Polishing the Windows of the Mind

The refinement of noninvasive functional imaging tools represents one of the most remarkable advances in psychiatric research over the past decade. These tools include functional magnetic resonance imaging (fMRI), event-related potentials, and magnetic encephalography, each of which measures activity in the living, working human brain. Advances in these techniques have occurred in parallel with an explosion in knowledge from basic cognitive and affective neuroscience that provides the necessary context for understanding brain function in mental disorders. The relatively widespread availability of imaging facilities and the standardization of data analytic approaches have brought neuroimaging front and center in such diverse psychiatric fields as nosology, genetics, and therapeutics. During this period, the *Journal* has provided considerable leadership in bringing high-quality clinical imaging studies to the psychiatric literature. Much also has been learned about the unique issues that can complicate the interpretation of results from functional imaging research on clinical disorders. The purpose of this editorial is to bring key issues into focus because they are considered when manuscripts are evaluated for publication in the *Journal*. These issues concern most centrally the role of behavioral data relevant to specific psychological theories in imaging experiments and standardization in data analytic approaches. We focus explicitly on studies examining the engagement of the brain during cognitive-affective processes, as typically probed with fMRI, event-related potentials, and magnetic encephalography.

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In the early days of cognitive-affective imaging, studies tended to be exploratory, based perhaps on the observed sensitivity of a particular psychological task-to-group difference in task performance. Current cognitive-affective imaging studies are most informative when they test a hypothesis framed by a specific theory positing relationships among three factors:

1. A between-subject variable, such as a disorder, a risk for a disorder, or a specific genetic polymorphism
2. A specific psychological process, as either directly measured or indirectly inferred, during a psychological task
3. Dysfunctional engagement of a specific neural circuit during task performance

This is most usefully accomplished when the study presents converging data in all three domains as they relate directly to the theory under investigation.

Because such converging data are difficult to obtain, few cogent examples exist in the literature. Typically, data have emerged in stages, with major theoretical perspectives stimulating the initial standardization of paradigms, which then have been refined for use in experimental laboratory-based studies. Finally, laboratory studies typically have led to neuroimaging research, in both healthy individuals and individuals with illnesses, that further refines experimental paradigms. Such refinements capitalize on emerging understandings of relationships between specific psychological processes engaged by the relevant task and functioning in specific brain structures.

Perhaps the most compelling example of a clinical research framework demonstrating this progression emerges in dementia, where studies benefit from the availability of rich data in human postmortem, rodent, and nonhuman primate research. Major the-

ories ascribe a key role for medial temporal lobe structures in declarative memory formation, based initially on clinical observations of amnesia after medial temporal lobe injury (1). Experimental paradigms implemented through the 1990s directly observed memory formation, first in the laboratory and then in the scanner, to test the hypothesis that memory encoding is associated with medial temporal lobe engagement. After generating evidence to support this hypothesis (2), clinical investigators have begun to use memory-encoding paradigms to identify without dementia individuals; who face a high risk for developing dementia (3).

It is important to note that the theoretical framework for this research on memory function and dementia did not need to be developed de novo; an established model from cognitive neuroscience was applied with great success. We believe that the appropriate use of established tools and models from the basic behavioral sciences and cognitive-affective neuroscience should be considered an important strength in clinical neuroimaging research.

Since the inception of cognitive-affective imaging, a particular challenge has been interpreting imaging findings in light of behavioral data. For example, many imaging studies assess perturbed neural engagement in the context of abnormal behavioral performance on a disorder-relevant task. With this approach, group differences in brain activity might be attributed to artifacts of psychological processes, such as reduced motivation, only secondarily related to the condition of interest. One approach to handling this confounder is to match groups on behavioral performance, either by providing differential amounts of task practice to each group or by selecting a priori groups to be matched. With this approach, a theory must be advanced in which no between-group differences in performance are expected in the context of between-group differences in neural activation. For example, one model of prefrontal cortical dysfunction in schizophrenia has hypothesized that risk for schizophrenia is reflected in a pattern of altered efficiency of prefrontal cortical activation in the context of normal working memory performance (4).

Alternative approaches attempt to design studies so that between-group differences in behavioral performance are captured while there is control for possible confounders created by performance differences. For example, studies using event-related designs have relied on tasks that engage a relevant cognitive system and provide behavioral evidence of impairment, but they restrict the analysis to correct responses. This ensures that subjects are "on task" while providing converging behavioral evidence that the cognitive system of interest is affected in the group being studied (5). Similarly, event-related designs can include a parametric manipulation in which task difficulty can systematically vary. This affords the opportunity to examine between-group differences in brain engagement during successful task performance across varying levels of difficulty. Regardless of the specific approach, these and other scenarios use imaging to test specific theory-driven hypotheses on relationships among a between-subject factor, behavior observed in the scanner, and engagement of a specific neural circuit.

Beyond these major issues concerning the role of behavioral data in imaging research, other issues also needing to be addressed in functional imaging studies concern standardization of data analytic approaches. On statistical grounds, imaging studies present a particular problem of multiple comparisons when activity in tens of thousands of voxels across the brain is tested for statistical significance. The range of established statistical methods that appropriately strike the balance between type I and type II error should be judiciously used in a principled manner. A critical related issue concerns statistical power to test hypotheses. Power should be explicitly considered when a study is designed, both in terms of task-design features, which ensure that sufficient data are collected for the relevant psychological processes, and in terms of subject selection features, in which studies typically require at least 12 subjects per group. It has also become standard in imaging studies, as in other fields in the biological and social

sciences, to use random effects statistical models that allow inference to the population level.

Data analytic issues also extend to principles of data presentation, namely, while overlaid "blobs" of group differences are informative regarding topography, functional imaging data are much more informative when time series or parameter estimates for each condition in each group are displayed for key brain regions. This presentation allows the reader to visualize the pattern of brain activity across different experimental conditions that might be accounting for group differences and to relate the findings of the study to the broader, basic cognitive, and affective neuroscience literature.

There is little doubt that functional imaging studies will become an increasingly fundamental part of our clinical neuroscience armamentarium, useful for understanding the nature of cognitive-affective deficits in disorders, the mechanisms of treatment effects, and the locus of functional expression of risk genes. The implementation of cognitive-affective imaging extends a wealth of other research in neuroscience that attempts to understand person-specific differences in behavior based on person-specific aspects of information processing. Given this perspective, it will be vital to focus attention equally on methods for the processing of brain imaging data as well as on the methods for elicitation of relevant information processing abilities in the scanner, in the laboratory, and potentially in the clinic. Through such focus, modern methods from neuroscience may ultimately be brought to bear on clinical questions that have traditionally been difficult to evaluate from the perspective of neuroscience. This includes questions relevant to the boundaries of some of our more challenging disorders, particularly developmental disorders, as well as questions relevant to early diagnosis, risk prediction, and the mechanisms of treatment. The *Journal* will play an important role in communicating these developments, which will meet the highest standards of innovation and experimental rigor, to our readers in the coming years.

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