Residual functional connectivity in the split-brain revealed with resting-state functional MRI

Lucina Q. Uddin[a], Eric Mooshagian[b], Eran Zaidel[b,c], Anouk Scheres[d], Daniel S. Margulies[a], A.M. Clare Kelly[a], Zarrar Shehzad[a], Jonathan S. Adelstein[a], F. Xavier Castellanos[a], Bharat B. Biswal[e] and Michael P. Milham[a]

[a]The Phyllis Green and Randolph Cowen Institute for Pediatric Neuroscience, New York University Child Study Center, New York, NY, [b]Department of Psychology, [c]Brain Research Institute, University of California Los Angeles, Los Angeles, California, [d]Department of Psychology, University of Arizona, Tucson, Arizona and [e]Department of Radiology, University of Medicine and Dentistry of New Jersey, Newark, New Jersey, USA

Correspondence to Dr Lucina Q. Uddin, PhD or Michael P. Milham, MD, PhD, New York University Child Study Center, 215 Lexington Avenue, 14th Floor, New York, NY 10016, USA
Tel: + 1 212 263 4673; fax: + 1 212 263 4675; e-mail: lucina.uddin@med.nyu.edu or milham01@med.nyu.edu

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Split-brain patients present a unique opportunity to address controversies regarding subcortical contributions to interhemispheric coordination. We characterized residual functional connectivity in a complete commissurotomy patient by examining patterns of low-frequency BOLD functional MRI signal. Using independent components analysis and region-of-interest-based functional connectivity analyses, we demonstrate bilateral resting state networks in a patient lacking all major cerebral commissures. Compared with a control group, the patient's interhemispheric correlation scores fell within the normal range for two out of three regions examined. Thus, we provide evidence for bilateral resting state networks in a patient with complete commissurotomy. Such continued interhemispheric interaction suggests that, at least in part, cortical networks in the brain can be coordinated by subcortical mechanisms. *NeuroReport* 19:703–709 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Patients who have undergone the 'split-brain' operation to relieve severe intractable epilepsy provide a unique opportunity for cognitive neuroscientists to examine mechanisms of interhemispheric interaction, neural plasticity, and compensatory reorganization. A somewhat surprising finding has been that aside from deficits visible under restricted testing conditions, these patients 'show a remarkable absence of functional impairment in nearly all ordinary behavior' [1]. Numerous studies of split-brain patients have shown evidence for continued interhemispheric transfer – albeit degraded – in the absence of cerebral commissures [2]. These patients can often transfer coarse perceptual visual information between the hemispheres [3]. The common assumption is that this is accomplished by subcortical pathways, which can compensate when low-level information transfer is required [3].

It is generally accepted that some interhemispheric transfer exists in these patients, yet our understanding of the coordination of processing between the split hemispheres remains limited. Although some studies of typical interhemispheric coordination in neurologically intact participants suggest entirely corticocortical connections, others implicate subcortical contributions [4]. Efforts to differentiate between these possibilities have relied on measures of coherence as indexed by electroencephalogram (EEG), with conflicting findings. Coherence analyses of EEG have been used as an indicator of functional corticocortical connections, with coherence decreases thought to reflect decreased interhemispheric connectivity [4]. Although some report residual coherence in human split-brains as well as in surgically callosotomized animals, supporting the idea of subcortical interhemispheric coordination [5], others report drastically reduced interhemispheric coherence postoperatively, suggesting that coherence is entirely mediated by corticocortical connectivity [6]. Unfortunately, EEG lacks the anatomical resolution required for studying specific networks. Recently developed functional connectivity measures applied to fMRI data provide an alternative method for studying interhemispheric coordination.

The discovery of resting-state functional connectivity in the motor system [7] has provided a new method for mapping major cortical networks. To date, coherent spontaneous fMRI activity has been used to identify attention systems [8], the default mode network [9], as well as several other resting state networks (RSNs) [10]. Resting state functional connectivity can also be used as a measure of interhemispheric coherence, with greater anatomical specificity than is possible with EEG. For example, a recent study has demonstrated that homologous regions of the anterior cingulate cortex in each hemisphere exhibit stronger correlations than nonhomologous regions [11].

Although the significance of these RSNs is not yet fully understood, they are widely thought to reflect intrinsic functional architecture. In a recent review, it is suggested that these signals serve to organize and coordinate neuronal activity [12]. In support of a putative functional role in organizing and coordinating neural activity across distributed networks, it has been shown that low-frequency oscillations (<0.1 Hz) serve to synchronize activity in large-scale networks, whereas higher frequency oscillations modulate more local events [13]. Thus, current models in the literature point to organizational functional properties of resting-state networks.

Functional connectivity, whether measured by EEG or fMRI, is thought to reflect structural connectivity. Given the known structural connectivity existing between homologous regions in each cerebral hemisphere, cortical commissural fibers have long been purported to mediate the majority of interhemispheric interactions. In split-brain patients, however, interhemispheric coordination, when it exists, must be mediated by extracallosal pathways.

Here, we used resting-state functional connectivity to establish the degree to which coordination of processing between the cerebral hemispheres can be supported by subcortical mechanisms. We used independent components analysis (ICA) and seed-based functional connectivity measures on fMRI data from a commissurotomy patient to test for the presence of continued patterns of bilateral connectivity in commonly observed RSNs. This patient has been previously characterized using several behavioral assessments [14], and surgical reports verify completeness of the commissurotomy [1].

Methods

Participant: patient N.G.

We tested patient N.G., a right-handed 74-year-old woman who underwent complete forebrain commissurotomy (single-stage midline section of the anterior commissure, corpus callosum, hippocampal commissure, and massa intermedia) in 1963 to relieve intractable epilepsy. A complete case history is reported elsewhere [1]. Structural MRIs confirmed complete commissurotomy. This patient reportedly sustained greater preoperative extracallosal structural damage to the right hemisphere (RH) [15]. Behavioral testing in this patient has indicated some preserved interhemispheric interaction as indexed by various neuropsychological tests [15]. Preoperative and postoperative full-scale IQ was 76 and 71, respectively. This study was approved by the Institutional Review Board at the University of Arizona and New York University School of Medicine. Consent was obtained from the patient according to the Declaration of Helsinki, and she was compensated for her participation.

Participants: adult controls

We used previously collected resting fMRI data from 42 adult participants (20 women, average age 29.5 ± 8.1 years) as a reference group for comparison with data from patient N.G. in secondary analyses (described in Methods). Subsets of this dataset have been used in earlier publications [11,16,17]. All participants in this sample were free of psychiatric disorders and had no history of head trauma. Participants signed informed consent and received monetary compensation for participation. The study complied with the Declaration of Helsinki and was Institutional Review Board approved at New York University and the NYU School of Medicine.

Functional MRI acquisition parameters: patient N.G.

Data were acquired on a General Electric 3.0 T HD Signa Excite scanner (General Electric, Milwaukee, Wisconsin, USA) equipped with Optimized ACGD Gradients located at the University of Arizona. A resting scan of 6 min duration was acquired during which the participant received no visual stimuli [TR=2000 ms; TE=25 ms; flip angle=90, 40 slices, matrix 64×64; field of view (FOV)=230 mm; acquisition voxel size=$3\times3\times4$ mm]. An additional functional scan was acquired (TR=2000 ms; TE=25 ms; flip angle=90, 40 slices, matrix 64×64; FOV=230 mm; acquisition voxel size=$3\times3\times3$), during which the participant was asked to complete a finger-tapping task, but was unable to comply with instructions. This functional scan was thus equivalent to a resting scan. A T1-weighted anatomical image was acquired for registration purposes and to confirm complete commissurotomy (Magnetization Prepared Rapid Gradient Echo, TR=2500 ms; TE=4.35 ms; TI=900 ms; flip angle=8; 176 slices; FOV=256 mm). A 25-direction diffusion tensor imaging (DTI) sequence was also acquired to rule out the existence of residual callosal fibers (TR=13000 ms; TE=72.1 ms; flip angle=90; matrix 128×128; FOV=25.6 cm; 3-mm slices).

Functional MRI acquisition parameters: adult controls

Functional images were acquired on a Siemens Allegra 3-Tesla scanner (Siemens, Erlangen, Germany) located at New York University using an echo planar imaging gradient echo sequence (TR=2000 ms; TE=25 ms; flip angle=90, 39 slices, matrix 64×64; FOV=192 mm; acquisition voxel size $3\times3\times3$ mm) while participants were instructed to rest with eyes open. For each participant, 197 contiguous echo planar imaging functional volumes were acquired, resulting in a 6 min 38 s scan. During this scan, the word 'Relax' was projected in white font against a black background. A T1-weighted anatomical image was also acquired for registration purposes (Magnetization Prepared Rapid Gradient Echo, TR=2500 ms; TE=4.35 ms; TI=900 ms; flip angle=8; 176 slices; FOV=256 mm).

Data analysis

The functional scans collected from patient N.G. were initially analyzed using FMRIB Software Library's Multivariate Exploratory Linear Optimized Decomposition into Independent Components (MELODIC) ICA (*http://www.fmrib.ox.ac.uk/fsl/*). ICA is a model-free approach for analyzing functional neuro-imaging data that decomposes a two-dimensional (time $\times$ voxels) data matrix into a set of timecourses and associated spatial maps, which describe temporal and spatial characteristics of underlying hidden signals, or components [18]. ICA was used as a primary approach to objectively identify RSNs, as described below. Subsequently, those networks readily identifiable with ICA were further characterized using a seed-based approach that has become standard in the field of resting-state functional connectivity [9,11,12] to detect interregional temporal correlations in fMRI signal fluctuations (see Table 1).

Independent components analysis

Data were analyzed using MELODIC Version ln(11), part of FMRIB Software Library (FMRIB's Software Library). The two functional scans were combined for this analysis to increase power. Preprocessing of the data was applied as follows: masking of nonbrain voxels; voxel-wise demeaning of the data; normalization of the voxel-wise variance. Preprocessed data were whitened and projected into a 75-dimensional subspace using probabilistic Principal Component Analysis in which the number of dimensions was estimated using the Laplace approximation to the Bayesian evidence of the model order [19]. The whitened observations were decomposed into a set of time-courses and spatial maps by optimizing for non-Gaussian spatial source distributions using a fixed-point iteration technique. Estimated component maps were divided by the standard deviation of the residual noise and thresholded by fitting a mixture model to the histogram of intensity values [19]. From this analysis, components were visually inspected to identify those corresponding to several previously identified RSNs [10]. Three additional bilateral networks were also observed. These were less reliably related to previously characterized networks, likely reflecting individual variability, possible reorganization in this patient, or effects of age, and have thus been excluded from the current analysis.

Seed-based functional connectivity

For this analysis, the first resting-state scan was used. We created spherical 'seed' regions of interest (ROIs) ($10\ 3\times3\times3$-mm voxels, volume=270 mm^3) using Talairach coordinate locations from previous work [10] (Table 1). These Talairach coordinates were converted to Montreal Neurological Institute space using the algorithm implemented in the MATLAB script tal2mni.m (*http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach*). Two ROIs for each RSN were used to extract an average hemodynamic time series for each network in each hemisphere by applying each ROI mask to the preprocessed time series, and averaging across all voxels within the ROI. We then carried out separate multiple regression analyses (using the General Linear Model as implemented in FMRIB Software Library's FMRI Expert Analysis Tool) for each set of seeds, with the seed time series regressors and nuisance covariates (global signal, cerebrospinal fluid, white matter), as well as six motion regressors. The global signal, which reflects a combination of physiological processes (such as cardiac and respiratory fluctuations) and scanner drift, was included in the General Linear Model to minimize the influence of such factors [17]. Each ROI time series was orthogonalized with respect to the nuisance covariates, to the six motion regressors, and to 19 artifact components identified by ICA. These methods are described in detail in a recent publication from our group [11], and are becoming standard practice in analysis of resting-state data [12].

Table 1 Montreal Neurological Institute coordinates of seed ROI locations

Network	Region	x	y	z
RSN 1	Left middle occipital gyrus	−22	−88	17
	Right middle occipital gyrus	22	−76[a]	17
	Left lingual gyrus	−8	−80	−8
	Right lingual gyrus	8	−80	−8
RSN 2	Left cingulate gyrus	−8	−54	27
	Right cingulate gyrus	8	−54	27
	Left medial frontal gyrus	−8	56	0
	Right medial frontal gyrus	8	56	0

ROI, region of interest.
[a]This coordinate was placed slightly more medially owing to accommodate artifact in the scan.

Interhemispheric correlations

To provide a quantitative comparison of interhemispheric connectivity between patient N.G. and the neurologically intact control group, for each seed, we calculated interhemispheric correlation scores for each participant. The hemodynamic time series for each coordinate listed in Table 1 was extracted for each participant and a correlation was computed between the time series from the left hemisphere and the time series from the homologous coordinate in the RH. Results from these comparisons are presented in Table 2 and Fig. 4.

Diffusion tensor imaging

Fractional anisotropy (FA) maps thresholded at 0.25 are presented in Fig. 1. A program implemented in MATLAB was used to calculate the diffusion tensor. For S_0 and S_i representing the signal intensity with b=0, and the signal intensity in the ith direction and b=diffusion weighting, $Y=[\ln(S_0/S_1)/b,\ \ln(S_0/S_2)/b, \ldots,\ \ln(S_0/S_M)/b]^T$. The noise in the data for each acquisition can then be expressed as $Y=Hd+\eta$, with $d=H^{-1}Y$. In cases with more than six directions, the H matrix is not a square matrix, so it is not possible to calculate the inverse H^{-1}. Psuedoinverse H^{ψ}, however, can be calculated such that $H^{\psi}H=I_{6\times6}$. $H^{\psi}H=(H^TH)^{-1}\ H^T$. The tensor $[\lambda_1, \lambda_2, \lambda_3]$=diagonalization of d. FA was calculated as:

$$\mathrm{FA}=\frac{\sqrt{3[(\lambda_1-\langle\lambda\rangle)^2+(\lambda_2-\langle\lambda\rangle)^2+(\lambda_3-\langle\lambda\rangle)^2]}}{\sqrt{2(\lambda_1^2+\lambda_2^2+\lambda_3^2)}}$$

As can be seen from the map, no residual commissural fibers exist in this patient.

Results

The ICA revealed two notable bilateral components (Fig. 2). The first appeared to be the posterior portion of what has come to be known as the default mode network [20], comprising posterior cingulate and lateral parietal cortices. The second closely matched a posterior network characterized by involvement of occipital cortex referred to in the literature as RSN 1 [10].

The seed-based functional connectivity analysis confirmed that the two networks revealed using ICA were indeed present bilaterally. Networks correlated with each of the seed ROIs are shown in Fig. 3. For seeds placed in various left hemisphere regions (Fig. 3a), a strongly bilateral network was revealed by the regression analyses. A similar, though weaker, bilateral pattern emerged for RH seeds (Fig. 3b). It is likely that preoperative structural damage to the RH in this patient contributes to the weaker functional connectivity from right to left regions. Results for a comparison of patient N.G.'s interhemispheric correlation scores with scores from 42 neurologically intact participants are shown in Fig. 4. Table 2 summarizes the average and standard deviation of interhemispheric correlation scores for the control participants and for patient N.G. For two out of three of the coordinates examined, patient N.G. fell well within the standard deviation (Table 2).

Discussion

In summary, we assessed interhemispheric coordination in a commissurotomy patient using ICA and seed ROI-based functional connectivity measures, both of which revealed a

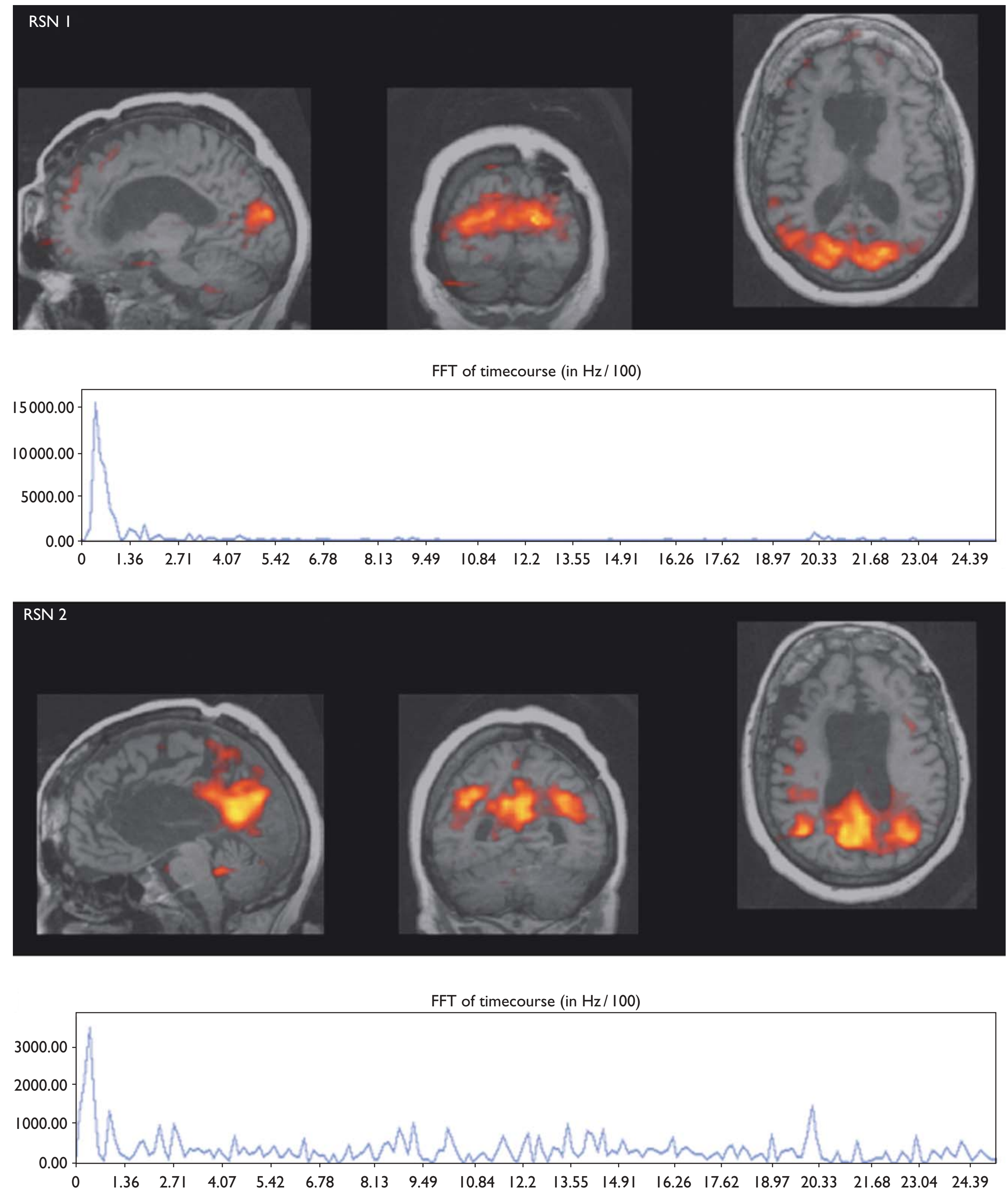

Fig. 1 Resting state networks identified using ICA. Two components were identified by ICA. These components had fast Fourier transform timecourses consistent with known resting state networks (< 0.1 Hz). ICA, independent components analysis.

surprisingly high degree of bilaterality. Such interhemispheric coordination in the absence of all major commissures, including the corpus callosum, suggests that the low-frequency BOLD signal that gives rise to large-scale RSNs can be coordinated subcortically. Behavioral analyses have shown large individual differences in interhemispheric transfer among split-brain patients [2]. The patient studied here shows remarkably spared visual transfer. Specifically, she is able to match meaningful as well as nonsense shapes of varying complexity, as well as letter shapes across the vertical meridian, but not letter names or facial identity [21]. This is consistent with the existence of strong bilateral connectivity

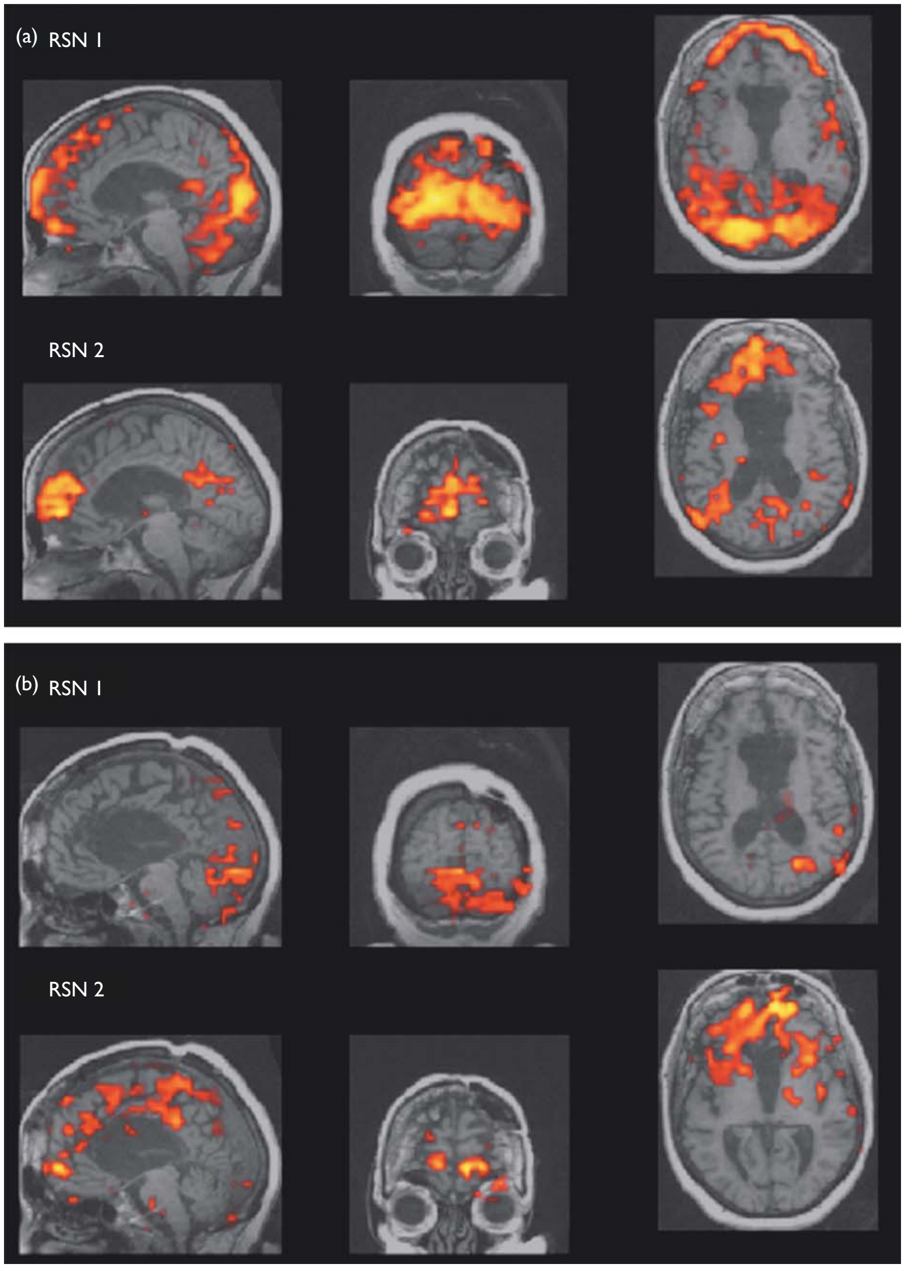

Fig. 2 Networks correlated with seeds in the LH (a) and RH (b). (a) Left seed ROIs: seeds placed in the LH (see Table 1 for coordinates) revealed bilateral patterns of connectivity. (b) Right seed ROIs: seeds placed in the homologous RH regions also revealed bilateral connectivity, though weaker. LH, left hemisphere; RH, right hemisphere; ROI, region of interest.

in primary visual cortex (RSN 1), as demonstrated here. Additionally, this patient shows preserved bilaterality in regions comprising the default mode network [20]. This network exhibits high baseline levels of activity that is attenuated during externally oriented cognitive tasks, and is thought to be involved in a variety of self-referential and social cognitive functions [22]. Recent work has shown decreases in connectivity between the anterior and posterior portions of this network with age [23], consistent with our data.

The fact that specific RSNs maintain bilateral presence after complete commissurotomy strongly suggests that their coordination is subcortical in origin, after surgery. It remains possible that in the intact brain, a dual mechanism exists such that both cortical and subcortical mechanisms work to coordinate networks, but the persistence of bilateral networks in our commissurotomy patient suggests that commissural connections are not the only fibers involved in maintaining interhemispheric coordination and coherence. It is likely that in the intact brain, commissural connections do exert a greater influence, but in the absence of such connections, the subcortical mechanism takes over. Such a dual mechanism model is consistent with the studies demonstrating greater contributions of subcortical structures during sleep than waking states [4]. Future work in neuroimaging of acutely postoperative patients will help to clarify this issue, and assess compensatory reorganization unfolding over time.

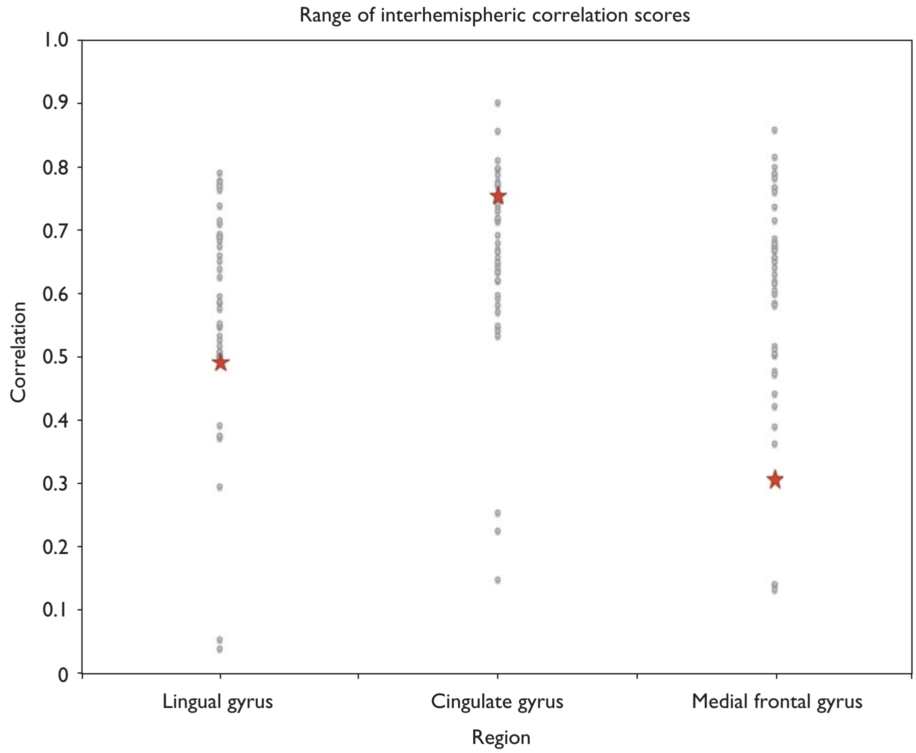

Fig. 3 Interhemispheric correlation scores. Interhemispheric correlation scores from 42 neurologically intact control participants show a wide distribution. Scores for patient N.G. (red stars) fall within the normal range for 2 out of 3 of the regions examined.

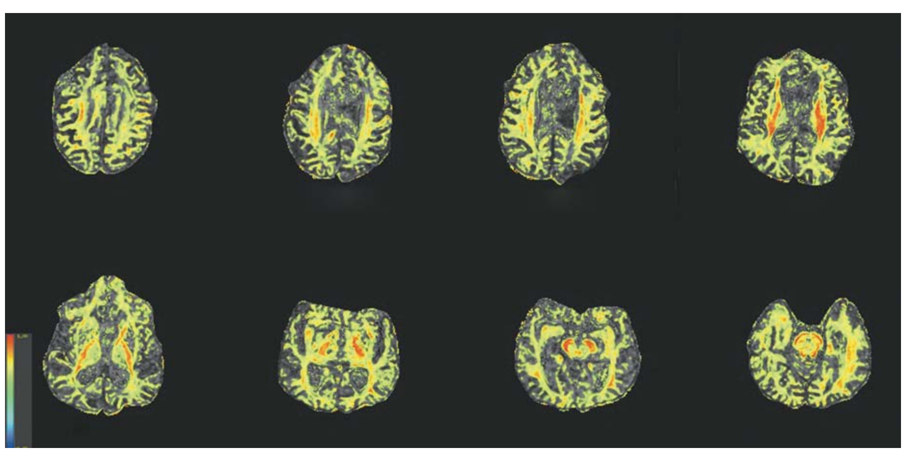

Fig. 4 Diffusion tensor imaging. Fractional anisotropy maps (horizontal sections, dorsal to ventral) from patient N.G. demonstrate completeness of commissurotomy. No residual interhemispheric fibers can be detected.

Table 2 Interhemispheric correlation scores

	Middle occipital gyrus	Cingulate gyrus	Medial frontal gyrus
Patient N.G.	0.4960	0.7384	0.3070
Controls (mean)	0.5776	0.6552	0.5982
Controls (SD)	0.1707	0.1537	0.1767

Understanding the mechanisms of interhemispheric coordination has been a central problem in the field of cognitive neuroscience. Given the vast literature on compromised interhemispheric coordination in commissurotomy patients, it has long been asserted that the commissural fibers are necessary for transfer of complex cognitive information [24]. In this and other split-brain patients, however, several investigators have noted that transfer of some types of visual information is usually spared [21]. The commonly accepted explanation for residual interhemispheric coordination in split-brain patients is that subcortical pathways suffice to transfer simple visual information [3,21,25]. Our data are consistent with the claim that such subcortical connections operate when the corpus callosum is surgically severed. We reasoned that if such subcortical pathways exist, then they should be detectable using the methods of resting-state functional connectivity. Here, we have demonstrated just such connectivity in a commissurotomy patient.

Limitations

A limitation of this study is the lack of task-related activation data. Unfortunately, owing to the patient's age and reduced motor ability, we were unable to collect additional data during a task paradigm (e.g. finger tapping) that would have allowed us to address the interesting question of functional connectivity during task performance after complete commissurotomy. Resting-state fMRI, however, is increasingly used to examine network integrity in clinical populations for which task-based paradigms are difficult to implement. One of the advantages of the resting-state approach is that it is 'cognitively unbiased', or independent of task performance, yet is related in meaningful ways to cognition and behavior [16].

Another limitation is the use of two different scanners (General Electric 3.0 T HD Signa Excite and Siemens Allegra 3-Tesla) for collection of data from the patient and normal adult control group, respectively. This was unavoidable owing to the geographical location of the patient, and precludes further direct comparison of data between the patient and control population.

Finally, our data represents the brain of one individual, and thus awaits replication by studies on other comparable patients. Unfortunately, such patients are rare as the complete commissurotomy surgery as treatment for intractable epilepsy has been largely replaced by pharmacological interventions.

Conclusion

We used two different methods, ICA and seed-based analyses, to demonstrate functional connectivity between homologous regions with a high degree of anatomical specificity, in the two disconnected cerebral hemispheres. This is the first neuroimaging evidence of bilateral RSNs in a patient with no cortical commissural fibers. Our findings suggest that RSNs in the brain are at least in part subcortically coordinated, and that the sparing of information transfer between the hemispheres of split-brain patients is mirrored in the specific bilateral RSNs.

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