

Functional Brain Imaging: Twenty-First Century Phrenology or Psychobiological Advance for the Millennium?

For those of us interested in neurochemical pathology of the major neuropsychiatric disorders—including schizophrenia, affective disorders, Alzheimer's disease and other dementias, and the addictions—the last several years have witnessed a marked paradigm shift. From reliance on animal models of psychopathology with all of their shortcomings (1) to the neuroendocrine window strategy with its pitfalls (2) to post-mortem studies with their inherent difficulties (3), the field has evolved to the use of multidisciplinary techniques, of which functional brain imaging represents one of the most promising yet least understood. This issue of the *Journal* contains three reports of research that used two functional brain imaging techniques, positron emission tomography (PET) and magnetic resonance spectroscopy (MRS). These two techniques, together with functional magnetic resonance imaging (MRI) and single photon emission computed tomography (SPECT), constitute the “big four” of functional brain imaging modalities most commonly used today. Below we briefly review the strengths and weaknesses of each of these techniques, their great promise for research in psychiatry, and how the reports contained in this issue advance their respective fields.

PET and the related SPECT represent planar radiometric functional imaging techniques. Both use the intravenous or inhalational administration of radiopharmaceuticals and detectors specialized for localizing photons (gamma rays) emitted by positron annihilation to support neurophysiologic, neuroreceptor, and neurochemical imaging. Neurophysiologic imaging refers to the use of cerebral blood flow radiotracers ($^{15}\text{OH}_2$, [^{15}O]butanol, C^{15}O_2 , ^{133}Xe , [$^{99\text{m}}\text{Tc}$]HMPAO) or metabolic radiotracers ([^{18}F]fluorodeoxyglucose) to spatially resolve the hemodynamic and metabolic correlates of neural circuit activity. The metabolic costs of synaptic transmission are high and relate largely to adenosine triphosphate (ATP) consumption in support of the ion pump activity that drives sodium and potassium gradients across neuronal membranes. Functional imaging of brain activity using PET or SPECT actually involves the localization of changes in oxygen and glucose utilization for ATP synthesis by oxidative glycolysis, which is correlated very highly with neuronal activity. Neuroreceptor imaging refers to the use of PET or SPECT radionuclides bound to ligands possessing a high and selective affinity for neurotransmitter receptors or transporters. Tracer kinetic models are used to convert local positron annihilations into estimates of receptor or transporter density, distribution, or occupancy. Neurochemical imaging refers to the use of PET or SPECT radionuclides bound to precursors (e.g., DOPA) of enzymatic reactions that support neurotransmitter synthesis.

Functional MRI refers to a variant of MRI that is sensitive to local changes in deoxyhemoglobin concentration. Because the regional blood flow increase associated with neuronal activity apparently surpasses the oxygen consumption, this results in an apparent *decrease* in deoxyhemoglobin. In the 1930s, Linus Pauling observed that the quantity of oxygen carried by hemoglobin is inversely proportional to the degree to which it perturbs a magnetic field. This property of differential paramagnetism was finally demonstrated in vivo in the late 1980s, and functional MRI was introduced (4, 5).

At present only functional MRI measures relative neural activity, whereas PET can provide either absolute or relative measures; many investigators study only relative

flow with PET to enhance ease of use. Consequently, neuroimaging experiments must be designed to quantify relative changes in activity. But relative to what? The most commonly used approach, subtractive mapping, extends an idea proposed more than 130 years ago. Franciscus Donders, a Dutch physiologist, proposed a method to study specific cognitive processes (6). Armed only with subjects' response times, he suggested that longer response times represented added mental processing. He subtracted the time to respond to any light from the time needed to respond to a particular colored light. He concluded that this difference, about 50 msec, represented the time to process color. One can easily imagine this exact experiment being repeated in either a PET or a functional MRI scanner, and instead of subtracting response times, subtracting brain activity maps.

The subtractive approach to neuroimaging has been used with great success over the past 10 years. The assumption is that levels of "brain activity" are additive in a linear fashion. Undoubtedly, this is not the case, but it is not yet clear under what circumstances it is a reasonable approximation. A second, and potentially more problematic, assumption is that cognitive processes are additive. Also referred to as the "pure insertion" hypothesis, this assumes that the addition of another cognitive process does not alter the original one.

Given the uncertainty in these assumptions, it is surprising that such impressive imaging results have been obtained at all. One might argue that because subtractive designs do work, the assumptions have not been disproved. Indeed, we see three imaging articles in this issue, each incrementally advancing the understanding of a particular aspect of mental illness. Each of these articles identifies state changes in the CNS of particular groups of subjects. Neuroimaging offers a powerful probe of brain state, but we are now faced with metaphysical questions; i.e., what is a brain state, and how is it related to the outward manifestations of behavior? This has the potential for degenerating into the old mind-body duality of Descartes, but it is really far more complex than such dichotomous models. Neuroimaging allows the identification of brain regions in which activity is correlated with some external baseline or outcome measure (e.g., Hamilton Depression Rating Scale score, cocaine use, antidepressant treatment). Whether a causal relationship exists remains obscure. How does this pattern of brain activity *result* in behavior X? This is the "hard" problem of brain imaging, and one for the twenty-first century.

Functional brain imaging techniques bridge the gap between neural systems and behavioral neurosciences. In doing so they provide novel and powerful insights into the changes in regionally distributed brain activity that underlie normal and abnormal behavior. The three reports that are the focus of this editorial are excellent examples of the breadth and depth of the evolving impact of such techniques on the field of biological psychiatry.

Chang and colleagues, using MRS, measured the frontal lobe concentrations of *N*-acetylaspartate in gray matter, a putative marker of glia integrity, and myoinositol in white matter, a putative marker of glia activation, in 64 young, asymptomatic, abstinent long-term cocaine abusers and 58 healthy comparison subjects. The abstinent cocaine users exhibited significant decreases in frontal lobe *N*-acetylaspartate and increases in myoinositol concentrations, indications of neuronal loss and glial infiltration, respectively, in those subjects. Such a study obviously has important implications for the persistent untoward neurobiological consequences of cocaine abuse. Previously, such data could only have been obtained by study of postmortem tissue or the rarely used method of brain biopsy. Of course, the technique has its limitations. We are, for example, not able to identify the neurons that are affected by long-term cocaine administration—are they dopaminergic, somatostatinergic, glutamatergic, GABA-ergic? These investigators also identified gender differences in cocaine-induced brain injury, which might underlie the increasingly recognized need for gender differences in addiction treatment strategies.

The two PET studies, by Mayberg et al. and Smith et al., both used glucose utilization, although the former study also used [^{15}O]water to measure regional cerebral blood flow as an index of neuroactivation. Both studies represent incremental advances in the neurobiology of affective disorders. The Mayberg et al. study is of particular interest for several reasons. First, it provides novel evidence that the brain regions that exhibit changes in activity after provocation of sadness in healthy volunteers are the very same that show opposite changes when depressed patients exhibit clinical recovery after fluoxetine treatment. Second, the circuits identified in both experiments were limbic and cortical sites previously posited to regulate affect, including neocortical and limbic areas (e.g., right dorsolateral prefrontal and inferior parietal cortices and subgenual cingulate and anterior insula regions). Finally, the cingulate-prefrontal circuit model of mood regulation offers a plausible converging point for the separate antidepressant effects of medication, cognitive behavioral, and psychosurgical treatments. Smith and colleagues sought to determine whether total sleep deprivation—a technique demonstrated to result in a rapid, but short-lived, antidepressant effect—combined with paroxetine, a selective serotonin reuptake inhibitor antidepressant, in elderly depressed patients and matched normal comparison subjects provided persistent reductions in glucose utilization in the anterior cingulate cortex, an effect observed after long-term paroxetine treatment. In this study, PET studies were obtained at baseline, after total sleep deprivation, after recovery sleep, and after 2 weeks of paroxetine treatment (patients only). Persistent reductions in glucose metabolism in the anterior cingulate cortex did occur in the depressed patients; no such effects were observed in the comparison subjects. The results suggest that in the depressed patients, improvement in depressive symptom severity associated with the combined treatment was, indeed, associated with reductions in glucose utilization in the right anterior cingulate cortex.

These studies, taken together, indicate that functional brain imaging methods are powerful tools in helping to answer hypothesis-driven investigations of neurochemical pathology, psychobiology, and treatment response in psychiatric disorders. There are also risks and limitations: statistical analysis of data from multiple brain regions in a limited number of subjects with the use of multiple comparisons in the absence of priori hypotheses can potentially result in both false positive and false negative findings that may redirect the field in spurious directions. Like the tools of molecular biology, functional brain imaging techniques represent powerful methods that, when used in conjunction with solid basic neuroscience, have much to contribute to the outstanding questions in our field.

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