Applications of Resting-State Functional MR Imaging to Epilepsy

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KEYWORDS

- fMR imaging • Memory • Language • Functional connectivity • Medial temporal lobe

KEY POINTS

- Surgical resection of the anterior temporal lobe in epilepsy can result in impairments in language and memory; functional MR imaging (fMR imaging) biomarkers of risk would be valuable.
- Resting-state fMR imaging may be superior to task-related activation as an indicator of functional capacity.
- Resting-state functional connectivity between hippocampus and posterior cingulate cortex is predictive of memory change following temporal-lobe resection.
- Less work has been done to relating resting-state functional connectivity to language ability in people with temporal-lobe epilepsy, although some reports show promise.

WHAT CAN FUNCTIONAL MR IMAGING ADD TO EPILEPSY SURGICAL EVALUATIONS?

Most surgeries in adults with epilepsy involve patients with medial temporal-lobe epilepsy (mTLE) who experience recurrent seizures arising from one medial temporal lobe (MTL), including the hippocampus and surrounding entorhinal and parahippocampal cortices. In this situation, the concern is whether removal of anterior and medial temporal-lobe structures for seizure control will result in significant morbidity in the form of postsurgical cognitive decline. With respect to language, functional decline can result from excision of the anterior temporal neocortex of the dominant (typically left) hemisphere.[1–3] For memory, the functional adequacy of the epileptogenic MTL is critical, as better preoperative capacity is associated with greater decline,[4,5] typically with verbal memory associated with the left MTL and visuospatial memory with the right.[6–8] Functional MR imaging (fMR imaging) provides the means to assess adequacy of the epileptogenic tissue and risk of cognitive decline postoperatively, as well as characterize potential reorganization or compensation of neural networks that support language and memory.[9]

Clinical fMR imaging research has been directed largely at questions of task-related patterns of activation, focusing on specific regions of interest. The most robust findings concern reduced MTL activation during encoding in patients with mTLE[10–14] compared with healthy controls. Additionally, the strength (magnitude, spatial extent) of activation in the left temporal lobe predicts the degree of decline in verbal episodic memory and naming after left temporal lobectomy.[15–17] Recently, a panel of the American Academy of

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Neurology evaluated the efficacy of fMR imaging in determining lateralization and predicting postsurgical memory and language outcome in patients with epilepsy, particularly focusing on comparison with the Wada procedure, which involves drug-induced inactivation of one hemisphere for assessing capacity of the contralateral hemisphere.[18] They reported evidence of material-specific asymmetry during verbal and nonverbal memory tasks (leftward and rightward, respectively), with fMR imaging as the superior predictor of verbal memory change postoperatively compared with the Wada procedure. In terms of language mapping, they argued that fMR imaging is as effective in lateralizing language functions as the Wada procedure, although data concerning language outcome were limited and relevant studies underpowered. The conclusion was that fMR imaging of language and verbal memory lateralization can be used as an alternative to the Wada procedure for predicting outcome in mTLE, although they cautioned that fMR imaging is not established as an alternative to the Wada procedure in terms of predicting global amnesia that can arise when functioning of the contralateral MTL is also impaired.

Although task-activation paradigms have shown considerable success in lateralizing language and predicting postoperative memory decline, there are important limitations. Relatively long scans with multiple runs are typically required for reliable data, and the capacity for full task engagement in patient populations is sometimes suspect. One must carefully consider task design and the sensitivity and specificity of various metrics of activation; for example, whether magnitude of activation in the epileptogenic MTL or asymmetry between hemispheres is a better indicator of capacity. Indeed, one study found that activation in a language task was superior to that from a memory task in predicting verbal memory decline following left anterior temporal lobectomy,[19] which may reflect relatively poor sensitivity or specificity to memory outcomes of the paradigms, the metrics, or both. Data analysis methods are also critical, including the selection method for regions of interest and how to determine appropriate thresholds. At this point, there is no consensus as to the best combination of methodologic features for clinical decisions, or the extent to which these variables affect the accuracy of predictions. Of importance, individual patients may use alternate strategies or activate different networks during a task, which can undermine a region of interest approach, and there is evidence that greater signal in the hippocampus does not correlate with better function.[20] Considerable effort has been aimed at identifying ideal task-activation paradigms for clinical use,[19,21,22] but there is increasing interest in exploring whether resting-state networks may provide greater insight into the functional capacity of neural systems, rather than what is being activated by a particular task or situation, under the assumption that capacity is what is most important in the clinical context.

RESTING-STATE FUNCTIONAL MR IMAGING AND MEMORY IN MEDIAL TEMPORAL-LOBE EPILEPSY

Resting-state fMR imaging (rsfMR imaging) scans can be used to derive networks characterized by intrinsic functional connectivity among brain regions. Such resting connectivity measures could potentially be superior to task-based measures of activation or connectivity, as they eliminate variance or “noise” associated with atypical strategies or compensatory networks in patients in whom some degree of functional reorganization may have already taken place.[23] Examination of the Default Mode Network (DMN) may be particularly well-suited to address questions of functional adequacy of the MTL because the hippocampus and parahippocampal gyrus are constituent nodes, and the overall DMN shows considerable overlap with the constellation of brain regions commonly engaged during episodic recollection.[24,25] Studies have documented abnormal connectivity between the MTL and other DMN regions in patients with mTLE,[26–29] but only a few have examined the consequence of that disrupted connectivity to functional integrity as indexed by memory performance.

Our first study[30] focused on 2 nodes of the DMN: the hippocampus and posterior cingulate cortex (PCC), the latter of which is a hub within the network and is typically activated in recognition and recall tasks.[24] Patients with left or right mTLE showed reduced connectivity to the epileptogenic hippocampus and increased connectivity to the contralateral one compared with controls. Furthermore, stronger connectivity on the epileptogenic side was associated with better presurgical memory and greater postsurgical memory decline, whereas greater connectivity on the contralateral side was protective. We collected rsfMR imaging in a subset of patients following temporal-lobe resection and found an increase in contralateral connectivity, the magnitude of which was correlated with memory preservation, and therefore is suggestive of compensatory plasticity. A subsequent study examined the relationship between current memory performance and functional connectivity throughout 20 nodes of the

DMN.[31] Consideration of the full network resulted in correlations with memory that were even stronger than the simple 2-node solution. Better memory was associated with stronger posterior and interhemispheric connectivity (ie, between MTL structures and medial and lateral parietal cortices), whereas poorer memory was associated with stronger long-range posterior-to-anterior intrahemispheric connections. Of interest, the latter finding is quite similar to the long-range connectivity we have seen in patients with left mTLE when they are recalling personal autobiographical memories that are impoverished in detail compared with memories retrieved by control participants.[32] As this alternate pattern of connectivity (**Fig. 1**) has been seen in different circumstances (resting state and directed memory retrieval), with distinct analytical techniques (multivariate correlations and structural equation modeling), and in association with different outcomes (reduced details in personal recollection and poorer performance on clinical measures of learning and recognition), it may signify a specific change in memory networks in mTLE.

Other studies, particularly a series by Voets and colleagues,[33] underscore the argument that networks beyond those considered "canonical" to memory processes in the healthy brain must be considered in patients with mTLE. They reported reduced resting-state functional connectivity

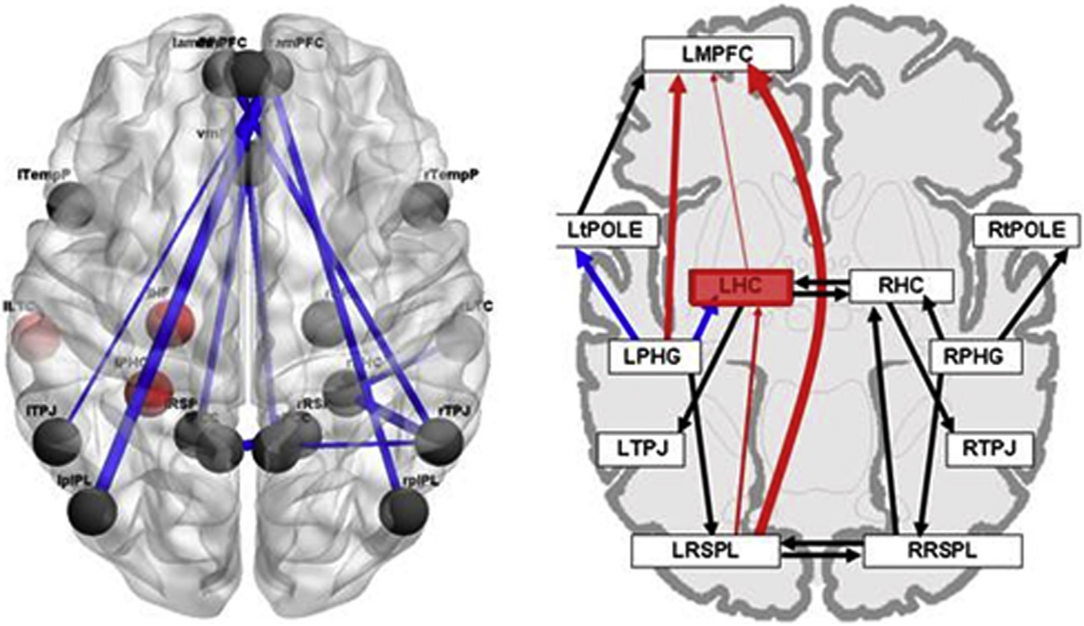

Fig. 1. Increased long-range intrahemispheric connectivity in patients with left mTLE. Figure on the left, in which blue lines indicate increased (relative to controls) long-range connectivity in rsfMR imaging from posterior medial and lateral parietal cortices to medial prefrontal regions in patients with left mTLE. Figure on the right indicates altered effective connectivity (relative to controls) during autobiographical memory retrieval, with increases in red and decreases in blue. Major differences are increased connectivity from retrosplenial to medial prefrontal cortex on the left and reduced connectivity involving left medial temporal regions. Red nodes in both figures indicate regions of reduced structural integrity of medial temporal cortex. dmPFC, dorsomedial prefrontal cortex; lamPFC, left anteromedial prefrontal cortex; LHC, left hippocampus; lHF, left hippocampal formation; lLTC, left lateral temporal cortex; LMPFC, left medial prefrontal cortex; lPCC, left posterior cingulate cortex; lPHC, left parahippocampal cortex; LPHG, left parahippocampal gyrus; lpIPL, left posterior inferior parietal lobule; lRSP, left retrosplenial cortex; LRSPL, left retrosplenial cortex; lTempP, left temporal pole; lTPJ, left temporoparietal junction; LTPJ, left temporoparietal junction; LtPOLE, left temporal pole; ramPFC, right anteromedial prefrontal cortex; RHC, right hippocampus; rHF, right hippocampal formation; rLTC, right lateral temporal cortex; rPCC, right posterior cingulate cortex; rPHC, right parahippocampal cortex; RPHG, right parahippocampal gyrus; rpIPL, right posterior inferior parietal lobule; rRSP, right retrosplenial; RRSPL, right retrosplenial cortex; rTempP, right temporal pole; rTPJ, right temporoparietal junction; RTPJ, right temporoparietal junction; RtPOLE, right temporal pole; vmPFC, ventromedial prefrontal cortex. (*From* [*Left*] McCormick C, Protzner AB, Barnett AJ, et al. Linking DMN connectivity to episodic memory capacity: what can we learn from patients with medial temporal lobe damage? Neuroimage Clin 2014;5:188–96; and [*Right*] Addis DR, Moscovitch M, McAndrews MP. Consequences of hippocampal damage across the autobiographical memory network in left temporal lobe epilepsy. Brain 2007;130:2327–42.)

(rsFC) between ipsilateral temporal neocortex and the DMN in patients with left mTLE, although unfortunately memory performance was not examined. A more recent study found that short-term memory was related to thalamic connectivity to specific regions in frontal and parietal cortices in the contralateral hemisphere, whereas long-term memory was associated with the strength of rsFC between ipsilateral thalamus and entorhinal cortex.[34] Of interest, when they assessed functional connectivity during memory encoding rather than rest, poorer subsequent memory performance was associated with reduced connectivity in a network that included bilateral MTL and extended to bilateral occipital and left orbitofrontal cortex.[28] There are too few studies comparing connectivity of networks during task activation versus rest to know whether "driving" the network could provide a better indicator of capacity. Nonetheless, these findings indicate that longstanding epilepsy may promote reorganization of networks supporting memory and indicate that consideration of both resting and task-based connectivity may be important in determining the most productive line to pursue for clinical purposes.

These are early days in the exploration of rsfMR imaging and memory in epilepsy, and of course there are many complexities to be addressed. For example, a few studies looking at connectivity and current memory capacity seeded from the hippocampus (HC) rather than PCC, as we had done. One found that higher contralateral HC-PCC connectivity was associated with better episodic memory, as we had, but also that connectivity between both hippocampi and other MTL structures (entorhinal cortex and parahippocampal gyrus) was negatively associated with memory performance.[35] Another group reported that connectivity between the ipsilateral left hippocampus and left PCC/precuneus and inferior parietal lobule (IPL) was negatively associated with memory, whereas stronger connectivity between the epileptogenic hippocampus and contralateral PCC/precuneus and IPL was associated with better memory.[36] A third pattern is represented by findings of poorer verbal memory in the context of strong ipsilateral hippocampus–to-PCC connectivity in patients with left mTLE, which aligns with the study by Holmes and colleagues[36] but contrasts with the study by McCormick and colleagues,[30] but stronger nonverbal memory in patients with right mTLE who demonstrated greater connectivity between the left hippocampus and medial prefrontal cortex.[37] Clearly, we need studies with larger cohorts and particularly those in which prediction of change after surgery is the primary outcome to discern the most robust patterns of connectivity that are reliable indicators of functional capacity and risk.

The functional imaging literature to date typically refers to the hippocampus as a homogeneous structure, and yet there is evidence of considerable variability in the distribution of histopathology along the longitudinal axis in mTLE.[38–40] Furthermore, there is evidence that greater mesial temporal sclerosis in the anterior half of the hippocampus is associated with increased probability of seizure freedom after surgery.[41] Of interest, recent studies in normative populations have shown that anterior and posterior segments of the hippocampus have distinct multisynaptic patterns of rsFC connectivity with neocortical regions, which likely has important implications for the type of memory processes they support.[42–44] These anterior and posterior networks have been characterized in several ways. One model proposes that posterior regions support the fine-grained representations that enable retrieval characterized by recollection of details, rather than coarser "gist" information that anterior networks support.[45] Another model hypothesizes that coupling between the anterior hippocampus and the dorsal attention network is important for encoding new information, whereas retrieval depends more on posterior hippocampus–DMN connectivity.[46] Our own work indicates that posterior hippocampus–to-neocortex networks are especially involved with the type of relational memory processes that are particularly impaired in patients with mTLE.[47,48] Clearly, this is an important avenue for future investigations in individuals with mTLE, marrying rsfMR imaging to well-designed cognitive assays of clinically meaningful memory processes.

A key question regarding the added value of these functional connectivity measures in the clinical context is whether they complement or exceed structural integrity or task-evoked activation as indicators of memory capacity. In their study assessing thalamo-cortical connectivity and memory, Voets and colleagues[34] noted that hippocampal volume added unique information to thalamic-frontal rsFC in explaining short-term memory performance but volume did not add to the relationship between long-term memory and thalamic-medial temporal rsFC. We have found that rsFC is a stronger predictor of performance on clinically relevant memory tasks than is structural damage to the MTL or other DMN nodes.[30,31] These findings align with concepts articulated in the study of the Human Brain Connectome, that structure influences but does not fully determine the brain's dynamic and flexible functional repertoire.[49,50] Indeed, we found that the correlation between hippocampal volume and memory was in fact mediated by functional activation in the hippocampus during encoding,[10] indicating that anatomic constraints may be less important than how readily the affected tissue can be engaged.

RESTING-STATE FUNCTIONAL CONNECTIVITY AND LANGUAGE IN MEDIAL TEMPORAL-LOBE EPILEPSY

rsfMR imaging is also emerging as a potentially valuable tool for mapping the language network, a network composed of the inferior frontal gyrus, superior temporal gyrus, supramarginal gyrus, IPL, and pre–motor cortex. Although most fMR imaging research on this network has been done using task-based fMR imaging,[51] reliable network characterization has also been shown using rsFC.[52,53] Here, we review the literature on rsfMR imaging mapping of language network connectivity, discussing its reliability and stability in temporal-lobe epilepsy and healthy individuals. We also compare presurgical rsFC network characterization with traditional methods of presurgical language mapping, such as task-based language fMR imaging, the Wada procedure, and electrical stimulation mapping (ESM), highlighting the potential advantages of each. Finally, we review research examining the ability of rsFC to predict postsurgical language change.

As with memory, there are compelling reasons to develop a strong clinical grounding for rsFC in language processes. Any patient may be incapable of performing language tasks adequately or in the manner we designate, and thus our task-based patterns of activation may include regions that are engaged for the fMR imaging task but not truly indicative of language capacity. Language networks can be characterized from rsfMR imaging data using univariate, seed-based approaches[53] or multivariate approaches such as independent component analysis.[52] Using a very large database, Tomasi and Volkow[53] examined more than 900 healthy people collected from 22 research sites around the world and used a standard seed-to-voxel approach with 2 regions of interest (the Broca and Wernicke areas) to interrogate language network connectivity. Across each research site, both seeds demonstrated robust connectivity to language regions, including the inferior frontal gyrus (IFG; composed of pars orbitalis, triangularis, and opercularis), middle frontal gyrus, superior frontal cortex, inferior temporal cortex, superior temporal gyrus, inferior parietal cortex, caudate, putamen, and cerebellum, with the Broca area showing stronger connectivity to anterior language regions, and the Wernicke area communicating more with posterior regions. Although the investigators found more bilateral connectivity than is typically captured by task-activation paradigms, they found leftward lateralization of connectivity, which supports lateralization of language to the left hemisphere, as is expected in the general population. These patterns were found to be highly reproducible within subjects across time intervals ranging from 45 minutes to 16 months,[54] providing evidence that rsFC reflects stable network measurements.

Although epilepsy specialists have noted the growing utility of rsfMR imaging in clinical decision making,[55] there are limited instances of this technique being applied in the presurgical mapping context. In one study involving patients with mTLE or tumor, language networks were extracted from rsfMR imaging scans using a machine-learning algorithm that was trained to classify voxels as being a part of canonical resting networks.[56] Before surgery, all patients also had ESM to identify eloquent cortex, and the investigators found strong agreement between ESM and rsFC language network classification. Because ESM is viewed as a gold standard for language mapping, this provides strong evidence that rsfMR imaging can identify eloquent cortex. In a comparison between language task–based fMR imaging and rsfMR imaging, greater leftward lateralization determined by task activation was associated with stronger resting-state connectivity between left IFG and other neocortical regions in the left hemisphere in controls and patients with mTLE.[57] In a subsequent study, this group showed that task-based patterns of activity and connectivity seem to be more left-lateralizing and selective, whereas resting language connectivity appears to reflect a broader, more bilateral set of “prepotent” language regions.[58] This suggests that task-based fMR imaging may be better suited for determining the language dominant hemisphere. However, Waites and colleagues[59] found that although task activation yielded similar language maps between patients and controls, resting-state connectivity produced striking differences between the 2 groups, with patients showing markedly less connectivity from seeded language regions at rest than controls. The investigators suggested that resting state was a more sensitive measure of difference in language networks between the 2 groups than task activation. Unfortunately, less has been done to compare resting-state connectivity with the Wada inactivation procedure in terms of predicting lateralization or functional capacity, although a recent study found that the 2 methods yielded highly concordant results of language lateralization.[60]

Although these findings are promising, if rsfMR imaging is to replace invasive procedures in surgical decision making, more work is needed to confirm that this measure is informative. Such work will need to compare rsfMR imaging with the current best practices of language activation tasks in a large sample, as well as investigate the ability of rsFC to predict postoperative language change. The few studies that have attempted to relate rsFC to presurgical and postsurgical language ability have used varying techniques with mixed success. For example, in one study, laterality indices produced from rsfMR imaging maps seeded from the IFG failed to predict preoperative language fluency in patients with left and right mTLE.[58] In another study, rsFC between language regions in the left hemisphere (posterior superior temporal gyrus, middle temporal gyrus, and pars triangularis of the IFG) was strongly correlated with verbal IQ in those with left mTLE.[61] Osipowicz and colleagues[62] used a multiscan approach to examine the ability of task-based fMR imaging, rsfMR imaging, and diffusion tensor imaging (DTI) to predict postoperative verbal fluency by examining the deviation of structure and function in patients from healthy controls at preoperative and postoperative time points. They found that a model including all 3 measures of postoperative deviation accounted for 52% of the variance in fluency outcome, with DTI explaining 32% of the variance, rsFC explaining 15%, and fMR imaging task-evoked activation explaining only 4%. No single modality significantly predicted outcome, nor did models using presurgical deviation from healthy controls, rendering this method ineffectual in the context of preoperative planning.

We previously reported that task-related connectivity between the left inferior frontal and left middle temporal gyri was a better indicator of current performance on clinical tests of naming and verbal fluency than magnitude of lateralized activation in individuals with mTLE.[21] For the present article, we probed a subset of these data (n = 10), which also included a resting-state scan, and here report that the correlation with naming (Boston Naming Test [BNT]) was stronger for task-based functional connectivity between those regions ($r = 0.50$), weaker for rsFC between those regions ($r = 0.25$), and weakest for the task-activation laterality index ($r = 0.16$). These preliminary findings appear to call into question the potential utility of rsFC to preoperative planning. However, we also found that when rsFC within a broader and more bilateral language network in individuals with left mTLE was compared with a healthy control template, greater similarity of patient connectivity to healthy control connectivity predicted better BNT performance after surgery ($r = 0.74$, **Fig. 2**). Thus, more "normal" connectivity of resting-state language networks was associated with better language outcome. Furthermore, patients with greater degree (here, a resting-state graph theory measure of functional integration) in to-be-resected nodes in the anterior temporal lobes showed the greatest decline in naming after surgery ($r = -0.64$), indicating that greater integration of the anterior temporal lobe with the rest of the language network predicts worse language outcome after its removal. Note these results are from previously unpublished data (Audrain and colleagues, 2017) and we are currently analyzing a larger data set to assess how robust these preliminary findings may be.

Further success in using rsfMR imaging to predict postoperative change has been found using graph theory metrics.[63] This study selected 7 regions involved in expressive language to examine their relationship to neuropsychological outcome following anterior temporal-lobe resection. They found that integration of the left inferior frontal cortex (ie, the path length to all other brain regions) was the most significant predictor of outcome, with higher integration (shorter path length) predicting better verbal outcome in the left mTLE group. Interestingly, they also reported a somewhat complex relationship between graph theory properties and verbal episodic memory, in which increased integration and reduced centrality of the left inferior frontal cortex was associated with better verbal memory outcome for patients with left mTLE. Surprisingly, the graph theory measures of the hippocampus were not predictive of postsurgical memory change in either the left mTLE or right mTLE group. This finding is somewhat at odds with our study using simple correlation of DMN nodes to predict postsurgical memory change[30] and speaks to the impact that analysis choices can have on prediction. These findings indicate that in addition to the many ways one can characterize language networks, there are also many ways to relate resting-state measures to clinically meaningful cognitive performance. There is substantial work needed to determine the best methods for characterizing functionally relevant patterns of connectivity in a clinically useful way.

RESTING-STATE FUNCTIONAL MR IMAGING AND OTHER CLINICAL QUESTIONS IN EPILEPSY

A substantial development in the past decade of clinical epilepsy is that even "focal" epilepsies are considered as "network" disorders, and presurgical investigations are aimed at characterizing

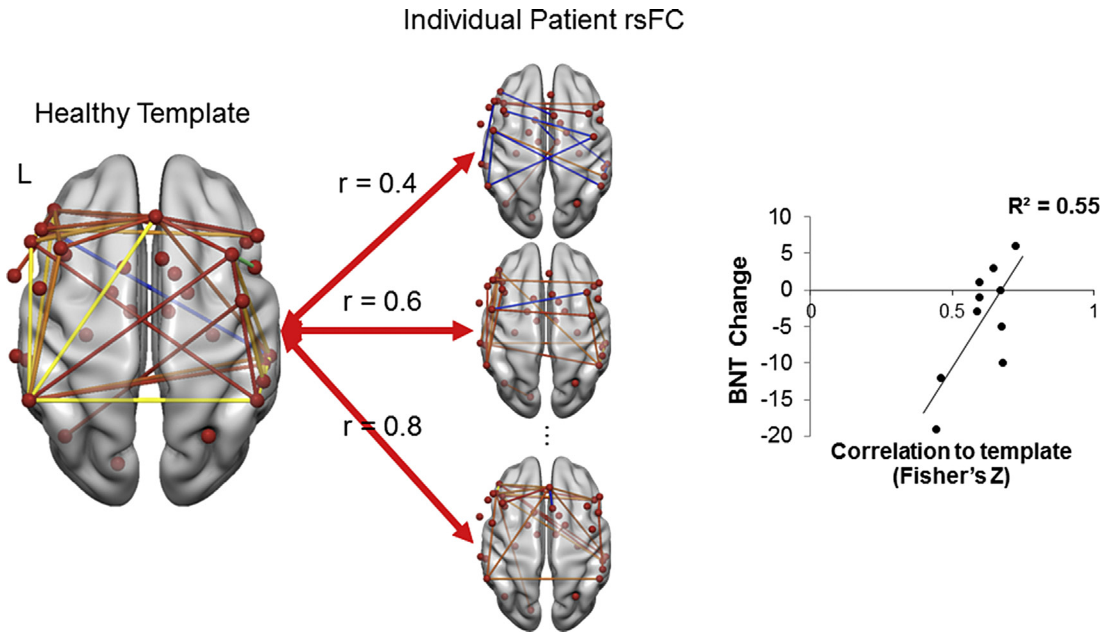

Fig. 2. Correlation with rsFC "template" for language in patients with mTLE. Each patient's language network rsFC was correlated with a healthy control template (created by taking the mean connectivity among language nodes in 19 healthy age-matched controls) to measure network similarity. The correlation coefficient was transformed into a *z*-score using a Fisher transformation and used to predict BNT performance, shown in the scatter plot on the right, which demonstrates that patients who had networks more similar to the template presurgically, had better language outcome. The brain maps are presented in neurologic convention with warmer-colored connectivity bars representing stronger connections between regions. Note: The brain maps displayed are for illustrative purposes only and are thresholded to demonstrate differences/similarities. The calculation of the correlation coefficients in this analysis included every pairwise connection among 33 bilateral brain regions involved in language.

that epileptic network to improve surgical outcomes.[64] Individuals with mTLE show a consistent pattern of disconnection of the MTL from the rest of the DMN in resting-state scans.[29,30,65,66] Simultaneous electroencephalogram (EEG)-fMR imaging data collection has allowed us to advance considerably on understanding the relationship between transient abnormalities associated with epileptiform discharges and intrinsic networks[67–69] and identifying patterns that may be predictive of postoperative seizure freedom.[70] Recently, there have been some important efforts to use resting-state connectivity, particularly coupled with measures of spatial clustering, to discern abnormalities associated with epileptic foci on an individual patient basis. One such study reported success in locating abnormal changes in connectivity that was closely related to EEG foci in 5 of 6 patients.[71] Although much work needs to be done, these early efforts are key steps in delivering on the promise of functional connectivity as a useful tool in the clinic, not dependent on capturing ictal events during a scanning session. To the extent that stable interictal defects that are clear biomarkers of epilepsy-associated damage can be identified, the need for more invasive intracranial recording in patients in whom scalp EEG is insufficient to determine the likelihood of surgical success will be reduced.

POSSIBILITIES AND LIMITATIONS

A fundamental tenet of this enterprise is that resting-state networks provide a valid reflection of brain activity that underlies task performance, otherwise the objective of linking rsFC patterns to cognitive outcomes is unlikely to succeed. In addition to the specific studies reviewed previously, there are important examples in the literature of strong correspondence in the topology of networks active during particular cognitive states or tasks, including basic sensory and motor as well as more complex cognitive operations, including working memory and emotional processing, and intrinsic connectivity at rest.[72–74] Using large-scale connectivity across many brain regions and multiple cognitive tasks, Cole and colleagues[72] found a high degree of overlap between rest and task-evoked connectivity even at the local pairwise connectivity level, suggesting that the network supporting a given cognitive operation is shaped primarily by intrinsic architecture together with a limited set of task-evoked changes. Some strong cautions to this view have been offered, noting a modest amount of shared variance between rest and tasks that engage similar networks, arguments that scans during instruction to "do nothing in particular" merely reflect a poorly constrained and highly dynamic set of cognitive operations, and that rest may offer little insight into cognitive networks that are based on versatile process-specific alliances that form within and between intrinsic networks during the execution of particular cognitive operations.[75–78] Nonetheless, using machine-learning techniques, one group has demonstrated that it is possible to predict task-activation maps for a range of functions at an individual subject level from that person's resting-state connectivity[79] and, highly relevant to the concerns of this article, that algorithms trained on control resting connectivity can be used to predict activations associated with verbal fluency in patients being considered for neurosurgery.[80] These studies demonstrated remarkably good predictive accuracy, with poorer performance of the model associated with lower quality of the resting-state scans rather than individual differences in disease state, behavior, age, or other characteristics. Exporting this strategy and training data set on a broad scale, if feasible, would afford an excellent opportunity to discern the accuracy of predicting task-related topology in a variety of clinical populations.

There are operational concerns that need to be addressed to ensure this is a practical enterprise in clinical settings. First, there are many analytical approaches that can be taken, and it is important to decide which is most appropriate or best suited to specific questions. Approaches that use seed regions that are based on existing literature (eg, from the well-characterized DMN) may capture those networks in the healthy brain but become difficult to interpret if there has been substantial reorganization in the target clinical population. For example, the selection of a damaged hippocampus as seed may not lead to identifying the effective memory network in mTLE. Independent component analysis and related approaches are data-driven means to extract networks, but can sometimes split networks into a variable number of components across different subjects and still require one to select components of interest for interpretation. A semiautomated approach has been proposed for identification of these networks based on training templates,[52] and machine-learning techniques can enable identification of atypical networks given there is sufficient homogeneity within the patient population of interest. Finally, issues of thresholding for single-subject analyses are equally important here as in activation paradigms; stringent yet arbitrary cutoffs may eliminate potentially meaningful connections, but without thresholds the signals can be noisy and uninterpretable.

In addition, there are concerns about reliability of resting-state connectivity metrics, particularly at the individual subject level. Test-retest reliability has been of concern in activation paradigms, particularly for complex tasks that can induce different strategies on subsequent scanning sessions.[81,82] There is some evidence that rsFC is more reliable than task-related activation magnitude or spatial extent,[83,84] and even sufficiently robust to identify individual subjects akin to a "fingerprint,"[85] but it is important to note that variables such as participant age, scan length, and other acquisition parameters can impact rsFC reliability.[86,87] Conversely, resting-state connectivity may be even more sensitive to nuisance variables, such as motion,[88,89] and to the extent that motion is confounded with the variable of interest (such as degree of cognitive impairment), it presents a genuine challenge for interpretation. In addition, investigations into the extent to which the pathology in mTLE and/or use of antiepileptic drugs in these conditions may influence (either globally or locally) the neurovascular coupling that is crucial for observing changes in local cerebral blood flow and blood oxygenation or other aspects of fMR imaging signals are just beginning.[90–93]

A final crucial step in advancing the clinical utility of rsfMR imaging, particularly for the individual patient with epilepsy considering surgery, is establishing sensitivity, specificity, and positive predictive value for these metrics. What is the degree of connectivity within the epileptogenic region that may signify a significant risk of cognitive morbidity should part of that network be excised? Our experience with postoperative memory change suggests that, even in the case of "lateralized" or material-specific memory functions, consideration of connectivity in the contralateral memory networks may be as important as characterizing adequacy of the to-be-resected MTL in devising clinical metrics. Fortunately, the barrier to conducting resting-state studies is considerably lower than with activation tasks in terms of amount of data required, the complexity of task influences, and the possibility of pooling data from multiple centers, making it more likely that the field will make rapid progress on some of these questions.

SUMMARY

Overall, there is very good evidence that rsfMR imaging is developing into a useful clinical tool for mapping language networks and characterizing functional integrity of memory networks in clinical populations and for providing predictions after surgical or other interventions. At present, however, much work still needs to be done in terms of comparisons to relevant “gold standards” in clinical practice, determining ideal analytical strategies and decision algorithms, and relating network properties to the behaviors we are most interested in measuring and predicting.

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