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Pretreatment regional brain glucose uptake in the midbrain on PET may predict remission from a major depressive episode after three months of treatment

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Abstract

In order to test the hypotheses that pretreatment metabolic activity in the midbrain and the rostral anterior cingulate may predict remission in response to medications enhancing monoaminergic transmission, we compared relative regional cerebral metabolic rate of glucose (rCMRglu) using positron emission tomography (PET) in medication-free patients with major depression who remitted after 3 months of monoaminergic medication, with non-remitters on the same treatment. [^{18}F]-FDG PET was conducted in a group of 33 drug-free DSM-IV major depression subjects prior to antidepressant treatment. Patients were prescribed paroxetine initially (61%) unless they had failed paroxetine previously. Treatment was then managed by the subjects' own physician with 91% receiving a selective serotonin reuptake inhibitor and 78% another non-selective monoamine reuptake inhibitor during the 3 months of treatment. Voxel-based parametric brain maps of remitters were compared with maps of non-remitters using SPM2. Remission was defined as a N50% decrease in and a final score of ≤10 on the 24-item Hamilton Depression Rating Scale. We found that treatment remitters have lower activity in a single contiguous brain region (with global maxima in the midbrain, cluster level P=0.013, corrected for multiple comparison (CMC)), prior to treatment, compared with non-remitters to 3 months of community-based monoaminergic antidepressant treatment. Degree of improvement correlated with pretreatment midbrain activity. Pretreatment clinical picture and intensity of treatment did not distinguish remitters. No other area of the brain showed a significant difference between remitters and non-remitters even with CMC completely disabled. Lower relative regional brain activity in the region of monoaminergic nuclei prior to treatment predicts remission in response to 3 months of antidepressant treatment, despite no clinical differences at baseline and no difference in treatment intensity. Brain imaging is a potential objective laboratory technique that may guide treatment selection where clinical methods have not shown promise. Prospective studies are needed to replicate these findings and determine whether outcome prediction is limited to a specific class of antidepressants.

Keywords

Depression; PET; FDG; Brain regions; Remission; Antidepressant treatment; Outcome; Positron emission tomography

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1. Introduction

Major depressive disorder (MDD) is one of the leading causes of disability and burden of illness worldwide (Evans and Charney, 2003) and estimated to be second only to cardiovascular disease by 2020 (Michaud et al., 2001). Despite this, the majority of patients with MDD are inadequately treated (Oquendo et al., 1999; Kessler et al., 2003). Even with adequate treatment, response to treatment, defined as a 50% improvement in the Hamilton Depression Rating Scale (HDRS) score, usually occurs in only 50–60% of individuals (Panel, 1999). Rates of remission after antidepressant treatment, defined as both a 50% decline in HDRS and a final 17-item score of <7 or <10 for the 24 item HDRS (Frank et al., 1991), are even lower, only 20%–35% (Mann, 2005). Antidepressants currently in clinical use (selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, selective norepinephrine reuptake inhibitors, and tricyclic antidepressants) primarily target monoaminergic transmission and much evidence has accumulated demonstrating abnormalities of the monoaminergic systems in mood disorders. It is unclear why some patients respond well and others respond poorly to antidepressant treatments that target the monoaminergic system. Nevertheless, prediction of remission in response to monoaminergic antidepressants requires an understanding of the biologic heterogeneity of the etiology and pathophysiology of major depression.

Ten studies, conducted after 1989, utilized F^{18}-fluorodeoxyglucose positron emission tomography (FDG-PET) to map brain regions that predict antidepressant treatment response in MDD (Wu et al., 1992; Little et al., 1996; Buchsbaum et al., 1997; Mayberg, 1997; Brody et al., 1999; Ketter et al., 1999; Kimbrell et al., 1999; Wu et al., 1999; Brannan et al., 2000; Brody et al., 2001; Kennedy et al., 2001; Saxena et al., 2003; Little et al., 2005); these are summarized in Table 1. The rCMRglu in various parts of the temporal lobe region predicted treatment response in 40% of studies (Little et al., 1996; Wu et al., 1999; Saxena et al., 2003; Little et al., 2005), various parts of the anterior cingulate in 60% of the studies (Mayberg 1997; Brody et al., 1999; Wu et al., 1999; Brannan et al., 2000; Kennedy et al., 2001; Little et al., 2005); various parts of the prefrontal cortex (PFC) in 70% of studies (Little et al., 1996; Buchsbaum et al., 1997; Wu et al., 1999; Brody et al., 2001; Kennedy et al., 2001; Saxena et al., 2003; Little et al., 2005). Note however, that in Table 1 the studies we found in the literature do not agree on the exact location (Brodmann area), direction or laterality of the metabolic change predicting response or non-response to treatment. There is no ready explanation for these disagreements, but we speculate that some of these differences may be explained in part by imaging methods and heterogeneity of relatively small patient samples. In addition, all of these studies investigated response to treatment and not remission. Remission is a valuable clinical endpoint because it indicates that treatment has been fully effective; therefore we sought to determine the brain regions associated with remission.

Brain regions that may predict clinical response may be hypothesized based on the monoamine deficiency hypotheses of depression that posit diminished brain monoaminergic function (Achor, 1959; Kur'Ianova, 1959; Stein, 1961; Koutsky et al., 1962; Bunney and Davis, 1965; Coppen, 1967; Feer, 1967; Schildkraut, 1967; Coppen, 1969; van Praag et al., 1969). We hypothesize that monoamine reuptake inhibitors are more likely to be therapeutic in cases of depression where monoaminergic deficiency is part of the abnormality contributing to the development of the depressive symptoms. If monoaminergic deficiency leads to abnormal glucose uptake, than FDG-PET may predict remission. Another hypothesized abnormality that may predict remission is hyperactivity in the rostral anterior cingulate that is reduced by antidepressant treatment regardless of whether drug or psychotherapy treatment is employed (Mayberg et al., 1997).

We conducted PET-FDG scans on 33 medication-free patients with MDD who were awaiting treatment for a major depressive episode (MDE), and then re-evaluated them after 3 months of naturalistic antidepressant treatment. Remission was defined *a priori* as a 50% decrease in the 24-item HDRS and a final score of ≤10 (Frank et al., 1991; Bschor et al., 2002; Smith et al., 2002). Baseline rCMRglu was mapped and compared between remitters and non-remitters. As is, evident from Table 1 there are no replicated and validated regions of interest (ROIs) predicting remission in the literature; therefore, we chose an unbiased voxel-based approach to analyze the data in addition to an ROI-based analysis.

2. Methods

2.1. Subjects

Thirty-three patients enrolled in a baseline PET study agreed to be followed during their community-based treatment and were included in this study. All patients met DSM-IV criteria for MDD (American Psychiatric Association. and American Psychiatric Association. Task Force on DSM-IV, 1994) and a current major depressive episode with a score greater than 16 on the 17-item HDRS (Hamilton 1960). The subjects gave written informed consent as approved by the Columbia University Medical Center institutional review board. Demographic data, psychiatric, medical, developmental and family history were recorded on Columbia University Baseline Demographic/History Form. History, physical, and laboratory results were assessed for inclusion/exclusion criteria. Exclusion criteria included other comorbid Axis-I disorders, significant medical conditions (especially those affecting the brain or serotonergic system, e.g.: Cushing's disease, Alzheimer's disease, migraine and temporal lobe epilepsy), family history of schizophrenia, pregnancy, the use of medication known to affect serotonin function (list may be provided upon request) or brain activity within 2 weeks of the scan except benzodiazepines (ativan, but not within 3 days of the scan) and electroconvulsive therapy (ECT) within 3 months of the scan. Pre-menopausal women were studied within 14 days of the onset of menses.

2.2. Treatment

Prior to PET scan, patients were medication-free for a minimum of 2 weeks (6 weeks for fluoxetine hydrochloride and 1 month for oral antipsychotic agents). Eleven (6 of 11 in the remitter (R) and 5 of 22 in the non-remitter group (NR)) patients were naïve to psychotropic medication. The R and NR groups did not differ in the class or type of medication taken (Table 2) prior to entering the study or in the number of days off medications prior to scanning (F=0.48, df=15, P=0.8; F=3.46, df=1, P=0.104, respectively).

Physicians employed in the General Clinical Research Unit at the New York State Psychiatric Institute treated and monitored inpatients. The decision to treat as outpatient or inpatient was determined based on clinical need. Inpatients were evaluated by their physicians at least three times weekly and were monitored continuously by clinical ward staff. Outpatients were evaluated at least once a week by their community-based psychiatrists. After 4 weeks, all outpatients in active treatment were seen monthly, unless clinical status indicated differently.

All patients were initially treated with paroxetine (61%) except for those who had failed paroxetine in the past or where the clinician felt the patient required ECT. For those initially receiving paroxetine, 20 mg was given daily for 3 weeks and then adjusted over 6 weeks depending on clinical response or side effects up to 60 mg per day. Additional pharmacotherapy was added as deemed necessary by the treating psychiatrist. Table 2 lists the average number of medications used per patient in each class of medication. Adequacy and intensity of treatment were determined by a computerized version (Oquendo et al.,

2003a,b) of the Antidepressant Treatment History Form (ATHF) (Sackeim et al., 1990). A therapeutic dose was defined as a score of 3 or greater on a scale of 0 to 5 on this instrument, which scores the adequacy of antidepressant treatment trials for the major pharmacological antidepressant categories and ECT and has been shown to have good reliability and validity (Sackeim et al., 1990; Prudic et al., 1996). For all categories of antidepressants, the minimum duration of the treatment with a specific dose is 4 weeks. The minimum adequate daily dose for the tricyclics is at least 200 mg of imipramine hydrochloride or its equivalent; for SSRIs, the minimum daily dose is at least 20 mg of fluoxetine or its equivalent; for phenelzine, the minimum is at least 61 mg; for venlafaxine, the minimum is 225 mg; for bupropion, the minimum is 300 mg; and for ECT, the minimum is more than six unilateral or bilateral treatments. See the work of Sackeim et al. (1990) for further details. One of the subjects within the remitter group did not have sufficient data to determine intensity of treatment.

2.3. Baseline evaluation and treatment response, remission assessment

Prior to initiating treatment, the severity of disease was measured using the 24-item HDRS and the Beck Depression Inventory (BDI) (Beck and Beamesderfer, 1974) within 24 h of the baseline PET scan and again at 3-months follow-up. The change in rating scales was calculated by subtracting post-treatment scores from pretreatment scores. One baseline and two 3-months BDI scores were not available for analysis. Remission was defined as both a 50% decline in 24-item HDRS and a final score of ≤10 at the 3-month assessment (Frank et al., 1991; Bschor et al., 2002; Smith et al., 2002). All ratings were done by clinicians without knowledge of the medication and not involved in the treatment of the patients.

2.4. Image acquisition and analysis

Acquisitions of PET and MRI images were preformed as previously described (Mann et al., 1996a,b). Five mCi of ^{18}F-FDG were administered and subjects looked at a cross-hair in a quiet room for the first 15 min of the uptake phase. Head movement was restricted in the scanner with an individually molded thermoplastic head holder. Image analysis was performed using Statistical Parametric Mapping software (SPM2; Institute of Neurology, University College of London, London, England) implemented in Matlab 6.5 (The Mathworks Inc, Natick, Mass) (Friston, 1994; Friston et al., 1995), with spatial normalization and adjusting for multiple comparisons (Wright et al., 1995). The effects of global metabolism were controlled by normalizing individual voxel counts to total gray matter counts (global normalization and proportional scaling in SPM2). Smoothing was done with an 8 mm Gaussian Kernel. A *t*-test on a voxel-by-voxel basis was used to identify clusters where remitters had significantly higher or lower rates of mean rCMRglu than non-remitters, while controlling for age and sex. Thresholds were set *a priori* to $P=0.01$ and to $P\leq 0.05$ for height and extent thresholds respectively after correction for multiple comparisons by SPM2.

We have previously published the neuroanatomic correlates of the objective psychopathologic components of MDD in the same cohort using the Hamilton Depression Rating Scale (Milak et al., 2005). Subgroups of this study population were the subject of other papers including: a subgroup who had a history of a suicide attempt were the subject of an earlier paper on regional brain correlates of suicidal behavior in major depression (Oquendo et al., 2003a,b); a subgroup with borderline personality disorder (Oquendo et al., 2005); regional brain responses to serotonin in MDD (Anderson et al., 2004); patients with history of familial mood disorder (Kegeles et al., 2003); and a subgroup that received ECT therapy (Nobler et al., 2001). Although this cohort has been studied before, the current article presents new data obtained by completing follow-up and has never been published before.

3. Results

3.1. Demographic and clinical characteristics

Eleven (33%) subjects met remission criteria at 3-month follow-up. Clinical and demographic data are summarized in Table 2. The remitters and non-remitters did not differ on demographic characteristics. There was a trend for more females in the non-remitters, and therefore sex was included in the final model as a nuisance variable. At baseline assessment, there was no difference in the pretreatment severity of MDD between groups on the HDRS (P=0.983) and BDI (P=0.113). There was no group difference in duration of current MDE (U=68.5; z=−1.5; P=0.122). As expected at 3 months, remitters had lower scores on the HDRS (6.2+2.8) and BDI (4.5+3.7) compared with non-remitters (HDRS=25.4+7.7, BDI=28.1+10.8, t=−10.4, −9.0; df=29.3, 27.3; P<0.001, respectively), and showed greater improvement on both HDRS and BDI scores (Table 2).

3.2. Treatment intensity

The adequacy and intensity of treatment as assessed by the ATHF score (Sackeim et al., 1990), and the average number of pharmacologic agents used per subject by medication class, *did not differ* between remitters and non-remitters during the treatment phase (Table 2).

3.3. Statistical Parametric Mapping analyses

3.3.1. Comparing responders vs. non-responders—The voxel-based analysis (see Figs. 1 and 2) reveals a single contiguous brain region where remitters have lower mean rCMRglu compared with non-remitters (2498 voxels, cluster level P=0.013 corrected for multiple comparisons, global maximum at Talairach (xyz) coordinates of 2, −24, −20, midbrain). This area encompasses parts of the midbrain, right parahippocampal gyrus, right putamen, right lateral globus pallidus and right thalamus (including the ventral lateral and ventral anterior nuclei). Based on this sample we determined whether higher midbrain metabolic activity may predict non-remission in MDE, finding specificity=0.64; sensitivity=0.82; positive predictive value (PPV)=0.82; negative predictive value (NPV)=0.64 (with sex and midbrain metabolic activity in the logistic regression model).

By conducting a correlation analysis on the entire patient sample restricted to this region of interest described above (SPM2, small search volume correction, SVC) we found a significant correlation between the percent decline in HDRS score in response to treatment and rCMRglu prior to treatment (927 voxels, cluster level r^2=0.32; P=0.01 corrected for multiple comparisons, global maximum at Talairach (xyz) coordinates of 0, −24, −24, midbrain).

Brodmann Area 24 relative activity did not differ between groups, although ventral limbic structures on the right side showed lower activity in remitters. Note, however, that we did not exactly replicate the study cited (Mayberg et al., 1997) as they compared responders and non-responders to healthy volunteers and not to each other. Moreover, they reported non-overlapping coordinates in and around the right anterior cingulate (24a/b) x=1 y=44 z=10 z-score=+2.10 for responders and x=10 y=38 z=12 z-score=−3.21 non-responders, where responders were hypermetabolic (24a/b mean rCMLGlc=1270±70) and non-responders hypometabolic (1134±111) compared to controls (1198±85). Nevertheless, in an attempt to avoid the possibility of washing out this finding with excessive correction for multiple comparisons, we repeated the analysis, turning off correction and restricting the search volume to an area located in the same part of BA 24a/b on either side individually, then combined, comparing remitters to non-remitters. Additionally, we surveyed the entire cingulate as well, then separately the entire brain and no suprathreshold voxels were found

exceeding a *z*-score of 1.96 (Mayberg et al., 1997) with either methods (outside of the area reported above in our current results).

3.3.2. Comparing remitters vs. non-remitters—Due to the preponderant use of responders vs. non-responders contrast in studies by others, instead of using remitters vs. non-remitters, we have reanalyzed the data using those definitions. However, we found no area in the brain where responders significantly differed from non-responders, when responder status is evaluated at the 3-months follow-up (with or without correction for multiple comparisons).

4. Discussion

We found a single contiguous region (with a global maximum in the midbrain) in depression where lower pretreatment relative metabolic activity predicts remission after 12 weeks of antidepressant treatment. This distinct difference was observed in the absence of baseline clinical differences and comparable antidepressant treatment in remitters and non-remitters. This finding, if replicated, suggests that brain imaging approach can detect differences, not seen clinically, that forecast clinical outcome and, as such, may be a step towards the development of an objective predictor of antidepressant treatment remission. Future studies need to determine whether brain imaging approaches can predict remission to specific subtypes of antidepressants in order to facilitate selection of the right antidepressant for the individual patient. Such predictors should shorten time to treatment response and remission from initial diagnosis by avoiding the current trial and error approach in antidepressant selection. This approach may reduce disease burden due to depression.

To date there is no biological marker in routine clinical use to predict treatment response or remission. This study shows that, despite the absence of pretreatment clinical differences, this PET scan can detect differences in regional metabolic brain activity that predict remission.

Our findings are consistent with a previous study (Wu et al., 1999) that found lower rCMRglu in responders in the right mesiotemporal cortex, parts of the basal ganglia and midbrain in responders (see Table 1). They also find differences between responders and non-responders in other brain regions, perhaps because they use sleep deprivation as the treatment.

Our study design and outcome measure of remission differ from the studies summarized in Table 1 only in part, because most studies examined degree of clinical improvement. We found that lower rCMRglu in midbrain and nearby regions predict remission, as well as degree of clinical improvement. Other studies identified regions such as prefrontal cortex, anterior cingulate and temporal lobe as related to clinical improvement. Differences in treatment modalities, patient population and scanning methodology may have contributed to differences in identified brain regions. Four studies (Little et al., 1996, 2005; Mayberg et al., 1997; Wu et al., 1999) compared rCMRglu in non-responders versus healthy controls. Some studies enrolled only outpatients (Little et al., 1996, 2005; Brody et al., 1999, 2001; Kennedy et al., 2001; Saxena et al., 2003) whereas others used inpatients exclusively (Mayberg et al., 1997; Wu et al., 1999), and the majority of the studies followed patients for only 6–8 weeks (Little et al., 1996, 2005; Mayberg et al., 1997; Brody et al., 1999; Kennedy et al., 2001; Saxena et al., 2003). Treatments for which response was assessed also varied amongst studies (see Table 1). Two studies enrolled subjects with comorbid Axis-I disorders (Saxena et al., 2003; Little et al., 2005). One included only male subjects (Kennedy et al., 2001).

Imaging methods varied with patients scanned at rest (Mayberg et al., 1997; Brody et al., 1999, 2001; Kennedy et al., 2001; Saxena et al., 2003) or performing variations of a continuous performance task during FDG uptake (Little et al., 1996, 2005; Buchsbaum et al., 1997; Wu et al., 1999). Studies also varied in method of image analysis, employing either a region of interest (Brody et al., 1999; Wu et al., 1999), Statistical Parametric Mapping (SPM) (Little et al., 1996, 2005; Kennedy et al., 2001) or both (Mayberg et al., 1997; Brody et al., 2001; Saxena et al., 2003). Three studies used correlation analysis to find regions that were associated with treatment response, correlating baseline rCMRglu and change in HDRS (Buchsbaum et al., 1997; Brody et al., 1999; Saxena et al., 2003), and Global Assessment Scale (GAS) (Saxena et al., 2003). There are also differences in the methods used to assess treatment response. Studies defined response based on changes in the HDRS (Buchsbaum et al., 1997; Mayberg et al., 1997; Wu et al., 1999; Brody et al., 2001; Kennedy et al., 2001), Clinical Global Impression Scale (CGI) (Little et al., 1996, 2005), or a combination of HDRS with other measures of depression severity, i.e. CGI (Brody et al., 1999) and GAS (Saxena et al., 2003) and set their criteria for response between 40 and 50% decrease in HDRS (Buchsbaum et al., 1997; Mayberg et al., 1997; Brody et al., 1999; Wu et al., 1999; Kennedy et al., 2001), and/or a CGI of moderate to marked response (Little et al., 1996, 2005; Brody et al., 1999). One study (Brannan et al., 2000) defined response as a score of ≤2 on the Lickert scale. Another study included subjects with decreases in the 17-item HDRS; but they were not separated into responders and non-responders (Brody et al., 2001). None of these methodological differences offer a direct explanation of the lack of reproducibility amongst the studies reviewed. An important problem in imaging studies is correction for multiple comparisons; note that most of these studies did not report whether such correction was used and/or how many other contrasts were tested. As mentioned in the Results section, we were not able to reproduce any of the findings listed in Table 1 (with one exception noted above), despite using a variety of different approaches, including one-tailed statistical contrasts without correction for multiple comparisons and/or restricting the search volume to specific regions of interest reported to be significant by studies in Table 1, which suggests that more standardized approaches and larger sample sizes are needed in order to avoid type-one error and sampling bias.

Several SPECT and PET scans using receptor-specific radioligands have found abnormal binding in the brainstem of depressed patients (Drevets et al., 1999, 2007; Morris et al., 1999; Dahlstrom et al., 2000; Willeit et al., 2000; Bhagwagar et al., 2004; Laasonen-Balk et al. 2004; Uusitalo et al., 2004; Newberg et al., 2005; Lehto et al., 2006, 2008; Meyer et al., 2006; Joensuu et al., 2007; Walter et al., 2007; Miller et al., 2008; Reimold et al., 2008). More recently, we and others have begun to scan indices of specific neurotransmitter systems, as predictors of antidepressant response. It has been reported that MDD patients with serotonin transporter (5-HTT) promoter region insertion were more responsive to placebo, as well as more responsive to SSRI than was the short allele group (Rausch et al., 2002). We found that lower serotonin transporter binding predicts poorer antidepressant response (Miller et al., 2006). Innis and colleagues found that higher pretreatment diencephalic 5-HTT availability significantly predicted better treatment response 4 weeks later (Kugaya et al., 2004). Linking these neurotransmitter-specific scan findings to more than just SSRI responses is an important future area of research. We also report elsewhere (Parsey et al., 2006a,b) that non-remission of major depression is associated with higher pretreatment brainstem 5-HT_{1A} binding (midbrain autoreceptors) and relate that to the higher autoreceptor expressing GG genotype. Based on this *imaging* finding the following model was proposed: the GG polymorphism is associated with greater 5-HT_{1A} gene expression in the midbrain raphe nuclei and hence the higher 5-HT_{1A} binding. As the 5-HT_{1A} receptors are presynaptic auto-inhibitory, more 5-HT_{1A} raphe autoreceptors would result in less serotonin neuron firing and decreased terminal field 5-HT release. This may be followed by a homeostatic upregulation of post-synaptic terminal field 5-HT_{1A} receptors.

The GG genotype by itself is also associated with resistance to a variety of antidepressant treatments (Albert 2004; Lemonde et al., 2004).

An important question is, how lower midbrain metabolic activity in remitters, in the present study, may be reconciled with fewer 5-HT_{1A} autoreceptors in the midbrain as predictors of better treatment outcome or, specifically, of remission? Since activating the 5-HT_{1A} receptors causes the opening of the potassium (K^+) channels, fewer available 5-HT_{1A} receptors are associated with the closing of the K^+ channels in the raphe serotonergic cell bodies. This in turn decreases the workload of the ATP-dependent K^+ pump, leading to lower metabolic activity in midbrain of the remitters. A major fraction of cerebral energy production is required for the extrusion of intracellular Na+ that enters during excitation and depolarization of neurons in other parts of the brain, suggesting higher firing leading to higher metabolic rates. However, in the raphe under wakeful rest and uneventful waking activity, serotonergic neurons display slow, clock-like activity of about 1 to 5 spikes/s (Jacobs and Fornal 1993; Frazer and Hensler, 1999). This slow firing barely changes (~1 to 1.25×) the resting workload of the Na/K-ATPase activity (Albers and Siegel, 1999). Therefore remitters with lower somato-dentritic 5-HT_{1A} receptor expression, and consequently closed K^+ channels, will have lower midbrain metabolic activity (despite slightly higher firing rates) than non-remitters.

Our results show that some subcortical ventral monoaminergic projection areas such as right parahippocampal gyrus, right putamen, right lateral globus pallidus and right thalamus, also have lower metabolic rates before treatment in remitters. We know from earlier studies that MDD subjects have higher rCMRglu in these regions prior to treatment (Milak et al., 2005), suggesting that those who later turn out to be remitters have less elevation in activity in these regions, prior to treatment, compared with patients who do not remit. In other words, less abnormality in those regions predicts better response. These findings are consistent with transmitter imaging studies of the 5-HT_{1A} and serotonin transporter binding sites where less abnormality predicts better treatment response (Parsey et al., 2006a,b).

It was first reported by Mayberg et al. (1997) that rCMRglu in the anterior cingulate may also be a predictor of favorable treatment response (not remission) by 60% of the studies. Note however, that there is disagreement between these studies in the location and direction of change in rCMRglu that discriminated responders from non-responders (see Table 1), moreover this metabolic abnormality was interpreted as an adaptive or compensatory response (not considered to be causally related) to depression and it was suggested that failure of this compensatory response may underlie poor outcome (Mayberg et al., 1997). We did not detect a relationship of remission or response with the subgenual anterior cingulate, perhaps in part because our study was designed for a different endpoint to improvement, but clearly this difference needs further research.

Limitations

This study involved a naturalistic community-based treatment, making the results more relevant to clinical practice, but as a consequence patients received a variety of treatments. Nevertheless 97% of the patients received antidepressant medications that increase monoaminergic transmission. Future controlled double blind cross-over studies are needed to determine whether brain imaging before treatment can predict improvement regardless of the mechanism by which the treatment enhances monoaminergic transmission, — or the findings described here are specific effects of a particular class of antidepressants.

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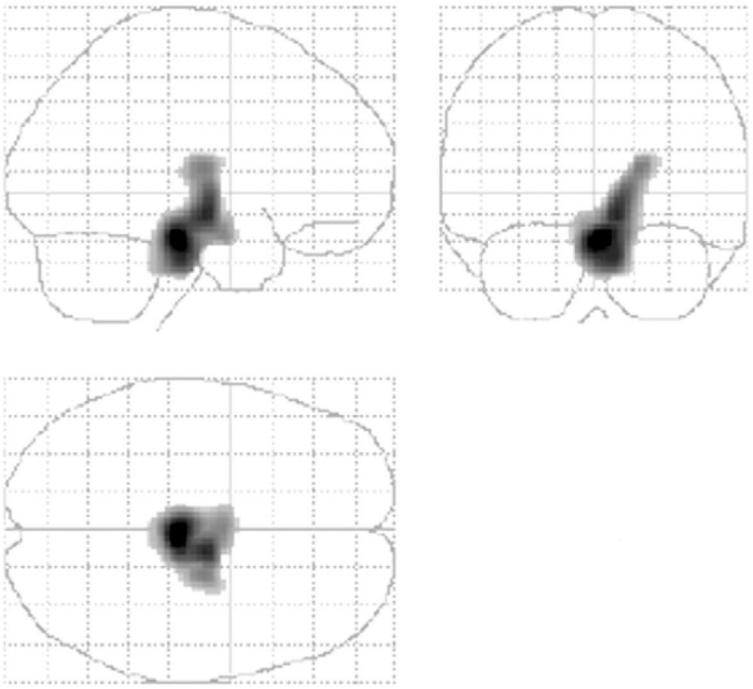

Fig. 1.
Statistical parametric map showing regions where major depression remitters after three months of treatment had lower rCMRglu than non-remitters. Regions shown as volume in glass brain.

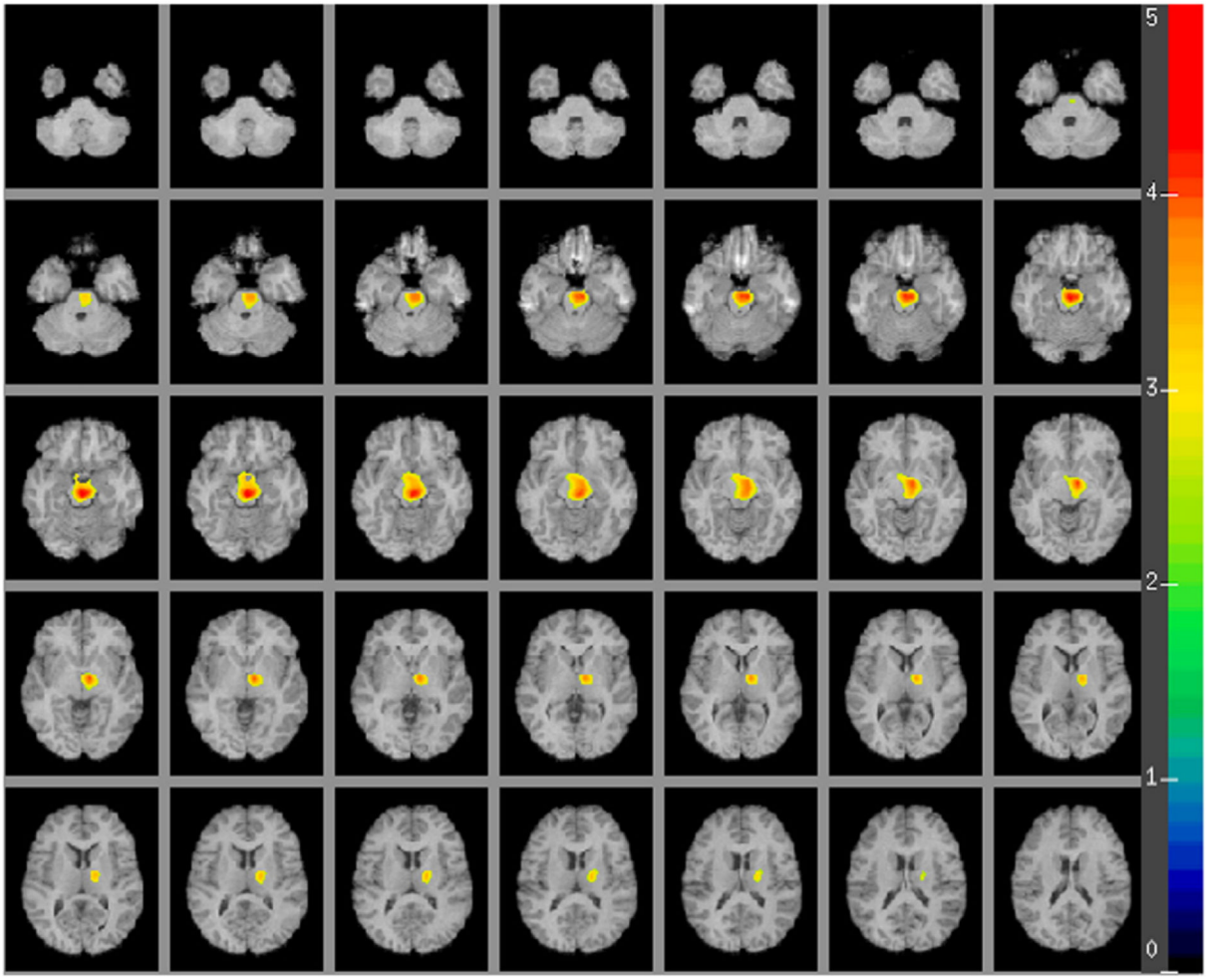

Fig. 2.

A human brain map in major depression depicting the region where antidepressant remitters demonstrate lower regional rates of cerebral glucose metabolism in comparison to the non-remitters. The color scale in the figure indicates the strength (*t*-score) of the correlation (*t*-score maps are overlaid on a series of transaxial slices (2 mm apart) of a coregistered MRI scan from 42 mm below to a 26 mm above a line connecting the anterior and posterior commissure).

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Table 1

FDG-PET studies of treatment outcome in major depression: table summarizes the ^{18}F-FDG-PET identified in the literature past 1996 that reported on regional brain glucose metabolic rate as a biological predictor of treatment outcome.

Authors and year	*N*	Treatment	Imaging analysis	Brain region																							
				Mesiotemporal cortex		Dorsal prefrontal cortex		Ventral prefrontal cortex		Anterior cingulate		Posterior cingulate		Insula		Parietal		Temporal		Occipital		Basal ganglia		Thalamus		Cerebellum		Midbrain	
				L/R/B		L/R/B		L/R/B		L/R/B		L/R/B		L/R/B		L/R/B		L/R/B		L/R/B		L/R/B		L/R/B		L/R/B		L/R/B	
				Rsp	NR	Rsp	NR	Rsp	NR	Rsp	NR	Rsp	NR	Rsp	NR	Rsp	NR	Rsp	NR	Rsp	NR	Rsp	NR	Rsp	NR	Rsp	NR	Rsp	NR
Little et al. (1996)	11	Venlafaxine or buproprion (randomized, with cross-over)	SPM			–/–/↓°												–/–/↓°								–/–/↓°			
Buchsbaum etal. (1997)	17	Sertraline (placebo-controlled, randomized)	BMP/correlation					↑/–/–																					
Mayberg (1997)	18	SSRI, TCA, buproprion	ROI							–/↑/–	–/↓/–																		
		(non-randomized)	SPM				↓/v/–[C]		–/–/↓	–/↑/–	–/↓/–	–/↓/–																	
Brody etal. (1999)	16	Paroxetine	ROI/correlation							↓/–/–																			
Wu et al. (1999)	36	Sleep deprivation	ROI				–/–/↑	–/↑/–			–/↓/–				–/↓/–			–/↓↑/–[D]	–/↓/–[D]		↑/–/–		–/↓/–					↓/–/–	–/↓/–
			*ROI	–/↓/–				↓/–/–		–/↑/↑[A]								–/–/↑										–/↓/–	
Brannan et al. (2000)	53	Antidepressants								↑/–/–												–/↑/–		–/–/↑					
Brody et al. (2001)	24	Paroxetine or ITP	ROI			–/↑/–		↑/–/–																					
		(non-randomized)	SPM			–/–/↑																–/–/↑		–/↑/–					
Kennedy et al. (2001)	13	Paroxetine	SPM			↓/–/–[phc]				–/↑/–												–/↓/–							
Saxena et al. (2003)	27	Paroxetine	ROI/correlation	–/↓/–																									
	44[B]		SPM			–/–/↑												–/↑/–											
Little et al. (2005)	20	Venlafaxine or buproprion	SPM	↓/–/–		–/–/↓		–/–/↓	–/–/↑	/–/↓[E]	–/↓/–[E]			–/↓/–			↓/–/–[F]	–/–/↓[C]		–/–/↑[G]	↑/–/–[G]	–/↓/↓°		–/–/↓[C]	c	–/–/↑			
		(randomized, cross-over)	SPM (absolute)																							↑/–/–			
			*SPM	↓/–/–				↓/–/–						–/–/↓		↑/–/–[F]		↓/–/–											
			*SPM (absolute)	↓/–/–				↓/–/–						–/–/↓															

Abbreviations: Comparison group are Controls unless otherwise indicated; *Comparison of Responders to Non-responders; *N*=number of depressed subjects, L/R/B=Left, Right, Bilateral, BMP=Biomedical Computer Program, SPM=Statistical Parametric Mapping, All SPM data are from normalized rCMRglu unless otherwise indicated. Results of Little et al. (1996) are from both absolute and normalized rCMRglu, A=data from 21 subjects not studied previously, B=MDD +/− comorbid OCD, C=decrease rCMRglu in right Brodmann area 44 and left Brodmann area 46/49 are unique to non-responders, phc=post hoc analysis, D=non-responders express decrease rCMRglu in Brodmann area 38/21, increase rCMRglu is seen in responders, decrease rCMRglu in responders is located in Brodmann area 37, E=non-responders to buproprion demonstrated decrease rCMRglu in right Brodmann area 32, while responders to venlafaxine demonstrated decrease rCMRglu in Brodmann area 32 bilaterally, F=non-responders to buproprion demonstrated decreased rCMRglu in left Brodmann area 4, responders to either medication demonstrated increase rCMRglu in left Brodmann area 40, G=venlafaxine non-responders only, buproprion responders only; ITP=Interpersonal therapy, °=coordinates not reported from SPM analysis.

Table 2

Characteristics of major depression study sample: comparison of remitters vs. non-remitters.

Characteristics	Remitters	Non-remitters		*P* value
Total *N*	11	22		
Female *N* (%)	4(36.4%)	17 (77.3%)		0.052[a]
Age	43.2±15.3	36.6±10.5		0.22
Years of education	16.8±3.0	15.6±2.3		0.25
Number of previous MDEs	4.9±5.6	3.1±2.4		0.33
Psychotic features (%)	0 (0%)	5(22.7)%		0.14[a]
HAMD-24				
Baseline	29.6±5.0	29.7±7.0		0.98
3 months	6.2±2.8	25.4±7.7		<0.001
Change in HDRS	− 23.5±5.2	−4.3±9.2		<0.001
BDI				
Baseline	26.8±9.4	32.9±9.8		0.11
3 months	4.5±3.7	28.1±10.8		<0.001
Change in BDI	− 23.4±8.1	−4.8±10.4		<0.001
Treatment intensity (ATHF)	3.5±0.5	3.6±1.3		0.74
On meds at 3 mos months (%)	10(90.9%)	21(95.5%)		1.00[a]
Average number of pharmacologic agents used			*t*	χ^2
Antidepressant	1.50±0.52	2.00±0.76	0.08	1.00[a]
SSRIs	0.91±0.30	0.91±0.61	1.00	0.64[a]
Paroxetine	0.45±0.52	0.68±0.48	0.22	0.27[a]
Antidepressant, other	0.18±0.40	0.68±0.72	0.04	0.67[a]
Tricyclics	0.36±0.50	0.23±0.43	0.42	0.44[a]
MAOI	0.09±0.30	0.18±0.39	0.51	0.64[a]
Anticonvulsant/mood stabilizer	0.18±0.40	0.59±0.73	0.10	0.13[a]
Lithium	0.09±0.30	0.32±0.48	0.16	0.22[a]
Antipsychotic, atypical	0.18±0.40	0.18±0.39	1.00	1.00[a]
Antipsychotic, typical	0.00±0.00	0.23±0.53	0.17	0.28[a]
Benzodiazepine	0.55±0.69	0.73±0.77	0.51	0.72[a]
Stimulant	0.00±0.00	0.18±0.50	0.24	0.54[a]
Hypnotic	0.00±0.00	0.05±0.21	0.49	1.00[a]
ECT	0.09±0.30	0.27±0.46	0.32	0.38[a]

Abbreviations: MDD (Major Depression Disorder); MDE (Major Depressive Episodes); HDRS (Hamilton Depression Rating Scale); ATHF (an automated version of the Antidepressant Treatment History Form; see methods (Oquendo et al., 2003a,b)). All *P* values are derived from paired *t*-test unless otherwise noted.

[a] *p*=Fisher's Exact *P* value for cross-tabulation.Values are mean±S.D. unless otherwise noted.