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Functional MRI at the Crossroads

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Abstract

Since the observation of the blood oxygenation level dependent (BOLD) effect on measured MR signal in the brain, functional magnetic resonance imaging (fMRI) has rapidly become the tool of choice for exploring brain function in cognitive neuroscience. Although fMRI is an exciting and powerful means to examining the brain *in vivo*, the field has sometimes permitted itself to believe that patterns of BOLD activity reveal more than it is possible to measure given the method's spatial and temporal sampling, while concurrently not fully exploring the amount of information it provides. In this article, we examine some of the constraints on the kinds of inferences that can be supported by fMRI. We critique the concept of reverse inference that is often employed to say some cognitive function must be present given activity in a specific region. We review the consideration of functional and effective connectivity that remain infrequently applied in cognitive neuroimaging, highlighting recent thinking on the ways in which functional imaging can be used to characterize inter-regional communication. Recent advances in neuroimaging that make it possible to assess anatomical connectivity using diffusion tensor imaging (DTI) and we discuss how these may inform interpretation of fMRI results. Descriptions of fMRI studies in the media, in some instances, serve to misrepresent fMRI's capabilities. We comment on how researchers need to faithfully represent fMRI's promise and limitations in dealing with the media. Finally, as we stand at the crossroads of fMRI research, where one pathway leads toward a rigorous understanding of cognitive operations using fMRI and another leads us to a predictable collection of observations absent of clear insight, we offer our impressions of a fruitful path for future functional imaging research.

Introduction

Since the discovery of the blood oxygenation level dependent (BOLD) effect on observable MR signal in the brain (Ogawa, Tank et al. 1992; Ogawa, Lee et al. 1993; Ogawa, Menon et al. 1993) and its application to cognitive stimulation in humans (Bandettini, Wong et al. 1992; Kwong, Belliveau et al. 1992; Bandettini, Jesmanowicz et al. 1993), functional magnetic resonance imaging (fMRI) has overtaken other modalities (e.g. EEG, PET, MEG) as the predominant means for measuring cognitively-induced changes in brain activity. This is evident in the over 2000 research articles published in the year 2007 alone concerning fMRI and its applications to understanding mental operations and their disorders in diseased

populations. Early findings using fMRI and related technologies (e.g. Positron Emission Tomography (PET)) provided considerable excitement during the Decade of the Brain and proved to be one of the major success stories from this NIH-sponsored program (Rosenberg and Rowland 1990; Roberts 1991; Huerta, Koslow et al. 1993; Shepherd, Mirsky et al. 1998).

In recent years, as researchers have turned to functional imaging with the goal of obtaining increasingly detailed information about the location of cognitively-induced brain activity, technical (Brett, Johnsrude et al. 2002), statistical (Smith, Jenkinson et al. 2004), experimental (Poldrack, Fletcher et al. 2007), as well as conceptual issues (e.g. Henson 2005; Rogers, Hocking et al. 2006) have been raised concerning how to best interpret patterns of brain activity. In the neuroimaging literature, static "blobs" of activation are often interpreted as reflecting specialized, independent modules that are necessary for the associated cognitive function. In characterizing such modules, researchers often justify these structure-function associations by cataloging previous studies finding similar activation and inferring that the same cognitive function is engaged in their study. As we will discuss below, this reasoning may be problematic for a number of reasons.

It has long been appreciated that a full understanding of brain function requires characterization of both functional specialization (which highlights the specific roles played by different regions) and functional integration (which highlights how those areas work together to achieve unified brain function) (Friston, Frith et al. 1993; McIntosh and Gonzalez-Lima 1994; Horwitz, McIntosh et al. 1995; McIntosh, Cabeza et al. 1998). However, in the cognitive neuroscience literature there is a much heavier focus on the analysis of regional activation as opposed to network analyses. It is sometimes claimed that the regions activated together in a study form a "network", but without specific analysis of the relationships between regional activation, it is not possible to state that a set of regions comprises a true network, which implies causal relations between regions.

Functional imaging holds a particular appeal for the lay public as communicated to them by the popular media. Stories of brain researchers using fMRI to peer deeply into human mental processes both frightens and fascinates non-scientists — at once, evoking visions of reading one's thoughts while also providing an intriguing rationale for human character. However, such articles often fail to capture the limitations of neuroimaging techniques, perhaps speaking to a need for the media to focus on sensationalized content that sells magazines as opposed to showcasing truly innovative work revealing new understanding of brain function. Communicating fMRI research findings to the public is an important aspect of this work but one that must be undertaken carefully if the field seeks sustained respectability moving forward.

We were asked by the editor of this special issue to speculate on those aspects in functional imaging that we felt needed improvement, clarification, or called for widespread change in the culture of brain mapping as we enter the next era of cognitive neuroimaging research. We are delighted to be able to offer our thoughts. We take full responsibility for the opinions expressed here but hope that these musings are informative, thought provoking, and constructive. Many of the points we raise could form their own exhaustive review and we regret not being able to address each in greater detail. In the space we have, our intent is to point out those areas where, as we interpret and communicate the results from these intricate studies and their rich data sets to each other and to the public, we need to take greater care to not misinterpret their meaning, overextend their significance, and fail to acknowledge the limits of the techniques. We hope that this review will serve as a small step toward forging a concerted effort to buttress functional imaging against becoming trivial or formulaic in its scientific approach to studying the living brain.

In this article, we appraise the common assumption that an activated brain region is specific to and necessary for some cognitive function; the use of reverse inference as the means for deciding upon its functional specificity; and the assumption that regions that co-activate are, indeed, the most functionally correlated. We examine how fMRI results might be considered in conjunction with functional and physical connectivity information to guide our understanding of regional communication in the brain. Finally, we discuss the relationship of functional neuroimaging research, investigators, and the media - importantly, how we, as scientists, should be inviting but cautious in how we deal with the media and how we might communicate results without being drawn into wild speculation or sensationalizing the capabilities of the methodology.

Assumptions of Specificity, Necessity, and the Difficulty of Reverse Inference

The promise of early functional imaging studies has been the ability to see the brain "in action" and to infer which brain regions contribute to basic mental processes (Posner, Petersen et al. 1988). In accordance with the Donderian Pure Insertion Model (Friston, Price et al. 1996; Brett, Johnsrude et al. 2002), when there is a relative increase in BOLD activity in a region during one task condition as compared to another, this is considered evidence of that region's functional involvement in the cognitive process under examination. It is not uncommon for a researcher to suggest that this brain region is not only necessary for but also specific to that component of cognition.

Yet the common practice of assigning function to brain regions suffers from logical associations that may be flawed in their reasoning. Most neuroimaging research to date has used an approach which Henson (2006) has defined as a process of "forward inference". In this approach, task conditions are compared that differ in the engagement of some supposed mental process. Those regions that show differences in activation between those conditions are inferred to take part in that mental process. This empirical method has been remarkably successful for gaining insights into the functional characteristics of individual brain structures and forms the basis for much of the published literature in cognitive brain mapping. However, potential problems with the approach were documented even in the early days of neuroimaging (Blaxton, Zeffiro et al. 1996) and, in general, may not hold as a valid assumption (Zarahn, Aguirre et al. 1999). Specifically, since it is a correlation-based approach, it is difficult to conclude that the activated regions are necessary or sufficient for the involvement of the mental process (Poldrack 2000).

Indeed, there are well-known examples of cases in which regions that are activated during a task are not necessary for the task. For instance, the hippocampus has been found to be activated during delay classical conditioning (Gabrieli, Carrillo et al. 1995) though lesions of the hippocampus have been shown not to impair this effect (Rosenbaum, Winocur et al. 2007). At the same time, the observation of little relative BOLD activity in a region does not imply that it is not involved in processing when a task has become highly automatic or efficient (Poldrack, Sabb et al. 2005). Furthermore, in many instances, as trials are repeated, there is a systematic attenuation of the BOLD signal even in the absence of conscious awareness. Several authors attempted to capitalize on this "repetition suppression" methodologically, particularly in the domain of face processing (Ishai, Pessoa et al. 2004). Additionally, studies by Cabeza (2004) and others have demonstrated that when participants are struggling with a task, they may recruit additional regions to compensate/bolster failing processes normally carried out by critical regions, but this does not imply that the compensatory regions are necessarily required by the task. Finally, for certain patient groups, for instance, they may find a task more challenging than would a "normal" subject — so challenging that they might ultimately demonstrate reduced activity in a region typically critical for task performance and the recruitment/activation of other areas to help in the processing (Fu, Suckling et al. 2005). This

may be the case in many patient populations and might help to explain some of the reports of hypo-activity in certain brain regions that have been interpreted as a consequence of the disease, *per se*.

Thus, the demonstration of the functional necessity of a region relies upon a manipulation of the region in question which cannot be achieved with neuroimaging alone. Assigning anatomical specificity for a cognitive operation and necessity as part of a cognitive system requires evidence from corresponding, non-neuroimaging, techniques demonstrating that normal function requires that the region is healthy and intact. Techniques that permit the examination of the effects of manipulating brain anatomy and its impact on function, either indirectly through lesion studies (e.g., Molenberghs, Gillebert et al. 2008), pharmacological probes (e.g., Honey and Bullmore 2004), or directly via transcranial magnetic stimulation (TMS) (e.g., Rushworth, Hadland et al. 2002), will thus remain crucial reference points for neuroimaging studies of cognitive processes.

Increasingly common in neuroimaging is the use of BOLD activation data to infer the presence of specific mental processes, an approach known as “reverse inference” (Aguirre 2003; Poldrack 2006). This approach has been particularly common in the neuroeconomics literature, where one of the main goals has been to identify emotional contributors to decision making (Sanfey, Rilling et al. 2003). This is also present in reports from the neuropsychiatric literature in which the objective is to identify differences in functional activity that underlie clinical diagnoses. In terms of deductive logic, reverse inference reflects the logical fallacy of *affirming the consequent* (Poldrack 2006). This is the logical fallacy that suggests the IF A THEN B is a commutative process; that is IF A THEN B; B, THEREFORE A.

For instance, an author might assign a specific function to a region according to the following argument: “Smith and Jones (2004) reported that Area MT is specific to the processing of visual motion. In our study we observed that Area MT is activated during Task X. Therefore, Task X is a visual processing task.” In this case “A” supposes Area MT specificity, while “B” is the processing of visual motion. However, this does not necessarily mean that the reverse is true; that is, “B” indicating that Task X elicits MT activity, and, therefore, “A” that Task X is a task containing visual motion. This common line of reasoning is evident in many fMRI activation studies and the field must be careful not to fall victim to and propagate such logic as these errors can become cumulatively embedded into future research.

While synthetic examples of this logic might seem somewhat contrived or perhaps unrealistic, we raise this issue to demonstrate the point of reaching conclusions based upon logical fallacies. Claims similar to these are only deductively true if, and only if, the specific mental process results in activation in the region of interest. However, brain regions observed with fMRI are rarely activated by only a single mental process. Given that the goal of cognitive neuroscientists is to construct explanations rather than deductive laws, reverse inferences may provide some information even if they are not deductively valid. Recent work (Poldrack 2006) has demonstrated that the amount of information provided by reverse inference can be estimated using Bayes’ theorem with the BrainMap database (Laird, Fox et al. 2005). This approach reveals that the quantity of information is relatively low as a consequence of brain activation being rarely selective (*e.g.* regions are often activated by a wide range of mental tasks and with sometimes large task-dependent variation across individual subjects).

One of the driving questions for cognitive neuroscience is how mental function is mapped to the brain, which necessitates knowledge of the range of mental processes that exist. Such a hierarchical arrangement of concept-based knowledge is more formally known as an “ontology” (Stevens, Goble et al. 2000; Bard and Rhee 2004; Smith, Ceusters et al. 2005; Bowden, Dubach et al. 2007). To date most brain imaging research has employed concepts

from cognitive psychology to map onto the brain, but this research has shown that these concepts do not map in a one-to-one fashion to brain regions. One conclusion from this outcome is that there is no faithful one-to-one mapping of mental processes to specific brain regions; for example, specific mental processes may only emerge through the interactions of multiple brain regions (Price and Friston 2005; Poldrack 2006). Another alternative is that there is a faithful mapping of mental processes onto specific brain regions, but that our currently ontology for mental processes is incorrect. Given that much of our current thinking about mental ontologies has not changed since the 19th century, some revision in light of more recent ideas about cognition may be in order. Developing useful ontologies of cognitive processes will first necessitate a formal explication of the various mental functions, their properties, and operations. Once in place, a coherent formalization would then allow the use of powerful informatics techniques to determine which approaches fit the data best.

The reverse inference approach described above represents one informal approach to predicting mental states from neuroimaging data. However, the question of how accurately mental states can be predicted from fMRI data is increasingly being examined using pattern classification methods from the fields of statistics and machine learning (Haynes and Rees 2006). Whereas standard computational approaches examine the statistical fit of a regression model to a sample of data, pattern classification methods focus instead on the accuracy of predictions to data that were not used to estimate the model (Fukunaga 1990). This can be obtained by "cross-validation" wherein the model is fit to subsets of the data and then tested on the remainder, thereby assessing the reliability of the model for predicting the cognitive state of the subject from their pattern of activation.

The growing use of pattern classification methods first occurred in the literature on visual object recognition. In response to localizationist claims regarding the representation of specific object categories (e.g., faces or houses) in the ventral temporal cortex, several studies (Haxby, Gobbini et al. 2001; Carlson, Schrater et al. 2003; Hanson, Matsuka et al. 2004) have used pattern classification approaches to show that the class of object being perceived could be predicted from patterns of activity in the ventral temporal cortex, even when the regions most selectively activated by a specific class of objects were excluded from the analysis. More recent work has shown that visual cortical regions contain information sufficient to identify specific visual scenes (Hariri, Tessitore et al. 2002) and specific faces (Gobbini and Haxby 2007). Whereas much of the work in this area has regarded visual information processes, other recent work has shown that such approaches can also be used to detect high-level cognitive processes such as intention (Kilner and Frith 2008), lying (Davatzikos, Ruparel et al. 2005), and consciousness (Haynes and Rees 2006).

Although most work to date has focused on classification within individuals, some studies have shown that it can be possible to successfully classify mental states across individuals (Mourao-Miranda, Bokde et al. 2005). The ability to classify across individuals would provide a basis for formal reverse inference, but doing this on a large scale would require a database of activation patterns against which any particular dataset could be compared. Although such classification has been demonstrated using a handful of tasks (Poldrack, Halchenko, & Hanson, Abstract, Society for Neuroscience Annual Meeting, San Diego, November 2007), it is not known how well it would scale to a large number of potential mental states. In addition, such large-scale classification would require databases that contain whole-brain voxelwise activation patterns. The only current database containing a large enough number of studies to be useful is the BrainMap database (Laird, Lancaster et al. 2005), but the representation in this database is too impoverished to support pattern classification (i.e., it only stores the coordinates of reported peak activations, and does not store patterns for individual subjects).

Measuring Functional Integration in Neuroimaging

The collection of regions whose above threshold activity results in a spatially distributed arrangement of significant relative change in BOLD are referred to by some as forming the network responsible for a given cognitive operation. This presumes that these areas are themselves physically or, at least functionally connected. However, it is well known that correlations between activation of different regions can occur even when those areas have no causal influence on one another (e.g., when both are being driven by a common third region). There is a wide range of methods available for the analysis of functional integration, which is usually broken into two classes (Friston, 1994). *Functional connectivity* analysis refers to techniques that examine the correlational structure of activity across voxels. This includes multivariate decomposition methods (such as principal components analysis and independent components analysis) as well as simpler methods involving correlation with seed regions. What is common amongst functional connectivity approaches is that they are exploratory and do not require a prior anatomical model; however, they also cannot support inferences regarding the causal relations of brain regions. Another set of methods, referred to as *effective connectivity*, are designed to test hypotheses regarding the causal influence of regions on one another. These models, which include path analysis, structural equation modeling, and dynamic causal modeling, require a prior anatomical model and are generally limited to a small set of regions.

Horwitz (2003) has argued that the conceptual formulations of functional and effective connectivity are far from clear. Specifically, the terms functional and effective connectivity are applied to quantities computed on types of functional imaging data (e.g., PET, fMRI, EEG) that vary in spatial, temporal, and other features, using different definitions (even for data of the same modality) and employing different computational algorithms. The more explicit concept of Effective Connectivity refers explicitly to the influence that one neural system exerts over another, either at a synaptic (*i.e.*, synaptic efficacy) or population level (Horwitz, Warner et al. 2005). Effective Connectivity is a dynamic process, *i.e.*, activity- and time-dependent, and (b) it depends upon having a model of region-wise interactions. Until it is understood in better detail how effective connectivity at the neuronal level is reflected in neuroimaging signals, comparisons of functional and/or effective connectivity across studies may appear inconsistent and should be performed with caution.

A large body of work in the last twenty years has focused on the characterization of structure in complex networks such as social networks. Building on a number of fields including graph theory, social psychology, and statistical physics, this approach has been highly successful in describing the features of a broad range of complex networks (Newman 2003). In particular, this work has shown that many real-world networks (from the World Wide Web to the *C. elegans* nervous system) exhibit “scale-free” properties, meaning that the connectivity of individual nodes decreases by a power law, such that there is a small number of highly connected nodes (“hubs”) each of which is also densely connected to its local neighbors. These networks exhibit “small world” characteristics (i.e. the “Six Degrees of Separation” phenomenon), such that the distance between any two nodes in the network is relatively small due to the presence of these hubs. Recent work has shown that both structural brain anatomy (Stephan, Hilgetag et al. 2000) and whole brain systems (Sporns, Chialvo et al. 2004) can be characterized as scale-free or small-world networks. This is an attractive conceptual framework for the organization of brain anatomical and functional networks because a small-world topology can support both segregated/specialized and distributed/integrated information processing (Bassett and Bullmore 2006). Moreover, small-world networks are economical, tending to minimize “wiring costs” while supporting high dynamical complexity (Achard and Bullmore 2007), and also appear to be amongst the most robust class of networks in the face of damage (Kaiser, Martin et al. 2007). However, the contributions of brain atlas registration errors to the voxelwise variance in these approaches is often not examined, though could be

addressed using manual region-of-interest style approaches to support conclusions drawn on registered data sets. Nevertheless, we are convinced that analysis methods based on these complex network modeling methods have great potential to better bridge the gap between functional specialization and functional integration in neuroimaging.

fMRI and the Emergence of Diffusion Weighted Imaging

Understanding brain function in terms of its connected architecture is a developing goal within the field of neuroimaging. However, direct investigation of the influence of brain circuitry on function has been hindered by the lack of a technique for exploring anatomical connectivity in the *in vivo* brain. Recent advances in MR diffusion imaging have given scientists access to data relating to local white matter architecture and, for the first time, have raised the possibility of in vivo investigations into brain circuitry. Use of this technology may reframe how we interpret the location of functional regions in the brain that will, furthermore, enable us to more carefully interpret individual differences in these patterns that may result from differences in cognitive strategies (Van Horn, Grafton et al. 2008). Establishing a direct relationship between regional boundaries based on diffusion imaging and borders between regions that perform different functions would not only be of great significance when interpreting functional results, but would also provide a first step towards the validation of diffusion-based anatomical connectivity studies (Upadhyay, Ducros et al. 2007).

Diffusion tensor imaging (DTI) has emerged over the past several years as an exciting way to measure, model, and explore the white matter pathways in the living brain. The approach is based on the notion that the diffusion of water molecules occurs more easily parallel to but is reduced perpendicular to densely arranged white matter fibers (Basser and Jones 2002). In diffusion weighted imaging, multiple magnetic field gradient directions are applied in a sequence of image volume acquisitions in which it is possibl to detect the magnitude of water diffusivity in each orientation. These image volumes are then systematically combined to determine the degree and preferred directionality of diffusion (Pierpaoli, Jezzard et al. 1996) and from these measurements provide a means for assessing white matter integrity (Assaf and Pasternak 2008). From this diffusion orientation information it is then possible to extract streamlines that are representative of the underlying white matter fiber tracts and to render and explore them using 3D graphical rendering software (Basser, Pajevic et al. 2000). Using a very large set of gradient directions permits even finer assessment of crossing fiber tracts and tract complexity (Chiang, Barysheva et al. 2008). DTI has now been widely applied in studies of normal subjects (Catani, Jones et al. 2005), Mild Cognitive Impairment and Alzheimer's Disease (Medina, Detoledo-Morrell et al. 2005), schizophrenia (Nakamura, McCarley et al. 2005), as well as other neuropsychiatric populations (Kubicki, Westin et al. 2002; Lim and Helpern 2002).

However, only recently have we begun to see how one MR modality can be used to inform the other. A study by Baird and coworkers (2005) combined fMRI and DTI to explore individual differences on a task that required the recognition of objects presented from unusual viewpoints. This task was chosen based on previous work that has established the necessity of information transfer from the right parietal cortex to the left inferior cortex for its successful completion. They measured reaction times to localize regions of cortical activity in the superior parietal and inferior frontal regions that were more active with longer response times. These regions were then sampled, and their signal change used to predict individual differences in structural integrity of white matter in the corpus callosum as assessed by white matter fractional anisotropy (FA). Results indicated that shorter RTs (and associated increases in BOLD response) were associated with increased FA (presumed to reflect greater white matter organization) in the splenium of the corpus callosum, whereas longer RTs were associated with increased FA in the genu. These results demonstrated that where multiple pathways exist

between regions or hemispheres, depending on the type of stimulus requiring processing, the routing of neural signals may take preferred pathways.

Still other work has matched functional and anatomical information using motor fMRI and white matter tractography inferred from DTI. Guye and colleagues (2003) performed coregistered DTI and motor task fMRI in healthy subjects and in one patient presenting with a left precentral tumor. They defined 3D connectivity maps within the whole brain, from seed points selected in the white matter adjacent to the location of the maximum of fMRI activation. Their results demonstrated, in all control subjects, strong connections from M1 to pyramidal tracts, premotor areas, parietal cortices, thalamus, and cerebellum. M1 connectivity in controls was asymmetric, being more extensive in the dominant hemisphere. The patient showed extensive differences in M1 connectivity as compared to the control group. Their study demonstrated the utility of leveraging both fMRI and DTI for use in measuring white matter pathway trajectories and how clinically relevant information can be extracted.

Communication of Research Results and Interactions with the Media

In the majority of published neuroimaging studies, full interpretation of patterns of BOLD activity and regional connectivity are difficult to convey in the space permitted. An understanding of how fMRI studies are typically conducted and the limitations of the BOLD technique are frequently assumed, having been discussed by others elsewhere or simply understood by other workers in the field. The popular press and news media, always on the watch for the latest developments in brain research, offers researchers the chance to expound on their findings and point out their larger implications to a lay audience.

With the media attempting to attract readership using provocative headlines but having their own limits of column length, reporters will tend to maximize speculation on the meaning of the findings while minimizing the details of how they were obtained. This can lead to gross misrepresentations of the underlying science and faulty impressions of what the technology can deliver. For instance, while the original studies represent novel applications of the fMRI technology (Fisher, Aron et al. 2006; Savic and Lindstrom 2008), headlines such as “Gay Men, Straight Women Have Similar Brains” (*Washington Post*, June 16, 2008) or “Loving with all your … brain” (*CNN*, February 15, 2007), may in fact detract from the neuroscience of gender differences, sexuality, and emotion by playing into Hollywood’s fascination with the titillating extremes of sex and interpersonal relationships.

Researchers can find their interactions with the media personally flattering and useful for spreading the word about their latest study. Moreover, making science more accessible to a lay audience is one of the greatest services that a scientist can perform. Yet having one’s research mentioned in the press or on television is not the same as its being described in the peer reviewed literature. In one recent example, an article in the op-ed page of the New York Times presented fMRI results concerning brain activation patterns of potential voters when viewing pictures of each of the then-current US presidential candidates (“This Is Your Brain on Politics”, *New York Times*, November 11, 2007). The outcry to this article, both by fellow scientists and other writers in the media, should serve as an example of how such attempts are likely to backfire on the authors, but it is up to the field to continue its insistence on careful presentation of imaging results in the press (Poldrack 2008).

The ways in which functional imaging is portrayed in the media have been addressed by Racine and colleagues (2005), who have expressed concern that fMRI researchers and the media have not done a good job presenting neuroimaging findings and their limitations to a mass audience. In what they term “neuro-realism” people believe that what is seen in the brain makes behavioral interpretations more real. In this way, findings concerning brain function tend to

get amplified when they appear in the press. However, in many cases the take home message is something that one didn't need fMRI to discover in the first place (e.g. "males responded positively to pictures of exotic automobiles, while females tended to be indifferent about them", etc.). Where irresponsible interactions with the media occur they can have clear negative effects. Non-scientist government leaders and other decision makers who determine the allocation of research funding may be alarmed to read such headlines and concerned indeed when they read pundits suggesting that human brain imaging is the stuff of hucksterism, false claims, or miracle cures (e.g. "Brain scans, the new snake oil", *Los Angeles Times*, December 11, 2007).

A solution for how the media and fMRI scientists might better communicate is multi-factorial. On the side of the media, newspapers and broadcasters might make a concerted effort to employ more people who have degrees in science, engineering, and mathematics in addition to journalism. This might help members of the media be more critical of what they are writing and be better able to express the limitations of the research being featured. Likewise, brain scientists and researcher should be encouraged to undertake media training at their local institutions to help them understand the audience that the media is trying to reach and the media's motivations and intentions for reporting on scientific outcomes. Finally, major scientific societies, such as the *Society for Neuroscience* (www.sfn.org) and the *International Organization of Psychophysiology* (www.world-psychophysiology.org), might consider hosting frequent round table dialogues between science, media, and policy leaders that serve to educate each other about the limits of these exciting technologies but what promise they may hold for understanding the brain and mind.

Discussion

As we enter the next era of human brain mapping, a greater awareness is settling in that the honeymoon period for fMRI is now over. It is not enough to simply gather data to see "what lights up" any longer. Rather, the field has recognized that we must now move beyond activation and toward predictive models of brain function that incorporate behavioral as well as regional interactions into comprehensive but testable models of brain function. Such approaches necessitate and will require concepts new to the neuroimaging community, for instance, coming from theories that are used to describe the architecture of communication and signal transmission in complex networks (Proakis and Salehi 1994), as well as taking into account brain metabolism and electrical activity.

To make such approaches maximally effective, it will be necessary to truly combine data from multiple modalities. By this we mean going several steps further than simply spatially co-registering fMRI and DTI images or computing the correlations between strategically placed seed voxels. We envision a conscientious movement toward a model in which scans of cortical anatomy, white matter integrity, BOLD functional activity, MRS, and possibly PET are all blended to better understand how the effects of functional signal change in one cortical region affect the properties of signal in another over white matter pathways. While each modality by itself will still be the source of many more research articles, we believe that those examinations in which the amount of available information available from multiple neuroimaging sources is taken to its fullest advantage will enable cognitive neuroimaging to properly consider how function and form interact to give rise to cognitive processes.

Other studies, too, will examine the effects of alterations of connectivity and their effects on the brain in damage or disease. For instance, schizophrenic subjects have previously been noted for showing relatively less activity in dorso-lateral prefrontal cortices as compared to control subjects (Weinberger and Berman 1996). These findings have been reported in both PET as well as in fMRI examinations. The question arises as to whether these subjects have reduced

working memory related activity or an over activity during the paired sensorimotor task condition. Conversely, the activity in these regions may simply be reduced overall in these subjects. However, alterations of the underlying white matter connectivity between these and other regions may mean that afferent signals are not getting through to the DLPFC as they should and this may degrade working memory task performance. One approach to this issue is more careful examination of double dissociations between external variables and pattern of brain activity — an approach which has become a cornerstone for brain lesion research (Neininger and Pulvermuller 2003; Mitchell and Dalrymple-Alford 2006; Ng, Noblejas et al. 2007) and may be suitable for fMRI as well. Rather than claiming to have the answer to these questions, we simply wish to note that it will not be through the application of a single imaging modality that will get to the heart of these questions but will require an empirical and multimodal approach that carefully integrates the data into a coherent explanation for phenomena such as schizophrenic hypofrontality.

Pharmacological manipulations can also serve as probes of cognitive function. Drugs such as amphetamines have been observed to enhance and focus activity in frontal regions (Mattay, Callicott et al. 2000) whereas alcohol (EtOH) serves to suppress activity in cerebellar nuclei (Van Horn, Yanos et al. 2006). Subtle manipulations of these and other drugs during fMRI has been termed pharmacological fMRI or more colloquially “phMRI” (Honey and Bullmore 2004). These studies can be important for assessing how the effects of a drug results in an alteration of the normal magnitude and extent of brain activity as compared to placebo across a range of clinical samples as well as practical applications.

With the ability to obtain genetic information with relative ease from only a saliva sample, the next era of neuroimaging will see an increase in the number of fMRI studies examining the role of various allelic gene variants on patterns of BOLD signal. Studies of Catechol-O-methyl transferase (COMT)-related gene variants have shown that this gene plays a role in working memory and may underlie a predisposition to dopaminergic dysfunction in schizophrenia (Shirts and Nimgaonkar 2004). In an event-related fMRI task dissociating component numerical WM sub-processes (Tan, Chen et al. 2007), baseline numerical size comparison engaged ventrolateral prefrontal cortical activation that correlated with COMT Val-allele load (COMT Val>Met), while performing arithmetic transformations further engaged this genotype effect in dorsolateral prefrontal cortex (DLPFC), as well as in parietal and striatal regions, disproportionately engaging greater COMT Val>Met effects only at DLPFC. COMT Val>Met effects were also observed in DLPFC during encoding of new information into WM, but not during subsequent retrieval. Thus, temporal updating operations, but less so the retrieval of already encoded representations, engaged relatively specific dopaminergic tuning at the DLPFC. These findings add to the integration of dopaminergic signaling in basic cortical assemblies with their roles in specific human brain networks during the orchestration of information processing in working memory. In our view, genomic neuroimaging studies such as these hold a considerable amount of promise for exploring the scale and scope of specific genetic effects on brain activity. The functional aspects of neuroimaging can be expected to provide considerable evidence for the functional role of genes that express themselves in the brain. However, it is important to recognize that the analysis of genetic associations is fraught with its own set of difficulties and pitfalls (Chanock and Thomas 2007) and that neuroimaging researchers must make themselves aware of these issues (see van Haren, Bakker et al. 2008, for considerations in structural imaging of clinical samples).

Finally, given the ubiquity of the internet as a medium for the sharing of data, resources, and ideas the next era of human brain mapping research will depend heavily on domestic and international collaborative efforts that leverage the transmission of digital information. Such efforts will be important for cross-cultural studies of cognitive processes, the sharing of compute resources, and for learning what researchers and colleagues in other areas of the globe

are learning about brain function. The construction and maintenance of comprehensive databases of primary research data, too, will promote the re-purposing of published data to examine alternative hypotheses, be examined using novel techniques, and combined with data from other studies (Van Horn and Ishai 2007). Neuroscientists and biologists can work together to link their respective resources to form larger, richer collaborations for information exchange pertaining to brain function and that will be essential for the training of the next generation of neuroscience researchers.

Functional neuroimaging research is stronger and more widespread than ever before and we expect its prominence to increase further with many new and interesting results in the coming years. The diversity of applications to brain function is boundless and the richness of the data capable of contributing to multiple domains of research. Yet, we must be careful to ask questions that avoid predictable interpretation but scientifically and clinically relevant questions whose answers lead to new knowledge about brain function. Cautious interpretation and reporting of findings in the peer reviewed literature is critical if the field is to maintain respectability. In the end, researchers in the field will then need to carefully but precisely communicate their research results in these areas to the public and to those who support and fund the research. As we take our next steps down the road of human functional imaging we can are confident that with careful understanding and communication of results, that path will be smooth and we can arrive at fruitful scientific destinations.

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