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Resting Inter-hemispheric fMRI Connectivity Predicts Performance after Stroke

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Abstract

Objective—Focal brain lesions can have important remote effects on the function of distant brain regions. The resulting network dysfunction may contribute significantly to behavioral deficits observed after stroke. This study investigates the behavioral significance of changes in the coherence of spontaneous activity in distributed networks after stroke by measuring resting state functional connectivity (FC) using functional MRI.

Methods—In acute stroke patients we measured FC in a dorsal attention and an arm somatomotor network, and determined the correlation of FC with performance (behavioral correlation) obtained in a separate session on tests of attention (n=23) and motor function (n=16). In particular we compared the behavioral correlation with intra-hemispheric FC to the behavioral correlation with inter-hemispheric FC.

Results—In the attention network disruption of inter-hemispheric FC was significantly correlated with abnormal detection of visual stimuli (Pearson's r with Field Effect = −0.624, p =0.002). In the somatomotor network disruption of inter-hemispheric FC was significantly

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Author ContributionsA.R.C. performed the analysis of most imaging data (BOLD functional connectivity analysis and stroke lesion segmentation analysis), imaging-behavior correlations, statistical analysis, assisted in the recruitment and scanning of subjects and wrote the paper. S.V.A. assisted in the scanning of subjects, image analysis, ROI creation, encoding of behavioral data, and developed the composite functional connectivity scores. C.E.L. contributed to the experimental design and development of an appropriate battery for testing motor behavior. L.T.C. contributed to the experimental design, behavioral battery and helped with the statistical analysis. J.R. recruited and consented patients, assisted in the scanning, administered the behavioral battery and analyzed the behavioral data. M.J.S. instructed the authors in statistical methods for comparing non-independent correlations. D.L.P. assisted in scanning and behavioral testing. G.L.S. and M.C. designed the study, oversaw data acquisition and analysis, and were principal editors of the paper. All authors discussed the results and commented on the paper.

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correlated with upper extremity impairment (Pearson's r with contralesional ARAT = 0.527, p = 0.036). In contrast, intra-hemispheric FC within the normal or damaged hemispheres, was not correlated with performance in either network. Quantitative lesion analysis demonstrated that our results could not be explained by structural damage alone.

Interpretation—These results suggest that lesions cause 'state' changes in the spontaneous functional architecture of the brain, and constrain behavioral output. Clinically, these results validate using FC for assessing the health of brain networks, with implications for prognosis and recovery from stroke, and underscore the importance of inter-hemispheric interactions.

Keywords

stroke; networks; attention; motor; connectivity; fMRI

Introduction

Recent developments in neuroscience emphasize the fundamental role of widely distributed neural networks for the control of behavior[1–3]. A network perspective suggests that physiological effects of brain injury are best assessed over entire networks rather than just locally at the site of structural damage[4–6]. However, it is entirely unknown what patterns of interaction within a network are most closely associated with behavioral deficits after injury. Here we compare the behavioral significance of intra-hemispheric vs. inter-hemispheric interactions. Various observations point to the importance of inter-hemispheric interactions. Inhibitory influences from the undamaged hemisphere onto the damaged hemisphere are decreased during motor recovery[7]. Moreover, following damage to right hemisphere-dominant neural systems that result in spatial neglect, activation of left and right parietal regions is unbalanced and inter-hemispheric functional connectivity in parietal cortex is decreased [8, 9].

Resting state functional connectivity (FC) magnetic resonance imaging [10] measures within a subject the temporal correlation of the blood oxygenation level dependent (BOLD) signal across regions without any imposed task, providing a measure of temporal coherence between brain regions. Recent studies indicate that functional networks identified from resting FC measurements strongly overlap with networks activated by task performance[11], and that spontaneous activity correlates with trial-to-trial fluctuations of task-evoked responses[12] and behavior[13, 14]. An initial report from our group showed that disruption of functional connectivity between structurally normal left and right posterior parietal regions correlates with the degree of spatial neglect in stroke patients [9].

To identify patterns of functional connectivity that are behaviorally significant following stroke, we measured FC at rest in patients with a first ever stroke and separately conducted behavioral measurements of spatial attention and arm function. We correlated subjects' level of impairment on different behavioral measures with the strength of FC in brain networks for attention and motor function previously defined in healthy controls. The results highlighted the critical behavioral significance of inter-hemispheric connectivity between homologous regions of a task-relevant network. Surprisingly, intra-hemispheric connectivity, even within the damaged hemisphere, showed much less relationship with behavioral performance.

Materials and Methods

Subjects

Twenty-three first time stroke patients (mean age 59.6 +/− 13 years (+/− s.d.), 12 women, 22 right-handed; Table 1) and 11 healthy controls were enrolled. Candidates were identified through daily monitoring of the stroke inpatient service at Barnes-Jewish hospital (BJH), and the Rehabilitation Institute of St. Louis (RISTL). Initial inclusion criteria of a first ever right hemispheric ischemic stroke with hemispatial neglect were broadened after recruitment of 8 subjects to include subjects with a first ever stroke in any distribution irrespective of neglect (n=15). The two groups were pooled. The remaining inclusion criteria remained unchanged throughout the study: a) age: over 18; b) four weeks or less since the time of infarct. Exclusion criteria were: a) prior strokes except for clinically silent lacunes (up to 2, each not greater than 15 mm), b) evidence of periventricular white matter disease grade 3 on the classification of de Groot et al[15] (corresponding to = or >grade 5 of Longstreth et al[16]), c) dementia, defined as a score greater than 13 on the Short Blessed scale, d) other medical conditions preventing survival for 12 months e) schizophrenia, bipolar, obsessive-compulsive, personality disorders and major depression.. All 23 subjects completed the attention task and 16 completed the motor battery. Resting state FC maps for the dorsal attention and motor networks were also calculated for 11 healthy individuals. All subjects provided informed consent according to Washington University Institutional Review Board guidelines and were compensated.

Behavioral Testing

Subjects underwent behavioral tests outside of the scanner. Spatial attention was evaluated using a computerized Posner Task[17], and reaction times (RT) and accuracy were recorded. Motor ability was measured by evaluating active range of motion at the wrist[18], grip strength[19], performance on the Action Research Arm Test (ARAT) [20], speed on the Nine Hole Peg Test (NHPT) [21] in pegs/sec, gait speed[22] and the Functional Independence Measurement – Walk Item[23] (See Supplementary Materials for additional details).

Resting State BOLD fMRI and Structural Scanning

A Siemens 3.0 Tesla Allegra MRI scanner was used. During resting-state BOLD fMRI scans, subjects were instructed to maintain fixation on a central cross projected onto a screen at the head of the magnet bore by a Sharp LCD projector (“Keep your eyes open, look at the cross”). Eye opening and wakefulness were confirmed by infrared camera. Participants viewed the stimuli through a mirror attached to the head coil. A gradient echo echo-planar sequence was used (TE = 25 ms, flip angle = 90°, 4×4×4 mm voxels, volume TR = 2.06 s) sensitive to blood oxygenation level-dependent (BOLD) contrast. Each BOLD fMRI scan consisted of 128 frames. As the TR was 2.06 seconds, each scan lasted 128 × 2.06 = 4.4 minutes. Six to eight resting scans were obtained for each subject. Whole brain coverage was obtained with 32 contiguous slices. Structural images for atlas transformation and lesion segmentation were acquired using a T1-weighted MP-RAGE (1×1×1.25 mm voxels; TE=3.93ms, TR=1810ms, TI=1200ms, flip angle=12 deg) and T2-weighted fast spin echo sequence (1.1×1.1×3.0 mm voxels; TE=96ms, TR=8430ms).

Atlas Transformation—A target atlas based on T1 weighted images from 12 healthy controls was generated (see Supplementary Methods).

Preprocessing of resting fMRI time-series data—The preprocessing sequence has been described in detail in our prior publications[9, 24] (see Supplementary Methods).

Definition of networks (ROIs)—Core regions for the somatomotor and attention networks were identified based on previous event-related fMRI studies. Those regions then served as seeds to generate voxel-wise FC maps (see Supplementary Methods, Supplementary Figure 1).

Voxel-wise correlation maps from a single seed ROI and ROI-to-ROI connectivity values—To compute FC maps corresponding to a selected seed ROI, the regional time course was correlated against all other voxels within the brain. To compute connectivity values between two ROIs for a subject, Pearson correlation coefficients (r) for region pairs were calculated and the Fisher z transform was applied to yield measures that are approximately normally distributed.

Lesion segmentation—Using T1-weighted MP-RAGE and T2-weighted spin echo images, lesion boundaries were determined with the aid of an unsupervised fuzzy class means based segmentation procedure. Voxels were classified into air, CSF, gray matter and white matter. Expert judgment was required to definitively determine the lesion CSF replacement of parenchyma boundaries.

Data Analysis

Definition of terms—The connectivity score for an ROI pair (e.g. between left and right frontal eye fields (FEF)) is the Fisher z-score that is computed from the correlation coefficient for the temporal correlation between the two ROIs. The average connectivity score for a group of ROI pairs is the average of the component Fisher z-scores for the corresponding ROI pairs. We report five kinds of average functional connectivity scores including homologous inter-hemispheric FC, heterologous inter-hemispheric FC, ipsilesional intra-hemispheric FC, contralesional intra-hemispheric FC, and across network FC (see Supplementary Methods for detailed definitions)

Statistical analysis of FC scores—Average connectivity scores were analyzed by repeated measures ANOVA according to connectivity pattern (homologous, heterologous, ipsilesional, contralesional) followed by pair-wise comparisons.

Results

Resting-state functional connectivity identifies specific networks

FC maps of the dorsal attention and somatomotor networks in 11 healthy control subjects are shown in Fig 1A and Fig 1B respectively, (full maps presented in Supplementary Figure 2). The average resting-state FC scores (Fig 1C) between regions belonging to the same network were much greater than the baseline connectivity (FC = 0.016) between regions belonging to different networks ($F(3, 30) = 145.85$, $p < 0.001$). Post-hoc comparisons with paired t-tests indicated a significant difference between each FC score within a network and the FC score across networks ($p < 0.001$).

To determine if behavior was correlated with FC after stroke, stroke patients were scored on tests of spatial attention and arm/hand motor function, and BOLD resting-state scans were obtained to determine FC measures. Patients' characteristics are listed in Table 1 and Table 2.

FC-behavior correlations in the dorsal attention network

Patients with visual neglect after stroke show impaired detection of stimuli in the contralesional visual field, a phenomenon we call the Field Effect. Based on our prior work[9] we first determined if resting inter-hemispheric connectivity between homologous regions of

the dorsal attention network (e.g. left and right posterior IPS) were predictive of the Field Effect. Decreased FC was associated with longer reaction times (RT) and more misses for contralesional than ipsilesional targets (negative correlation in Fig 2A). This FC-behavior correlation was strong for pIPS (Fig 2B) but was also present throughout the network (Supplementary Table 1). Statistical comparison revealed no difference in the strength of these FC-behavior correlations for either Field Effect RT (Chi-square = 3.97, p = 0.26, n = 22) or Field Effect accuracy (Chi-square = 3.10, p = 0.38, n = 23). This analysis replicated and extended our prior work by showing that an imbalance in inter-hemispheric coherence in regions involved in the control of spatial attention, measured at rest, correlates with spatial attention deficits. Interestingly, this relationship generalizes across the whole network.

To further investigate network-wide FC, four topographic patterns of FC were calculated: inter-hemispheric homologous, inter-hemispheric heterologous, intra-hemispheric ipsilesional and intra-hemispheric contralesional FC (Fig 3A; see Supplementary Methods for definitions). A repeated measures ANOVA including these four scores and a fifth score of across-network connectivity to control for non-specific correlations revealed a significant within group difference ($F(4,88) = 61.18$, $p < 0.001$, n=23). Post-hoc pairwise t-tests confirmed that homologous FC was greater than ipsilesional ($t(22) = 5.99$, $p < 0.001$), contralesional ($t(22) = 4.20$, $p < 0.001$) or heterologous ($t(22) = 9.89$, $p < 0.001$) FC. Each within-network FC score (e.g. contralesional FC) was greater than across network FC (each at $p < 0.001$).

Next, we asked if any of these network-wide patterns of functional connectivity were predictive of spatial attention deficits. Strikingly, inter-hemispheric homologous FC proved a much more powerful predictor of behavioral deficits following stroke than did FC within either hemisphere. A significant negative correlation was observed between homologous FC and the Field Effect (RT: $r = -0.624$, $p = 0.002$; % miss: $r = -0.491$, $p = 0.017$; Fig 3B, and Fig 3C upper panel) and between heterologous FC and the Field Effect RT ($r = -0.510$, $p = 0.015$). However, no correlation between ipsilesional (Fig 3C, lower panel) or contralesional FC and the Field Effect was observed. Statistical comparison of FC-Field Effect RT correlations confirmed a significant within-group difference among pattern of FC (Chi-Square = 14.33, p = 0.0025). Post-hoc pairwise comparisons demonstrated that behavioral correlation with homologous FC was significantly greater than with ipsilesional FC (Chi-Square = 4.04, p = 0.044). These findings indicate that inter-hemispheric FC is of particular behavioral importance in the dorsal attention network.

FC-behavior correlations in the arm somatomotor network

To determine if these results generalized to other networks, we studied the somatomotor network for arm control. We first determined if resting inter-hemispheric connectivity between homologous regions of the somatomotor network was predictive of arm function. A significant correlation was observed between left-right CS FC and multiple measures of arm performance (Fig 4). Using performance on the ARA test as a representative example, FC-behavior correlations were variable among the six ROI pairs (L-R CS: $r = 0.598$, $p = 0.014$; L-R Put: $r = 0.423$, $p = 0.103$; L-R S2: $r = 0.352$, $p = 0.181$; L-R Thal: $r = 0.187$, $p = 0.488$; L-R SMA: $r = 0.160$, $p = 0.553$; L-R CB: $r = -0.008$, $p = 0.977$). However, statistical comparison of these FC-behavior correlations revealed no significant within group difference among these homolgous ROI pairs (Chi-Square = 4.86, p = 0.43).

To further investigate network-wide FC in the somatomotor network, the same four measures of network resting connectivity previously described (homologous, heterologous, ipsilesional and contralesional FC) were calculated (Fig 5A). Across network FC served again as a baseline. A repeated measures ANOVA revealed a significant within group

difference ($F(4,88) = 118.81$, $p < 0.001$, n = 23). Post-hoc paired t-tests showed that homologous FC was again greater than ipsilesional ($t(22) = 14.11$, $p < 0.001$), contralesional ($t(22) = 7.55$, $p < .001$) or heterologous FC ($t(22) = 14.82$, $p < 0.001$). Ipsilesional FC was also significantly decreased compared to contralesional FC ($t(22) = -4.91$, $p < 0.001$). Again, each of the four within network FC scores was significantly greater than across network FC ($p < 0.001$ for each comparison).

Next, we asked if any of these network-wide patterns of functional connectivity were predictive of arm function. As in the dorsal attention network, inter-hemispheric homologous FC in the arm network predicted performance following stroke (e.g. for ARAT Pearson r = 0.527, p = 0.036). No significant behavioral correlation was observed with heterologous, ipsilesional, or contralesional FC (Fig 5B, and Supplementary Table 2). Statistical comparison of FC-ARAT correlations indicated that correlation with homologous FC was greater than that with heterologous (Chi-Square = 5.08; p = 0.024) or contralesional (Chi-Square = 6.41; p = 0.011) FC. The difference with ipsilesional connectivity was marginal (Chi-Square = 3.71, p = 0.054).

Specificity of FC-behavior correlations

Whereas homologous FC in the attention network was highly correlated with Field Effect RT (r = −0.624, p = 0.002), homologous FC in the somatomotor network was not (r = −0.35, p = 0.11, Fig 6). In contrast, homologous FC in the attention network was as predictive of motor performance (for total ARAT: Pearson r = 0.55, $p < 0.05$) as homologous FC in the somatomotor network (Pearson r = 0.53, $p < 0.05$)(Fig 6).

Analysis of connectivity-behavior correlations for a measure of lower extremity function, the FIM-walk item, supported this difference in specificity between the attention and somatomotor networks. The FC-behavior correlation for FIM-walk was high with attention-homologous FC (Pearson r = 0.81, $p < 0.01$) but low with motor-homologous FC (Pearson r = 0.08, Fig 6). Statistical comparison confirmed a significant difference (Chi-Square = 7.74, $p < 0.01$). These results are consistent with the central role that attention plays in human behavior and suggest that our somatomotor network was specific to arm-related behaviors.

Impact of ROI damage and size on FC-behavior correlations

A quantitative analysis of stroke lesion distribution (Fig 7A) and ROI damage in our stroke population revealed that the main areas affected were left putamen, left S2 and left thalamus (Fig 7B). Only a very small percentage of the voxels defining the ROIs for each network was damaged (0.28% in the dorsal attention network, and 2.16% in the somatomotor network). Critically, strong and significant correlation between homologous interhemispheric connectivity and behavior occurred in regions that showed no structural damage (e.g. in attention network: pIPS and vIPS in Fig 2A, and in somatomotor network: CS in Fig 4). Finally, the observed FC-behavior correlations remained even when data from damaged motor ROIs were excluded from the analysis (Supplementary Table 3). Therefore, ROI damage cannot account for the observed FC-behavior correlations.

Asymmetry in ROI size in the left versus right hemisphere may represent another source of bias as our ROIs were determined by activation studies (see definition of network ROIs in Supplementary methods). To investigate the effects of asymmetric ROI size we recalculated a portion of our analysis for select ROIs in the dorsal attention network and all ROIs in the somatomotor network that showed more variability in size between the left and the right hemisphere. They were replaced with spherical ROIs of the same size in each hemispheres. This procedure had no effect on measured FC scores (Supplementary Figure 3). In the dorsal attention network, FC-behavior correlations between L-R pIPS FC and Field Effect RT

remained significant ($r = -0.443$, $p = 0.039$) but correlation with Field Effect % miss did not ($r = -0.344$, $p = 0.108$). In the somatomotor network, FC-behavior correlations between homologous, ipsilesional, or contralesional FC and measures of arm function were unchanged (Fig 8, compare with Fig 5B). Overall, our main findings were resistant to changes in ROI size and symmetry.

Discussion

This is the first study to demonstrate that following stroke, the loss of coherence in spontaneous BOLD fluctuations in different functional networks at rest predicts behavioral deficits. Loss of *inter-hemispheric* functional connectivity between homologous regions of the dorsal attention network correlated with deficits in the detection of contralesional targets. This result generalized to the motor system, where loss of *inter-hemispheric* resting connectivity in an arm-defined somatomotor network correlated with measures of upper extremity function.

Network specificity in relation to behavior

The behavioral significance of resting FC reflected the involvement of neural networks in specific behavioral domains. The breakdown of somatomotor inter-hemispheric FC was significantly correlated with measures of motor performance but not with measures of attention. In addition, connectivity changes in our arm-defined network correlated with arm/hand function measures but not with the two walking measures. In the dorsal attention network, the breakdown of inter-hemispheric functional connectivity correlated with difficulty in detecting targets in the contralesional visual field, characteristic of spatial neglect[25]. However, connectivity scores in the dorsal attention network also correlated with measures of upper extremity (ARA) and walking function (FIM walk). Physiological studies indicate that the dorsal attention network is important not only for stimulus selection, but also for selection of limb responses[26, 27] especially early after injury[28]. Therefore, the broader behavioral significance of the dorsal network corresponded to its involvement in a larger range of behavioral functions.

Inter-hemispheric functional connectivity in relation to behavior

A striking finding was that resting-state FC scores between the two hemispheres, specifically between homologous regions, were the best predictor of behavioral performance. The special significance of inter-hemispheric interactions may reflect the importance of proper equilibrium between excitation and inhibition across hemispheres for optimal function[29, 30]. Inter-hemispheric competition, for example, has been postulated to underlie the balance of attention toward the left vs. right visual fields[31]. Physiologically, the locus of attention in cortical regions is coded by the relative rather than the absolute level of activity between attended and unattended cortical representations[32–34]. Accordingly, we have reported that an inter-hemispheric imbalance of task-driven responses is observed at the acute stage after stroke, and that this task-driven imbalance correlates with visual neglect[8]. Our current results extend these observations by showing that abnormalities of inter-hemispheric coherence of the spontaneous resting-state BOLD signal also correlate with spatial neglect.

Similarly, in the somatomotor system, normal inter-hemispheric coherence is quite important for normal function[7, 35]. A recent study using dynamic causal modeling of fMRI BOLD signal reported that subcortical strokes are associated with decrements in inter-hemispheric neuronal coupling at rest, increased inter-hemispheric inhibition onto affected M1 motor cortex during paretic hand movement, and decreased inter-hemispheric

facilitation during bilateral hand movement[36]. However, these findings do not preclude the behavioral significance of resting intrahemispheric connectivity between specific ROI pairs.

Lesions cause 'state' changes in spontaneous network activity that constrain behavioral output

The most important result in our study is that inter-hemispheric FC measured during resting wakefulness is related to behavioral output during a task. While traditional theories assume that behavior depends only on task-driven activity[37, 38], alternative views emphasize the importance of spontaneous activity as a mechanism for maintaining anticipatory signals related to prediction [39, 40], for synchronizing neural representations for stimulus and response coding[41] and for the emergence of spontaneous neuronal rhythms[42, 43]. There is also growing evidence for a direct relationship between slow spontaneous BOLD signal fluctuations and power in neuronal activity at both slow and fast frequencies[44–46].

Our results are consistent with the view that lesions modify the spontaneous coherence between regions that belong to a functional network, and presumably between different related functional networks. This change in baseline communication may affect the way these regions are recruited and communicate during active behavior. A recent study by Lewis et al. shows that in healthy subjects the ability to learn a novel task is associated with task-specific changes in both resting functional connectivity and evoked activity and provides more direct proof for a relationship between spontaneous coherence, task-evoked activity and function[47].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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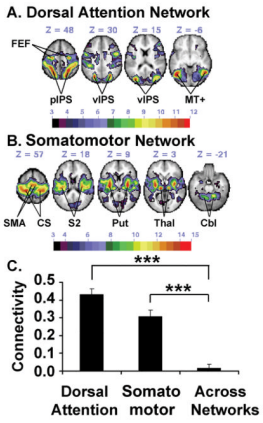

Figure 1. Dorsal attention and somatomotor networks identified by resting state functional connectivity MRI

(A and B) Selected sections of the functional connectivity map for the (A) dorsal attention network and (B) the somatomotor network that highlight the nodes in each network in healthy controls. The full map is presented in Supplementary Figure 2. (C) One-way ANOVA with neuronal network as the within subjects factor, and FC score as the dependent variable, shows that the FC within networks was significantly greater than across networks ($F(3, 30) = 145.85$, $p < 0.001$), and post-hoc comparisons with paired t-tests indicated a significant difference between each score within a network and the FC score across networks ($p < 0.001$); pIPS = posterior intraparietal sulcus; vIPS = ventral intraparietal sulcus; FEF = frontal eye field; MT+ = middle temporal complex; CS = central sulcus; SMA = supplemental motor area; Put = putamen; Thal = thalamus; Cbl = cerebellum; error bars are S.E.M.; *** = $p < 0.001$.

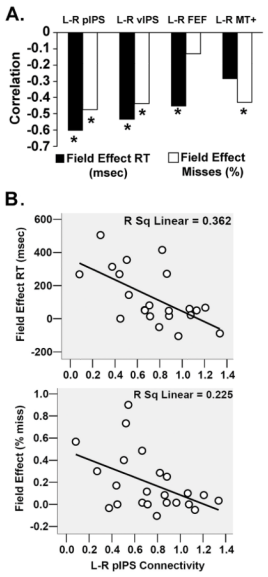

Figure 2. Correlation between the Field Effect and FC scores in four homologous ROI pairs in the dorsal attention network

A) Significant correlation between the Field Effect and most homologous pairs in the dorsal attention network was observed. A significant Field Effect reflects an increase in reaction times (RTs) and increase in % misses when targets are presented to the contralesional side as compared to when they are presented to the ipsilesional side. B) A negative correlation between left-right resting connectivity in the posterior intraparietal sulcus and Field Effect indicates that as FC decreases, the amplitude of the Field Effect RT (left panel) and percent misses (right panel) increases. pIPS = posterior intraparietal sulcus; vIPS = ventral intraparietal sulcus; FEF = frontal eye fields; MT+ = middle temporal complex; L =left; R =right; RT = reaction time; * = $p < 0.05$.

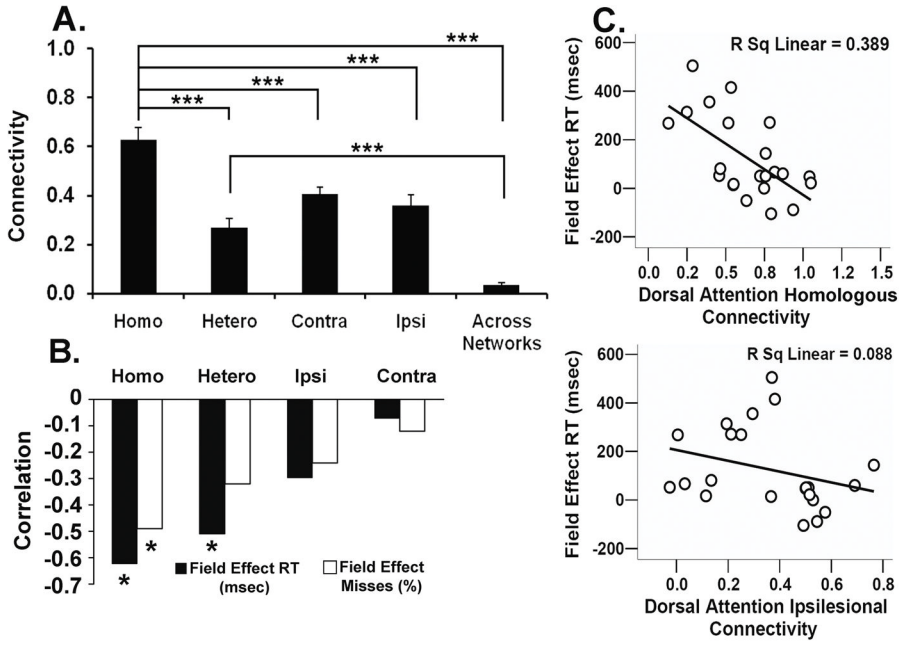

Figure 3. Inter-hemispheric connectivity in the dorsal attention network predicts attentional deficits

A) Strength of resting connectivity scores for four patterns of connectivity in the dorsal attention network. Repeated measures ANOVA followed by multiple paired t-test shows that homologous resting connectivity is greater than other connectivity patterns. B) The Field Effect RT and % misses are significantly correlated with homologous FC scores but not with ipsilesional or contralesional FC scores. C) Scatter plots demonstrate that this correlation is specific to inter-hemispheric (upper panel) and not intra-hemispheric (lower panel) connectivity. pIPS = posterior intraparietal sulcus; vIPS = ventral intraparietal sulcus; FEF = frontal eye field; MT+ = middle temporal complex; homo = homologous; hetero = heterologous; ipsi = ipsilesional; contra = contralesional; RT =reaction time; * = $p < 0.05$; *** = $p < 0.001$.

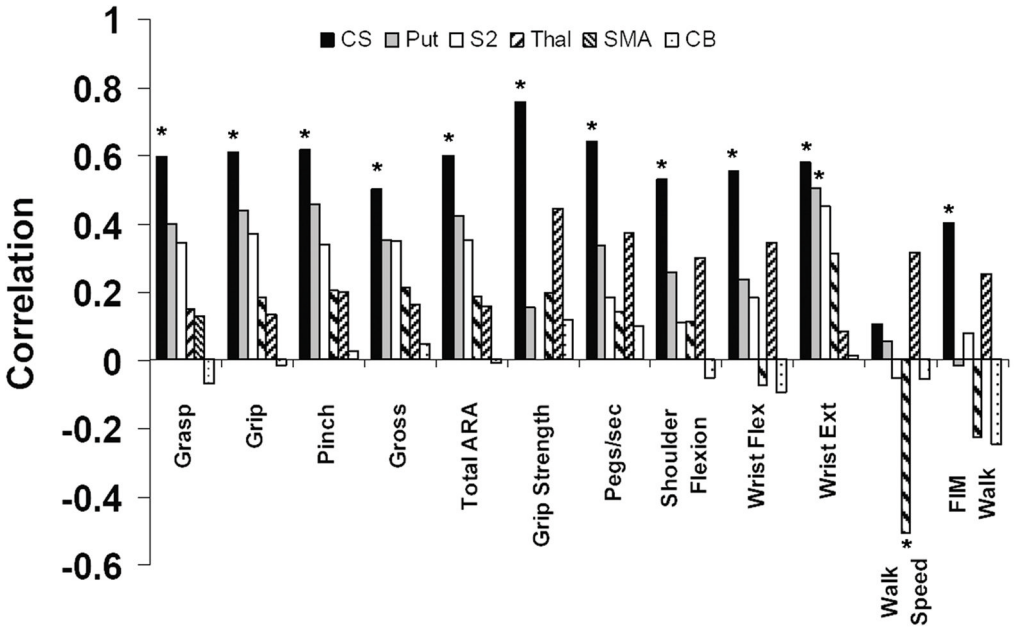

Figure 4. Correlation between motor function and resting connectivity in the six homologous ROI pairs in the somatomotor network

Grasp, Grip, Pinch, and Gross are all subtests of the action research arm test (ARA test). Pegs/sec = performance measure on nine hole peg test; FIM = Functional Independence Measure; flex = flexion; ext = extension; CS = central sulcus; Put = putamen; Thal = thalamus; SMA = supplementary motor area; CB = cerebellum; * = $p < 0.05$.

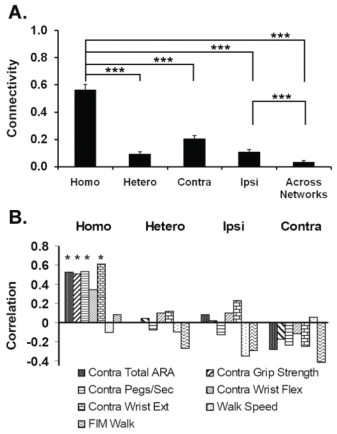

Figure 5. Homolgous inter-hemispheric FC in the somatomotor network predicts arm performance

A) Strength of resting connectivity scores for four patterns of connectivity in the arm somatomotor network. Repeated measures ANOVA followed by multiple paired t-tests shows that homologous resting connectivity is greater than other connectivity patterns. B) Four out of five measures of arm function are significantly correlated specifically with homologous FC scores. Neither of the two measures of leg function is significantly correlated. Homo = homologous connectivity; hetero = heterologous connectivity; contra = contralesional connectivity; ipsi = ipsilesional connectivity. ARA = action research arm test; FIM = functional independence measure; Flex = flexion; Ext = extension; contra = Contralesional; * = $p < 0.05$; *** = $p < 0.001$.

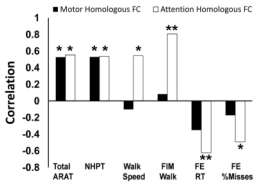

Figure 6. Differential specificity of FC-behavior correlations in the somatomotor network compared to the attention network

Homologous FC scores in the somatomotor network are correlated with measures of hand function (total ARAT score, 9 Hole Peg Test (NHPT)), but not with measures of leg function (walking speed, FIM walk), nor with measures of visuo-spatial attention (FE RT, FE % misses). Homologous FC scores in the dorsal attention network on the other hand are significantly correlated with all the measures shown. ARA = action research arm test; FIM Walk = Functional Independence Measure walk item; NHPT = nine hole peg test; FE = Field Effect; RT = reaction time; * = $p < 0.05$; ** = $p < 0.01$.

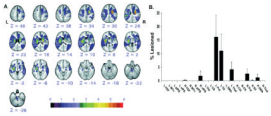

Figure 7. Lesion distribution and ROI damage

A) Distribution of stroke lesions in 22 subjects. Color scale indicates number of subjects with lesioned voxel. B) Percentage of the total voxels in each ROI lesioned by infarct. ROI labels are same as in Figure 1. L = left; R = right; n = 22; error bars = SEM.

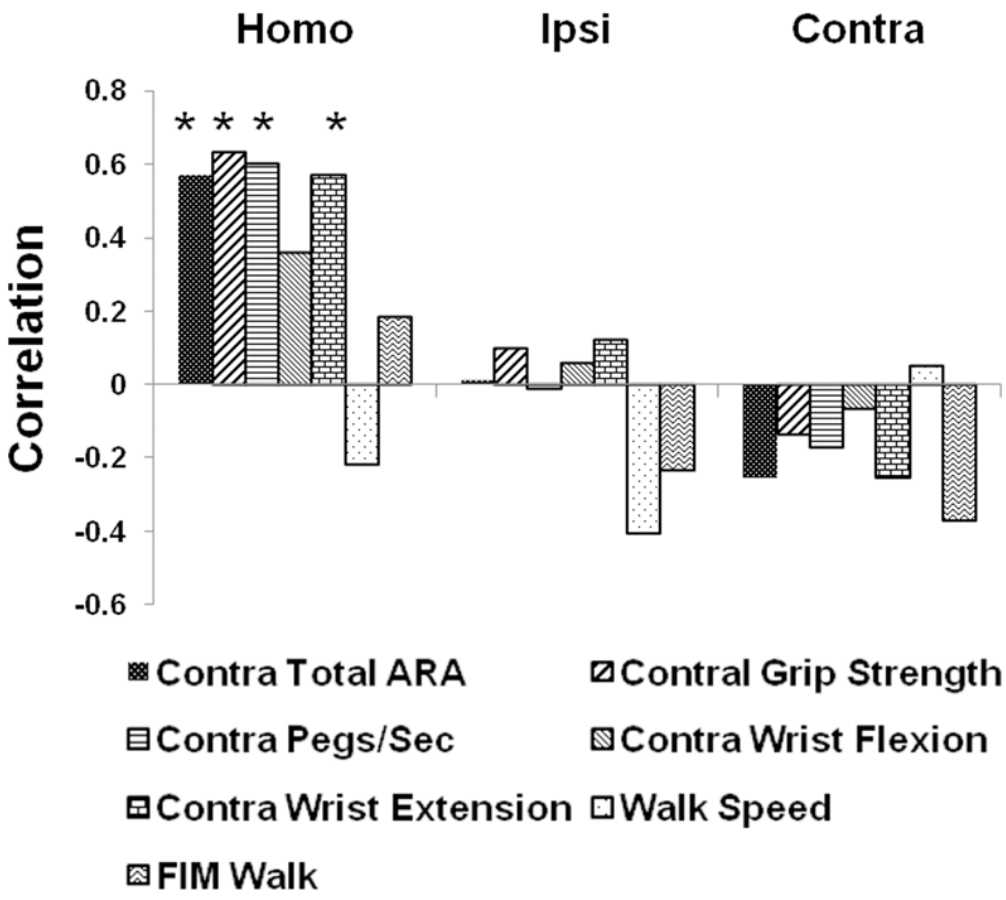

Figure 8. Effect of ROI size and asymmetry on FC-behavior correlations

Repeat analysis using spherical uniform ROIs did not affect FC-behavior correlations in the somatomotor network. Homologous intra-hemispheric FC remained predictive of scores on the ARA, Grip strength, 9 hole peg, and wrist extension tests. The two measures of leg function remained uncorrelated. Homo = homologous connectivity; hetero = heterologous connectivity; contra = contralesional connectivity; ipsi = ipsilesional connectivity. ARA = action research arm test; FIM = functional independence measure; Flex = flexion; Ext = extension; contra = Contralesional; * = $p < 0.05$.

Table 1

Demographic and clinical characteristics of the subjects in the stroke group

ID	Age	Sex	Handedness	Days since stroke	tPA	Type of lesion	Side of lesion	Lesion volume (voxels)	Main clinical symptoms	Initial NIHSS (normal = 0)
1	44	M	R	23	N	I	R	6831	Ne, HP	10
2	42	M	R	27	N	I	R	7115	Ne, HP	9
3	51	F	R	14	N	I	R	3178	Ne, HP	12
4	52	F	R	10	N	H	L	3702	HP	23
5	61	F	R	30	N	I	R	2103	Ne, HP, A	13
6	63	M	R	18	N	I	R	5264	Ne, HP	8
7	80	F	R	10	N	I	R	683	Ne, HP	9
8	51	F	R	12	N	I	R	344	Ne, HP	6
9	83	F	R	18	N	I	L	638	HP	11
10	82	F	R	29	N	I	L	*	A	3
11	57	M	R	25	N	H	R	290	Ne, HP	9
12	78	F	R	23	N	I	R	274	HP	9
13	52	F	R	10	N	H	L	3532	HP	9
14	56	M	R	31	Y	I	L	62	Ne, HP	6
15	45	M	R	12	N	I	L	5073	HP	3
16	48	M	R	13	N	I	L	2036	HP	8
17	58	M	R	20	N	I	R	2205	HP	15
18	54	M	R	14	N	I	R	208	HP	12
19	47	F	L	9	N	I	L	42	Ne, HP, A	1
20	57	M	R	27	N	H	L	12156	HP, A	29
21	75	M	R	10	N	I	L	198	Ne, HP	6
22	76	F	R	15	N	I	R	865	HP	14
23	58	F	R	11	N	H	L	403	HP	3
		11M/	**1LH/**		**1Y/**		**11L/**		**11Ne/3A/**	
Total	**-**	**12F**	**22RH**	**-**	**22N**	**18I/5H**	**12R**	**-**	**22HP**	**-**
Mean (SD)	**59.6 (13.0)**			**17.9 (7.5)**				**2600 (3099)**	**-**	**9.9 (6.3)**

n=23. M = male; F = female; L = left; R = right; Y = yes; N = no; I = ischemic; H = hemorrhagic; A= aphasia; HP = hemiparesis; Ne = neglect; NIHSS = NIH stroke scale; tPA = tissue plasminogen activator treatment; sd = standard deviation.

* In 1 patient with evidence of small areas of restricted diffusion on the MRI diffusion sequence but no abnormal signal on standard T1 or T2 sequences, lesion volume could not be quantified.

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Table 2

Behavioral characteristics of the subjects in the stroke group

ID	Posner Field Effect RT (msec)	Posner Field Effect % Misses	Total ARAT	Grip strength (kg)	9 hole peg test (Pegs/s)	FIM Walk
1	313.5	−3%	.	.	.	.
2	504.5	30%	.	.	.	.
3	52.3	49%	.	.	.	.
4	414.9	29%	.	.	.	.
5	355.3	40%	.	.	.	.
6	270.9	8%	.	.	.	.
7	143.5	73%	54	8	0.08	4
8	66.6	8%	.	.	.	.
9	50.3	−5%	0	0	0	4
10	16.9	25%	57	15	0.23	5
11	80.7	12%	38	18	0.13	5
12	−50.8	−11%	38	6	0.11	3
13	59.8	10%	10	2	0	4
14	−88.7	3%	57	38	0.43	5
15	47.9	2%	57	42	0.32	7
16	50.2	2%	56	42	0.21	4
17	268.9	17%	3	0	0	3
18	−105.1	2%	40	12	0.08	4
19	−14.1	0%	56	30	0.29	4
20	.	90%	0	0	0	2
21	0.0	0%	41	27	0.06	4
22	267.9	57%	0	0	0	1
23	21.8	0%	57	13	0.26	7
Mean	**124.0**	**19%**	**35.3**	**15.8**	**0.14**	**4.1**
SD	**168.8**	**27%**	**23.9**	**15.4**	**0.14**	**1.5**
Normal	**3.66**	**0%**	**57**	**M 40.7**	**M 0.43**	**7**
				W 25.0	**W 0.50**	**7**

n=23 (one subject missed all the invalid targets in the neglected field and had no reaction time in the Posner task). 23 subjects underwent attention testing, 16 subjects underwent motor testing. RT = reaction time in msec; ARAT = action research arm test; FIM = functional independence measure; M = men; W = women; Field Effect = [(contralesional invalid + contralesional valid) (ipsilesional invalid + ipsilesional valid)]/2; sd = standard deviation.