Poster

Neurochemical brain imaging of treatment response in geriatric depression

Since the renewed emphasis on the heterogeneity of geriatric depression and the impact on treatment response variability over a decade ago,[1] neuroimaging methods have been increasingly applied to understand the underlying neurobiology of treatment response variability in geriatric depression.[2] The application of neuroimaging methods has resulted in fundamental observations with respect to the neural circuitry and the role of the serotonin system. The observations that some patients remain symptomatic after adequate treatment with a selective serotonin uptake inhibitor (SSRI) and that despite remission of mood symptoms, residual cognitive and other behavioral deficits persist, suggest that other neurochemical mechanisms may be involved. This review will focus on neurochemical imaging research in geriatric depression that has led to an initial understanding of the neurobiological mechanisms underlying remission of depression in late life. Future research directions to investigate the mechanisms underlying treatment resistance of mood and cognitive aspects of the illness will be discussed.

Geriatric depression is a clinically and neurobiologically heterogeneous disorder.[1,2] The treatment of depression in the elderly is complicated by age-related changes in cognition, brain structure, function, and neurochemistry ,and by comorbid medical illnesses and the contribution of neurodegenerative and cerebrovascular disease processes. The issue of treatment response is complex in the elderly, as several domains of symptomatology must be considered, including mood, reward sensitivity, and cognitive function. These domains of symptomatology may have different mechanistic bases. For example, cognitive deficits persist in some patients even after remission of mood symptoms.[3,4] Deficits in several domains of cognition have been reported in geriatric depression. The most consistent cognitive deficits observed in depressed patients who do not meet thecriteria for early Alzheimer's disease (AD) or other dementias are slowed speed of processing and deficits in executive function and memory.[5-8] Given the advances in single photon emission computed tomography (SPECT) positron emission tomography (PET), radiotracer chemistry, and instrumentation and methodology development in magnetic resonance imaging (MRI), functional and structural imaging methods can be applied and integrated to understand the pathophysiological mechanisms underlying the different symptom domains and differential response to treatment. The focus of this report will be to discuss the role of PET neuroimaging methods to: (i) identify the neural circuitry associated with depression remission; (ii) investigate the role of drug occupancy in treatment response; and (iii) elucidate the potential utility of studying interactions between monoamine systems in developing a mechanistic basis of treatment remission across domains of symptomatology in geriatric depression.

The functional neuroanatomy of treatment response

The *neural circuitry* of geriatric depression has been investigated using functional MRI (fMRI), diffusion tensor imaging and PET methods.[9-12] Studies of the cerebral metabolic and blood flow effects of antidepressant interventions have been performed mainly in younger (midlife) depressed patients (as reviewed in ref 2). The neuroimaging data, in addition to preclinical and postmortem neurochemical studies, have been integrated to develop a functional neuroanatomic model of antide-

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pressant effects involving increased metabolism in dorsal structures and decreased metabolism in ventral structures.[13] Many of the brain regions that comprise this model have been implicated in a recent meta-analysis of neuroimaging studies in major depression.[14] The regions that are hypoactive at rest and show a lack of activation during negative mood states and an increase with selective serotonin reuptake inhibitor (SSRI) treatment include the dorsal pregenual cingulate gyrus, middle and dorsolateral prefrontal cortex, insula, and superior temporal gyrus. A second network identified was a cortical-limbic network including the medial and inferior frontal cortex and basal ganglia, structures that were overactive at rest and during induction of negative mood states and reduced in activity with antidepressant treatment. The amygdala and thalamus were also implicated in the network in some studies. Other regions highlighted in the meta-analysis were the cerebellum (which showed increased activity at rest), posterior cingulate, and medial temporal lobe (including the parahippocampal gyrus), all of which show abnormal activation in mood induction paradigms.

Studies performed in patients with late-life depression suggest that there may be differences between the functional neuroanatomic alterations in older depressed patients compared with younger patients.[11,12,15] With respect to "baseline" (pretreatment metabolism), studies in geriatric depression show that glucose metabolism is increased in the patients relative to the demographically matched control subjects in both anterior and posterior regions that also showed evidence of atrophic changes in patients compared with controls. These regions included the right superior and middle frontal gyrus, left superior (BA 9) and inferior frontal gyrus (BA 45), left precentral gyrus, right middle temporal gyrus (BA 22), precuneus (bilaterally) and inferior parietal lobule (bilaterally), left cuneus and right cerebellum (Smith et al, unpublished data). In younger patients, many of these regions have relatively decreased activity including the dorsolateral prefrontal cortex, posterior cingulate, and precuneus.[13,16] Thus, differences in the "baseline" state between midlife and geriatric depressed patients may contribute to the differences observed between the age groups in the cerebral metabolic effects of treatment.

With respect to the cerebral metabolic effects of treatment, a similar pattern of increases and decreases has been observed with both total sleep deprivation and medication (citalopram) in patients who show a significant decrease in depressive symptoms to meet the criteria for remission.[11,12] Decreases in metabolism have been observed in right anterior cingulate gyrus (BA 24), superior and middle frontal gyrus (bilaterally) and right inferior frontal gyrus, superior and middle temporal gyrus (bilaterally) and left inferior temporal gyrus, precuneus and posterior cingulate (bilaterally), midbrain (bilaterally), right pons, parahippocampal gyrus, and amygdala (bilaterally). Increases in metabolism were observed in the putamen (bilaterally), right thalamus (pulvinar and medial dorsal nuclei), inferior parietal lobule (bilaterally) occipital cortex (right cuneus and left middle and inferior occipital gyrus) and cerebellum (bilaterally). The decreases and increases in metabolism superimposed on an MR rendering are shown in *Figure 1*.

Thus, in geriatric depression, the brain regions observed to be hypermetabolic that show evidence of atrophic changes include structures that comprise the "default network" that has been shown to be hyperactive in the resting state in younger depressed patients and hypoactive in patients with AD.[17,18] These regions are also activated in mood induction paradigms, attentional and memory tasks, and during conditions of hunger and satiety,[19-21] and may be related to the cognitive and vegetative, in addition to mood, symptoms. The cortical hypermetabolism may be a compensatory mechanism for neurodegenerative changes such as amyloid deposition or neuroinflammation, or may be the result of a primary or secondary increase in glutamate concentrations as glutamate is the primary neurotransmitter with these cortico-cortical pathways.[22]
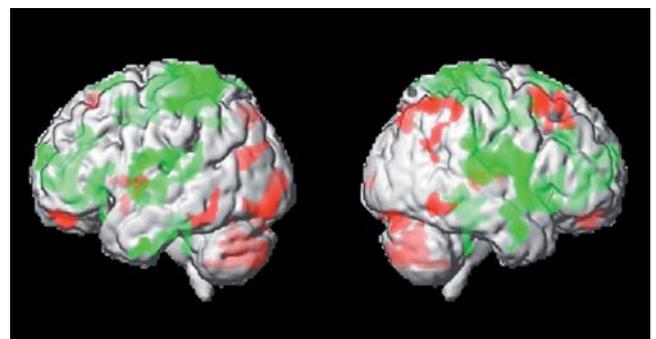

Figure 1. The effects of chronic citalopram treatment on cerebral glucose metabolism in geriatric depression. Regions of metabolic decrease (green) and increase (red) are superimposed on an MR rendering from a representative subject. MR, magnetic resonance

Poster

Serotonin transporter occupancy and treatment response

While studies of cerebral glucose metabolism provide invaluable information regarding changes in neural circuitry, PET neuroreceptor radiotracers can be applied to evaluate the neurochemical substrates of the cerebral metabolic effects observed. The serotonin transporter is a logical initial target, as this is the primary binding site of the SSRIs, and the serotonin transporter is located in cortical, striatal, and limbic regions shown to be affected by citalopram and related to treatment response. Neuroimaging studies of the serotonin transporter have been performed mainly in midlife depressed patients. Reduced serotonin transporter binding in the midbrain (including the raphe nuclei) has been reported in midlife depressed patients.[23] In one of the initial studies of the effects of SSRI treatment (paroxetine and citalopram) on serotonin transporter binding, Meyer et al[24] observed a high degree of serotonin transporter occupancy at relatively low SSRI plasma concentrations.

Serotonin transporter occupancy by citalopram has been studied in patients with geriatric depression.[25] Seven patients underwent studies with the selective serotonin transporter radiotracer [11C]-DASB developed by Wilson and colleagues.[26] The patients demonstrated 70% occupancy by citalopram in the striatum and thalamus, which was not correlated with the change in depression ratings over the treatment interval, in addition to citalopram dose and plasma concentration. Exploratory, voxel-wise analyses revealed that the magnitude of serotonin transporter occupancy by citalopram was observed in regions in which significant decreases (anterior cingulate, middle frontal gyrus, superior and middle temporal gyrus, precuneus) and increases (inferior parietal lobule, cuneus) in cerebral glucose metabolism have been observed. The [11C]-DASB images from a representative subject are shown in *Figure 2*. These results indicate that serotonin transporter occupancy in cortical regions, which can be measured using higher-resolution PET scanners implemented in the past decade, may be relevant to the clinical and cerebral metabolic effects of citalopram in geriatric depressed patients.

Neuroimaging of monoamine interactions

Several observations suggest that the mechanism of action of the SSRI and an understanding of the neurochemical basis of treatment response variability may involve alterations in the ability of serotonin to modulate other neurotransmitter systems. Firstly, both acute and chronic citalopram treatment is associated with significant occupancy of the serotonin transporter, the initial target site of action (greater than 70%)[24-28] Despite significant transporter occupancy, clinical antidepressant effects are not observed acutely, and persist in some patients even after chronic serotonin transporter occupancy. Secondly, the observation that despite remission of mood symptoms, some patients have persistent cognitive deficits (eg, executive dysfunction) and other symptoms (eg, sleep disturbance) suggests involvement of other neurotransmitter systems.[28,29] The modulatory role of serotonin and the SSRIs with respect to other neurotransmitters including dopamine, glutamate, and acetylcholine has been well described.[30-33] Given the nature of the residual symptoms in depression that may have a substrate in the dopamine system, the inability of serotonin to modulate dopamine function in such patients is a mechanistic hypothesis that can be evaluated using neurochemical imaging methods.

Such hypotheses involving dynamic interactions between neurotransmitter systems can be evaluated with *in vivo* imaging. The demonstration that endogenous neurotransmitter concentrations and interactions between neurotransmitter systems could be measured in vivo by combining neurotransmitter receptor binding measures with acute pharmacologic interventions has been an important development in neurochemical brain imaging
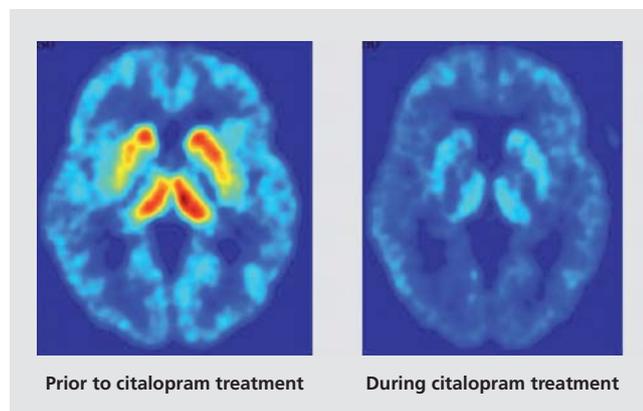

Prior to citalopram treatment   **During citalopram treatment**

Figure 2. Serotonin transporter occupancy by chronic citalopram treatment: parametric [11C]-DASB images at the level of the striatum, prior to and following citalopram treatment for a representative subject.[25]

methodology, particularly with respect to the dopamine system.[34-36] The development and application of methods to evaluate dopamine modulation by other neurotransmitter systems is an opportunity to test alternative hypotheses regarding pathophysiology and drug mechanisms of action. Serotonin modulation of dopamine function has been a particular focus of PET dopamine (D_2) receptor studies.[36,37-39] Several human studies have observed that a pharmacologic increase in serotonin concentrations produced a reduction in striatal D_2 receptor availability secondary to an increase in striatal dopamine concentrations. As shown in *Figure 3*, an acute dose of
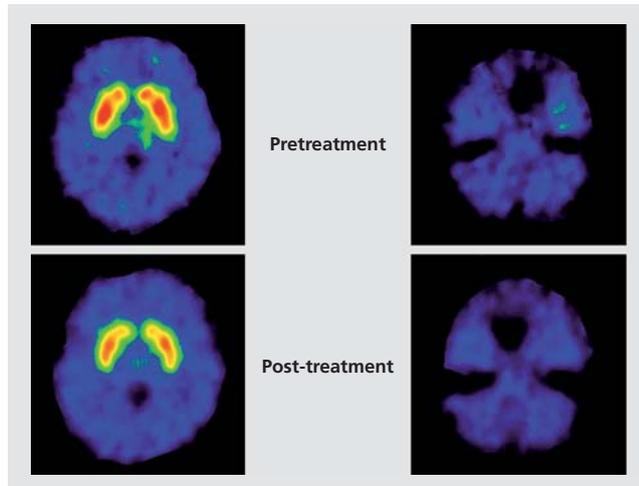

Figure 3. Serotonin modulation of striatal dopamine concentrations measured with PET and [11C]-raclopride. Parametric [11C]-raclopride images after saline infusion (top row) and after acute citalopram administration (40mg, IV; bottom row). Images are shown at the level of the striatum (left) and cerebellum (right) to show regions of specific and nonspecific binding, respectively.[37] PET, positron emission tomography

citalopram that has been shown to produce significant effects on cerebral metabolism as well as serotonin transporter occupancy also produces a decrease in striatal D_2 binding of the radiotracer [11C]-raclopride, consistent with an increase in endogenous dopamine concentrations.[37] Such a paradigm could be used to evaluate the functional integrity of serotonin/dopamine interactions in geriatric depression as a potential mechanistic basis of such symptoms as executive dysfunction, apathy, and sleep disturbance. While the focus of methodology development for imaging of dynamic neurotransmitter concentrations and interactions has been the dopamine sys-

tems, other potentially relevant neurotransmitter systems such as serotonin and acetylcholine have been the focus of methodology development as well.[40,41]

Future directions

Thus far, neuroimaging methods have been applied to the understanding of the neurobiological substrates of treatment response variability, and have shown the functional neural circuitry associated with treatment response, as well as the role of serotonin transporter occupancy by antidepressant medications. Given the advances in radiotracer chemistry and instrumentation, other neurobiological mechanisms can be investigated in smaller brain regions that could not be imaged reliably with PET previously.

The application of dynamic measures of monoamine function, such as those described in the previous section, may be more sensitive than static measures such as transporter or receptor availability. Active areas of radiotracer development which might be potentially important include adrenergic and glucocorticoid systems, as well as tracers that could be used to measure trophic responses.[42] There are several neuropathological processes that can be imaged with PET, such as amyloid deposition and neuroinflammation, that might have implications for understanding the basis of persistent cognitive impairment in geriatric depression.[43-46] Another important approach to understanding the neurobiological basis of treatment resistance is to investigate the mechanism of action of somatic treatments such as electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), and potentially magnetic seizure therapy (MST), that are effective in treating patients who respond poorly to antidepressant medications. Both TMS and MST are also interesting research tools that can be applied to understanding the function of specific neural circuits.[47]

In summary, molecular brain imaging can potentially make contributions to fundamental questions in geriatric depression that would have significant implications for the design of more effective treatments. Such questions include: what is the neurobiological basis of glucose hypermetabolism in geriatric depression; does the clinical management of depression in late life have a neuroprotective effect; what is the mechanism by which combined medication and psychotherapy is more effective; what is the mechanism of action of somatic therapies that are effective in treatment-resistant depression? ❏

Poster

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