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Neural basis and recovery of spatial attention deficits in spatial neglect

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The syndrome of spatial neglect is typically associated with focal injury to the temporoparietal or ventral frontal cortex. This syndrome shows spontaneous partial recovery, but the neural basis of both spatial neglect and its recovery is largely unknown. We show that spatial attention deficits in neglect (rightward bias and reorienting) after right frontal damage correlate with abnormal activation of structurally intact dorsal and ventral parietal regions that mediate related attentional operations in the normal brain. Furthermore, recovery of these attention deficits correlates with the restoration and rebalancing of activity within these regions. These results support a model of recovery based on the re-weighting of activity within a distributed neuronal architecture, and they show that behavioral deficits depend not only on structural changes at the locus of injury, but also on physiological changes in distant but functionally related brain areas.

Injury to a brain area causes behavioral deficits that are thought to reflect the local dysfunction of neurons at the site of injury. This logic (the local injury hypothesis) has been used for over 150 years by physicians to localize lesions in the brain. Neuropsychologists have built on the same logic to show the independence of mental processes (for example, see ref. 1).

However, as originally pointed out by Hughlings Jackson, the localization of normal functions (or mental operations) may or may not correspond to the localization of behavioral deficits. A lesion may cause dysfunction in other nodes of a functional brain network[2,3], impairing processes other than those mediated by neurons at the site of injury (the distributed injury hypothesis). Accordingly, recovery of function may depend on the restoration and rebalancing of activity in structurally normal, but functionally impaired, nodes of a task-relevant network. Here, we test whether the distributed injury hypothesis applies to spatial neglect, one of the main attentional syndromes following injury to the human brain.

Spatial neglect occurs in about 25–30% of all stroke-affected individuals (an estimated 3–5 million a year, worldwide)[4,5]. It is a complex syndrome characterized by a failure to attend to, look at and respond to stimuli (objects, food, people) located on the side of space or of the body opposite to the side affected by a brain lesion[6–8]. This spatial bias coexists with difficulties in maintaining alertness and detecting targets that are not lateralized to one side of space and has been linked to (non-spatial) deficits in attentional capacity (spatial and temporal) and impaired vigilance[9–11].

Over 90% of individuals with spatial neglect have right hemisphere injury and neglect of the left side of space or body. The most frequent sites of damage are right inferior parietal, ventral frontal[12,13] and superior temporal cortex[14], along with subcortical nuclei[12,15]. Although the contribution of different regions to the different processing deficits in neglect is unclear (but see refs. 16 and 17), it is currently assumed that these regions serve as specialized nodes of a network that mediates spatial attention, visuomotor behavior (eye-hand coordination) and vigilance[6,8].

Notably, the lesion anatomy of spatial neglect does not closely match the pattern of brain activation associated with spatial attention and visuomotor behavior. When subjects direct attention, eye movements or hand movements to visual objects—tasks on which individuals with neglect show a rightward bias—parietal and frontal regions are activated that are more dorsal than those anatomically damaged in neglect (**Fig. 1a**). These regions form a bilateral dorsal frontoparietal network (**Fig. 1a**, blue regions) that governs spatial attention and visuomotor control (eye-hand movement)[18–21], contains visuotopic maps of contralateral space[22,23] and is involved in goal-directed stimulus and response selection[24]. This network is a plausible, neural substrate of spatial biases in neglect.

The location of anatomical damage and its right hemisphere lateralization more closely matches a set of ventral temporoparietal and frontal regions related to the detection of salient sensory events[18,25,26](**Fig. 1a**). These regions form a ventral attention network that redirects the dorsal network to novel and behaviorally relevant stimuli, especially when these are unattended[24] (**Fig. 1a**, orange regions). Damage to these ventral regions may directly mediate deficits in 'non-spatial' processes such as vigilance or (attentional capacity[10]) as well as in attentional reorienting.

We hypothesize that spatial attention deficits in neglect arise from the structural or functional dysfunction of both dorsal and ventral attention networks. A stroke in ventral cortex (either frontal or parietal) should interfere with attentional reorienting. Moreover, as the ventral

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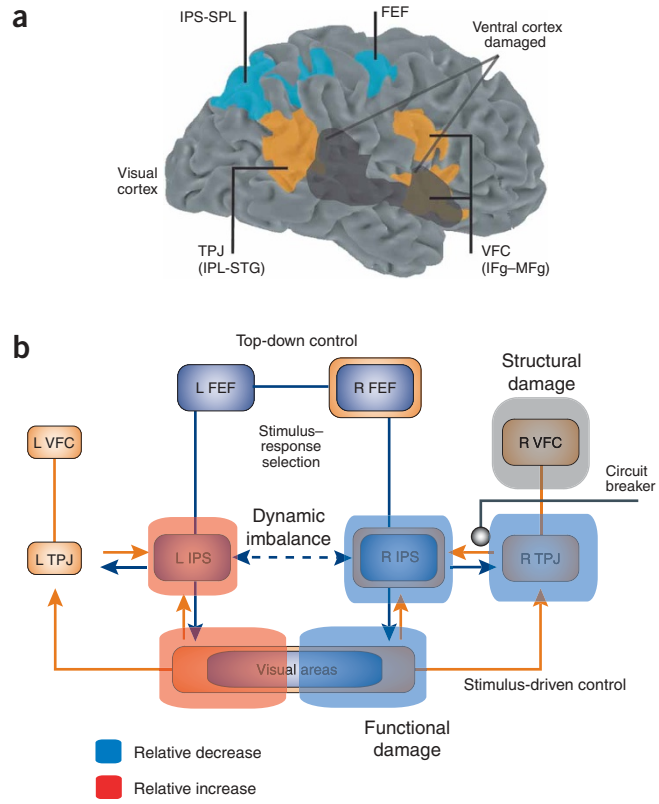

Figure 1 Functional-anatomical model of attention. (**a**) Dorsal (blue, top-down) and ventral (orange, stimulus-driven) regions of the human attention system. Black, hypothetical cortical lesion in ventral frontal, insular and perisylvian cortex, causing spatial neglect. (**b**) Anatomical model of attention and changes in relative activation after acute damage to right ventral frontal cortex. Areas in blue (dorsal system) mediate top-down stimulus-response selection and bias the activity in visual cortex. Areas in orange (ventral system) mediate stimulus-driven reorienting. The shading in light blue and red indicate, respectively, relative decreases and increases in functional activity. IPS-SPL, intraparietal sulcus–superior parietal lobule; FEF, human frontal eye field; VFC, ventral frontal cortex; TPJ, temporoparietal junction; IFG, inferior frontal gyrus; STG, superior temporal gyrus; MFG, middle frontal gyrus; IPL, inferior parietal lobule.

network normally sends the dorsal network a 'circuit-breaking' signal during target detection, a ventral lesion should also decrease activity of the (ipsilateral) right dorsal network (**Fig. 1b**). The resulting hemispheric imbalance could produce a rightward spatial bias in visual processing.

A final prediction is that the recovery of these attentional deficits is associated with a normalization of activity in both dorsal and ventral attention networks. Previous work shows that the recovery of neglect is associated with the restoration of normal activity in ipsilateral subcortical nuclei after frontal damage in monkeys[27] or in right hemisphere regions after cortical-subcortical damage in humans[17,28,29]. However, no study to date has measured functional task-evoked brain activity in a relatively numerous and anatomically homogenous group of individuals with spatial neglect during both acute and chronic stages of recovery and related brain activity to behavioral performance.

Here we show that spatial attention deficits in neglect after right frontal damage correlate with abnormal functional activation of structurally intact regions of the dorsal and ventral attention networks and that recovery of these deficits correlates with the normalization of activity within these regions.

RESULTS

To test the above predictions, we performed a prospective longitudinal study of individuals with spatial neglect ($n = 11$) following unilateral strokes. Subjects were enrolled on the basis of the presence of extinction to double simultaneous stimulation, omission of targets during visual search or evidence of clinical neglect in activities of daily living within the first week of their stroke (see inclusion criteria in **Supplementary Methods** online). All subjects underwent standard rehabilitation for at least 3 months after stroke. They were tested at the acute ($\sim$4 weeks, mean $\pm$ s.d. $=$ 32 $\pm$ 22.8 days) and chronic stages of recovery ($\sim$39 weeks, mean $\pm$ s.d. $=$ 39 $\pm$ 11.5 weeks) using a battery of neuropsychological and computerized tasks which assessed the presence of spatial or body neglect, anosognosia, vigilance, spatial attention and reaching deficits.

Anatomy

The majority of subjects (63%, or 7 of the 11) had lesions centered in the perisylvian region, including superior temporal gyrus (STG), frontal operculum, insula and putamen (**Fig. 2a**,**d**). The temporoparietal junction (TPJ), including the supramarginal gyrus (SMG) and underlying white matter, was damaged in 45% of subjects (5 of 11; **Fig. 2a**,**b**), whereas no subject had lesions that extended into dorsal posterior parietal cortex (specifically, intraparietal sulcus, IPS) or frontal cortex (specifically, frontal eye field, FEF) (**Fig. 2c**). One subject had a lesion in the parahippocampal gyrus, but otherwise the visual cortex was completely spared. On average this group was representative of the most common lesion sites in neglect[15]. The location of TPJ damage matched the location of maximal damage after middle cerebral artery strokes[13].

Behavior

Clinically, from the acute to the chronic stage of recovery, all subjects improved on traditional measures of spatial neglect (**Supplementary Table 1**). Whole-brain functional magnetic resonance imaging (fMRI) of the blood oxygenation level–dependent (BOLD) signal, an indirect

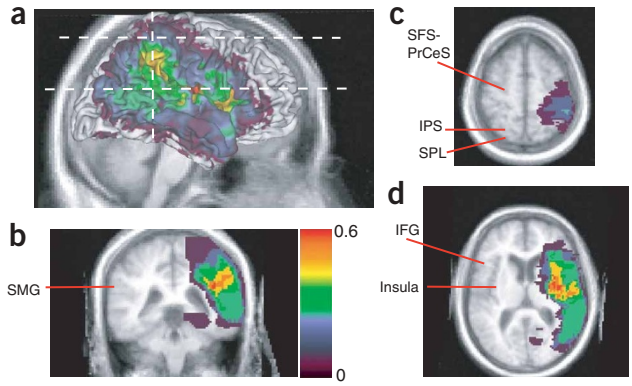

Figure 2 Lesion anatomy. (**a**) Atlas brain; right hemisphere, anatomical average of individual lesions. Color scale indicates percentage of subjects with lesion overlapping a specific voxel. Red-yellow areas, 50–70% overlap; yellow-green areas, 30–50% overlap; purple-blue areas, $<$10% overlap. Dashed lines indicate sections at the level of (**b**) the TPJ (coronal view; SMG, supramarginal gyrus), (**c**) dorsal frontoparietal regions (transverse view; SFS-PrCeS, superior frontal sulcus-precentral sulcus: that is, locations of FEF and IPS-SPL) and (**d**) ventral frontal and insular cortex (transverse view; IFG, inferior frontal gyrus).

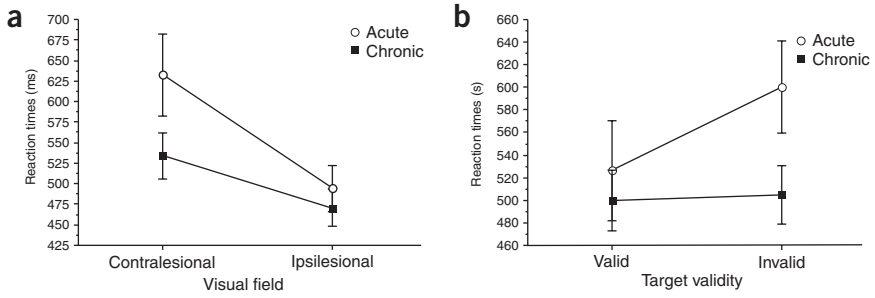

Figure 3 Behavioral results. (**a**) Recovery in contralesional visual field. (**b**) Recovery in reorienting to invalid targets.

noninvasive indicator of neuronal activity, was acquired at 4 weeks and 39 weeks after stroke. Subjects were scanned while performing a Posner visual orienting task used to define dorsal and ventral frontoparietal attention networks in normal observers[24] and previously used to study spatial neglect[30]. Subjects viewed a central arrow cue that covertly directed their attention to a left or right location on a computer screen. After a random delay, a target (an asterisk) was briefly flashed at one of the two locations. On 75% of the trials the target was presented at the location indicated by the cue (valid), whereas on 25% of the trials it was presented at the opposite location (invalid). Subjects pressed a key with their right hand as soon as they detected the target, and accuracy and reaction times were measured. Activity induced by the presentation of the cue stimulus was not separated from activity induced by the presentation of the target. All subjects were tested before scanning to establish that they could see the stimuli, maintain accurate fixation on a large majority of trials (> 90%) and carry out the task. Eye movements were not recorded in the scanner.

The behavioral data were analyzed with a three-way analysis of variance (ANOVA), using stage (acute or chronic), visual field (left or right) and cue validity (valid or invalid) as factors. Overall, subjects detected more targets at the chronic than acute stage (87.7% versus 81.1%; $F_{1,10} = 6.46$, $P < 0.05$), in the ipsilesional (right) than contralesional (left) visual field (87% versus 82%; $F_{1,10} = 8.35$, $P = 0.01$) and when the target was validly cued rather than invalidly cued (87% versus 81%; $F_{1,10} = 6.62$, $P = 0.03$). Similar effects were found for the reaction time to detect targets.

Recovery was indexed by two measures. First, there was a significant decrement in the rightward processing bias, as shown by a greater improvement in reaction time to targets in the contralesional (left) rather than the ipsilesional (right) visual field (two-way ANOVA of stage × visual field; $F_{1,10} = 4.77$, $P = 0.053$; **Fig. 3a**). Second, there was a significant improvement in attentional reorienting, expressed as an improvement in the hit rate and reaction time for detecting invalidly cued rather than validly cued targets (hit rates for acute valid and acute invalid were 87% and 76%, respectively; hit rates for chronic valid and chronic invalid were 88% and 87%, respectively; $F_{1,10} = 14.35$, $P = 0.004$; reaction time: $F_{1,10} = 4.79$, $P = 0.053$, **Fig. 3b**). Rightward bias and impaired attentional reorienting (or the "disengage deficit"; ref. 30) are robust measures of the spatial impairment in neglect and correlate with the severity of, and recovery from, spatial neglect as assessed by more traditional measures[31].

Functional MRI

The normal pattern of brain activation on the Posner task, as shown previously[18] for a group of young adults, involves large swaths of occipital, parietal, temporal and frontal cortex bilaterally, except in right TPJ (**Fig. 4a**). These maps are not directly comparable to those in the stroke-affected subjects but provide a qualitative baseline for comparison.

In the neglect group, at 4 weeks after stroke (**Fig. 4b**), a significant alteration was evident in the activation pattern. In the damaged right hemisphere, large portions of occipital visual cortex, posterior parietal cortex (especially IPS and superior parietal lobule (SPL)) and dorsolateral prefrontal cortex (DLPFC) showed weak or no task-related activity, even though these regions were anatomically intact. In the left hemisphere, there was decreased activity in occipital visual cortex and prefrontal cortex but robust activation in parietal cortex and sensory motor cortex (SMCX; **Fig. 4b**). At 39 weeks, a strong reactivation occurred in many right hemisphere regions but also in many left hemisphere regions (**Fig. 4c**).

Dorsal parietal cortex (IPS-SPL)

To determine which brain regions changed their level of activation from 4 to 39 weeks, we carried out a random-effect voxel-wise ANOVA using the MR frame (frames 1–8) and stage (acute or chronic) as factors. One notable pattern was observed in dorsal parietal cortex, the posterior core of the dorsal attention network (**Fig. 5a,b**). In the right hemisphere, dorsal parietal cortex (specifically, IPS-SPL) was not active at the acute stage but strongly reactivated at the chronic stage (pIPS-SPL 23, –73, 51, $P = 0.0001$; ventral IPS (vIPS)-precuneus 14, –76, 36, $P = 0.005$). This reactivation was independent of the visual field in which the target was presented. In contrast, in the left hemisphere, dorsal parietal cortex activity was stronger at the acute than at the chronic stage (SPL –21, –60, 58, $P = 0.008$; IPS –26, –54, 24 $F_{7,70} = 3.54$, $P = 0.003$). Dorsal parietal cortex was the only brain region that showed this interhemispheric 'push-pull' pattern from the acute to the

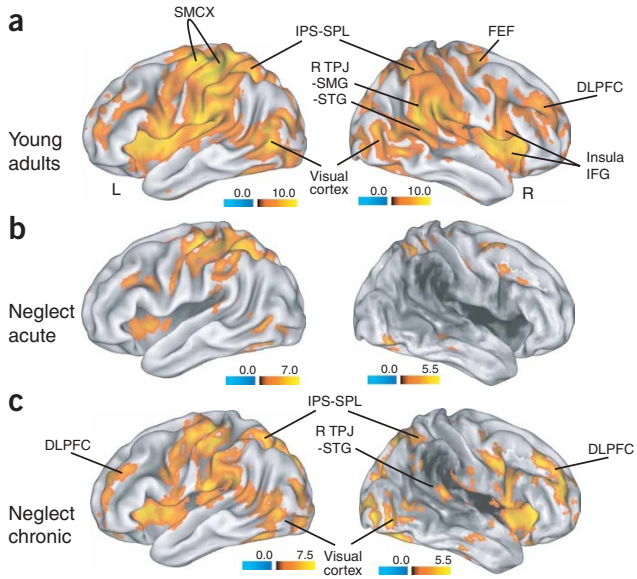

Figure 4 Functional maps of the Posner task. (**a**) In young adult observers. (**b**,**c**) In subjects with neglect at (**b**) the acute and (**c**) the chronic stage. Anatomical abbreviations as in previous figures. DLPFC, dorsolateral prefrontal cortex; SMCX, sensory-motor cortex.

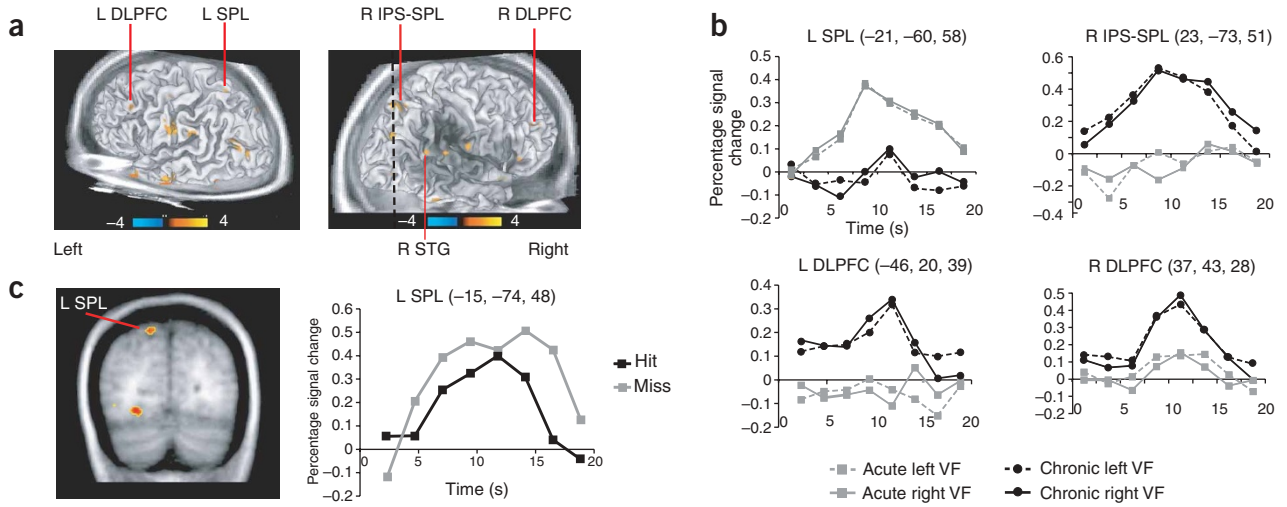

Figure 5 BOLD correlates of rightward bias in parietal cortex. (**a**) BOLD changes from acute to chronic stage in parietal and frontal cortex (thresholded at $z = 2.5$, $P < 0.01$ uncorrected), superimposed on three-dimensional atlas brain with average lesion embedded. The dashed black line indicates slice through SPL in panel **c**. (**b**) BOLD signal time courses for targets in left and right visual fields at acute and chronic stages. (**c**) BOLD signals for missed targets in left SPL. Graph, BOLD time course for hits and misses in left SPL.

chronic stage. For example, prefrontal cortex reactivated bilaterally at the chronic stage (left DLPFC: –46, 20, 39, $P = 0.009$; right DLPFC: 37, 43, 28, $P = 0.001$; **Fig. 5a**,**b**); left FEF activity did not change, whereas adjacent clusters in right FEF showed opposite patterns (right precentral gyrus: 31, –15, 61, $P = 0.02$ acute > chronic; right precentral gyrus: 40, –10, 43, $P = 0.01$ chronic > acute). See **Supplementary Table 2** for a complete list of coordinates.

To confirm that dorsal posterior parietal cortex was the site of activity imbalance, we carried out a regional ANOVA using regions of interest (ROIs) from the young adult group in IPS (anterior and posterior) and FEF (medial and lateral), regions previously shown to be involved in controlling spatial attention[18]. This analysis confirmed an imbalance in dorsal parietal cortex but not in the FEF (**Supplementary Fig. 1**).

The interhemispheric push-pull pattern in dorsal parietal cortex is consistent with the hypothesis that the lateralized (rightward) bias in neglect is caused by a left hemisphere–orienting mechanism that is relatively hyperactive[32]. If left parietal cortex hyperactivity mediates the rightward spatial bias, then greater activity in left SPL should correlate with a greater number of missed targets; this invariably occurred in the left visual space. A voxel-wise ANOVA identified several left hemisphere regions active for missed targets; one of the most significant regions was the left SPL (–15, –79, 40; **Fig. 5c**). In a second analysis, we directly compared hit and miss trials in a voxel-wise ANOVA. Once again we found significant effects in left SPL (graph in **Fig. 5c**) where the response was significantly stronger for miss than for hit trials ($F_{7,70} = 3.85$, $P = 0.001$), especially at the acute stage (response × stage × MR frame; $F_{7,70} = 3.16$, $P = 0.006$). Finally, we found a positive significant correlation between rightward bias and left SPL activity ($r^2 = 0.36$, $P = 0.051$) at the chronic stage (see **Supplementary Fig. 2**), confirming that hyperactivity in this region correlated with poor orienting toward the left visual field.

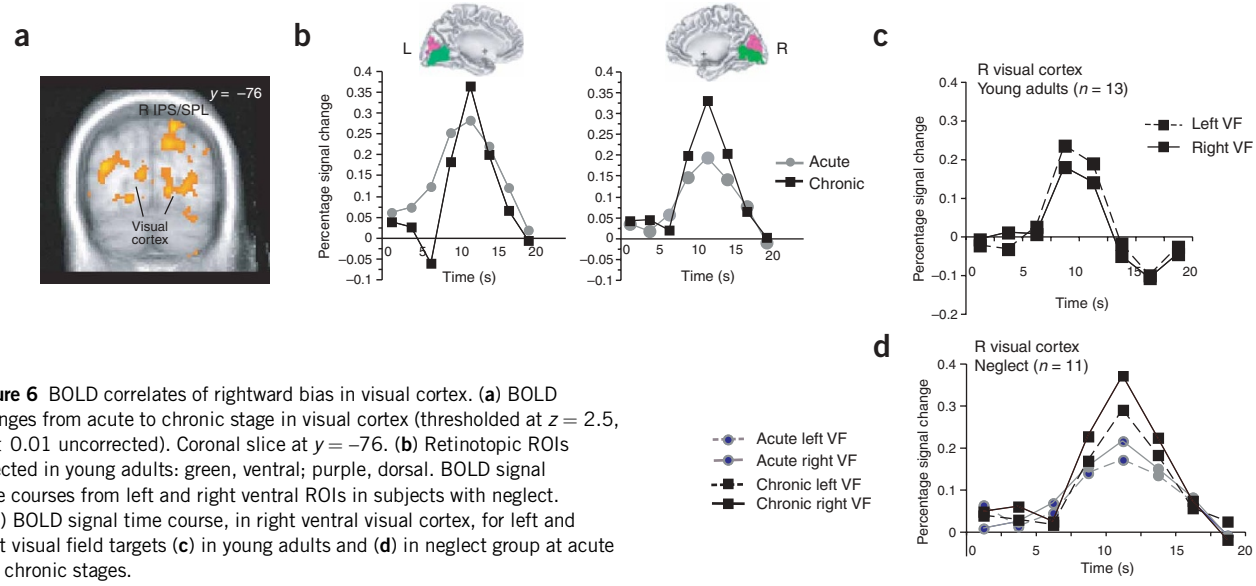

Figure 6 BOLD correlates of rightward bias in visual cortex. (**a**) BOLD changes from acute to chronic stage in visual cortex (thresholded at $z = 2.5$, $P < 0.01$ uncorrected). Coronal slice at $y = –76$. (**b**) Retinotopic ROIs selected in young adults: green, ventral; purple, dorsal. BOLD signal time courses from left and right ventral ROIs in subjects with neglect. (**c**,**d**) BOLD signal time course, in right ventral visual cortex, for left and right visual field targets (**c**) in young adults and (**d**) in neglect group at acute and chronic stages.

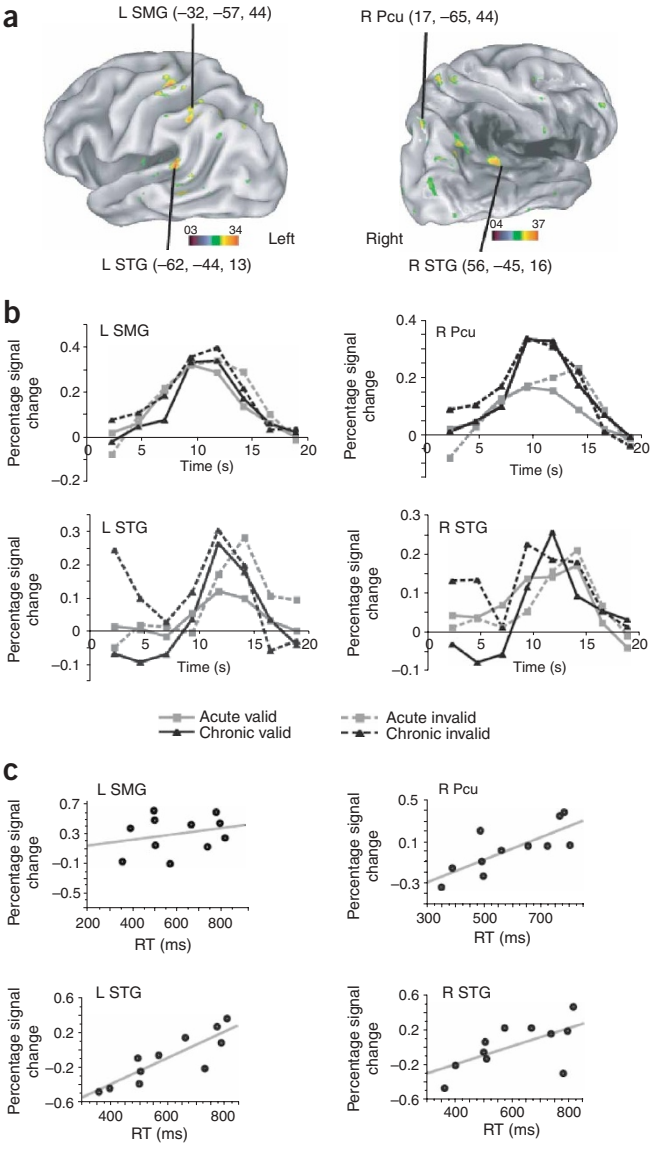

Figure 7 BOLD correlates of attentional reorienting. (**a**) Regions involved in the recovery of reorienting. ANOVA (stage × validity × MR frame) interaction map (expressed as *z*, thresholded at $z = 2.5$, $P < 0.01$ uncorrected). (**b**) BOLD signal time courses for valid and invalid trials at acute and chronic stages, averaged over left and right visual fields. (**c**) Correlation across subjects between the magnitude of the BOLD signal and reaction, on invalid trials at the acute stage. Pcu, precuneus.

Visual cortex

Neural models of attention[24,33] postulate that posterior parietal cortex interacts with visual cortex for the selection of relevant objects. Our hypothesis predicted that activity in visual cortex should mirror the push-pull interhemispheric pattern observed in posterior parietal cortex. Many regions in visual cortex showed significant changes in task-related BOLD activity from the acute to the chronic stage (**Fig. 6a**). To test this hypothesis, dorsal and ventral retinotopic ROIs were selected from visual cortex in the young adult group (see **Supplementary Methods**), and signal time courses were extracted from these ROIs in the neglect group at the acute and chronic stages. In both ventral and dorsal retinotopic ROIs, we observed a relative imbalance at the acute stage with more activity in the left than right hemisphere, and a rebalancing at the chronic stage with a reactivation of the right hemisphere (graph in **Fig. 6b**). This was confirmed by a significant interaction of stage (acute or chronic) × hemisphere (left or right) × time in ventral visual cortex (three-way ANOVA; $F_{7,70} = 2.62$ $P = 0.02$) and stage × hemisphere × visual field × time in dorsal visual cortex (four-way ANOVA; $F_{7,70} = 2.59$, $P = 0.02$). In right dorsal occipital cortex, the reactivation was larger for targets in the left (contralesional) than in the right (ipsilesional) visual field. All results were confirmed when using only hit trials.

We also observed a disruption of spatially selective responses in right visual cortex. In the young adult group (**Fig. 6c**), targets in the contralateral visual field evoked stronger responses than did targets in the ipsilateral visual field ($F_{7,84} = 3.18$, $P = 0.0049$), especially in the right hemisphere ($F_{1,12} = 6.4$, $P = 0.03$). In the neglect group (**Fig. 6d**), a normal lateralization was observed in left visual cortex, whereas in right visual cortex, targets in the left (contralesional) visual field evoked significantly less activity than did those in the right (ipsilesional) visual field (three-way ANOVA: MR frame × hemisphere × visual field; $F_{1,10} = 4.83$, $P = 0.05$). When compared to the young adult group, this inversion was significant at the acute stage (four-way ANOVA: hemisphere × visual field × MR frame × group; $F_{7,154} = 2.38$, $P = 0.02$) but not at the chronic stage, even though the time course of the BOLD signal was not qualitatively different (**Fig. 6d**). Correlation analyses showed only marginal correlations between left or right visual cortex activity and measures of rightward bias (all comparisons, $0.05 < P < 0.10$).

Temporoparietal junction

The second index of behavioral recovery was the improved ability to reorient to unattended locations. This function is known to correlate with the recovery of spatial neglect[31] and is specifically associated with damage to the STG[16]. The TPJ region was defined in our laboratory as the clusters of activation in SMG and STG that show a differential response to unattended (invalidly cued) versus attended (validly cued) visual targets (**Fig. 1**). This region was damaged in 5 of 11 subjects (**Fig. 2a**).

We observed some reactivation in the ventral part of the TPJ from the acute to the chronic stage (right STG: 63, –44, 21, $P < 0.001$; right parietal operculum: 57, –35, 35, $P < 0.01$; see **Supplementary Table 2**), but the degree of reactivation depended on the presence of anatomical damage (**Supplementary Fig. 3**).

To identify regions whose activity varied as a function of both the stage of recovery and attentional reorienting, as indexed by target validity, we ran a voxel-wise ANOVA with MR frame, stage (acute or chronic) and target validity (valid or invalid) as factors. We identified several regions that showed an interaction of stage × validity × time, including left and right STG (ventral part of TPJ), but also dorsal regions such as the right precuneus and left IPS (**Fig. 7a** and **Supplementary Table 3**). This reorienting network in stroke-affected subjects largely overlapped with that recruited in normal subjects under the same conditions. Time-course analysis indicated that the interaction was carried by a weaker and delayed response at the acute stage, especially for invalid targets (**Fig. 7b**). This interaction was very clear in right TPJ when the time-course analysis compared subjects with and without anatomical damage to this region (**Supplementary Fig. 3**).

The modulation of right TPJ by both the stage of recovery and attentional reorienting (that is, target validity) was confirmed by replicating the stage × validity × time interaction in a regional ANOVA, in which the ROI was independently selected from the

young adult group. Only the hit trials were included to avoid contamination from error related signals. Finally, we observed, in TPJ and other regions of the reorienting network, a specific correlation at the acute stage between the magnitude of the BOLD signal and the reaction time to invalidly cued targets (left STG: –62, –44, 13, $r^2 = 0.73$, $P < 0.001$; right STG: 56, –45, 16, $r^2 = 0.39$, $P = 0.04$; right precuneus: 13, –43, 60, $r^2 = 0.54$, $P = 0.01$; **Fig. 7c**). No relationship was found for validly cued targets except in left STG ($r^2 = 0.49$, $P = 0.02$), eliminating an effect of time on task as an explanation for the correlation. None of these effects interacted with the visual field of the target (all comparisons, $P > 0.05$).

DISCUSSION

We showed that attentional deficits in spatial neglect did not depend just on neuronal dysfunction at the site of injury, but were mediated by the combined structural and functional dysfunction of two interacting frontoparietal attention networks. The recovery of spatial attention deficits, accordingly, correlates with the reactivation and rebalancing of normal activity within these networks.

BOLD signals in human stroke model

There is growing evidence that BOLD signals may be abnormal in individuals with stroke; hence an important issue is whether our findings might be artifactual. Mechanisms linking local neuronal activity to local hemodynamic changes (blood flow or BOLD)—so-called neurovascular coupling—may be impaired after a stroke, even in the unaffected hemisphere[34–36]. Although these findings suggest caution in relating BOLD-fMRI signals to neuronal changes in stroke-affected individuals, they cannot explain the current findings. First, changes in the BOLD response during recovery showed a strong correlation with performance. Second, although in many areas recovery was associated with larger BOLD responses, in other areas recovery induced an attenuation of a relatively hyperactive response. Third, none of the strokes in our sample were lacunar—the type associated with artifactual decrement in task-evoked BOLD response[35]. Finally, most of the results we report occurred in areas that were distant from the core of the lesion where time-dependent changes have been reported[36].

Rightward bias and reorienting

We found different neural correlates for two separate spatial attention deficits and their recovery: rightward spatial bias and the reorienting deficit.

The rightward spatial bias, a relative impairment in detecting targets in the left visual field, was associated with a relative functional imbalance at the acute stage in dorsal parietal cortex (IPS-SPL) and visual cortex. At the chronic stage, activity in these regions rebalanced in parallel with behavioral recovery.

Our interpretation is that the decreased BOLD responses at the acute stage in dorsal parietal cortex reflects the lack of an excitatory 'circuit-breaking' stimulus-driven signal from injured ventral areas during target detection (**Fig. 1**). Under normal conditions this signal reorients the dorsal system to relevant events, but after VFC damage, its absence induces a relative deactivation of ipsilateral (right) dorsal parietal cortex. The resulting functional imbalance, at the acute stage, in dorsal parietal and visual cortices is manifested as a relative hyperactivation on the left and relative deactivation on the right (dynamic imbalance, **Fig. 1**). This imbalance and the rebalancing that occurs over time are consistent with competitive (possibly cross-inhibitory[37]) interactions between oppositely lateralized orienting mechanisms for directing attention and visual representations, as previously hypothesized[32]. The results of our experiment provide evidence for these competitive interactions, localize the site of competition to dorsal parietal cortex and show a clear functional interaction between dorsal parietal and visual cortices.

The relationship between activity changes in dorsal parietal cortex and the rightward spatial bias was supported by two independent analyses. There was a relatively higher response in left SPL in subjects who detected fewer targets in the left visual field and in those who responded more slowly to left, as compared to right, visual field targets. Notably, the shape of the BOLD response, in left SPL, to missed targets was sustained and outlasted the response to detected targets (**Fig. 5**), suggesting that the orienting bias in SPL was tonic and endogenous. Tonic oculomotor biases that are independent of visual stimulation have been described in neglect[38].

The response in right visual cortex, especially at the acute stage, not only was decreased but also did not show a normal lateralization—that is, a stronger response to contralateral (left) than to ipsilateral (right) visual targets (**Fig. 6**). One interpretation of these results is that unbalanced top-down modulation from dorsal parietal cortex decreased both stimulus-evoked responses and spatial selectivity of visual neurons, weakening the relative salience of stimuli presented in the left visual field. That is, the rightward spatial bias may reflect both abnormal orienting mediated by imbalanced IPS-SPL activity and abnormal sensory processing of stimuli in the left visual field. However, as there was no clear relationship between BOLD response in visual cortex and rightward bias, the role of visual neurons in mediating the rightward bias will require further tests, such as the separation of cue- and target-related activity or the correlation, trial by trial, of brain activity and behavioral performance.

A second key deficit in spatial neglect is the inability to reorient to behaviorally relevant stimuli presented at unattended locations: the so-called disengage deficit[30]. Our subjects with neglect showed good recovery of reorienting, with faster and more accurate responses over time to unattended targets. Previous work correlated stimulus-driven reorienting with a right hemisphere–dominant ventral and dorsal network, including TPJ[24]. Here, we found that reorienting deficits and their recovery also correlated with functional changes in a similar network. In subjects with lesions restricted to ventral frontal cortex and related subcortical structures (**Supplementary Figs. 2** and **3**), right TPJ reactivated from the acute to the chronic stage (**Supplementary Fig. 3**), and this reactivation was modulated by whether the target was attended or unattended (**Fig. 7**). For targets presented at unattended locations, BOLD signals in right and left STG (a subregion of TPJ) were delayed at the acute stage as compared to the chronic stage (**Fig. 7** and **Supplementary Fig. 3**). Moreover, at the acute stage, subjects with stronger STG activity responded more slowly to targets at unattended locations. One interpretation is that signals in the TPJ indexed the time it takes to reorient to a novel location of interest, a process that was delayed at the acute stage.

A new anatomical model of spatial neglect

These results provide a new framework for thinking about the pathophysiology of spatial neglect and reconcile functional neuroimaging results with the anatomy of neglect. Ventral lesions in frontal or temporoparietal cortex[12–14] cause dysfunction of dorsal parietal areas that seem to mediate a rightward bias during spatial attention.

However, isolated damage to these dorsal areas does not typically cause neglect, even though it can produce deficits of eye movements, attention and visuomotor hand coordination[39,40]. Therefore, damage (functional or structural) to both dorsal and ventral attention networks is necessary for neglect to occur. This result rules out the possibility that spatial neglect results from the critical dysfunction of one brain area[14].

The TPJ region is crucial because it provides a signal that marks sensory events of interest for the dorsal system, especially when they are unattended. Damage to TPJ produces two effects that contribute to neglect. First, it decreases the overall detection capacity—that is, the capacity across the visual field[11]. Second, it biases competitive interactions between orienting mechanisms in dorsal parietal cortex[32]. Therefore, a stimulus in the left visual field will be at a disadvantage, as compared to a stimulus in the right visual field, on two counts: (i) a decreased stimulus-driven capture resulting from damage of right TPJ and (ii) a top-down bias against exploring leftward locations, owing to imbalanced orienting mechanisms in left and right IPS. The idea that non-spatial processing deficits contribute to spatial neglect and may exacerbate spatial biases has been suggested before[9,10], but we provide a new anatomical framework in which to think about these interactions.

The right hemisphere dominance of spatial neglect has previously been explained by theories that emphasize hemispheric asymmetries in spatial maps, with right parietal cortex coding for both sides of space and left parietal cortex coding predominantly for the contralateral (right) space[6,8,41]. However, recent studies, in normal observers, that mapped visuotopic responses in frontal and parietal cortices have not revealed any hemispheric asymmetry in spatial representations or orienting signals[22,23]. In contrast, there is compelling evidence for a right hemisphere–dominant ventral attention system, including TPJ (reviewed in ref. 24). Therefore, our current hypothesis is that the higher frequency of left-sided neglect is a function of the right hemisphere dominance of non-spatial processes mediated by right TPJ, coupled with their physiological impact on ipsilateral spatial processes mediated by IPS- SPL.

Implications regarding mechanisms of recovery of function

These results show that a neurological deficit after focal brain injury does not reflect only local dysfunction at the site of injury, but also is determined by the distributed impairment of connected neural systems that are structurally intact[2,3]. This dysfunction may be reflected neurally—not just by diaschisis at rest, as shown in previous studies[17,27,28]—but also by deactivation, hyperactivity or interhemispheric imbalance during task processing, as shown here.

Although this distributed impairment principle has been demonstrated here for spatial neglect, it is likely to apply to other deficits such as aphasia or sensory-motor deficits, and thus have widespread implications for the fields of neuropsychology and neurology. For example, the localization of specific neuropsychological syndromes on the basis of anatomical information should be re-examined by combining both anatomical and functional information.

That a behavioral deficit reflects a distributed dysfunction does not imply that different nodes of a functional network do not perform specialized operations. The notion of distributed injury is neutral with respect to the issue of whether cognitive operations in the intact brain are carried out in specialized nodes (one-to-one mapping) or over many nodes (one-to-many), or whether different operations are mapped to the same node as a function of task demands (many-to-one). Nonetheless, in our case the evidence strongly indicates a relative specialization of different nodes—as in the case of IPS-SPL for directing attention or TPJ for reorienting attention.

The notion of competition between hemispheres and the negative influence of activity in the intact hemisphere is emerging as an important principle at the systems level to understand recovery of function, not only in spatial neglect, but also in studies of motor and language recovery[42,43]. Modulation of these competitive interactions either by increasing the excitability of the ipsilesional cortex or by decreasing the excitability of the intact cortex should have a beneficial effect[44]. For example, we predict that in individuals with chronic neglect who show a persistent rightward bias despite extensive rehabilitation, there should be persistent left SPL hyperactivation; reducing that hyperactivity should be beneficial. This hypothesis has been tested with some success in TMS studies that have broadly targeted the left parietal cortex of individuals with neglect[45]. Our results suggest a more specific site where TMS treatment might have a favorable therapeutic effect.

METHODS

Participants were eleven patients (mean age 60 years; 8 male) with right frontoparietal stroke and clinical neglect. Both behavioral testing and fMRI were conducted first in the acute stage (3–4 week post-stroke) and then at the chronic stage (>6 months post-stroke). Individual lesions were segmented (in atlas space) using a supervised fuzzy class-means procedure on the basis of co-registered T1- and T2-weighted structural data acquired in the chronic stage. The Posner task was implemented during fMRI as previously described[18,24]. Details of functional scanning procedures (sequence parameters and data analysis techniques) are as previously described[18,21]. Additional technical details are given in the **Supplementary Methods**.

Note: Supplementary information is available on the Nature Neuroscience website.

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COMPETING INTERESTS STATEMENT

The authors declare that they have no competing financial interests.

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