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Understanding Psychiatric Disorders Through Functional Brain Imaging

By Clinton D. Kilts, PhD

ABSTRACT *~ Functional brain imaging technologies, such as positron emission tomography (PET) and single-photon emission tomography (SPECT), are widely used to measure hemodynamic and metabolic neural events associated with psychiatric illness or an experimental challenge. Psychopharmacologic treatment produces adaptive changes in neural circuitry that correspond with changes in behavior. This concept has been tested in studies that were designed to visualize changes in neural receptors and transporters subsequent to pharmacotherapy. The use of functional neuroimaging in distributed neural processing studies offers the hope of identifying individuals at risk of developing psychiatric disorders in addition to treatment responders and non-responders. This technology also has the potential to identify new treatments and novel uses for existing treatments.* Psychopharmacology Bulletin. *2004;38(Suppl 1): 21-24.*

INTRODUCTION

In vivo neuroimaging is a broadly applied and multimodal (informs at multiple levels of brain function) technology that has accelerated our understanding of the pathophysiology of mood and anxiety disorders. Through the use of neuroimaging studies, we now have a deeper appreciation of the structural and functional brain changes that occur in persons at risk for psychiatric disorders as well as in patients who are clinically ill. Neuroimaging studies also enable examination of the effects of medication and psychotherapy at different levels of brain function, from the molecular level of receptors and transporters to the more macro level of distributed neural systems. The radiometric tomographic imaging technologies, positron emission tomography (PET) and single-photon emission tomography (SPECT), are widely used to measure hemodynamic (ie, cerebral blood flow) or metabolic (ie, glucose metabolism) responses of neural circuits that occur in response to a psychiatric illness or an experimental challenge (eg, anxiety provocation). A relatively new application for the use of functional brain imaging is visualization of the density, distribution, and occupancy of neural receptors and transporters before,

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during, and after drug therapy.[1] Functional neuroimaging will further our knowledge of illness, therapeutic response, and treatment resistance, and offers the hope of identifying new therapeutic agents and novel uses for existing treatments.

MECHANISM OF ACTION STUDIES

Although in vivo functional neuroimaging is a useful tool for studying the molecular mechanism of pharmacologic agents, it can also challenge existing dogma. For example, the mechanism of the antidepressant paroxetine is widely believed to be related primarily to antagonism of the serotonin transporter (SERT).[2] However, a PET study conducted in depressed patients demonstrated that increasing serum paroxetine concentrations did not result in corresponding increases in striatal occupancy rates of brain regional SERT.[3] These findings of saturation of SERT by low doses suggested that non-serotonergic mechanisms, such as inhibition of norepinephrine (NE) reuptake, may contribute to the clinical effect of high-dose paroxetine treatment. An ex vivo study was conducted to measure NE reuptake by cells transfected with the human NE transporter gene inhibition by the serum of depressed patients treated with escalating doses of paroxetine up to 60 mg/day. Paroxetine resulted in a dose-related effect, with approximately 40% inhibition of NE reuptake at the highest dose.[4] Thus, the unexpected findings of a functional brain imaging study[3] prompted the discovery of a potentially novel multiple mechanism of action for an antidepressant whose molecular pharmacology was once thought to be well understood.

FUNCTIONAL BRAIN CORRELATES OF TREATMENT RESPONSE

Receptor and transporter pharmacology describes the actions of antidepressants at the molecular level, but does not fully explain therapeutic effects, such as the delayed onset of clinical response, partial response, or non-response. Beyond acute receptor and transporter effects, psychopharmacologic treatment is believed to result in adaptive changes in distributed neural circuits that are more proximal to behavior. This concept has been tested in several studies that were designed to localize the functional brain correlates of response to SSRI treatment in patients with major depression.

In an elegant series of PET studies, Mayberg and associates measured regional patterns of change in cerebral glucose metabolism, a correlate of synaptic activity, in depressed patients before and after antidepressant treatment.[5,6] In the first study, patients who were eventually determined to be antidepressant nonresponders exhibited hypometabolism in the rostral anterior cingulate. In contrast, responders were hypermetabolic in this brain region, and no other regional metabolic rates differentiated the two

groups. These results suggest that a hypermetabolic anterior cingulate may be an important adaptive response to depression, and that failure to adapt translates into a poor response to treatment. In a subsequent study by this group, depressed patients were scanned before treatment with fluoxetine and after one and six weeks of treatment.[5] At week one, time-dependent, regional patterns of change in cerebral glucose metabolism in subcortical, limbic/paralimbic, and neocortical areas were observed that were similar for both eventual responders and non-responders. However, at week six, the initial one-week pattern was reversed in responders, who exhibited decreased glucose metabolism in the limbic/paralimbic and striatal areas and increased metabolism in the brain stem and cortex. Conversely, the initial metabolic pattern observed at week one did not change in nonresponders, who also did not exhibit changes in the subgenual cingulate or prefrontal cortex.[5] Related findings were observed in a similar PET study of cerebral glucose metabolism in depressed patients treated with sertraline. Patients were scanned while medication-free and again at least one month after therapeutic response stabilized. As in the study by the Mayberg group, clinical response was associated with reduced metabolism in the subgenual cingulate cortex, as well as in the amygdala.[7]

The physiological integrity of neural information processing for a given brain area can be assessed by the imaged response to a stimulus or task demand. Using such an approach with functional magnetic resonance imaging (fMRI), Siegle and colleagues[8] demonstrated that depression was associated with a sustained response of the amygdala to emotionally negative words.

It is hoped that distributed neural processing studies such as these will be a springboard for developing clinical models to identify treatment nonresponders. In the meantime, this area warrants further study, including large, collaborative trials to more clearly define the adaptive neural circuitry associated with administration of psychopharmacologic agents. The findings of these studies also hold the potential for use as a standard against which to test new therapeutic agents for potential efficacy.

CONCLUSIONS

Functional brain imaging is a burgeoning field of study that is enabling a deeper understanding of the pathophysiology of mood and anxiety disorders at a molecular level as well as at the level of distributed neural circuitry. It is anticipated that neuroimaging technology will benefit clinical care in the not so distant future by identifying treatment non-responders as well as patients who are at risk for development of disorders. Indeed, functional brain imaging may play a pivotal role in preventive psychiatry. ✤

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