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In Vivo Neuroimaging Correlates of the Efficacy of Paroxetine in the Treatment of Mood and Anxiety Disorders

By Clinton Kilts, PhD

ABSTRACT *~ The advent of neuroimaging technology has brought with it a deeper understanding of brain function and structure in health and psychiatric illness. This article overviews pertinent findings from neuroimaging studies in mood and anxiety disorders. Paroxetine is a particularly well-studied psychopharmacologic agent in this regard. The findings of neuroimaging studies of paroxetine will be placed into perspective for a better understanding of the interaction of this selective serotonin reuptake inhibitor (SSRI) with the serotonergic and noradrenergic systems in the brain that mediate clinical efficacy. When considered in the context of a burgeoning literature on neuroimaging research of the pathophysiology of mood and anxiety disorders, the findings of paroxetine studies suggest a neurobiological explanation for the mechanisms whereby chronic administration of paroxetine affects neural systems involved in the pathophysiology of major depression and several anxiety disorders such as obsessive-compulsive disorder, posttraumatic stress disorder, and social anxiety disorder.* Psychopharmacology Bulletin. *2003;37(Suppl 1):19-28.*

INTRODUCTION

Disorders dominated by dysregulation of mood or anxiety have plagued societies for centuries. Medical attempts to treat their manifest symptoms were often misguided by a lack of understanding of the neurobiological bases of such disorders. It was not until the second half of the 20th century that the serendipitous discovery of symptom improvement by drugs that inhibited monoamine neurotransmitter transporters or monoamine oxidase provided an evidence-based strategy for treating mood disorders. An increasing awareness of the in vitro

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actions of such medications led to the ill-informed distinction of "serotonergic" and "noradrenergic" depressions. Interestingly, it is these neurotransmitters that remain as the primary molecular targets of antidepressants some 40 years later. An important discovery during this period of time, led by the introduction of the selective serotonin reuptake inhibitors (SSRIs), has been the demonstrated therapeutic efficacy of paroxetine and other SSRIs in the treatment of anxiety disorders.

Of the classic neurotransmitters, serotonin, or 5-hydroxytryptamine (5-HT), exhibits perhaps the most widespread influence on brain function. Its effects are mediated by at least 15 discreet 5-HT receptor subtypes and transduced by a myriad of transmembrane signaling mechanisms. Similar to the catecholamine neurotransmitters, the moment-to-moment changes in synaptic transmission at 5-HT neurons that contribute to the coordinated modulation of behavior are critically dependent on the actions of a 5-HT transporter (SERT) to clear the synapse of 5-HT and ready receptive neurons for future information coded by 5-HT release. It is the selective and potent ability of paroxetine to inhibit SERT function that initiates its efficacious use in the treatment of mood and anxiety disorders.[1,2]

Along with other SSRIs, paroxetine has unquestionably and significantly reduced the immense personal and social burden of mood and anxiety disorders. It is also increasingly evident that different members of the class of SSRIs are clinically distinguishable, and that these distinctions are associated with differences in their molecular pharmacology.

This discussion seeks to highlight the emerging role of in vivo functional and structural imaging technology and approaches providing an important new understanding of the pathophysiology and pharmacotherapy of mood and anxiety disorders. The ability to track brain events associated with mood and anxiety disorders, define these alterations in brain function that accompany emotion and fear processing, and define the effect of psychotherapeutic interventions at multiple levels of brain function has dramatically changed our perspective on how the brain responds to mood and anxiety disorders and to their treatment. These realizations confirm the biological basis of mood and anxiety disorders, point to new targets for future medication development, and provide initial answers to the long-respected problem of treatment resistance. Moreover, in vivo structural brain-imaging studies are now providing important new clues to the neurobiology of the causes (eg, early trauma) of mood disorders. Converging lines of discovery related to the application of in vivo neuroimaging technology hold new promise for unraveling the long-held mysteries of why and how certain individuals suffer from crippling mood and anxiety disorders.

IN VIVO NEUROIMAGING APPROACHES

Historically, exploration of the neurobiology of mood and anxiety disorders was dependent on the examination of the neurochemistry, morphology, and morphometrics of postmortem brain tissue, or on the neurochemistry of blood and cerebrospinal fluid obtained from living subjects. The confounded and indirect nature of these avenues of investigation limited the interpretability and significance of the results obtained. Until the 1980s, electroencephalography (EEG) and evoked-potential research claimed the sole ability for identifying temporally resolved changes in brain activity related to symptoms of major depression. At this time, radiometric tomographic-imaging techniques such as single photon emission tomography (SPECT) and positron emission tomography (PET),[3] and nonradiometric magnetic resonance imaging (MRI) techniques (fMRI)[4] emerged technologically as in vivo functional brain-imaging approaches. The application of such techniques to behavioral neuroimaging in living, awake humans offered possible answers about the identity of those temporally and spatially resolved functional signals that define the relationship between the brain and normal and abnormal behavior. Soon after the introduction of these

TABLE 1

IN VIVO FUNCTIONAL NEUROIMAGING MODALITIES

EEG/ERP	Maps bioelectric activity
MEG	Maps biomagnetic activity
PET	Regional cerebral blood flow (rCBF) Regional metabolic rate Receptor/transporter density, distribution, occupancy
SPECT	Similar to PET
fMRI	Regional cerebral blood flow and volume
MRS	Quantitative neurochemistry In vivo pharmacokinetics Neurotransmitter turnover, Krebs cycle
OPTICAL	Regional cerebral blood flow and volume

EEG=electroencephalography; ERP=event-related potential; MEG=magnetoencephalography; MRS=magnetic resonance spectroscopy; fMRI=functional magnetic resonance imaging; PET=positron emission tomography; SPECT=single photon emission tomography.

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techniques as research tools, investigators applied them to the study of the brain anatomical and functional correlates of psychiatric disorders. In essence, the human brain has evolved to a point where it can develop technologies for studying itself.

A growing number of in vivo functional brain-imaging modalities are available for behavioral neuroscience research (Table 1). These modalities differ in the brain function imaged and the spatial and temporal resolution of the functional signal that is measured. Several techniques such as PET and SPECT are capable of imaging multiple, distinct aspects of brain function based on the use of different radiopharmaceuticals that target different physiological or pharmacological properties. As examples, PET has been used as a neurophysiological imaging tool when coupled with radiolabeled blood flow tracers (eg, $[^{15}O]H_2$, $[^{15}O]$-butanol) to generate images of the hemodynamic correlate of neural activity.[5] When used with other radioligands that target neurotransmitter receptors and transporters, PET has been used to support in vivo molecular-imaging studies. Although the number of available PET radiopharmaceuticals that possess the essential physiochemical and pharmacological properties to support reliable and accurate in vivo molecular imaging remains limited,[6] radioligands have been developed for imaging dopamine, 5-HT, opiate, benzodiazepine, and acetylcholine receptors, as well as dopamine, 5-HT, and vesicular monoamine transporters. Recently, in vivo molecular imaging studies have been of particular utility in mapping the in situ relationships between administered drug doses or drug effects and the extent of occupancy of the putative molecular targets in the central nervous system (see below). By the use of different radiofrequency (RF) pulse programs, magnetic gradient sets, and head coils, MRI similarly has multipotential applications including in vivo neurochemistry and pharmacokinetics by spectroscopic imaging and neurophysiological imaging, typically by blood oxygen level-dependent (BOLD) imaging. The future power of using in vivo functional brain imaging to define the neural correlates of behaviors, cognitions, and emotions will be realized in part by the integration of complementary imaging modalities to resolve spatially and temporally the related neural activations and to define their underlying neurotransmitters.

NEUROIMAGING AND THE PHARMACOLOGY OF PAROXETINE

The following discussion reviews the extant in vivo neuroimaging findings related to the pharmacodynamics of paroxetine in the treatment of mood and anxiety disorders. Ten years of clinical experience with paroxetine have also yielded significant insights from such studies as to the interaction of paroxetine with its primary molecular target in the human brain, and into the identity of those changes in distributed

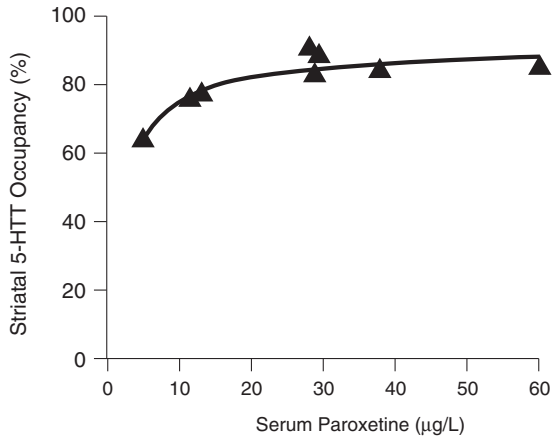
neural activity that mediate its clinical efficacy. Integrated with a growing neuroimaging research literature concerning the pathophysiology of mood and anxiety disorders, these findings point to a neurobiological explanation of how prolonged paroxetine administration influences those neural systems that mediate the mood and anxiety dysregulation characteristic of major depression and anxiety disorders, such as obsessive-compulsive disorder (OCD), posttraumatic stress disorder (PTSD), and social anxiety disorder.

INTERACTION OF PAROXETINE WITH MOLECULAR SITES OF ACTION

Prior to its approval for clinical use, paroxetine had widespread research use as a selective, high-affinity inhibitor of SERT. A recent fMRI study in healthy subjects used a single dose of paroxetine to demonstrate the role of serotonin in motor control and its neural activation correlates in executive motor areas of the cerebral cortex.[7] It is widely accepted that significant clinical improvement for the great majority of patients with mood and/or anxiety disorders treated with indicated medications exhibits a delay of 3 to 5 weeks from the initiation of treatment.[8] Consistent in vitro evidence indicates that these delayed clinical responses are initiated by the acute antagonism of monoamine transporters, particularly the SERT.[1,2]

FIGURE 1

RELATIONSHIP BETWEEN SERT OCCUPANCY AND SERUM PAROXETINE CONCENTRATION 6 TO 13 HOURS FOLLOWING THE LAST DOSE



Relationship between striatal serotonin transporter (SERT) occupancy and serum paroxetine concentration 6 to 13 hours following the last dose of a 4-week trial with paroxetine administration (20 mg/d)

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However, this molecular interaction and the influence of cellular, transynaptic, brain regional, and pharmacokinetic factors had not been confirmed in the living human brain. The emergence and refinement of PET and SPECT scanners, and the development of targeted radiopharmaceuticals and models and methods of quantitating emission data, have permitted the in situ study of the density, distribution, and occupancy of neurotransmitter receptors and transporters with picomolar sensitivity.[9]

An initial estimate of the ability of acute paroxetine administration to occupy the human brain SERT assessed the effect of an oral dose of 60 mg paroxetine on the in vivo binding of the candidate PET SERT ligand (+)-[^{11}C]McN 5652.[10] Paroxetine administration decreased (+)-[^{11}C]McN 5652 binding in the amygdala, striatum, thalamus, and midbrain, suggesting that (+)-[^{11}C]McN 5652 binding in these brain regions reflects binding to the SERT. A subsequent PET study of individuals with major depression and using the superior PET SERT ligand [^{11}C]DASB examined the extent of brain regional SERT availability before and after a 4-week trial with either 10 mg or 20 mg/day of paroxetine.[11] Six to 13 hours following the last dose, the mean occupancy of striatal SERT was 83%; comparable values were obtained for the thalamus and the prefrontal and anterior cingulate cortex. Interestingly, a comparison of the relationship between serum paroxetine concentration and striatal SERT occupancy indicated a relatively flat hyperbolic relationship such that a 12-fold increase in serum paroxetine was associated with minimal increases in SERT occupancy (Figure 1).[11]

These in vivo neuroimaging findings support the high affinity of paroxetine for the human brain SERT, and suggest that other non-SERT mechanisms may mediate the clinical effects of moderate to high doses of paroxetine. Inhibition of the norepinephrine transporter (NET) may represent one such mechanism because significant inhibition of in vitro NET function was observed for serum from depressed patients obtained following a 7-week forced-titration study of paroxetine administration.[12] NET function was decreased by 27% and 43% at average serum paroxetine concentrations of 100 and 200 ng/mL. Unfortunately, PET or SPECT ligands for the brain NET are not yet available to directly compare the differential occupancy of brain regional SERT and NET sites associated with paroxetine administration. A critical extension of these PET studies to testing molecular mechanism of action hypotheses would incorporate the determination of the relationship between the extent of SERT and NET occupancy and clinical symptoms. For example, such studies have been conducted for the relationship between striatal D_2 dopamine receptor occupancy and the therapeutic and side effects of antipsychotic drug administration to patients with schizophrenia.[13]

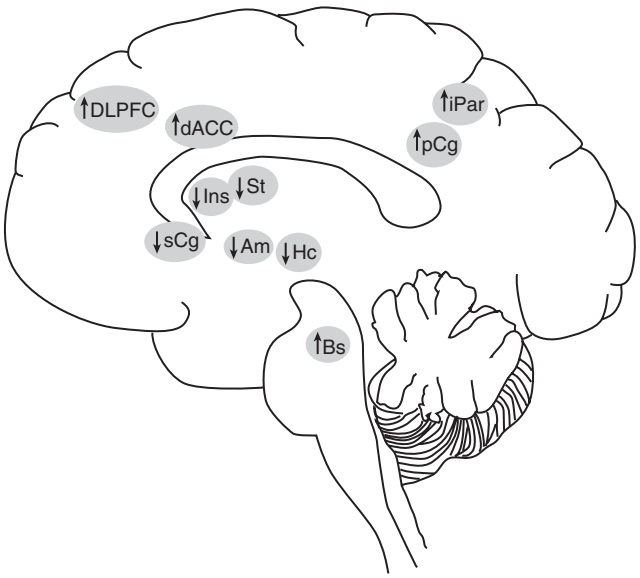
ADAPTIVE MOLECULAR AND NEURAL RESPONSE TO PAROXETINE

Although SERT inhibition is generally regarded as the molecular target of paroxetine and other SSRIs in producing their clinical effects, this action is also not regarded as representing the final common pathway of their antidepressant and anxiolytic effects. Rather, the prolonged inhibition of the SERT (and perhaps other monoamine transporters) is thought to precipitate an adaptive alteration in the activity of distributed brain areas involved in mood or anxiety regulation. Thus, changes in mood- and anxiety-related neural circuits are thought to be more proximally related to antidepressant and anxiolytic responses.

Recent in vivo neuroimaging studies have shed exciting new light on the functional anatomy of antidepressant response. Mayberg and colleagues[14] demonstrated, using serial [^{18}F]-FDG PET studies of the metabolic correlate of neural activity, that significant antidepressant response to a 6-week trial with fluoxetine was associated with decreases relative to baseline in activity in limbic/paralimbic (subgenual cingulate, hippocampus, insula) regions, and increases in activity in brain stem and

FIGURE 2

NEURAL CIRCUIT MODEL OF ANTIDEPRESSANT DRUG RESPONSE



Adapted from Mayberg et al[14] and Drevets et al.[16] Brain areas and anticipated direction of drug-induced change in magnetic resonance imaging [^{18}F]-FDG PET estimate of neural activity signal are illustrated. DLPFC=dorsolateral prefrontal cortex; dACC=dorsal anterior cingulate cortex; iPar=inferior parietal cortex; pCg=posterior cingulate gyrus; Ins=insula; St=striatum; sCg=subgenual cingulate gyrus; Am=amygdala; Hc=hippocampus; Bs=brainstem.

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dorsal neocortical (dorsolateral prefrontal, anterior and posterior cingulate, and inferior parietal cortex) areas. Nonresponders at the 6-week end point continued the pattern of brain activity changes observed at 1 week. A recent comparative PET study of responders to placebo versus fluoxetine administration indicated that altered activity in the brain stem, striatum, insula, and hippocampus was unique to active medication response, and that response-related changes in the remaining limbic/paralimbic and neocortical brain areas were more robust in fluoxetine responders.[15] Drevets and colleagues[16] also used serial [^{18}F]-FDG PET studies to demonstrate that antidepressant response to sertraline administration was associated with decreased estimated activity, relative to baseline, in the amygdala and subgenual cingulate cortex; the medication-induced decrease in amygdala metabolism was significantly correlated with improvement in depressive symptoms. These in vivo neuroimaging findings support the role of a neural circuit (Figure 2)[14,16] in treatment-related improvement in the mood, cognitive, motor, and somatic symptoms of major depression. Future imaging studies will assess the role of this functional anatomical model as a final common pathway for antidepressant treatment response and remission.

Similar experimental designs have been used to define, using in vivo functional neuroimaging approaches, the neural correlates of the efficacy of paroxetine administration in the treatment of major depression or OCD. Clinically significant response to a paroxetine dose titration to a target of 40 mg/day was associated with decreases from baseline in ventrolateral prefrontal (VLPFC) and orbitofrontal (OFC) metabolism; improvement in depressive symptoms was significantly correlated with decreased estimated activity in the VLPFC and inferior frontal gyrus.[17] In a separate PET study, clinically significant response of geriatric depression to a 2-week trial of paroxetine administration (preceded by total sleep deprivation) was associated with decreased estimated activity in the anterior cingulate and medial frontal cortex.[18] These cortical effects may be related to the recent demonstration using PET and [^{18}F]setoperone of a downregulation in cortical 5-HT$_{2A}$ receptors following 6 weeks of treatment of depressed patients with paroxetine.[19]

A recent [^{18}F]-FDG PET study examined the neural correlates of response to paroxetine pharmacotherapy in groups of patients with major depression, OCD, or concurrent OCD and depression.[20] Pretreatment to posttreatment decreases in estimated activity in the OFC, thalamus, and VLPFC were noted for OCD responders: decreased OFC and anterior temporal pole metabolism characterized the OCD nonresponders. In contrast, responders with major depression exhibited relative decreases in a large frontal area encompassing the VLPFC and medial, inferior, and

dorsolateral frontal cortex, as well as the superior frontal and occipital cortex; nonresponders to paroxetine demonstrated only a decrease in putamen metabolism. Responders with concurrent OCD and major depression exhibited a significant metabolic increase in the superior temporal cortex; nonresponders exhibited significant metabolic decreases in the VLPFC. The most salient conclusion of this study is that the neural effects of paroxetine pharmacotherapy differ for different mood and anxiety disorder diagnoses, and between those individuals who respond or don't respond clinically to paroxetine. In turn, these differences most probably reflect a dependence of the effect of paroxetine on brain function on the underlying pathophysiology of the patient, and vary with the extent of symptomatic improvement.

Finally, in vivo structural brain-imaging studies of mood and anxiety disorders have demonstrated significant volumetric changes in selective brain regions consistent with the association of functional or structural neuropathology. Decreased hippocampal and increased thalamic volumes have been associated with PTSD[21,22] and pediatric OCD,[23] respectively. Interestingly, paroxetine monotherapy seems to normalize these volumetric changes. These early findings suggest that paroxetine has complex interactions with the pathophysiology of anxiety disorders and that treatment response may be best described by a compilation of multiple brain responses.

CONCLUSION

In vivo functional, as well as structural, brain-imaging approaches are providing a new understanding of the relationship of the brain and behavior. In so doing, this technology is changing the face of psychiatric disorders. This discussion focused on the emerging understanding of the molecular and neural system level response of patients with mood and/or anxiety disorders to treatment with paroxetine. At the molecular level, SERT occupancy following therapeutic dosing with paroxetine approaches 80% and suggests that additional molecular sites of action are involved. At the neural system level, significant clinical response to paroxetine pharmacotherapy seems to be related to adaptive alterations in neocortical and paralimbic cortical areas, and perhaps to events associated with volumetric changes in subcortical structures. Although more systematic, hypothesis-driven and model-based in vivo neuroimaging research is necessary, the extant findings from this technology support the promise of eventually elucidating the neural substrates of paroxetine response and nonresponse. Such knowledge will be critical to the rational development of future medications for the improved management of mood and anxiety disorders. ✤

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