EDITORIAL

Defining the Neural Circuitry of Depression: Toward a New Nosology With Therapeutic Implications

Defining structural, functional, and chemical abnormalities with in vivo neuroimaging methods has been a mainstay of depression research for more than 20 years (reviewed in Drevets 2000; Mayberg 2003). Recent studies have both replicated and extended previous findings by capitalizing on advances in imaging physics, analytic strategies, and the growing ease of acquiring complementary structural and functional studies in the same individual. The field has further matured to now emphasize more than just individual regions but also their organization within integrated pathways and distributed neural networks (Anand *et al.* 2005; Drevets 1999; Mayberg 1997; Seminowicz *et al.* 2004).

This strategy starts with the assumption that depression is unlikely a disease of a single gene, brain region, or neurotransmitter system (Manji *et al.* 2001; Nestler *et al.* 2002). Rather, the syndrome is conceptualized as a systems disorder with a depressive episode viewed as the net effect of failed network regulation under circumstances of cognitive, emotional, or somatic stress (Mayberg 2003). Even in the absence of specific pathogenetic mechanisms mediating such dysfunction, the current state of the "network" can be characterized with complementary functional and structural imaging approaches. Differential modulation of the defined "network" by various treatments can also be evaluated, adding a new perspective to understanding mechanisms mediating clinical response and remission. Variability in baseline or change patterns can be further evaluated against known clinical phenotypes. Such a model does not dismiss the critical contribution of genetic, neurochemical, or environmental factors but rather provides a potential brain-based framework to systematically examine their interactions.

Neural interactions, defined broadly, refer to the way in which different elements or components within the central and peripheral nervous system influence one another. This can involve activity at a single synapse or ensembles of neurons working in concert to mediate local and widespread processes (Lee *et al.* 2003). With imaging data, the examination of neural interactions emphasizes not the absolute change in activity occurring between groups or within individuals with an acute or chronic change in state but, rather, the way in which activity changes in different locations influence one another. Several different approaches have been adopted to quantify these interactions with functional imaging data (Horwitz *et al.* 2000; McIntosh and Loblaw 2004; Peltier *et al.* 2003; Zuendorf *et al.* 2003), and most involve the measurement of pairwise interactions, usually with correlations or covariances. This approach is now commonly termed "functional connectivity" (Arfanakis *et al.* 2000; Friston 1994). An advantage of the functional connectivity strategy over past approaches is that it can be performed with or without a specified model or hypothesis (i.e., data driven), meaning that patterns of maximum covariance can be extracted with minimal constraints. The versatility of these methods also allows systematic testing of theoretical models informed by complementary imaging and preclinical information (Carmichael and Price 1996; Haber *et al.* 2000; Vogt and Pandya 1987).

Such a conceptual shift might seem unnecessary given the converging findings across many studies demonstrating the involvement of a consistent set of limbic and cortical regions in both unipolar and bipolar depression as well as replicable change patterns with various treatments (reviewed in Drevets 2000; Mayberg 2003). Nonetheless, there is a certain sense of urgency to further define subtleties of abnormal brain function in these patients, fueled in part by the emerging consensus that current classification schemes are inadequate to characterize biological heterogeneity inherent in these disorders and converging evidence that available treatments leave many depressed patients with residual symptoms that place them at increased risk for relapse or recurrence. As such, delineation of brain-based illness models defined with a combination of imaging methods and informed by post-mortem studies and animal models (Nestler *et al.* 2002; Rajkowska 2003) is seen as a promising strategy for redefining our depression nosology, with additional opportunities for developing algorithms that might guide treatment selection in individual patients.

Imaging-based diagnostic tests are routinely used in the clinical management of many medical illnesses. In ischemic heart disease, for example, evaluation of the integrity and caliber of the coronary arteries combined with tests of myocardial function are critical determinants of the interventional strategy initiated after the diagnosis of an acute myocardial infarction (Antman *et al.* 2004). The decision by a cardiologist to treat medically or surgically is neither arbitrary nor conciliatory. Rather, it is based on objective measurements of the primary organ of interest considered in context of other contributing risk factors, including genetics, comorbid medical conditions (i.e., hypertension, diabetes, hyperlipidemia), life-style factors (smoking, diet, exercise), and past cardiac problems. Currently, no such comparable biological algorithms exist for treating a major depressive episode nor are there biomarkers that can even reliably distinguish a unipolar depression from a first presentation of depression in bipolar disorder (American Psychiatric Association 2000). In prioritizing a role for direct measures of brain functioning in the development of new algorithms for diagnosis and management of depressed patients, a systematic characterization of pretreatment patterns predictive of unambiguous remission to standard treatments is a necessary first step. Short term, this approach aims to identify brain biomarkers that can predict which patients are likely (or unlikely) to remit to a given first-line intervention. Long-term similar approaches might also identify which patients are vulnerable to relapse or recurrence during continuation or maintenance treatments as well as define endophenotypes that predict illness vulnerability and resilience (Pezawas *et al.* 2005). It is envisioned that in the future a psychiatrist making a decision to treat a patient with major depression will choose a pharmacological, psychotherapeutic, or somatic intervention on the basis of objective measures of brain function in the context of known risk factors, including genetics, comorbid conditions, psychosocial issues, and past history (Mayberg 2003).

This issue of the *Journal* reports several new findings that further define key nodes involved in these putative depression circuits with a range of structural and function approaches in both patients and animal models. As demonstrated with the systematic characterization of neural circuits mediating normal

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and abnormal motor functioning in patients with Parkinson's disease (Wichmann and DeLong 2006), a similar strategy for depression holds great promise for significant diagnostic and treatment advances in the care of depressed patients. (Ongur *et al.* 1998).

Helen S. Mayberg

Emory University School of Medicine
Department of Psychiatry
101 Woodruff Circle
WMB 4-313
Atlanta, GA 30327
Phone: 404 727-6740
Fax: 404 727-6743
E-mail: hmayber@emory.edu

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Dr. Mayberg consults to Advanced Neuromodulation Systems and Cyberonics and has filed a patent application for Deep Brain Stimulation (DBS) for depression.

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