Influence of motor deficiency and spatial neglect on the contralesional posterior parietal cortex functional and structural connectivity in stroke patients

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Abstract

The posterior parietal cortex (PPC) is a key structure for visual attention and upper limb function, two features that could be impaired after stroke, and could be implied in their recovery. If it is well established that stroke is responsible for intra- and interhemispheric connectivity troubles, little is known about those existing for the contralesional PPC. In this study, we aimed at mapping the functional (using resting state fMRI) and structural (using diffusion tensor imagery) networks from 3 subparts of the PPC of the contralesional hemisphere (the anterior intraparietal sulcus (aIPS), the posterior intraparietal sulcus (pIPS) and the superior parieto-occipital cortex (SPOC) to bilateral frontal areas and ipsilesional homologous PPC parts in 11 chronic stroke patients compared to 13 healthy controls. We also aimed at assessing the relationship between connectivity and the severity of visuospatial and motor deficiencies. We showed that interhemispheric functional and structural connectivity between PPCs was altered in stroke patients compared to controls, without any specificity among seeds. Alterations of parieto-frontal intra- and interhemispheric connectivity were less observed. Neglect severity was associated with several alterations in intra- and interhemispheric connectivity, whereas we did not find any behavioral/connectivity correlations for motor deficiency. The results of this exploratory study shed a new light on the influence of the contralesional PPC in post-stroke patients, they have to be confirmed and refined in further larger studies.

Keywords: stroke, connectivity, resting state, DTI, posterior parietal cortex, fronto-parietal networks

Introduction

Stroke is a leading cause of acquired disability in the world. Among all stroke-induced deficiencies, upper limb paresis is one of the most frequent, represents a key factor for autonomy (Veerbeek et al. 2011) and its rehabilitation remains a challenge. Spatial neglect, defined as a failure to acknowledge or explore stimuli towards the contralesional side (Heilman et al. 1983), is another disabling consequence of stroke because it largely impedes stroke recovery and patients' autonomy (Di Monaco et al. 2011). The posterior parietal cortex (PPC), a region composed of areas located along the intraparietal sulcus (IPS) and of the superior parieto-occipital cortex (SPOC), is a key structure for sensori-motor integration, upper limb movement planning and control of spatial attention (Corbetta and Shulman 2002; Buneo and Andersen 2006; Davare et al. 2011; Vesia and Crawford 2012). Beyond specific brain areas, brain connectivity studies have shown that the effect of a brain lesion must be studied at the level of networks it impacts. Indeed, multiple recent connectivity studies have identified altered connectivity patterns that correlate with behavior and cognition using either functional (Bournonville et al. 2018), structural (Griffis et al. 2019; Wiesen et al. 2019), or effective connectivity (Allart et al. 2017) methods.

The PPC is part of the dorsal attention network (DAN), which is involved in the voluntary orientation of attention and the generation of attentional sets (top-down attention) (Corbetta and Shulman 2002). In neglect patients, the lesion is most often responsible for an intrahemispheric disconnection with the right DAN, leading to an interhemispheric trouble in the balance between activity of both DANs (Corbetta and Shulman 2002; He et al. 2007; Baldassarre et al. 2014; Ramsey et al. 2016). This induces an hyperexcitability of left parieto-frontal networks that can be directly assessed by transcranial magnetic stimulation (TMS) (Allart et al. 2017; Koch et al. 2008a). This hyperexcitability is a target of non-invasive brain stimulation protocols proposed in neglect patients, most often consisting in inhibitory protocols over the contralesional posterior part of the intraparietal sulcus (pIPS), with encouraging first results (for a review, see (Jacquin-Courtois 2015)). However, little is known about the specificity of the involvement of each contralesional PPC subpart in the connectivity troubles observed in neglect patients and their relationships with the severity of the disability. In a previous work, we studied the contralesional PPC-M1 connectivity in stroke patients from the 3 subparts of the PPC using a paired-pulse TMS (ppTMS) protocol (Allart et al. 2017). We showed, as already demonstrated for pIPS (Koch et al. 2008a), that SPOC-M1 connectivity was modified in neglect patients, whereas aIPS-M1 connectivity was not modified. However, we only assessed intrahemispheric connectivity (and not interhemispheric features), ppTMS protocols only address some particular features of brain effective connectivity (assessing an indirect response via M1) (Rothwell 2011), and to the best of our knowledge no study investigated specifically modifications of structural connectivity of the contralesional PPC networks.

In addition to its role in spatial attention, the PPC plays a role in the planning and control of visually-guided movements of the upper limb. This role is well demonstrated in healthy humans by connectivity studies using transcranial magnetic stimulation (Busan et al. 2009; A. Karabanov et al. 2012; G Koch et al. 2008; Koch et al. 2007, 2010; Vesia et al. 2013) or functional imaging (Filimon et al. 2009; Cavina-Pratesi et al. 2010; Reichenbach et al. 2011; Konen et al. 2013; Monaco et al. 2015). These works particularly showed that most caudal structures of the PPC (pIPS, SPOC), as well as the dorsal premotor cortex (dPMC) to which they are connected, are mostly involved in the reaching phase of movement. On the other hand, the anterior part of the

intra-parietal sulcus (aIPS), connected to the ventral premotor cortex (vPMC), are involved in the grasping phase. In addition, there are some evidence indicating that the PPC exerts a direct influence on M1 and upper limb movements, since an excitatory modulation of the PPC by NIBS techniques is able to enhance M1 excitability (Rivera-Urbina et al. 2015), PPC-M1 connectivity (Chao et al. 2015) and to modify movement timing in healthy subjects (Krause et al. 2012). In post-stroke patients, if the integrity of the pyramidal tract and interhemispheric imbalance between primary motor cortices (M1) are the main features associated with motor deficiency and recovery (Calautti et al. 2007; Bembenek et al. 2012; Stinear et al. 2012; Thiel and Vahdat 2015; Koch et al. 2016), interactions between lesioned M1 and bilateral non-primary motor areas seem to play a role. Firstly, it is well known that movement production with the paretic upper limb is associated with activations of ipsilesional M1, but also of the PMC and the PPC (Buma et al. 2010). In addition, the influence of the PMC and the supplementary motor area (SMA) of both hemisphere on lesioned M1 has been more widely studied (James et al. 2009; Sharma et al. 2009; Park et al. 2011; Rehme and Grefkes 2013; Wang et al. 2014; Zheng et al. 2016; Zhang et al. 2016) and recently led to the first applications of non-invasive brain stimulation (NIBS) protocols targeting PMC (and not directly M1) for motor recovery (Cunningham et al. 2015; Plow et al. 2015; Andrade et al. 2017). Data concerning connectivity of the PPC with M1 are scarcer but of interest. First, recent imaging studies of functional and structural connectivity showed that ipsi- and contralateral connectivity of both PPC to lesioned M1 was altered in the subacute phase post-stroke (Wang et al. 2010; Park et al. 2011; Inman et al. 2012; Schulz et al. 2015, 2016; Zhang et al. 2016), and suggested that ipsilesional parieto-frontal networks could play a role in motor deficiency and recovery after stroke (Inman et al. 2012; Schulz et al. 2015, 2016). This has been confirmed in a recent connectivity study using EEG (Bönstrup et al. 2018). Taken together, these data may underline a potential positive impact of a modulation of the PPC on recovery of the upper-limb disability. Moreover, as applying NIBS over the unaffected hemisphere is easier and more and more widely used, they point the contralesional PPC as a potential adjuvant target in addition to M1 in such protocols. However, as for spatial neglect, little is known about the specificity of the involvement of each contralesional PPC subpart, the modifications of contralesional PPC connectivity and their relationships with the severity of motor deficiency.

In order to answer the points raised for both neglect and upper-limb function, we therefore aimed at mapping the functional and structural networks associated with each of the 3 PPC areas (aIPS, pIPS and SPOC) of the contralesional hemisphere in chronic stroke patients compared to healthy controls using a resting state fMRI (rs-fMRI) and a diffusion tensor imaging (DTI) analyses. We also aimed at assessing the relationship between connectivity and the severity of visuospatial and motor deficiencies. We hypothesized that patients would show intra- and inter-hemispheric modifications in the contralesional PPC functional and structural connectivity, particularly evident for the two caudal parts of the PPC (pIPS and SPOC) regarding neglect status.

Methods

Participants

Patients were recruited among in- and outpatients in the Neurorehabilitation Unit at Lille University Medical Center (Lille, France) between August 2014 and March 2016. A majority of them had already participated in a previous study evaluating PPC-M1 connectivity in the left (contralesional for patients) hemisphere using a ppTMS protocol (Allart et al. 2017). All patients had suffered a single right ischemic or hemorrhagic

hemispheric stroke (diagnosed by MRI) for at least 6 months before inclusion and had displayed left hemiparesis; the presence of spatial neglect was not an inclusion criterion but was assessed in all included patients. We also included healthy age-matched controls. We excluded patients with bilateral lesions and subjects who were unable to consent to or understand the study protocol due to language, cognitive or psychiatric disorders, and those presenting contraindications to MRI. All participants were right-handed (according to the Edinburgh Handedness Inventory (Oldfield 1971)) and gave their informed written consent to participation. The study was approved by the local investigational review board (*Comité de protection des personnes Nord Ouest IV*, Lille, France; reference 2013-A01766-39), and was conducted in accordance with the tenets of the Declaration of Helsinki.

Clinical assessment of spatial neglect and motor deficiency

Patients were classified as suffering from spatial neglect (“N+”) or not (“N-”) with regard to their performance in the three following tests. Peripersonal visual neglect was assessed using the Bells test (Gauthier et al. 1989) and patients were considered as neglect if they omitted at least 6 bells (Gauthier et al. 1989; Rousseaux et al. 2001). Personal (body) neglect was assessed with the fluff test (cut-off score: ≤ 13) (Cocchini et al. 2001). Lastly, behavioral neglect was assessed via the examiner’s part of the Catherine Bergego Scale (cut-off score: > 10) (Azouvi et al. 2003). Motor impairment was evaluated via the upper extremity subsection of the Fugl-Meyer Assessment (FMA-UE), which assesses the motor function of the upper arm, wrist and hand, and overall coordination (Fugl-Meyer et al. 1975).

MRI data acquisition

All exams were performed on a 3T Philips Achieva Scanner (Philips Healthcare, Best, The Netherlands) using an 8-channel phased-array head coil and a whole-body coil transmission. The imaging protocol included an anatomical three-dimensional T1-weighted (3DT1), a rs-fMRI, and a diffusion tensor imaging (DTI) sequences:

- 3D T1 FFE sequence was acquired using the following parameters: voxel size= $1 \times 1 \times 1$ mm³; matrix= $256 \times 256 \times 176$; TR=7.2 ms; TE=3.3 ms and FA=9°.
- rs-fMRI was performed with a T2*-weighted EPI sequence lasting 10 min: voxel size= $3 \times 3 \times 3$ mm³; matrix= $64 \times 64 \times 40$; TR=2.4 s, TE=30 ms and FA=90°. Patients were required to remain quiet, stay awake and close their eyes.
- DTI was acquired using a single-shot EPI sequence with 32 directions of the diffusion gradient: voxel size= $2 \times 2 \times 2$ mm³; matrix= $128 \times 128 \times 66$; TR=12 s; TE=56 ms; b=1000 s/mm². To correct B0 field inhomogeneity-induced distortion, another non-diffusion weighted images (b=0 s/mm²) with opposite phase-encoding direction was also collected (Holland et al. 2010).

T1 processing

Structural T1 images were processed using the Freesurfer software (v.5.6 Massachusetts General Hospital, Boston, MA; <http://surfer.nmr.mgh.harvard.edu/>). This included the preprocessing steps of non-uniform signal correction, signal and spatial normalizations, skull stripping and brain tissues automatic parcellation (Dale et al. 1999). Then a non-linear registration was applied to match the preprocessed 3DT1 data to the MNI template, using Statistical Parametric Mapping software (SPM12 <http://www.fil.ion.ucl.ac.uk/spm/software/spm12>

Regions of interest and lesion masks

Three regions of interest (ROIs) corresponding to the 3 left PPC regions (aIPS, pIPS and SPOC) were manually segmented on 3DT1 images of all subjects by a single expert (EA), on the basis of coronal and transversal slices. The aIPS was defined as the region located over the intersection between the postcentral sulcus and intraparietal sulcus (Frey et al. 2005; Cavina-Pratesi et al. 2010). The pIPS was situated over the caudal part of the intraparietal sulcus (Karabanov et al. 2013; Koch et al. 2007). The SPOC was defined as the region along the medial surface of the parietal lobe, anterior to the parieto-occipital sulcus, posterior to the subparietal sulcus and medial to the intraparietal sulcus (Cavina-Pratesi et al. 2010; Vesia et al. 2013). Volume of each seed was comparable between subjects and controls and the quality of overlap between subjects was good (appendix 1). These ROIs were used as seeds in the rs-fMRI analysis (see below).

In stroke patients, lesion masks were similarly manually segmented by the same expert on 3DT1 images using the same methodology as for ROIs for information about lesion localization and volume.

rs-fMRI analysis

Preprocessing and registration with MNI template

Preprocessing of rs-fMRI data were performed using a combination of SPM and in-house software implemented in MATLAB Version: 8.3.0.532 (R2014a) (Mathworks Inc., Natick, MA, USA). Preprocessing of rs-fMRI data included the removal of the first three image volumes (to avoid T1 equilibration effects), rigid-body head motion correction, slice-timing correction using a mean frame as reference, and registration to 3DT1 images. Nuisance signals were removed using a two-step linear regression. The first regression removed linear/quadratic trends (to account for scanner drift) and six motion parameters (time frames with excessive motion were suppressed). The second regression removed five “nuisance signals” obtained by means of a principal component analysis of white matter and ventricle signals using the component-based noise correction (CompCor) approach (Behzadi et al. 2007). Residual data were filtered for high temporal frequencies (low-pass of the frequency filter 0.1 Hz). Then, preprocessed rs-fMRI data were spatially normalized to match the Montreal Neurological Institute (MNI) template. For that the transformation computed during 3DT1 preprocessing was applied to preprocessed rs-fMRI data and resampled by spline interpolation into a final voxel size of $2 \times 2 \times 2 \text{ mm}^3$. Finally, preprocessed rs-fMRI data were spatially smoothed using a 3D 6-mm full width at half maximum Gaussian kernel.

Seed-based connectivity analysis

All seed-based connectivity analyses were performed using the functional data sets that had been previously preprocessed and registered to the MNI standard space. CONN functional connectivity toolbox 16.a (<http://www.nitrc.org/projects/conn>) (Whitfield-Gabrieli and Nieto-Castanon 2012) was used for analysis, using ROI (aIPS, pIPS and SPOC) as seeds. Additional denoising steps were proceed: Band-pass filter were set to [0.01 0.1] Hz, detrending removes cubic trends, and despiking applies a squashing function to reduce the influence of potential outlier scans. Functional connectivity analyses use a General Linear Model for bivariate correlation measures of the association between the seed BOLD timeseries and each voxel BOLD timeseries. Thus, a functional connectivity map was obtained for each seed per subject. Voxel-wise group comparisons were

performed on these maps by a non-parametric approach based on 10000 permutations. Differences were considered significant at $p < 0.05$ corrected for multiple comparisons by family-wise error approach.

Network analysis

As we focused on the role of frontoparietal and inter-PPC connectivity, we only considered these last networks in the functional connectivity network analysis. To take into account for the small sample size, patients' and controls' resting-state connectivity was compared using another approach based on networks. Networks corresponded to regions functionally connected to seeds and were extracted from one-sample T-test control's maps. Regions per hemisphere were identified by selecting 100 voxels around the peak of each significant cluster ($p < 0.05$ False Discovery Rate corrected) respecting a minimal distance of 50 mm. Thus, 3 networks corresponded to each seed were obtained, and for each network mean functional connectivity for identified ROIs were extracted and compared between patients and control groups using a two-sided Mann-Whitney U test, with a significant level at $p < 0.05$ (FDR corrected).

DTI data analysis

Preprocessing and coregistration with 3DT1

DTI images were corrected for Eddy currents, geometrical and signal distortions (Glasser et al. 2013). Eddy current artifacts were corrected using the `eddy_correct` FSL function (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/>). Then, the distortion field, inherent to EPI images in the phase encoding direction and responsible for geometric and signal artefacts, was calculated using a pair of spin echo EPI scans with opposite phase encoding directions (Holland et al. 2010). The “`epiunwarp`” function in the Computational Morphometry Toolkit (CMTK 3.2.2 <http://www.nitrc.org/projects/cmtk/>) was used to estimate the distortion field and applied it to DTI images. 3DT1 image was coregistered to corresponding DTI space using the rigid registration provided by SPM12.

White matter fiber tractography

Preprocessed DTI data were analyzed using the MRtrix software (v0.2.9, <http://www.brain.org.au/software/mrtrix/>) (Tournier et al. 2012). For each subject, fractional anisotropy (FA) map was calculated and threshold ($FA > 0.7$) to determine the response function of highly anisotropic voxels, further used for constrained spherical deconvolution in order to provide sharp fiber orientation distribution (FOD) estimates (Tournier et al. 2007). Whole-brain fiber tracts were generated using a probabilistic tracking algorithm (Tournier et al. 2012). Tracking parameters were left to defaults (step size = 0.1 mm, minimum radius curvature = 1 mm, FOD cutoff = 0.1, minimum length = 10 mm), the maximum harmonic order set to 10 and the number of generated tracts set to 1,500,000. The tracking mask was defined by the union of the 1-mm dilated white matter mask and the subcortical labels (provided by FreeSurfer) resampled to the DWI space. The rigid transformation matrix, computed during preprocessing steps, was then applied to seeds (aIPS, pIPS & SPOC) initially defined in 3DT1 space. Clusters extracted from functional connectivity analysis of controls, originally in MNI standard space, were then moved to each subject's diffusion space using registration implemented with FSL software. To estimate integrity of white matter pathways connecting seeds (aIPS, pIPS and SPOC) and functional clusters previously extracted in the rs-fMRI network analysis, the FA was computed for each subject. It represents a common measurement used in DTI studies and ranges from 0 = isotropic movement of water

molecules (e.g., cerebrospinal fluid), to 1 = anisotropic movement of water molecules (e.g., fiber bundles). The FA was sampled along fibers and then averaged (mean FA). Difference between groups was evaluated with a two-sided Mann-Whitney U test with a significant level at $p < 0.05$ (FDR corrected). As for functional connectivity, only structural connectivity from each seed to ipsi- and contralesional frontal areas and ipsilesional PPC have been studied.

Statistical analysis

The normality of the distribution of demographic and behavioral data was checked with a Shapiro-Wilk test and Q-Q plots. Intergroup comparisons were performed using the Student's t test (or the Mann-Whitney U test, for non-normally distributed data) for quantitative variables and Fisher's exact test for qualitative variables. Correlations between connectivity indices and behavioral assessments were performed using a Spearman correlation test. The threshold for statistical significance was set to $p < 0.05$ and all tests were two-tailed. All statistical analyses were performed with either SPSS software (version 20.0, IBM Corp., Armonk, NY, USA) or MATLAB.

Results

Participants

We recruited 11 stroke patients ($N^+ = 5$; $N^- = 7$) and 13 healthy controls. However, DTI acquisition was not performed in 2 patients (due to discomfort in the MRI scanner, the DTI sequence being performed last) and DTI preprocessing was impossible in one other (due to lesion size), so results of the DTI analysis were available for only 8 patients (3 in the N^+ group and 5 in the N^- group) (Appendix 2). The characteristics of the study population are summarized in Table 1. There were no significant differences between patients and healthy controls in terms of the mean age ($p = 0.602$) and the gender ratio ($p = 0.649$).

Lesion distribution in stroke patients included in the fMRI and DTI analyses are shown in Fig. 1. The highest overlap was situated subcortically and lesions were highly variable in size. They involved mainly the middle cerebral artery territory. Median lesion volume and interquartile interval were 7.5 [15.3] cm^3 in the fMRI analysis, 6.8 [20] cm^3 in the DTI one.

Functional connectivity

Seed-based analysis

The results of the cluster analysis in stroke patients and healthy controls are shown in Fig. 2 and Table 2. We will only focus on the networks of interest. In healthy controls, the left aIPS was connected to the left inferior frontal region (in two separate clusters, the posterior one encompassing the vPMC) and to the aIPS homologous PPC region within the ipsilesional (right) hemisphere and to the right inferior frontal gyrus. In patients, the aIPS intrahemispheric connections were driven to frontal areas, located slightly more medially compared to controls (middle and superior frontal gyri), whereas links with the ipsilesional hemisphere were only found with the homologous aIPS.

In healthy controls, the left pIPS showed functional connections with the contralesional inferior and middle frontal gyri (borderline between ventral and dorsal premotor cortices) and interhemispheric connections with the homologous pIPS and the posterior part of the middle frontal gyrus. As we showed for the aIPS, the pIPS network was less broad in patients, particularly for the connectivity pattern towards parietal and frontal regions in the ipsilesional hemisphere, whereas the connectivity within the contralesional hemisphere was globally the same as in controls.

In healthy controls as in stroke patients, the SPOC was functionally connected to the posterior part of the middle frontal gyrus (dPMC) within the contralesional hemisphere and to its homologous region within the ipsilesional hemisphere.

Between-group comparisons did not reveal any significant difference in functional connectivity between healthy controls and patients for any of the 3 seed ROIs.

Network analysis

Figure 3 shows the significant differences between stroke patients and healthy controls in terms of functional connectivity from contralesional PPC to bilateral frontal areas and ipsilesional PPC using a network-based analysis (cf methods). For the aIPS network, stroke patients showed a significant decrease of connectivity with the left inferior frontal gyrus, the homologous aIPS and inferior frontal regions in the lesioned hemisphere. The connectivity of the pIPS network was decreased to the ipsilesional middle frontal gyrus. Finally, the SPOC network only showed interhemispheric alterations with the ipsilesional SPOC. Levels of functional connectivity were overall more variable in stroke patients than in healthy controls (whatever the hemisphere we considered).

Neglect demonstrated relationship with functional connectivity data (Fig. 4), conversely to motor deficiency. Peripersonal and behavioral neglect was more severe when alterations of intrahemispheric connectivity from aIPS and pIPS to ipsilateral frontal regions were present. Concerning interhemispheric connectivity, the severity of spatial neglect was only significantly correlated to the level of connectivity between the aIPS and ipsilesional middle frontal gyrus (in the Bells test). However, there was a trend indicating that the decrease of interparietal connectivity between pIPS, SPOC and their homologous areas within the ipsilateral hemisphere may be associated with the severity of spatial neglect ($p < 0.1$ in the 3 tests of neglect for the pIPS, $p = 0.089$ in the Fluff test for the SPOC).

Structural connectivity

For each seed, interhemispheric structural connectivity (mean FA) of the PPC was significantly decreased in patients with the homologous region in the ipsilesional PPC (Fig. 5). Moreover, the SPOC network was the only to show modifications of intrahemispheric connectivity with the dPMC (middle frontal gyrus).

We only found a relationship between mean FA data and spatial neglect and to a much lesser extent compared to what we found for functional connectivity. The number of total omissions in the Bells Test was all the more higher when the connectivity between SPOC areas was decrease ($r = -0.679$; $p = 0.044$). Thus, this result indicated that interhemispheric anatomical disconnection between SPOC areas was associated with the severity of peripersonal neglect.

Discussion

The present exploratory study is the first proposing a combined functional (rs-fMRI) and structural (DTI) approach to map intra- and interhemispheric connectivity of 3 distinct regions of the contralesional (left) PPC (aIPS, pIPS and SPOC) in chronic post-stroke patients. We also sought to study whether connectivity was associated with the severity of visuospatial and motor deficiencies. We showed that functional and structural connectivity of the PPC was altered in patients, these alterations were particularly obvious to homologous PPC structures in the ipsilateral hemisphere. Interestingly, we demonstrated several links between functional connectivity and the severity of spatial neglect, but not with motor deficiency. Structural connectivity data were less linked to clinical scores. The results of the present study, even if preliminary ones, may confirm the role of the imbalance of interhemispheric connectivity in spatial neglect, particularly between homologous caudal parts of the PPC. The relationship between contralesional PPC connectivity and upper limb function is less obvious and must be further evaluated in future studies that will have to take into account the difficulty to properly assess the multiple determinants of this function.

Functional connectivity in healthy controls

Functional networks identified in the healthy controls were in accordance with previous studies. Concerning intrahemispheric connectivity, and despite their proximity, the 3 PPC sites exhibited functional connectivity to different neural networks in healthy controls. Consistent with previous results, we observed a segregation between the two caudal sites (pIPS and SPOC) on the one hand and the anterior one (aIPS) on the other. Therefore, aIPS was functionally and anatomically connected to inferior frontal regions, particularly to the vPMC (Cavina-Pratesi et al. 2010; Uddin et al. 2010), whereas the pIPS (Koch et al. 2010; Cavina-Pratesi et al. 2010; Konen et al. 2013) and the SPOC (Cavina-Pratesi et al. 2010; Konen et al. 2013) were connected to the dPMC. Each ROI was also connected with surrounding parietal areas, especially the supramarginal gyrus for the aIPS (two regions operating in the control of the grasping phase during arm function (Koch et al. 2007, 2010)), the superior part of the angular gyrus for the pIPS and the SPOC (both involved in the control of the reaching phase of upper limb movements) (Koch et al. 2010; Vesia et al. 2013).

Interhemispheric connections were driven to the contralateral homologous parietal areas in the contralateral (right) hemisphere. This is in line with previous results (Corbetta and Shulman 2002) and it has been demonstrated that these interactions were supported by transcallosal fibers belonging to the posterior part of the corpus callosum (Koch et al. 2011). The aIPS and pIPS ROIs were also connected to contralateral frontal regions homologous to those to which they are connected in the ipsilateral hemisphere (especially frontal and temporal areas). Together with the interparietal influences, this result highlights the importance of interhemispheric relations between bilateral fronto-parietal networks and more globally between bilateral attentional networks (Corbetta and Shulman 2002).

Alterations of functional connectivity in stroke patients

As highlighted in previous works about motor deficiency and neglect, interhemispheric functional resting-state connectivity was modified in stroke patients (He et al. 2007; Park et al. 2011; Rehme and Grefkes 2013; Baldassarre et al. 2014). Although quite visually evident (Fig 2), particularly between the 3 contralesional PPC areas and their homologous regions in the ipsilesional hemisphere, interhemispheric connectivity was not significantly different between stroke patients and healthy controls based on the whole-brain seed-based analysis (probably due to a lack of statistical power because of the small sample size). We have anticipated this result by **a** priori planning networks analyses comparing connectivity between patients and healthy controls on the basis of the connexions we identified in healthy controls. These analyses revealed that interhemispheric connectivity was altered to the homologous aIPS and SPOC regions but not to the pIPS one. In neglect patients, such a disconnection has been demonstrated at the subacute stage between bilateral pIPS, SPOC and more broadly between bilateral DANs (He et al. 2007; Baldassarre et al. 2014).

Intrahemispheric functional connectivity within the contralesional hemisphere was overall less altered than interhemispheric connectivity. Parieto-frontal connections were less efficient only from the aIPS seed, which could be a consequence of their alterations in the lesioned hemisphere in relation to motor deficit (Inman et al. 2012; Schulz et al. 2015, 2016).

When modified compared to patients, functional connectivity was always altered in patients in our study, unlike some previous works that found it could be increased for both its intra- and interhemispheric aspects (Wang et al. 2010; Baldassarre et al. 2014; Ramsey et al. 2016). However, such an increase in functional connectivity in these studies was shown using a different methodology (a principal component analysis) and patients were assessed at the subacute phase. Thus, the observed modifications in functional connectivity could be the reflect of transitory functional adaptations due to post-lesional spontaneous cerebral plasticity (Wieloch and Nikolich 2006). In our study, patients were assessed at the chronic stage when spontaneous post-lesional plasticity is no longer present; so, the alteration in connectivity we noticed seem to be the reflect of a long-term intra- and interhemispheric functional disconnection of the contralesional PPC.

Contrary to what we expected, motor deficiency was not related to functional connectivity between the PPC (whatever the ROI) and the ipsi- and contralesional frontal frontal areas (especially the PMC). However, motor deficiency is not only determined by paresis, it also encompasses pyramidal hypertonia, muscle contractures, sensory loss and disturbances of motor intention or control (Gracies 2005); secondly, motor deficiency is mainly determined by the amount of involvement of the pyramidal tract in the lesion (Stinear et al. 2012; Puig et al. 2017) and by interhemispheric imbalance between sensori-motor networks (Loubinoux et al. 2003; Calautti et al. 2007). Future works should address other parameters of upper limb function (such as spatio-temporal parameters of movement, activity limitations) to further study the implication of the contralesional PPC in upper limb function deficiency and recovery.

In contrast to motor deficiency, functional connectivity showed links with neglect severity, dependent on the PPC site considered. Previous studies have already found that contralesional connectivity in fronto-parietal networks within the contralesional hemisphere, from pIPS and SPOC, was modified and correlated to peripersonal neglect severity (Allart et al. 2017; Baldassarre et al. 2014; Corbetta et al. 2005; He et al. 2007; Koch et al. 2008a; Ramsey et al. 2016). The present study extends the relationship to behavioral neglect and outlines for the first time (to the best of our knowledge) such relations for aIPS connectivity network. Finally, previous works demonstrated that neglect severity was strongly associated with a decrease in interhemispheric

functional connectivity between caudal parts of the PPC and more broadly between DANs (He et al. 2007; Carter et al. 2010; Baldassarre et al. 2014; Ramsey et al. 2016), which was normalized in recovered patients (Ramsey et al. 2016).

Alterations of structural connectivity in stroke patients.

In monkeys, it is well demonstrated that the PPC of one hemisphere has dense structural connections to homologous regions in the contralateral one, but studies have also evidenced a smaller number of direct transcallosal connections to motor and somatosensory areas (Neal 1990; Padberg et al. 2005). In humans, interparietal pathways have been identified crossing the splenium of the corpus callosum (part IV) (Koch et al. 2011), but to the best of our knowledge direct interhemispheric connections between the PPC and PMC or M1 have never been demonstrated by imaging studies. In our study, structural connectivity was reduced between each of the left PPC area and their homologous brain region in the lesioned hemisphere (extended to surrounding parietal and middle or inferior temporal regions). Such an interparietal anatomical disconnection has been previously evidenced in chronic neglect patients, and was associated with the severity of neglect and a poorer recovery (Bozzali et al. 2012; Lunven et al. 2015). Consistent with this result, even if only found for SPOC, we demonstrated such an association between the severity of peripersonal neglect and the amount of decrease in interparietal connectivity. Impaired interhemispheric structural connectivity has also been demonstrated after stroke in the medial transcallosal fibers, joining the lesioned M1 to the contralesional M1 and surrounding non-primary motor regions, and were related to motor deficit (Chen and Schlaug 2013). We did not find any difference in structural connectivity between left PPC and frontal areas of the lesioned hemisphere and no relationship between connectivity within any of the network of the PPC areas and motor function. But as we already stated for functional connectivity, upper limb function is determined by many other factors.

Intrahemispheric structural connectivity was preserved except for the SPOC network where it was decreased to frontal, anterior parietal and temporal areas. Such abnormalities within the contralesional hemisphere have already been shown in chronic stroke patients and could be signs of secondary degeneration of areas (and networks) connected to the lesion (Crofts et al. 2011).

In the present study, we used fMRI to guide DTI analyses in order to reduce the number of fiber tracts to be considered and make the analyses more focused and efficient (Zhu et al. 2014). Comparing the results of these two analyses may inform on the underlying mechanisms explaining abnormalities of functional connectivity. Especially, our results showed a convergent decrease in functional and structural connectivity of the PPC networks to homologous parietal areas located in the lesioned hemisphere, suggesting that white matter abnormalities explained functional abnormalities (Lunven et al. 2015). But we have to bear in mind that abnormalities in functional but not structural connectivity may be observed when the region is not directly anatomically connected to the contralesional PPC (but functionally connected to it via a relay), or if abnormalities are only due to a functional reorganization without microstructural lesions.

Study Limitations

The present study suffered from several limitations. Above all, the sample size was small (particularly considering the N+ patients) and we had to further exclude patients due to difficulties in the preprocessing phase; this may have led to a lack of statistical power in comparative (patients vs controls) and correlations analyses. To minimize this limit, we *a priori* planned to compare functional and structural connectivity data in patients vs controls based on the networks individualized in controls (minimizing the number of comparisons compared to a whole brain voxel analysis or a tracks analysis, as confirmed by results of SLF components and inter-parietal structural connectivity analyses we retrospectively performed (appendix 3)). However, this approach did not allow to make subgroup comparisons (especially N+ vs N- patients) and to study the effect of age, gender and time since stroke as covariables. Instead, we considered the continuous aspect of each clinical score when correlate it with connectivity data to improve statistical power. Moreover, in the network analysis we compared patients and controls connectivity on the basis of functional networks identified in controls; this approach did not take into account the possible alternative connections in patients due to brain plasticity. In order to take the step, from association to causal interaction, a quite interesting perspective could be to use effective connectivity approaches. Indeed, Granger causality (Bajaj et al. 2015), dynamic causal modelling (DCM) (Bajaj et al. 2016), or Bayesian search methods, often enable more precise causal inferences, though they are not without their own limitations (Reid et al. 2019). Afterwards, as shown in Fig 1, the distribution of the lesions was widespread and not homogenous in terms of cortical or subcortical involvement, and we did not study at this time the involvement of right parietal areas in the lesion; in order to better characterize connectivity modifications, an alternative should have been to include only patients who presented subcortical lesions, and an assessment of lesion localization and of connectivity of fronto-parietal networks within the lesioned hemisphere will have to be performed in future studies. Finally, the population of patients was quite heterogeneous with regard to disease characteristics. To reduce this heterogeneity, we included only chronic stroke patients. However, this choice complicated the inclusion of patients with neglect because this impairment often disappears in the months following stroke. Both for spatial neglect and motor deficit, modifications of functional connectivity are more frequent in the subacute than in the chronic phase since they reflect plasticity occurring after a lesion. Nevertheless, this study is of interest and complementary to those performed at the subacute stage since the modifications we observed at the chronic stage are no longer due to transient plastic phenomena but to long lasting brain rearrangements. Taken as a whole, the results of the present exploratory study shed new lights on parieto-frontal networks plasticity after stroke but have to be considered with caution, and further studies dealing specifically with spatial neglect and motor deficiency, or better integrating holistically these two deficiencies, are still required to better characterize the role of the contralesional PPC areas in post-stroke patients.

Conclusion

Our results revealed that functional and structural connectivity of the contralesional PPC was altered in chronic post-stroke patients. We particularly showed alterations of intrahemispheric functional connexions between the contralesional PPC and posterior frontal regions (especially premotor areas), and interhemispheric functional and structural abnormalities between each part of the contralesional PPC and their homologous area in the ipsilesional hemisphere. Neglect severity but not motor deficiency was associated with alterations in some intra- and interhemispheric connectivity patterns. Even if the results of this exploratory study must be confirmed and

refined in further larger studies, they shed a new light on the influence of the contralesional PPC in post-stroke patients.

Conflicts of interest: none

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fMRI (n=11)

DTI (n=8)

Fig. 1 Lesion overlap map for patients included in the fMRI analysis (at the top) and the DTI analysis (at the bottom). The color scale at the end of each row indicates the proportion of patients with a lesion in that voxel (with higher proportions for colors towards the top of the scale).

Fig. 2 Functional connectivity of left aIPS (a), pIPS (b) and SPOC (c) in healthy controls (HC) and stroke patients (P), determined in a seed-based approach.

L: left hemisphere (lesioned hemisphere in stroke patients) lateral and medial views; SUP: superior view; INF: inferior view; R: right hemisphere medial and lateral view.

Fig. 3 Functional connectivity of the left aIPS (a), pIPS (b) and SPOC (c) to bilateral frontal areas and the ipsilesional PPC, determined using a network approach.

The large red dot represents each seed in the PPC, and green points refer to connected areas identified in healthy controls in a seed-based analysis, considering only bilateral frontal areas and the ipsilesional PPC. Box plots represent the functional connectivity in healthy controls and stroke patients for each network considered; bold lines linking the seed to clusters represent clusters whose connectivity with the seed differed significantly when comparing healthy controls with stroke patients. * $p < 0.05$

a.

b.

c.

Fig. 4 The relationship between the functional connectivity of each PPC area (a=aIPSP, b=pIPSP, c=SPOC) and the severity of neglect (as assessed by the bells test, the fluff test and the Catherine Bergego scale (CBS) score). The large red dot represents each seed in the PPC, and green points refer to connected areas identified in healthy controls in a seed-based analysis, considering only bilateral frontal areas and the ipsilesional PPC. The scatter plot of functional connectivity vs. clinical scores highlights the correlations. Bold lines represent networks whose function is correlated with a given clinical score ($p < 0.05$).

a.

b.

c.

Fig. 5 Structural connectivity of left aIPS (a), pIPS (b) and SPOC (c).

The large red dot represents each seed in the PPC, and green points refer to connected areas identified in healthy controls on the basis of the cluster analysis in the rs-fMRI analyses, considering only bilateral frontal areas and the ipsilesional PPC. Box plots represent the FA in healthy controls and stroke patients; bold lines linking the seed to ROIs represent regions whose structural connectivity with the seed differed significantly when comparing healthy controls with stroke patients. * $p < 0.05$

Table 1 Characteristics of stroke patients and healthy controls

	Gender	Age (y)	Stroke type	Median time since stroke (m)	FMA-UE score (out of 66)	Neglect status	Bells test score (total omissions)	Fluff test (left score, out of 15)	CBS score (out of 30)
Patients (n=11)	M=9 (81.8%)	53.4±14.8	I=8 (72.7%)	11 (158)	36.7±21				
1	F	64	I	7	24	+	7	10	11
2*	M	58	I	6	60	+	4	12	7
3*	M	69	I	186	6	+	6	15	4
4*	M	67	H	6	7	+	9	13	9
5*	M	40	H	11	33	-	0	15	0
6*	M	54	I	13	59	-	0	15	0
7*	M	55	I	99	38	-	3	15	0
8*	M	67	I	202	33	-	0	14	0
9	M	20	I	164	23	-	2	15	2
10	M	41	H	6	62	-	0	15	0
11*	F	62	I	8	59	-	0	15	0
Controls (n=13)	M= 10 (75%)	52.8±11.4	-	-	-	-	-	-	-

Stroke type: I=ischemic; H=hemorrhagic; FMA-UE: upper extremity subsection of the Fugl-Meyer Assessment; CBS: Catherine Bergego Scale

** patients included in the DTI analysis*

Table 2. Regions showing significant connectivity with each ROI in the PPC (the aIPS, pIPS and SPOC) in healthy controls and stroke patients.

Healthy controls					Stroke Patients				
	Region	Peak MNI Coordinates				Region	Peak MNI Coordinates		
		X	Y	Z			X	Y	Z
aIPS	<i>Left aIPS and surrounding parietal areas (L. aIPS)</i>	-38	-46	52		<i>Left aIPS and surrounding parietal areas (L. aIPS)</i>	-40	-52	60
	Left ant inferior frontal gyrus (L. IFG1)	-46	34	-10		Left middle frontal gyrus (L. MFG)	-44	34	34
	Left post inferior frontal gyrus (L. IFG2)	-46	4	36		Left superior frontal gyrus (L. SFG)	-18	2	70
	Right inferior frontal gyrus (R. IFG)	46	42	14		Right aIPS and superior parietal lobule (R. aIPS)	52	-38	48
	Right aIPS and superior parietal lobule (R. aIPS)	32	-68	46		Left inferior temporal gyrus (Left ITG)	-52	-58	0
	Left middle temporal gyrus (L. MTG)	58	-60	-2		Right middle temporal gyrus (Right MTG)	58	-56	-8
	Right postcentral gyrus (R. PG)	58	-22	48					
	Right cingulate gyrus (R. CG)	8	20	44					
	Right middle temporal gyrus (R. MTG)	-50	-52	-14					
pIPS	<i>Left pIPS and surrounding parietal areas (L. pIPS)</i>	-28	-70	38		<i>Left pIPS and surrounding parietal areas (L. pIPS)</i>	-32	-72	46
	Left middle frontal gyrus (L. MFG)	-28	12	62		Left middle frontal gyrus (L. MFG)	-44	30	34
	Left inferior frontal gyrus (L. IFG)	-54	22	16		Left middle temporal gyrus (L. MTG)	-60	-44	-14
	Right pIPS and superior parietal lobule (R. SPL)	26	-68	44		Right inferior parietal lobule (R. IPL)	40	68	38
	Right middle frontal gyrus (R. MFG)	48	12	34		Right cerebellar posterior lobe (R. C)	34	-72	-38
	Left postcentral gyrus (L. PG)	-62	-24	34					
	Left inferior temporal gyrus (L. ITG)	-50	-56	-16					
	Right inferior temporal gyrus (R. ITG)	56	-54	-16					
SPOC	<i>Left SPOC and surrounding parietal areas (L. SPOC)</i>	-18	-68	58		<i>Left SPOC and surrounding parietal areas (L. SPOC)</i>	-16	-68	60
	Left middle frontal gyrus (L. MFG)	-20	2	68		Left middle frontal gyrus (L. MFG)	-20	-2	58
	Right SPOC (R. SPOC)	20	-70	50		Right SPOC (R. SPOC)	8	-66	60
	Left postcentral gyrus (L. PG)	-54	-34	50		Left inferior parietal lobule (L. IPL)	-56	-32	32
	Left middle occipital gyrus (L. MOG)	-50	-64	-8		Left lingual gyrus (L. LG)	-16	-86	-18

Appendix 1

Table. Volume of seeds (mean and standard deviation) in mm³ for patients and controls in the native T1 space.

	<i>Patients (n=11)</i>	<i>Controls (n=13)</i>	<i>P value</i>
<i>aIPS</i>	2472 ± 334	2346 ± 405	0.41
<i>pIPS</i>	2223 ± 314	2208 ± 536	0.93
<i>SPOC</i>	2148 ± 515	2366 ± 876	0.46

Figure. aIPS, pIPS and SPOC overlap between subjects in the MNI space

Appendix 2. Flow chart of the study

Appendix 3. Results of fiber tracks analyses on SLF components and inter-parietal fibers.

Attentional networks (Dorsal and Ventral) are largely involved in spatial neglect. We focused our study on pathways linking the parietal to the frontal lobe (Superior Longitudinal Fasciculus (I, II and III)) and on intercallosal fibers linking both parietal lobes.

Our processing pipeline is illustrated below. From the whole brain tractography described the article, tracts segmentation was done with TractQuerier a “White Matter Query Language (WMQL)” (b) (1), whereas others track operations (linear registration (c) (2), outlier removal (d) (3), clustering (e)(4) and parametric maps extraction (FA, MD, S0, MO, L1, L2 and L3)) were done using the “DIPY” python package, version 0.14.0 (5). Groups comparisons were performed using Mann-Whitney U test, while correlation analysis between clinical scores (Bells test, Catherine Bergego Scale, Fluff test, FMA) and diffusion parameters were performed using Spearman’s correlation test.

After correction for multiple comparisons (using the False Discovery Rate of Benjamin-), threshold for statistical significance was set to $p < 0.05$.

No significant results were obtained on contralesional and interhemispheric tracks. Only ipsilesional SLF I ($p=0.0195$) and SLF II ($p=0.0223$) FA was significantly altered in patients vs controls. In addition, we did not show any behavioral/connectivity correlation.

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