The Relationship Between the Acute Cerebral Metabolic Response to Citalopram and Chronic Citalopram Treatment Outcome

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Objectives: Given the challenges in the clinical management of geriatric depression, research over the past decade has focused on developing early neurobiological markers of antidepressant treatment response. This study tested the hypothesis that lower baseline glucose metabolism and greater acute cerebral metabolic responses to a single, intravenous (IV) dose of the selective serotonin reuptake inhibitor (SSRI) citalopram would be associated with greater improvement of depressive symptoms after 12 weeks of citalopram treatment in geriatric depression. Methods: Sixteen geriatric depressed patients underwent two scans to measure cerebral glucose metabolism after administration of either a saline placebo or citalopram infusion (40 mg, IV). Then, the patients were treated with the oral citalopram medication for 12 weeks. Results: Greater improvement of depressive symptoms was associated with lower baseline metabolism in anterior cingulate, superior, middle, and inferior frontal gyri (bilaterally), inferior parietal lobule (bilaterally), precuneus (right), insula (left), parahippocampal gyrus (right), caudate (bilaterally), and putamen (left) regions. Greater improvement of depressive symptoms was associated with greater reductions in metabolism after acute citalopram administration in similar brain regions, including additional posterior cortical regions. Conclusions: Lower baseline cerebral metabolism and greater decreases with acute citalopram administration are associated with better antidepressant response to chronic citalopram treatment. These data are consistent with previous studies of total sleep deprivation and suggest that dynamic, early adaptive changes or normalization of cerebral metabolism may represent early neurobiological markers of chronic SSRI treatment response in geriatric depression. (Am J Geriatr Psychiatry 2010; 19:53–63)
The early development of in vivo neurochemical brain imaging methods was strongly motivated by an interest in developing early neurobiological markers of psychotropic drug response in psychotic and affective disorders. The majority of studies measured the effects of a single drug dose or acute interventions on global measures of brain function (cerebral glucose metabolism and blood flow) or, more directly, on endogenous neurotransmitter activity. Studies to measure serotonin transporter occupancy by antidepressants or D2 occupancy by antipsychotics have not shown associations with affective or psychotic symptom improvement, respectively (e.g., Refs. 3 and 4). These occupancy measures reflect whether the medications act on the primary target sites of action. The secondary effects of medication, measured by the dynamic response of the brain (global brain function or endogenous neurotransmitter activity), may be better associated with clinical outcome than measures of transporter or receptor occupancy. The underlying assumption is that the initial, dynamic brain response to acute treatment is indicative of the capacity of the brain to respond to a course of chronic treatment and, thus, greater clinical improvement.

Research over the past decade has focused on developing early neurobiological markers of antidepressant (e.g., total sleep deprivation [TSD] or selective serotonin reuptake inhibitor [SSRI]) treatment response in geriatric depression (as reviewed in Ref. 5). Early indicators of treatment response are particularly important in geriatric patients because more than half of geriatric depressed patients are either mixed/partial responders or nonresponders to an adequate course of treatment. The ability to identify which patients would respond best to an SSRI versus those who would require another class of antidepressant medication or more intensive treatment would have a significant impact on the clinical management of geriatric depression. This is especially important for some classes of antidepressants that are associated with greater side effects (e.g., selective noradrenergic reuptake inhibitors). Thus far, structural neuroimaging and genetic methods have been applied to distinguish treatment responders from nonresponders. The neurobiological measures associated with poorer response to antidepressant (SSRI) treatment include magnetic resonance (MR) measures of decreased anterior cingulate volumes (Brodmann area [BA]: 24, 32) and greater cerebrovascular burden (hyperintensities in the white matter and deep gray matter structures), decreased functional connectivity of white matter pathways in cortical and limbic regions, and the s allele of the serotonin transporter promoter polymorphism. These data suggest that dysfunction in cortical and limbic structures and decreased serotonin function may be associated with poorer antidepressant response.

With respect to the predictive value of dynamic measures of brain function in geriatric depression, the cerebral metabolic response to TSD and one night of recovery sleep were both associated with the clinical antidepressant response to 12 weeks of treatment with the SSRI paroxetine. Greater reductions in cerebral glucose metabolism in the rostral anterior cingulate (BA: 24, 32), superior and middle frontal gyri, and precuneus after TSD and recovery of sleep were associated with greater improvement of depressive symptoms after chronic paroxetine treatment. These data suggest that acute metabolic responses may represent an early neurobiological marker of chronic treatment response in geriatric depression. It is important to note that TSD is not a neurochemically selective intervention but has multiple effects including increases in concentrations of monoamines, acetylcholine and trophic factors (as reviewed in Ref. 1). This study was undertaken to evaluate whether a neurochemically selective acute intervention, the most selective of the SSRIs, citalopram, would produce similar changes in neural circuitry associated with antidepressant treatment response. The cerebral glucose metabolic response to acute citalopram administration (40 mg, IV) was measured in geriatric depressed patients who then underwent a 12-week treatment trial with the oral citalopram medication.

Based on prior observations of increased pretreatment cerebral glucose metabolism in geriatric depression and reductions in metabolism with...
treatment, it was hypothesized that lower pretreatment metabolism in the rostral anterior cingulate gyrus (BA: 24), superior and middle frontal cortex, and precuneus would be associated with greater improvement of depressive symptoms. Greater reductions in cerebral metabolism after acute citalopram in these brain regions were hypothesized to be associated with a greater antidepressant effect after 12 weeks of citalopram treatment.

**METHODS**

**Subjects**

Sixteen depressed patients were enrolled in the study (seven men and nine women), who met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for major depression (nonbipolar and nonpsychotic; mean age, 65.3 ± 9.1 years; mean education level, 14.3 ± 2.9 years; Mini-Mental State Examination score [MMSE] 28.7 ± 1.1). The mean age at onset of depression was 60.0 ± 4.4 years, and the mean duration of the current episode was 7.1 ± 2.8 months. There were no significant differences in these demographic variables as a function of gender (age: men, 66.3 ± 8.5 years and women, 64.4 ± 9.9 years; age at onset: men, 66.3 ± 8.5 years and women, 61.4 ± 9.6 years; duration: men, 6.9 ± 2.7 and women, 7.2 ± 3.0; education level: men, 14.0 ± 1.5 and women, 13.7 ± 3.4; and MMSE: men, 29.1 ± 0.7 and women, 28.3 ± 1.2, p > 0.1). Subjects were recruited through the Geriatric Psychiatry Outpatient Clinic of the Zucker Hillside Hospital and by advertisements in the community. The protocol and consent forms were approved by the Institutional Review Board and the Radiation Safety Committee of the North Shore-Long Island Jewish Health System. The clinical and neuroimaging data from this patient sample have been reported previously.12,14,15

Participants underwent psychiatric screening using the Structured Clinical Interview for DSM-IV Axis I Disorders—Patient Edition.16 Depression severity was measured using the Hamilton Depression Rating Scale-24 items (HDRS17), Beck Depression Inventory,18 and Geriatric Depression Scale.19 Participants underwent laboratory testing (CBC, blood chemistry, glucose levels, thyroid function, and toxicology) and MR imaging to rule out structural abnormalities (e.g., stroke and brain tumor; GE 1.5 T Magnetom Vision, General Electric Medical Systems, Milwaukee, WI). Exclusionary criteria were 1) history or current other DSM-IV, Axis 1 disorders, 2) unstable medical conditions or insulin dependent diabetes, and 3) use of medications with central nervous system effects within the past 2 weeks (including beta blockers and over-the-counter medications). Twenty-five percent (%) of the patients were taking antihypertensive medications (either an angiotensin converting enzyme inhibitors or a calcium channel blocker, as patients taking beta blockers were excluded). The mean blood pressure for the patients was systolic 130.0 ± 15.3 and diastolic 75.3 ± 11.3. The majority of patients enrolled in this study were never treated previously with an antidepressant or other psychotropic medication (12 patients or 75%). Three of four previously medicated subjects had been treated with sertraline but were medication free for 6 months or more before study enrollment. The fourth subject was treated with nortriptyline and was not responding to treatment. She was tapered off the medication 2 weeks before the first positron emission tomography (PET) scan and did not have detectable plasma nortriptyline levels at the time of scanning.

**Citalopram Administration and PET Scan Procedures**

The study procedures, including the PET scans, have been described previously.12,14,15 Before starting citalopram treatment, patients underwent PET scans on 2 consecutive days, after placebo infusion (250 mL saline) on Day 1 and citalopram infusion (40 mg, IV) on Day 2. The study was single blinded in that the investigators, not the patients, were aware of the identity of the infusions. The placebo was always administered on Day 1.

The PET scans were acquired on a GE Advance Tomograph (General Electric Medical Systems, Milwaukee) in the Center for Neurosciences, Feinstein Institute for Medical Research, Manhasset, New York.
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Institute for Medical Research. On each of the days of the PET scans, subjects arrived at the laboratory and catheters were placed in each arm for placebo/ citalopram and radiotracer infusion and for blood sampling (opposite arm). The radiotracer was injected approximately 30 minutes after the end of infusion, at which time the greatest effect of citalopram on cerebral metabolism has been observed.\(^5\) \(5 \pm 10\%\) mCi of 18F-2-deoxy-2-fluoro-d-glucose was injected as an IV bolus. Then, a 25-minute radiotracer uptake period occurred in a quiet, dimly lit room with eyes and ears unoccluded. Then, the subjects were positioned in the PET scanner. A 10-minute transmission scan was performed followed by a 5-minute, two-dimensional emission scan for attenuation correction. A 10-minute, three-dimensional emission scan was performed approximately 40 minutes after the injection of the radio-tracer. At the completion of the scan, subjects were removed from the scanner and debriefed as to their perceptions of the study. Twenty percent of the subjects experienced transient headache and nausea that coincided with the peak plasma concentration of citalopram, from the end of infusion to 30 minutes postinfusion.

Two days after the acute, IV administration of a single dose of citalopram, the patients began treatment with the oral citalopram medication at a dose of 10 mg/day for 3 days. The dose was increased to 20 mg on the 4th day. If significant clinical improvement was not observed at the 20-mg dose after 4 weeks of treatment (measured as a rating of \(\geq 3\) on the Clinical Global Impression Scale\(^21\)), the dose was increased to 30 mg, and then, if needed, to 40 mg. One patient was titrated to a dose of 50 mg. Patients were monitored on a weekly basis in the Geriatric Outpatient Clinic of the Zucker Hillside Hospital, at which time clinical ratings were administered, and side effects were assessed. All patients who began treatment completed the 12-week course of treatment and were included in this report.

PET Data and Image Analyses

The quantification of glucose metabolism was performed on a voxel-wise basis using validated methods as described previously.\(^1\) Image preprocessing and voxel-wise statistical analyses were performed with SPM5 (Institute of Neurology, London, UK\(^22\)). Images were smoothed using an isotropic Gaussian kernel (full-width half-maximum, 8 mm for all directions). Global normalization of the images to a mean of 50 was performed after confirming that the global means for the two conditions (placebo/citalopram) did not differ significantly \((p > 0.05)\). Two primary analyses were performed: 1) the paired \(t\) test option with change in HDRS as a covariate was used to correlate baseline cerebral metabolism with change in HDRS score from baseline to 12 weeks and 2) the flexible factorial option was used to compare change in cerebral metabolism from pretreatment to the acute citalopram challenge and change in HDRS score from baseline to 12 weeks. Thus, treatment response (change in HDRS score) was treated as a continuous variable. Results are reported for a \(t\) threshold >3.51 \((z > 2.98, p < 0.001, uncovcorr for multiple independent comparisons)\) and a cluster size of greater than 50 voxels. To address the possibility that the magnitude of reduction in HDRS score after treatment may be related to greater baseline depression severity, a correlation was computed between baseline HDRS scores and changes in HDRS scores. The relationship between the baseline scores and the magnitude of change was not significant \((r = 0.016, p = 0.953)\).

RESULTS

Clinical Data

The biweekly clinical ratings and citalopram doses are shown in Table 1. The patients demonstrated significantly decreased observer and self-report depression ratings after 12 weeks of citalopram treatment. Significant reductions in HDRS scores (baseline: 27.8 ± 3.7, treatment at Week 12: 6.6 ± 5.6; range: −27 to −12 \([F = 302.4, df = 1, p < 0.001]\)), Beck Depression Inventory scores (baseline: 11.4 ± 3.1, treatment Week 12: 3.3 ± 3.1; range: −13 to 5 \([F = 53.9, df = 1, p < 0.001]\)), and Geriatric Depression Scale scores were observed (baseline: 20.44 ± 5.6; treatment Week 12: 8.0 ± 8.1; range: −21 to 5 \([F = 52.1, df = 1, p < 0.001]\)).

Although treatment response status was treated as a continuous variable in the statistical analysis, to compare with the literature, the patients were characterized as responders or nonresponders. The definition of response was HDRS change of 50% and
a score of <10 at Week 12 of citalopram treatment. On this basis, 25% of patients met criteria for non-response. There were no significant differences in the demographic variables as a function of treatment response (age: responders, 65.6 ± 7.8 years and non-responders, 64.3 ± 13.6 years; age at onset: responders, 64.7 ± 7.8 years and non-responders, 60.3 ± 13.3 years; duration: responders, 6.5 ± 2.1 and non-responders, 8.8 ± 4.3; education level: responders, 13.9 ± 2.9 and non-responders, 13.5 ± 1.9; MMSE: responders, 28.6 ± 1.2 and non-responders, 29.0 ± 0.8; and Week 12 citalopram dose: responders, 32.5 ± 8.7 and non-responders, 42.5 ± 5.0, p > 0.05). In fact, at the end of the study, the nonresponders were taking a higher dose of citalopram than responders.

**Correlations Between Baseline Metabolism and Change in HDRS Score From Pretreatment to Week 12 of Citalopram Treatment**

The correlations between baseline metabolism and change in HDRS score from pretreatment to Week 12 of citalopram treatment are shown in Tables 2 and 3 and Fig. 1. Positive correlations (higher baseline glucose metabolism is associated with greater reductions in HDRS score with treatment) were observed in the left medial frontal gyrus, right superior temporal gyrus, left fusiform gyrus, and cerebellum (culmen, bilaterally).

Negative correlations (lower baseline metabolism associated with greater reductions in HDRS score with treatment) were observed in the left anterior cingulate gyrus (BA 24 and BA 32, bilaterally), superior frontal gyrus (bilaterally), middle frontal gyrus (bilaterally), inferior frontal gyrus (bilaterally), precentral gyrus (bilaterally), left superior parietal lobule, inferior parietal lobule (bilaterally), right postcentral gyrus, right precentral gyrus, right precuneus, right cuneus, right parahippocampal gyrus, left insula, caudate (bilaterally), and left putamen.

**Correlations Between Change in Metabolism From Placebo to Acute Citalopram Administration and Change in HDRS Score From Pretreatment to Week 12 of Citalopram Treatment**

The correlations between change in metabolism from placebo to acute citalopram administration and change in HDRS score from pretreatment to Week 12 of citalopram treatment are shown in Tables 4 and 5 and Fig. 2. Positive correlations (greater reductions...
TABLE 3. Negative Correlations (Lower Baseline Glucose Metabolism is Associated With Greater Reductions in HDRS Scores During Treatment)

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FIGURE 1. Correlations Between Lower (Blue) or Higher (Red) Baseline Metabolism and Improvement of Depressive Symptoms. Significant Regions Are Displayed on a Three-Dimensional MR Rendering of a Representative Subject.

In metabolism from baseline to acute challenge are associated with greater reductions in HDRS score with treatment) were observed in the left anterior cingulate gyrus (BA 23), right anterior cingulate (BA 32), superior and medial frontal gyri (bilaterally), right inferior frontal gyrus, left precentral gyrus, right superior parietal lobule, inferior parietal lobule (bilaterally), postcentral gyrus (bilaterally), left precuneus, right supramarginal gyrus, right posterior cingulate gyrus (BA 31), middle occipital gyrus (bilaterally), cuneus (bilaterally), left lingual gyrus, right fusiform gyrus, left superior temporal gyrus, left middle temporal gyrus, right parahippocampal gyrus, left insula, and culmen (bilaterally). Negative correlations (increases in metabolism from baseline to acute challenge are associated with greater reductions in HDRS score with treatment) were observed in the left middle frontal gyrus.

Although gender differences in the baseline or change in HDRS score with citalopram treatment were not observed, voxel-wise comparisons of the correlations between gender groups in SPM5 showed that the correlations between the change in metabolism and change in HDRS scores were significantly greater in men than women. Significantly greater positive correlations in men were observed in the right (BA 24) and left (BA 32) anterior cingulate gyrus (right: 8 37–2 and 3.03 and left: -7 36 18 and 3.82; Talairach coordinates and z score, respectively), right medial frontal gyrus (27 26–27 and 3.15), bilateral precentral gyrus (right: 58 1 29 and 3.01; left: -46 0.49 and 3.19), right superior temporal gyrus (BA 22; 66 –28 13; and 4.05), right postcentral gyrus (22 –29 67 and 3.49), and left precuneus (BA 7; -15 –58 55; and 3.32). Significantly greater negative correlations...
in men than women were observed in the left occipital cortex (BA 17; −7 −83 12; and 3.44).

CONCLUSIONS

In this study, greater improvement of depressive symptoms (reductions in HDRS score) with chronic citalopram treatment was associated with lower pretreatment cerebral glucose metabolism and greater reductions in cerebral glucose metabolism after acute, IV administration of citalopram. At baseline, higher glucose metabolism in the rostral anterior cingulate (BA 24, 32), frontal and parietal cortices, striatum (caudate and putamen), and limbic/paralimbic regions (insula and parahippocampal gyrus) was associated with less improvement of depressive symptoms with citalopram treatment. This finding is consistent with observations of cortical hypermetabolism in geriatric depressed patients relative to controls and of correlations between higher metabolism and greater severity of depression and anxiety symptoms in the patients before treatment. Several regions including the left medial frontal gyrus, right superior temporal gyrus, left fusiform gyrus, and bilateral cerebellum showed the opposite association (greater improvement associated with higher metabolism), which may represent a compensatory response in these mainly sensory and motor regions for change in other brain regions.

The reductions in cerebral metabolism after acute citalopram administration that were correlated with improvement of depressive symptoms occurred in many of the same regions in which the baseline associations were observed. The notable differences between the baseline and acute citalopram analyses...
were that the striatal regions showed correlations with baseline metabolism only, whereas more extensive changes in posterior cortical regions were observed in the acute citalopram condition only (e.g., right supramarginal and fusiform gyri, left lingual gyrus, left superior, and middle temporal gyri). The correlations between less depressive symptom improvement and higher striatal metabolism in the baseline condition and not the acute citalopram condition suggest that the underlying mechanism may be another neurotransmitter aside from serotonin. Other neurochemical mechanisms might be involved including increased glutamate concentrations or structural pathology in fronto-striatal circuitry that might result in an increase of striatal metabolism by disinhibition. The left middle frontal gyrus was the only region that showed the opposite association (increased metabolism was associated with greater improvement of depressive symptoms). This was the only region that showed decreased metabolism in the geriatric depressed patients compared with controls which may explain this opposite finding. With respect to gender differences, the male depressed patients showed significant greater correlations between metabolic responses and clinical improvement than women even though the magnitude of clinical improvement did not differ significantly between groups. The greater association between clinical and metabolic responses in men is consistent with reports of greater serotonin metabolism in men than women and may be associated with the greater vulnerability of women than men to depression.

In comparing the correlations with treatment response for the acute citalopram study to the earlier study of correlations between the metabolic effects of TSD and paroxetine response, similar anterior cortical regions show correlations in both studies. The acute citalopram data show a more extensive brain network of correlations including more posterior cortical regions. This observation may be explained by a greater neurochemical effect of acute citalopram compared with TSD or possibly differences in patient characteristics, although the samples are similar in such variables as magnitude and rate of treatment response. Neurochemical brain imaging studies of the acute effects of IV administration of citalopram have shown significant serotonin transporter occupancy in striatum, thalamus, brainstem, amygdala, and hippocampus and increases in striatal dopamine concentrations. Thus, both primary and secondary neurochemical effects of citalopram have been observed in the same time frame as the cerebral metabolic effects observed in this study. Given the regional distribution of the correlations, the alterations in cerebral metabolism may reflect the effects of serotonin transporter occupancy on cortico-cortical circuits that are likely to be mediated through a glutaminergic mechanism. In addition, many of the regions that are “hypermetabolic” at baseline and are affected by citalopram treatment are regions that comprise the “default network” and that demonstrate beta-amyloid deposition in demented and nondemented elderly. As increased glutamate activity is observed in amyloid transgenic mouse models and serotonin inhibits cortical glutamate, a secondary consequence of beta-amyloid deposition and decreased serotonin functional integrity could be glutamate hyperactivity, which would increase glucose metabolism. Citalopram treatment may decrease metabolism by decreasing glutamate concentrations. Thus, correlations in the resting state and after acute citalopram administration
provide different functional neuroanatomic and mechanistic information associated with depressive symptom improvement.

The majority of studies that have evaluated baseline or acute cerebral metabolism or neuroreceptor measures relative to clinical treatment outcome have been performed in midlife depressed patients. There is some evidence, consistent with findings of this study, that baseline hypermetabolism of the pregenual and subgenual cingulate cortices (BA 24 and BA 32) predicts worse treatment response to venlafaxine or cognitive behavior therapy. Lower midbrain metabolism was also associated with better antidepressant treatment response. Other studies of SSRI treatment and TSD in midlife depressed patients have reported opposite findings in the rostral anterior cingulate cortex and frontal cortex. As described, the findings in older depressed patients may be a secondary consequence of neuropathological processes, in contrast to findings in some studies of midlife depressed patients. MR spectroscopy studies suggest that bioenergetic abnormalities related to mitochondrial dysfunction may be associated with treatment response. These studies have shown that 1) lower basal ganglia beta nucleoside triphosphate and purine intensities (in women) was associated with better treatment response to fluoxetine and 2) higher baseline phosphocreatine was associated with better treatment response to T3 augmentation. Serotonin imaging studies have shown that increased 5-HT1A binding in cortical and limbic regions and the raphe nuclei and lower serotonin transporter (SHTT) binding in the anterior cingulate, amygdala, and midbrain were associated with poorer SSRI treatment response. As increased 5-HT1A binding may represent an upregulation due to decreased serotonin concentrations and the lower transporter binding may suggest a loss of serotonin projections, these observation suggest serotonin hypofunction in nonresponders. These observations are consistent with the findings of this study that suggest a blunted metabolic response to acute citalopram is associated with a poorer antidepressant response.

Several issues should be considered in the interpretation of the data from this study. As described in the Methods section, the acute citalopram administration was performed in a fixed order. The chronic citalopram treatment phase was open labeled, and a placebo-treated group was not included. It is important to note that the rate of treatment nonresponse to citalopram in this study (25%) was similar to that of placebo controlled trials. Another important consideration is that the HDRS measures the core symptoms of depressed mood, in addition to the vegetative signs of depression, so the correlations represent metabolic alterations associated with the net effect on different aspects of depressive symptomatology.

In summary, lower pretreatment cerebral glucose metabolism in the rostral anterior cingulate, prefrontal cortex, striatum, and limbic/paralimbic regions was associated with greater improvement of depressive symptoms in geriatric depressed patients. Furthermore, greater decreases in cerebral glucose metabolism after acute serotonin intervention were associated with a greater antidepressant effect of citalopram. The regions affected uniquely in the acute citalopram condition compared with baseline metabolism were temporal, parietal, and occipital cortical regions. The anterior cortical findings are consistent with the prior study that showed an association between the cerebral metabolic effects of TSD and the antidepressant response. The regional pattern of the acute citalopram effects in cortical and limbic regions includes the targets of serotonergic projections, which suggest that the changes in metabolism reflect the functional integrity of the serotonin system or serotonin modulation of glutamate concentrations. These regional cerebral metabolic findings are consistent with the results of other studies in geriatric depression that have shown correlations between poorer treatment response and white matter connectivity in similar cortical and limbic pathways. The results of this study suggest that the dynamic response of the brain to an acute increase in serotonin, the cerebral metabolic response to acute citalopram, is indicative of the capacity of the brain to respond to a course of chronic citalopram treatment. Future studies should evaluate the extent to which the acute metabolic and neurochemical changes associated with other pharmacologic classes of antidepressants (e.g., selective noradrenergic reuptake inhibitors), somatic treatments (ECT and transcranial magnetic stimulation), and psychotherapy are associated with improvement in depressive symptoms to determine whether the early metabolic neurochemical changes represent biomarkers of treatment response. Although the integration of neuroimaging studies into clinical trials is logistically challenging,
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such studies are critical to developing neuroimaging biomarkers of treatment response in psychiatric disorders.

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References