NeuroImage 62 (2012) 2271–2280

Contents lists available at SciVerse ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Review

Why use a connectivity-based approach to study stroke and recovery of function?

Alex R. Carter [a,*], Gordon L. Shulman [a], Maurizio Corbetta [a,b,c]

[a] Department of Neurology, Washington University School of Medicine, St. Louis, MO 63110, USA
[b] Malinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, MO 63110, USA
[c] Department of Anatomy and Neurobiology, Washington University School of Medicine, St. Louis, MO 63110, USA

ARTICLE INFO

Article history:
Accepted 24 February 2012
Available online 5 March 2012

Keywords:
Stroke
Recovery
fMRI
Resting state
Connectivity
Inter-hemispheric

ABSTRACT

The brain is organized into a set of widely distributed networks. Therefore, although structural damage from stroke is focal, remote dysfunction can occur in regions connected to the area of lesion. Historically, neuroscience has focused on local processing due in part to the absence of tools to study the function of distributed networks. In this article we discuss how a more comprehensive understanding of the effects of stroke can be attained using resting state functional connectivity BOLD magnetic resonance imaging (resting state fcMRI). Resting state fcMRI has a number of advantages over task-evoked fMRI for studying brain network reorganization in response to stroke, including the ability to image subjects with a broad range of impairments and the ability to study multiple networks simultaneously. We describe our rationale for using resting state connectivity as a tool for investigating the neural substrates of stroke recovery in a heterogeneous population of stroke patients and discuss the main questions we hope to answer, in particular whether resting state fcMRI measures in the acute phase of stroke can predict subsequent recovery. Early results suggest that disruption of inter-hemispheric connectivity in the somatomotor network and the dorsal attention network is more strongly associated with behavioral impairment in those domains than is intra-hemispheric connectivity within either the lesioned or unaffected hemisphere. We also observe in the somatomotor network an interesting interaction between corticospinal tract damage and decreased inter-hemispheric connectivity that suggests that both processes combine to contribute to neuromotor impairment after stroke. A connectivity-based approach will provide greater insight into network reorganization in the acute and chronic phases after stroke and will contribute to improving prognostic ability and the development of therapeutic interventions.

Contents

* Corresponding author. Fax: +1 314 362 6911.

1053-8119/$ – see front matter © 2012 Elsevier Inc. All rights reserved.
doi:10.1016/j.neuroimage.2012.02.070

From local structural damage to physiological impairment in distributed functional networks

Stroke is unlike many other neurologic disorders. For example, most progressive neurodegenerative diseases are insidious in onset, but stroke occurs suddenly in a system that is intact until the onset of symptoms. Moreover, structural damage from stroke is focal rather than diffuse, although stroke is associated with both local and global changes in brain function. Also, because the disease process is generally static after the initial insult, subsequent changes in brain function represent how the brain responds to injury rather than representing ongoing pathologic processes. These and other features of stroke discussed below create unique challenges and opportunities with regard to the use of a connectivity-based approach to studying the effect of focal lesions on brain function and recovery, as well as the organization of normal neurological systems. We will discuss the use of resting state functional connectivity MRI (fcMRI) to study stroke in the context of our ongoing NIH-funded longitudinal study of stroke recovery.

Historically, the observation that certain patterns of neurologic impairment were often associated with damage to different brain regions represented a very significant advance in our understanding of the brain. As a result, the mapping of symptoms to focal lesions has been a mainstay of neurology research since the early 19th century and continues to this day (Bartolomeo, 2011; Gillebert et al., 2011; Kalenine et al., 2010). Although this approach has taught us a lot about the specialization of different brain regions, it has also blinded us to a network perspective. Consequently, researchers are often befuddled when experimental results suggest that lesions in different brain locations are associated with a similar clinical picture, as in hemispatial neglect. Recent studies of neglect have suggested that white matter lesions may be just as important as cortical damage, emphasizing anatomical connectivity (Bartolomeo et al., 2007; Doricchi et al., 2008; He et al., 2007a; Karnath et al., 2009; Urbanski et al., 2011). We believe our understanding of central neurological disorders is limited by the longstanding focus on local function within brain regions, and that a conceptual framework based on connectivity and neural communication across regions (He et al., 2007b) provides a useful heuristic that is consistent with most recent views of the brain as organized in an ensemble of functional networks.

Functional connectivity MRI (fcMRI) as a tool to study the functional organization of the brain

Measurement of temporal correlation of the BOLD signal between different regions at rest (functional connectivity MRI, or fcMRI) has emerged as a powerful tool to map the functional organization of the brain (see Van Essen et al., 2012). A growing number of studies are employing this technique to map the spatio-temporal covariance structure of networks of spontaneous activity in the brain at rest. It is now well established that many networks are robust, i.e. consistent across subjects, and involve sensory (visual, auditory, somatosensory) and motor regions of the brain, as well as a number of associative 'control' networks (default, dorsal attention, fronto-parietal, ventral attention) (Fox et al., 2005; Greicius et al., 2003; Vincent et al., 2007). From a theoretical perspective, the main appeal of fcMRI is that it allows a direct and fairly straightforward measure of interaction between areas of the brain, and that the signal, not depending only on direct mono-synaptic connections (Honey et al., 2009; Vincent et al., 2007), provides a fairly large scale view of different functional systems across the whole brain. It is therefore an ideal tool to study the remote physiological effects of lesions on distant areas.

Advantages of resting state fcMRI over task-evoked fMRI

It is appropriate to discuss herein the relative pros and cons of traditional task fMRI vs. fcMRI to study behavioral deficits in stroke and their recovery. Task-based functional neuroimaging has been used to study recovery of function (Corbetta et al., 2005; Saur et al., 2006; Ward et al., 2003) and has provided important information on the patterns of functional reorganization post-stroke in several domains including motor (Loubinoux et al., 2003; Ward et al., 2003); language (Buckner et al., 1996; Meinzer et al., 2011; Saur et al., 2006); and attention (Corbetta et al., 2005). In a typical example subjects with stroke producing a specific deficit, e.g. hemiparesis secondary to subcortical strokes (Chollet et al., 1991) are selected, and then scanned either at one or multiple time points post-stroke for comparing patterns of activation produced by the normal and impaired hand. A primary requirement for this experiment to work is that patients must have enough function to be able to carry out the experimental task. This profoundly limits the number of patients that can be studied, and their severity since only mild-to-moderate patients will be able to participate. Even if subjects can perform the task, the interpretation remains problematic if performance is not matched between patients and controls. To overcome this problem parametric designs have been proposed (Ward et al., 2003). Another limitation is that neuroimaging studies based on activation paradigms are tailored to a particular neural system, while stroke symptoms may reflect dysfunction across multiple systems. More generally it is an intellectual abstraction that one study is about 'motor' or 'language' recovery since most patients present with a combination of deficits in different domains that are not usually controlled for in the enrollment. Finally, task-evoked studies traditionally provide little information about temporal interactions between regions. While a number of methods have been proposed to study interaction and directional influences, these methods have had limited application because either they require strong assumptions or their signal-to-noise is relatively modest, especially for experimental paradigms (e.g. event-related designs) in which regional interactions are relatively limited in time.

We believe that fcMRI studies provide a number of distinct advantages over task-evoked fMRI to study the pathogenesis of behavioral deficits in brain disorders, especially for conditions such as stroke, multiple sclerosis, traumatic brain injury and Alzheimer's disease in which the communication among regions/networks is impaired. As mentioned above the main strength of fcMRI is that it provides a fairly direct and simple measure of regional interaction. The measure is robust because it is based on the computation of a Pearson's r-score between two time-series (one for each region) of the BOLD signal over long periods of time (10–30 min). As a result fcMRI measures are not only robust at the group level, as in most task fMRI studies,

but also in single subjects. This provides potentially the opportunity to use data in single subject for individual diagnosis, prognosis or monitoring of therapy. Another major advantage of fcMRI is that it can be easily obtained even in severe patients that cannot participate in cognitive testing in the scanner. We have scanned comatose intubated patients, and although these more severe cases are technically challenging, it is possible to study with this method even single cases of unusual presentations. A third major advantage is that in a single scan it is possible to obtain a survey of multiple networks at once, in contrast to task fMRI in which only regions driven by the task will be seen.

There are also major potential limitations. The major weakness of fcMRI is that brain signals and behavioral measures are obtained in different sessions. In the early days of SPECT and FDG-PET, the ability to measure simultaneously behavior and brain function first with O15-water PET, then with fMRI was hailed as a major step forward. Today, nearly 20 years later from those first studies in neurological patients, we are assuming again that it is sensible to measure behavior and brain physiology separately. This belief is based on a growing literature in normal subjects (Albert et al., 2009; Hampson et al., 2006; Lewis et al., 2009; Tambini et al., 2010; van den Heuvel et al., 2009) showing that in healthy subjects behavioral parameters and learning are significantly correlated with patterns of resting functional connectivity. The Human Connectome Project (see Van Essen et al., 2012) is seeking to demonstrate inter-individual variability of such relationship. Work in numerous clinical conditions including stroke (Carter et al., 2010; Grefkes and Fink, 2011; He et al., 2007a; James et al., 2009; van Meer et al., 2010; Westlake and Nagarajan, 2011) have also shown an association between behavioral deficits and their recovery and changes in fcMRI. It remains, however, to be seen in a large prospective study (such as the NIH-sponsored project we are currently conducting) whether, and what patterns of functional connectivity more closely predict behavioral deficits, and whether fcMRI explains more behavioral variability than simple structural measures of lesion volume or location (see below). It remains also to be seen whether fcMRI changes in stroke reflect a state or a trait change, i.e. are they robust across different sessions? Or, do they reflect idiosyncratic patterns related to recent behavioral activity? A final important point is whether fcMRI signals will be sensitive and correlate with changes in behavior over time. In preliminary work on a small sample of subjects (N = 11), for instance, we found good correlation between attention scores in neglect subject at the acute stage in structurally normal regions of posterior parietal cortex, and improvement of connectivity over time (from 3–4 to 39 weeks), but no correlation with recovery of function. This issue resonates with the trait vs. state issue, because if fcMRI were to underlie the latter, then behavioral correlations at each stage (acute, chonic) may be easier to obtain than behavioral correlation across time points.

What do we hope for from a connectivity approach?

The answers fall into two main categories, clinical and theoretical. From a clinical perspective, we hope that examining stroke through the lens of connectivity may improve our ability to correlate behavioral deficits to structural/functional indices of dysfunction. We expect that each behavioral deficit and its variability across patients will likely be explained by a combination of structural variables (location, volume) and their interaction with measures of structural (e.g. integrity of the white matter and pathways), and functional connectivity (see below).

A second promise is that measures of connectivity will improve our prediction of clinical outcomes. Previous attempts based on structural damage alone have been disappointing. Analysis of some large cohorts such as the Copenhagen study have provided some general guidelines, but at the individual patient level, predicting which stroke patient will reintegrate into society and which will be relegated to a life of disability is difficult. Multiple studies have considered factors like stroke lesion volume (Protopsaltis et al., 2009), location (Pan et al., 2006) and etiology as prognostic factors of long-term outcome, but results are conflicting and conventional MRI scans have not yielded conclusive added value in the prediction of resuming activities of daily living in the long term (Schiemanck et al., 2006). The ability to assess multiple networks at once and their interaction may be especially valuable since in the real world stroke patients rarely have deficits in just one functional domain (e.g. neglect patients may also show profound motor impairments). Hence, assessments of the functional integrity or reconfiguration of multiple networks may be necessary for accurate prediction. For instance a recent study showed that patterns of functional connectivity across multiple networks were able to predict the developmental age of normal children (Dosenbach et al., 2010).

Finally, understanding disorders of network connectivity may lead to a more rational approach to developing novel therapeutic interventions. For instance, the discovery of pathological increases in connectivity between regions after stroke might suggest that disruption of such connectivity via non-invasive brain stimulation could have a therapeutic effect.

It is appropriate to mention that as exciting as these developments may appear, similar promises have been made before at the inception of each of the various neuroimaging methods developed in the last 25 years (PET, SPECT, fMRI, MEG). Even so, and based on our own experience of using different methods in the last 15 years or so of research in this area, our impression is that fcMRI is the most promising of the methods thus far available to study stroke recovery.

Connectivity analysis in patients can also provide new theoretical insights. First, the timing and extent of changes in connectivity can extend our understanding of mechanisms of neuroplasticity at the network scale. Task-based fMRI has already taught us some lessons about network reorganization after stroke. A consistent observation is the activation of more extensive cortical areas after stroke (Feydy et al., 2002; Saur et al., 2006; Tombari et al., 2004; Ward et al., 2003). Initially it was thought that this widespread activation reflected the recruitment of adjacent or contralateral cortical regions to compensate for the deficit, but several studies have determined both cross-sectionally and longitudinally that persistent over-activation is negatively associated with function and recovery (Bestmann et al., 2010; O'Shea et al., 2007; Riecker et al., 2010) and, that conversely re-focusing and normalization of activation patterns to pre-injury levels and topography correlates with better outcome. Accordingly efforts are under way to use this model to 'down-regulate' regions of brain over-activation with methods that transiently disrupt cortical function like transcranial magnetic stimulation (TMS). Functional connectivity analysis of similar conditions would allow to understand whether the regional interaction, and not just the focal level of activation, is disrupted, and what patterns separate good from poor outcome. In relation to the question of contralateral over-activation, study of intra- vs. inter-hemispheric patterns of functional connectivity seems especially relevant (see below). Second, patterns of connectivity may contribute to testing of neuro-cognitive models based in healthy subjects. A relevant example is a model of attention that posits physiological interactions between two cortico-cortical network of regions involved in the control of visual attention (Corbetta and Shulman, 2002). The putative interaction between networks was demonstrated in a series of studies in neglect subjects in which lesions overlapping with the more ventral network cause physiological, both task-evoked and functional connectivity, abnormalities in the structurally intact dorsal network (Corbetta et al., 2005; He et al., 2007b). Third, in combination with behavioral analyses, we can begin to dissect which connections in a widely distributed brain network are most relevant for neuro-rehabilitation. Again in neglect, a recent analysis based in part on functional and structural connectivity results argues that different behavioral deficits in neglect emerge from damage to different networks for attention (Corbetta and Shulman, 2011). These deficits

are amenable to different interventions, and it would be valuable to be able to assess physiologically which pattern of behavior/functional connectivity impairment a specific patient suffers from. Fourth, effective connectivity approaches can show us which nodes in a network are driving which other nodes, thereby providing crucial knowledge about the direction of information flow and ultimately what kinds of computations are being performed in the system. In a recent study we showed that dorsal parietal and frontal areas commonly recruited by spatial attention generate a top-down signal onto visual cortex during orienting to spatial locations (Bressler et al., 2008). Based on this result we used TMS to disrupt top-down signals in visual cortex during spatial attention, and were successful in causing behavioral deficits in healthy subjects (Capotosto et al., 2011). In parallel, occipital rhythms associated with the allocation of spatial attention were also disrupted. Measurement of similar signals in patients with visual disorders would be very important not just for clinical reasons, but also to demonstrate top-down influence of fronto-parietal regions on visual cortex.

A theoretical framework for connectivity-based approach to reorganization

We propose that stroke impairs behavioral functions because it disrupts communication in distributed brain networks that are relatively specific to particular behavioral domains, yet are widely distributed in the brain. The degree of initial disorganization and then dynamic reorganization over time of these functional brain networks may determine the amount of acute impairment and then the level of post-stroke recovery, respectively. An important idea here is that recovery of function is largely determined by a reorganization of activity in existing cortical/subcortical networks, and that this reorganization is present not only during active tasks, i.e. when the networks are recruited, but also at rest. Therefore a stroke causes a 'functional state' change in the distributed landscape of spontaneous brain activity. This 'state' change at rest will impact the way these networks are recruited during active behavior. This relationship explains why measures of resting state activity may relate to behavioral deficits. We can think of this state change as a new set of hills and valleys in the landscape of spontaneous activity across multiple networks in the brain. In non-linear dynamics, this landscape can be formalized as a set of attractors. Recovery is the process with which the brain settles back into a nearly normal landscape, while poor outcome may be thought of as a reorganized state whose output is non-optimal. This framework makes it clear why multi-network assessment may be key to understanding or prognosis. Preliminary support for this framework comes from proof-of-concept studies in neglect and motor deficits (Deco and Rolls, 2004; Grecucci et al., 2008; Krebs et al., 2009; Park et al., 2011; J. Wang et al., 2010). In the last 2 years we have embarked on a large scale study trying to test some of the above ideas in a much larger sample of stroke patients studied prospectively and longitudinally.

Our experimental approach

This study prospectively enrolls patients with a first-ever stroke regardless of the nature and severity of their neurologic deficits, as long as they are medically stable and can safely tolerate MRI scanning and behavioral testing. This design feature is important to highlight because the frequency, severity, and co-occurrence of deficits in this sample reflects what is observed in the community. Patients are studied longitudinally within the first 2 weeks from symptom onset when their deficits are still severe, at 3 months, and finally at 12 months. These time points capture the recovery curve of most deficits. At each time point, we obtain resting state fcMRI, anatomical imaging and behavioral performance on a battery of clinical and cognitive tasks that reflect the function of networks of interest (attention, language, motor, memory, vision and default). While neuropsychological studies often involve homogeneous samples based on a common behavioral or anatomical categorization (e.g. 'neglect' patients or 'right intraparietal lobule (R IPL)' patients), a large ($n = 200$) heterogeneous sample can be analyzed without the use of categorizations, which can involve arbitrary thresholds or cut-off scores. Essentially, a large variation in behavioral scores and connectivity scores across stroke patients allows a sensitive assessment of how connectivity relates to behavior while controlling for the presence of stroke and for lesion volume. The use of a heterogeneous sample is most advantageous when the integrity of multiple networks can be assessed efficiently, as with resting state fcMRI, and when a broad range of behavioral measures is collected.

Questions

A set of complementary goals have been developed around the major resting state networks, addressing the question of how networks are affected by and reorganized after a focal lesion. First, we use resting state functional connectivity to explore how focal structural lesions lead to dysfunction in brain regions that are structurally intact, but connected to the area of structural damage. This "distributed injury hypothesis" is the basis for all studies of altered connectivity after a focal lesion. Second, the separation of the brain into two hemispheres is arguably the most obvious structural/functional organizing principal. However, the relative importance of intra-hemispheric versus inter-hemispheric connectivity seems to be important on the basis of task fMRI studies (see above). Third, network connectivity can be examined at different scales, and connectivity measures may reflect whole network connectivity, as in some graph measures of network properties (Bullmore and Sporns, 2009) or local connectivity between two specific ROIs. Whether global network connectivity or connectivity between specific ROI pairs is more behaviorally relevant is not known. Fourth, is it possible to disentangle the relative contributions of structural damage and altered physiology to behavioral deficits? Fifth, how are deficits within single or multiple behavioral domains related to interactions between different networks? And finally, does how any (or all) of these relationships change over time predict the course and ultimate level of recovery?

Methodological considerations

BOLD image acquisition and quality assurance

Patient groups may show poorer quality BOLD resting data than control groups because of physiological artifacts such as increased movement which has recently been shown to cause an underestimation of long-range BOLD correlations and an overestimation of short-range correlations (Power et al., 2012). In addition to assessing the prevalence of artifacts across groups, the use of procedures for identifying and removing MR frames with high artifact from the resting time-series is advisable. We have examined several automatic procedures based on quantitative assessments of subject movement and image variance. Preliminary results show that these procedures can increase the signal-to-noise ratio. To some extent, these problems are mitigated by the use of a large heterogeneous sample in which patients essentially serve in both experimental and control groups.

Cerebrovascular status

Arterial spin labeling (ASL) can be used to investigate and control for changes in overall cerebral perfusion (see Supplementary data). We will also control for carotid stenosis. We will have access to clinical information on carotid Doppler studies to evaluate the impact of the degree of carotid obstruction on fcMRI and perfusion measures.

The degree of obstruction can be used as a covariate of no interest in the analysis.

Atlas transformation

Theoretically, the local deformation of the brain of stroke patients due to ischemia, edema or hemorrhage might interfere with optimal image registration. However, although we mask out the lesion in the final stages of computing the atlas transform, we have observed minimal effects of a lesion on image registration.

Lesion segmentation and symptom mapping

Using atlas-transformed T1-weighted MP-RAGE and T2-weighted spin echo images, lesions are manually segmented using the Analyze biomedical imaging software system. As much as possible, hyperintensities on T2 weighted images are matched to hypointensities on T1W images. All segmented lesions are reviewed by one of 2 neurologists with special attention given to distinguishing lesion from CSF and hemorrhage from surrounding vasogenic edema. Lesions can then be quantified and conjunction analyses performed to develop lesion density maps or to quantify the amount of overlap between lesion and other structures of interest such as white matter tracts in a given subject.

Quantification of lesion extent and location can be of particular value in studies of stroke recovery. Although we have focused primarily on functional connectivity here, there is a growing appreciation for understanding the anatomical connectivity underlying distributed brain networks.

Several recent methods have been proposed to map symptoms or deficits on structural lesions. This mapping involves either a binary contrast between groups of patients with more or less severe deficits, or a linear regression of severity of deficits onto presence/absence of damage in a voxel. Several studies have used this approach to map language (Bates et al., 2003; Borovsky et al., 2007), attention (Committeri et al., 2007; Molenberghs et al., 2008; Verdon et al., 2010), motor planning (Kalenine et al.) and general intelligence (Glascher et al., 2010). An open issue is whether structural, physiological, or both sets of measures constitute a better predictor of current deficits or future outcome.

Behavioral measures

One of the strengths of fcMRI analysis is that all networks can be studied simultaneously. However to harness the full power of the approach, connectivity should be correlated with behavior. Therefore, careful selection of behavioral measures across multiple domains is important. Many measures that index rehabilitation are ordinal, but because of the frequent use of correlation and regression analyses, more statistical power is achieved when the dependent variable is continuous rather than ordinal, as in measures of reaction time or percent correct responses. As noted above, use of a correlational or multiple regression framework for relating behavior to connectivity avoids the classification of patients into groups using cutoffs. Finally, data simplification can be achieved by using factor-analytic approaches to combine multiple measures.

The behavioral battery includes:

Vision battery

We plan to measure visual impairment using an automated perimetry system (Humphrey Zeiss perimeter, www.zeiss.com) to determine the contrast sensitivity over the visual field and the dimensions of any detected scotoma.

Memory battery

The memory battery consists of three tests: The Wechsler Memory Scales-III (Wechsler, 1997) Spatial Span block tapping test (forward and backward) (Wilde et al., 2004); the Hopkins Verbal Learning Test (HVLT) (immediate recall, delayed recall, recognition) (Stewart et al., 2002); and the Brief Visuospatial Memory Test (BVMT) (immediate recall, delayed recall, recognition) (Benedict et al., 1998).

Functional outcome battery

Assessments will be administered including the Short Form 36 (SF-36) (Anderson et al., 1996), the Reintegration to Normal Living Index (RNL) (Wood-Dauphinee et al., 1988), the Geriatric Depression Scale (Williams et al., 2005), the FIM/FAM (McPherson et al., 1996), and the Stroke Adapted Sickness Impact Profile (van Straten et al., 1997).

Attention battery

We will use the Posner Task, a computerized target detection task with directional cueing. The subject must maintain central fixation throughout but must covertly shift attention as directed by the directional cue and press a button upon the appearance of the target. However, 25% of the time, the cue is misleading (Friedrich et al., 1998; Posner, 1980; Posner et al., 1984). We have recently demonstrated that the computerized Posner Task is the most sensitive test for the detection of hemispatial neglect at the acute and especially the chronic phase after stroke (Rengachary et al., 2009).

The Mesulam random array symbol cancelation subtest is a pen and paper target cancelation task where participants must cross out each occurrence of a target (Lowery et al., 2004; Mesulam, 1985).

The Behavioral Inattention Test: star cancelation subtest. Like the Mesulam, this is a pen and paper target cancelation task where participants must cross out each occurrence of a target (Wilson et al., 1987).

Motor battery

Assessment included goniometric measurements of the active range of motion in joints of the upper and lower extremities (Lang and Beebe, 2007), against gravity; grip strength with a dynamometer (Schmidt and Toews, 1970); the lower extremity Motricity Index (Collin and Wade, 1990); the Action Research Arm Test (Lyle, 1981) and the 9 Hole Peg Test (Mathiowetz et al., 1985) . Lower extremity function is assessed with the Functional Independence Measure (FIM) walking item (Granger and Hamilton, 1993), gait speed (Richards et al., 1993) and ankle dorsiflexion with a dynamometer (Sunnerhagen et al., 1999).

Language battery

The Boston Diagnostic Aphasia Examination (BDAE) (Goodglass et al., 2001) is a widely used standardized test battery for evaluating adults with acquired brain damage on reading, writing, verbal production, and auditory comprehension and includes summary scores across subtests (e.g., the Language Competency Index, LCI). We designed a test battery for aphasia that was substantially shorter than the 2-hour BDAE, yet evaluated expression and comprehension components of language. A *Verbal Expression composite score* includes the 15-item Boston Naming, Oral Sentence Reading, Stem Completion, and Nonword Reading. The latter two tests came from a computerized battery of verbal production developed in our lab for which we have substantial experience and data from people with aphasia (Blasi et al., 2002; Connor et al., 2006; Rosen et al., 2004). Our *Comprehension composite score* includes Word Discrimination, Commands, Complex Ideational Material, Oral Word Reading, and Oral Sentence Comprehension. Each BDAE subtest in the composite measures have reliability coefficients greater than 0.89, with the 15-item Boston Naming Test having a reliability of 0.90 (Graves et al., 2004).

Testing for the emergence of new or modified networks

Resting state functional connectivity analyses can be performed in a seed-based fashion using predefined ROIs or in a data driven fashion using independent component analysis (ICA) (Arfanakis et al., 2000). This method involves the identification of spatio-temporal components and the clustering of these components across subjects based on their spatial similarity. While seed-based analyses exploit prior information

on the organization of functional brain networks in healthy subjects and test their modification post-stroke, this approach would not be sensitive for detecting the recruitment of new areas into a network, or detecting changes in the topography of a network in response to the focal structural lesion of stroke. In preliminary studies using ICA we observed the fractionation of a bilaterally represented motor network into two unilateral networks consistent with the breakdown of inter-hemispheric connectivity seen using seed-based fcMRI. Recent reports of long-range neuroplasticity in monkey cortex also would suggest that the formation of novel networks may not be unexpected.

Preliminary results on functional connectivity and behavioral deficits post-stroke

Local destruction but distributed dysfunction: evidence from hemispatial neglect and motor impairment

Neuroimaging studies of task-evoked activity have shown that regions involved in directing attention to spatial locations are localized in dorsal frontal and posterior parietal cortex (Corbetta et al., 1993; Nobre et al., 1997) and overlap regions involved in eye movement planning/execution (frontal and parietal eye regions) (Corbetta et al., 1998; Luna et al., 1998). Dorsal fronto-parietal regions contain topographic maps of contralateral space (Sereno et al., 2001; Silver et al., 2005), and they generate top-down signals that bias sensory processing in visual regions (Bressler et al., 2008; Ruff et al., 2006). These regions form a 'dorsal attention network' that controls stimulus–response selection both under goal-driven and stimulus-driven conditions (Corbetta and Shulman, 2002). However, these regions are not generally damaged in neglect patients.

Instead, regions much more ventrally located are typically damaged in neglect (Fox et al., 2006; Friedrich et al., 1998; He et al., 2007a; Rengachary et al., 2011; Shomstein et al., 2010; Shulman et al., 2010). These regions correspond to a second system whose core regions include temporo-parietal junction (TPJ) cortex and ventral frontal cortex (VFC). This ventral network is co-activated with the dorsal network during orienting to novel or behaviorally relevant stimuli presented outside the focus of attention and is 'non-spatial' in the sense that it responds equally well to stimuli presented on both sides of space and signals the presence of novel salient stimuli even when they do not require a shift of attention (Corbetta et al., 2008).

However, a right hemisphere stroke that structurally damages the ventral network and induces neglect also has remote effects on the dorsal attention network, which is more hypoactivated in the right than left hemisphere. Furthermore, He et al. (2007a, 2007b) showed that at two weeks after stroke, the normally high resting state functional connectivity (rsFC) between left and right dorsal parietal cortex was disrupted and the degree of breakdown correlated with the severity of left spatial neglect.

Connectivity analyses have revealed evidence of similar remote network dysfunction after a focal lesion in the motor network (Carter et al., 2010; Grefkes et al., 2008; van Meer et al., 2010; Ward et al., 2007). In a group of subacute stroke patients, structural damage to the corticospinal tract (CST) was correlated with decreased inter-hemispheric rsFC in the motor network upstream from the site of the lesion (Carter et al., 2012). This effect could not be accounted for by damage to the selected motor ROIs or to the interruption of transcallosal motor fibers. Therefore, while stroke induces a sudden local structural lesion, widespread changes in network functional connectivity take place immediately and may have important implications for behavior and recovery.

Intra-hemispheric versus inter-hemispheric connectivity

Connectivity measures of networks after stroke may reveal important principles about network organization and reorganization, particularly when those measures are correlated with behavioral measures of impairment. For instance, although contralateral control is a general feature of sensorimotor organization, a large body of experimental evidence, implicates inter-hemispheric interactions as important in spatial attention and disrupted in hemispatial neglect. Accordingly, we reported that acute changes in inter-hemispheric fcMRI in spatial attention networks correlate with the severity of neglect while intra-hemispheric changes in connectivity were not predictive. Similarly in motor physiology there is a growing awareness that disrupted inter-hemispheric functional interactions may underlie motor behavioral deficits and post-stroke recovery (Grefkes and Fink, 2011; Westlake and Nagarajan, 2011). Movement parameters are impaired after stroke not only in the contralesional hand, but also to a lesser degree in the ipsilesional hand. As discussed above prominent contralateral changes in activation have been reported post-stroke during movements of the affected limb, which could depend on abnormal interaction between the two hemispheres (Chollet et al., 1991; Gerloff et al., 2006; Grefkes et al., 2008; Rehme et al., 2011; Ward et al., 2003). These results have led to the hypothesis (Ward and Cohen, 2004) that the primary goal of inter-hemispheric interaction in the motor system is to prevent the execution of symmetrical movements or mirror movements, and that these interactions are impaired post-stroke. The hypothesis of impaired cross-inhibitory motor control is in line with theories of inter-hemispheric competition in attention (Kinsbourne, 1977). Correspondingly, we have reported that inter-hemispheric decreases in connectivity are more predictive of motor deficits than intra-hemispheric decreases. Surprisingly neither ipsilesional nor contralesional intra-hemispheric functional connectivity was predictive of behavioral deficits in a group of stroke patients with subcortical lesions and very little cortical damage (Fig. 1). This result will need replication in a larger group of subjects. Using a dynamic causal modeling approach in subacute stroke patients, Grefkes et al. (2008) found a significant decrease in intrinsic ipsilesional SMA-M1 coupling that was correlated with motor behavior. In addition, during movement of the paretic hand, increased inhibition from contralesional M1 onto ipsilesional M1 was detected that correlated with motor impairment. Whether this increased inhibition during movement in this DCM analysis corresponds to the decreased inter-hemispheric resting state connectivity and drives the correlation we observed between inter-hemispheric connectivity and motor performance remains to be determined.

Local connectivity versus global network integrity

Both global vs. local measure of functional connectivity can be used to describe the damage or reorganization to a network. Which of the two sets of measures (local, global) is more relevant to behavior and outcome is a key issue for the future. Networks can be described with different mathematical tools, which provide global indices about the spatial properties of the network (e.g. centrality, betweeness), (Bullmore and Sporns, 2009; J. Wang et al., 2010; L. Wang et al., 2010). While global measures have been related to behavior (Li et al., 2009), and shown to be differentially affected in different pathological states such as Alzheimer's disease (Sanz-Arigita et al., 2010); schizophrenia (Bassett et al., 2008); alcoholism (Chanraud et al., 2011); and obsessive compulsive disorder, (Zhang et al., 2011) their clinical and behavioral relevance is unknown. In our own work, while initial results from attention and motor networks point to the importance of inter-hemispheric interactions at the network level, this result does not preclude the importance of changes in local connectivity between two specific ROIs either between or within hemispheres. For example, the correlation between inter-hemispheric connectivity and motor behavior is particularly strong for regions within the central sulcus (Carter et al., 2010). The relative importance of regional vs network-wide connectivity is an open issue.

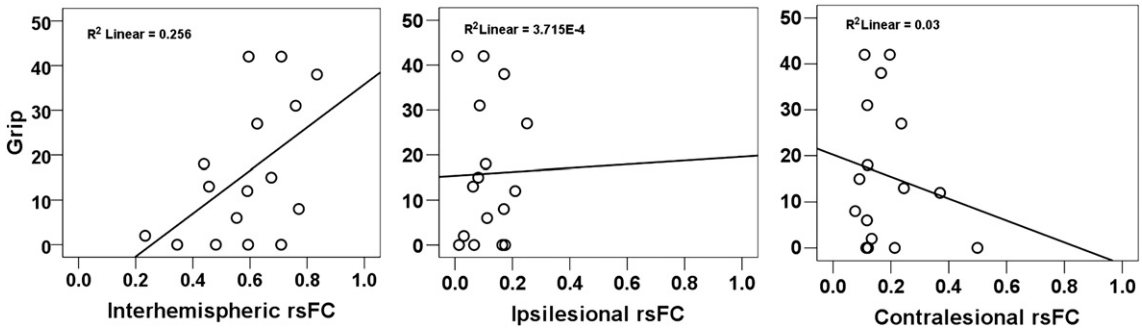

Fig. 1. Correlation of motor function with large scale patterns of resting state functional connectivity in the somatomotor network. In a study of 23 subacute stroke patients, grip strength (in kg) was significantly correlated with inter-hemispheric connectivity (left panel) but not with intra-hemispheric connectivity either within the lesioned hemisphere (middle panel) or the unaffected hemisphere (right panel). Inter-hemispheric connectivity represents the average of the connectivity scores between homologous regions in the left and right hemispheres (e.g. average of the Fisher z score for the temporal correlation between left and right hemisphere ROIs in the network). Ipsilesional intra-hemispheric rsFC represents the average of the connectivity scores between each ROI in the damaged hemisphere and all other ROIs in the same network within the damaged hemisphere. Contralesional intra-hemispheric FC is the same as the ipsilesional score but all ROI pairs are in the unaffected hemisphere. rsFC: resting state functional connectivity.

Relative contributions of structural damage and functional connectivity

It is currently debated whether fcMRI signals relate to structural anatomy. Lesions that affect the cortex or the white matter will necessarily have an effect on fcMRI signals recorded. Whether the impact of lesions goes beyond the simple anatomical disconnection is controversial. In some cases, as in the case of frontal lesions causing posterior parietal abnormalities the effects must be transynaptic hence reflect a true physiological remote effect. Also, a growing number of studies using diffusion tensor imaging (DTI) have demonstrated correlations between white matter integrity and behavioral performance. For instance, the degree of aphasia in chronic stroke

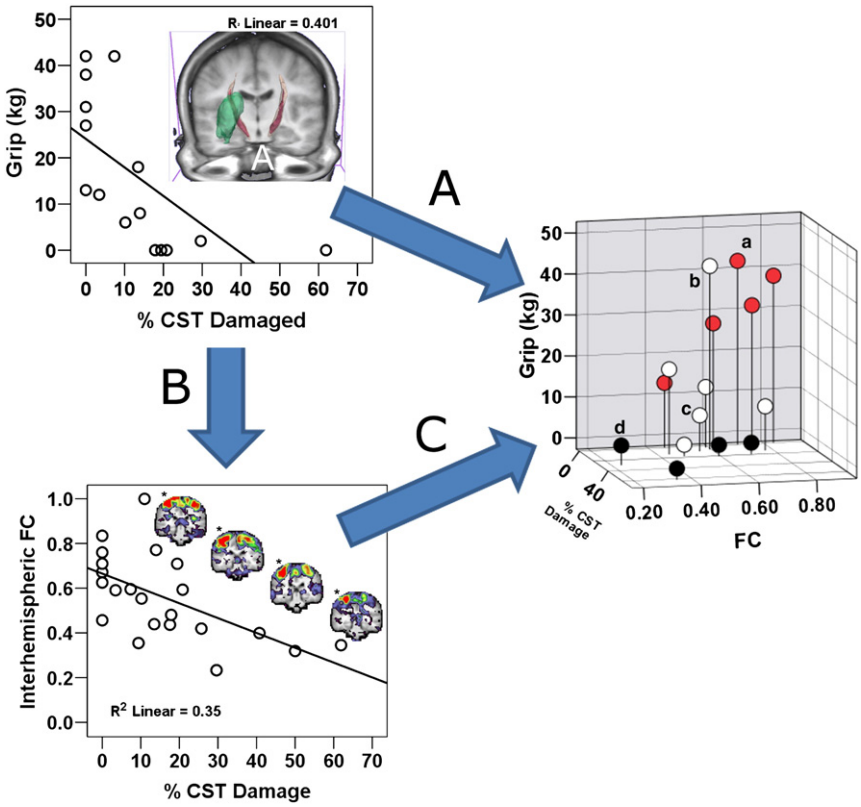

Fig. 2. A model for how interactions between structural damage and network dysfunction contribute to behavioral impairment. A template of the corticospinal tract (CST) was developed based on diffusion tensor imaging in 12 healthy controls (colored in pink in top panel). Each stroke patient's lesion was segmented out (colored in green in top panel) and overlaid on the CST template to obtain the % CST damage. Structural damage to the CST had a direct effect on behavior (arrow A to right panel), as illustrated by the scatter plot (top panel) demonstrating that as % CST damage increased grip strength decreased. In addition, CST damage affected inter-hemispheric resting connectivity (arrow B to bottom panel). As % CST damage increased, inter-hemispheric functional connectivity decreased as shown in the scatter plot and functional connectivity maps from 4 subjects with increasing amounts of CST damage (note the decreased connectivity with the hemisphere contralateral to the hemisphere that was seeded (*) for the analysis). Effects of structural damage and altered connectivity (arrows A and C respectively) converge to impact motor behavior (right panel). In this three dimensional representation, black circles in the foreground have severe CST damage; white circles in the midground have moderate CST damage; red circles in the background have little or no CST damage. When CST damage is severe, grip performance is not correlated with functional connectivity. However, when CST damage is moderate or mild, then grip performance improves with higher inter-hemispheric connectivity (white and red circles). FC: inter-hemispheric resting state functional connectivity in somatomotor network.

patients is correlated with the extent of white matter damage specifically to the arcuate fasciculus and not to other with matter bundles like the extreme capsule or the uncinate fasciculus (Marchina et al., 2011). In chronic stroke patients, the extent of CST damage, rather than overall lesion volume, is correlated with motor performance (Zhu et al., 2010). In addition, fractional anisotropy (FA) values in the CST predict the amount of motor improvement in response to training (Schaechter et al., 2009; Stinear et al., 2007). Furthermore, DTI studies suggest that the integrity of other pathways such as cortico-rubro-spinal or cortico-reticulospinal tracts and transcallosal motor pathways may contribute to the potential for functional recovery (Lindenberg et al., 2011). The implication of a role for transcallosal motor pathways is interesting in light of our recent study of the effects of corticospinal tract damage on resting state functional connectivity in the somatomotor network in subacute stroke patients (Carter et al., 2012). CST damage was significantly correlated with inter-hemispheric connectivity but not with ipsilesional intra-hemispheric connectivity or contralesional intra-hemispheric connectivity. Because % CST damage influences the strength of inter-hemispheric rsFC but is also highly correlated with motor impairment, it was important to disentangle the relative importance of % CST damage and inter-hemispheric connectivity on motor behavior. We found that when CST damage was mild or moderate, then inter-hemispheric rsFC was correlated with behavior but that at higher levels of CST damage, neuromotor impairment was driven primarily by the CST damage, although inter-hemispheric rsFC was quite altered. We concluded that both the focal lesion and its remote effects on network function are relevant to understanding network reorganization after stroke (Fig. 2).

Conclusion

Resting state functional connectivity analysis is well suited to the study of how multiple distributed networks are disrupted by and reorganize after stroke. In conjunction with analysis of behavioral performance it is possible to determine what patterns of connectivity are most likely to be behaviorally relevant. Initial results suggest that rsFC is behaviorally relevant and that in the dorsal attention network and the somatomotor network, inter-hemispheric rsFC in subacute stroke is a better predictor of behavior than is intra-hemispheric rsFC. Whether this relationship holds true at the chronic stage and whether acute rsFC predicts chronic performance remains to be determined. Given the difficulty of the challenges faced in stroke rehabilitation and the uncertainty of an individual patient's recovery, the promise of a roadmap for individual treatment long held out by functional neuroimaging is appealing. Because of individual variability, individual rsFC measures for a patient may not be interpreted as normal or abnormal with any certainty, but the use of multivariate classification techniques may improve diagnostic accuracy.

Acknowledgments

This work is supported by the National Institute of Mental Health [R01 HD061117-05A2 to M.C.]; NIH [5K08NS064365-02 to A.R.C.], the Robert Wood Johnson Foundation Amos Medical Faculty Development Program [65592 to A.R.C.], and the Rehabilitation Institute of St. Louis.

Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.neuroimage.2012.02.070.

References

Albert, N.B., Robertson, E.M., Miall, R.C., 2009. The resting human brain and motor learning. Curr. Biol. 19, 1023–1027.
Anderson, C., Laubscher, S., Burns, R., 1996. Validation of the Short Form 36 (SF-36) Health Survey Questionnaire among stroke patients. Stroke 10, 1812–1816.
Arfanakis, K., Cordes, D., Haughton, V.M., Moritz, C.H., Quigley, M.A., Meyerand, M.E., 2000. Combining independent component analysis and correlation analysis to probe interregional connectivity in fMRI task activation datasets. Magn. Reson. Imaging 18, 921–930.
Bartolomeo, P., 2011. The quest for the 'critical lesion site' in cognitive deficits: problems and perspectives. Cortex 47 (8), 1010–1012.
Bartolomeo, P., Thiebaut de Schotten, M., Doricchi, F., 2007. Left unilateral neglect as a disconnection syndrome. Cereb. Cortex 17, 2479–2490.
Bassett, D.S., Bullmore, E., Verchinski, B.A., Mattay, V.S., Weinberger, D.R., Meyer-Lindenberg, A., 2008. Hierarchical organization of human cortical networks in health and schizophrenia. J. Neurosci. 28, 9239–9248.
Bates, E., Wilson, S.M., Saygin, A.P., Dick, F., Sereno, M.I., Knight, R.T., Dronkers, N.F., 2003. Voxel-based lesion-symptom mapping. Nat. Neurosci. 6, 448–450.
Benedict, R.H.B., Schretlen, D., Groninger, L., Brandt, J., 1998. The Hopkins Verbal Learning Test-Revised: normative data and analysis of interform and test–retest reliability. Clin. Neuropsychol. 12, 43–55.
Bestmann, S., Swayne, O., Blankenburg, F., Ruff, C.C., Teo, J., Weiskopf, N., Driver, J., Rothwell, J.C., Ward, N.S., 2010. The role of contralesional dorsal premotor cortex after stroke as studied with concurrent TMS-fMRI. J. Neurosci. 30, 11926–11937.
Blasi, V., et al., 2002. Word retrieval learning modulates right frontal cortex in patients with left frontal damage. Neuron 36, 159–170.
Borovsky, A., Saygin, A.P., Bates, E., Dronkers, N., 2007. Lesion correlates of conversational speech production deficits. Neuropsychologia 45, 2525–2533.
Bressler, S.L., Tang, W., Sylvester, C.M., Shulman, G.L., Corbetta, M., 2008. Top-down control of human visual cortex by frontal and parietal cortex in anticipatory visual spatial attention. J. Neurosci. 28, 10056–10061.
Buckner, R.L., Corbetta, M., Schatz, J., Raichle, M.E., Petersen, S.E., 1996. Preserved speech abilities and compensation following prefrontal damage. Proc. Natl. Acad. Sci. 93, 1249–1253.
Bullmore, E., Sporns, O., 2009. Complex brain networks: graph theoretical analysis of structural and functional systems. Nat. Rev. Neurosci. 10, 186–198.
Capotosto, P., Babiloni, C., Romani, G.L., Corbetta, M., 2011. Differential contribution of right and left parietal cortex to the control of spatial attention: a simultaneous EEG-rTMS study. Cereb. Cortex 22, 446–454.
Carter, A.R., Astafiev, S.V., Lang, C.E., Connor, L.T., Rengachary, J., Strube, M.J., Pope, D.L., Shulman, G.L., Corbetta, M., 2010. Resting interhemispheric functional magnetic resonance imaging connectivity predicts performance after stroke. Ann. Neurol. 67, 365–375.
Carter, A.R., Patel, K.R., Astafiev, S.V., Snyder, A.Z., Rengachary, J., Strube, M.J., Pope, A., Shimony, J.S., Lang, C.E., Shulman, G.L., Corbetta, M., 2012. Upstream dysfunction of somatomotor functional connectivity after corticospinal damage in stroke. Neurorehabil. Neural Repair 26, 7–19.
Chanraud, S., Pitel, A.L., Pfefferbaum, A., Sullivan, E.V., 2011. Disruption of functional connectivity of the default-mode network in alcoholism. Cereb. Cortex 21, 2272–2281.
Chollet, F., DiPiero, V., Wise, R.J.S., Brooks, D.J., Dolan, R.J., Frackowiak, R.S.J., 1991. The functional anatomy of motor recovery after stroke in humans: a study with positron emission tomography. Ann. Neurol. 29, 63–71.
Collin, C., Wade, D., 1990. Assessing motor impairment after stroke: a pilot reliability study. J. Neurol. Neurosurg. Psychiatry 53, 576–579.
Committeri, G., Pitzalis, S., Galati, G., Patria, F., Pelle, G., Sabatini, U., Castriota-Scanderbeg, A., Piccardi, L., Guariglia, C., Pizzamiglio, L., 2007. Neural bases of personal and extrapersonal neglect in humans. Brain 130, 431–441.
Connor, L.T., et al., 2006. Cerebellar activity switches hemispheres with cerebral recovery in aphasia. Neuropsychologia 44, 171–177.
Corbetta, M., Shulman, G.L., 2002. Control of goal-directed and stimulus-driven attention in the brain. Nat. Rev. Neurosci. 3, 201–215.
Corbetta, M., Shulman, G.L., 2011. Spatial Neglect and Attention Networks. Annu. Rev. Neurosci. 34, 569–599.
Corbetta, M., Miezin, F.M., Shulman, G.L., Petersen, S.E., 1993. A PET study of visuospatial attention. J. Neurosci. 13, 1202–1226.
Corbetta, M., Akbudak, E., Conturo, T.E., Snyder, A.Z., Ollinger, J.M., Drury, H.A., Linenweber, M.R., Petersen, S.E., Raichle, M.E., Van Essen, D.C., Shulman, G.L., 1998. A common network of functional areas for attention and eye movements. Neuron 21, 761–773.
Corbetta, M., Kincade, M.J., Lewis, C., Snyder, A.Z., Sapir, A., 2005. Neural basis and recovery of spatial attention deficits in spatial neglect. Nat. Neurosci. 8, 1603–1610.
Corbetta, M., Patel, G., Shulman, G.L., 2008. The reorienting system of the human brain: from environment to theory of mind. Neuron 58, 306–324.
Deco, G., Rolls, E.T., 2004. A neurodynamical cortical model of visual attention and invariant object recognition. Vision Res. 44, 621–642.
Doricchi, F., Thiebaut de Schotten, M., Tomaiuolo, F., Bartolomeo, P., 2008. White matter (dis)connections and gray matter (dys)functions in visual neglect: gaining insights into the brain networks of spatial awareness. Cortex 44, 983–995.
Dosenbach, N.U., Nardos, B., Cohen, A.L., Fair, D.A., Power, J.D., Church, J.A., Nelson, S.M., Wig, G.S., Vogel, A.C., Lessov-Schlaggar, C.N., Barnes, K.A., Dubis, J.W., Feczko, E., Coalson, R.S., Pruett Jr., J.R., Barch, D.M., Petersen, S.E., Schlaggar, B.L., 2010. Prediction of individual brain maturity using fMRI. Science 329, 1358–1361.
Feydy, A., Carlier, R., Roby-Brami, A., Bussel, B., Cazalis, F., Pierot, L., Burnod, Y., Maier, M.A., 2002. Longitudinal study of motor recovery after stroke: recruitment and focusing of brain activation. Stroke 33, 1610–1617.

Fox, M.D., Snyder, A.Z., Vincent, J.L., Corbetta, M., Van Essen, D.C., Raichle, M.E., 2005. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc. Natl. Acad. Sci. U. S. A. 102, 9673–9678.
Fox, M.D., Corbetta, M., Snyder, A.Z., Vincent, J.L., Raichle, M.E., 2006. Spontaneous neuronal activity distinguishes human dorsal and ventral attention systems. Proc. Natl. Acad. Sci. U. S. A. 103, 10046–10051.
Friedrich, F.J., Egly, R., Rafal, R.D., Beck, D., 1998. Spatial attention deficits in humans: a comparison of superior parietal and temporal–parietal junction lesions. Neuropsychology 12, 193–207.
Gerloff, C., Bushara, K., Sailer, A., Wassermann, E.M., Chen, R., Matsuoka, T., Waldvogel, D., Wittenberg, G.F., Ishii, K., Cohen, L.G., Hallett, M., 2006. Multimodal imaging of brain reorganization in motor areas of the contralesional hemisphere of well recovered patients after capsular stroke. Brain 129, 791–808.
Gillebert, C.R., Mantini, D., Thijs, V., Sunaert, S., Dupont, P., Vandenberghe, R., 2011. Lesion evidence for the critical role of the intraparietal sulcus in spatial attention. Brain 134, 1694–1709.
Glascher, J., Rudrauf, D., Colom, R., Paul, L.K., Tranel, D., Damasio, H., Adolphs, R., 2010. Distributed neural system for general intelligence revealed by lesion mapping. Proc. Natl. Acad. Sci. U. S. A. 107, 4705–4709.
Goodglass, H., Kaplan, E., Barresi, B., 2001. Boston Diagnostic Aphasia Examination. Pro-Ed, Austin, TX.
Granger, C.V., Hamilton, B.B., 1993. The Uniform Data System for Medical Rehabilitation report of first admissions for 1991. Am. J. Phys. Med. Rehabil. 72, 33–38.
Graves, R.E., Bezeau, S.C., Fogarty, J., Blair, R., 2004. Boston naming test short forms: a comparison of previous forms with new item response theory based forms. J. Clin. Exp. Neuropsychol. 26, 891–902.
Grecucci, A., Crescentini, C., Siugzdaite, R., 2008. Vicarious function in the motor cortex. A computational investigation. Neurosci. Lett. 434, 185–190.
Grefkes, C., Fink, G.R., 2011. Reorganization of cerebral networks after stroke: new insights from neuroimaging with connectivity approaches. Brain 134, 1264–1276.
Grefkes, C., Nowak, D.A., Eickhoff, S.B., Dafotakis, M., Kust, J., Karbe, H., Fink, G.R., 2008. Cortical connectivity after subcortical stroke assessed with functional magnetic resonance imaging. Ann. Neurol. 63, 236–246.
Greicius, M.D., Krasnow, B., Reiss, A.L., Menon, V., 2003. Functional connectivity in the resting brain: a nework analysis of the default mode hypothesis. Proc. Natl. Acad. Sci. U. S. A. 100, 253–258.
Hampson, M., Driesen, N.R., Skudlarski, P., Gore, J.C., Constable, R.T., 2006. Brain connectivity related to working memory performance. J. Neurosci. 26, 13338–13343.
He, B.J., Snyder, A.Z., Vincent, J.L., Epstein, A., Shulman, G.L., Corbetta, M., 2007a. Breakdown of functional connectivity in frontoparietal networks underlies behavioral deficits in spatial neglect. Neuron 53, 905–918.
He, B.J., Shulman, G.L., Snyder, A.Z., Corbetta, M., 2007b. The role of impaired neuronal communication in neurological disorders. Curr. Opin. Neurol. 20, 655–660.
Honey, C.J., Sporns, O., Cammoun, L., Gigandet, X., Thiran, J.P., Meuli, R., Hagmann, P., 2009. Predicting human resting-state functional connectivity from structural connectivity. Proc. Natl. Acad. Sci. U. S. A. 106, 2035–2040.
James, G.A., Lu, Z.L., VanMeter, J.W., Sathian, K., Hu, X.P., Butler, A.J., 2009. Changes in resting state effective connectivity in the motor network following rehabilitation of upper extremity poststroke paresis. Top. Stroke Rehabil. 16, 270–281.
Kalenine, S., Buxbaum, L.J., Coslett, H.B., 2010. Critical brain regions for action recognition: lesion symptom mapping in left hemisphere stroke. Brain 133, 3269–3280.
Karnath, H.O., Rorden, C., Ticini, L.F., 2009. Damage to white matter fiber tracts in acute spatial neglect. Cereb. Cortex 19, 2331–2337.
Kinsbourne, M., 1977. Hemi-neglect and hemisphere rivalry. In: Weinstein, E.A., Friedland, R.L. (Eds.), Hemi-inattention and Hemispheric Specialization. Raven Press, New York, pp. 41–52.
Krebs, H.I., Volpe, B., Hogan, N., 2009. A working model of stroke recovery from rehabilitation robotics practitioners. J. Neuroeng. Rehabil. 6, 6.
Lang, C.E., Beebe, J.A., 2007. Relating movement control at 9 upper extremity segments to loss of hand function in people with chronic hemiparesis. Neurorehabil. Neural Repair 21, 279–291.
Lewis, C.M., Baldassarre, A., Committeri, G., Romani, G.L., Corbetta, M., 2009. Learning sculpts the spontaneous activity of the resting human brain. Proc. Natl. Acad. Sci. U. S. A. 106, 17558–17563.
Li, Y., Liu, Y., Li, J., Qin, W., Li, K., Yu, C., Jiang, T., 2009. Brain anatomical network and intelligence. PLoS Comput. Biol. 5, e1000395.
Lindenberg, R., Zhu, L.L., Rüber, T., Schlaug, G., 2011. Predicting functional motor potential in chronic stroke patients using diffusion tensor imaging. Hum. Brain Mapp. (Apr 29). Epub ahead of print.
Loubinoux, I., Carel, C., Pariente, J., Dechaumont, S., Albucher, J.F., Marque, P., Manelfe, C., Chollet, F., 2003. Correlation between cerebral reorganization and motor recovery after subcortical infarcts. Neuroimage 20, 2166–2180.
Lowery, N., Ragland, J.D., Gur, R.C., Gur, R.E., Moberg, P.J., 2004. Normative data for the symbol cancellation test in young healthy adults. Appl. Neuropsychol. 11, 218–221.
Luna, B., Thulborn, K.R., Strojwas, M.H., McCurtain, B.J., Berman, R.A., Genovese, C.R., Sweeney, J.A., 1998. Dorsal cortical regions subserving visually-guided saccades in humans: an fMRI study. Cereb. Cortex 8, 40–47.
Lyle, R.C., 1981. A performance test for assessment of upper limb function in physical rehabilitation treatment and research. Int. J. Rehabil. Res. 4, 483–492.
Marchina, S., Zhu, L.L., Norton, A., Zipse, L., Wan, C.Y., Schlaug, G., 2011. Impairment of speech production predicted by lesion load of the left arcuate fasciculus. Stroke 8, 2251–2256.
Mathiowetz, V., Weber, K., Kashman, N., Volland, G., 1985. Adult norms for the nine-hole peg test of finger dexterity. Occup. Ther. J. Res. 5, 24–38.
McPherson, K.M., Pentland, B., Cudmore, S.F., Prescott, R.J., 1996. An inter-rater reliability study of the Functional Assessment Measure (FIM + FAM). Disabil. Rehabil. 7, 341–347.
Meinzer, M., Harnish, S., Conway, T., Crosson, B., 2011. Recent developments in functional and structural imaging of aphasia recovery after stroke. Aphasiology 25, 271–290.
Mesulam, M., 1985. Principles of Behavioral Neurology. In: Mesulam, M. (Ed.), F.A. Davis Company.
Molenberghs, P., Gillebert, C.R., Peeters, R., Vandenberghe, R., 2008. Convergence between lesion-symptom mapping and functional magnetic resonance imaging of spatially selective attention in the intact brain. J. Neurosci. 28, 3359–3373.
Nobre, A.C., Sebestyen, G.N., Gitelman, D.R., Mesulam, M.M., Frackowiack, R.S.J., Frith, C.D., 1997. Functional localization of the system for visuospatial attention using positron emission tomography. Brain 120, 515–533.
O'Shea, J., Johansen-Berg, H., Trief, D., Gobel, S., Rushworth, M.F., 2007. Functionally specific reorganization in human premotor cortex. Neuron 54, 479–490.
Pan, S.L., Wu, S.C., Wu, T.H., Lee, T.K., Chen, T.H., 2006. Location and size of infarct on functional outcome of noncardioembolic ischemic stroke. Disabil. Rehabil. 28, 977–983.
Park, C.H., Chang, W.H., Ohn, S.H., Kim, S.T., Bang, O.Y., Pascual-Leone, A., Kim, Y.H., 2011. Longitudinal changes of resting-state functional connectivity during motor recovery after stroke. Stroke 42, 1357–1362.
Posner, M.I., 1980. Orienting of attention. Q. J. Exp. Psychol. 32, 3–25.
Posner, M.I., Walker, J.A., Friedrich, F.J., Rafal, R.D., 1984. Effects of parietal injury on covert orienting of attention. J. Neurosci. 4, 1863–1874.
Power, J.D., Barnes, K.A., Snyder, A.Z., Schlaggar, B.L., Petersen, S.E., 2012. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. Neuroimage 59, 2142–2154.
Protopsaltis, J., Kokkoris, S., Korantzopoulos, P., Milionis, H.J., Karzi, E., Anastasopoulou, A., Filioti, K., Antonopoulos, S., Melidonis, A., Giannoulis, G., 2009. Prediction of long-term functional outcome in patients with acute ischemic non-embolic stroke. Atherosclerosis 203, 228–235.
Rehme, A.K., Eickhoff, S.B., Wang, L.E., Fink, G.R., Grefkes, C., 2011. Dynamic causal modeling of cortical activity from the acute to the chronic stage after stroke. Neuroimage 55, 1147–1158.
Rengachary, J., d'Avossa, G., Sapir, A., Shulman, G.L., Corbetta, M., 2009. Is the posner reaction time test more accurate than clinical tests in detecting left neglect in acute and chronic stroke? Arch. Phys. Med. Rehabil. 90, 2081–2088.
Rengachary, J., He, B.J., Shulman, G.L., Corbetta, M., 2011. A behavioral analysis of spatial neglect and its recovery after stroke. Front. Hum. Neurosci. 5, 29.
Richards, C.L., et al., 1993. Task-specific physical therapy for optimization of gait recovery in acute stroke patients. Arch. Phys. Med. Rehabil. 74, 612–620.
Riecker, A., Groschel, K., Ackermann, H., Schnaudigel, S., Kassubek, J., Kastrup, A., 2010. The role of the unaffected hemisphere in motor recovery after stroke. Hum. Brain Mapp. 31, 1017–1029.
Rosen, H.J., et al., 2004. Neural correlates of recovery from aphasia after damage to left inferior frontal cortex. Neurology 55, 1883–1894.
Ruff, C.C., Blankenburg, F., Bjoertomt, O., Bestmann, S., Freeman, E., Haynes, J.-D., Rees, G., Josephs, O., Deichmann, R., Driver, J., 2006. Concurrent TMS-fMRI and psychophysics reveal frontal influences on human retinotopic visual cortex. Curr. Biol. 16, 1479–1488.
Sanz-Arigita, E.J., Schoonheim, M.M., Damoiseaux, J.S., Rombouts, S.A., Maris, E., Barkhof, F., Scheltens, P., Stam, C.J., 2010. Loss of 'small-world' networks in Alzheimer's disease: graph analysis of FMRI resting-state functional connectivity. PLoS One 5, e13788.
Saur, D., Lange, R., Baumgaertner, A., Schraknepper, V., Willmes, K., Rijntjes, M., Weiller, C., 2006. Dynamics of language reorganization after stroke. Brain 129, 1371–1384.
Schaechter, J.D., Fricker, Z.P., Perdue, K.L., Helmer, K.G., Vangel, M.G., Greve, D.N., Makris, N., 2009. Microstructural status of ipsilesional and contralesional corticospinal tract correlates with motor skill in chronic stroke patients. Hum. Brain Mapp. 11, 3461–3474.
Schiemanck, S.K., Kwakkel, G., Post, M.W., Kappelle, L.J., Prevo, A.J., 2006. Predicting long-term independency in activities of daily living after middle cerebral artery stroke: does information from MRI have added predictive value compared with clinical information? Stroke 37, 1050–1054.
Schmidt, R.T., Toews, J.V., 1970. Grip strength as measured by the Jamar dynamometer. Arch. Phys. Med. Rehabil. 51, 321–327.
Sereno, M.I., Pitzalis, S., Martinez, A., 2001. Mapping of contralateral space in retinotopic coordinates by a parietal cortical area in humans. Science 294, 1350–1354.
Shomstein, S., Lee, J., Behrmann, M., 2010. Top-down and bottom-up attentional guidance: investigating the role of the dorsal and ventral parietal cortices. Exp. Brain Res. 206, 197–208.
Shulman, G.L., Pope, D.L., Astafiev, S.V., McAvoy, M.P., Snyder, A.Z., Corbetta, M., 2010. Right hemisphere dominance during spatial selective attention and target detection occurs outside the dorsal frontoparietal network. J. Neurosci. 30, 3640–3651.
Silver, M.A., Ress, D., Heeger, D.J., 2005. Topographic maps of visual spatial attention in human parietal cortex. J. Neurophysiol. 94, 1358–1371.
Stewart, K.J., Gale, S.D., Diamond, P.T., 2002. Early assessment of post-stroke patients entering acute inpatient rehabilitation: utility of the WASI and HVLT-R. Am. J. Phys. Med. Rehabil. 81, 223–228.
Stinear, C.M., Barber, P.A., Smale, P.R., Coxon, J.P., Fleming, M.K., Byblow, W.D., 2007. Functional potential in chronic stroke patients depends on corticospinal tract integrity. Brain 130, 170–180.

Sunnerhagen, K.S., Svantesson, U., Lönn, L., Krotkiewski, M., Grimby, G., 1999. Upper motor neuron lesions: their effect on muscle performance and appearance in stroke patients with minor motor impairment. Arch. Phys. Med. Rehabil. 80, 155–161.
Tambini, A., Ketz, N., Davachi, L., 2010. Enhanced brain correlations during rest are related to memory for recent experiences. Neuron 65, 280–290.
Tombari, D., Loubinoux, I., Pariente, J., Gerdelat, A., Albucher, J.F., Tardy, J., Cassol, E., Chollet, F., 2004. A longitudinal fMRI study: in recovering and then in clinically stable sub-cortical stroke patients. Neuroimage 23, 827–839.
Urbanski, M., Thiebaut de Schotten, M., Rodrigo, S., Oppenheim, C., Touze, E., Meder, J.F., Moreau, K., Loeper-Jeny, C., Dubois, B., Bartolomeo, P., 2011. DTI-MR tractography of white matter damage in stroke patients with neglect. Exp. Brain Res. 208, 491–505.
van den Heuvel, M.P., Stam, C.J., Kahn, R.S., Hulshoff Pol, H.E., 2009. Efficiency of functional brain networks and intellectual performance. J. Neurosci. 29, 7619–7624.
Van Essen, D.C., Ugurbil, K., Auerbach, E., Barch, D., Behrens, T.E., Bucholz, R., Chang, A., Chen, L., Corbetta, M., Curtiss, S.W., Della Penna, S., Feinberg, D., Glasser, M.F., Harel, N., Heath, A.C., Larson-Prior, L., Marcus, D., Michalareas, G., Moeller, S., Oostenveld, R., Petersen, S.E., Prior, F., Schlaggar, B.L., Smith, S.M., Snyder, A.Z., Xu, J., Yacoub, E., WU-Minn HCP Consortium, 2012. The Human Connectome Project: A data acquisition perspective. Neuroimage. Epub ahead of print.
van Meer, M.P., van der Marel, K., Wang, K., Otte, W.M., El Bouazati, S., Roeling, T.A., Viergever, M.A., Berkelbach van der Sprenkel, J.W., Dijkhuizen, R.M., 2010. Recovery of sensorimotor function after experimental stroke correlates with restoration of resting-state interhemispheric functional connectivity. J. Neurosci. 30, 3964–3972.
van Straten, A., de Haan, R.J., Limburg, M., Schuling, J., Bossuyt, P.M., van den Bos, G.A., 1997. A stroke-adapted 30-item version of the Sickness Impact Profile to assess quality of life (SA-SIP30). Stroke 11, 2155–2161.
Verdon, V., Schwartz, S., Lovblad, K.O., Hauert, C.A., Vuilleumier, P., 2010. Neuroanatomy of hemispatial neglect and its functional components: a study using voxel-based lesion-symptom mapping. Brain 133, 880–894.
Vincent, J.L., Patel, G.H., Fox, M.D., Snyder, A.Z., Baker, J.T., Van Essen, D.C., Zempel, J.M., Snyder, L.H., Corbetta, M., Raichle, M.E., 2007. Intrinsic functional architecture in the anaesthetized monkey brain. Nature 447, 83–86.
Wang, J., Zuo, X., He, Y., 2010a. Graph-based network analysis of resting-state functional MRI. Front. Syst. Neurosci. 4, 16.
Wang, L., Yu, C., Chen, H., Qin, W., He, Y., Fan, F., Zhang, Y., Wang, M., Li, K., Zang, Y., Woodward, T.S., Zhu, C., 2010b. Dynamic functional reorganization of the motor execution network after stroke. Brain 133, 1224–1238.
Ward, N.S., Cohen, L.G., 2004. Mechanisms underlying recovery of motor function after stroke. Arch. Neurol. 61, 1844–1848.
Ward, N.S., Brown, M.M., Thompson, A.J., Frackowiak, R.S., 2003. Neural correlates of motor recovery after stroke: a longitudinal fMRI study. Brain 126, 2476–2496.
Ward, N.S., Newton, J.M., Swayne, O.B., Lee, L., Frackowiak, R.S., Thompson, A.J., Greenwood, R.J., Rothwell, J.C., 2007. The relationship between brain activity and peak grip force is modulated by corticospinal system integrity after subcortical stroke. Eur. J. Neurosci. 25, 1865–1873.
Wechsler, D., 1997. Manual of the Wechsler Memory Scale-3rd Edition (WMS-III). The Psychological Corporation.
Westlake, K.P., Nagarajan, S.S., 2011. Functional connectivity in relation to motor performance and recovery after stroke. Front. Syst. Neurosci. 5, 8.
Wilde, N.J., Strauss, E., Tulsky, D.S., 2004. Memory span on the Wechsler Scales. J. Clin. Exp. Neuropsychol. 26, 539–549.
Williams, C.L., Rittman, M.R., Boylstein, C., Faircloth, C., Haijing, Q., 2005. Qualitative and quantitative measurement of depression in veterans recovering from stroke. J. Rehabil. Res. Dev. 42, 277–290.
Wilson, B., Cockburn, J., Halligan, P., 1987. Development of a behavioral test of visuospatial neglect. Arch. Phys. Med. Rehabil. 68, 98–102.
Wood-Dauphinee, S., Opzoomer, A., Williams, J., Marchand, B., Spitzer, W., 1988. Assessment of global function: the Reintegration to Normal Living Index. Arch. Phys. Med. Rehabil. 69, 583–590.
Zhang, T., Wang, J., Yang, Y., Wu, Q., Li, B., Chen, L., Yue, Q., Tang, H., Yan, C., Lui, S., Huang, X., Chan, R.C., Zang, Y., He, Y., Gong, Q., 2011. Abnormal small-world architecture of top-down control networks in obsessive–compulsive disorder. J. Psychiatry Neurosci. 36, 23–31.
Zhu, L.L., Lindenberg, R., Alexander, M.P., Schlaug, G., 2010. Lesion load of the corticospinal tract predicts motor impairment in chronic stroke. Stroke 5, 910–915.