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Long-term effects of motor training on resting-state networks and underlying brain structure

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ABSTRACT

Acquired motor skills are coded in fronto-parietal brain networks, but how these networks evolve through motor training is unclear. On the one hand, increased functional connectivity has been shown immediately after a training session; on the other hand, training-induced structural changes are visible only after several weeks. Based on known associations between functional and structural network development during human ontogeny, we hypothesised that learning a challenging motor task leads to long-lasting changes in functional resting-state networks and the corresponding cortical and sub-cortical brain structures. Using longitudinal functional and structural MRI at multiple time points, we demonstrate increased fronto-parietal network connectivity one week after two brief motor training sessions in a dynamic balancing task, although subjects were engaged in their regular daily activities during the week. Repeated training sessions over six consecutive weeks progressively modulate these changes in accordance with individual performance improvements. Multimodal correlation analyses showed an association between structural grey matter alterations and functional connectivity changes in prefrontal and supplementary-motor areas. These coincident changes were most prominent in the first three weeks of training. In contrast, changes in fronto-parietal functional connectivity and the underlying white matter fibre structure developed gradually during the six weeks. Our results demonstrate a tight correlation between training-induced functional and structural brain plasticity on the systems level and suggest a functional relevance of intrinsic brain activity for morphological adaptation in the human brain.

Introduction

The coordination and planning of complex motor skills is controlled by fronto-parietal brain networks (Rizzolatti and Luppino, 2001). Apraxia patients with lesions in parietal or premotor areas as well as their anatomical connections have severe deficits in coordinating complex visuomotor movements (Leiguarda and Marsden, 2000). Functional magnetic resonance imaging (fMRI) studies have found that prefrontal, premotor, supplementary motor and parietal brain areas are recruited when acquired motor skills are executed (Hallett and Grafman, 1997; Halsband and Lange, 2006; Pascual-Leone et al., 1995). However, it is uncertain how motor skill learning changes the underlying functional and structural network architecture.

The brain's functional network architecture is apparent in its intrinsic functional connectivity (IFC) patterns. IFC in the brain can be assessed by functional MRI of blood-oxygen-level-dependant (BOLD) signal fluctuations in the resting-state (Biswal et al., 1995; Fox and Raichle, 2007). Different from task-evoked BOLD signal changes, fMRI in the resting-state measures ongoing, spontaneous fluctuations of the BOLD signal. These fluctuations are not random but temporal coherent between distinct regions in the brain, thus, providing a measure of IFC (Fox and Raichle, 2007). IFC closely resembles patterns of anatomical connectivity through white matter fibre pathways and also co varies with cortical grey matter volume (Hagmann et al., 2008; Seeley et al., 2009).

Longitudinal brain imaging studies revealed a pronounced degree of training-induced structural plasticity in the adult human brain. For example, three months of juggling training resulted in profound changes in parietal grey matter structure (Draganski et al., 2004). A recent study also found training-induced changes in parietal white matter microstructure after six weeks of juggling training (Scholz et al., 2009). However, the functional role of these learning-induced grey and white matter changes for functional network integrity is unclear. Do structurally modified grey matter regions or white matter fibre tracts contribute to refinements in functional network connectivity? Cross-sectional studies thus far have demonstrated a correlation between increasing IFC and white matter fibre proliferation from childhood to adolescence, suggesting slowly-evolving changes in brain architecture during human ontogeny (Hagmann et al., 2010; Power et al., 2010). Instead, motor training can modulate IFC in

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resting-state networks immediately after a training session. For instance, learning a visuomotor tracking task enhanced IFC between frontal and parietal brain regions during subsequent resting wakefulness (Albert et al., 2009). However, it is unclear whether long-term changes in IFC can be induced by motor training and whether IFC changes coincide with structural alterations in the underlying grey matter and white matter fibre structure.

Therefore, we trained human subjects in a dynamic balance task for 45 min once a week (always on Monday) over six consecutive weeks (see Methods; Figs. 1a, b, c). FMRI during resting-state was performed 30 min prior to training in the first (fMRI 1), third (fMRI 2) and fifth week (fMRI 3) as well as in the seventh week (fMRI 4), thus, leaving always one week between a training session and the subsequent fMRI scan (Fig. 1c). The functional data was acquired in the course of a previous study where we reported structural grey and white matter changes in response to balance training (Taubert et al., 2010). IFC was measured as linear correlation between BOLD signal time courses in each brain voxel (Fox and Raichle, 2007). To identify patterns of IFC changes across the whole brain, we used a novel graph-based network analysis technique called eigenvector centrality mapping (ECM) (Lohmann et al., 2010). ECM attributes a centrality value to each voxel ($3\times3\times3$ mm) in the brain such that a voxel receives a larger value if it is more strongly correlated with many other voxels which are central within the network themselves (Fig. 1d). Subsequently, seed-based correlation maps were computed, using peak coordinates from ECM clusters as seed regions, in order to identify to which regions IFC increased as a result of training. The seed-based correlation analysis was performed to unfold the spatial topography of learning-induced IFC changes across the brain. Third, multimodal correlation analyses were applied to investigate the structure–function relationship with our previously published structural data (Taubert et al., 2010). We tested whether functional and structural changes that occur in the same brain networks within the same participants have comparable temporal dynamics across the six weeks of training.

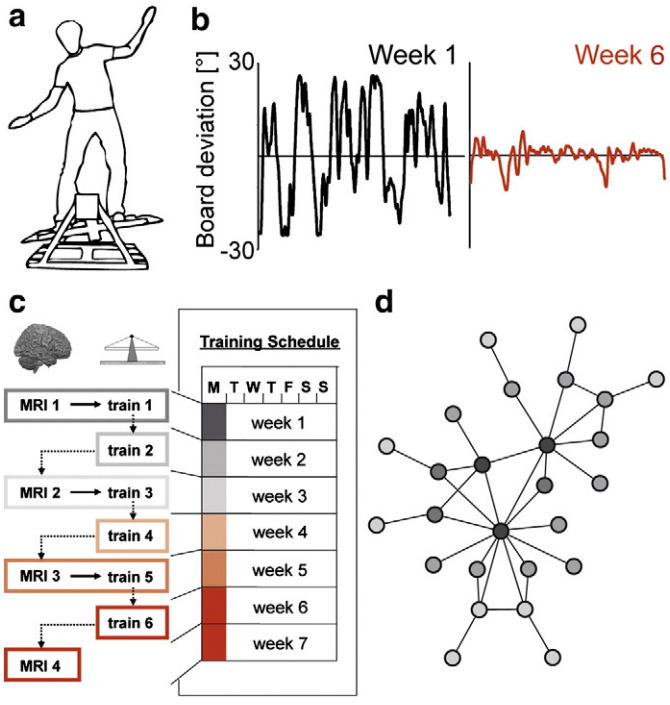

Fig. 1. Experimental procedure. (a) Dynamic balancing task. (b) Board deviation (maximum deflection ±26°) from horizontal line on training day (train) 1 (black; fifth trial) and 6 (red; fifth trial) in one representative subject. (c) Motor training and MRI scanning schedule. Scanning was always performed prior to training (M: Monday). (d) Schematic network representation showing brain voxel (nodes) and their functional connections (edges). Dot colour represents increasing eigenvector centrality (white to black; see Methods).

Methods

Participants

Twenty-eight right handed subjects (25.9 years ± 2.8 y; 14 females) were recruited for the study after obtaining written informed consent approved by the local ethics committee. All subjects underwent a neurological examination before participation. Subjects were naive to the experimental setup with no prior experience of other highly coordinative balancing skills.

Training and experimental procedure

Fourteen subjects were trained once a week (always on Monday) in a dynamic balance task (DBT) for six consecutive weeks (Fig. 1a). In each training session, subjects performed 15 trials of 30 s in the DBT, trying to keep an unstable stabilometer platform (Lafayette Instrument, US) in a horizontal position as long as possible (Fig. 1b). We measured time in balance within a range of 3° to each side from the horizontal during the trial length of 30 s and provided subjects with verbal feedback after each trial. Subjects received 2–3 min rest between each trial to ensure that no fatigue effects will influence the results. Thus, the total time for each training session was approximately 45 min for each subject (7.5 minutes balance training and 35 minutes rest). MRI was performed as follows: baseline scan before learning (fMRI 1), two intermittent scans in week 3 and 5 (fMRI 2 and 3) and a final scan one week after completion of the learning period (fMRI 4). Scanning was performed prior to training on training days 1, 3 and 5 (for further details see (Taubert et al., 2010)). The control group, consisting of 14 age- and gender-matched subjects scanned at baseline and 2 weeks later, did not practise the balancing task during the two weeks.

Scanning protocol and preprocessing

FMRI data were acquired under eyes-closed condition on a Siemens Magnetom Tim Trio 3 Tesla scanner equipped with a 32-channel head coil using the following parameters: 400 whole brain volumes, acquisition matrix = 64×64, slice thickness = 3 mm (1 mm gap), voxel dimensions = $3\times3\times4$ mm, 34 slices, TR = 2300 ms, TE = 30 ms, flip angle = 90°, bandwidth = 1825 Hz. The total time for the resting-state fMRI session for each subject was approximately 15 min. Preprocessing of fMRI data was performed according to Lohmann et al. (2010) and included removal of first 10 volumes, motion correction, bandpass filtering and spatial smoothing. Preprocessed data sets were registered into standard MNI152 (Montreal Neurological Institute) brain space and resampled to an isotropic voxel grid with a resolution of $3\times3\times3$ mm. The functional data were acquired at the beginning of each MRI session followed by a T1-weighted anatomical (approx. 13 min.) and diffusion-weighted (approx. 15 min.) scan. The pre-processing procedures and statistical analyses of previously published diffusion-weighted and structural MRI data were described in Taubert et al.(2010).

ECM and seed-based correlation analyses (SBCA)

ECM analysis for each subject and scanning time point was performed according to Lohmann et al. (2010). We believe that ECM is more appropriate in our study than other centrality measures such as betweenness or degree centrality because ECM is parameter-free, computationally fast and does not depend on prior assumptions (a priori information). Previous studies commonly used an anatomical

template of 90 regions-of-interest (Achard et al., 2006; He et al., 2009). However, similar to the structural grey matter analysis, we aimed to perform voxel-wise analyses with the functional data. This required a large region-of-interest of ~40000 voxels in our study which makes measures like betweenness centrality computationally intractable (Lohmann et al., 2010). The computational speed of ECM enabled us to obtain whole brain centrality maps and use them in a manner similar to contrast maps obtained in standard regression analyses (Lohmann et al., 2010). Furthermore, in contrast to degree centrality, ECM does not depend on a pre-specified threshold for correlation values and captures small-world characteristics of the human brain which degree centrality does not (Bonacich, 2007; Lohmann et al., 2010).

We manually defined a region-of-interest containing about 52,000 voxels covering the entire cerebrum to which subsequent ECM analysis was applied. Negative correlations were set to zero. Also, correlations between voxels that were less than 3 voxels (9 mm) apart were set to zero focussing on long-range connectivity. ECM procedure is independent from a priori information regarding selection of specific seed regions and therefore constituted a perfect starting point to apply subsequent SBCA. SBCA were used to find changes in BOLD signal correlations from centrality clusters (Supplementary Table 2) to other areas across the whole brain. For SBCA we performed temporal filtering of preprocessed fMRI data in a range between 0.1 and 0.01 Hz (Fox and Raichle, 2007).

Probabilistic tractography of diffusion-tensor imaging data

The aim of this analysis was to show anatomical connections from a white matter region in the left anterior centrum semiovale where we previously observed learning-induced microstructural alterations in the same subjects (Taubert et al., 2010), and left SMA/pre-SMA and mPL showing gradually increasing IFC (Fig. 3). Thus, we aimed to show that increased functional connectivity between SMA/pre-SMA and mPL coincides with structural alterations in interconnecting fronto-parietal fibre tracts (Fig. 3). We used probabilistic tractography analysis of diffusion-weighted imaging data from each subject at baseline ($n=14$). For image acquisition parameters and pre-processing procedure see Taubert et al. (2010). A cluster in left anterior centrum semiovale which showed negative correlation between individual performance improvements and changes in mean diffusivity across the four scanning time points (Taubert et al., 2010) (thresholded at $p<0.001$ uncorrected on voxel-level and $p<0.05$ corrected for multiple comparisons on cluster-level) was used as a seed region-of-interest (ROI) for the tractography algorithm. Because the white matter diffusion results were group results localised in MNI space and tractography was carried out in each individual's native space, we first mapped the diffusion results onto each participant's anatomy. Paths from seed ROI were determined using a Monte-Carlo algorithm with multiple samples per seed voxel. The resulting images represent empirically determined probability distributions of anatomical connectivity from the seed ROI in native space.

Statistical analysis

Statistical analysis was performed using the programme package Lipsia (Lohmann et al., 2001). ECM for each subject on each scanning time point was computed according to Lohmann et al. (2010). Subsequent SBCA allowed detection of IFC changes between peak centrality coordinate (bilateral SMA/pre-SMA, right vPMC and left mPL; Table S1) and other areas across the brain. Correlations were detected using linear correlation between BOLD signal time courses in peak voxel of centrality cluster (Table S1) and all other voxel across the brain. Note that all SBCA statistics were computed on Fisher Z-transformed correlation (r) values. Centrality and IFC changes between fMRI scans were detected using two-tailed paired samples t-tests. Performance-related centrality and functional connectivity changes across all scanning time points were detected using parametric correlations with average (train1: 7; train2: 13; train4: 17; mean average of last five trials on train6: 20 s) as well as individual performance values from training day 1 (average of initial five trials), 2, 4 (average of 15 trials) and 6 (average of last five trials). Similarities in the temporal dynamics between grey matter and centrality changes were assessed in a further parametric correlation analysis using grey matter eigenvalues from peak coordinate in left and right SMA/pre-SMA and left OFC grey matter cluster across the four scanning time points (Taubert et al., 2010). Results were corrected for multiple comparisons using cluster-size and cluster-value thresholds obtained by Monte-Carlo simulations (Poline et al., 1997) using significance level of $p<0.05$. Clusters were obtained using an initial z-value threshold of 2.33.

Results

Functional changes from fMRI 1 to fMRI 2 (after 2×45 min of training)

The whole-brain ECM analysis revealed a centrality increase in bilateral supplementary/pre-supplementary motor areas (SMA/pre-SMA) and right ventral premotor cortex (vPMC) in the training group from fMRI 1 to fMRI 2 (baseline to the third week of training; paired samples *t*-test, $n=14$, $p<0.05$, corrected for multiple comparisons; Fig. 2a) while no changes in these areas could be observed in the control group that performed no balance training (region-of-interest (ROI) analysis for bilateral SMA/pre-SMA and right vPMC; paired samples *t*-test, $n=14$, $p>0.05$, corrected). Significant centrality changes in the training group but not in controls were confirmed by interaction analyses (ANOVA with group×time interaction for left SMA/pre-SMA: $F_{(1,13)}=4.54$, $p=0.038$; right SMA/pre-SMA: $F_{(1,13)}=6.18$, $p=0.016$; right vPMC: $F_{(1,13)}=5.44$, $p=0.024$; see Fig. 2d).

These results are consistent with the key role of SMA/pre-SMA and vPMC in motor learning (Hallett and Grafman, 1997; Halsband and Lange, 2006). Given that our graph-based network analysis assesses local differences in eigenvector centrality (Lohmann et al., 2010), we subsequently conducted seed-based correlation analyses (SBCA) for the peak coordinates found in SMA/pre-SMA and vPMC (Supplementary Table 1). SBCA for left SMA/pre-SMA revealed increased IFC in a medial network of SMA/pre-SMA, medial orbitofrontal cortex (OFC) and medial parietal cortex (mPL) in the left hemisphere (Fig. 2b). SBCA for right vPMC revealed increased IFC to bilateral dorsolateral prefrontal cortex (DLPFC) (Fig. 2c; Supplementary Table 2 for all IFC changes). These results demonstrate training-induced IFC increases between prefrontal cortex, SMA/pre-SMA and parietal areas that persist for at least one week after training (Albert et al., 2009; Lewis et al., 2009; Tambini et al., 2010).

Functional changes after the initial learning phase (after fMRI 2)

Next, we wanted to test the stability and modifiability of centrality changes through additional balance training between fMRI 2, fMRI 3 and fMRI 4 (Fig. 1c). We found that centrality changes in the right vPMC but not in bilateral SMA/pre-SMA were significantly smaller at fMRI 3 as compared to fMRI 2 (whole-brain analysis using paired samples *t*-test; $n=14$; corrected for multiple comparisons). ROI analysis revealed that centrality in right vPMC at fMRI 3 and fMRI 4 decreased back to baseline (fMRI 1) levels (Fig. 2d; repeated measures ANOVA with main effect fMRI-timepoint $F_{(3,39)}=5.393$; $p=0.003$; post-hoc comparisons: fMRI 1 to fMRI 2, $p=0.019$; fMRI 1 to fMRI 3 and fMRI 1 to fMRI 4, each $p>0.05$, corrected for multiple comparisons). In contrast, centrality in left SMA/pre-SMA remained elevated at fMRI 3 but not fMRI 4 as compared to baseline (repeated measures ANOVA with main effect fMRI-timepoint $F_{(3,39)}=2.867$; $p=0.049$; post-hoc comparisons: fMRI 1 to fMRI 2, $p=0.002$; fMRI 1

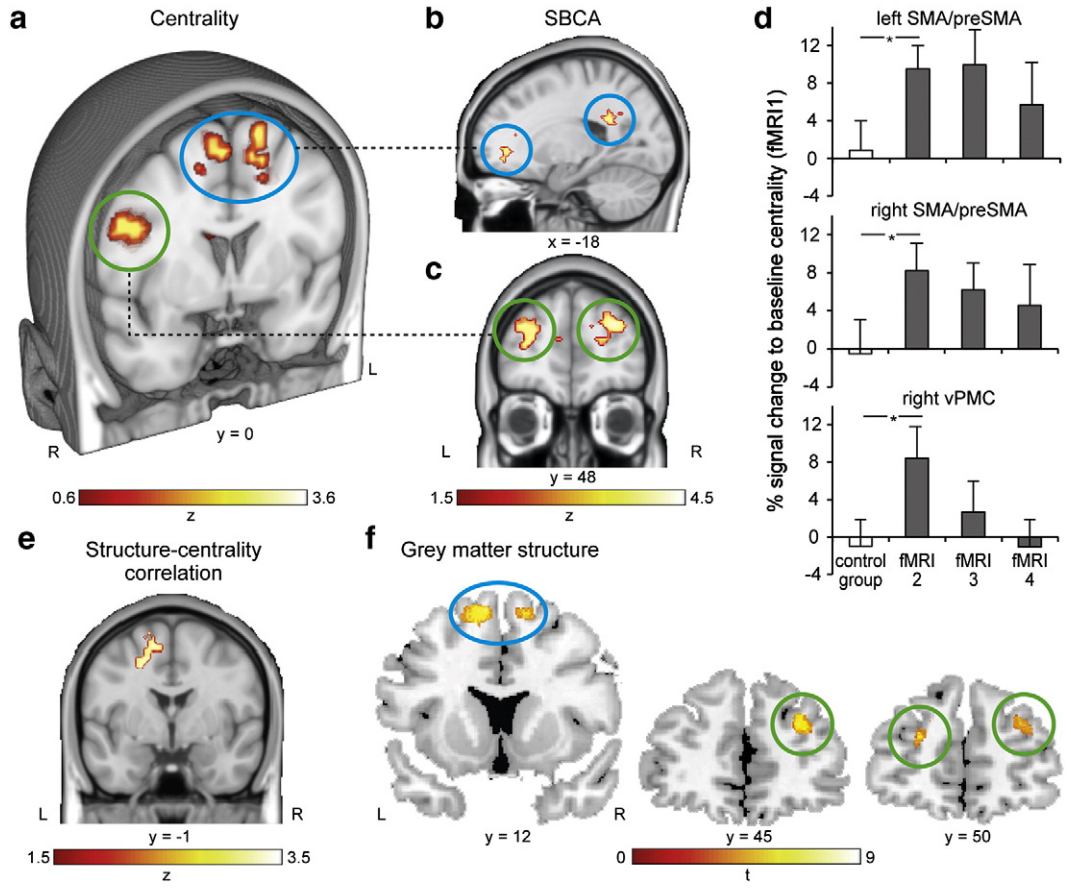

Fig. 2. Functional and structural changes after 2×45 min of training. (a) Centrality increase in bilateral SMA/pre-SMA (cyan) and right vPMC (green) from fMRI 1 to fMRI 2 (baseline to week 3; n = 14, $p<0.05$ corrected for multiple comparisons). No centrality decrease was detected. (b, c) Seed-based correlation analyses (SBCA) showed increased connectivity from left SMA/pre-SMA (cyan) and right vPMC (green) from fMRI 1 to 2 (n = 14, $p<0.05$ corrected; no decrease detected). Bars indicate Z values. (d) Percent signal change in left and right SMA/pre-SMA and right vPMC in the balance training group (fMRI 2, fMRI 3 and fMRI 4; n = 14) and the age- and gender-matched controls (n = 14) (group × time interaction for left SMA/pre-SMA: $F_{(1, 13)} = 4.54$, $p = 0.038$; right SMA/pre-SMA: $F_{(1, 13)} = 6.18$, $p = 0.016$; right vPMC: $F_{(1, 13)} = 5.44$, $p = 0.024$). Bars show average centrality values (± standard error) within a 9 mm sphere around the peak voxel (Supplementary Table 1). Asterisks indicate significant differences between groups. (e) Parametric correlation between grey matter eigenvalues and centrality in left SMA/pre-SMA (n = 14, $p<0.05$ corrected). (f) Grey matter volume increase from baseline to week 3 (structural data from Taubert et al., 2010). Bar indicates t value. Distance between functional and structural peak coordinate in left SMA/pre-SMA is <0.4 mm (Supplementary Table 1). L, Left; R, Right.

to fMRI 3, $p = 0.019$; fMRI 1 to fMRI 4, $p>0.05$, corrected for multiple comparisons) while no significant changes over time could be observed in right SMA/pre-SMA (repeated measures ANOVA with no significant main effect fMRI-timepoint $F_{(3,39)} = 2.141$; $p = 0.111$). Additionally, whole-brain analyses (paired samples *t*-test) for fMRI 1 to fMRI 3 and fMRI 1 to fMRI 4 suggest no further centrality changes in other brain regions at fMRI 3 (n = 14, $p>0.05$ corrected) but a significant centrality increase in the left medial parietal cortex (mPL) at fMRI 4 (n = 14, $p<0.05$ corrected for multiple comparisons across the whole brain) relative to fMRI 1. These results suggest that additional balance training sessions after the initial learning phase caused different temporal dynamics of centrality changes in vPMC and SMA/pre-SMA as well as in mPL.

Performance-related functional changes during six weeks of motor training (fMRI 1, fMRI 2, fMRI 3 and fMRI 4; 6×45 min of training)

As a next step, we aimed to test whether performance improvements in the dynamic balance task during the whole training period (fMRI 1, fMRI 2, fMRI 3 and fMRI 4) correlate with individual centrality changes across the whole brain. It has been suggested that memory retrieval-induced reconsolidation processes are crucial for the integration of new information into existing memory networks (Sara, 2000; Tronson et al., 2006). Assuming that further motor training in the dynamic balance task progressively modifies functional changes in specific brain regions, we tested for performance-related changes in centrality across the four scanning time points (fMRI 1–4). The parametric analysis for both average (thick black line in Fig. 3f; see Methods) as well as individual (average initial five trials on train 1; average of all trials on train 2 and 4; average of last five trials on train 6) performance improvements revealed a positive correlation in left mPL (fMRI 1–4; n = 14; $p<0.05$ corrected for multiple comparisons across the whole brain; Figs. 3a, b, d). A cluster in the contralateral right mPL was only significant for the parametric correlation with average performance improvements (Figs. 3a and b).

The parametric SBCA for left mPL showed steadily increasing connectivity to left SMA/pre-SMA (Figs. 3c, e; Supplementary Table 2) in correlation with individual performance improvements. This pattern of SMA/pre-SMA - mPL connectivity was already enhanced at fMRI 2, however, with SMA/pre-SMA being the cortical locus of increased centrality (Fig. 2a). Hence, these results suggest core IFC changes between parietal and SMA/pre-SMA areas during the entire motor training period (Supplementary Fig. 1) (Hallett and Grafman, 1997).

Structure–function relationship

Although, studies with rats demonstrate an association between experience-dependent neuronal activity changes in a cortical brain area and corresponding structural changes that are dedicated to the

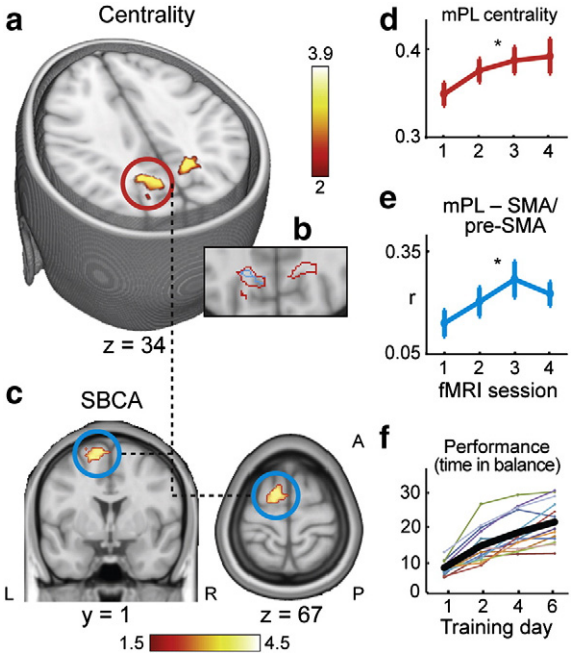

Fig. 3. Performance-related functional and structural changes. (a) Positive correlation between centrality increase in bilateral mPL (red) and average performance improvements (black line in *f*) across the six weeks ($n=14$; $p<0.05$ corrected for multiple comparisons). No negative correlation was detected. Bar indicates Z value. (b) Outlines indicate spatial overlap for positive correlations between centrality changes and performance improvements (see *f*; red: average; blue: individual improvements). Image is thresholded at $Z>3$. (c) SBCA (left mPL) revealed a connectivity increase to left SMA/pre-SMA (cyan) that correlated with individual performance values ($n=14$; $p<0.05$ corrected; no negative correlation). Bar indicates Z value. (d, e) Group averaged (d) centrality and (e) correlation values (± standard error) for fMRI 1–4 (main effect, centrality $F_{(3,39)}=3.9$, $p=0.015$; correlation $F_{(3,39)}=4.8$, $p=0.006$). (f) Average (black line) and individual (coloured lines) motor performance (y-axis shows time in balance) used for parametric correlation analyses. L, Left; R, Right; A, Anterior; P, Posterior.

formation of new synaptic connections (Maviel et al., 2004), no previous study found an association between training-induced macroscopic structural alterations and functional connectivity changes in the human brain. Therefore, we tested for temporal and spatial relationships between functional network changes and macroscopic structural changes in cortical grey matter regions and white matter fibre tracts. We used multimodal correlation analyses between centrality/IFC changes and balance training-related structural grey and white matter changes obtained from the same participants that were described previously by our group (Taubert et al., 2010). Specifically, we tested whether increased centrality or IFC occurs in the same brain networks and with comparable temporal dynamics to structural grey and white matter changes (Taubert et al., 2010). We previously found transient, initial and widespread grey matter changes in bilateral SMA/pre-SMA, bilateral DLPFC and the left inferior parietal lobe as well as slowly-evolving and performance-related changes in the orbital part of the left superior frontal gyrus (Fig. 2f and Supplementary Fig. 2). Figs. 2a, c, f illustrate coincident centrality, IFC and grey matter changes from fMRI 1 to fMRI 2 in SMA/pre-SMA and DLPFC. Using a parametric correlation analysis, we showed that the temporal dynamics of grey matter and centrality changes in left SMA/pre-SMA (across all scanning time points) positively correlate with each other (Fig. 2e, see also Supplementary Fig. 3). Second, we tested the hypothesis that core IFC changes between left SMA/pre-SMA and left mPL coincide with structural white matter changes in interconnecting fibre tracts. In addition to grey matter changes in bilateral SMA/pre-SMA, we previously found slowly-evolving mean diffusivity decreases across the four scanning time points within white matter regions in bilateral anterior centrum semiovale (Fig. 3f) (Taubert et al., 2010). Using probabilistic tractography analysis with diffusion-tensor imaging data (DTI baseline scan; $n=14$), we therefore aimed to track the fibre connections from the cluster in left anterior centrum semiovale in each subject. The individual data shows anatomical connections to left SMA/pre-SMA via transcallosal fibres and left mPL via cingulate fibres (Fig. 4), indicating slowly-evolving structural changes in functionally-relevant anatomical pathways during the whole learning period.

Discussion

Developmental studies suggest reciprocal relations between intrinsic long-range functional connectivity and white matter fibre structure from childhood to adolescence, potentially supporting improved information processing in distributed networks (Hagmann et al., 2010; Power et al., 2010). According to Hebb's postulate (Hebb, 1949), the correct timing of neural signals is a prerequisite for the occurrence of learning-related synaptic plasticity in neural networks. The velocity and synchrony of neural transmission between distant cortical regions is regulated by the structure of white matter fibre tracts (Fields, 2008). Accordingly, motor learning has been shown to change the white matter microstructure in parietal regions (Scholz et al., 2009). Our data provide novel evidence for the functional relevance of training-induced white matter changes showing that intrinsic functional connectivity changes between left SMA/pre-SMA and mPL coincide with microstructural alterations in the underlying white matter fibre tracts (Fig. 3). Moreover, we can show that both, white matter and IFC changes correlate with individual performance improvements during the six weeks of training (Fig. 3). Data from our previous study also indicate performance-related grey and white matter changes in the left anterior prefrontal lobe (Supplementary Fig. 2; (Taubert et al., 2010)). Importantly, this region is anatomically and functionally connected with mPL via the cingulum bundle (Margulies et al., 2009; Petrides and Pandya, 2007; Vincent et al., 2008), indicating training-induced functional and structural brain plasticity in a large-scale network comprising interconnected regions across the entire cerebrum.

Furthermore, we provide evidence that cortical changes in functional centrality in left SMA/pre-SMA directly correlate with structural grey matter changes in this area (Fig. 2). A previous study demonstrated coincident changes in occipital grey matter volume and the task-evoked BOLD signal response after two weeks of daily mirror reading training (Ilg et al., 2008). Our results extend these findings showing that local grey matter changes also coincide with alterations in the functional connectivity patterns of the corresponding brain region. But what does this evidence tells us about possible physiological mechanisms of training-induced changes in intrinsic brain activity?

Electrophysiological studies suggest that intrinsic BOLD fluctuations may result from changes in slow cortical potentials (SCP; <4 Hz) (He et al., 2008; Raichle, 2010). SCPs most consistently correlate with BOLD signal fluctuations (He et al., 2008). Similar to BOLD signal fluctuations, SCPs can be modulated by prior motor learning (Huber et al., 2004). These learning-induced modulations were most prominent within the low delta band (<2 Hz) and at frequencies corresponding to the slow oscillation (<1 Hz) and correlated with the amount of motor skill retention (Huber et al., 2004). It has been suggested that SCPs are generated by excitatory postsynaptic potentials at apical dendrites in pyramidal neurons (Birbaumer et al., 1990; McCallum and Curry, 1993). Recent animal studies, using long-term imaging of dendritic arbours, demonstrate the learning-induced formation and growth of spines on apical dendrites (Holtmaat and Svoboda, 2009). Spine changes are functionally relevant and lead to increased stimulus-evoked postsynaptic potentials (Trachtenberg et al., 2002; Wilbrecht et al., 2010). Furthermore,

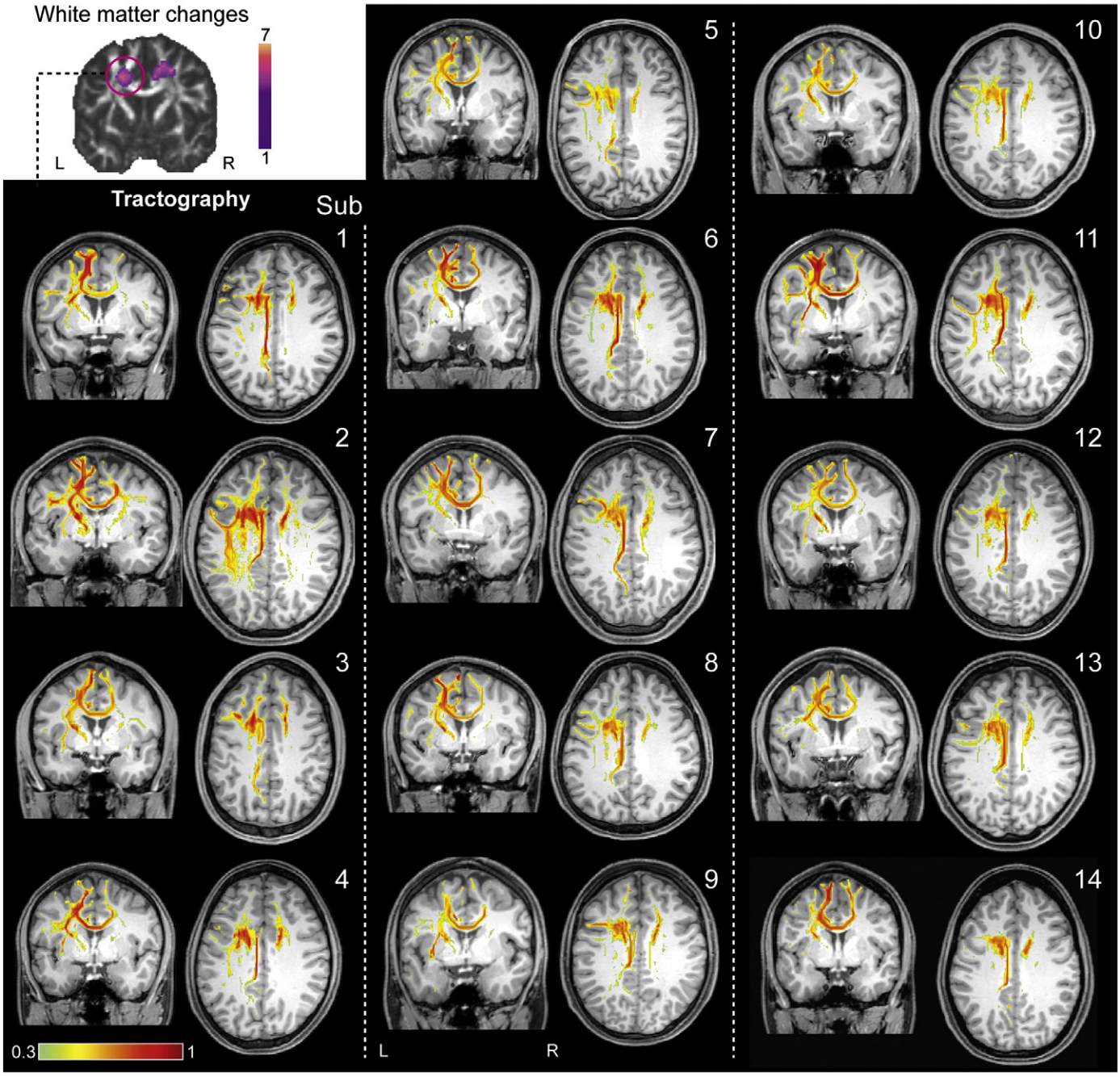

Fig. 4. Probabilistic tractography from seed region in left anterior centrum semiovale. (a) Parametric (with individual performance values) mean diffusivity decrease in anterior centrum semiovale (mean diffusivity data from Taubert et al., 2010). (b) Individual maps from probabilistic tractography using left anterior centrum semiovale as a seed region (purple circle). Connectivity maps were overlaid on individual T1-weighted images. The bar was scaled according to the individual maximum probability value (value of 1) in each image. L, Left; R, Right.

they occur, like MRI-detectable grey matter changes in humans, very rapidly after an intervention (Tost et al., 2010; Xu et al., 2009). Although, the cellular mechanisms of training-induced grey matter changes, as measured with MRI, are largely unknown, recent evidence suggests that the remodelling of neuronal processes (encompassing presynaptic terminals that form synapses with dendritic spines) seems to be a reasonable mechanisms (Lerch et al., 2011). Based on these findings, we speculate that grey matter changes in SMA/pre-SMA may reflect the total amount of dendritic spine changes induced by motor training. The spine changes could lead to SCP alterations which can be inferred from changes in intrinsic BOLD signal fluctuations (He et al., 2008). Although, we demonstrate a correlation between grey matter changes and alterations in intrinsic functional connectivity within the same area, future longitudinal studies using simultaneous EEG-fMRI recordings may unfold direct interactions between SCPs and BOLD signal changes as a result of training.

In summary, we demonstrate (1) a tight correlation between intrinsic functional connectivity and structural changes in SMA/pre-SMA and corresponding connections to mPL as well as (2) the longevity of balance training-induced functional changes under resting conditions. The latter suggests a new way to examine the spatial extent and fate of learning-related functional brain plasticity.

The former provides a general framework how internal or external alterations influence the structure and function of large-scale brain networks in humans.

Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.neuroimage.2011.05.078.

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