Parietofrontal motor pathways and their association with motor function after stroke

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Corticocortical interactions between the primary motor cortex, the ventral premotor cortex and posterior parietal motor areas, such as the anterior and caudal intraparietal sulcus, are relevant for skilled voluntary hand function. It remains unclear to what extent these brain regions and their interactions also contribute to basic motor functions after stroke. We hypothesized that white matter integrity of the underlying parietofrontal motor pathways between these brain regions might relate to residual motor function after stroke. Twenty-five chronic stroke patients were recruited (aged 64 ± 8.8 years, range 46–75, 17 males, one left-handed) and evaluated 34 months after stroke (range 12–169 months) by means of grip force, pinch force and the Fugl-Meyer assessment of the upper extremity. Based on these measures, motor function was estimated applying a factor analysis with principal component extraction. Using diffusion tensor imaging and probabilistic tractography we reconstructed probable intra-hemispheric trajectories between the primary motor cortex, the ventral premotor cortex and the anterior and caudal intraparietal sulcus in each patient. White matter integrity was estimated for each individual tract by means of fractional anisotropy. Generalized linear modelling was used to relate tract-related fractional anisotropy to the motor function. We found that the white matter integrity of the fibre tracts connecting the ventral premotor cortex and the primary motor cortex (P < 0.001) and the anterior intraparietal sulcus and the ventral premotor cortex (P < 0.01) positively correlated with motor function. The other tracts investigated did not show a similar structure-behaviour association. Providing first structural connectivity data for parietofrontal connections in chronic stroke patients, the present results indicate that both the ventral premotor cortex and the posterior parietal cortex might play a relevant role in generating basic residual motor output after stroke.

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Abbreviations: IPS = intraparietal sulcus; SLF = superior longitudinal fascicle; UEFM = Fugl-Meyer assessment of the upper extremity
Introduction

A stroke causing a motor deficit leads to widespread time-dependent alterations of motor-related neural activity (Rehme et al., 2012) which is paralleled by changes of functional (Wang et al., 2010) and effective interregional connectivity patterns (Greikkes et al., 2008; Rehme et al., 2011). Numerous studies have contributed to the understanding of the primary motor cortex (M1), the premotor cortices and the supplementary motor area as important nodes for motor recovery and functioning after stroke (Rehme and Greikkes, 2013). For instance, on the ipsilesional hemisphere, a positive prefrontal–premotor coupling was found to increase after stroke (Sharma et al., 2009) while premotor–premotor (Sharma et al., 2009) and prefrontal–motor couplings were reduced (Greikkes et al., 2008, 2010; Rehme et al., 2011). Such alterations in brain connectivity have been found functionally relevant as the reinstatement of normal coupling patterns within the ipsilesional hemisphere over time has been related to the amount of recovery (Rehme et al., 2011).

Compared to other secondary motor areas, less is known about the functional relevance of the ventral premotor cortex and the posterior parietal cortex after stroke. Studies in healthy participants have confirmed that the posterior parietal cortex and its pathways linking different secondary motor areas along the intraparietal sulcus (IPS) with ventral premotor cortex and ipsilateral M1 (Rizzolatti et al., 1998; Greikkes and Fink, 2005) mediate skilled voluntary movements, such as reaching and grasping and using objects and tools (Vingerhoets, 2014). These features account for dexterous hand function which is often critically affected after stroke. As an important node in a dorsolateral parietofrontal circuit, the anterior portion of the lateral bank of the IPS has been found to contribute critically to grasping (Davare et al., 2010, 2011), precision grip (Ehrsson et al., 2001) and online-adjustment of grip force (Dafotakis et al., 2008) during object manipulation and exploration (Binkofski et al., 1999). Anterior IPS provides ventral premotor cortex with visual information about object properties and influences the interactions between ventral premotor cortex and M1 to generate task-specific motor commands. Also more posterior regions along the intraparietal sulcus, homologous to the caudal IPS in monkeys, showed grasp-related activation (Faillenot et al., 1997; Culham et al., 2003). Animal (Tsutsui et al., 2003) and human studies (Shikata et al., 2001; Filimon et al., 2007; Koch et al., 2010; Mruczek et al., 2013) have documented that caudal IPS might contribute to the integration of spatial object features relevant for further movement planning and execution.

Structural connections between M1 and ventral premotor cortex as well as ventral premotor cortex and both anterior and caudal IPS have been found in animals (Cavada and Goldman-Rakic, 1989; Luppino et al., 1999; Rozzi et al., 2006; Schmahmann et al., 2007; Borra et al., 2008; Gharbawie et al., 2011) and humans (Makris et al., 2005; Tomassini et al., 2007; Koch et al., 2010). Sparse pathways linking also the anterior IPS-associated supramarginal gyrus and caudal IPS-related angularis gyrus with M1 have been recently described in humans (Koch et al., 2010). The structural substrate of the parietofrontal connections is the superior longitudinal fascicle (SLF). Its major component SLF II predominantly connects caudal inferior-parietal brain regions corresponding to the angularis gyrus with dorsal lateral frontal cortices. Its ventral component (SLF III) mainly derives from the more anterior supramarginal gyrus and targets predominantly ventral premotor and prefrontal cortices while a dorsal component (SLF I) connects mediodorsal parts of the parietal cortex with the mediodorsal frontal lobe (Makris et al., 2005).

There is only limited knowledge about the relevance of the parietofrontal motor pathways after stroke. A recent meta-analysis has described a consistent activation of anterior IPS during various movements of the affected limb (Rehme et al., 2012). Resting-state functional MRI has shown an increased connectivity between the contralesional superior parietal lobule and the ipsilesional dorsal premotor cortex that positively related to motor function after subcortical stroke (Wang et al., 2010). Effective connectivity analyses have revealed a decreased coupling of the ipsilesional superior parietal cortex on M1 and the supplementary motor area (Linnman et al., 2012).

Given the importance of the parietofrontal interactions for skilled hand function in healthy participants and growing evidence for stroke-related alterations of neural activity in the posterior parietal cortex, we questioned whether the microstructural integrity of specific parietofrontal white matter pathways might contribute also to basic residual motor function after stroke. Indeed, previous imaging studies have clearly shown that the structural integrity of corticocortical pathways is an important basis for neuronal information throughput and relevant for behaviour (Schulz et al., 2014). Using diffusion-tensor imaging we aimed at (i) reconstructing probable intrahemispheric connections between M1, ventral premotor cortex, anterior IPS and caudal IPS; and (ii) examining the extent to which tract-related microstructural integrity correlates with preserved motor function in the chronic stage of recovery after stroke.

Materials and methods

Subjects

Twenty-five patients (aged 64 ± 8.8 years, range 46–75, 17 male, one left-handed) with a broad spectrum of first-ever cortical and subcortical ischaemic strokes (10 in the dominant hemisphere, see Fig. 1 for lesion location and Table 1 for clinical data) were recruited. Patients were evaluated 34 months after stroke (range 12–169 months) by means of grip force, pinch force, the Fugl-Meyer assessment of the upper
extremity (UEFM) and the modified Rankin Scale. Based on grip and pinch force and the UEFM score, one composite motor function score was calculated for the affected hand using a factor analysis with principal component analysis. Explaining 73.4% of the variance, the first eigenvariate was used for further correlative analysis. To account for general inter-subject variability in motor performance, a motor function score was also calculated for the unaffected hand.

Table 1 Clinical data

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Age (in years) and gender (M = male; F = female), dominant hemisphere (L = left; R = right), stroke location (MED = media infarct; POS = posterior infarct; PLIC = posterior limb of the internal capsule; CR = corona radiate; CI = capsula interna; TC = thalamocapsular; LC = lenticocapsular; MO = medulla oblongata; BG = basal ganglia; PRE = precentral gyrus; PON = pons), affected hemisphere (AH), time in months after stroke. Absolute grip and pinch force values (in kg), and the UEFM are merged to one composite motor function score (MF) for the affected hand (A). Grip and pinch force values of the unaffected hand (U) were also merged to one composite motor function score.

Figure 1 Stroke lesions. All masks of stroke lesions were brought to the right hemisphere (affected hemisphere, AH) and overlaid on T1 template in MNI standard space. Axial slices were chosen with given z-values. The colour bar indicates the number of subjects in which voxels lay within a stroke lesion. UH = unaffected hemisphere.
based on grip and pinch force variability. A group of 20 healthy age- (67 ± 2.4 years) and gender-matched (10 male) participants was also recruited. Participants gave written informed consent according to the Declaration of Helsinki. The study was approved by the local ethics committee.

Brain imaging

A 3 T Siemens Skyra MRI scanner was used to acquire both diffusion-weighted and high-resolution T1-weighted anatomical images. For diffusion-weighted imaging, 75 axial slices were obtained covering the whole brain with gradients (b = 1500 mm²/s) applied along 64 non-collinear directions with the sequence parameters: repetition time = 10 000 ms, echo time = 82 ms, field of view = 256 × 204, slice thickness = 2 mm, in-plane resolution = 2 × 2 mm. The complete data set consisted of 2 × 64 × 1500 images and additionally one b0 image at the beginning and one after the first 64 images. For anatomical imaging, a 3D magnetization-prepared, rapid acquisition gradient-echo sequence (MPRAGE) was used with the following parameters: repetition time = 2500 ms, echo time = 2.12 ms, field of view = 240 × 192 mm, 256 axial slices, slice thickness = 0.94 mm, in-plane resolution = 0.94 × 0.94 mm

Preprocessing

The analysis of the diffusion-weighted and anatomical images was conducted using the FSL software package 5.1 (http://www.fmrib.ox.ac.uk/fsl). After correcting for eddy currents and head motion and brain extraction, fractional anisotropy maps were calculated fitting the diffusion tensor model at each voxel. Individual fractional anisotropy maps were then registered non-linearly to the Montreal Neurological Institute (MNI) standard space. The non-linear transformation was also performed with the anatomical images after non-linear co-registration to the individual fractional anisotropy map.

Creation of cortical seed masks

To calculate cortical seed and target masks for the tractography, the T1 structural image was used for brain segmentation into white and grey matter. The Freesurfer image analysis suite (http://surfer.nmr.mgh.harvard.edu/) was used for subsequent automatic cortical parcellation. Surface-based cortical grey matter masks were then transferred to FSL, refined in an automated fashion and used to calculate individual masks related to the boundary between white and grey matter including the whole extent of M1, ventral premotor cortex and the intraparietal sulcus. To bias the tract reconstruction towards the hand representation within each motor area of interest, functional imaging and electrophysiological data were incorporated into the mask creation as recently introduced for the reconstruction of corticospinal (Schulz et al., 2012) and corticocortical connections in young and older participants (Schulz et al., 2014): 500 voxels adjacent to peak coordinates of interest (Supplementary Table 1) within each region were automatically selected using an in-house Matlab script (Matlab R2010b, Mathworks) (Supplementary material) providing small motor masks within each anatomical region related to hand function and standardized in size and relation to the cortical grey matter/white matter boundary.

Probabilistic tractography of corticocortical and corticospinal trajectories

Probabilistic tractography was used to reconstruct the connections between (i) M1 and ventral premotor cortex; (ii) M1 and anterior and caudal IPS; (iii) ventral premotor cortex and these two parietal brain regions; and also (iv) between anterior and caudal IPS. Therefore, 100 000 streamlines were sent bidirectionally from both the seed and target regions applying exclusion masks to guide this first tractography. The thresholded and refined combination of both resulting output distributions (Hughes et al., 2012) was then used to estimate a tract-specific exclusion mask in which the second tractography was conducted to avoid erroneous trajectories. This procedure was found to allow a reliable reconstruction of the trajectories with—compared to others—even very small structural connectivity probabilities. The probabilistic tractography distribution was finally analysed applying a spectrum of different thresholds from 1% to 20% to estimate the tract-related fractional anisotropy—a measure of white matter integrity for both the affected and unaffected hemisphere. Details on the tractography and the fractional anisotropy calculation can be found in the online Supplementary material. In agreement with previous studies, proportional fractional anisotropy values (ratio affected/unaffected hemisphere) were calculated to assess fractional anisotropy asymmetry and used for the correlative analyses (Schulz et al., 2012). To assess white matter disintegrity in the stroke patients in comparison to healthy controls, 20 healthy age- and gender matched controls were also recruited and underwent brain imaging. To account for the distribution of dominant and non-dominant hemispheres affected, the right and left hemispheres of the control subjects were randomly assigned to the ‘affected’ (right) and ‘unaffected’ (left) hemisphere, respectively. As the corticospinal tract from M1 critically involves residual motor function after stroke (Schulz et al., 2012), we aimed at addressing structure-function relationships for the corticocortical connections between parietal brain region and M1 and premotor cortex while accounting for the integrity of the corticospinal tract. The corticospinal tract reconstruction was conducted in the controls as recently suggested (Schulz et al., 2012), seeding from the hand representation in M1 downwards via the posterior limb of the internal capsule, the pontomedullar junction and the ventral medulla oblongata. After thresholding each output distribution and binarization, the common group average of the corticospinal tract was defined by those voxels that were found in at least 65% of the number of subjects contributing to the tract (Schulz et al., 2012). For the stroke patients, the binarized corticospinal tracts were used to estimate individual fractional anisotropy values at the level from the mesencephalon to the cerebral peduncle (MNI coordinates z = −25 to z = −20). Finally, tract-related fractional anisotropy values were reported as proportional values (ratio affected/unaffected hemisphere). Details on the corticospinal tract reconstruction can be found in the Supplementary material.

Statistics

For within- and between-group comparison of behavioural outcome measures, tract topography and proportional fractional anisotropy values we used Student’s t-tests. False discovery
rate (FDR) correction was applied to correct for multiple comparisons. The relationship between the asymmetry of the tract-related fractional anisotropy values and motor function was inferred using generalized linear modelling. Including the proportional fractional anisotropy value of each tract of interest individually, we estimated six models. Corticospinal tract integrity (proportional fractional anisotropy) and motor function of the unaffected hand were included as covariates. Moreover, own observations and previous reports (Harris and Eng, 2006) have suggested that patients with lesions to the dominant hemisphere demonstrate better motor function than those with the non-dominant hand affected. Thus, this information was also included as a categorical factor. Model assumptions were met after \( z \)-transformation of the dependent and continuous independent variables. Statistical significance was assumed at \( P \)-values \( \leq 0.05 \). All results are given as mean ± standard error of the mean (SEM). Statistical analysis was conducted using SPSS 21 software (IBM Corp.).

Results

Probabilistic tractography of intrahemispheric parietofrontal motor pathways

Probable trajectories connecting M1 with premotor cortex, M1 with anterior and caudal IPS as well as tracts connecting premotor cortex with anterior IPS and caudal IPS were successfully obtained in stroke patients and healthy controls (Fig. 2). More specifically, the fibre tracts between M1 and both premotor cortex and anterior IPS as well as between premotor cortex and anterior IPS were continuously reproducible in all stroke patients. By contrast, connections targeting caudal IPS were much more difficult to reconstruct: for caudal IPS–premotor cortex, three stroke patients had to be excluded from further analysis, for caudal IPS-M1 11 patients, for caudal IPS-anterior IPS two patients due to invalid tract reconstructions. Figure 2 provides an overview of the 3D spatial courses of the different tracts of interest. It shows that for M1 and premotor cortex, there is significant convergence of fibres towards the hand knob area in M1 and the anterior bank of the caudal precentral gyrus for ventral premotor cortex. Contrarily, the spatial variability is increased in deeper white matter with a more distributed course along the fibre tracts. For M1–premotor cortex, the present results are in good agreement with previous diffusion tensor imaging data on corticocortical connectivity in young and older participants (Schulz et al., 2014). In contrast to M1 or premotor cortex, the 3D spatial variability of the trajectories targeting the parietal cortex was higher. This is in line with the considerable inter-subject variability in local (i.e. gyral) brain anatomy of the parietal cortex. The trajectory variability map clearly shows that the fibres towards...
caudal IPS target an area on the medial wall of the caudal intraparietal sulcus whereas the seed/target region for anterior IPS was located—as hypothesized and calculated—on the anterior lateral aspect of the intraparietal sulcus.

In addition to the 3D spatial overlap of binarized, individual trajectories, a centre of gravity analysis allowed a more detailed assessment of topographic aspects of the long-range parietofrontal motor pathways contributing to the SLF.

As illustrated in Fig. 3, the four tracts connecting the parietal brain regions with M1 and premotor cortex exhibited spatially distinct courses within SLF II and III. At the mid-level of the parietofrontal connections (\(y = -34\), MNI, Fig. 3), the tracts connecting anterior IPS and premotor cortex were located in a lateral and caudal location, likely within SLF III whereas fibres targeting M1 were located in a more medial and cranial position. Connections from caudal IPS to M1 and caudal IPS to premotor cortex seem to continue this distinct lateromedial and caudocranial topography and belong to SFL II (Fig. 3). Corroborating the 3D results from the trajectory variability maps in Fig. 2, the centre of gravity analysis also showed significant convergence with decreasing distance to the seed/target regions. Tractography was also conducted in healthy participants to compare the distributions between stroke patients and healthy controls. On visual inspection, there were similar parietofrontal connections in both groups (Supplementary Fig. 2). More specifically, stroke patients and controls showed comparable tract-related centres of gravity at the mid-level of the parietofrontal connections (Table 2 and Supplementary Fig. 3 for trajectories of the healthy controls). To correct the influence of the microstructural parameters of the parietofrontal connections to the integrity of the corticospinal tract, we also performed a probabilistic tractography of the corticofugal fibres from M1. These results are presented in the Supplementary Fig. 1.

**Tract-related white matter integrity and motor function after stroke**

Table 3 summarizes the tract-related absolute fractional anisotropy values for the affected and unaffected hemispheres of the stroke patients and the data for the healthy controls. Individual Student’s \(t\)-tests did not reveal significant differences between the groups (Supplementary Fig. 4A). This was also shown by an additional repeated-measures ANOVA including the subset of 12 stroke patients and 19 controls in which all tracts were successfully reconstructed (Supplementary material). The proportional fractional anisotropy values were also comparable between stroke patients and controls (Supplementary Fig. 4B).

For each tract of interest, one generalized linear model was estimated to infer the association between white matter integrity and motor function whose predictors are summarized by forest plots in Fig. 4 (see Supplementary Table 2 for statistical details). We found significant positive contributions of the microstructural integrity of the fibre tracts connecting ventral premotor cortex with M1 (\(B = 0.352; P < 0.001\)) and also anterior IPS with premotor cortex (\(B = 0.298; P < 0.01\)) as well caudal IPS and premotor cortex (\(B = 0.287; P = 0.07\)), M1 (\(B = -0.068; P = 0.82\)) and anterior IPS (\(B = 0.003; P = 0.99\)) did not show significant associations with the preserved motor function after stroke (Fig. 4). Notably, across all parietofrontal connections both the integrity of the corticospinal tracts and the motor function of the unaffected hand were relevant predictors of residual motor function of the affected hand after stroke.

**Discussion**

**White-matter integrity of parietofrontal motor pathways and motor function after stroke**

As a main finding of the present study, tract-related proportional fractional anisotropy as a marker for microstructural white matter integrity showed a significant association with basic residual motor function of the affected hand for M1–ventral premotor cortex and anterior IPS–ventral premotor cortex connections. Thus, the present analysis provides first probabilistic structural connectivity data in chronic stroke patients which indicate that, aside from interactions with M1, i.e. between ventral premotor cortex and M1, also interactions between secondary parietal and frontal motor areas (anterior IPS and ventral premotor cortex) influence residual motor function after stroke. These data extend prior knowledge about motor-related parietofrontal interactions, both in stroke patients and healthy participants.

So far, some studies have contributed to the understanding of M1, ventral premotor cortex and the posterior parietal cortex as important areas for motor recovery and residual motor function after stroke. For instance, animal studies showed that ventral premotor cortex was able to increase its connections to the somatosensory cortex (Dancause et al., 2005) or enlarge its hand representation after a lesion to M1 (Frost et al., 2003). In chronic stroke patients, a meta-analysis has recently evidenced an increase in task-related premotor cortex activation both on the ipsilesional and contralesional hemisphere compared to controls (Rehme et al., 2012). Early after stroke, a positive coupling onto the ipsilesional M1 was found to be significantly reduced in the stroke patients, which could be related to the residual motor function (Rehme et al., 2011). Providing structural connectivity data for M1–premotor cortex, the present study strengthens these functional data by showing that the integrity of the underlying
white matter tracts connecting M1 with ventral premotor cortex also influences the residual motor function. In terms of the functional role of parietal brain regions for recovery and motor function after stroke, the available data are still limited. We found that the integrity of the anterior IPS–premotor cortex connection appears to be relevant for hand motor function after stroke. This importance of anterior IPS was similarly suggested by a meta-analysis on functional imaging data in chronic stroke patients, which found a consistent task-related activation of anterior IPS during various movements of the affected limb (Rehme et al., 2012). Also structural analyses on cortical strokes have demonstrated that deficits in parietal sensorimotor integration areas significantly impact on residual motor function and recovery after stroke: for instance, one longitudinal study has found that parietal cortex lesions impaired the overall outcome while lesions to M1 influenced rather the dynamics of motor recovery after stroke (Abela et al., 2012). Another study reported that grey matter atrophy in a cluster on the angularis gyrus was associated with less favourable recovery after cortical sensorimotor stroke (Abela et al., 2014). Providing structural data, the present results corroborate previous functional connectivity data: for instance it was shown that increased functional connectivity between ipsilesional M1 and ipsilesional inferior parietal lobe was

**Figure 3  Centre of gravity analysis of parietofrontal connections in chronic stroke patients.** Tract-related centres of gravity were calculated for each subject and each tract and threshold from $y = -90$ to $y = 10$ in steps of 2 mm. For the final coordinate, centres of gravity were averaged across the thresholds. Notably, only those $y$-values were presented in which more than two thresholds contributed to the final coordinate. The centre of gravity distribution is shown on sagittal slices individually for the affected (AH) and unaffected (UH) hemisphere, on one horizontal slice and one coronal slice at $y = -34$ in MNI standard space. Table 2 provides statistics on the centre of gravity analysis at the coronal level. Please note that the caudal course from M1 from $y = -20$ towards higher $y$-values is caused by individual variability of fibres trajectories.

$aIPS = \text{anterior IPS}; cIPS = \text{caudal IPS}; PMv = \text{premotor cortex}.$
associated with improved motor recovery whereas a decreased parietofrontal connectivity was related to bad outcome (Yin et al., 2012). Similar findings were also obtained for functional connectivity between the superior parietal cortex and M1 suggesting that motor control deficits following stroke might be partly caused by a disconnection between parietal higher-order motor guidance systems and the primary motor network (Inman et al., 2012). Another study (Park et al., 2011) has addressed recovery-related changes of altered parietofrontal functional connectivity. The authors found a reduced connectivity between contralateral posterior parietal cortex and M1 shortly after stroke. In the early subacute stage 1 and 6 months after the ischaemic event the connectivity between M1 and ipsilateral posterior parietal brain regions was increased while the reduction of connectivity with the contralateral posterior parietal cortex was persistent. However, an association with behaviour was not detected. Adding structural connectivity data for the connection between anterior IPS and premotor cortex, the present study strengthens the view that posterior parietal areas might contribute to motor function after stroke via corticocortical interactions with frontal brain regions such as premotor cortex.

Previous studies in healthy participants have commonly related M1, ventral premotor cortex and anterior IPS-related brain activity and their interactions to rather skilled hand functions, such as visually guided precision grip (Ehrsson et al., 2001), power grip (Ehrsson et al., 2000) and reaching and grasping (Ehrsson et al., 2001; Witt et al., 2008; Davare et al., 2010, 2011). Specifically, ventral premotor cortex activity concerns the integration of information processed by parietal secondary motor areas such as anterior IPS into more M1-related executive information processing. In this context, anterior IPS was found to contribute also to object manipulation and exploration (Binkofski et al., 1999) by continuously converting spatial specification of target location into motor plans (Olivier et al., 2007; Davare et al., 2010, 2011). Thereby, anterior IPS provides premotor cortex with visual information about object properties and influences grasp-related and muscle-specific premotor cortex-M1 interactions (Tunik et al., 2005; Olivier et al., 2007; Koch et al., 2008; Davare et al., 2009, 2010; Reichenbach et al., 2011; Karabanov et al., 2013). The present data suggest that, different from healthy participants, in chronic stroke patients, this structure-behaviour relationship is not only observed in such complex grasp- or reach-related functions but already in basic hand and arm motor functions.

The question arises why we did not find similar associations between tract-related white matter integrity and motor function for the other four pathways of interest. For the direct connections between caudal IPS and M1 the tract reconstruction was difficult, though not caused by a specific co-localization of the tract courses and the stroke lesions (Supplementary material and Supplementary Table 3). Koch et al. (2010) found only sparse connections

Table 2 | Tract-related centres of gravity at y = −34 (MNI) in stroke patients and healthy controls

<table>
<thead>
<tr>
<th></th>
<th>Anterior IPS-premotor cortex</th>
<th>Caudal IPS-premotor cortex</th>
<th>Anterior IPS-M1</th>
<th>Caudal IPS-M1</th>
</tr>
</thead>
<tbody>
<tr>
<td>x Stroke</td>
<td>38.4 ± 0.35</td>
<td>38.5 ± 0.73</td>
<td>27.5 ± 1.06</td>
<td>25.7 ± 0.83</td>
</tr>
<tr>
<td>Control</td>
<td>37.5 ± 0.74</td>
<td>37.4 ± 0.87</td>
<td>35.5 ± 1.01</td>
<td>25.1 ± 0.9</td>
</tr>
<tr>
<td>P-value</td>
<td>0.65</td>
<td>0.65</td>
<td>0.65</td>
<td>0.65</td>
</tr>
<tr>
<td>z Stroke</td>
<td>35.4 ± 0.31</td>
<td>35.9 ± 0.45</td>
<td>41.4 ± 0.65</td>
<td>43.5 ± 0.8</td>
</tr>
<tr>
<td>Control</td>
<td>35.6 ± 0.25</td>
<td>35.8 ± 0.6</td>
<td>43.0 ± 1.26</td>
<td>44.3 ± 0.8</td>
</tr>
<tr>
<td>P-value</td>
<td>0.86</td>
<td>0.98</td>
<td>0.65</td>
<td>0.65</td>
</tr>
</tbody>
</table>

Centres of gravity of parietofrontal connections targeting M1 and premotor cortex at the mid-level of the connections (y = −34) for stroke patients and controls. x and z values are presented individually for the affected (AH) and unaffected (UH) hemisphere. Results are given as mean ± SEM. Individual Student’s t-tests were used to compare tract-related coordinates between stroke patients and controls. P-values were fully FDR-corrected for multiple comparisons.

Table 3 | Tract-related white matter integrity in stroke patients and healthy controls

<table>
<thead>
<tr>
<th></th>
<th>Premotor cortex-M1</th>
<th>Anterior IPS-premotor cortex</th>
<th>Caudal IPS-premotor cortex</th>
<th>Anterior IPS-M1</th>
<th>Caudal IPS-M1</th>
<th>Caudal IPS-anterior IPS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AH</td>
<td>UH</td>
<td>AH</td>
<td>UH</td>
<td>AH</td>
<td>AH</td>
</tr>
<tr>
<td>Fractional anisotropy Stroke</td>
<td>0.35 ± 0.001</td>
<td>0.38 ± 0.005</td>
<td>0.35 ± 0.001</td>
<td>0.38 ± 0.006</td>
<td>0.38 ± 0.001</td>
<td>0.39 ± 0.009</td>
</tr>
<tr>
<td>Control</td>
<td>0.37 ± 0.007</td>
<td>0.38 ± 0.009</td>
<td>0.38 ± 0.007</td>
<td>0.38 ± 0.001</td>
<td>0.39 ± 0.007</td>
<td>0.4 ± 0.007</td>
</tr>
<tr>
<td>P-value</td>
<td>0.29</td>
<td>0.96</td>
<td>0.29 ± 0.06</td>
<td>0.96</td>
<td>0.29 ± 0.01</td>
<td>0.47 ± 0.08</td>
</tr>
</tbody>
</table>

We estimated fractional anisotropy in individual white matter tracts of these six connections in the affected (AH) and unaffected (UH) hemisphere of stroke patients and healthy control subjects. Results are given as mean ± SEM. Comparing stroke patients with healthy controls we performed individual Student’s t-tests. The P-values were fully FDR corrected for multiple testing.
between the angularis gyrus and M1 in healthy participants. Given the positive findings for functional connectivity between parietal brain regions and M1 (Koch et al., 2007, 2008; Karabanov et al., 2013; Chao et al., 2015) this might indicate that the connectivity from the parietal areas of interest with M1 is probably mediated indirectly via premotor cortex rather than directly. This was suggested by a recent study which combined transcranial magnetic stimulation and diffusion-tensor imaging in healthy participants (Koch et al., 2010) and might explain why anterior IPS–M1 and caudal IPS–M1 did not show significant relationships with motor function. For caudal IPS-related connections, the absent association with motor function could also be explained by its predominant role in integrating visual information in grasping and reaching movements and tool use (Faillenot et al., 1997; Shikata et al., 2001; Culham et al., 2003; Tsutsui et al., 2003; Filimon et al., 2007; Koch et al., 2010; Mruczek et al., 2013). Therefore the present structural data suggest that caudal portions of the intraparietal sulcus do not relate to rather basic hand and arm function after stroke. In this context future studies are needed to further assess possible associations between parietofrontal connections and more complex movements in stroke patients such as reaching and grasping in space.

Generalized linear models were used to infer tract-related structure-behaviour relationships of corticocortical parietofrontal connection in chronic stroke patients while adjusting the associations for the integrity of the corticospinal tract. In agreement with previous work, this measure was found to critically contribute to motor function after stroke (Schulz et al., 2012). Aside from the corticospinal integrity, we found that the integrity between M1 and premotor cortex as well as anterior IPS and premotor cortex explained additional variance in motor function. The positive influence of the third covariate, whether the dominant or non-dominant hand was affected by the stroke, was also in agreement with one previous report (Harris and Eng, 2006), likely caused by more intensive training and use of the dominant hand.

**Topography of intrahemispheric parietofrontal motor pathways**

Probable intrahemispheric trajectories connecting hand representations of anterior IPS, caudal IPS, ventral premotor cortex and M1 were successfully reconstructed in chronic stroke patients. Similar results with comparable individual trajectories were also obtained in a group of age- and
gender-matched healthy controls suggesting valid tract reconstruction in patients, even with cortical stroke locations. A centre of gravity analysis revealed detailed insights into a distinct topography of intrahemispheric long-range fibres connecting anterior and caudal IPS with both premotor cortex and M1. We found a lateromedial and caudocranial distribution of the fibres in the order anterior IPS–premotor cortex, anterior IPS–M1, caudal IPS–M1 and caudal IPS–premotor cortex localizing with distinct components of the SLF. Thereby, anterior IPS–premotor cortex and anterior IPS–M1 were most likely localized in the SLF III component at the laterocaudal extent of the distribution. This localization is in good agreement with previous imaging data in healthy humans (Croxson et al., 2005; Makris et al., 2005; Koch et al., 2010) and anatomical animal work suggesting that SLF III predominantly originates from the supramarginal gyrus and connects prominently to ventral premotor cortex and prefrontal brain regions (Petrides and Pandya, 1984; Schmahmann et al., 2007). In addition we also found a connection to M1. By contrast, a recent probabilistic tractography analysis between the supramarginal gyrus and both premotor cortex and M1 showed only very sparse connections targeting M1 (Koch et al., 2010). Moreover, in animals, connections to M1 were observed even only for the superior parietal lobe (Johnson et al., 1996). Tract reconstructions for caudal IPS-related connections were found to localize in SLF II (Croxson et al., 2005; Makris et al., 2005), the major component of the SLF. SLF II originates predominantly from areas around the angularis gyrus and targets not only dorsolateral frontal brain regions (Petrides and Pandya, 1984; Luppino et al., 1999; Makris et al., 2005; Rozzi et al., 2006; Schmahmann et al., 2007) but also ventral premotor cortex (Croxson et al., 2005). However, compared to anterior IPS, the tract reconstruction between caudal IPS and M1 was less reliable, as previously reported (Koch et al., 2010).

In summary, the present analysis adds further structural probabilistic data on parietofrontal connectivity in the human brain, both in healthy participants and stroke patients. Previous imaging studies on parietofrontal connectivity and SLF topography have either used visual image inspection on relative location and orientation of diffusion properties of the tissue for each SLF component (Makris et al., 2005) or probabilistic tractography from large seed and target masks (Koch et al., 2010). Here we performed individual probabilistic tractography from and to rather circumscribed hand representations. This approach of using functional imaging or electrophysiology-based hand representations within functional brain regions for probabilistic tractography has been recently introduced for probabilistic tractography of corticospinal (Schulz et al., 2012) and corticocortical connections (Schulz et al., 2014). As similar trajectories and measures of integrity were obtained in 25 stroke patients and 20 healthy controls, we conclude that the actual trajectories are of reasonable quality to be used for correlative analysis.

**Limitations of the study**

Some limitations of the present study have to be mentioned. First, we found significant associations between a composite motor function score and proportional fractional anisotropy values within the tracts of interest. The question arises whether this relationship is stroke-specific or a general age-related phenomenon also found in healthy controls. Unfortunately, in the present control sample we did not have behavioural data. Hence we were not able to answer this question. However, a recent analysis of multiple corticocortical connections including M1–premotor cortex in healthy aged participants did not find a significant association between tract-related white matter integrity and motor performance (Schulz et al., 2014). These data favour the view that the present findings might be rather stroke-specific than a general phenomenon. Future studies will have to include correlative analyses in controls to investigate the stroke specificity of the present structural findings. Second, we used probabilistic tractography to reconstruct individual fibre tracts between M1, ventral premotor cortex, anterior IPS and caudal IPS. Seed and target masks were individually tailored according to the subject’s brain anatomy. Exclusion and waypoint masks were used to guide the individual tract reconstruction. Still, the courses of the tracts remain probabilistic and might differ in the individual brain. Third, previous functional imaging and electrophysiological data published were used to bias the tract-reconstruction to probable hand representations. To what extent cortical reorganization after stroke might change gross cortical representations and therefore influence the courses of the corticocortical connections remains unclear. The combination of functional and diffusion tensor imaging in the individual participant might help to improve the estimation of task-related seed and target regions and the reconstruction of the tracts. Fourth, the aim of the present work was to investigate the association between white matter integrity of corticocortical parietofrontal pathways and residual motor function after stroke, adjusting to the integrity of the corticospinal tract. It has to be stated that, despite the amount of variance explained, the corticocortical network analysed here was limited to areas of interest, M1, ventral premotor cortex, anterior IPS and caudal IPS, and thus not complete. More complex modelling on larger sample sizes is needed to assess the involvement of parietofrontal structural connectivity in the context of the structural properties of extended neuronal subcortico-cortico-cortical circuits, including also prefrontal, subcortical and cerebellar structures.

**Conclusion**

In conclusion, the present results provide structural connectivity data in chronic stroke patients which indicate that the integrity of the connection (i) between ventral premotor cortex and M1; and (ii) between anterior IPS and
ventral premotor cortex contribute to motor function after stroke. This supports the view that not only frontal secondary motor areas but also parietal brain regions along the IPS might play a relevant role in generating basic residual motor output after stroke.

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Supplementary material

Supplementary material is available at Brain online.

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Harris JE, Eng JJ. Individuals with the dominant hand affected following stroke demonstrate less impairment than those with the nondominant hand affected. Neurorehabil Neural Repair 2006; 20: 380–9.


