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Clinical Applications and Future Directions of Functional MRI

Daniel Orringer, MD, David R. Vago, PhD, and Alexandra J. Golby, MD

First described for use in mapping the human visual cortex in 1991, functional MRI (fMRI) is based on blood-oxygen level dependent (BOLD) changes in cortical regions that occur during specific tasks (1). Typically, an overabundance of oxygenated (arterial) blood is supplied during activation of brain areas. Consequently, the venous outflow from the activated areas contains a higher concentration of oxy-hemoglobin, which changes the paramagnetic properties of the tissue which can be detected during a T2-star acquisition. fMRI data can be acquired in response to specific tasks or in the resting state. fMRI has been widely applied to studying physiologic and pathophysiologic diseases of the brain. This review will discuss the most common current clinical applications of fMRI as well as emerging directions.

The role of fMRI in brain tumor surgery

Functional MRI is a useful tool in the surgical care of brain tumor patients. By highlighting the relationship of the tumor to eloquent functional areas, functional MRI may be used as a means of devising a surgical plan (2). A case series of 17 patients with lesions adjacent to the primary motor cortex provides the strongest evidence of the usefulness of fMRI in predicting the relationship of lesions to motor areas (3). Similarly, multiple case series have demonstrated that fMRI can also be used to estimate the location of cortical areas involved in speech and language in relationship to brain tumors (4–7). Though there is less published evidence, fMRI can also be used to map cognitive functions such as calculation in brain tumor patients (8). Defining the relationship of a lesion to an eloquent region may help determine whether intraoperative mapping via direct cortical stimulation is needed for safe resection. (Figure 1)

Several case series, including a recent description of 87 glioma patients, suggests that fMRI is more accurate in predicting the location of motor areas compared to language areas (9, 10). Some investigators have found that fMRI activation was not closely correlated with key speech areas documented during surgery (10). Still other investigators have appreciated high concordance between fMRI and intraoperative mapping data (11). The discrepancy is most likely related to the difficulty of utilizing an fMRI task protocol that corresponds to those used during intraoperative mapping (4, 10). In addition, fMRI is an observational study which demonstrates all areas activated during the performance of a task, and thus does not demonstrate necessity for task performance; in contrast deactivation or temporary lesion tests such as electrocortical mapping or the intracarotid amytal (Wada) test which are able to demonstrate necessity for task performance.

Nevertheless, fMRI has been embraced as an important component of multimodal navigational data used during brain tumor surgery. In a case series of 167 patients utilizing multimodal navigation, functional MRI was felt to be responsible for the low rate of permanent neurologic deficits following surgery (12). Several smaller case series also have confirmed the importance of fMRI-based navigation in optimizing surgical results in glioma patients (13, 14). Some have suggested that intraoperative acquisition of fMRI (15, 16) may also be useful and has the advantage of using real-time anatomical data (rather than preoperative studies) for predicting the location of eloquent areas.

A wide variety of imaging and electrophysiologic techniques have been designed to assist surgeons in achieving maximal safe brain tumor resections. fMRI is increasingly being combined with other techniques, such as diffusion tensor imaging (17) (discussed elsewhere in this issue), direct cortical and subcortical white matter stimulation (18), to deliver optimal surgical results. In our clinical practice, we have found the combination of fMRI, DTI and direct cortical stimulation to be most useful in planning and executing the resection of primary brain tumors in eloquent regions.

It is also important to note the limitations of fMRI for applications in brain tumor patients. The BOLD signal, which provides localization of functional cortex in brain tumor patients, is affected by tissue-level changes induced by the presence of the tumor. Specifically, patient age, previous surgery, edema, mass effect, tumor neovasculature and tumor blood volume have been shown to affect BOLD signal (19–22). Some reports have suggested that BOLD signal is decreased in magnitude or lost adjacent to gliomas due to loss of autoregulation in the neovasculature (23–25). In addition, practical concerns related to lengthy, sometime complex imaging studies on patients with neurologic deficits have also been raised (26).

(The following text could be presented in a table format)

Summary: Uses and Limitations of fMRI in Brain Tumor Surgery

Uses:

- Defining the relationship of lesions to eloquent areas prior to surgery
- Determining the need for intraoperative electrocortical mapping
- Defining a surgical plan for resection
- Determining Language lateralization

Limitations:

- fMRI is better at demonstrating motor areas than language areas
- BOLD signal can be affected by biological aspects of brain tumors
- fMRI may be difficult to acquire in patients with profound neurologic deficits
- fMRI does not demonstrate essential cortex

Strengths:

- Available pre-operatively (thus allows more informed decision making by surgeon and patient)
- Non-invasive
- Can be overlaid with anatomy
- Visualize in 3D
- Repeatable

The role of fMRI in the care and treatment of epilepsy

The role of fMRI in the management of epilepsy has become increasingly well defined in the last decade. In particular, fMRI has had a major impact on the planning and execution of epilepsy surgery. Given the normal variation in the anatomic position of cortical functions as well as the cortical reorganization common in patients with epilepsy, electrophysiologic or image-based methods for mapping of eloquent cortex is required before planning surgical

intervention. As in brain tumor surgery, fMRI has become a central component of mapping of eloquent regions responsible for motor, somatosensory, language, and memory functions needed for planning surgical interventions for epilepsy. fMRI-based motor mapping is particularly useful when lesional borders are intimately related to important motor or somatosensory areas. Given the variability in fMRI based motor mapping, however, direct electrocortical stimulation should be used to make the ultimate decision regarding resectability of a specific region (10).

Defining language dominance and predicting verbal outcome after temporal lobectomy has historically been accomplished through intracarotid amytal testing. A large number of studies, reviewed in detail elsewhere (27), have formed the basis for a shift in the mainstream of clinical practice towards reliance primarily on fMRI for language lateralization. In most studies, concordance between fMRI and WADA testing for predicting the language laterality ranges between 80–90% (28). Differences among estimates of the reliability of fMRI for language lateralization are explained in part by the variability in the specific fMRI task paradigms and interpretation of fMRI BOLD threshold used. Numerous approaches related to selection of regions of interest, baseline task, and thresholding have been examined for their effect on accurate prediction of language lateralization. For example, threshold-independent approach for assigning language laterality that improves agreement with the clinical gold standard (29). Assessment of the validity of fMRI is hampered by the fact that even in patients undergoing epilepsy surgery, the vast majority have left lateralized language making atypical language dominance a relatively rare finding and thereby complicating assessment of the predictive value of the test.

While predicting laterality of speech dominance is important, the overall goal of WADA testing is to predict language outcome. Several studies, using divergent methodology and analyses have recently compared the ability of fMRI and WADA testing in predicting language outcomes. In a series of 24 consecutive patients undergoing left ATL, fMRI was found to have a stronger correlation with naming outcome than WADA testing. In this study, the fMRI had a positive predictive value of 81% for predicting significant naming decline in comparison to WADA, which had a positive predictive value of 67% (30). Using a multivariate analysis, Binder et al., evaluated the predictive value of fMRI for language decline after ATL. In this, age at epilepsy onset, preoperative language and fMRI laterality index, a measure of the predominant side in which language functions are localized, were strongly correlated with language outcome. Interestingly, 27% of the variance in outcome was predicted by clinical variables, while 23% of the variance was predicted by fMRI laterality index. WADA testing did not account for a significant variance in predictive power (31). Taken together, the work of these two investigations provides compelling evidence of the utility of fMRI for predicting language outcome after ATL. The intracarotid amytal test is still recommended for patients in whom agitation, cognitive or perceptual impairment preclude completion of tasks in the MRI environment or if fMRI is inconclusive for language lateralization (32).

Beyond predicting language dominance, fMRI may also be useful in defining the anatomic borders of key language centers in the vicinity of a planned resection. Language mapping is particularly important in the setting of planned surgery since the language network in patients with epilepsy, particularly left temporal lobe epilepsy and cortical dysplasia, is frequently reorganized (33–35). If a resection is planned near language cortex, direct electrical stimulation of the cortex is typically performed to provide detailed mapping either prior to or during surgery (36). At our institutions, the clinical practice has been to use fMRI in planning of placement of subdural grids followed by detailed mapping of language function by direct stimulation through the grids.

Material specific memory deficits after temporal lobectomy have been described (37, 38). Behavioral paradigms for memory testing have usually used encoding tasks. Such task-based fMRI provides a diagnostic method for predicting the sequelae of temporal lobectomy. In a case series of 15 patients with unilateral temporal lobe epilepsy undergoing ATL, verbal memory decline was most severe in patients with ipsilateral memory activation, as determined by preoperative fMRI. The same pattern was observed for non-verbal memory in patients undergoing non-dominant ATL. In this study, verbal memory activation was mapped to the dominant hippocampus, and appeared to predict decline after ipsilateral ATL (39). In a related study, lateralization of hippocampal activation was found to be related to decline of visuospatial memory following ATL targeting the side with greater activation (40). In addition, several fMRI-based studies utilizing auditory semantic (41), scene encoding (42) and picture memorization tasks (43) in patients with temporal lobe epilepsy confirm the common theme that activation of mesial temporal structures contralateral to the planned resection is associated with better memory outcomes (Figure 2). At this time, there is no consensus on a single or specific group of fMRI paradigms that can be reliably used to predict memory outcomes after ATL. A prospective evaluation of various paradigms might yield a standard battery that could be used widely to predict memory outcomes in ATL patients.

In addition to mapping normal language and memory-related cortical activity in response to specific tasks, fMRI can also be used in conjunction with EEG to identify seizure foci. Although it is technically demanding, EEG-fMRI offers an alternative means of localizing epileptogenic lesions in patients where the EEG and imaging data are insufficient. EEG-fMRI is performed by simultaneous collection of scalp EEG data during resting-state BOLD acquisition. A seizure focus is identified in EEG-fMRI when interictal discharges (spikes and sharp waves) are temporally correlated to localized BOLD signal changes (44). Among a series of 29 patients deemed to be poor surgical candidates due to presumed multifocality or an unclear focus, EEG-fMRI revealed specific sites of recurrent interictal discharge in 8 patients, 4 of whom were reclassified as surgical candidates based on EEG-fMRI results. In the remainder of the patients in the series, unclear focus or multifocality was confirmed by EEG-fMRI (45). In another study focusing on 9 patients diagnosed with non-lesional frontal epilepsy, EEG-fMRI was capable of demonstrating focal spike-related BOLD signal-changes in 8 patients (46).

Summary: Uses for fMRI in management and treatment of Epilepsy

- Determining lateralization of language dominance and predicting risk for language function decline
- As an adjunct to direct cortical stimulation for mapping relationship of lesion to language, motor, and somatosensory areas
- Predicting memory deficits following ATL
- Simultaneous fMRI-EEG may help localize lesions where EEG and imaging data and EEG are discordant

The role of fMRI in the diagnosis and management of Alzheimer's disease

Functional MRI has been shown in many studies to be capable of demonstrating impairment of the activation of the hippocampus and parahippocampal gyrus during memory encoding tasks in patients with Alzheimer's disease (47–50). fMRI has also shed light on the network of structures involved in the memory encoding process aside from the hippocampus including the ventrolateral and other prefrontal regions, precuneus, cingulate and lingual gyri (50–54). Synthesis of current fMRI data on impairment of cognitive processes may

ultimately yield a clinical biomarker for AD. However, variations in clinical definitions of cognitive impairments, fMRI task design, imaging parameters and data interpretation have precluded definition of a single or set of imaging abnormalities that could be considered diagnostic for AD (55, 56).

The discovery of an fMRI-based biomarker present in patients at risk for Alzheimer's disease has also been an active area of research. Efforts in screening at risk individuals with mild cognitive impairment have revealed divergent results when investigating medial temporal lobe activity, with some studies showing decreased activity with the medial temporal lobe (57–60) and others showing an increase in medial temporal lobe activity (53, 61–63) in comparison to normal subjects. A decrease in the activation of the medial temporal lobe in patients with mild cognitive impairment is not unexpected given the fact that many studies have observed diminished activation of the hippocampus and associated structures in Alzheimer's patients. The increase in medial temporal lobe activity in some patients with mild cognitive impairment may be explained by the theory that hippocampal hyperactivity is thought to compensate for declining function early in Alzheimer's disease (64). The heterogeneity of observed fMRI findings in patients with early cognitive impairment creates a barrier to the identification of a consistent fMRI-based biomarker capable of screening for early Alzheimer's disease. Nonetheless, it is possible that such a marker will emerge as more is understood about the imaging correlates of early Alzheimer's disease (65).

Beyond screening, fMRI also provides a useful tool in monitoring and predicting the course of Alzheimer's disease as well as evaluating the effects of pharmacologic agents on disease activity. Resting MRI studies offer insight into the functional cognitive networks that deteriorate in Alzheimer's disease (66, 67). A cohort study of 68 patients (25 controls, 31 with mild cognitive impairment and 12 with Alzheimer's disease) suggests that disrupted connectivity of cognitive networks parallels disease progression from mild cognitive impairment to full-blown Alzheimer's disease (68). Multiple studies now support the broad dysfunction of networks in AD including mnemonic and default mode networks using a variety of task-based and resting state fMRI (reviewed in (65)). (Figure 3) Several small clinical studies have evaluated the effects of cholinesterase inhibitors on cognitive networks known to be dysfunctional in Alzheimer's disease. Saykin et al. correlated improvement in cognitive function in patients on donepezil with an increase in the activity of frontal cognitive areas on fMRI (69). Shanks et al. evaluated changes in brain activation over a 20-week period of treatment with galantamine and demonstrated an increase in brain activation in the semantic association and target detection tasks after treatment among patients with early AD (70). In addition to contributing to our understanding of the biological basis for cholinergic therapies in Alzheimer's disease, these trials demonstrate the potential for resting state or task-specific fMRI studies in the process of drug discovery for Alzheimer's disease.

Summary: Applications of fMRI to Alzheimer's Disease

- Understanding the pathophysiologic basis of memory loss in AD
- Predicting decline in cognitive function
- Evaluating alterations in brain physiology in response to pharmacologic agents

Insights into the pathophysiology of traumatic brain injury gained from fMRI

Functional MRI has also been used, primarily over the past decade, to study the alterations in cognitive processes associated with traumatic brain injury. Early fMRI studies in TBI evaluated cognitive networks by tracking the activity within working memory circuitry during an auditory-verbal recall task. This paradigm stimulates activation within frontal, parietal, cerebellar and basal ganglia areas. In two cases studies with 30 mild TBI and 33 health control subjects, TBI patients were found to have increases in bifrontal and biparietal cortical activity in comparison to healthy controls (71, 72). Interestingly, in these studies, TBI patients reported more difficulty with the tasks presented during the fMRI yet performed as well as the controls. A follow-up study of a subset of patients in these studies demonstrated that the fMRI differences between TBI patients and controls persisted from 1–12 months (73). Studies have also shown changes in declarative memory systems even in mild TBI. Stulemeijer et al. reported a series of 43 mild TBI patients matched with 20 controls in which mesial temporal activation was increased during an auditory-verbal recall task which was designed for equivalent performance behaviorally (74). This implies that like some stages of dementia, increased cognitive effort is required to achieve equivalent performance in the setting of functional disruption. Taken together, these studies provide evidence that modulation of activity in cognitive and memory networks may be impaired in TBI. Other studies have demonstrated that mild TBI patients have abnormal activation in frontal and parietal cortex that are thought to explain deficits in attention, episodic memory and executive function (73, 75, 76). It remains to be seen whether fMRI will emerge as a useful clinical tool in traumatic brain injury.

Due to military operations in Iraq and Afghanistan, traumatic brain injury in veterans is receiving increased attention with particular interest in how military injury differs from civilian head injury. Veterans suffering from TBI have been enrolled in a number of studies that have advanced our understanding of the pathophysiologic mechanisms underlying cognitive and psychological dysfunction commonly associated with TBI. Schiebel et al. evaluated 30 soldiers (15 with mild TBI, 15 controls) using a stimulus-response compatibility task-based fMRI. In comparison to the controls, mild TBI subjects demonstrated increased activation in a network involving the cingulate gyri, medial frontal cortex, and parieto-occipital regions (77). The pattern of increased activation within cognitive networks was felt to be consistent with McAllister's original work with TBI patients discussed above. Another interesting finding in this report was the negative correlation of activity in the posterior portion of the cognitive network with PTSD among study subjects. Matthews et al. also investigated psychologic sequelae of TBI in a study of 11 blast victims who developed major depressive disorder. In comparison to controls (11 blast victims who did not develop major depressive disorder), subjects who developed major depressive disorder were found to have greater activation in the bilateral amygdalae during an emotional face-matching task. The results of this study support the hypothesis that mild TBI can cause dysregulation of the brain networks involved in the fear response (78).

Functional MRI has also been used to study the abnormalities in the neurochemistry of brain activation following TBI. Several studies have investigated abnormal catecholamine metabolism in TBI patients. One study, which enrolled 26 individuals who suffered mild TBI and 31 controls, tested the hypothesis that responsiveness to dopamine was altered following TBI. Using a task to test the verbal working memory, bromocriptine, a dopamine agonist, was found to improve working memory in controls, but not in TBI patients. This difference was thought to arise from activation of cortical and subcortical areas outside of the task-specific region (79). Another study on altered catecholamine responsiveness focused on the effect of guanfacine, an α_2 receptor agonist on working memory in 13 patients with mild

TBI. Among the control group, there was no improvement in working memory with guanfacine administration. However, among TBI patients, there was an increase in working memory performance that correlated with an fMRI finding of increased activity in the right prefrontal and middle frontal gyri on fMRI. This study is of particular interest both because it suggests that guanfacine may be useful in improving memory after TBI and because it demonstrates how fMRI can be used to better understand specific neurochemical pathways involved in the cognitive sequelae of TBI and therapeutic strategies.

The role of fMRI in psychiatric disease

In recent years, the advent of functional neuroimaging, along with advances in the cognitive and affective neurosciences, has revolutionized our understanding of the functional and structural neuroanatomy of psychiatric disorders. Novel developments in structural and functional neuroimaging have provided guidance for early interventions, for finding biomarkers of risk/resilience, and for subtyping and predicting responses to treatment. Advancements in multivariate techniques and complex network analyses are contributing to our improved understanding of the brain circuitry that regulates dysfunctional mood states. Here we review findings from neuroimaging studies of depression and describe an emerging neurocircuitry model of mood disorders, focusing on critical circuits of cognition and emotion, particularly those networks involved in the regulation of evaluative, expressive and experiential aspects of emotion. The relevance of this model for neurotherapeutics is discussed.

Functional imaging has played a key role in the significant progress that has been made in delineating the neural circuitry underlying major depression and related psychopathology. In fact, several reviews have focused on final common pathways for psychopathology using major depressive disorder (MDD) as the model disorder. Consistently across the majority of neuroimaging studies, psychopathology is shown to arise due to functional disturbances in cortico-limbic-insular-pallidal-striatal-thalamic (CLIPST) circuitry, a network of brain regions implicated in the wide variety of symptoms that comprise depression, including regulation of mood and executive function, anxiety, fear, reward processing, attention, motivation, somatic function, and management of stress. Psychopathology may arise due to dysfunction in one area specifically, because of failure in the coordinated interactions within the circuitry, or with elements of the hypothalamic-pituitary-adrenal axis (80–83). Many functional neuroimaging studies have demonstrated basal abnormalities, while others demonstrate dysfunction during emotion provocation. Volumetric reductions of the hippocampus, basal ganglia, orbitofrontal cortex (OFC), and subgenual anterior cingulate cortex (sgACC) are also consistently found in MDD patients, with atrophy preceding neurologic insult or onset of neurodegenerative disease increasing the likelihood of later onset of depression. Atrophy in the left sgACC (BA25) has been the most prominently (19–48%) reported reduction (84, 85). The failure to account for these reductions using corrections for partial volume effects often lead to directional discrepancies in reporting functional abnormalities.

More persistent forms of depressive symptoms and abnormal findings in CLIPST circuitry have been found to depend upon longer illness duration, experience of multiple episodes, or repeated relapse (82, 86). Other mediators that have been shown to affect the nature of the findings in a regionally specific manner include age, medication, genetic predisposition or family history, stress reactivity, stage of illness, and behavioral factors for risk and resiliency (87, 88). In order to fully understand how the CLIPST circuitry functions to produce symptoms of psychopathology, future fMRI research must provide a clear understanding of the critical role these factors play in facilitating dysfunction and/or decreasing efficiency of sub-networks with the circuitry. Distinct neuroplastic changes in

CLIPST circuitry have been found to co-vary with enduring cognitive-behavioral schemas related to maladaptive processing of emotion and memory. Indeed, functional abnormalities (glucose metabolism or cerebral blood flow) of the prefrontal cortex (PFC) and limbic structures (e.g., amygdala and hippocampus) are among the most robust findings in depressive mood symptoms. Increases in resting amygdala metabolism is one the most consistent finding reported in individuals reporting mood disorders during both symptomatic and asymptomatic states. There is also consistently hypoactivity in dorsal and lateral portions of PFC and dorsal ACC, and hyperactivity in ventral and medial regions, including ventromedial PFC (VMPFC), orbitofrontal cortex (OFC), ventrolateral PFC (VLPFC), and anterior insula (84, 85, 89). Ventral PFC abnormalities have been found most consistently in sgACC (BA 25), supporting prominent structural abnormalities found in this region (84). Decreased sgACC metabolism and CBF has been demonstrated in both medicated and unmedicated patients with depression using fMRI (90–92). In contrast, there have also been reports of increased activity in the depressed versus remitted state, including the subgenual and pregenual ACC (93–95), a finding supported by activation in healthy subjects during experimentally induced sadness (96–98). Future work in this area will clarify discrepancies. Decreased functional connectivity has been reported between dorsal ACC and limbic structures in depressed individuals, suggesting decreased control over emotional expression (92), while hyperconnectivity between sgACC and task negative self-reflective networks has been found to correlate with depressive symptoms like rumination (99). A summary of the most consistent structural-functional MRI findings are presented in Figure 4.

Dorsal PFC circuitry is often categorized as regulating executive functions and cognitive forms of appraisal, whereas, ventral PFC circuitry is more often characterized as regulating affective, evaluative, and self-relevant processing (85, 100, 101). In alignment with these distinctions, symptoms arising from ventral circuitry lesions or atrophy may reflect dysregulated attempts to interrupt unreinforced aversive thoughts and emotions. Lesions or atrophy in dorsal lateral circuitry lead to deficits in working memory and executive function, while dorsomedial dysfunction leads to deficits in reason and emotional expression. Critically, the imaging data appear to support a dysfunctional integration of dorsal and ventral circuitry in depression due to the overwhelming evidence for dysfunction in rostral ACC (BA24a), a structure with extensive reciprocal connections between both dorsal and ventral circuitry, and the evidence that pretreatment metabolism in this area has been shown to predict treatment response (89). The research also indicates that individuals with MDD are impaired in their ability to sustain the up-regulation of positive affect by cognitive means, and this is associated with reduced dorsomedial prefrontal cortex (DMPFC)-striatal connectivity and decreased ventral striatal activity in response to positive words (102) or decreases in sustained nucleus accumbens activity while up-regulating positive affect (103).

Normalization of many of the abnormal functional findings in CLIPST circuitry and reduction of symptoms of depression has been shown after successful pharmacologic therapy (89), cognitive behavioral therapy (CBT) (104), or deep brain stimulation of the ventral striatum (105, 106) or sgACC (107).

The investigational use of functional MRI in the field of neuropsychiatry is currently flourishing as a tool for probing brain-mind function, and dysfunction in the setting of disease. Studies using fMRI are not only increasing our understanding of the pathophysiology of neuropsychiatric disorders and underlying circuitry, but are also becoming a prerequisite for developing, monitoring and screening new, targeted biological therapies and for identifying final common pathways among disease states. Although there is yet to be a standard, scientifically validated role for neuroimaging techniques in the clinical evaluation of individual patients suffering from mental illness, future studies using fMRI with advanced statistical modeling techniques will ultimately be used to diagnose

pathophysiology based subtypes of psychiatric disease, guiding early treatment approaches, and predicting treatment response. The increasing ability to monitor and modulate activity in the identified circuitry will continue to provide potential for circuitry-based diagnosis and treatment via deep brain stimulation, magnetic stimulation, or even focused ultrasound.

Conclusion

Since its discovery, fMRI has been applied to the study and treatment a wide range of neurologic disorders. Functional MRI has shown great utility identifying the anatomic location corresponding with specific motor, somatosensory, language and cognitive processes. In addition, it has expanded our understanding of the neuroanatomic and pathophysiologic changes that occur in response to brain tumors, epilepsy, movement disorders, dementia and trauma. In addition, fMRI may be helpful in defining targets for functional neurosurgery. fMRI also holds great promise in creating biomarkers that can be used for monitoring diseases of the central nervous system and for assessing the utility of existing and experimental treatments.

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Figure 1.

Three dimensional rendering, coronal slice and axial slice showing relationship of recurrent brain tumor (yellow) to motor activations for hand (blue) and foot (purple) as well as associated tracts obtained from Diffusion Tensor Imaging. Note presence of foot associated activation lateral to hand, confirmed at surgery, and suggestive of reorganization in this longstanding tumor.

Figure 2. Coronal fMRI acquired at 3T during scene encoding in a patient with left mesial temporal sclerosis and MTL epilepsy shows asymmetric activation in the hippocampal formations.

Figure 3.

Investigation of default mode network using resting state (task-free) fMRI in healthy older control subjects (OC), patients with mild cognitive impairment (MCI), and patients with mild Alzheimer's disease (AD) dementia. Functional connectivity in the default network declines with greater clinical impairment. Figure courtesy of Reisa Sperling.

Figure 4. Consistent abnormalities in CLIPST (cortico-limbic-insular-pallidal-striatal-thalamic) circuitry for major depressive disorder. Arrows indicate direction of volumetric change (reduction/increase) or metabolic change (decrease/increase). Structures without arrows indicate absence or inconsistent results. Figure courtesy of David Vago.