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Behavioral/Cognitive

Discrete Patterns of Cross-Hemispheric Functional Connectivity Underlie Impairments of Spatial Cognition after Stroke

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Despite intense research, the neural correlates of stroke-induced deficits of spatial cognition remain controversial. For example, several cortical regions and white-matter tracts have been designated as possible anatomic predictors of spatial neglect. However, many studies focused on local anatomy, an approach that does not harmonize with the notion that brain-behavior relationships are flexible and may involve interactions among distant regions. We studied in humans of either sex resting-state fMRI connectivity associated with performance in line bisection, reading and visual search, tasks commonly used for he clinical diagnosis of neglect. We defined left and right frontal, parietal, and temporal areas as seeds (or regions of interest, ROIs), and measured whole-brain seed-based functional connectivity (FC) and ROI-to-ROI connectivity in subacute right-hemisphere stroke patients. Performance on the line bisection task was associated with decreased FC between the right fusiform gyrus and left superior occipital cortex. Complementary increases and decreases of connectivity between both temporal and occipital lobes predicted reading errors. In addition, visual search deficits were associated with modifications of FC between left and right inferior parietal lobes and right insular cortex. These distinct connectivity patterns were substantiated by analyses of FC between left- and right-hemispheric ROIs, which revealed that decreased interhemispheric and right intrahemispheric FC was associated with higher levels of impairment. Together, these findings indicate that intrahemispheric and interhemispheric cooperation between brain regions lying outside the damaged area contributes to spatial deficits in a way that depends on the different cognitive components recruited during reading, spatial judgments, and visual exploration.

Key words: attention network; functional connectivity; parietal lobe; spatial cognition; spatial neglect; visual attention

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Significance Statement

Focal damage to the right cerebral hemisphere may result in a variety of deficits, often affecting the domain of spatial cognition. The neural correlates of these disorders have traditionally been studied with lesion-symptom mapping, but this method fails to capture the network dynamics that underlie cognitive performance. We studied functional connectivity in patients with right-hemisphere stroke and found a pattern of correlations between the left and right temporo-occipital, inferior parietal, and right insular cortex that were distinctively predictive of deficits in reading, spatial judgment, and visual exploration. This finding reveals the importance of interhemispheric interactions and network adaptations for the manifestation of spatial deficits after damage to the right hemisphere.

Introduction

Traditionally, the study of spatial impairments after focal brain injury has focused heavily on local cortical anatomy (Vallar and Perani, 1986; Doricchi and Tomaiuolo, 2003; Mort et al., 2003; Karnath et al., 2004; Committeri et al., 2007; Golay et al., 2008; Medina et al., 2009). Only recently has this focus shifted toward possible structural disconnections underlying clinical syndromes, such as spatial neglect (Urbanski et al., 2011; Thiebaut de Schotten et al., 2014). Voxel-based lesion-symptom mapping (VLSM) and diffusion tensor imaging (DTI) have led to a complex picture, suggesting that numerous regions and fiber tracts

contribute to such deficits (Chechlacz et al., 2012; Molenberghs et al., 2012; Pedrazzini and Ptak, 2020). This could reflect the observation that patients, though sharing an underlying "core" component, may differ on dimensions, such as egocentric/ allocentric, personal/extrapersonal, or near/far space neglect (Corbetta and Shulman, 2011; Sperber and Karnath, 2018). Alternatively, different inclusion criteria or issues of statistical power in an area of study that strongly relies on familywise error (FWE) control may have contributed to these intricate findings.

Despite decades of research, the nature of the association between brain anatomy and cognitive function remains difficult to specify, even more so as it may differ across brain areas and the class of function under investigation (Price and Friston, 2002). Functional imaging has led to the dismissal of the idea that this association is rigid (as in a one-to-one relationship), in favor of a more flexible connection (one-to-many, many-to-one), or even the hypothesis that anatomic correlates of a function vary across situations according to current computational requirements (many-to-many) (Shallice and Cooper, 2011; Cole et al., 2013; Poldrack and Farah, 2015; Ptak et al., 2017). The latter perspective describes a brain that is highly dynamic and adaptable, which contrasts with the relatively static picture of brain function provided by lesion overlap methods.

Measures of resting-state functional connectivity (FC) provide the possibility to study distributed networks and their alteration as predictors of behavioral deficits after stroke in a complementary way to VLSM and DTI methods (Buckner et al., 2013; Bassett and Sporns, 2017). Connectome studies show that the human brain is intrinsically organized into large-scale networks (Yeo et al., 2011; Petersen and Sporns, 2015), which, when damaged, may give rise to widespread patterns of functional disconnection (Alstott et al., 2009; Buckner et al., 2009; Gratton et al., 2012). FC-behavior relationships have been revealed for deficits of spatial cognition, where some studies reported that interhemispheric FC between dorsal frontoparietal regions predicts deficits of lateralized attention after hemispheric stroke (He et al., 2007; Carter et al., 2010). Likewise, intrahemispheric frontoparietal disconnection was found to be associated with impairments of goal-directed attention (Fellrath et al., 2016). Interactions between functional networks within and across hemispheres appear to be particularly affected in patients with spatial neglect, suggesting that changes of functional networks may provide a specific signature of this disorder (Baldassarre et al., 2014).

Behavioral studies with brain-damaged patients regularly report dissociations of performance in different tests of spatial attention, a finding reflecting the involvement of discrete cognitive mechanisms. For example, damage to posterior and inferior parietal or premotor cortex differently affects cancellation and line bisection (Pedrazzini et al., 2017; Toba et al., 2017), personal and extrapersonal space (Committeri et al., 2007; Baas et al., 2011), orienting of attention (Molenberghs et al., 2008; Vandenberghe et al., 2012; Pedrazzini and Ptak, 2019), and reading (Lee et al., 2009; Medina et al., 2009). Here, we examined whether such distinct patterns of performance in tests of spatial cognition are predictable from resting-state FC. We assessed cancellation, line bisection, and reading performance in patients with right hemisphere stroke and established correlations with brainwide FC. Our findings identify distinct intrahemispheric and interhemispheric connectivity patterns as predictors of stroke-induced deficits of spatial cognition.

Materials and Methods

Participants. We recruited 30 patients (11 women) with first-ever right-hemisphere stroke while they were hospitalized at the Division of Neurorehabilitation, University Hospitals Geneva. Approval for this study was obtained from the local ethical committee (Geneva, Switzerland), and all participants gave written informed consent before being enrolled. Exclusion criteria were as follows: (1) presence of prior strokes or multiple lacunar lesions; (2) inability to participate to MRI (e.g., presence of metallic parts in the body); (3) severe cognitive impairment precluding administration or interpretation of clinical tests (e.g., severe hypovigilance, confusion, or dementia); and (4) presence of other neurologic or psychiatric diseases (e.g., major depression). We did not select participants based on their performance in any of the clinical tests.

Mean age of patients was 63 ± 13.1 years, and the mean delay of testing after stroke onset was 42.6 d. All participants had a standard neurologic examination, including visual field testing through digital confrontation and/or a campimetry test (detection of running numbers on a 24 inch screen).

Experimental procedures and stimuli. They were administered the following clinical tests: line bisection (Ronchi et al., 2012), symbol cancellation (the Bells test) (Gauthier et al., 1989), letter cancellation (Ptak et al., 2007), and word reading (Ptak et al., 2012). The reading test consisted of 40 compound words presented in 5 columns on an A4 sheet of paper. This test has previously been used to identify patients with spatial dyslexia, a reading disorder associated with left neglect that is characterized by omissions and substitutions of word beginnings.

Performance in these tests may be taken as cutoff criterion to identify clinical groups for group-based FC analyses, or may be entered as continuous measure in regression-based FC analyses. In this study, we performed both types of analyses and therefore defined groups showing clinically relevant neglect in line bisection, symbol cancellation, or reading tests based on cutoff criteria from previous normative studies. For the reading test, we first applied the criteria of Ellis et al. (1987) to classify reading errors as omissions, substitutions, additions, or mixed errors. Patients were then classified as belonging to a spatial dyslexia group if they reached the cutoff of $n \geq 4$ lateralized reading errors. Seven patients were identified as spatial dyslexics using this criterion. They missed on average 13.7 ($\pm$ 9.5) words completely and transformed 7.2 ($\pm$ 5.5) words compared with 2.6 ($\pm$ 3) words missed and 0.3 ($\pm$ 0.6) transformations by the nondyslexia group. Neglect on line bisection was defined by using the cutoff of ≥ 2 SDs of healthy control performance. This criterion identified 9 patients, who had an average bisection error of 9% ($\pm$ 5.1) compared with 1.4% ($\pm$ 1.6) of the non-neglect group. Finally, the cutoff score used to define left neglect on the cancellation test was ≥ 3 omissions on the left side of the sheet. This criterion identified 13 patients, who missed on average 10.6 ($\pm$ 3.6) items on the left, compared with 1 ($\pm$ 1.3) item for the non-neglect group. Table 1 provides clinical characteristics and individual test results of all patients.

Experimental design and statistical analysis. The study focused on 30 human stroke patients of both sexes who to different degrees expressed deficits in simple tasks probing spatial cognition. We used clinical tests that evaluate elementary visuospatial performance and in which performance of healthy participants score at ceiling (e.g., a cutoff of two for the difference between left and right omissions is considered as pathologic performance on the Bells test) (Azouvi et al., 2002), precluding any correlational analysis with measures of connectivity. We therefore renounced testing controls and instead compared global patterns of connectivity in the patient group with anatomic and resting state (rs)-fMRI data of middle-aged healthy subjects from a previous study (Goveas et al., 2013) (data freely available through the 1000 Functional Connectomes Project at http://fcon_1000.projects.nitrc.org). We selected from this dataset the 27 oldest participants (12 women). The mean age of the control group was 55.9 ($\pm$ 6.1) years.

Group comparisons of ROI-to-ROI FC data were performed with ANOVA. Group comparisons of seed-based data applied independent-samples t tests with a significance level $p < 0.001$ and FWE-adjusted cluster-size correction.

MRI acquisition. Structural and functional MRI scans were acquired on a 3T Trio scanner (Siemens Medical Solutions) in a single session,

Table 1. Clinical characteristics and test results of the patient sample (inf./sup. quad.: inferior/superior quadrant)

No.	Age (yr)	Time post stroke (days)	Visual field	Bells left omissions (of 15)	Letters left omissions (of 27)	Bisection (% bias)	Reading errors	Spatial dyslexia errors
1	61.8	53	Intact	15	0	−0.05	0	0
2	78.9	13	Hemianopia	0	15	5.14	23	4
3	69.0	48	Intact	0	0	0	0	0
4	78.5	65	Intact	6	20	3.18	11	8
5	62.6	56	Intact	1	2	0	0	0
6	66.0	38	Intact	11	3	11.31	4	1
7	71.7	39	Hemianopia	15	27	21.41	6	4
8	66.2	30	Intact	1	0	−0.94	1	0
9	81.4	35	Intact	0	5	2.89	2	1
10	66.6	50	Hemianopia	15	11	8.1	33	0
11	33.6	21	Intact	0	0	0	0	19
12	79.3	21	Intact	8	11	−0.72	3	0
13	51.8	43	Intact	0	2	2.82	1	0
14	42.1	91	Intact	7	4	2.45	4	2
15	69.5	48	Inferior quadrant	10	21	5.79	38	4
16	65.6	52	Intact	0	—	7.11	1	0
17	46.3	23	Intact	0	6	2.24	9	0
18	62.2	37	Intact	7	6	3.96	6	0
19	58.7	54	Intact	3	3	0.4	1	0
20	59.4	73	Hemianopia	10	9	2.78	3	0
21	70.3	37	Intact	15	27	8.58	15	4
22	76.4	26	Hemianopia	3	3	4.9	24	0
23	65.3	33	Hemianopia	13	12	8.22	6	1
24	78.7	23	Intact	6	9	0.94	11	0
25	55.9	55	Intact	2	3	0.78	2	1
26	63.6	50	Superior quadrant	3	5	2.44	4	0
27	28.3	18	Intact	2	0	2.73	5	1
28	72.2	45	Intact	0	1	3.53	0	0
29	77.6	45	Intact	3	1	−0.57	5	4
30	48.0	33	Intact	0	0	1.32	0	0
Mean	63.6	41.8		5.2	7.1	3.69	7.3	1.8

which took place within a week from behavioral testing. A high-resolution (voxel size: 1 mm³) T1-weighted MPRAGE sequence (TR: 2300 ms; TE: 1.94 ms; flip angle 9°) and a T2-weighted (TR: 3200 ms; TE: 407 ms; flip angle 120°) structural scan were acquired for normalization and lesion delineation. The rs-fMRI scan consisted of 320 volumes acquired using T2*-weighted GRE EPI sequence (TR: 1500 ms; TE: 35 ms; voxel size $3 \times 3 \times 5$ mm; flip angle 85°). During acquisition, each subject's head was fixed with cushions to prevent motion, and participants lay in the dark, eyes closed. Control data were acquired on a 3T Signa GE scanner (GE Healthcare Technologies) and consisted of a high-resolution (voxel size: 1 mm³) 3D spoiled gradient-recalled echo anatomic scan (TR: 10 ms; TE: 4 ms; flip angle 12°) and 175 volume EPI sequence (TR: 2000 ms; TE: 25 ms; voxel size $3.75 \times 3.75 \times 4$ mm; flip angle 90°).

Lesion delineation and preprocessing of structural and functional MRI data. For each patient, a volumetric mask was created by delineating every lesion manually on the T2-weighted MRI scan in MRIcron software (Rorden et al., 2007). The structural T2 scan and the lesion mask were realigned and coregistered with the structural T1 using SPM12 (www.fil.ion.ucl.ac.uk/spm). Structural T1 scans were then segmented and normalized to the MNI (http://www.bic.mni.mcgill.ca) template space. These steps were performed with the Clinical Toolbox (Rorden et al., 2012), which offers an age-specific MRI template and automatically applies an enantiomorphic lesion mask to minimize normalization artifacts induced by abnormal tissue (Nachev et al., 2008). Normalization produced images of $2 \times 2 \times 2$ mm voxel size.

Analysis of rs-fMRI data. We used the CONN toolbox (Whitfield-Gabrieli and Nieto-Castanon, 2012) to normalize patients' functional volumes and for the complete preprocessing of control's structural and functional images (including segmentation of the structural T1 and normalization to MNI). Normalized images were smoothed with an 8 mm FWHM function. ART-based scrubbing was used to identify outlier volumes (Power et al., 2012). We corrected nuisance (physiological and movement artifacts) with a linear regression model, by inserting the

following as confounds: (1) the six rigid-body parameters estimated from realignment, (2) averaged BOLD signals of white matter and CSF, and (3) the scrubbing parameters. Moreover, data were filtered with a bandpass of 0.008-0.09 Hz to remove low-frequency drift and high-frequency noise. Scrubbing identified on average 0.25% outlier scans in controls, and maximum framewise displacement was <0.5 mm in all subjects. Two patients had an excessive number of outlier scans (>13%) and were therefore eliminated from further analysis. The remaining 28 patients had on average 1.82% outlier scans identified by scrubbing and a maximal framewise displacement <0.5 mm.

We next defined seven cortical seeds (or ROIs) based on the AAL atlas (Tzourio-Mazoyer et al., 2002). We focused on regions that lie in the ventral and dorsal stream and are either central nodes in attention networks (angular gyrus [Ang]; supramarginal gyrus [SMG]; superior parietal lobule [PSup]; superior frontal cortex [FSup]; lateral inferior frontal cortex [FInf]) or have previously been identified as important predictors of spatial dyslexia (fusiform gyrus [Fus]; superior temporal gyrus [STG]) (Lee et al., 2009; Ptak et al., 2012). For seed-based FC analyses, we computed Fisher-transformed correlation and applied a threshold of $p < 0.001$ (uncorrected) at the voxel level. The significance level for clusters was set to $p < 0.05$, with an FWE correction for cluster volume (testing performed with $n = 1000$ permutations). In all analyses, we examined seed-based FC of right-hemispheric ROIs and of homotopic regions of the left hemisphere. In a second step, we also computed ROI-to-ROI connectivity between ipsilateral and contralateral ROIs. While we focused on cortical ROIs, seed-based FC was always computed with the rest of the brain, including subcortical regions, such as the thalamus; any involvement of the latter would therefore be identified in our analyses.

A major problem when examining FC in brain-injured patients is that the degree of connectivity in the injured area is unknown, as the damage seen on MRI is at the best a modest predictor of residual activity and areas with altered neurovascular coupling cannot easily be
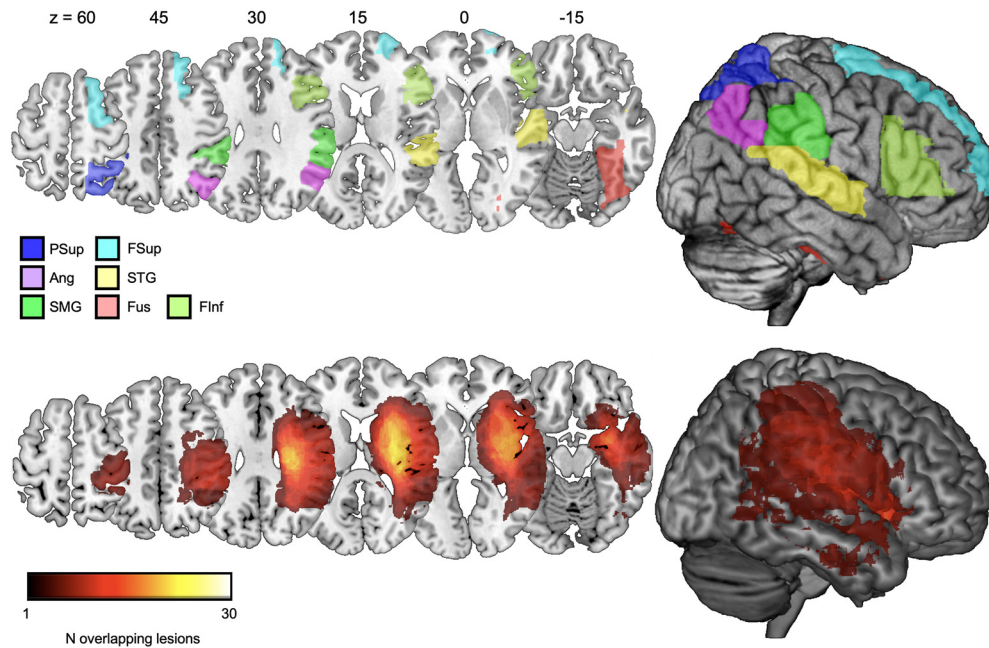
Figure 1. Top, Axial slices of the MNI-template brain showing the five ROIs entered as seeds in FC analyses (z values show MNI coordinates). Bottom, Rendering of brain lesions of all participants. Color scale represents the number of patients with damage at each specific voxel.

identified. Stroke may affect the BOLD signal outside the damaged area and even in the intact hemisphere (Pineiro et al., 2002; Amemiya et al., 2012), and brain regions that are close to, but do not overlap with, damaged tissue may exhibit significant changes of connectivity (Lv et al., 2013; Siegel et al., 2017). More importantly, areas with decreased BOLD responses may exhibit significant neural activity as measured with evoked potential methods (Rossini et al., 2004). Because of the insecurities regarding changes of neurovascular coupling in our patients, we decided to include injured voxels in the FC analyses. We quantified the relative damage to each ROI as well as the total lesion volume and examined their impact on FC by including them as covariates in the connectivity analyses.

Results

Lesion distribution and overlap with ROIs
Figure 1 shows the distribution of lesions in the patient group. Most patients shared damage in periventricular white matter, whereas cortical lesions were comparatively less frequent. The average overlap of each patient's lesion with each ROI was, respectively, as follows: 5.7% (Fus), 7.2% (Ang), 15.4% (SMG), 2.1% (PSup), 15.4% (STG), 0.03% (FSup) and 10.2% (FInf). Thus, there was a modest involvement of damaged tissue in seed-ROIs used in the FC analyses.

Global patterns of connectivity
Before examining specific FC predictors of behavioral performance, we assessed global patterns of seed-based connectivity for both groups of participants. These analyses applied one-sample t tests ($p < 0.001$ and FWE cluster-size correction), examining whether connectivity at each voxel was significantly different from zero. In order to ensure that these analyses were based on a comparable number of functional images, we included only the first 175 volumes of the patient data. Figure 2 shows significant voxels identified in these seed-based analyses.

Analyses of control data revealed bilateral and largely symmetrical functional networks that were specific for each seed-ROI (Fig. 2). These networks implicated the following: (1)

inferior and superior temporal cortex, lateral and superior occipital cortex, as well as the precentral and postcentral gyrus for the Fus seed; (2) inferior parietal, mid-temporal, premotor, dorsal prefrontal, frontopolar, and retrosplenial cortex for the Ang seed; (3) inferior and superior parietal cortex, STG, lateral PFC, and insula for the SMG seed; (4) superior and inferior parietal, dorsal premotor, lateral prefrontal, and lateral occipital cortex for the PSup seed; (5) the superior and middle temporal and lateral occipital cortex, SMG, insula, as well as the precentral and postcentral gyrus for the STG seed; (6) dorsal and ventral PFC, Ang, and middle temporal gyrus for the FSup seed; and (7) lateral PFC, SMG, medial, and STG for the FInf seed. As Figure 2 shows, there were only few negative correlations, mainly contralateral and with the SMG and Ang seeds. In strong contrast to controls, stroke patients exhibited FC with regions lying in the vicinity of the seed-ROI, whereas contralateral connectivity was limited to regions that were homologous with the seed.

These analyses identified the global patterns of connectivity but did not provide a direct comparison of absolute connectivity values across the two groups. We therefore ran a further analysis, which compared FC of both groups at the voxel level with an independent-samples t test. The results revealed a pattern of significant differences that closely matched the general connectivity pattern of the control group (Figs. 2, left, 3), showing that controls had higher connectivity than stroke patients in cortical networks ipsilateral and contralateral to all right-hemisphere seed regions under focus.

We next performed ROI-to-ROI analyses by extracting correlations between right- and left-hemispheric ROI pairs and compared them across groups. This analysis was motivated by previous findings showing that focal damage after stroke is associated with a significant decrease of FC between homotopic regions (Siegel et al., 2016; Tang et al., 2016). We computed average connectivity values for each combination of the five right- and left-hemispheric ROIs and classified them according to one of four conditions: interhemispheric homotopic, interhemispheric heterotopic, left intrahemispheric, and right intrahemi-
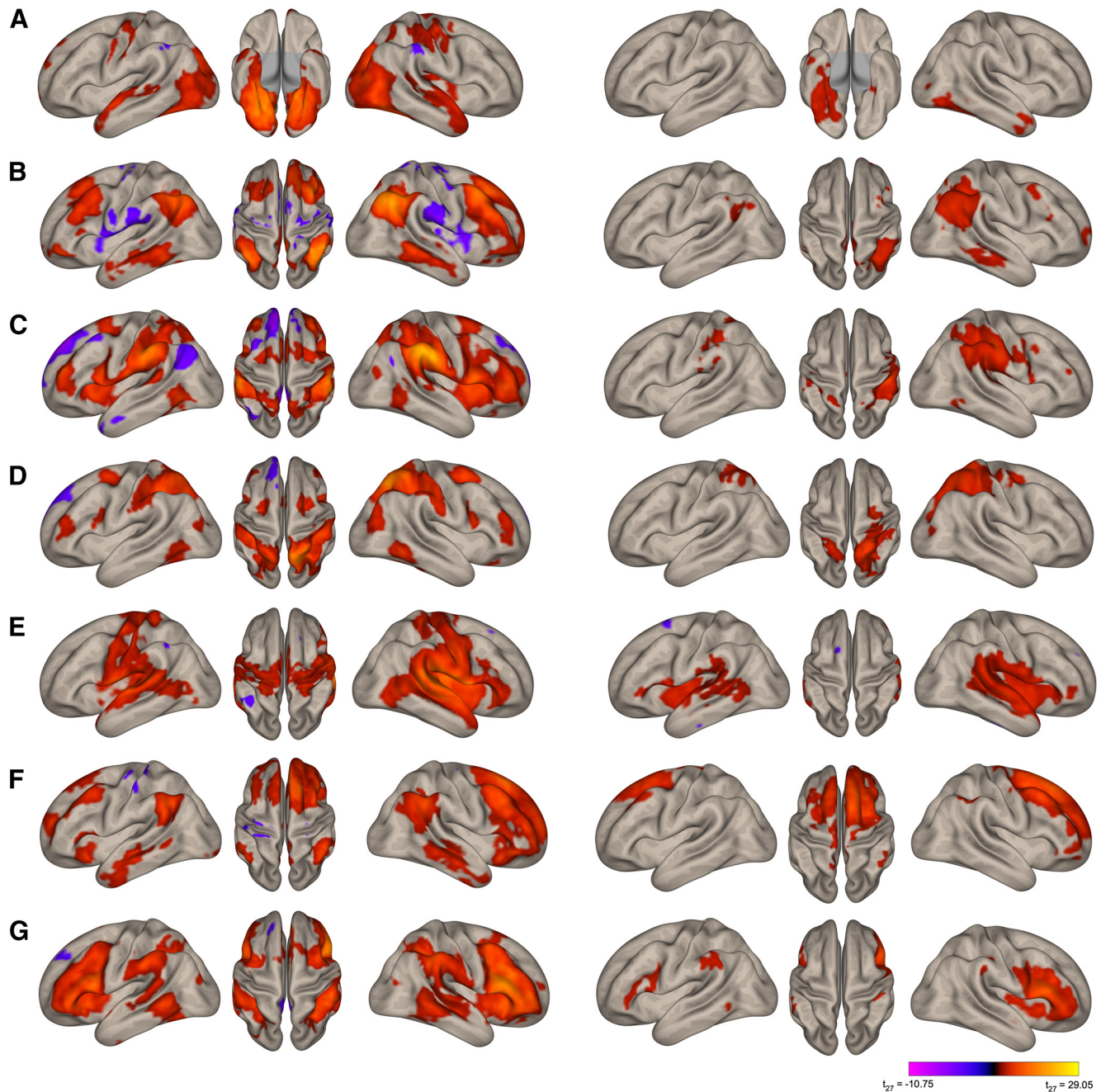
Figure 2. Connectivity of each seed-ROI with the rest of the brain (left column, healthy controls; right column, stroke patients). Seed-ROIs are as follows: (**A**) Fus, (**B**) Ang, (**C**) SMG, (**D**) PSup, (**E**) STG, (**F**) FSup, and (**G**) FInf. Reddish tones represent positive correlations. Bluish tones represent negative correlations.

spheric FC. Figure 4 shows a color-rendered matrix of mean connectivity for each ROI pair. Connectivity in controls was highest between homotopic region pairs (mean: 0.71 ± 0.1), followed by right intrahemispheric (mean: 0.56 ± 0.12), left intrahemispheric (mean: 0.48 ± 0.12), and heterotopic FC (mean: 0.45 ± 0.14). In patients, homotopic FC was highest (mean: 0.54 ± 0.22), followed by left intrahemispheric (mean: 0.49 ± 0.17), right intrahemispheric (mean: 0.42 ± 0.16), and heterotopic FC (mean: 0.28 ± 0.18). To examine these data statistically, we performed a mixed ANOVA with Group as between-factor and ROI-to-ROI condition as within-factor. This analysis yielded significant main effects of Group ($F_{(1,53)} = 13.21$, $p = 0.001$, $\eta^2 = 0.20$) and Condition ($F_{(3,159)} = 51.53$, $p < 0.0001$, $\eta^2 = 0.493$), as well as a Group × Condition interaction ($F_{(3,159)} = 8.41$, $p < 0.0001$, $\eta^2 = 0.137$). Independent-

samples t tests comparing groups across different conditions showed that, in all conditions, controls exhibited higher connectivity than patients ($t_{(53)} > 3.76$, $p < 0.001$), except for left intrahemispheric FC ($t_{(53)} = 0.23$).

To summarize, the seed-based analyses revealed a consistent pattern of connectivity between each seed and neighboring regions of the same hemisphere, where distant within-hemisphere connections reflected known functional networks (in particular, frontoparietal networks identified in FC analyses with the Ang, PSup, FSup, and FInf seeds). ROI-to-ROI analyses showed that interhemispheric connections involving homotopic areas had the highest degree of efficiency in both groups. In addition, except for the intact left hemisphere, controls had consistently higher FC than patients.
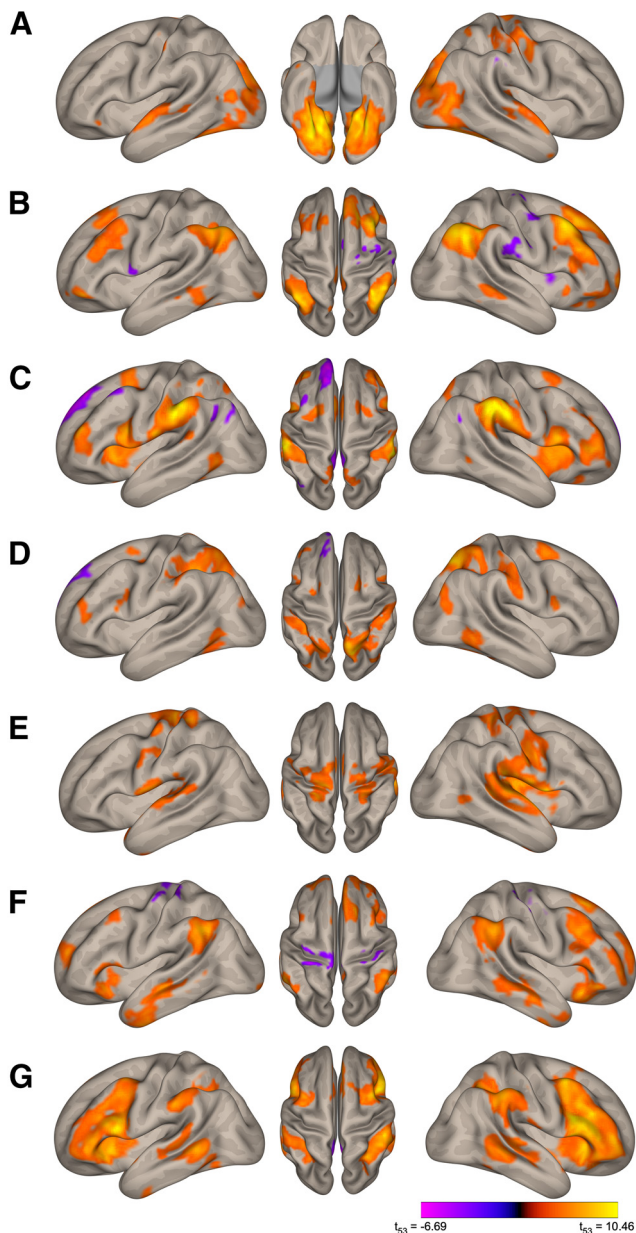
Figure 3. Direct contrast of seed-based connectivity between controls and stroke patients. Yellow-orange tones represent areas where controls had significantly higher correlations than patients. Pink represents areas of higher correlation in patients. Seed-ROIs are as follows: (**A**) Fus, (**B**) Ang, (**C**) SMG, (**D**) PSup, (**E**) STG, (**F**) FSup, and (**G**) FInf.

## FC predictors of spatial cognition

We next performed seed-based regression analyses that examined whether regional connectivity predicted behavioral scores in reading, line bisection, and cancellation. First, we examined FC predictors of reading performance. Unfortunately, reading errors were not linearly distributed across patients, as most patients made none or very few transformations characteristic of spatial dyslexia. Consequently, our cutoff identified only 7 patients with spatial dyslexia. Since these data did not lend themselves for regression analysis, we compared connectivity across groups with independent-samples t tests. The main finding of these analyses was that patients with spatial dyslexia had increased FC between the right Fus and anterior inferior temporal cortex (cluster size: 192 voxels; MNI coordinates: −60, −32,

−18; FWE-corrected $p < 0.02$; Fig. 5), but decreased FC between the left Fus and right posterior inferior temporo-occipital cortex (cluster size: 430 voxels; MNI coordinates: −8, −64, −8; FWE-corrected $p < 0.0001$; Fig. 6B). In dyslexic patients, the left Fus seed additionally exhibited higher connectivity with the left insula (cluster size: 511 voxels; MNI coordinates: −34, −10, 4; FWE-corrected $p < 0.0001$) and anterior temporal cortex (cluster size: 146 voxels; MNI coordinates: −28, 16, −46; FWE-corrected $p < 0.05$). We repeated these analyses by including total lesion volume (instead of the relative volume of damage to the seed-ROI) as covariate and identified the same clusters of positive or negative connectivity. Thus, positive predictors of impaired reading were located in the left hemisphere, whereas negative predictors were all located in the right hemisphere.

We next searched for positive or negative predictors of the line bisection bias (where higher values indicate more severe deficit) by treating line bisection data as a continuous measure in a regression analysis. Of all right- and left-hemispheric seed-ROIs, only FC of the right Fus revealed clusters of significant FC-behavior relationship. In the larger of two clusters (located in the left superior occipital cortex), a significant decrease of connectivity was associated with greater ipsilesional bias on line bisection (Fig. 6A; cluster size: 930 voxels; MNI coordinates: −26, −86, 28; FWE-corrected $p < 0.0001$). Figure 6B shows the negative relationship between mean cluster-FC and line bisection performance. These data followed a linear trend, which was very similar if the whole dataset was considered ($R^2 = 0.343$), or only values of patients with pathologic scores (>2 SDs of the control mean; $R^2 = 0.308$). In a smaller cluster, located in the right occipital pole, increased connectivity predicted worse performance on the line bisection task (cluster size: 188 voxels; MNI coordinates: 18, −104, −10; FWE-corrected $p < 0.05$). Repeating these analyses with total lesion volume as covariate confirmed the same FC-clusters without identifying any further significant results. We additionally performed group-based analyses by comparing 9 patients with a pathologic bias on line bisection to 19 unimpaired patients. Only FC of the right Fus identified a cluster of significant FC-behavior relationship, which was remarkably similar to the cluster identified with the regression analysis shown in Figure 6A (cluster size: 884 voxels; MNI coordinates: −28, −86, 26; FWE-corrected $p < 0.0001$). Thus, regression and group-based analyses yielded very similar results, showing involvement of only one ROI (Fus) and identifying a cluster in the left superior occipital cortex in which FC predicted bias on line bisection.

Next, we examined predictors of left omissions in the Bells test, a sensitive measure of visual search deficits characterizing spatial neglect. Regression analyses yielded two clusters in which FC was negatively correlated with increasing numbers of omissions: one cluster was identified through the right SMG seed and was located in the left SMG (Fig. 7A; cluster size: 185 voxels; MNI coordinates: −54, −30, 18; FWE-corrected $p < 0.02$). A linear fit of these data was significant and very similar if computed across the whole dataset ($R^2 = 0.568$), or only with the pathologic data (>3 omissions; $R^2 = 0.574$). Analysis of left SMG FC revealed a second cluster located in the right insula (Fig. 7B; cluster size: 634 voxels; MNI coordinates: 50, 4, −10; FWE-corrected $p < 0.0001$). Again, the linear fit of these data was similar whether it was computed across the entire dataset ($R^2 = 0.718$) or with pathologic scores only ($R^2 = 0.757$). These two clusters were confirmed after repeating these analyses by including total lesion volume rather than the degree of damage to seed-ROIs as covariate. We also performed a group-based analysis on patients separated into an impaired ($N = 13$) and a nonimpaired group
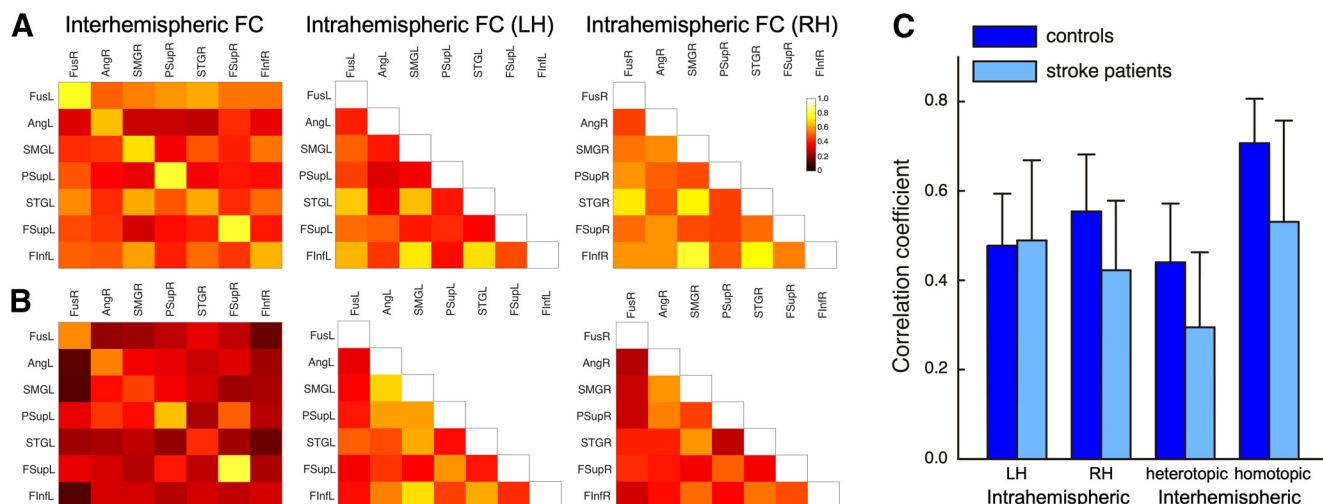
Figure 4. ROI-to-ROI–based analyses of interhemispheric and intrahemispheric connectivity. **A**, Data of healthy controls. **B**, Data of stroke patients. The colored matrices represent average interhemispheric FC for homotopic ROIs (shown on the descending diagonal axis) and heterotopic ROIs, as well as intrahemispheric FC of the left hemisphere (LH) and right hemisphere (RH). **C**, Average connectivity of controls and stroke patients for intrahemispheric and interhemispheric ROI pairs.
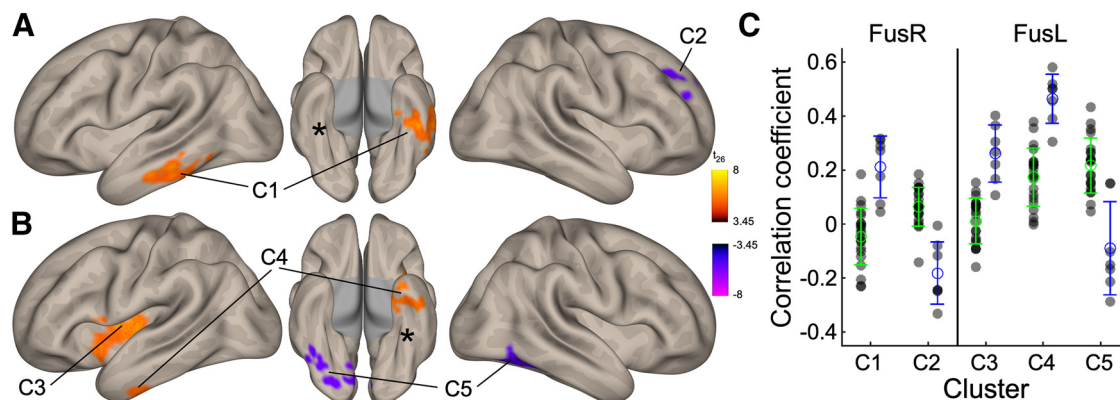
Figure 5. Seed-based analysis of FC as predictor of spatial dyslexia. **A**, Clusters identified with the right Fus ROI (*). **B**, Clusters identified with the left Fus ROI. **C**, Average correlation values in each of the five clusters shown in **A** and **B**. Green represents patients with spatial dyslexia. Blue represents nondyslexic patients.
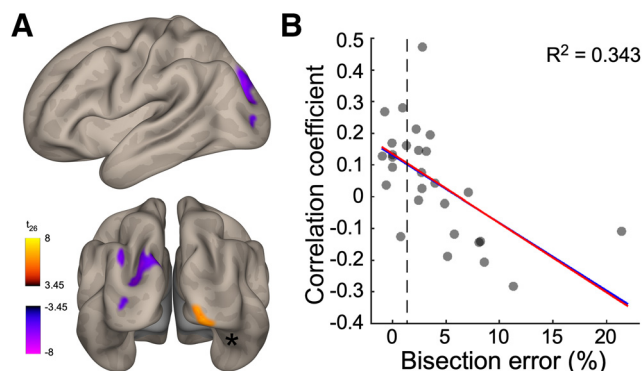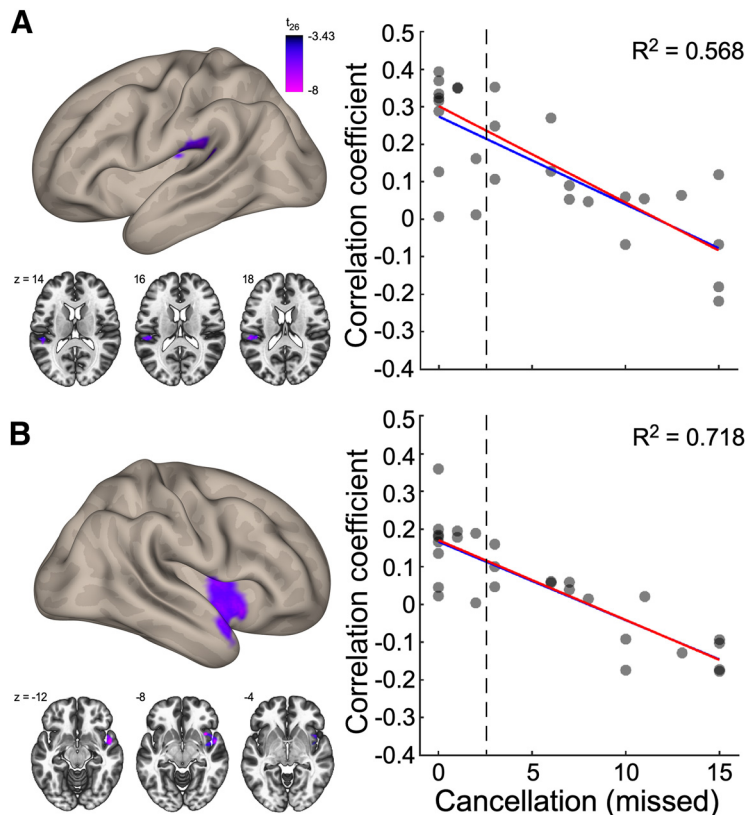

Figure 6. Seed-based analysis of FC as predictor of line bisection performance. **A**, Clusters that significantly correlated with the right Fus ROI (*). **B**, Linear fit of bisection error and mean correlation within the cluster of negative correlation shown in **A**. Stippled vertical line indicates the cutoff of normal performance. Blue line indicates fit for the whole dataset. Red line indicates only pathologic data.

($N = 15$) by computing independent-samples t tests. Of all seven ROIs, only FC of the left SMG revealed a cluster with a significant FC-behavior relationship. This cluster was similar to the cluster identified by the regression analysis and shown in Figure

7*B*, although smaller (cluster size: 290 voxels; MNI coordinates: 36, 14, −8; FWE-corrected $p < 0.0011$). Thus, regression and group-based analyses confirmed that connectivity between the left SMG and right insular cortex is a significant predictor of cancellation performance.

We finally explored the FC-behavior relationship between left- and right-hemisphere seeds by focusing on ROI-to-ROI interactions. For this analysis, we first extracted average correlations between interhemispheric and intrahemispheric ROI pairs and then correlated these with behavioral scores (line bisection bias and left omissions in the cancellation test). Figure 8*A* illustrates color-rendered correlation matrices between connectivity and bias in line bisection, and Figure 8*B* shows the correlation matrices for the number of omissions in the cancellation test. We performed one-way ANOVAs to compare FC between homotopic, heterotopic, left intrahemispheric, and right intrahemispheric ROI pairs. A significant effect ($F_{(3,90)} = 10.39$, $p < 0.0001$) indicated that heterotopic (-0.22 ± 0.16; $p < 0.003$) and homotopic interhemispheric FC (-0.34 ± 0.14; $p < 0.001$) were better (though negative) predictors of line bisection bias than left (-0.07 ± 0.13) and right intrahemispheric FC (-0.07 ± 0.16). The analysis of the cancellation data was also significant ($F_{(3,90)} = 14.79$, $p < 0.001$); right intrahemispheric FC

Figure 7. Seed-based analysis of cancellation performance. **A**, Cluster functionally connected with the right SMG seed that negatively predicted the number of missed cancellation targets. **B**, Cluster connected with the left SMG seed that negatively predicted the number of missed cancellation targets. Scatterplots represent individual connectivity. Stippled vertical line indicates the cutoff of normal performance. Blue line indicates fit for the whole dataset. Red line indicates only pathologic data.

(-0.22 ± 0.14) and interhemispheric FC (heterotopic: -0.16 ± 0.16; homotopic: -0.19 ± 0.14) were better (negative) predictors of cancellation bias than left intrahemispheric FC (0.6 ± 0.14; all $p < 0.001$). Thus, although FC-behavior relationships based on ROI-to-ROI analysis were relatively weak in terms of the amplitude of correlation, a general pattern was that interhemispheric FC was a better predictor of behavioral deficits than left intrahemispheric connectivity.

Discussion

The present data show that behavioral scores in clinical tests commonly administered to assess deficits of spatial cognition are associated with distinct patterns of FC across the hemispheres. Seed-based analyses identified functional networks in healthy individuals that involved frontoparietal (Ang, SMarg, PSup, FSup, and FInf seed), occipito-temporal (Fus seed), and temporo-insular cortex (STG seed). These networks were well segregated and exhibited a high degree of bilateral symmetry, although the seed-ROIs were located in the right hemisphere. In contrast, patients showed intrahemispheric connectivity patterns that were largely limited to regions surrounding the seed. In addition, whereas controls showed a widespread connection pattern comprising homotopic and heterotopic regions of the contralateral hemisphere, interhemispheric connectivity in patients was restricted to homotopic cortex. This finding suggests that areas of the injured hemisphere maintain collaboration with homotopic areas but fail to connect to more distant and heterotopic regions located in the contralateral hemisphere. Indeed, ROI-to-ROI analyses of our patient sample showed that intrinsic connectivity of the damaged right hemisphere and between

hemispheres was significantly decreased, whereas intrahemispheric FC of the left hemisphere was comparable to healthy controls. Disruption of connectivity with distant brain regions is in agreement with previous modeling (Alstott et al., 2009) and empirical studies (Carter et al., 2010; Gratton et al., 2012), suggesting a particular vulnerability of functional interactions which are conveyed by indirect structural connections (van den Heuvel and Hulshoff Pol, 2010; Hermundstad et al., 2013). Local cortical or subcortical damage may thus have widespread consequences on functional interactions between relatively distant brain regions. This principle provides a possible solution to controversies surrounding the anatomy of behavioral symptoms after stroke, in particular the contribution of preserved right-hemispheric cortex and areas of the undamaged left hemisphere, to spatial dyslexia or visual search deficits.

Our observation that cross-hemisphere changes of FC predict reading deficits is of direct relevance to the possible contribution of dorsal and ventral pathways to spatial reference frames used in reading. Spatial dyslexia is a reading disorder that is characterized by perceptual or attentional impairments, whereas phonological and semantic processes are intact (Ellis et al., 1987; Vallar et al., 2010). The defining feature of spatial dyslexia is an object-centered deficit (i.e., reading errors are determined by a reference frame centered on the word) that gives rise to lateralized omissions and substitutions (Hillis and Caramazza, 1995). Some previous lesion studies have shown that such object-centered failures reflect damage to superior or inferior parietal cortex (Ptak et al., 2012; Pedrazzini et al., 2017), whereas others pointed to more ventral regions, such as the lateral occipital or inferior temporal cortex (Lee et al., 2009; Medina et al., 2009). The present study indicates that, even if the Fus is nearly unaffected by stroke (only ~6% of the Fus-ROI was damaged in the present study), its connectivity with the language-dominant left hemisphere is determinant for the occurrence of spatial dyslexia. We observed two patterns of FC changes that appear to be critical for spatial reading deficits. On the one hand, we found decreased connectivity between right inferior occipitotemporal cortex and the left Fus, a region known to play a central role in peripheral reading processes. Damage to the left Fus results in pure alexia, a disorder whose main characteristic is a letter-by-letter reading strategy (Gaillard et al., 2006; Pflugshaupt et al., 2009; Di Pietro et al., 2012). Decreased FC between left fusiform and right occipitotemporal cortex may therefore reflect the functional isolation of the right hemisphere from left-hemisphere areas that are essential for the visual and phonological aspects of reading. On the other hand, patients with spatial dyslexia had increased connectivity between the left and right Fus and more anterior temporal and insular cortex of the language-dominant hemisphere. This might be a
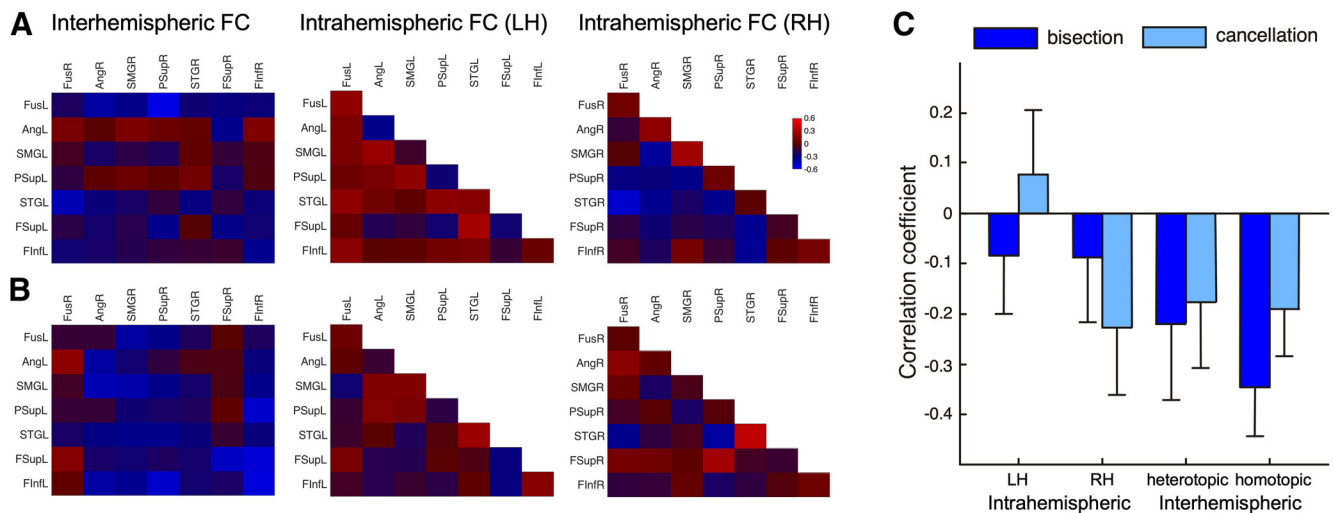
Figure 8. ROI-to-ROI–based analyses of connectivity-behavior relationships for homotopic, heterotopic, and intrahemispheric region pairs. ***A***, Correlation between FC and the line bisection task. ***B***, Correlation between FC and the number of missed left cancellation targets. ***C***, Average connectivity in the line bisection and cancellation tasks for intrahemispheric and interhemispheric ROI pairs.

compensatory adaptation, possibly reflecting increased recruitment of areas necessary for the interpretation of the degraded textual information.

In contrast to the FC increases observed in the reading task, the connectivity analyses of line bisection and cancellation revealed a negative association between connectivity and degree of deficit. Thus, negative FC between the right Fus and the left superior occipital cortex predicted line bisection bias. Several previous studies have observed a positive association between line bisection and reading, suggesting that both tasks may share common object-centered reference frames (Azouvi et al., 2002; Lee et al., 2009; Pedrazzini et al., 2017). This association might particularly engage the right Fus, which emerged as significant seed in the present study, both for reading and line bisection. However, while a connection between the right and left inferior temporal cortex was of significance for reading, FC with dorsal occipital cortex is more compatible with recruitment of processes necessary for stimulus-based spatial judgment in the line bisection task (Fink et al., 1997; Rorden et al., 2006). Thus, although the right Fus might mediate object-centered processing for reading and line bisection, its connections with distinct left-hemispheric regions differentiate between the two tasks.

Contrasting with the two stimulus-centered tasks, FC predictors of cancellation involved the right and left SMG, a region lying at the right temporoparietal junction that was previously identified by anatomic studies as crucial for the occurrence of spatial exploration deficits (Golay et al., 2008; Chechlacz et al., 2012; Molenberghs et al., 2012; Pedrazzini and Ptak, 2020). These analyses identified two interesting interactions: impaired performance was associated with decreased FC between the right SMG and its left homotopic region as well as decreased FC between the left SMG and the right insula. A decrease of interhemispheric FC between both SMGs has been observed previously (He et al., 2007) and is in line with the classic proposal that spatial neglect reflects a lack of balance between attention resources of both hemispheres. This hypothesis is based on the assumption that awareness is biased rightward in neglect because of the stronger allocation of attention to right space by the left hemisphere than to left space by the right hemisphere (Kinsbourne, 1993; Koch et al., 2008, 2011; Szczepanski et al., 2010). However, while previous studies related this attentional imbalance to

impaired interhemispheric FC between superior parietal cortices (He et al., 2007; Baldassarre et al., 2014; Ramsey et al., 2016), none of our regression or group-based analyses implicated specifically this region. Our patient group as a whole showed decreased interhemispheric FC between all ROIs, not only the superior parietal cortex. One possible reason for this discrepancy is our focus on postacute patients, who exhibit less specific alterations of FC between dorsal parietal regions than patients in early phases of disease (Corbetta et al., 2005). Alternatively, the differences in findings may reflect different definitions of neglect: as a clinical syndrome defined by combined deficits in visual search, spatial extinction, and activities of daily life (Corbetta et al., 2005), or as independent cutoff performance in reading, line bisection, or cancellation. Since these different spatial tasks engage discrete cognitive processes, neglect defined in the latter way may reflect engagement of distinct brain regions.

Studying FC-behavior relationships in stroke patients may provide complementary information that helps to confirm or clarify some findings of previous VLSM or DTI studies. One such finding is our observation of decreased connectivity between the left SMG and the right insula, a region whose contribution to spatial attention and stimulus selection is currently under debate. Some authors have proposed that this region acts as a "switch" that biases or interrupts ongoing cortical activity to redirect attention toward stimuli that threaten homeostasis (Menon and Uddin, 2010; Uddin, 2015). Although lesion evidence supports a specialization of the insula for bodily awareness rather than attention for external stimuli (Jones et al., 2010; Pedrazzini and Ptak, 2019), some studies noted that insular damage might contribute to spatial neglect (Golay et al., 2008; Molenberghs et al., 2012). The fact that the present study only found involvement of the right insula when cancellation performance was measured suggests a specific contribution of this region to spatial exploration, but not to object-based measures, such as reading or line bisection. Another important finding of previous studies is the importance of transcallosal connections for the recovery of spatial neglect (Lunven et al., 2015) and the effectiveness of inhibitory contralesional stimulation to alleviate this disorder (Nyffeler et al., 2019). These observations are complemented by our finding that greater impairment in line

bisection and cancellation is associated with decreased cross-hemispheric FC, supporting the importance of interhemispheric cooperation in spatial cognition tasks.

In conclusion, our study indicates that cortical regions well outside the area of damage may contribute to deficits of spatial cognition. FC predictors were specific for each of the three tasks examined (reading, line bisection, and cancellation), supporting the assumption that interregional connectivity reflects distinct cognitive processes recruited during behavioral performance. These findings indicate that, similarly to direct tissue damage, functional adaptations distant from the lesion site are important predictors of deficit after stroke. Thus, the study of functional networks complements lesion mapping and DTI in the effort to acquire a deeper understanding of impaired spatial cognition after focal brain injury.

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