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Normalization of network connectivity in hemi-spatial neglect recovery

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Abstract

Objective—We recently reported that spatial and non-spatial attention deficits in stroke patients with hemi-spatial neglect are correlated at 2 weeks post-onset with widespread alterations of inter-hemispheric and intra-hemispheric functional connectivity (FC) measured with resting state fMRI (R-fMRI) across multiple brain networks. The mechanisms underlying neglect recovery are largely unknown. In this study we test the hypothesis that recovery of hemi-spatial neglect correlates with a return of network connectivity toward a normal pattern, herein defined as ‘*network normalization*’.

Methods—We measured attention deficits with a neuropsychological battery, and FC in a large cohort of stroke patients at, on average, 2 weeks (n=99), 3 months (n=77), and 12 (n=64) months post onset. The relationship between behavioral improvement and changes in FC was analyzed both in terms of a priori regions and networks known to be abnormal sub-acutely, and in a data driven manner.

Results—Attention deficit recovery was mostly complete by 3 months, and was significantly correlated with a normalization of abnormal FC across many networks. Improvement of attention deficits, independent of initial severity, was correlated with improvements of previously depressed inter-hemispheric FC across attention, sensory, and motor networks, and a restoration of the normal anti-correlation between dorsal attention/motor regions and default-mode/frontoparietal regions, particularly in the damaged hemisphere.

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Author contributions

Study concept and design by MC, GS, R, AB. Data acquisition and analysis was done by LR, JS, AB, NM and KZ. The manuscript was written by LR, MC, GS.

Potential Conflicts of interest

None

Interpretation—These results demonstrate that abnormal network connectivity in hemi-spatial neglect is behaviorally relevant. A return toward normal network interactions, and presumably optimal information processing, is therefore a systems level mechanism that is associated with improvements of attention over time after focal injury.

Introduction

Hemi-spatial neglect is a syndrome affecting approximately 20–30% of stroke patients ^{1,2}. Recovery occurs mostly within the first three months post-stroke ^{1,3}. The amount of recovery depends on the severity of the acute deficit ⁴ and is incomplete in most cases ^{3,5}.

Anatomically, neglect can be caused by damage to multiple cortical and subcortical regions ^{5–7}. Neuroimaging studies have related more severe attention deficits in hemi-spatial neglect to a relative imbalance of task-evoked activity between the two hemispheres and a loss of inter-hemispheric correlations ^{6,8–11}, as well as damage to intra-hemispheric fronto-parietal connections ^{12,13}. These results support the idea that this syndrome is associated with widespread disruption of cortical activity ¹⁴, especially in networks related to attention that can manifest abnormal physiology even when structurally intact (reviewed in ¹¹).

In contrast, the mechanisms underlying neglect recovery are largely unknown. Hypothetical mechanisms of recovery include remapping, i.e. a shift of function to neighboring maps; normalization of activity, i.e. a return of the pre-stroke state of activity within/across regions; or reorganization, i.e. a compensatory shift of activity to different regions/networks. Different physiological correlates have been reported in small case series including: normalization of regional cerebral perfusion (¹⁵, n=8 patients); shift of activity back to the damaged hemisphere (¹⁶, n=3); rebalancing of stimulus-evoked activity between left and right hemisphere regions for attention and visual perception (⁸ n=11); normalization of depressed inter-hemispheric correlations in the dorsal (DAN) and ventral (VAN) attention networks (⁶, n=11). Importantly, a direct correlation with behavioral improvement was measured only in some studies ^{6,8,9}.

In a recent large study (¹⁰, n=84) we confirmed that attention deficits typical of neglect were strongly associated with widespread, multi-network disruption of inter-hemispheric functional connectivity (FC) measured with resting state (R-fMRI). In contrast to previous work⁶, we found that the disruption of inter-hemispheric FC did not involve only dorsal and ventral attention regions, but also extended to auditory, motor, and visual networks. In addition, we found that intra-hemispheric attention and motor regions became positively correlated with regions of the fronto-parietal (FPN) and default mode (DMN) networks, which are negatively correlated or uncorrelated in the intact brain. This pattern accounted for over 40% of the variance in behavior-to-FC correlation.

Based on ¹⁰, we hypothesized that recovery of neglect would be associated with a normalization of the abnormal patterns of network connectivity demonstrated at the sub-acute stage. Normalization of network connectivity, while not excluding other explanations, would be consistent with previous work showing normalization of task-evoked patterns of activation in motor, language, and attention regions ^{17,18}, and network theories suggesting

that the normal architecture of brain connections, structural and functional, is the best compromise between metabolic demands and computational efficiency¹⁹.

To test this hypothesis we examined neglect recovery in a large cohort of first time stroke individuals (n=77) with an extensive neuropsychological battery and multiple neuroimaging methods. We defined a behavioral measure of neglect that captured spatial and non-spatial impairments and assessed this measure at, on average, 1–2 weeks, 3, and 12 months post onset. We related behavioral recovery to FC changes in networks that have been found in our prior work to be associated with neglect¹⁰. Finally, we conducted a data-driven analysis across all brain regions to show that patterns related to recovery, accounting for large fractions of variance in the behavior-to-FC correlation, correspond to those found sub-acutely.

Methods

Participants

172 subjects were recruited. All participants provided informed consent with Washington University Institutional Review Board oversight. The inclusion criteria were (1) Clinical diagnosis of stroke; (2) Persistent stroke symptom(s) at hospital discharge; (3) Awake, alert, and able to complete study tasks; (4) Age 18 or older. Exclusion criteria were: (1) Previous stroke; (2) Multifocal stroke; (3) severe psychiatric condition; (4) Dementia; (5) other neurological disorder; (6) Brain injury; (7) Other diagnosis with a life expectancy less than 1 year; (8) Premorbid functional disability as measured by a Modified Rankin score of 2 or higher; (9) Claustrophobia; (10) Implanted metal precluding 3T MRI. 132 met the post-enrollment inclusion criteria (5 could not tolerate scanning, 8 had a bilateral lesion, 12 had no detectable lesion, 11 had incomplete data collection, and 4 for other reasons). Of these 132, 99 patients had a full set of neuro-imaging and attention battery measures collected. 77 of the 99 patients returned for their 3-month data collection and this set of 77 patients is used in the following analyses (Table 1). 64 of these patients were retested one-year post stroke. Twenty-two patients with attention and imaging data at the sub-acute stage did not return for their 3 month data collection and therefore were not included in the analyses. There was no difference in attention scores between the patients that did and did not return for their 3 month visit ($t(97)=-1.45, p=0.15$) or 1 year visit ($t(75)=0.05, p=0.96$).

Information about medications was recorded at the time of enrollment, but no attempt was made to control what medications subjects used in the course of the study.

The same behavioral and imaging measures were collected twice, 3 months apart, in 31 age- and education-matched controls.

Behavioral testing

Subjects were tested approximately two weeks after their stroke (sub-acute, $M=12.8$ days, $SD=4.49$), and again at 3 months ($M=111.1$, $SD=17.5$) and 12 months ($M=392$, $SD=52.6$). These time points were selected based on previous observations that sensory-motor deficits recover within 3 months, while cognitive deficits take longer up to 1 year. A comprehensive battery of behavioral tests was used to assess motor, memory, attention, language and visual

deficits (fully described in Corbetta et al ²⁰). Core deficits of hemi-spatial neglect were assessed by the Posner Visual Orienting Task ²¹ and two cancellation tasks, the Mesulam Unstructured Symbol Cancellation Test ²² and the Behavioral Inattention Test ²³. These tests were selected based on their high accuracy in detecting hemi-spatial neglect even at the chronic stage as reported in our previous study ²⁴ and are described in more detail in ¹⁰.

Measures of spatial attention

The Posner task yields 4 measures: (1) Overall Performance (performance averaged for stimuli in both visual fields and both cueing conditions); (2) Visual Field Bias (difference between ipsi- and contra-lesional targets); (3) Validity Effect (difference between valid and invalid targets); and, (4) Disengagement Effect (difference of validity effect between ipsi- and contra-lesional targets). Each measure is computed for both accuracy and reaction time (RT). For the Mesulam and BIT we calculated the center of cancellation (CoC), which corresponds to the lateralized center of mass of hits for stimuli positioned in the contra-lesional and ipsi-lesional side of stimulus array ²⁵.

A principal component analysis was applied to the sub-acute data across the 10 scores to reduce noise and the number of variables (Table S1, fully described in Corbetta et al ²⁰). Since the first component explained the largest component of the variance (29%), and encompassed both a bias in processing lateralized visual stimuli (spatial attention) and an overall impairment in speed and accuracy (non-spatial attention), it was chosen for further analyses. Hereafter Factor 1 will be defined as the Visual Attention Deficit (VAD) as in Baldassarre et al. 2014 ¹⁰.

Functional magnetic resonance imaging (fMRI) scanning and data preprocessing

Scanning was performed on a Siemens 3T Tim-Trio scanner at the Washington University School of Medicine in St. Louis. Each subject was scanned at the sub-acute timepoint, 3 months, and 1 year. Structural scans included: (1) a sagittal MP-RAGE T1-weighted image (2) a transverse turbo spin-echo T2-weighted image and, (3) a sagittal FLAIR (fluid attenuated inversion recovery) (for more detail see ¹⁰). 7 functional scans were acquired with a gradient echo EPI sequence (TR=2000 msec, TE=27 msec, 32 contiguous 4 mm slices, 4×4 in-plane resolution, 128 volumes each) for a total acquisition time of ~30 minutes. Resting-state functional MRI scans were obtained while subjects were asked to lie still and fixate a central cross (resting fMRI or R-fMRI). Eye closures were monitored with a video camera. The fMRI data was preprocessed and motion contaminated frames were removed as in Baldassarre et al (¹⁰).

Lesions

The lesions were manually segmented using Analyze biomedical imaging software (www.mayo.edu) by inspecting all structural images (the MP-RAGE, T2 and FLAIR) in atlas space and distinguishing the lesion from healthy tissue, CSF and surrounding vasogenic edema. This was evaluated in all three directions (slices of 2 mm thickness), and was independently double-checked by two neurologists (Alex Carter MD, and MC).

Resting state functional connectivity networks and mapping

169 seed regions of interest (ROIs) were identified as described in ¹⁰ in a group of healthy controls, separated into 10 networks ²⁶. Correlations (Pearson r) between the time courses of each of the nodes and all voxels in the rest of the brain were calculated, creating full brain, voxel-wise functional connectivity (FC) maps for each ROI, for each subject, for each of the two sessions. ROIs overlapping with the lesion and lesioned voxels in the voxel-wise maps were excluded from all analyses. The Pearson correlations were Fisher z -transformed, generating $z(r)$ maps, for further analyses.

Functional connectivity – behavior correlations

Based on previous work indicating the importance of a region in posterior parietal cortex, part of the DAN, for the recovery of neglect ⁶, we first explored the relationship between neglect and FC patterns from a single region of the DAN (right medial IPS or RmIPS) to the rest of the brain, using methods previously employed ^{27,10}. Difference FC maps were created for each subject by subtracting the 2-weeks maps from the 3-month maps. These maps were subsequently correlated across subjects with the improvement in VAD scores (3 months minus sub-acute). Since behavioral recovery is highly correlated with the degree of sub-acute deficit, the same procedure was repeated using change behavior scores while regressing out the sub-acute deficit scores, examining changes specific to recovery.

Second, to quantify FC recovery effects at the network level, we focused on the two most robust FC correlates of sub-acute attention deficits, namely a decrement of inter-hemispheric FC in DAN, DMN, visual, auditory, and motor networks, and an increase of intra-hemispheric FC between DMN and DAN, motor, visual, and auditory networks. ¹⁰. Two-factor ANOVAs with Group (N+,N-) and Time (2 weeks, 3 months, 12 months) as factors were conducted on inter-hemispheric FC scores averaged across the homotopic ROI pairs of each network (see Table S2 for ROI list). Similar ANOVAs were conducted on intra-hemispheric FC scores, which consisted of averaged ROI to ROI FC of each DMN ROI vs. each ROI of the other networks.

Finally, to examine the relationship between recovery of attention deficits and FC across the whole brain in a data-driven manner, we employed a procedure introduced in ¹⁰. A separate analysis was conducted for each hemisphere involving 91 nodes consisting of the nodes belonging to the hemisphere and the nodes falling on the midline. The overarching logic of the analysis was to 1) generate voxel-wise functional connectivity maps for each node for the sub-acute and three-month time-points, which are then subtracted to create change FC maps, 2) compute the correlation across subjects between these maps and behavioral change scores, 3) determine through a data reduction operation with PCA whether these voxel-wise functional connectivity:behavior correlation maps were consistent across nodes, 4) select the most representative nodes and networks, i.e. those yielding the maps with the highest loadings on the first principal component of the PCA, and 5) display the average functional connectivity:behavior maps from the most representative nodes. The Pearson r -values were transformed into t -scores and then Z -scores over the population. These maps were then thresholded ($|Z| > 2.25$, $P < 0.05$, cluster-size of 53 voxels) to only retain the statistically

significant clusters, accounting for multiple comparisons. This method is explained in greater detail in Baldassarre et al ¹⁰.

Effects of Lag

Siegel et al ²⁸ developed methods for detecting hemodynamic lags in undamaged tissue within the same vascular distribution as a stroke, and found significant hemodynamic lags in ~30% of sub-acute stroke subjects, which were associated with decrements of FC and with behavioral deficits. However, significant FC:behavior correlations persisted after the effect of lag was removed. Given this prior work, we performed a control analysis to determine if changes of inter-hemispheric FC in the DAN in relation to changes in VAD scores were affected by lags.

For each of the ROIs of the 9 homotopic DAN pairs, the hemodynamic lag was determined as follows: lags in the contralesional hemisphere were assumed to be zero and lags in the ipsilesional hemisphere were defined as the latency of the peak in the cross-correlation between any region and its contralesional homologue. Lags were computed both at 2 weeks and 3 months. For each ROI pair the change in pairwise lag between sub-acute and chronic timepoints was regressed from the change in FC score. The correlation between behavioral improvement (VAD change score) and the average FC residuals across all 9 pairs was calculated.

Results

Lesion topography

The lesion distribution in the 77 stroke subjects shows the highest overlap subcortically, involving the central white matter and basal ganglia, while cortically the lesions involved mainly the middle cerebral artery distribution (Figure 1A). The mean lesion volume was 20.5 cm^3 ($SD \pm 23.4$).

Based on the acute (admission) NIH stroke scale scores, the majority of patients (90%) had motor deficits, 21% had aphasia and 17% had hemi-spatial neglect. At the time of our first data collection 7% of the patients were classified as having neglect according to the NIH stroke scale, but our more sensitive neuropsychological battery classified 32% ($N=25/77$, $N+$) of the subjects with hemi-spatial neglect at ~2 weeks post stroke, based on a VAD score that was 2 standard deviations below the average score of healthy age matched controls, and 68% ($52/77$, $N-$) without neglect.

The lesion distributions for the two groups are shown in Figure 1B ($N+$: 7 left hemisphere damaged (LHD), 18 right hemisphere damaged (RHD); $N-$: 32 LHD, 20 RHD). The mean lesion volume of patients with neglect was larger ($N+=34.8 \text{ cm}^3$ versus $N-=11.3 \text{ cm}^3$, $t(75)=4.28, p<0.001$). For analyses relating behavior to FC analyses, lesion and fMRI maps were flipped in LHD patients so that the right hemisphere was always the damaged hemisphere (Fig.1C).

Measures of hemi-spatial neglect and its recovery

The frequency distribution of VAD scores in control and stroke subjects is shown in Figure 2A. The distribution of VAD scores was significantly lower in patients than controls sub-acutely ($t(105) = -3.00$, $p=0.003$), at 3 months ($t(105) = -2.71$, $p=0.008$), and on average got closer to normal at 1-year post stroke ($t(92) = -1.40$, $p=0.165$). There was no correlation between the time of testing post stroke and the severity of neglect (sub-acute: $r=0.06$; $p=0.59$, 3 months: $r=0.124$, $p=0.28$; 1 year: $r=0.054$, $p=0.67$).

The recovery of attention was evidenced by an increase of VAD scores over time (Fig.2A). Based on the 2 SD below control cut-off score, neglect was observed in 25 patients (32%) at ~2 weeks, 14 patients (18%) at ~3 months, and 7 (11%) patients at ~1 year, respectively (inset Fig.2A). Most patients, however, remained impaired as indexed by VAD scores greater than 1 SD below the control mean (84% at 3 months, and 55% at 12 months).

We compared VAD scores in N+ and N- groups (Fig.2B) using an ANOVA with time (sub-acute, 3 and 12 months) and group (N+, N-) as factors. A significant interaction ($F(2,61)=32.3$, $p<0.001$) indicated recovery in the N+ group. In the first 3 months there was approximately a 59% improvement from the initial deficit ($p<0.001$), but no significant improvement occurred between 3 months and one-year (Fig.2B). N+ maintained significant deficits as compared to the N- group at 12 months ($p=0.002$, Fig.2B). Performance in the healthy control group and N- patients was not significantly different and was stable across time points, indicating good inter-session reliability. There was no effect of having received TPA ($n=10$) on the recovery of attention deficits ($F(2,61)=0.36$, $p=0.70$).

Finally, we examined whether sub-acute impairment on attention scores and their recovery correlated with acute impairment or recovery of other domains (language, left or right motor function, spatial or verbal memory). At the sub-acute stage, VAD scores correlated with left limb motor ($r=0.51$, $P<0.001$) and spatial memory ($r=0.52$, $p<0.001$) scores (Fig.2C). However, the improvement of VAD scores within the first three months correlated with an improvement in spatial memory ($r=0.47$, $P<0.001$), but not left motor function, language, or verbal memory (Fig.2D). These behavioral results indicate that recovery of attention is more related to recovery of spatial memory than motor or language. This issue is relevant with respect to the functional connectivity correlates of attention recovery, and their specificity, as discussed later on.

Functional connectivity and neglect recovery: R parietal to/from rest of the brain

We performed three different analyses to test the hypothesis that a normalization of the pattern of FC abnormality sub-acutely after stroke (a decrement of inter-hemispheric correlations and abnormal increase of FC within each hemisphere, as seen in ¹⁰) was associated with recovery from neglect. The first analysis related neglect recovery to the whole-brain FC of the structurally normal R mIPS (indicated by a star symbol in Fig.3), which has been implicated in the pathophysiology of neglect ^{6,8-10}.

We confirmed that sub-acutely neglect was associated with widespread decrements of inter-hemispheric FC between R medial intraparietal sulcus (mIPS) and left hemisphere regions of the DAN, visual, auditory, and motor networks (Fig.3B, green/blue regions). As an

example the scatter plot indicates that decreases of FC between right and left mIPS were significantly related to VAD (Fig.3A). Moreover, there was a positive correlation between the strength of FC between R mIPS and large swaths of the right hemisphere corresponding to the DMN and FPN (yellow/orange regions), with stronger connectivity corresponding to stronger deficits (Fig.3C). In both cases the effects were stronger in right hemisphere patients.

Figures 3D–F show the relationship between the change (3 months – sub-acute) in FC from R mIPS and the improvement (3 months – sub-acute) of VAD scores. Figure 3E indicates that an increment of inter-hemispheric FC between R mIPS was positively correlated with an improvement of attention (Fig.3D). Similarly a decrement of intra-hemispheric FC also correlated with an improvement of attention (Fig.3F). Notably, the topography of FC:behavior correlation at the sub-acute timepoint is similar to the inverse of the topography of change ($r = -0.78$).

However, these correlations may be biased by the level of initial severity given the severity of attention deficits sub-acutely is strongly related to the degree of improvement from sub-acute to 3 months ($r = -0.89$, $P < 0.001$). Hence we re-computed the FC:behavior change maps after regressing out the sub-acute VAD scores. This procedure decreased the strength of the FC:behavior change correlation, but the correlation remained highly significant, both in terms of improvement in inter-hemispheric correlation as well as in a return of the normal negative correlation between right mIPS and the DMN (e.g. supramarginal gyrus)(Figs.3G–I).

Overall, the first set of analyses indicated that the improvement of attention deficits was linked to an increase in inter-hemispheric connectivity across DAN, visual, auditory, and motor networks, and an increase of negative correlation between DAN and DMN/FPN regions. Both results correspond to a normalization of physiological patterns of functional connectivity toward that observed in healthy subjects.

Functional connectivity and neglect recovery: DAN, DMN, and other networks

While the first analysis focused on FC to/from mIPS to the rest of the brain, here we examine the same question focusing on two networks: DAN and DMN. To improve signal-to-noise, we averaged ROI to ROI correlations across networks, e.g. all inter-hemispheric DAN pairs or DAN to DMN pairs within each hemisphere and we looked at the recovery in N+ and N– groups (Fig. 4). There was a statistically significant interaction between the two groups ($F(2,62) = 7.265$, $p < 0.001$). Post-hoc tests revealed a decrease in inter-hemispheric DAN connectivity in both groups, but more severely for the N+ group ($p = 0.005$), which recovered to the level of the N– group by 3 months. The decrease for both groups however remained below that of the healthy controls ($F(2,93) = 5.725$, $p = 0.005$)(Fig.4A).

For DAN-DMN connections there was also a significant interaction of time by group ($F(2,62) = 5.784$, $p = 0.005$ and $F(2,62) = 2.940$, $p = 0.06$ for the left and right hemisphere respectively), which showed that the negative correlations decreased more strongly in the N+ (as compared to the N–) group ($p = 0.001$ and $p = 0.007$ respectively) recovering within the first three months to the level of the N– group (Fig.4B–C). FC in the N+ group recovered to

the level of the age matched controls in the left hemisphere ($F(2,93)=1.653$, ns), but not the right (damaged) hemisphere ($F(2,93)=6.560$, $p=0.02$).

Given our previous work showing multi-network FC changes associated with attention deficits at the sub-acute stage¹⁰, we extended the same analysis to motor, auditory and visual networks (Fig. 5A–C). Acute decrements of inter-hemispheric FC in the N+ patients, and improvement within the first three months was robust in the motor and auditory networks, but not in the visual network (Figure 5). Similarly, there was an improvement toward negative correlation with the DMN in motor, auditory, and visual network.

Overall these analyses support at the level of multiple networks that recovery of attention was related to a normalization of inter-hemispheric and intra-hemispheric FC.

Principal component analysis of correlation maps between functional connectivity and neglect recovery

In the third analysis, we employ a data driven approach in which we relate changes in attention performance from 2 weeks to 3 months to changes in FC across the whole set of 169 ROIs. This approach is similar to¹⁰, except that FC and behavioral *change* scores are used for the correlation of FC-to-behavior. Voxel-wise maps of FC:behavior correlation for each ROI are summarized by spatial principal component analysis (PCA) to highlight the most consistent maps across ROIs.

Left hemisphere PCA—The PCA from left hemisphere ROIs yielded three components that explained respectively 20%, 12%, and 9% of variance across ROIs. The first PC loaded most on ROIs in dorsal parietal and frontal cortex within the DAN and motor network (Figs. 6A, 6B and Table S3). The average FC:behavior correlation map from the top 10% nodes showed a widespread positive correlation between changes in inter-hemispheric FC and improvement in VAD scores (yellow/orange). For example, figure 6C shows the correlation between change scores for FC between the top 10% ROIs and a region in the right supramarginal gyrus with VAD change scores. There were also significant negative correlations (green-blue) from the ROIs in DAN and motor network between improvement in VAD and decreases in FC in DMN and FPN regions such as the dorsolateral prefrontal region (DLPFC)(Fig. 6D).

Right hemisphere PCA—The PCA from right hemisphere ROIs yielded three components that explained 19%, 11%, and 11% of variance across ROIs, respectively. As in the left hemisphere, the first PC loaded most on the DAN, but also on auditory and FPN (not shown). The top 10% regions were predominantly DAN regions, posteriorly located around the IPS (Table S3). The correlation maps from these top 10% regions also showed a strong positive correlation between improvement in attention deficits and inter-hemispheric FC across large swaths of cortex, and negative correlations within the right hemisphere with posterior DMN regions.

Comparison of sub-acute and change PCA results—Finally, to demonstrate that behaviorally relevant FC changes at 2 weeks normalized during recovery, we compared the top 10% maps from a PCA run on sub-acute FC:behavior maps to the change maps using

spatial correlation (after regressing out the sub-acute VAD scores). We found that the sub-acute and change PCA maps (after regressing out the acute scores) were highly correlated: with an r of -0.41 and -0.50 for the maps of the left and right hemisphere respectively (-0.80 and -0.88 sub-acute versus change PCA maps without acute regressed out).

Therefore, the data-driven analysis indicated that recovery of attention deficits correlated with a normalization of inter-hemispheric FC, especially in DAN and motor networks, and a relative decrease of intra-hemispheric FC between DAN/motor and DMN/FPN.

Specificity of network connectivity changes to attention

An important issue is whether these changes in FC are specific to attention or more generally depend on the presence of a lesion or the severity of neurological impairment. To address this concern we performed an analysis in which we correlated changes (3-month-acute) voxel-wise FC to/from right mIPS with changes in motor and language scores derived from a PCA of the neuropsychological battery as in ²⁰. Figure 7A shows the original voxel-wise correlation with VAD change scores showing strong inter-hemispheric FC increases in sensory-motor and attention networks, and FC decrements with DMN/FPN regions. Figs. 7B–C show FC patterns related to language and motor recovery that appear quite different from attention recovery (Fig. 7A). Fig. 7D shows FC changes related to attention recovery after regressing out motor change scores. The pattern albeit slightly decreased is still present. Finally, Fig. 7E quantifies these relationships for DAN and DMN ROIs. The strength of FC:behavior correlation, both inter-hemispheric FC increases and intra-hemispheric FC decreases, for attention recovery is not attenuated after regressing out language or motor scores. These analyses confirm the specificity of the reported FC network changes for attention recovery.

Controls for lag, lesion size, lesion type, and arousal

Prior studies have identified perilesional delays in the resting BOLD signal post-stroke using cross-correlation analysis, i.e. by comparing the latencies of signal time series in the stroke hemisphere with either homologous signal time series in the normal hemisphere or a global signal computed over the whole brain or gray matter (^{29,30}). These delays or ‘hemodynamic lags’ correspond to areas of hypoperfusion and can artificially lower observed FC values ³¹. Here, we present a limited analysis of the potential effect of hemodynamic lags on the normalization of FC in relation to neglect recovery in nine homotopic pairs of ROIs in the DAN, the network in which we found the strongest effects of recovery ($r=0.63$, $p<0.001$, Fig. 8A). Consistent with the recovery of lag reported in Siegel et al. ²⁸, the lags decreased as the interhemispheric FC recovered ($r=-0.47$, $p<0.001$). However, when the recovery of lag was regressed out of each ROI pair, the inter-hemispheric FC in the DAN ROIs showed a slightly weaker, but still strong correlation with behavioral recovery ($r=0.55$, $p<0.001$, Fig. 8C).

Another possible confound is the volume of the lesion. The volume of stroke in N+ patients was larger than in N- patients. However, we found no relationship between changes in inter-hemispheric FC (DAN) and lesion-size ($r=0.18$, ns). Also regressing out lesion-size from the change in FC only slightly decreased the correlation between FC and behavioral recovery

($r=0.58$, $p<0.001$, Fig. 8D). Moreover, there seems to be no difference in this relationship between FC and behavioral recovery for different lesion types (subcortical, cortical and cortical-subcortical, Fig. 8B). A larger dataset is however needed to quantify this.

Finally, we examined if changes in FC were influenced by the state of vigilance of our patients in the scanner. We used an eye tracker in the scanner in 44 of the patients to determine the percentage of time patients had their eyes open during each resting scan. There was no relationship between the time patients kept their eyes open and homotopic DAN FC (sub-acute: $r=-0.23$, $p=0.11$, 3 months: $r=-0.13$, $p=0.35$) and no difference between the neglect and non-neglect groups on the amount of time they had their eyes open ($t(48)=1.30$, $p=0.197$).

Discussion

This study examined network-level correlates of hemi-spatial neglect recovery, the most common cognitive syndrome after right hemisphere stroke. Attention deficits mostly recovered within the first three months post stroke, with little additional improvement between three months and one year. Correspondingly, we observed changes in FC of structurally normal brain regions also significantly stronger between 2 weeks and 3 months, then plateauing between 3 and 12 months. Attention deficit recovery was significantly correlated with increases in inter-hemispheric FC between regions of the dorsal attention, motor, visual, and auditory networks, and more negative intra-hemispheric FC between dorsal attention/motor and default mode/frontoparietal regions. Notably these changes correspond to a relative normalization by 3 months of the abnormal network FC observed at approximately 2 weeks post-injury. These findings support the behavioral relevance for hemispatial neglect of abnormal network interactions at the sub-acute stage, and indicate that their normalization is associated with recovery of function.

Recovery of attention deficits

The VAD factor loaded on lateralized spatial biases in visual perception and a general decrement in performance consistent with sustained attention impairment. Both features correspond to the most common processing deficits of the hemi-spatial neglect syndrome³. Compatible with prior work, performance improved during the first three months post stroke but then plateaued without reaching normal levels³⁻⁵.

Interestingly, while VAD scores sub-acutely correlated with both left motor and spatial memory deficits, consistent with a right hemisphere localization of neglect, changes in VAD scores from 2 weeks to 3 months were significantly correlated with spatial memory deficits, but not motor deficits. Spatial attention and spatial memory are cognitive functions that rely on the integration of information across multiple regions of the brain, and are closely intertwined both behaviorally and neurally. Functionally, attention determines what enters in working memory³², while information in working memory can bias what is attended³³. Neurally, both spatial attention and memory involve distributed networks of frontal-parietal cortical and subcortical regions^{33,34}. Accordingly, disorders of both functions depend on widespread cortical dysfunction due to structural or functional disconnection³⁵, and their recovery may depend on the restoration of communication across multiple brain regions. In

contrast, motor behavior is an output function. Several studies have reported that one of the strongest predictors of motor impairment and recovery is the degree of damage to the corticospinal tract^{36,37}. Interestingly, cortico-spinal damage is a stronger predictor of motor impairment than functional connectivity³⁸. Therefore, while deficits of attention and left limb motor function are correlated sub-acutely, possibly due to the co-localization of related cortical regions in the vascular territory of the most common middle cerebral artery stroke, the recovery of attention and motor function may underlie different mechanisms, with attention more related to functional interactions between distributed brain regions, while motor recovery more related to local structural reorganization.

Functional Connectivity & Attention Recovery

Inter-hemispheric connectivity—Both animals and human stroke studies show correlated decreases in inter-hemispheric functional connectivity (or signal temporal correlation) with motor^{9,39}, and attention deficits^{6,9,10}.

Our results show for the first time in a large cohort of human subjects (see³⁹ for a corresponding result in rats) that improvement of inter-hemispheric connectivity over time is associated with behavioral recovery. An improvement of VAD scores from sub-acute to 3 months was correlated with an increase of functional connectivity between inter-hemispheric regions in multiple networks, predominantly the DAN and the motor network, but also auditory and visual regions. Our previous work had showed that hemi-spatial neglect sub-acutely is associated with disrupted inter-hemispheric connectivity in the same networks¹⁰. Therefore, the results for both the sub-acute deficit and the recovery of that deficit over time strongly support the behavioral relevance of FC measures.

An improvement of inter-hemispheric FC over time in stroke has been reported in other studies of motor recovery^{40,41}. For instance, Park et al⁴² observed an improvement of inter-hemispheric FC from 1 to 6 months post stroke in a small group (n=12) of patients by performing a ROI based analysis from the primary motor cortex. They also showed that the degree of acute inter-hemispheric FC impairment correlated with the degree of motor recovery. These studies therefore are also consistent with the notion of normalization of abnormal network interactions in the motor system as a possible mechanisms underlying recovery of function.

Default mode network and DAN—The second pattern of abnormal connectivity associated with the recovery of neglect is a return toward a negative intra-hemispheric coupling between the DMN and the DAN as well as sensory and motor networks. In the healthy brain, regions involved in the processing of ‘external’ information (e.g. DAN, visual, auditory, motor during visual or auditory processing tasks) are negatively correlated with regions of the DMN, which are instead more involved in the processing of ‘internal’ information (e.g. memory retrieval, theory of mind, self-referential tasks)(reviewed in⁴³). This competitive pattern of task activation is behaviorally relevant. Positive responses in the DAN and negative responses in the DMN relate to accuracy on a perceptual task, while the reverse pattern holds during memory retrieval⁴⁴. Conversely, a failure to suppress DMN activity underlies lapses and deficits in attention^{45,46}. The DAN and DMN are also

negatively coupled in the resting state, even after accounting for the effects of global signal regression ⁴⁷, and this coupling is absent in several pathological states. For instance, decreases in segregation between DMN and DAN is found in patients with ADHD ⁴⁸. Our results show that a recovery of negative coupling between DAN and DMN within each hemisphere (both damaged and normal) is related to the behavioral recovery of neglect. Subjects with more severe inter-hemispheric disruption have less negative or abnormally positive coupling intra-hemispherically.

Behavioral recovery as improvement of network efficiency

Animal and human neuroimaging studies in the last two decades have shown after stroke that performance of motor or language tasks lead to abnormal recruitment and over-activation of cortical regions, often in the undamaged hemisphere, that are not typically present in healthy subjects. This abnormal recruitment typically occurs more strongly in individuals who are more severely impaired ^{17,18}. In the course of recovery, activity shifts back to the damaged hemisphere often with a re-mapping of function near the lesion (peri-lesional), especially in patients with better recovery ^{17,49}. These dynamic alterations in task-evoked activation must be reconciled with acute alterations and chronic normalization of inter-regional signal temporal correlation reported here.

We propose that observed changes in activity and connectivity reflect a tendency of brain networks toward energy optimization. The brain weighs only 2% of the body weight yet uses about 20% of the total energy ⁵⁰. Most energy consumption relates to intrinsic, not task-driven, signaling ⁵⁰. Recent theoretical work in network science indicates that the brain's structural and functional architecture is the best energetic compromise for a system that requires both specialized local processing and distributed integration of information ¹⁹.

This architecture renders the system relatively resistant to perturbations ⁵¹, but necessarily local and distributed injuries will affect the system processing capacities. While local damage to cortex can be compensated for by highly interconnected neighboring neuronal populations that are part of a network with similar input and output connections ¹⁹, damage to white matter pathways, especially regions in which multiple pathways intersect¹⁰, will lead to disconnection of wide swaths of cortex and more severe and long lasting deficits ^{20,52}. For example, in the case of hemispatial neglect damage to white matter pathways connecting frontal and temporo-parietal regions leads to severe and persistent impairment ^{3,12,13,20}.

A key insight from our work on network abnormalities in stroke is that sub-acutely large parts of cortex show patterns of connectivity that are highly similar, and that similarly correlate with behavioral deficits. For instance, the two characteristic connectivity abnormalities found sub-acutely in hemispatial neglect, i.e. a loss of inter-hemispheric correlation and an abnormally increased correlation between normally segregated networks, is found in over 40% of cortical regions ¹⁰. In other words, the pattern of resting synchronization across brain regions is highly simplified, i.e. the brain noise variability is decreased. This is also clear from EEG/MEG studies in which the damaged hemisphere typically show slower and less variable brain rhythms ⁵³, and EMG studies of muscle synergies, in which the variability of motor patterns during movement is also reduced in

stroke⁵⁴. Apparently, during task performance, these abnormal and low variability intrinsic brain rhythms give rise to abnormally strong patterns of task activation that are not only behaviorally, but also metabolically inefficient. To the extent that sub-acute abnormal patterns also include compensatory adjustments, they may reflect an attempt to link regions that are disconnected, either by increasing neural activity upstream of the lesion or by re-routing activity through accessory regions.

Through rehabilitation and possibly neuromodulation (e.g.^{55,56}) connections and networks may return toward more normal patterns of intrinsic synchronization, which in turn relate to more efficient task patterns of activation. Normalization will result in more efficient energy utilization and increased neural state variability, hence better behavior. Normalization of functional connectivity, as shown here, could be mediated either through undamaged parts of white matter tracts that still connect these regions, or indirectly through regions of the same network⁵⁷ that share intact structural connections. A similar trend toward normalization of connectivity states has been observed after traumatic brain injury⁵⁸. In a recent study Lee and colleagues⁵⁹ observed a global increase of network efficiency (again measured as a shorter characteristic path length) in the first three months post stroke, and showed that increased efficiency shortly after stroke predicted the amount of motor recovery.

In summary, then, a normalization of the brain's functional architecture toward a healthy state appears to be a property of brain networks after injury that also relates to behavioral recovery.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Topography of stroke. Lesion overlap image in atlas space for all patients (A), patients without and with neglect (B) and all patients, with lesions flipped to the right side (C). The color scale indicates the number of subjects with lesions at each voxel.

Figure 2.

Neglect and recovery. The distribution of neglect scores in controls and in patients sub-acutely and 3 months and 1 year post stroke (A). Visual attention deficit (VAD) scores over time for patients with and without sub-acute deficits and controls (B). Correlation of VAD scores with scores in other behavioral domains at the sub-acute timepoint (C). Correlation of the improvement (3 months minus sub-acute) of VAD scores with the improvement of scores in other behavioral domains (D).

Figure 3.

Right medial IPS functional connectivity (FC) with the rest of the brain in relation to behavior. FC by behavior maps: sub-acutely post stroke (B), recovery (E) and recovery with sub-acute behavior regressed out (H). Red/yellow indicates a positive correlation and green/blue a negative correlation. Scatter plot of FC versus behavior for an inter-hemispheric region (A, D, G) and intra-hemispheric region (C, F, I) highlights the correlations. Each dot is a patient and blue indicates patients with right hemisphere lesions, red with left hemisphere lesions.

Figure 4.

DAN and DAN-DMN functional connectivity (FC). Inter-hemispheric DAN (A), left hemisphere DAN to DMN (B) and right hemisphere DAN to DMN (C) FC over time for the deficit (red) and no deficit (blue) patients and controls (green). The brain figures show a subset of the connections that were averaged in the graphs (blue dots represent DAN ROIs and red dots DMN ROIs).

Figure 5.

Inter- and intra-hemispheric functional connectivity (FC). Homotopic FC (A) for each network and intra-hemispheric FC for the DMN versus other networks in the left (B) and right (C) hemisphere over time for the deficit (dashed line) and no deficit (solid line) patients and controls (dotted line).

Figure 6.

Behaviorally relevant functional connectivity (FC) recovery of the left hemisphere. The loadings for each of the 10 networks of the first component of the principal component analysis of voxel-wise FC and behavior change maps of the left hemisphere (A). The voxelwise FC change maps of the top 10% ROIs (depicted in B) are averaged and correlated with the VAD change. The inter-hemispheric FC to VAD change is shown on the left hemisphere (C) and the within hemisphere FC to VAD change is shown on the left hemisphere (D). On the lateral views of the brain red/yellow indicates a positive FC-VAD correlation and green/blue a negative correlation (Z-statistic of Pearson r , thresholded at $|Z| > 2.25$, $P < 0.05$, Monte Carlo corrected). The scatterplots depict the correlation between the average FC change of the top 10% seeds and the black circle and behavioral improvement (C: Supramarginal gyrus, Talairach coordinates: +45 -38 +34; D: PFC, -32 +46 +23). Each dot is a patient and blue indicates patients with right hemisphere lesions, red with left hemisphere lesions. Networks: VNF = visual foveal representation; VNP = visual peripheral representation; DAN = dorsal attention; MN = motor; AN = auditory; VAN = ventral attention; CON = cingulo-opercular; LN = language; FPN = frontoparietal; DMN = default mode. Labels: FEF, frontal eye fields; IPS, intraparietal sulcus; TPJ, temporal parietal junction; pIns, posterior insula; aIns, anterior insula; MT+, middle temporal complex; PFC, prefrontal cortex; dPoCe, dorsal post central gyrus.

Figure 7. R mIPS correlations with recovery of other deficits in patients with right hemisphere lesions. Whole brain functional connectivity improvement correlations of the right medial IPS with behavioral recovery of A. Attention (n=37), B. Language (n=34) and C. Motor (n=34) recovery. In each of these correlations the sub-acute behavioral deficits are regressed out. In D attention recovery is depicted, while regressing out the left limb motor recovery (n=34). E shows the inter-hemispheric dorsal attention network (DAN) and intra-hemispheric DAN to default mode network (DMN) connectivity changes correlated with attention, language and motor improvement as well as attention with language and motor regressed out.

Figure 8.

Lesion type, Lag and Lesion size. The scatterplots show the correlation between behavior (VAD) change and FC change between sub-acute and 3 months post stroke for the average of the homotopic DAN nodes (A), the correlations of VAD change and FC change separated out by lesion type: subcortical, cortical and cortical-subcortical (B), the correlation between VAD change and FC change when lesion size is regressed out (C) and the correlation between VAD change and FC change with lag change regressed out (D). Each dot is a patient and grey triangles indicate patients with right hemisphere lesions, black circles patients with left hemisphere lesions.

Table 1

Variables	Stroke (n=77)	Controls (n=31)	Stroke vs Controls
Age (years)	53 ± 10	55 ± 12	ns
Women	35 (45%)	16 (52%)	ns
Right handed	68 (88%)	29 (94%)	ns
Left hemisphere lesion	39 (51%)	–	–
Lesion type			–
Ischemic	65 (84%)	–	
Hemorrhagic	8 (10%)	–	
Other	4 (5%)	–	
TPA	10 (13%)	–	–
Race			ns
White	24 (31%)	10 (32%)	
Black or African American	53 (69%)	20 (65%)	
Other	0 (0%)	1 (3%)	
Years of education	13.1 ± 2.5	13.6 ± 2.6	ns
Risk factors			
Hypertension	51 (66%)	8 (26%)	p<0.01
Diabetes Mellitus	27 (35%)	5 (16%)	ns
CAD	7 (9%)	2 (6%)	ns
Smoking	40 (52%)	13 (42%)	ns
Depression	5 (6%)	1 (3%)	ns
Measurement (days (range))			
Sub-Acute	13 (6–27)	0	
3 Month	111 (81–181)	96 (66–155)	ns
1 year (n=64)	392 (349–749)	–	