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COMMENTS AND CONTROVERSIES

Imaging Brain Plasticity: Conceptual and Methodological Issues—A Theoretical Review

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The neural plasticity associated with learning and development is increasingly being studied using functional neuroimaging methods such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). In this paper I outline a set of conceptual and methodological issues that are particularly relevant for the study of neural plasticity. A number of confounds, related to changes in performance and the inherently temporal nature of learning and development, must be addressed when imaging plasticity. The interpretation of changes in imaging signals is greatly underdetermined, suggesting that hypothesis-driven research approaches may be most fruitful. Finally, I argue that the imaging of learning-related and developmental plasticity can enhance the ability of functional neuroimaging to identify and characterize the underlying neural basis of cognition.

INTRODUCTION

The first two decades of cognitive neuroimaging research have provided a constantly sharpening snapshot of the neural organization of cognitive processes. Many cognitive functions can now be associated with particular neural structures, and ongoing research promises to clarify this picture further, providing a fine-grained mapping between cognitive function and neural function. This snapshot, however, belies the constantly changing and essentially plastic nature of the nervous system. The nervous system is altered on the basis of development and experience throughout the lifespan. These changes occur at multiple levels of neural organization, from molecules and synapses to cortical maps and large-scale neural networks (reviewed by Buonomano and Merzenich, 1998). After a long period of focusing on static functional neuroanatomy, researchers using neuroimaging are now turning their interest toward the characterization of both developmental and experience-dependent change in the nervous system.

The primary goal of this paper is to outline those conceptual and analytic issues that are particularly important in the context of imaging changes in neural function, including developmental and learning-related plasticity. However, many of the issues discussed here are relevant to a wide range of neuroimaging studies of various cognitive processes, such as group comparisons of patient populations with normal controls. This review focuses primarily on studies using functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) to image brain function (via measuring blood oxygenation or blood flow, respectively), but most of the issues raised here are also relevant to studies using other functional imaging modalities such as electroencephalography (EEG) and magnetoencephalography (MEG) as well as structural neuroimaging.

RELATING IMAGING SIGNALS TO NEURAL PLASTICITY

Changes in neural function on the basis of experience occur at several levels of neural organization, both in development and in learning. For example, developmental studies with nonhuman animals have shown that sensory experience leads to changes at the molecular level (gene transcription, receptor expression), the cellular level (synaptic density, receptive field properties), the columnar level (organization of ocular dominance columns), the cortical map level (organization of spatial maps), and the systems level (cross-modal plasticity). Because PET and fMRI are indirect measures of synaptic activity, only those changes resulting in differential (task-related) changes in synaptic activity will be detectable using these methods. Although some of the known plastic changes should clearly result in changes in the level of synaptic activity (e.g., synaptogenesis or synaptic pruning, expansions of cortical maps), there is relatively little evidence at present about the biophysical effects of plastic neural changes on functional imaging signals.

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In addition to plastic changes in brain function, both learning and development are associated with plastic changes in brain morphology, and the impact of these changes on functional imaging signals is also unknown. This issue is further discussed under Functional Imaging in the Face of Morphological Change. Because of the lack of evidence about the biophysical relation between plastic changes and imaging signals, it is difficult at present to map particular changes in imaging signals to particular neurobiological mechanisms of plasticity.

MULTIPLE SYSTEMS FOR LEARNING AND PLASTICITY

Just as there are multiple types of plasticity at the neural level, there are also multiple forms of learning at the cognitive level, which have been described in terms of multiple memory systems (Cohen and Eichenbaum, 1993; Squire, 1992). A primary distinction has been made between the declarative memory system, which relies on the medial temporal lobe (hippocampus and related cortices), and the nondeclarative memory system, which is independent of the medial temporal lobe. The declarative memory system supports conscious explicit memory for prior events and facts, whereas the nondeclarative system supports changes in behavior that do not necessarily involve conscious memory of the past. This review concentrates on nondeclarative memory phenomena, but many of the issues raised here are relevant for studies of declarative memory as well. Within the domain of nondeclarative memory, a number of different forms of learning have been identified, including skill learning (acquisition of novel task procedures), repetition priming (changes in performance on particular stimuli), classic conditioning (acquisition of novel stimulus–response associations), and adaptation-level effects. The common feature of these forms of learning is their independence of the medial temporal lobe (as demonstrated by intact learning in amnesic patients) and their independence from conscious recollection. However, nondeclarative memory is not unitary; both neuroimaging studies (e.g., Blaxton *et al.*, 1996; Demb *et al.*, 1995; Grafton *et al.*, 1992, 1995; Poldrack *et al.*, 1998, 1999) and neuropsychological studies (e.g., Gabrieli *et al.*, 1997; Heindel *et al.*, 1989; Keane *et al.*, 1995) have suggested that nondeclarative learning on different tasks may involve different neural substrates.

From the standpoint of imaging plasticity, the importance of the multiple memory systems framework is that different forms of learning may involve radically different underlying neural mechanisms, depending on the cognitive demands placed by the task. This is particularly clear at the level of the declarative/nondeclarative distinction, as has been seen in the literature on motor sequence learning. Subjects learning a sequence of finger movements explicitly (i.e., using conscious declarative memory for the sequence) engage a very different set of brain regions than subjects learning the same sequence implicitly (i.e., using nondeclarative learning mechanisms), even as the behavioral demands of the task remain identical (Grafton *et al.*, 1995; Hazeltine *et al.*, 1997). Similarly, in the context of learning auditory–visual associations, interactions between frontal and other cortical regions differ depending on whether the subjects were aware of the relations between stimuli (McIntosh *et al.*, 1999). These findings suggest that well-designed supplemental behavioral tasks (such as probe tasks to determine whether performance is based on declarative or nondeclarative memory) may often be necessary to fully understand the results of neuroimaging studies. They also highlight the importance of theory-driven experimental design, a point to be taken up later in this review.

STRATEGIES FOR IMAGING PLASTICITY

There are two fundamental strategies for examining plasticity. In the longitudinal approach, individuals are examined multiple times over the course of learning or development. For example, a typical neuroimaging study of skill learning assesses activation in a cognitive task before and after (and sometimes during) training on a task, in comparison with a baseline task that is not practiced. Data analysis techniques are then used to determine whether brain activity (measured as a difference between the trained and untrained tasks) has changed in association with training on the task. Longitudinal approaches are also useful in other situations, such as imaging recovery from neurological conditions, particularly when that recovery occurs over a relatively short period (e.g., Small *et al.*, 1998).

An alternative strategy is to compare individuals with varying levels of a given skill and identify differences in neural function or structure related to their skill level; this is known as a cross-sectional approach. This approach is often used in studying developmental changes that occur over the course of many years, where the longitudinal study of the individuals can be very difficult. For example, Amunts *et al.* (1997) examined the relation between the length of the precentral gyrus and the number of years of practice at a musical skill. They found that the length of this gyrus in both hemispheres was correlated with the number of years of practice, suggesting that structural variability in this structure was a result of experience-dependent plasticity rather than reflecting initial individual differences (see below for discussion of possible artifacts in this type of study). The cross-sectional approach is also useful in examining plasticity following brain insults such as stroke (e.g., Weiller *et al.*, 1995), where a longitudinal approach would require months or even years of follow-up.

Each of these approaches has distinct advantages and disadvantages. The advantage of the longitudinal approach is that it provides optimal power to identify changes because of its within-subject nature, given that variability between subjects is much greater than the variability between imaging sessions for a given subject. The cross-sectional design suffers in power from this between-subjects variability. Cross-sectional designs may also suffer from cohort effects, in which different groups (e.g., different age groups, skilled vs unskilled musicians) differ from each other by factors other than the factor of interest. For example, in the Amunts *et al.* (1997) study of cerebral structure in musicians, it is not possible to rule out that children who go on to become skilled musicians start out with different cerebral structure (although the correlation between age of practice onset and cerebral structure argues against this possibility). Cohort effects can also reflect cultural changes over time; for example, children growing up within the last 5 years will have received much more early experience with computers than children growing up 25 years ago. Any comparisons between these two groups would thus confound developmental differences with differences in specific group experiences. Longitudinal designs do not suffer from cohort effects, since the same individual is studied at every point. However, longitudinal designs can suffer from experiential or practice effects, since subjects are examined on multiple occasions and thus may acquire particular knowledge or skills related to participation in the study. This issue is examined in detail below (see Time Confounds).

POSSIBLE CONFOUNDS AND REMEDIES

Because plasticity by definition involves changes in behavior over time, there are intrinsic confounds inherent in any neuroimaging study of developmental or learning-related changes.

Performance

Development and learning are defined by their associated changes in behavior. For example, the index of skill learning or repetition priming on most tasks is a decrease in response time (often following a characteristic power law: Newell and Rosenbloom, 1981) and an increase in accuracy. Thus, comparisons between imaging data acquired between pretraining and posttraining are confounded with differences in performance. It is known that neural activation differs as a function of duty cycle (the proportion of time spent on task) or task pacing (D'Esposito *et al.*, 1997; Sadato *et al.*, 1997), and changes in activation between pretraining and posttraining may thus reflect changes in these factors rather than reflecting true changes in the underlying neural architecture of the task.

It is important to note that performance-related changes may extend beyond simple linear changes in the amount of activation. For example, there is evidence that anterior cingulate and other prefrontal regions may be engaged in relation to task difficulty (e.g., Barch *et al.*, 1997). If task difficulty changes drastically across learning or development (e.g., the automaticity generally associated with skill acquisition), then such regions could exhibit qualitative changes in their activity that would be mistakenly identified as reflecting the skill acquisition process rather than reflecting the consequences of skill acquisition. This problem can be addressed by including parametric manipulations of task difficulty at each level of skill or development, such that the relation between task difficulty and brain activity can be identified independent of the level of skill or development.

One remedy for performance confounds is to constrain performance to remain roughly constant. For example, in a study of motor sequence learning, Karni *et al.* (1995) asked subjects to make their finger movements in rhythm with the constantly timed noise of the magnetic resonance scanner. Comparisons of motor cortex activation were thus not confounded by changes in the rate of finger tapping, although it remains possible that other aspects of performance (e.g., movement speed, attentional demands) may have differed.

Another remedy for performance confounds is to vary some aspect of the task or stimulus to equate difficulty between conditions. For example, one might vary stimulus contrast to equate response time across two perceptual decision tasks. If one wishes to use this strategy, it is essential that one first test behaviorally to determine that the effect of the difficulty manipulation is additive with the condition effect of interest. If such additivity does not hold, then one cannot uniquely determine whether activation differences between conditions are due to the conditions themselves or to the difficulty in manipulation; even when they are additive, one must be cautious in interpreting the results because of the possibility of (behaviorally unobservable) changes in processing caused by the manipulation.

Differences in performance arising from response time changes seem to be more problematic than changes in accuracy, because of the direct relationship between response time and duty cycle. Thus, another possible remedy for performance confounds is the use of speeded tasks where changes in performance are seen in accuracy rather than response time. For example, Poldrack *et al.* (1998) presented words in mirror-reversed text for 2 s during scanning, whereas subjects generally need more than 3 s to perform the task with high accuracy. Accuracy increased significantly between pretraining and posttraining whereas response time remained constant, reducing the possibility of duty cycle confounds. A problematic aspect of the speeded presentation technique is that it may change the way that the task is performed by the subject.

Performance confounds can be particularly drastic in cross-sectional studies, where differences in the level of skill across subjects may be large. For example, in comparing normal and dyslexic readers on a nonword rhyme task, Shaywitz *et al.* (1998) found that normal readers had an error rate of 9.3% whereas dyslexic subjects had an error rate of 31.5%. These differences can result in duty cycle confounds as discussed above, making it difficult to interpret differences in activation between groups. In addition, there may be both cognitively driven and emotionally driven confounds related to failure on a task, particularly for subject groups such as dyslexics for whom the failure to read can have strong emotional consequences. Such failure could result both in activation of areas related to emotional processing of failure-related anxiety and in a lack of activation if the subject abandons the task when failure becomes imminent. One approach to this problem is to employ the simplest possible version of the task that still taps the cognitive process of interest (cf. Price and Friston, 1999). For example, in studies of dyslexic adults, Paulesu *et al.* (1996) and Shaywitz *et al.* (1998) both employed a simple letter-rhyming task that could be performed at an equally high level by all subjects but that still engaged the cognitive processes of interest. Although possible performance confounds remain, this approach is useful in the comparison of groups on tasks where subjects have a history of failure.

Time

Plasticity is inherently confounded with time, and there are a number of possible nonspecific confounds related to this effect. First, many subjects exhibit anxiety when taking part in neuroimaging studies, and this anxiety is reduced with experience in the scanner, both within a single session and across multiple sessions. The initial anxiety may express itself in a number of ways, from increasing head motion (which can decrease signal-to-noise initially and thus result in spuriously identified increases in activation) to increasing vigilance or attention (which can increase activation initially and thus result in spuriously identified decreases in activation as this initial activation subsides). Other time effects may arise from changes in scanner performance across time.

Time confounds are generally less problematic than performance confounds, because they reflect primarily main effects whereas performance confounds reflect time × condition interactions; that is, some time-varying effects (such as head motion) should equally affect all conditions, whereas performance confounds are by definition condition-specific. Thus, employing a general linear model approach in which one can estimate separately main effects of time and task and their interaction allows one to examine specific learning-related changes independent from time confounds. However, there may be cases in which the effects of time interact with condition; for example, vigilance effects might increase activation specifically in a difficult task relative to a resting baseline.

In some task designs there are multiple possible versions of the task that do not exhibit transfer of training between versions, for example, motor sequence learning tasks in which a particular sequence is trained. In these cases, one can image a direct comparison between untrained and trained versions of the task, which does not involve a temporal component. This approach has been applied in a number of cases of motor skill learning (e.g., Jenkins *et al.*, 1994), but is not viable for the study of tasks where there is no appropriate untrained comparison. In addition, it is important to confirm behaviorally that training on the task of interest does not transfer to the control task.

ANALYSIS APPROACHES

A number of analysis approaches have been applied to identify plastic changes in neuroimaging data, and relatively little is known about the comparative virtues of these approaches. In many cases the choice of analysis technique will depend upon the task design; for example, whether learning is analyzed within a single imaging session or across multiple sessions with interleaved training. In addition, the choice of analysis technique depends on whether one wants to generalize to the entire population (random-effect approach) or to determine the average characteristics of the particular sample (fixed-effect approach).

General Linear Model Approaches

An analysis approach that is becoming standard in the functional imaging community uses the general linear model (GLM) to estimate the effects of a set of variables (e.g., Friston *et al.*, 1995). In the context of a simple learning experiment in which one examines a particular task comparison at multiple points in time, effects are tested using an analysis of covariance (ANCOVA). Time and task condition are treated as main effects, whereas specific effects of learning are indexed by the time × condition interaction (because they reflect differences in condition effects over time). In event-related fMRI, time × condition interactions can be used to identify regions where the hemodynamic response to particular event types changes as learning occurs (e.g., Buchel *et al.*, 1998).

The use of ANCOVA in the context of the GLM allows one to examine effects of interest while removing the effects of other possibly confounding variables.

For example, one can remove (linear or nonlinear) effects of time, effects of performance variables such as response time, and head motion parameters. Alternatively, one can examine directly the effects of performance variables (e.g., the level of skilled performance or the amount of change due to training) to identify regions whose activity varies with performance. For cross-sectional studies of skill learning, this is particularly important since subjects are not assigned randomly to groups and thus may differ systematically.

Subtraction Analyses

In some cases, simpler subtraction analyses have been used to analyze learning data. In particular, one can directly subtract PET images from separate points in development or learning since PET images have a quantitative interpretation (unlike fMRI data). However, this approach has the drawback that one cannot directly determine whether changes reflect activation or deactivation. For example, Raichle *et al.* (1994) found increased activation in the insular cortex related to practice on a word generation task by directly comparing PET images between unpracticed and practiced trials. However, comparison of unpracticed word generation to a baseline task (word repetition) revealed that this insular region was deactivated compared with baseline. Thus, the "increase" in activity of the insular region may have actually reflected a reduction in the level of deactivation of that region, which would have very different implications for the interpretation of the results.

Connectivity Analyses

The previously described analyses identify localized brain regions whose activity is associated with a particular task. However, it is equally important to understand how these localized regions work together as large-scale neural networks. A different set of analytic techniques, known as network analyses or connectively analyses, have been used to identify networks of brain regions and their interactions. A major distinction among these techniques has been made between functional connectivity and effective connectivity analyses (see Friston, 1994). Functional connectivity analyses examine the correlation between activity in particular brain regions in a model-free manner. For example, principal-components analysis has been used to determine sets of regions demonstrating interrelated neural activity (e.g., Mcintosh *et al.*, 1994). Such analyses provide unbiased information about covariation between regions, but they cannot determine the causal structure of this covariation. Effective connectivity analyses, on the other hand, are used to determine the causal structure of influences on different brain regions. These approaches (which include structural equation modeling and path analysis) require a particular model of the neurobiological systems under investigation (i.e., which regions are involved and how they are connected). Thus, the casual effects of one region on another can be identified, but such estimates require some knowledge of the neural architecture. Both functional and effective connectivity analyses show great promise in the understanding of neural plasticity. To date, they have been primarily applied to understanding learning-related plasticity (discussed below), but it is likely that they will also provide strong insights into the nature of brain maturation and cognitive development as well.

Subjects: Random or Fixed Effect?

The statistical treatment of multisubject imaging data requires that one choose between treating subjects as a fixed effect and as a random effect (see discussion in Friston *et al.*, 1999). In a random-effect analysis, each subject contributes only a single observation per condition, whereas in a fixed-effect analysis all observations for each subject may be included. The choice between these approach revolves, in essence, around the desired target of inference for the particular study. When treating subjects as a fixed effect, inferences based on the particular sample of subjects extend only to that particular sample. By treating subjects as a random effect, inferences are extended to the entire population from which the subjects were sampled. The penalty for this extension of inference is that more subjects are generally required to find a particular effect, because the degrees of freedom are much greater in the fixed-effect analysis, particularly given the small numbers of subjects generally run in neuroimaging studies.

For cross-sectional studies of group differences (such as differences in age or skill), a random-effects approach is essential. If a fixed-effects approach is used to analyze group differences, the conclusions can only be of the form "One particular group of subjects differed from another particular group of subjects," with no inference to the population from which those subjects were drawn.

One note of caution should be raised, however, with respect to the use of random-effects models. Although one can legitimately make inferences from a sample to a population when using a random-effects model, the true nature of the "population" is determined by the sampling techniques employed in the study. That is, the population consists of all persons who could conceivably have been included in the study based on the sampling techniques employed. Whereas in studies of normal cognitive function one would like to generalize to all normal humans, perhaps qualified by age and education, in reality the true population is often a greatly limited subset of all possible normal humans (generally consisting of college undergraduates and graduate students).

INTERPRETING ACTIVATIONS IN STUDIES OF LEARNING AND DEVELOPMENT

The goal of neuroimaging studies of developmental or learning-related change is to map the observed changes in imaging onto putative changes in the underlying neural and cognitive processes. However, any particular change in neuroimaging data can reflect a number of different underlying effects, which are discussed here.

Interpreting Changes in Activation

Processing time. The simplest cause of decreased activation is a reduction in the amount of neural activity resulting from reduced time of processing. This could reflect faster settling of the particular neural network on a given output, at which point it would return to its baseline level of activity. Conversely, in tasks where learning or development is associated with increased time on task (e.g., rotary pursuit learning), increases in activation may reflect this increase in processing time. It is important to note that processing time for a particular neural region need not be linearly related to response time; recent mathematical models of response time (e.g., Townsend and Schweickert, 1989) demonstrate that the time to complete a particular mental process may bear a complex relationship to the observed response time.

Changes in cortical representation. Neurophysiological studies have demonstrated changes in the organization of cortical representations, both on the basis of development and on the basis of experience in mature animals and humans (Buonomano and Merzenich, 1998). Decreases in observed activation may occur due to the sharpening of responses in a particular neural network with experience or development. In this case, a minority of neurons would come to fire strongly to a particular stimulus or task but the majority of neurons would exhibit decreased firing for that stimulus or task. Such an explanation has been offered for the reductions in activation observed due to repetition priming; neurophysiological recordings have demonstrated that repetition results in smaller sets of activated neurons with suppression of activity in the majority of other neurons (Miller and Desimone, 1994). This effect can be conceptualized as a contraction of the neural representation of the newly learned stimulus. In regions with topographically organized cortex such contraction could result in a reduction in the spatial extent of activated cortex, whereas it likely results in a reduction in the level of activation in cortices with distributed representations.

In the context of learning, a great deal of attention has been paid to the search for learning-related expansion of cortical representations like that seen using neurophysiology. In topographically organized cortex this might be observed as an increased spatial extent of activation. Karni *et al.* (1995), for example, examined motor cortical activation during motor sequence learning, and found that the number of significantly active voxels increased with practice. They suggested that this result reflected the recruitment of additional cortical units with practice, because the strength of activation in the neighboring constantly active voxels did not increase. Although it may sometimes be possible to determine whether changes reflect expansion of extent or strengthening of response, the scale of changes in cortical representations is often below the spatial resolution of current imaging techniques, in which case spatially expanded representations might be reflected in increased strength of activation. The development of increasingly powerful imaging techniques that allow imaging at submillimeter resolution may obviate this problem. The spatial smoothing that is often applied to functional imaging data further reduces the ability to distinguish changes in strength and extent. In areas with distributed cortical representation, expanded representations are likely to be reflected in both level of activation and spatial extent.

Monitoring/control processes. Many tasks used in learning studies are initially difficult and require intense executive control of mental processing. As the task becomes less effortful with practice or developmental change, performance requires less control until, in the asymptote, it can be performed automatically (Logan, 1988; Schneider and Shiffrin, 1977). This reduction in executive control can lead to a reduction of activation that is correlated with learning or development. In particular, one would expect regions in the prefrontal cortex to reflect changes in executive control (Cohen *et al.*, 1996). For example, the right prefrontal cortex has been associated with the inhibition of irrelevant responses (Garavan *et al.*, 1999; Konishi *et al.*, 1999) and left prefrontal cortex has been linked to the selection among competing verbal responses (Thompson-Schill *et al.*, 1997); each of these processes is likely to be decreasingly necessary as learning or development progress.

Another aspect of novice performance in learning and development lies in monitoring for errors on the task. Thus, as skill is acquired less error detection is necessary, and regions involved in this process may exhibit decreases in activation. A particular region thought to be involved in error detection is the anterior cingulate cortex (Badgaiyan and Posner, 1998; Carter *et al.*, 1998). Whereas regions such as the cingulate may play general monitoring functions, other regions may exhibit monitoring functions that are specific to a particular task or domain. The cerebellum may be involved in the detection of errors during motor activity (Flament *et al.*, 1996), and decreases in cerebellar activation have been noted in studies of skill learning in cases where the task is highly automatized (Friston *et al.*, 1992). However, the cerebellum is also involved in error monitoring on linguistic tasks (Fiez *et al.*, 1992), and learning on linguistic tasks has resulted in decreased right cerebellar activation (Raichle *et al.*, 1994). Even within the same domain, different regions may be active depending on the nature of the task. For example, Fink *et al.* (1999) found separate areas of the right prefrontal cortex that were activated by a mismatch between visual and somatosensory feedback during hand movement, depending on whether movement was intentional or passive.

Awareness. Learning may involve changes in the degree to which subjects are aware of the task or stimulus structure, and these differences may result in different neural activity. In the study of motor sequence learning, it has been shown that subjects exhibit different patterns of neural activity depending on whether they are aware of the sequential structure of the task (e.g., Grafton *et al.*, 1995). Furthermore, transcranial magnetic stimulation (TMS) has been used to demonstrate that motor cortical activity changes when subjects become aware of this sequential structure (Pascual-Leone *et al.*, 1994). Beyond changes in region activation, differences in awareness may also be reflecting in connectivity. In an audiovisual associative learning task, McIntosh *et al.* (1999) found that the connectivity of left prefrontal cortex to a widespread set of other regions varied depending on whether subjects were aware of the relationship between stimuli. The importance of awareness in learning highlights the need for exquisite behavioral data to determine whether and when subjects become aware of a particular task manipulation.

Inhibition. In the context of inhibition, it is first important to note that functional imaging techniques such as fMRI and PET measure the level of synaptic activity rather than neuronal firing (Magistretti and Pellerin, 1999). As such, both excitatory and inhibitory synaptic activity will result in increased activation (although activation is thought to reflect primarily the effects of glutamate, an excitatory neurotransmitter, on glial cells: Magistretti and Pellerin, 1999). The effects of increased inhibition may be seen at later points in a given neural pathway when excitatory input from the inhibited area becomes reduced. However, such downstream effects have yet to be demonstrated convincingly using functional imaging. Within the context of well-understood functional networks, effective connectivity techniques may allow the determination of negative influences between regions, but the relationship between these negative influences and inhibition at the neural level remains unclear.

Process switching. It is thought that a particularly powerful strategy for learning may be found in switching between initial general-purpose processes and later use of processes that are more task-specific. For example, Poldrack *et al.* (1998) hypothesized that learning in a mirror-reading task involved switching between general-purpose spatial transformation processes and item-specific object recognition processes. Process switching predicts the coordinated increase and decrease of activation in separate brain regions. The reduction in neural activity in this case simply reflects less engagement of a particular cognitive process and thus reduced activity in the neural substrates of that process. Similarly, increased activation with learning can indicate the increased engagement of an existing system (as suggested by Raichle *et al.*, 1994) or alternatively can indicate the development of new representations or processes (as suggested by Poldrack *et al.*, 1998, in the case of mirror reading).

Altered neural synchronization. Synchronization of neural responses, both within and between cortical regions, is argued to be a powerful mechanism by which neural computations are achieved (Phillips and Singer, 1997), and it is likely that neural connectivity changes during learning and development. Recent modeling results (Chawla *et al.*, 1999) show that the level of synaptic activity is likely to increase in concert with neural synchronization, suggesting that functional imaging signals should be sensitive to synchronization. Developmental or learning-related changes in neural synchronization may thus be reflected in changes in regional neural activation. In addition, changes in synchronization can be identified using connectivity analyses, which have provided compelling evidence of learning-related changes in connectivity between brain regions. For example, Büchel *et al.* (1999) found that the connectivity of dorsal and ventral visual regions increased as subjects learned visual–spatial associations. In another study that examined artificial grammar learning, Fletcher *et al.* (1999) demonstrated a set of dynamic changes in the connectivity of frontal and parietal networks as subjects learned to classify items according to a set of rules.

Changes in neural synchronization have also been examined more directly using electrophysiological techniques. For example, Thatcher (1992) has demonstrated changes in the phase coherence of EEG recordings over the course of brain development. Other studies have demonstrated changes in synchronization related to motor skill acquisition (Andres *et al.*, 1999; Semmler and Nordstrom, 1998).

Resting-state processes. As performance of a task becomes automatic and requires less executive control, the subject may have a greater amount of cognitive resting time. There is evidence that subjects naturally engage in conceptual processing during resting states

(Binder *et al.,* 1999), and regions involved in these processes may become engaged more often as skill becomes automatized. Binder *et al.* suggest that this includes a network of left-hemisphere regions involved in semantic/linguistic processing. In addition, the precuneus region that is often more active during passive than active tasks is a possible candidate for such changes.

Changes in signal/noise ratio (SNR). Decreases in activation may result artifactually from reduced SNR during particular imaging blocks or sessions. Within a single session, reduced SNR over time may arise from restlessness on the part of the subject which results in increased head motion which can reduce SNR. When scans are performed across an interval of days, SNR may vary due to day-to-day variation in scanner stability. Although these are likely to be insignificant causes of apparent decreases in activation, it may be worthwhile to examine motion and image SNR parameters to rule them out.

Interpreting Constant Activations

Changes in activation are generally thought to be the sine qua non of a successful neuroimaging study of learning. In fact, some studies only report regions of significant change without reporting regions showing constant activation. However, there are a number of reasons that regions exhibiting constant activation with learning may nonetheless be of interest in the attempt to understand the neural basis of learning.

Limited time window. Some brain regions that are initially important in performing a task may decrease in activity over a very long window of training or development. Imaging studies that do not span this entire window may see only constant activity in these regions. For example, Poldrack *et al.* (1999) examined subjects as they learned to perform a probabilistic classification task. Previous neuropsychological studies had shown that initial learning on this task requires intact basal ganglia (Knowlton *et al.*, 1996), but that the basal ganglia become less important as training progresses. Poldrack *et al.*, however, found that the caudate nucleus was constantly active throughout the window of training examined in their study, with a small but nonsignificant decrease toward the end of training. Given the neuropsychological results, this basal ganglia activation is very likely to reflect processes that are essential to learning, yet it did not exhibit a learning-related change and thus may not have been highlighted without the guidance of the lesion studies. Had the study been continued through additional training trials, a significant decrease may have been observed.

Another example comes from cerebellar activation in studies of motor learning. Although neurophysiological studies suggested that the cerebellum should become less active as motor learning occurs and performance becomes less error-prone, a number of studies have failed to find significant decreases in cerebellar activation with motor learning (Grafton *et al.*, 1992; Seitz and Roland, 1992; Seitz *et al.*, 1990). Some of the studies that found such decreases used very simple motor tasks on which performance can be highly automatized and kept movement frequency constant (e.g., Friston *et al.*, 1992), suggesting that the decrease occurs only when performance becomes asymptotically skilled. Thus, the time window of training may simply have been too short in most studies to find this decrease.

A limited time window may also prevent the identification of learning-related changes if those changes require time for consolidation. Shadmehr and Holcomb (1997) trained subjects on a particular set of arm movements using a robotic manipulator, and performed PET imaging during initial learning and then again after 5.5 h had passed. They found a set of neural changes at the later scan that were not present in the earlier scans, consistent with the fact that learning on this task becomes progressively less susceptible to interference over that period. Other forms of learning appear to have consolidation periods of up to 8 h (e.g., visual perceptual learning: Karni and Sagi, 1993), suggesting that studies in many domains could benefit from follow-up scans after the consolidation period has passed.

Perseveration of nonessential processes. The activation of a particular brain region during performance of a task does not demonstrate that the region is necessary for performance of that task; as will be discussed further below, imaging results must be combined with data from lesion studies and other techniques (such as transcranial magnetic stimulation) to demonstrate that a region is necessary for performance of a particular task. A prominent example of this point comes from studies of classic conditioning. One version of classic conditioning in which the conditioned stimulus (CS) and unconditioned stimulus (UCS) overlap in time (known as delay conditioning) does not require an intact hippocampus for learning to occur (Gabrieli *et al.*, 1995), whereas another version in which the CS and UCS do not overlap in time requires the hippocampus (McGlinchey-Berroth *et al.*, 1997). However, neurophysiological studies in animals (Berger *et al.*, 1983) and imaging studies in humans (Blaxton *et al.*, 1996) have both shown that the hippocampus remains active during delay conditioning even though its activity is not necessary for task performance. In the context of plasticity, the implication of this point is that a region that has become unnecessary for task performance with learning or development may remain active even after it is no longer necessary.

FUNCTIONAL IMAGING IN THE FACE OF MORPHOLOGICAL CHANGE

The drastic changes in neural morphology that occur during child development are well known (Giedd *et al.*, 1996, 1999; Pfefferbaum *et al.*, 1994), as are the concomitant changes in brain metabolism (Chugani *et al.*, 1987) and myelination (Klingberg *et al.*, 1999; Paus *et al.*, 1999; Yakovlev and Lecours, 1967). These changes must be taken into account when comparing imaging data across age groups, but to date little is known about the effects of these changes on functional imaging signals. Although some functional imaging studies have found similar activation patterns between children and adults using fMRI (Thomas *et al.*, 1999), further work is necessary to determine whether the hemodynamic response to neural activity changes as a function of development.

Equally important are the changes in brain structure that occur due to experience. Learning of complex motor skills in animals is associated with changes not only in the functional organization of cortical motor maps (Nudo *et al.*, 1996) and physiologic changes such as early immediate (Fos) gene expression (Kleim *et al.*, 1996), but also with changes in a number of structural features of the cortex. In particular, motor skill learning is associated with changes in synaptic number (Anderson *et al.*, 1996; Greenough *et al.*, 1985), dendritic volume (Green *et al.*, 1983), mitochondrial and vascular density (Black *et al.*, 1991), and glial volume (Sirevaag and Greenough, 1991). At a much longer time scale, skill acquisition is associated with morphological changes such as gyral size (Amunts *et al.*, 1997). The effects of such microstructural changes on functional imaging results are currently unknown. However, given that the coupling of blood flow and neural activity is thought to involve the sensing of synaptic activity by glial cells (Magistretti and Pellerin, 1999), the finding of increased contact between glia and synapses following complex environmental experience (Jones and Greenough, 1996) suggests that experience-related structural changes may have direct effects on functional imaging signals. Future research must delineate the impact of these structural changes on functional imaging signals if plasticity-related changes in functional imaging are to be fully understood.

NECESSITY, SUFFICIENCY, AND NEUROIMAGING

The goal of cognitive neuroscience is to build an explanatory bridge between cognitive function and neural processing and structure, providing a description of the necessary and sufficient neural systems for a particular cognitive process along with a computational description of the neural processing performed by those systems. Functional neuroimaging plays an important role in this enterprise, by determining which brain regions exhibit differential neural activity in association with particular cognitive processes (putatively isolated by the experimental design). It must, however, be noted that neuroimaging alone cannot establish either necessity or sufficiency for particular brain regions in cognitive processing.

Necessity

Establishment of necessity requires independent manipulation of the putative causal agent. Thus, to establish that a particular neural structure or network is necessary (i.e., causal) for a particular cognitive process, one must manipulate neural processing in that region and observe the resulting effect on the cognitive process. Neuroimaging does exactly the opposite: It manipulates cognitive processes and observes the effect on neural activity.

Strict demonstration of necessity is possible only by using techniques such as transcranial magnetic stimulation (TMS) to manipulate neural processing (e.g., Kosslyn *et al.*, 1999) or by relying on nature to manipulate the brain through naturally occurring lesions (Price *et al.*, 1999). However, learning and development both provide variation in neural processing that could, in principle, be useful in the determination of necessary neural systems. For example, whereas demonstration of activation in a particular brain region during a particular cognitive process would not provide evidence of necessity, the additional demonstration that the development of that brain structure is strongly correlated with the development of that cognitive process would provide relatively strong support for the necessity of that structure. To additionally show that training on the particular cognitive process resulted in changes in activation in the neural structure of interest would provide even more evidence in favor of its necessity. Although it is not possible to conclusively demonstrate necessity using these means, they do provide additional information compared with the imaging of static adult function.

Sufficiency

In theory functional imaging could delineate the entire neural network that is sufficient for performing a particular cognitive operation, but in practice this is not possible because it requires that the imaging technique be able to identify all neural activity related to the putative process. There are several reasons that brain regions in this network can fail to be detected by functional imaging. First, current neuroimaging techniques are relatively weak (relying on relatively small changes in blood flow or oxygenation related to neural activity), and there are likely to be many regions whose activity falls outside the power of these methods. Second, some methods are intrinsically limited in imaging particular brain regions; for example, orbitofrontal cortex and lateral temporal cortex exhibit dropouts in fMRI signal due to magnetic susceptibility artifact (Ojemann *et al.*, 1997). Third, some regions may exhibit responses that are not measurable using current neuroimaging methods; for example, the neurons in a particular region may represent stimuli in terms of relative timing of spikes rather than frequency of spikes (e.g., Decharms and Merzenich, 1996), which would not change the total amount of local synaptic activity and thus would not generate a signal in fMRI or PET. Finally, some regions may exhibit constant levels of activity across a task manipulation because the cognitive process in question cannot be "turned off" during baseline conditions, an example of which is the resting-state activity outlined by Binder *et al.* (1999). Each of these issues makes it difficult to determine with certainty that one has outlined the entire neural network involved in a particular cognitive process, and it is unlikely that imaging of learning or development will provide significant leverage on these issues.

THE ROLE OF NEUROIMAGING IN COGNITIVE NEUROSCIENCE

The foregoing review and discussion makes two important main points. First, the interpretation of changes in neuroimaging data is greatly underdetermined by the data; any particular finding is open to a number of interpretations as either real or artifactual, and the data may be of little help in adjudicating between these choices. Second, neuroimaging cannot establish causality of neural structures in cognitive processing. Given these relatively pessimistic conclusions, one might ask whether neuroimaging has anything to offer to the understanding of the neural basis of cognition other than pretty pictures? I believe that neuroimaging can play two essential roles in understanding the neural basis of cognition. First, neuroimaging is an important tool for the initial discovery of relations between particular cognitive and neural processes. Indeed, most neuroimaging research to date has been directed at the discovery of such relations, rather than testing specific hypotheses about the neural basis of cognition, and the tools of neuroimaging have proven remarkably successful in this context. Although these discoveries using neuroimaging cannot support strong inferences about causal relations, they do provide important guidance for studies using other methods that can determine causality.

Second, neuroimaging can be important for testing hypotheses derived from explicit theories of the neural basis of cognition. A compelling example comes from the current controversy over the role of the fusiform gyrus in face recognition. One theory claims that part of this region is specialized for face processing (e.g., Kanwisher *et al.*, 1997), whereas another theory proposes that the same region in the fusiform is specialized for expert recognition regardless of stimulus type (e.g., Gauthier *et al.*, 1999). These theories make differential predictions about the effects of perceptual expertise on the activity of the fusiform region; the face-specific theory predicts that the region should not exhibit learning-related changes in activation for nonface objects, whereas the expert-recognition theory predicts that the region should exhibit increased activity for skilled compared with novice perception of any stimulus type. Imaging of neural plasticity has provided some evidence in favor of the expert-recognition theory. Imaging of learning with synthetic nonface objects ("Greebles") demonstrated increasing activation as subjects became experts at recognizing the objects (Gauthier *et al.*, 1999), and comparison of experts at bird or car recognition demonstrated activation of the fusiform region directly related to expertise (Gauthier *et al.*, 2000). As more explicit theories of the neural basis of cognition are developed, this kind of hypothesis-driven experimentation should become more commonplace.

SUMMARY

In this paper I have outlined a number of the conceptual and methodological issues that are involved in the study of brain plasticity using neuroimaging methods. Neuroimaging of learning and development is one of the most exciting and quickly growing areas of cognitive neuroscience, and will no doubt continue to grow as new techniques, such as optical imaging (Villringer and Chance, 1997) and diffusion tensor imaging (Klingberg *et al.*, 1999, 2000), are added to the quiver of neuroimaging methods. It is important, however, to take into account the limitations of functional neuroimaging in examining learning and development. A full understanding of the plastic brain will require the combination of neuroimaging methods with the other methods of cognitive neuroscience, such as lesion studies, TMS studies, and studies of developmental brain–behavior relationships.

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