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Mapping Cognitive Function

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Synopsis

Cognitive functions are fundamental to being human. Although tremendous progress has been made in the science of cognition using neuroimaging, the clinical applications of neuroimaging are just beginning to be realized. A unifying theme of this chapter is the concept that a more complete understanding of cognition only comes through integration of multimodal structural and functional imaging technologies.

Introduction

Cognitive functions are fundamental to being human. Although tremendous progress has been made in the science of cognition using neuroimaging, the clinical applications of neuroimaging are just beginning to be realized. Rather than give an exhaustive review of the neuroimaging of cognition, this review focuses on selected technologies, analysis techniques, and applications that have direct or soon-to-have direct clinical impact. We discuss how cognition can be imaged using magnetic resonance imaging (MRI), functional MRI (fMRI), positron emission tomography (PET), magnetoencephalography and electroencephalography (MEG/EEG), and on MRI diffusion tensor imaging (DTI). Many of these technologies have been topics in other chapters, so we will briefly introduce a few new ones in terms of image integration across the more familiar modalities.

Technologies for Functional Imaging

Cognition is a large topic and we will focus on cognition of primary sensory areas, language, and memory. A unifying theme of this chapter is the concept that a more complete understanding of cognition only comes through integration of imaging technologies. The imaging technologies are structural [MRI, DTI, computed tomography (CT)] and functional (PET, fMRI, MEG/EEG, optical) techniques and both have important roles in imaging cognition. Further, functional techniques can be thought of as originating from two sources: neuroelectrical (EEG and MEG) and hemodynamic [PET, single photon computed tomography (SPECT), fMRI, optical]. Exploring the relationship of the structure-function relationships found with neuroimaging is an area of intense research. It requires the integration across imaging modalities, and even by integrating behavioral metrics [1].

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Each imaging technology has its own individual strengths and weaknesses, typically with some trade-off between temporal and spatial resolution. The electromagnetic imaging techniques include MEG and EEG, which may not be thought of as imaging at all, yet do have excellent temporal resolution since they measure the underlying neural currents directly, on the order of milliseconds — although with limited spatial localization. fMRI has excellent spatial resolution, on the order of millimeters, but is dependent on the hemodynamic response, which limits the temporal resolution. By combining imaging technologies, it is possible to optimize the temporal and spatial scale, to accurately localize and characterize cognition non-invasively.

Using Sensory Stimulation to Probe for Disorders of Higher Cognitive Function

Although cognitive studies often employ tasks that involve higher cognitive function, there has been a long history of using sensory stimuli that have a cognitive correlate, such as the mismatch negativity and steady state responses (for review, see [2]).

Mismatch negativity

The auditory mismatch response [3-7] is a component of the MEG/EEG response elicited by any change ('deviant') in auditory stimulation ('standard'), usually peaking at 80–200 ms from change onset [8-10]. The mismatch response is elicited, for example, when a sound changes in frequency, duration, or intensity. Importantly, the mismatch response is elicited in the absence of attention, i.e., when no task performance is required, although clear modulation by attention of the mismatch responses has been described [11,12]. MEG/EEG source analysis [13-16], and depth recordings in humans [17] and animals [18] suggest that the mismatch response is generated in the posterior superior temporal gyrus (STG, in or near Heschl's Gyrus). Prior work [19] has suggested that the mismatch response is a composite of several different neural generators including parietal and frontal in addition to STG sources. Others [20] suggest that the STG source of the mismatch response results from anterior and posterior components of the N1 response— known as N1a and N1p, respectively [21,22]. The N1p may be generated in the associative auditory cortex and the planum temporale (earlier latency than the anterior component) and the N1a may have a genesis just anterior and lateral to the primary auditory cortex (Figure 1). The mismatch response may originate in or near the N1a generator or slightly anterior to it [3,19].

Most (reviewed by Javitt [23]) but not all [24] studies have reported a reduced mismatch response in neural diseases that have a reduction in inhibition such as schizophrenia. Electrophysiologic investigations suggest that the reduced mismatch response is localized in the posterior STG [25], the site of reduced volume measurements in the STG as measured by MRI. The mismatch response reliability is excellent [26], which makes it a good tool for clinical use.

For use in the imaging of normal and impaired cognition, the mismatch response may be used to determine the integrity of particular neurotransmitter systems. For example, some studies indicate that the excitatory glutamate receptors interacting with the inhibitor gamma-aminobutyric acid (GABA) system are closely related to the abnormalities of the mismatch response in many disorders of cognition, and typified by schizophrenia [27-29]. The monkey equivalent of the human mismatch response was abolished by microinjections of both competitive and non-competitive glutamate NMDA receptor antagonists, without noticeable effects on the temporally preceding activity in lower laminae or the deviant alone stimuli [18]. A similar inherent modulation was observed on surface potentials in schizophrenia [30-32]. Further, Javitt [18,23,29,33] has shown that exogenously administered NMDA receptor antagonists also result in a reduction of the mismatch response similar to that observed

in schizophrenia. These findings are supported by animal models that demonstrate recurrent inhibition of NMDA-receptor neurons via GABAergic interneurons [27]. These results suggest that non-invasive imaging of the mismatch negativity may have a direct impact on the clinical care of patients, such as in schizophrenia, especially when combined with other measures measurements and imaging techniques.

Spectral Analysis of Cognitive Processes using Visual Stimuli

Bertrand and colleagues [34-38] have investigated visual cognition using a variety of paradigms and showed that during a visual object recognition a burst of neural activity near 40 Hz (known as the gamma-band frequency) correlates strikingly with many cognitive acts. The gamma band activity typically occurs within two time windows after presentation of a visual stimulus: one phase-locked (evoked) to the stimulus at about 180ms and another, which is not phase-locked to the stimulus (induced), peaks at approximately 400 msec after stimulus presentation [39].

The timing of neural events is crucial for normal brain function, and probably most especially important for coordination of cognitive acts — especially for object recognition. Disruption of the precise timing of cortical events may explain the diverse cognitive deficits in dyslexia, depression, and schizophrenia [40]. Neural activity in the gamma frequency band (30 - 80 Hz or broader, centered on 40 Hz) has been hypothesized to reflect the synchronization of neural assemblies involved in “binding” of various features of an object both within a single sensory modality and across modalities, and also across time [41]. At the cellular level, Traub and colleagues [42-46] have presented evidence that interneurons with GABA_A-mediated synaptic transmission interacting with glutamate-mediated cells provide the substrate for gamma oscillations in the cortex. A rich literature suggests that gamma band activity may bind information across distant sites in the brain, known as the temporal binding hypothesis [41]. Neural modeling, using sophisticated biologically-based simulations based on cellular physiology, suggest that there is a complex interplay in the excitatory and inhibitory cells in generating intrinsic rhythms in the brain, and that different frequency bands have complementary roles in brain function [47], which is supported by recent cellular research [42-46].

Auditory steady-state response (ASSR)

A robust early neural response is the auditory steady state response (ASSR). It has a maximal peak when the stimulation frequency, typically presented as brief auditory clicks, is presented at 40 Hz. Several studies using the ASSR in schizophrenia shows a deficit in the 40 Hz response (Figure 2) in the ability to follow the stimulus, both in frequency and phase, in schizophrenia [48-50]. In a separate study, the auditory steady-state response (ASSR) was increased in Alzheimer's disease patients as compared to normal controls, which was suggested to represent decreased inhibition and adaptation in auditory processing [51].

Connectivity

Although early sensory processes may be used to measure processes that are involved in disorders of cognition, cognitive functions require precise coordination of neural activity across long distances in the brain. These connections are typically made through large white matter tracts in the brain, which ensure precise timing across distant brain areas. Imaging connectivity in the brain involves both structural and functional components, both of which are accessible through functional imaging. The non-structural connectivity is often also further classified as functional connectivity and effective connectivity. Functional connectivity quantifies the *correlation* of activity between two areas, and effective connectivity measures how the *influence* of one area on another. The covariance approach is a type of *effective* connectivity

of a large-scale interconnected network. This is in distinction with traditional subtraction methods (stimulus type contrasts) that assumes that there is a change in activation in discrete brain areas [52,53].

Structural Connectivity

Diffusion Tensor Imaging—Structural connectivity measures, such as DTI, have recently demonstrated the capability to detect subtle white matter microstructural variations across the brain and among individuals, as well as to find alterations in a number of brain disorders. Microscopic white matter alterations have been observed with DTI in a number of conditions including Alzheimer's disease, human immunodeficiency virus (HIV) infection, premature birth, chronic alcoholism, autism, multiple sclerosis, schizophrenia, and numerous other conditions [54,55]. Fractional anisotropy (FA) reflects diffusion anisotropy presumably from microstructural obstacles that cause water molecules to diffuse in a particular direction. The obstacles that the water may encounter may be due to the amount and integrity of myelin sheaths around axons, the diameter of the neurons, and the degree of facilitated diffusion that may reflect active transport within neurons.

DTI Combined with Other Neuroimaging Technologies—In order to understand the relationship of structure-function, diffusion measures such as FA and function (PET or fMRI) may be correlated within subjects or across subjects. The function might be the age of the subject, the timing of a behavioral response, or the latency of an evoked potential. For example, it has been shown that the normal aging prefrontal white matter is selectively susceptible to FA decline, consistent with prefrontal cognitive impairment in normal aging [56,57]. Antisaccade latency in schizophrenia is strongly correlated with FA in established white matter pathways in the antisaccade processing network.

Another study found a relationship between the timing of behavior, in this case the choice reaction time (CRT), and the physical properties of white matter [58]. Using DTI, the FA was found to be regionally correlated with the choice reaction time on a visual task. Specifically, the timing of CRT across a group of young, healthy subjects was highly correlated with the FA in visual projection and association pathways supporting visuospatial attention (Figure 3). The authors suggest that localization of the CRT-FA correlations to predominately visual and parietal fiber tracts, but not to motor pathways or the corpus callosum indicates that individual differences in visual CRT performance are associated with variations in the white matter underlying the visuospatial attention network as opposed to pathways supporting motor movement or interhemispheric transmission.

Clinically, it has been shown that evoked potentials and evoked magnetic fields may also be correlated with measures from DTI in disorders that affect cognition. Evoked potentials and neuromagnetic fields are an effective clinical diagnostic tool in a wide number of neurological and psychiatric disorders [59-61]. Despite the clinical utility of evoked fields and potentials, the exact underlying mechanism causing evoked potential abnormalities, such as prolonged latency or reduced magnitude, now are better understood with the use of structural and functional neuroimaging. Recent reports have demonstrated correlations between neuromagnetic and neuroelectric evoked response abnormalities and atrophy of the supporting white matter in a wide range of disorders, e.g., multiple sclerosis [62], schizophrenia [63,64], and cognitive impairment in normal aging [65]. For example, white matter lesion load in multiple sclerosis correlates with prolonged latencies [62]. The concordance between evoked response abnormalities and white matter pathology has promoted a model for neurological cognitive impairment based on alterations in nerve conduction velocity. One controversial model maintains that white matter degeneration, e.g., demyelination and/or axon loss, leads to

altered nerve conduction velocity, which disrupts the proper temporal synchronization of nerve impulses that are required for normal cognitive function [65,66].

Klingberg et al. [67] found certain function-structure relationships in the human brain by investigating patients with reading dyslexia. They reported that the FA values in the bilateral temporal junction were decreased in subjects with poor reading ability compared to age-matched control subjects. Specifically, the FA was correlated with the reading ability score. This finding suggests that there is decreased myelination in or near the classical Wernicke's area in patients with reading disorders.

Functional Connectivity

Resting state connectivity—A particular case of functional connectivity is the so-called default mode or resting state first characterized using PET and extended with fMRI studies. It quantified the spatial correlation of brain activity in the absence of a cognitive task. Typically, this is performed by having the subjects fixate on a visual cue, such as a cross-hair, without any other cognitive task [68]. The resting state map is typically computed by calculating the resting state *connectivity*, using a seed voxel to calculate voxels that are correlated with the seed voxel (Figure 4). This baseline activity in the resting state has spatial correlations that involve the same prefrontal, medial temporal lobe, and parietal lobe systems involved in some memory tasks. Although speculative, it may be that the memory system, especially the declarative memory system, might be activated in the so-called resting state [69].

Effective Connectivity

As functional connectivity measures the correlation of activity among brain regions, effective connectivity measures the influence of brain nodes on each other. Two types of effective connectivity are often used in functional neuroimaging: Covariance structural equation modeling (SEM) [52] and Granger causality [70]. The connectivity of brain activity can be studied by implementing the covariance SEM (for review, see [52]). Originally, SEM was applied to PET studies, and later to fMRI, to quantify causal interactions between brain regions [52,53,71-73]. This method estimates both the strengths of connectivity between areas and statistically infers the causal effects of *a priori* determined connectivity models of large-scale cerebral networks. For example, application of SEM modeling of human working memory for faces has suggested that the network of underlying activity changes as the task requirements change [74]. The resulting time-varying connectivity models can be used to image large-scale dynamic neural networks underlying language processing (Figure 5).

Granger causality, another type of effective connectivity, offers a powerful unbiased dynamic estimate of driving relationships within a large-scale neural network that tests all possible direct, indirect, and combinations of connections without any need for *a priori* connectivity information [70].

Cognitive Applications with an Emphasis on Mapping Brain Connections

Imaging Language

Preoperative determination of language areas is a recognized clinical application of neuroimaging of cognition. Language is important in understanding cognition. Speech and reading require a variety of intact cognitive and sensory-motor functions. For language comprehension to function normally requires numerous cortical and subcortical areas, including the sensory cortex, the classical language systems (Wernicke's area and Broca's areas) and memory networks. Preoperative or operative mapping is important prior to the removal of brain areas near eloquent cortex, such as in cases of brain tumor or epilepsy neurosurgery. Language function is disrupted in a wide range of cognitive disorders including

schizophrenia, Alzheimer's disease, and dyslexia. There is increasing evidence that language regions in the brain—even the classic Broca's area—are not necessarily specific to language, but rather involve more specific processes that give rise to both language and nonlinguistic functions. Functional neuroimaging also has indicated a far greater involvement of the right hemisphere in some aspects of language processing than previously has been appreciated.

In patients with brain tumors involving the perisylvian cortex, lateralization and localization of language processing is critical. Although fMRI is routine at some medical centers, the intracarotid injection of amobarbital, known as the Wada test, still may be considered the gold standard for presurgical determination of hemispheric dominance [75]. The Wada test yields a lateralization index (LI) based on the number of correct answers during the barbiturate administration of one hemisphere compared to the other hemisphere. Despite a long history and general acceptance of the results, the Wada test has been criticized because of potential cross-flow to the contra-lateral hemisphere, the lack of evaluation of the territory supplied by the posterior circulation, and the lack of data regarding reproducibility. There are several reports of fMRI being used to successfully determine the hemispheric dominance for language, and occasional for regional language mapping of individual language areas [76-86]. FitzGerald et al. [80] found a good correspondence between fMRI and electrocorticostimulation for presurgical language mapping purposes. Roux et al. [84] recently compared the results of fMRI language mapping using a verb generation task with stimulation arrest language. They found, however, an imperfect correlation of fMRI with intraoperative mapping.

Mapping language in a research subject or a patient requires designing a paradigm that best activates the language processing stream. Specific language processes include phonological, lexical, and syntactic processing. Concurrent memory storage and retrieval occurs with any language paradigm. Supporting processes include attention, motor planning (speech), and basic visual or auditory processing. Tasks requiring a decision are probably the most widely used since they require a response from the subject, such as a forced binary decision, allowing for one to monitor the quality of the subject's responses. Some consider covert responses desirable, as overt (spoken) responses can lead to unacceptable motion artifacts. For example, a verb generation task consists of having a noun read out loud while the subject is asked to think of an action verb to go with it (i.e., Car/drive). A semantic decision task might consist of presenting a series of nouns on a video monitor while the subject decides whether it is “abstract” or “concrete” (i.e., love/abstract or book/concrete). Still, passive sensory paradigms requiring no subject response also are reported to be successful, and circumvent the potential of movement related artifacts.

Hemispheric Dominance for Language—Determination of the language-dominant hemisphere is critical in many clinical applications [87]. Wada and Rasmussen determined that over 93% of patients are left language dominant, and that over 96% of right-handed patients are as well; yet, more recent studies indicate more bilateral representation of language than originally thought [88,89]. Among left-handed individuals, only about 70% demonstrate left hemispheric dominance for language, while approximately 15% demonstrate bilateral language lateralization.

The laterality of language is usually achieved with fMRI or PET by activating language areas and comparing the relative strength of activation between the right and left hemispheres [77, 85,87]. The lateralization index, analogous to the Wada LI is computed by the following

formula [77,87]: $LI = \frac{(LH - RH)}{(LH + RH)}$, where LI is the lateralization index, LH is the number of activated pixels in the left hemisphere, and RH is the number of activated pixels in the right hemisphere. A similar index is used in PET except that the counts in each hemisphere is used instead of number of pixels. No matter what the modality, when LI is 1, the subject is left-

hemisphere dominant, and when LI is -1, the subject is right dominant; for $LI \sim 0$, language function is bilaterally represented. Multiple groups report a strong correlation with fMRI and PET compared with both intraoperative mapping techniques and the results of the Wada test [77,81,83-86,90,91].

Regional Language Mapping—Task-activated fMRI and PET can locate, with a high spatial resolution, both receptive and productive language areas. This has led to a revolution in the understanding of the basic neuroscience principles involved in where and how the brain processes information. The practical needs for the presurgical evaluation of brain tumor patients, however, and the needs of basic neuroscience are fundamentally different. First, the neurosurgical application requires precise localization in the individual patient, while the neuroscientist can average the response over several subjects in order to increase the signal-to-noise ratio of small activations. Second, the neurosurgeon usually requires mapping the *essential language areas*, not just the participating areas. Essential language areas are ones that when removed result in a language deficit. *Participating* areas are activated during language paradigms, but do not result in a post-operative language deficit after resection, either because there are areas of redundant processing or because other areas learn to take over the same functions. Currently, there is no way to distinguish essential from participating areas with non-invasive imaging, and improving the detection of essential areas is a major goal of clinical functional imaging.

Four distinct language areas are strongly lateralized to the left hemisphere, and are readily found with a variety of language tasks [80]: (1) Prefrontal (inferior frontal gyrus, superior frontal gyrus, and the anterior cingulate); (2) angular gyrus, excluding the supramarginal gyrus; (3) ventrolateral temporal lobe (superior temporal, middle temporal, inferior temporal, and fusiform gyri); and (4) retrosplenial cortex. These areas of activation are seemingly at odds with the neurological dogma of language processing. Binder 77,78 suggests that the imaging findings may not be so different from these prior theories. The differences may be due to the fact that lesion studies of anterior lateral prefrontal cortex (Broca's area) may be overemphasized with respect to their role in Broca's aphasia, since pure Broca lesions cause apraxic deficits of articulation with only temporary disruptions of language function. A permanent Broca's aphasia requires a more extensive lesion—involving the anterior inferior frontal gyrus, middle frontal gyrus, and peri-central gyri—than simply a lesion involving Broca's area. Thus, the historical lesion studies and fMRI activation areas may not be so divergent as originally thought, as both suggest a wide area of frontal lobe participation in language processing outside the classical confines of Broca's area. Lesions studies also suggest that people with large frontal infarctions often present with a receptive aphasia, which later may evolve into a so-called expressive aphasia. Task-activated fMRI can provide evidence of cortical reorganization of language areas, due to mass lesions or after surgical resection.

Imaging Memory

Presurgical mapping of memory may have greater clinical impact in the coming years than mapping of language [92,93]. Conscious memory of events, also known as episodic memory, is known to involve processing in the medial temporal lobes and on the prefrontal cortex. Frontal lobe activity is thought to relate to both the encoding and retrieval of memory events, for both long-term and for short-term memory.

Declarative memory is explicit memory for facts and events, and the formation of such memories is often studied using the so-called, “subsequent memory effect”, which is the brain activity during *encoding* of items that are subsequently forgotten. The *retrieval* of declarative memory is typically studied with the “old/new effect”, which is the comparison of brain activity recorded during correctly recognized old versus correctly identified new items. There are been

numerous studies that have investigated the sites of declarative memory using PET, fMRI, and MEG/EEG (for review, see [94,95]). Increased theta activity in the medial temporal lobe is the hallmark of memory encoding, imaged best with MEG/EEG and MRI (Figure 6).

Episodic memory refers to knowledge about events and is dependent on medial temporal lobes [96]. Episodic and semantic memory might recruit different brain areas [97]. However amnesic patients with medial temporal lobe damage show intact priming, category learning, and even learning of artificial grammars. Semantic encoding left prefrontal cortex and retrieval increases right prefrontal cortex activity. More recent neuroimaging studies implicate the parietal lobe in episodic memory (for review, see [94]).

Working Memory—Studies in monkeys suggest that the prefrontal cortex is involved in working memory, a finding that is supported by numerous functional imaging studies, intraoperative mapping, and transcranial magnetic stimulation (TMS). Working memory is associated with activation of the dorsolateral prefrontal cortex (DLPF), reflecting spatial or physical features of the stimuli, different aspects of the tasks, and/or expected rewards (for review, see [98]). Working memory has overlapping brain mechanisms with attention [99] and associative learning in the prefrontal cortex [100,101]. Behaviorally, there is an association between perception and working memory [102], and some functional data suggest that these neural correlates may overlap [103].

Multimodal Imaging of language and memory—In order to improve the temporal resolution of PET and fMRI, the activation maps from these cross-sectional imaging modalities can be combined with the high-temporal resolution information provided by other sources, such as MEG/EEG. Additional information on tissue oxygenation can be obtained from diffusion optical tomography. Both MEG and EEG, unlike other hemodynamic techniques such as fMRI and PET, directly measure neural activity. MEG is similar to EEG and, in fact, the neural generators of the measured signals are identical. The principle difference is that MEG preferentially detects activity in superficial, non-radial areas of cortex, i.e., the fissural cortex of the cerebral hemispheres. This is particularly advantageous if the area of activity is in the walls of the sulci, such as in the motor cortex, somatosensory, and auditory cortices. Further, nearly all activity measured by MEG is related to post-synaptic activity in the pyramidal cells of the cerebral cortex. Recently developed methods of statistical combination of structural MRI, fMRI, and EEG/MEG may provide the greatest benefit to the neurosurgeon in the near future (Figure 7) [104,105].

The combination of fMRI and MEG can be particularly illuminating for regional language mapping. The mapping of equivalent current dipoles of the late auditory evoked fields can be used for both posterior temporal and frontal operculum mapping [106,107]. Temporal maps of activation have similar profiles as determined by invasive electro-corticography. The latency of Wernicke's area is typically between 210 and 420 msec, and Broca's area ranges 400 msec – 1100 msec, depending on the individual subject and the particular language paradigm [107, 108]. Generally, the peak activation of Wernicke's area precedes Broca's area, although occasionally other temporal profiles have been reported [109]. Thus, maps based on both the activity latency as well as the spatial location can be used to identify language related areas, increasing the accuracy of the functional map.

A disadvantage of fMRI is that, especially at lower field strengths (3.0T and below), significant activity is detected due to large draining veins, which can be some distance from the cortical sites, leading to confusion in the localization of eloquent cortex. PET centers utilizing activation techniques are relatively limited currently. MEG is useful in cases of compromise of the hemodynamic response mechanisms; for example, in situations of abnormal blood flow response, such as arteriovenous malformations and, importantly, tumors [110]. This is

especially true if the functional cortex is located within the radiologically defined extent of the tumor, such as those of a slow-growing, low-grade nature. Inoue [111] who found two examples where the tumor and associated edema and mass effect led to disruption of the normal hemodynamic response and caused an incorrect localization. Holodny [112,113] found decreased blood oxygenation level dependent (BOLD) activation of the motor and somatosensory cortices adjacent to brain tumors, despite normal neurological function. Thus, an abnormal vascular supply may decrease the hemodynamic response measured by fMRI. MEG, on the other hand, is a direct measure of neural activity and is immune to the constraints imposed by the vascular system [110]. The future of functional brain mapping will require the intelligent integration of various imaging modalities into a single, composite image that encompasses the strengths of each technique.

Spectral Spatiotemporal Maps of Memory Maps—Cortical and subcortical oscillations are especially important in memory formation and retrieval, and may be abnormal in diseased brains. Specifically, the oscillations in Alzheimer's disease and mild cognitive impairment (MCI) subjects have been reported to be abnormal, yet in distinct ways than can be detected with non-invasive imaging techniques with PET, fMRI and MEG/EEG. In non-impaired healthy subjects declarative memory encoding and retrieval is associated with increased gamma band activity in the occipital lobe and increased theta frequency band in the right temporal lobe. The gamma-band specific activity was in and near the calcarine fissure, suggesting that there may be a top-down influence on primary sensory areas. Additionally, theta activity was found in the medial temporal lobe (Figure 6).

Some studies suggest that spectral power differences in underlying neural activity exist during declarative memory tasks in patients with Alzheimer's disease compared to age-matched controls. The MCI difference in terms of spectral power show a decreased alpha and beta bands [114,115]. Others have examined the alpha and beta band coherence across various brain areas [116]. Well-documented cholinergic deficits in Alzheimer's disease (e.g., [117-119]) and MCI can thus underlie EEG/MEG abnormalities observed in these memory disorders. The cholinergic neurotransmitter system (ACh) may synchronize large-scale brain oscillations that functions for declarative memory. In this hypothesis, the ACh from the cortex is high during EEG desynchronization and decreased when the brain activity is synchronized [120]. Pharmacologically, this is supported by the fact that with the administration of ACh antagonists, such as scopolamine, high amplitude slow wave activity is produced. PET and fMRI studies have shown increased mesial temporal and inferior prefrontal activity in areas that are successfully encoded in the subsequent memory effect, but anterior prefrontal cortex, parietal cortex, and medial-frontal areas are activated during the old/new effect.

Conclusion

Functional imaging technologies have advanced the understanding of the neural mechanisms underlying cognition over the last two decades. First with PET imaging, and next with fMRI and MEG, the clinical relevance of much of this basic research has only recently been realized. The current clinical applications of using functional neuroimaging to map cognitive function include lateralization and presurgical mapping of language processing and memory mapping. The development of advanced techniques and the intelligent combination of imaging technologies is further expanding the basic understanding of cognitive thought and is extending the clinical applications of functional neuroimaging into new areas. Future applications will include multimodal functional neuroimaging of schizophrenia, Alzheimer's disease, and a variety of learning disorders.

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Figure 1. Auditory mismatch response and combining MEG with fMRI data

Upper panel shows both a three-dimensional (3-D) rendering of a brain computed from the subject's MRI with the corresponding inflated cortex patch around the auditory areas. Labeled areas include Heschl's gyrus (HG), planum temporale (PT), superior temporal gyrus (STG), superior temporal sulcus (STS), and middle temporal gyrus (MTG). The middle panel depicts the equivalent current dipole (ECD) method, which is traditionally used for MEG source estimation. On the left is a sagittal MRI with the ECD source estimate location with the black bar indicating the dipole direction. On the right, the dipole representing the peak in the magnetic mismatch response is registered onto an inflated cortex. Notice that in this case the dipole is near the anterior portion of Heschl's gyrus. Integration of the fMRI, MEG data, and the inflated

cortex data are combined (lowest panel) to create a 'movie' or spatiotemporal map. The fMRI data superimposed on source echoplanar imaging (EPI) BOLD MRI images, which is then transformed onto the inflated cortex. This illustrates how the activity from MEG are transformed using the minimum norm estimate (MNE), onto an inflated cortical source. Next, the fMRI data and the MNE results are combined into a spatiotemporal movie (dSPM). Some activity of the mismatch response is seen at 93 ms, which peaks at approximately 103 ms, and is diminished by 113 ms.

Auditory Steady State Potential in Schizophrenia

Figure 2. ASSR in Schizophrenia

(A) Magnetic field strength (fT/cm) versus time (stimulus presented at time 0, lasting ~ 500msec) in a single MEG channel over the temporal lobe. Note the appearance of middle latency evoked response (N100m) as well as the overriding sustained field. (B) Power spectral density in a temporal lobe gradiometer (maximal response for auditory stimuli) over the time interval 0-500ms. Note that in the control subjects, the 40Hz is the largest response (greater than both the 20Hz and 30Hz power peaks, often twice the magnitude). In this case, however, the 40Hz power is less than half the power in either the 20Hz or the 30Hz power, although the 20Hz response is maximal at a frequency somewhat less than 20Hz. (C) Time frequency representation (TFR) showing the spectral power as a function of time. Sustained neuromagnetic field from MEG gamma band response to periodic auditory clicks at 40Hz in a control subject. The color scale shows increased spectral power of the Morlet wavelet (blue to red for increasing power). (D) Source estimation localization using the same response to same auditory clicks from (A) [121], with the fMRI spatial information (not shown) using a

Morlet wavelet-based minimum norm estimate (MNE) centered at 40Hz at time 230msec after beginning of click train. It is displayed on an inflated cortical surface of the same subject. The activity appears to involve middle and medial Heschl's gyrus, extending into the planum temporale. Note that the MEG power spectrum calculated with a FFT in (B) does not include any temporal information unlike the wavelet-transformed measures such as the TFR in (C) and the spectral spatiotemporal map (dSPM) in (D).

Figure 3. Cognition and white matter from diffusion MRI

The correlation coefficient (r_s) between CRT and FA is displayed as map overlaid on the T1 template from a standard atlas. The small frames show axial slices through the optic radiation. The superior-inferior level of the axial slices is indicated by the yellow lines in the sagittal images. The sagittal images at top right are the Montreal Neurological Institute (MNI) individual T1 template (Left) and the group average FA map (Right). The correlation map shows the trajectory of the right visual pathway from lateral geniculate nucleus (LGN) through Meyer's loop (ML) to the optic radiation (OR), terminating at the junction between the optic radiation and the posterior forceps of the corpus callosum (OR-PF). [Used with permission by the author in Tuch DS, Salat DH, Wisco JJ, Zaleta AK, Hevelone ND, Rosas HD. Choice reaction time performance correlates with diffusion anisotropy in white matter pathways supporting visuospatial attention. *Proc Natl Acad Sci U S A*. Aug 23 2005;102(34):12212-12217].

Figure 4. Resting State Networks

Correlation maps are illustrated for the four seed regions. Left middle temporal (L MT+) and Right middle temporal (R MT+) are left and right regions defined around the MT+ complex; L HF and R HF are left and right regions defined within the hippocampal formation. Each image shows the mean voxel-wise correlation (a measure of functional connectivity) to the specific region displayed on the left. Four independent participant groups were analyzed. Only positive correlations are shown. Correlation maps are overlaid onto the average anatomic image for each group. Note the consistency of the difference between correlation with MT+ vs. HF seed regions and also the reproducibility of the topography across independent data sets. [Used with permission from author. Copyright belongs to Vincent JL, Snyder AZ, Fox MD, Shannon

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Figure 5. Connectivity Analysis of Visual Language using Magnetoencephalography

A. MEG Equivalent Current Dipole (ECD) location for a visually-presented word in the occipital lobe. B. ECD localization of temporal lobe dipole for same stimulus in (A). C. Current dipole time course of ECD in occipital lobe (solid line) and temporal lobe (dashed line). D. Time Frequency Representation of spectral power in the occipital lobe showing both upper alpha band activity (centered ~10Hz) and beta band activity (20Hz). E. Intratrial coherence of activity in the occipital ECD. F. Granger causality demonstrating two periods of occipital (labeled V1) and the temporal ECD (STG), without any significant temporal to occipital influence.

Figure 6. Theta Oscillations in Memory

Theta Inflated cortex with MEG/EEG activity in the medial temporal lobe during a visually presented semantic memory task. Note that the activity represents the spatiotemporal map [121] of the theta-band activity ($\sim 5\text{Hz}$) which is known to modulate recall and encoding in the medial temporal lobe structures.

Figure 7. Presurgical Mapping of language

Multimodal approach using MEG, DTI and fMRI. Blue regions represent MEG language localizations. Red areas represent fMRI language activations. Brown tracts represent white matter tractography. Note regions where MEG and fMRI language overlap, as these co-localizations were used as seeding points for tractography generation. Where MEG and fMRI language overlap, these co-localizations were used as seeding points for tractography generation. Images provided by Dr. Alexandra Golby, M.D. and Dr. Ralph Suarez, Brigham and Women's Hospital, Boston, MA.