

# Greater than the sum of its parts: a review of studies combining structural connectivity and resting-state functional connectivity

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**Abstract** It is commonly assumed that functional brain connectivity reflects structural brain connectivity. The exact relationship between structure and function, however, might not be straightforward. In this review we aim to examine how our understanding of the relationship between structure and function in the ‘resting’ brain has advanced over the last several years. We discuss eight articles that directly compare resting-state functional connectivity with structural connectivity and three clinical case studies of patients with limited white matter connections between the cerebral hemispheres. All studies examined show largely convergent results: the strength of resting-state functional connectivity is positively correlated with structural connectivity strength. However, functional connectivity is also observed between regions where there is little or no structural connectivity, which most likely indicates functional correlations mediated by indirect structural connections (i.e. via a third region). As the methodologies for measuring structural and functional connectivity continue to improve and their complementary strengths are applied in parallel, we can expect important advances in our diagnostic and prognostic capacities in diseases like Alzheimer’s, multiple sclerosis, and stroke.

**Keywords** Resting-state functional connectivity · Structural connectivity · DTI · fMRI

## Introduction and aims

One of the new trends in functional neuroimaging is studying ‘resting-state fMRI’. This approach focuses on spontaneous, rather than task-induced, fluctuations in the blood oxygenation level-dependent (BOLD) signal. In standard task-activation fMRI, an experimental task of interest is presented alternately with a control task and the BOLD signal during the experimental task is compared to the BOLD signal during the control task. The difference between baseline and task-related activation accounts for about 1–5% of the total BOLD signal. Thus, compared to ongoing ‘baseline’ brain activity, only a small percentage is needed to respond to an external stimulus. However, the function of this vast amount of baseline activity remains unclear.

Resting-state fMRI is one approach used to study this baseline activity of the brain. The most common fMRI analysis techniques were, and still are, model-based, using the onset and offset of an external stimulus to specify the model. In resting-state fMRI, by definition, no external stimulus is presented; therefore new analytic approaches had to be applied. In the first resting-state fMRI study (Biswal 1995), the time course of a seed region-of-interest (ROI) in the left motor cortex was correlated with the time course of all other brain voxels. The resulting map demonstrated functional connectivity between the left and right motor cortex even in the absence of a task. Since its initial demonstration, this correlation approach has been widely applied. A limitation of this approach, however, is that the seed ROI must be selected by the investigator, possibly inducing a selection bias. Furthermore, in such a correlation approach the global signal is usually regressed out, a preprocessing step that can induce false negative correlations between brain regions (Murphy, et al. 2009). To avoid

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these issues, data-driven approaches such as independent component analysis (ICA) have become increasingly common. ICA decomposes the 4-dimensional (brain volume over time) BOLD signal into a set of spatially distinct maps and their associated time courses. Among these independent components are several readily identified functional brain networks, but also artifacts related to movement and physiological noise (Beckmann et al. 2005). A general limitation to resting-state fMRI is that it is very difficult to separate physiological noise, induced by the cardiac pulse and respiration, from the BOLD signal. ICA does separate these signals to a large extent but residual noise might still be present in the components of interest (Birn et al. 2008). A possible solution to this problem is to collect physiological data and remove the corresponding signal from the fMRI data.

The abovementioned analysis approaches (seed-based correlations and ICA) both provide measures of functional connectivity between neighboring and/or distant brain voxels. It is generally assumed that functional connectivity reflects the brain's structural connectivity (i.e. the anatomical connections between brain regions) but the exact relationship between structure and function might not be straightforward. Structural brain connectivity is most commonly measured using diffusion tensor imaging (DTI). DTI is a relatively new imaging technique that measures the diffusion of water molecules in the brain (Le Bihan 2003; Moseley et al. 1990). In an unrestricted environment, water molecules diffuse freely in any direction. In the brain however, diffusivity is restricted by the brain's architecture such that water diffuses more readily along axons rather than across them. Measuring the direction of diffusivity can be used, therefore, to infer the orientation of white matter tracts in the brain. Several measures are used to quantify white matter integrity using DTI, the most common being fractional anisotropy (FA), mean diffusivity (MD), fiber count and probabilistic tractography. FA is a scalar measure of the degree of anisotropy (direction selectivity) and MD is a scalar measure of the total diffusivity. These two measures are calculated within a voxel. The remaining two measures, fiber count and probabilistic tractography, result from tracking the principle diffusion direction of every voxel between ROIs. Fiber count results in a total number of fibers connecting a seed region with a target region and probabilistic tractography produces a measure of the likelihood that two regions are connected.

The development of DTI has been an important contribution to the neuroimaging field by making it possible to study structural connectivity in vivo in humans. For all its strengths, however, there are also some important limitations to DTI including susceptibility-induced signal loss and difficulty resolving small tracts as they cross large tracts. A given voxel can contain several small fiber tracts

coursing in multiple directions. This can lead to an incorrect measure of the principal diffusion direction for a particular tract, resulting in both false positives and false negatives, making it difficult to discern crossing or “kissing” fibers. In addition, interpreting DTI data can be challenging, as the precise histological features reflected in the various DTI measures remain poorly characterized. Thus, while higher FA values are generally interpreted as reflecting healthier white matter the specific cellular level changes that can contribute to reduced FA have not been worked out in detail.

The number of studies directly comparing resting-state functional and structural connectivity is still relatively small, but leaped from only one study before 2008 to six published studies in 2008. In this review we will evaluate the existing literature and discuss the main findings and unresolved issues across studies. We aim to examine how knowledge of the relationship between structure and function of the ‘resting’ brain has advanced, and suggest directions for future research.

### Direct comparisons of functional and structural connectivity

We have found eight articles that directly compare resting-state functional connectivity with a measure of structural connectivity using DTI.

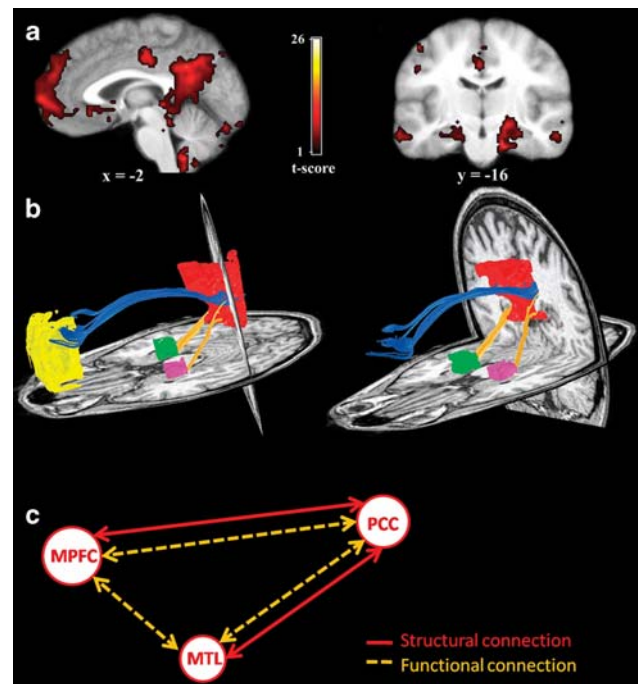
The first study that directly compared anatomical connectivity with functional connectivity was published in 2002 (Koch et al. 2002). In this study fMRI and DTI data were collected in one 5 mm axial slice. The authors used a similar approach to measure functional connectivity as in the paper by Biswal and colleagues described above. They differed however in that here the authors examined the correlation of spontaneous fluctuations in the BOLD signal of brain voxels in cortical gyri of the same hemisphere and not of symmetric areas in opposite hemispheres. They compared this measure of functional connectivity with anatomical connectivity, i.e. the probability that a tract can be traced between two points using DTI. Their results showed a positive correlation between functional and anatomical connectivity of regions along the central sulcus only. Furthermore, across all voxel pairs they observed high functional connectivity in the presence of low structural connectivity but not the opposite. That is, when structural connectivity was high between voxels, functional connectivity also tended to be high.

This study was the only one of its kind for several years but the issue has recently been revisited. Following the growing interest in resting-state fMRI, seven more papers have been published in 2008/early 2009 investigating the relationship between resting-state functional and structural

connectivity. Because the origin of resting-state networks (i.e. patterns of correlations in the BOLD signal measured during rest) is still a matter of considerable debate (Morcom and Fletcher 2007; Raichle and Snyder 2007), exploring the relationship between functional connectivity and the underlying anatomy may contribute to the discussion.

A resting-state network of particular interest is the default mode network (DMN). This group of brain regions—encompassing the posterior cingulate cortex (PCC) and the adjacent precuneus (pCu) and retrosplenial cortex (RSC); the inferior parietal cortex (IPC); the medial prefrontal cortex (MPFC) and somewhat less consistently the medial temporal lobe (MTL)—is active during rest and deactivates during most externally oriented tasks (Greicius et al. 2003; Raichle et al. 2001). Greicius et al. (2009) used ICA to define the DMN and then investigated the structural connections of four separate regions within this functional network: the PCC, MPFC, and bilateral MTL. DTI tractography revealed the cingulum bundle connecting the PCC and the MPFC and the descending cingulum bundles connecting the PCC and the bilateral MTL (see Fig. 1). The authors highlight the fact that these two separate white matter tracts contacted the large functional PCC cluster in two distinct locations. The MTL clusters connected to the more ventral or caudal aspect of the PCC cluster, presumably corresponding to the RSC, whereas the MPFC cluster connected to the more dorsal or rostral aspect of the PCC cluster likely corresponding to the PCC proper. These findings point to the potential of DTI to inform resting-state fMRI by parsing large functional clusters into adjacent but distinct subclusters. The other point made in this study is that functional connectivity does not always reflect structural connectivity. Though the MPFC and MTL were functionally connected, the authors were not able to detect any white matter tracts connecting these two regions structurally. This suggests either that (a) these two regions do not share a direct structural connection and so functional connectivity must be mediated through a third party (like the PCC) or (b) the absent structural connectivity reflects a false negative result in the tractography analysis.

Van den Heuvel et al. (2008b) extended this qualitative approach by taking two of the same DMN regions (PCC and MPFC) and quantifying the relationship between functional and structural connectivity. The authors obtained these PCC and MPFC regions from the DMN map created by their previously described voxel-based “normalized cut group clustering” approach (van den Heuvel et al. 2008a). This clustering approach also yielded six other resting-state networks (RSNs). As a functional measure they calculated, in each of 45 subjects, the partial correlations between the PCC and MPFC (factoring out the contribution of all the 15 other separate brain clusters



**Fig. 1** Functional connectivity reflects structural connectivity in the DMN. **a** Task-free, functional connectivity in the DMN is shown in a group of six subjects. The PCC/RSC and MPFC clusters are best appreciated on the sagittal view. Prominent bilateral MTL clusters are seen on the coronal image (left side of image corresponds to left side of brain). **b** DTI fiber tractography in a single subject demonstrates the cingulum bundle (blue tracts) connecting the PCC/RSC to the MPFC. The yellow tracts connect the bilateral MTL to the PCC/RSC. Note that generally the tracts from the MPFC enter the more rostral aspect of the PCC/RSC ROI corresponding to the PCC proper, whereas the tracts from MTL enter the more caudal aspect of the PCC/RSC ROI corresponding to the RSC proper. Left and right columns show slightly different views of the same tracts to highlight the distinct entry points into the PCC/RSC. There were no tracts connecting the MPFC to the MTL. **c** Schematic representation of the structural and functional connections between these three nodes of the DMN. Adapted with permission from Greicius et al. (2009)

within the DMN and other RSNs). The structural measure for each subject was the mean FA value of the cingulum bundle connecting the PCC to the MPFC. Including age as a covariate in their model, they found a significant positive correlation between FA in the cingulum bundle and the partial correlation between PCC and MPFC. This correlation seems to be specific to the cingulum bundle and PCC–MPFC connectivity, as no other significant association was observed between PCC–MPFC functional connectivity and mean FA of any of the other reconstructed white matter tracts. Furthermore, no significant correlations were found between mean FA of the cingulum bundle and functional connectivity between other brain regions.

A different, wider-scale approach was undertaken by Skudlarski et al. (2008). They studied the overall agreement of functional and structural connectivity using a

voxel-wise approach. They segmented the brain to obtain grey and white matter masks, both of which contained 5,000 voxels. Functional connectivity was then determined by the cross-correlation between the time courses of 5,000 × 5,000 voxel pairs within the grey matter. Structural connectivity was obtained by counting the number of white matter tracts connecting 5,000 × 5,000 white matter voxel pairs. In order to combine these two measures, structural connectivity values of the original white matter voxels were transposed to the nearest grey matter voxels. Functional connectivity values of grey matter voxel pairs were subsequently correlated with number of tracts connecting these voxel pairs. They found a significant overall agreement between the two connectivity measures, with the strongest agreement for regions showing high connectivity on either measure (Skudlarski et al. 2008).

While Greicius and van den Heuvel focused on the relation between structural and functional connectivity within a specific network and Skudlarski measured the structural/functional relations of 5,000 voxels, Hagmann et al. (2008) and Honey et al. (2009) employed an intermediate approach. The functional and structural units in these studies consisted of a low-resolution set of 66 predefined anatomical regions, see (Desikan et al. 2006), and a high resolution set of these same 66 regions parsed into 998 equally sized smaller regions. As a functional measure they used the correlation between each pair of ROI's mean time series, after regressing out mean cortical, white matter and ventricular signals. Using a tractography approach, the number of white matter tracts connecting the ROIs determined structural connectivity. In their paper Hagmann et al. (2008) focused mainly on structural connectivity. Their graph theoretical analysis approach revealed a structural core within the parietal cortex (PCC, pCu, IPC, etc.), as well as a number of distinct temporal and frontal hubs. Regions within this structural core form major hubs that link efficiently to all structural hubs. These structural core regions resemble the brain areas that form the posterior components of the DMN. The authors subsequently compared the strength of both structural connectivity and resting-state functional connectivity, within and outside of core regions and found a positive association between these two measures. In a second paper the same group followed up on this work by studying the relationship between structural and functional connectivity in more detail (Honey et al. 2009). In particular, they reported that when structural connectivity is present, its strength is robustly related to functional connectivity strength. The contrary, as suggested in the paper by Greicius et al., is not necessarily true in that the presence of functional connectivity does not automatically imply structural connectivity. Honey and colleagues showed that this imperfect correlation between functional and structural connectivity was not merely a

manifestation of the practical limitations of fMRI, as the correlations observed in the empirical data were about equal to those obtained by a computational model free of physiological and scanner noise. The authors additionally examined the reliability of resting-state functional connectivity by comparing data acquired on two separate occasions. They found unexpectedly low test–retest reliability within and across scanning sessions. However, they did find that functional connectivity between anatomically connected regions is more consistent than between unconnected regions. Systems with strong structural connectivity such as the DMN, therefore, showed more reliable functional connectivity across sessions.

The above studies investigated the relationship between functional and structural connectivity within a group of healthy subjects. Two other studies investigated changes in functional and structural connectivity between groups: comparing younger and older healthy subjects (Andrews-Hanna et al. 2007) and healthy controls and patients with multiple sclerosis (MS) (Lowe et al. 2008). Andrews-Hanna and colleagues were primarily interested in selective disruption of two networks, the DMN and what they refer to as the dorsal attention system which includes the intraparietal sulcus, frontal eye fields, inferior precentral sulcus and middle temporal area. They selected several bilateral ROIs from both networks and cross-correlated the average time series of the ROIs within a network. They found decreased connectivity strength in older subjects across most ROIs in both networks. Because age-related decreases in white matter integrity have been observed in previous studies (Damoiseaux et al. 2009; Good et al. 2001), they additionally studied white matter tract integrity within a subset of the older subjects using DTI. Mean FA values within a coarsely defined bilateral white matter ROI (including all white matter bundles within one axial slice, such as the corona radiata, superior longitudinal fasciculus and cingulum) correlated positively with functional connectivity between the pCu/RSC and MPFC.

The other two-group study by Lowe et al. (2008) examined bilateral sensorimotor areas and their structural connection, the transcallosal motor pathway, in healthy subjects and patients with MS. They selected an ROI in the left sensori-motor cortex based on task-activation data, averaged the time series, and correlated this reference time series with every other voxel in the brain. Functional connectivity was calculated as the percent of voxels within a right hemisphere ROI that significantly correlated with the left hemisphere ROI. No significant difference in functional connectivity was observed between patients and controls. The same left hemisphere seed region used in the fMRI data was used to track the fibers of the transcallosal motor pathway in the DTI data. For every subject mean FA, MD, parallel and transverse diffusivity, were used as



measures of structural connectivity. None of these measures were significantly different between groups. Mean FA correlated positively with functional connectivity when combining the two groups but not with the groups separately. They did, however, find an inverse correlation between transverse diffusivity and functional connectivity for all subjects combined and for the patient group alone. It is difficult to interpret these results as no significant group differences were observed but this inverse correlation may indicate that demyelinating lesions, which are believed to increase transverse diffusivity, can result in reduced functional connectivity.

Although the above studies use slightly different approaches (whole brain versus ROI, mean FA versus number of tracts (fiber count), etc.) their results are largely convergent. All studies show that the strength of resting-state functional connectivity correlates positively with structural connectivity strength. Furthermore, both Koch et al. (2002) and Honey et al. (2009) found that increased structural connectivity predicts increased functional connectivity, but increased functional connectivity does not as consistently predict increased structural connectivity. However, in the first study data were acquired in only one axial slice, so that anatomical connections extending out of the plane of this single slice could have been missed. Moreover, the presence of functional connectivity in the absence of structural connectivity, as mentioned earlier, may reflect either false negatives in DTI, false positives in resting-state fMRI or the fact that two functional ROIs may be functional connected via a third ROI without a direct structural connection (as is depicted in Fig. 1c where the MPFC and MTL show functional connectivity but no direct structural connection). This last option is supported by the findings of Honey et al. (2009) that showed that indirect connections accounted for some of the variance in functional connectivity that was unexplained by direct structural connectivity.

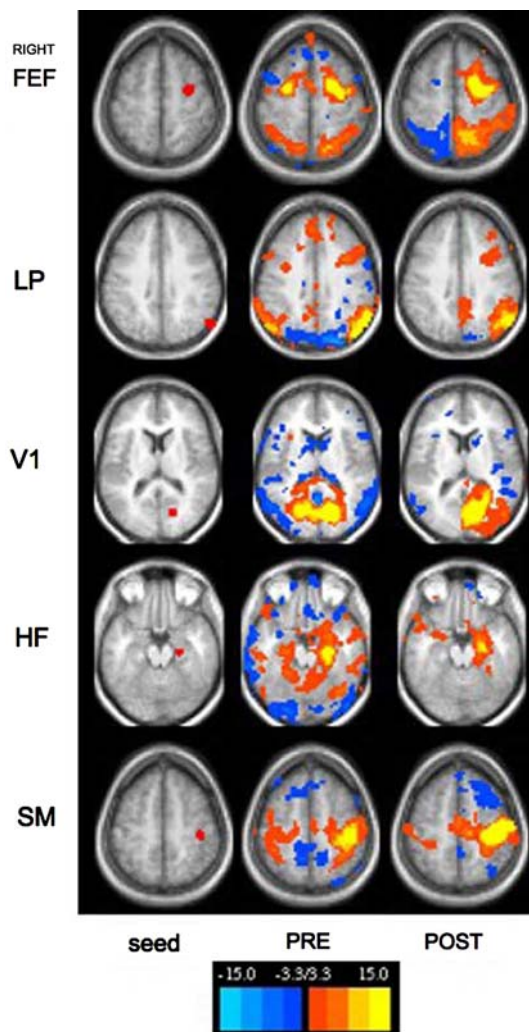
### Clinical case studies

Another way to gain insight into the relationship between brain structure and function is through clinical case studies of patients who lack normal anatomical connections between the hemispheres. In one such recent case (Johnston et al. 2008), the authors acquired resting-state fMRI data in a 6-year-old child with intractable seizures before and after complete section of the corpus callosum, including the splenium and dorsal hippocampal commissure. The anterior and posterior commissures were left intact. They studied connectivity patterns of several bilateral ROIs (located in the dorsal attention system, DMN, hippocampal formation, amygdala, auditory, somatomotor

and visual cortex) with the rest of the brain. Before section of the corpus callosum, correlations with the seed regions were found both ipsilaterally and contralaterally. After the section, mostly intrahemispheric correlations were preserved (see Fig. 2 for representative pre- and post operation correlation maps). Two bilateral regions studied here (hippocampus and somatomotor cortex) revealed some remaining interhemispheric correlations. The preserved interhemispheric hippocampal connectivity was believed to be mediated by the anterior commissure which was not sectioned. The preserved interhemispheric somatomotor connectivity was postulated to be caused by synchronous ascending information sent out through somatomotor thalamocortical projections.

Around the same time the above paper came out, another case study of a patient with a complete commissurotomy was published (Uddin et al. 2008). This patient underwent a single-stage midline section of the anterior commissure, corpus callosum, hippocampal commissure and massa intermedia in 1963. Uddin and colleagues investigated resting-state functional connectivity using both ICA and an ROI analysis. Their ICA resulted in two notable components showing spatial maps of bilateral connectivity, one resembling the posterior part of the DMN and the other the lateral visual cortex. From these two ICA maps the authors selected four bilateral seed regions (middle occipital, lingual, cingulate and medial frontal gyri). Each ROI's mean time series was correlated with all other brain voxels while regressing out the mean global, white matter and ventricular signal, six motion parameters and 19 artifact components identified by ICA. Similar to ICA this ROI analysis revealed interhemispheric functional connectivity. Furthermore, compared with a group of 42 healthy controls, the patient's interhemispheric functional connectivity scores of two out of the three ROIs examined fell within the normal range. The authors suggested that the observed interhemispheric connectivity in this patient could be coordinated subcortically.

An earlier study investigated whether congenital defects in the corpus callosum substantially diminish interhemispheric functional connectivity, by studying three patients with agenesis of the corpus callosum (Quigley et al. 2003). A structural MRI scan of all three patients confirmed an absent corpus callosum, and revealed colpocephaly in one patient, an interhemispheric cyst in another and both colpocephaly and an interhemispheric cyst in the last patient. In all three patients two task-related fMRI scans were collected (passive listening and finger tapping) and one resting-state scan. Resting-state functional connectivity analysis was performed using voxels activated during the task conditions as seeds and correlating the corresponding time courses with all other voxels in the brain. The authors found substantially less interhemispheric than



**Fig. 2** Functional connectivity computed before and after corpus callosotomy for right-sided seed regions. Seed regions defined in the right hemisphere (first column of each set) were used to generate correlation maps both before (second column) and after (third column) complete transection of the corpus callosum. Seed ROIs were placed laterally in the hemispheres to avoid confusion that might arise because of partial volume averaging associated with ROIs close to the midline. Preoperatively, functional connectivity maps using the selected seed regions revealed a pattern of correlations that is consistent with the published literature, including symmetric correlations with the contralateral hemisphere. For example, a seed in the right lateral parietal (LP) region demonstrates correlations with the left lateral parietal as well as with medial prefrontal cortex and posterior cingulate/precuneus (second row). Postoperatively, contralateral correlations that were present before transection are almost completely absent [frontal eye field (FEF), top row; LP, second row; V1, third row]. Correlations with the hippocampal formation (HF) seed and the somatomotor (SM) seed do not show complete loss of contralateral correlations. These regions have neuroanatomical connections with the opposing hemisphere through fibers that do not cross in the corpus callosum. The hippocampus, for example, is able to communicate with the contralateral hemisphere through the anterior commissure. Adapted with permission from Johnston et al. (2008)

intra-hemispheric resting-state connectivity in the motor and auditory cortices in these three patients. In healthy control subjects the difference between inter- and intra-hemispheric connectivity appears much smaller than that observed in the patients.

The results of the abovementioned case studies appear to be inconsistent, but the variability in the ROIs used and the difference in clinical status of the patients studied here could explain at least part of this inconsistency. The clinical status of the cases described in the first two surgical studies differ because in the first study a 6-year-old child was scanned under anesthesia within a few days after the surgery, and in the second a 74-year-old woman was scanned 45 years after surgery. The observed inter-hemispheric connectivity in the second study may therefore be a result of brain plasticity, reflected in reorganized subcortical mechanisms. This theory does not appear to be completely supported by the results of the agenesis study. However, these clinical cases may be difficult to compare as plasticity in a relatively normal brain after a surgical section of the corpus callosum may be different from plasticity in a congenitally abnormal brain. Nevertheless, even though comparison between these clinical cases is not straightforward, we can conclude that functional connectivity appears to depend to a large degree on intact inter-hemispheric connections but that subcortical mechanisms may help reestablish inter-hemispheric connectivity in patients with limited white matter connections between the cerebral hemispheres. Clearly, longitudinal follow-up imaging on the patient reported by Johnston and colleagues will help us understand the rate and potential mechanisms of plasticity in these callosotomy patients.

## Conclusions and discussion

It is commonly assumed that functional connectivity reflects structural connectivity in the brain. From surveying the current literature, we can conclude this is true to a large extent. However functional connectivity is also observed between regions where there is little or no structural connectivity. This likely indicates BOLD signal correlations mediated by indirect structural connections (i.e. via a third region), though we also need to be wary of the possibility of false negatives in DTI. Another potential problem worth mentioning is that correlations between structural and functional connectivity could be introduced because of near-distance spatial effects in fMRI (due to noise, hemodynamic or vascular artifacts) and greater likelihood to complete short fibers in DTI/tractography. In two of the

studies discussed here the authors corrected for these distance effects (Honey et al. 2009; Skudlarski et al. 2008), but this is not yet commonly done. Growing, convergent evidence for a quantitative relationship between resting-state functional connectivity and structural connectivity is reassuring for proponents of resting-state fMRI. This strongly indicates that these resting-state networks are of neuronal origin.

In this review two types of connectivity measures have been discussed, resting-state functional connectivity measured by fMRI and structural connectivity measured by diffusion imaging. As both resting-state fMRI and DTI are relatively new and somewhat controversial methods, verifying results of one such method with the other might not be ideal. The observed agreement between the results of both techniques is encouraging, but more research, both in healthy controls and patient populations, is needed to substantiate these findings and address some lingering inconsistencies. Regarding the question of test–retest reliability, for example, one study presented here (Honey et al. 2009) found low test–retest reliability in functional connectivity within and across scanning sessions, whereas other studies have shown reasonable consistency and reliability of resting state connectivity (Damoiseaux et al. 2006; Shehzad et al. 2009). Furthermore, most of the studies presented here mainly investigated connectivity between cortical brain regions, but subcortical connections certainly also play an important role. Resting state networks have previously been shown to encompass subcortical structures. In order to get a more complete picture of the brain's structure-function correlations, it will be essential to include subcortical connectivity in future studies. Resting-state fMRI and diffusion imaging are developing fields, and hopefully with time many methodological limitations will be overcome. For example, a recently developed diffusion imaging technique called diffusion spectrum imaging (DSI) has been shown to be particularly sensitive in detecting fiber crossings and might therefore provide a more suitable technique for fiber tracking than DTI. The studies by Hagmann and Honey and colleagues presented in this review have employed this technique.

Another way to confirm the correspondence between structural and functional connectivity is by studying multiple imaging modalities. For instance in the studies presented here the brain's grey matter was studied with fMRI and the white matter with DTI. But as has been shown previously, structural connectivity can also be assessed by studying grey matter (He et al. 2007; Mechelli et al. 2005; Seeley et al. 2009). Mechelli and colleagues calculated the grey matter density of 12 ROIs and used voxel-based morphometry to find patterns of positive and negative covariance across subjects between these ROIs and

multiple cortical regions. Positive associations were found both inter- and intrahemispherically. Negative associations were also found inter- and intrahemispherically but inter-hemispherically only between heterotopic regions and not between homotopic regions. He and colleagues investigated anatomical connection patterns by using cortical thickness measurements from structural MRI. Two areas were considered anatomically connected if they showed statistically significant correlations in cortical thickness across subjects. Connections were also found both intra- and interhemispherically, many of which were consistent with known neuroanatomical systems. Seeley and colleagues demonstrated that structural covariance maps derived from specific ROIs are strongly spatially correlated with maps of functional connectivity derived with the same ROIs. However, it needs to be noted that correlations between such grey matter measures do not necessarily imply structural connectivity, they could arise from shared function, or shared genetic influence. Nevertheless, it is very intriguing to see that different connectivity measures as used in these studies appear to be in agreement with the previously discussed fMRI and DTI measures. Precisely how these measures relate is an interesting question for further research.

Additional information could also be gained by (intracranial) electroencephalography (EEG/iEEG) and magnetoencephalography (MEG) or a combination of these methods with functional and structural MRI and diffusion imaging. Teipel and colleagues combined EEG with DTI to study convergence between functional and structural connectivity. Their results corroborate the conclusion of this review in that structural and functional measures demonstrated convergent connectivity patterns (Teipel et al. 2009).

A combined approach of different imaging modalities may be more fruitful than using either one alone. It can be especially helpful in studying disease. In Alzheimer's disease, for example, different modalities have already yielded convergent results. Functional connectivity of the DMN is decreased in patients with Alzheimer's disease compared to healthy controls (Greicius et al. 2004). The same brain regions also seem to be the main areas targeted by grey matter atrophy and deposition of  $\beta$ -amyloid plaques as measured by PET (Buckner et al. 2005) and appear to be modulated early in life in young adult APOE e4 carriers (Filippini et al. 2009). However, one technique alone may not have sufficient sensitivity and specificity to be used as a diagnostic tool. Obtaining additional information via a second modality may, however, allow for sufficient diagnostic accuracy to be achieved. For example, a recent study in Alzheimer's disease has shown that the combination of hippocampal volume and mean FA of an ROI in the posterior cingulum improved the separation of



patients and controls considerably compared to the hippocampal volume measure alone (Zhang et al. 2007). The combination of DTI measures with resting-state functional connectivity could be an even more efficient classification tool. As the methodologies for measuring structural and functional connectivity continue to improve and their complementary strengths are applied in parallel, we can expect important advances in our diagnostic and prognostic capacities in diseases like Alzheimer's, multiple sclerosis, and stroke.

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## References

- Andrews-Hanna J, Snyder A, Vincent J, Lustig C, Head D, Raichle M, Buckner R (2007) Disruption of large-scale brain systems in advanced aging. *Neuron* 56(5):924–935
- Beckmann CF, DeLuca M, Devlin JT, Smith SM (2005) Investigations into resting-state connectivity using independent component analysis. *Philos Trans R Soc Lond B Biol Sci* 360(1457):1001–1013
- Birn R, Murphy K, Bandettini P (2008) The effect of respiration variations on independent component analysis results of resting state functional connectivity. *Hum Brain Mapp* 29(7):740–750
- Biswal B (1995) Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *MRM* 34:537–541
- Buckner RL, Snyder AZ, Shannon BJ, LaRossa G, Sachs R, Fotenos AF, Sheline YI, Klunk WE, Mathis CA, Morris JC, Mintun MA (2005) Molecular, structural, and functional characterization of Alzheimer's disease: evidence for a relationship between default activity, amyloid, and memory. *J Neurosci* 25(34):7709–7717
- Damoiseaux JS, Rombouts SA, Barkhof F, Scheltens P, Stam CJ, Smith SM, Beckmann CF (2006) Consistent resting-state networks across healthy subjects. *Proc Natl Acad Sci USA* 103(37):13848–13853
- Damoiseaux J, Smith S, Witter M, Arigita E, Barkhof F, Scheltens P, Stam C, Zarei M, Rombouts S (2009) White matter tract integrity in aging and Alzheimer's disease. *Hum Brain Mapp* 30(4):1051–1059
- Desikan R, Ségonne F, Fischl B, Quinn B, Dickerson B, Blacker D, Buckner R, Dale A, Maguire R, Hyman B, Albert M, Killiany R (2006) An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage* 31(3):968–980
- Filippini N, MacIntosh BJ, Hough MG, Goodwin GM, Frisoni GB, Smith SM, Matthews PM, Beckmann CF, Mackay CE (2009) Distinct patterns of brain activity in young carriers of the APOE-epsilon4 allele. *Proc Natl Acad Sci USA* 106(17):7209–7214
- Good CD, Johnsrude IS, Ashburner J, Henson RN, Friston KJ, Frackowiak RS (2001) A voxel-based morphometric study of ageing in 465 normal adult human brains. *Neuroimage* 14(1 Pt 1):21–36
- Greicius MD, Krasnow B, Reiss AL, Menon V (2003) Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. *Proc Natl Acad Sci USA* 100(1):253–258
- Greicius MD, Srivastava G, Reiss AL, Menon V (2004) Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI. *Proc Natl Acad Sci USA* 101(13):4637–4642
- Greicius M, Supekar K, Menon V, Dougherty R (2009) Resting-state functional connectivity reflects structural connectivity in the default mode network. *Cereb Cortex* 19(1):72–78. Epub 2008 Apr 9
- Hagmann P, Cammoun L, Gigandet X, Meuli R, Honey C, Wedeen V, Sporns O (2008) Mapping the structural core of human cerebral cortex. *PLoS Biol* 6(7):e159
- He Y, Chen ZJ, Evans AC (2007) Small-World anatomical networks in the human brain revealed by cortical thickness from MRI. *Cereb Cortex* 17(10):2407–2419. Epub 2007 Jan 4
- Honey C, Sporns O, Cammoun L, Gigandet X, Thiran J, Meuli R, Hagmann P (2009) Predicting human resting-state functional connectivity from structural connectivity. *Proc Natl Acad Sci USA* 106(6):2035–2040
- Johnston J, Vaishnavi S, Smyth M, Zhang D, He B, Zempel J, Shimony J, Snyder A, Raichle M (2008) Loss of resting interhemispheric functional connectivity after complete section of the corpus callosum. *J Neurosci* 28(25):6453–6458
- Koch M, Norris D, Hund-Georgiadis M (2002) An investigation of functional and anatomical connectivity using magnetic resonance imaging. *Neuroimage* 16(1):241–250
- Le Bihan D (2003) Looking into the functional architecture of the brain with diffusion MRI. *Nat Rev Neurosci* 4(6):469–480
- Lowe M, Beall E, Sakaie K, Koenig K, Stone L, Marrie R, Phillips M (2008) Resting state sensorimotor functional connectivity in multiple sclerosis inversely correlates with transcallosal motor pathway transverse diffusivity. *Hum Brain Mapp* 29(7):818–827
- Mechelli A, Friston K, Frackowiak R, Price C (2005) Structural covariance in the human cortex. *J Neurosci* 25(36):8303–8310
- Morcom A, Fletcher P (2007) Does the brain have a baseline? Why we should be resisting a rest. *Neuroimage* 37(4):1073–1082
- Moseley M, Cohen Y, Kucharczyk J, Mintorovitch J, Asgari H, Wendland M, Tsuruda J, Norman D (1990) Diffusion-weighted MR imaging of anisotropic water diffusion in cat central nervous system. *Radiology* 176(2):439–445
- Murphy K, Birn R, Handwerker D, Jones T, Bandettini P (2009) The impact of global signal regression on resting state correlations: are anti-correlated networks introduced? *Neuroimage* 44(3):893–905
- Quigley M, Cordes D, Turski P, Moritz C, Haughton V, Seth R, Meyerand M (2003) Role of the corpus callosum in functional connectivity. *AJNR Am J Neuroradiol* 24(2):208–212
- Raichle M, Snyder A (2007) A default mode of brain function: a brief history of an evolving idea. *Neuroimage* 37(4):1083–1090 (discussion 1097–1099)
- Raichle M, MacLeod A, Snyder A, Powers W, Gusnard D, Shulman G (2001) A default mode of brain function. *Proc Natl Acad Sci USA* 98(2):676–682
- Seeley WW, Crawford RK, Zhou J, Miller BL, Greicius MD (2009) Neurodegenerative diseases target large-scale human brain networks. *Neuron* 62(1):42–52
- Shehzad Z, Kelly AM, Reiss PT, Gee DG, Gotimer K, Uddin LQ, Lee SH, Margulies DS, Roy AK, Biswal BB, Petkova E, Castellanos FX, Milham MP (2009) The resting brain: unconstrained yet reliable. *Cereb Cortex*. Feb 16 [Epub ahead of print]
- Skudlarski P, Jagannathan K, Calhoun V, Hampson M, Skudlarska B, Pearlson G (2008) Measuring brain connectivity: diffusion tensor imaging validates resting state temporal correlations. *Neuroimage* 43(3):554–561
- Teipel S, Pogarell O, Meindl T, Dietrich O, Sydykova D, Hunklinger U, Georgii B, Mulert C, Reiser M, Möller H, Hampel H (2009) Regional networks underlying interhemispheric connectivity: an EEG and DTI study in healthy ageing and amnesic mild cognitive impairment. *Hum Brain Mapp* 30(7):2098–2119
- Uddin L, Mooshagian E, Zaidel E, Scheres A, Margulies D, Kelly A, Shehzad Z, Adelstein J, Castellanos F, Biswal B, Milham M



- (2008) Residual functional connectivity in the split-brain revealed with resting-state functional MRI. *Neuroreport* 19(7):703–709
- van den Heuvel M, Mandl R, Hulshoff Pol H (2008a) Normalized cut group clustering of resting-state fMRI data. *PLoS ONE* 3(4):e2001
- van den Heuvel M, Mandl R, Luigjes J, Hulshoff Pol H (2008b) Microstructural organization of the cingulum tract and the level of default mode functional connectivity. *J Neurosci* 28(43):10844–10851
- Zhang Y, Schuff N, Jahng G, Bayne W, Mori S, Schad L, Mueller S, Du A, Kramer J, Yaffe K, Chui H, Jagust W, Miller B, Weiner M (2007) Diffusion tensor imaging of cingulum fibers in mild cognitive impairment and Alzheimer disease. *Neurology* 68(1):13–19