor circuits underlying the controlled execution of movements, but also the neural processes engaged in movement planning. One implication of this finding is that the decline in motor functioning observed behaviourally in older adults can potentially

have two underlying neural sources and that the high number of injuries stemming from falls and other harmful movements in older adults might not only reflect reduced motor control, but also reduced motor planning. In turn, our findings highlight the importance of physical activity as part of the process of healthy ageing and suggest that preventative behavioural training engaging MI might provide a promising tool to reduce the likelihood of future movement injuries in older adults. Such MI training might prove especially useful for older individuals who suffer from restricted physical mobility as a result of non-neurological age-related pathologies, such as rheumatism. In this context, it is important to note that our sample of older adults was relatively young, with the majority of participants being in their early 60s, and, therefore, not suffering from severe non-neurological age-related pathologies. In addition, the finding that the same age-related changes in motor functioning can be observed during ME and MI has clinical implications in that our results imply that functional neuroimaging of brain activity underlying MI could potentially serve as a reliable tool to diagnose pathological changes in the neural organization underlying motor dysfunctions, such as dyskinesia. In conclusion, our results demonstrate that increased motor-related brain activity in older adults might characterize neural dedifferentiation and an increase in GABAergic inhibition. Together, our findings provide the first evidence for a link between neurotransmitter imbalance and neural dedifferentiation in healthy ageing.

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Figure Captions

FIG 1. Task Layout. In each trial, participants were instructed to either move or imagine moving the fingers of their right or left hand, starting from a default position of all fingers extended. They curled in or extended specific fingers according to sequentially presented auditory cues. At the end of a cue sequence, participants were asked to indicate whether the configuration of their fingers matched the configuration of the displayed target hand.

FIG 2. Task Performance. Accuracy scores for the four experimental conditions and two imaging modalities (left = MEG; right = fMRI). **YA** = young adults; **OA** = older adults; **RE** = right-hand execution; **LE** = left-hand execution; **RI** = right-hand imagery; **LI** = left-hand imagery. Error bars denote the standard error of the mean.

FIG 3. MEG Results. Movement-related beta desynchronization in left and right primary motor cortex during the four experimental conditions. **YA** = young adults; **OA** = older adults; **RE** = right-hand execution; **LE** = left-hand execution; **RI** = right-hand imagery; **LI** = left-hand imagery; **M1** = primary motor cortex. Time-frequency plots show changes in power over time (x-axis, in seconds) for the beta-frequency band (15-30 Hz; y-axis, in Hz). Bar plots show MRBD, *i.e*., average power changes (in %) in the time window 250 to 500 msecs post-stimulus onset (dashed vertical line) relative to the pre-stimulus baseline (-1500 to -500 msecs). Brain images show location of the two ROIs in the left and right M1. Error bars denote the standard error of the mean.

FIG 4. fMRI Results: Whole-Brain Activity. Left: A pattern of whole-brain activity depicting areas active during motor execution and motor imagery (yellow/red) *vs*. fixation (blue/green). Right: Brain scores related to whole-brain activity seen on the left across the five conditions, for the two groups of participants. **YA** = young adults; **OA** = older adults; **RE** = right-hand execution; **LE** = left-hand execution; **RI** = right-hand imagery; **LI** = left-hand imagery; **FIX** = fixation. Error bars denote 95% confidence intervals calculated from the bootstrap procedure.

FIG 5. fMRI Results: Brain-Behaviour. Left - activity in somatosensory cortex (**top**: right M1 in crosshairs; **bottom**: left M1 in crosshairs). **Right** - correlations between activity in left M1, right M1, and accuracy during left-hand execution (**top**) and right-hand execution (**bottom**). Error bars denote 95% confidence intervals for the correlations calculated from the bootstrap procedure. When the error bars cross zero, the correlation is not significant. **YA** = young adults; **OA** = older adults; **L M1** = left primary motor cortex; **R M1** = right primary motor cortex; **ACC** = accuracy.

Table 1. Means, standard deviations, and ranges of the proportion accuracy on the task (per condition and group).

			BEHAVIOURAL RESULTS					
			MEG			**fMRI**		
	RE	**LE**	**RI**	**LI**	**RE**	**LE**	**RI**	**LI**
YOUNG $\bar{x}$	0.94	0.92	0.93	0.85	0.92	0.89	0.90	0.86
YOUNG SD	0.05	0.06	0.09	0.15	0.08	0.11	0.12	0.12
RANGE (min/max)	0.75/1	0.88/1	0.75/1	0.50/1	0.75/1	0.56/1	0.63/1	0.56/1
OLD $\bar{x}$	0.89	0.88	0.81	0.80	0.84	0.88	0.83	0.80
OLD SD	0.12	0.13	0.20	0.16	0.14	0.13	0.16	0.16
RANGE (min/max)	0.60/1	0.60/1	0.50/1	0.53/1	0.53/1	0.56/1	0.50/1	0.56/1

Legend: $\bar{x}$ = mean; **SD** = standard deviation; **MEG** = magnetoencephalography; **fMRI** = functional magnetic resonance imaging; **RE** = right-hand execution; **LE** = left-hand execution; **RI** = right-hand imagery; **LI** = left-hand imagery.

Table 2. Means, standard deviations, and range of the power change (%) during the task (per condition and group)

			MEG RESULTS					
		LEFT M1				RIGHT M1		
	RE	LE	RI	LI	RE	LE	RI	LI
YOUNG x̄	-33.0	-16.6	-3.4	-7.7	-18.4	-31.0	-5.2	-12.1
YOUNG SD	16.1	19.6	19.3	14.2	18.5	20.9	17.1	15.3
RANGE (min/ max)	-6.5/ -66.0	19.9/ -48.8	34.7/ -33.2	14.6/ -33.5	18.1/ -52.9	4.4/ -56.8	37.2/ -31.4	14.7/ -46.1
OLD x̄	-27.7	-30.4	-25.6	-23.2	-24.1	-28.4	-19.4	-24.5
OLD SD	16.2	16.4	16.4	14.1	17.5	20.9	16.4	15.7
RANGE (min/ max)	1.5/ -51.7	0.5/ -53.4	3.9/ -44.7	7.5/ -38.5	5.7/ -53.8	8.9/ -57.8	8.9/ -42.6	5.0/ -52.1

Legend: **x̄** = mean; **SD** = standard deviation; **MEG** = magnetoencephalography; **M1** = primary motor cortex; **RE** = right-hand execution; **LE** = left-hand execution; **RI** = right-hand imagery; **LI** = left-hand imagery.

Table 3. Brain-behaviour correlations during motor execution with left and right hand (per seed, accuracy, and group)

	BRAIN-BEHAVIOUR CORRELATIONS					
		LEFT HAND			**RIGHT HAND**	
	L M1	**R M1**	**ACC**	**L M1**	**R M1**	**ACC**
YOUNG	-0.08	0.73	-0.15	0.47	0.14	-0.30
OLD	0.79	0.65	-0.47	0.73	0.76	-0.72

Legend: L M1 = left primary motor cortex; **R M1** = right primary motor cortex; **ACC** = accuracy.