Functional anatomical correlates of antidepressant drug treatment assessed using PET measures of regional glucose metabolism

Wayne C. Drevets a, b, *, Wendy Bogers b, Marcus E. Raichle c, d, e, f

a Neuroimaging in Mood and Anxiety Disorders Section, National Institutes of Health, NIMH/MIB, Bethesda, MD, USA
b Departments of Psychiatry and Radiology, University of Pittsburgh, Pittsburgh, PA, USA
c Department of Neurology and Neurological Surgery (Neurology), Washington University School of Medicine, St. Louis, MO 63110, USA
d Department of Anatomy and Neurobiology, Washington University School of Medicine, St. Louis, MO 63110, USA
e Division of Radiological Sciences, Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, MO 63110, USA
f McDonnell Center for the Studies of Higher Brain Function, Washington University School of Medicine, St. Louis, MO 63110, USA

Abstract

Neurophysiological studies of major depression performed using PET imaging have shown abnormalities of regional cerebral blood flow (CBF) and glucose metabolism in multiple prefrontal cortical and limbic structures that have been more generally implicated in emotional processing. The current study investigated the effects of antidepressant drug treatment in these regions using PET measures of glucose metabolism. Subjects with primary MDD (n=27) were imaged while unmedicated and depressed, and, of these, 20 were rescanned following chronic antidepressant drug treatment. Regional metabolism was compared between unmedicated depressives and controls and between the pre- and post-treatment conditions in regions-of-interest (ROI) where metabolism or flow had previously been shown to be abnormal in unmedicated depressives. At baseline, the mean metabolism was increased in the left and right lateral orbital cortex/ventrolateral prefrontal cortex (PFC), left amygdala, and posterior cingulate cortex, and decreased in the subgenual ACC and dorsal medial/dorsal anterolateral PFC in the unmedicated depressives relative to controls, consistent with the results of previous studies. Following treatment, metabolism significantly decreased in the left amygdala and left subgenual ACC, and corresponding changes in the orbital and posterior cingulate cortices approached significance. The metabolic reduction in the amygdala and right subgenual ACC appeared largely limited to those subjects who both responded to treatment and remained well at 6 months follow-up, in whom the reduction in amygdala metabolism tightly correlated with the reduction in HDRS scores. The magnitude of the treatment-associated, metabolic change in the amygdala also correlated positively with the change in the stressed plasma cortisol levels measured during scanning. These data converge with those from other PET studies to indicate that primary MDD is associated with abnormal metabolism in limbic and paralimbic structures of the mesiotemporal and prefrontal cortices. Chronic antidepressant drug treatment reduces metabolism in the amygdala and ventral ACC in subjects showing a persistent, positive treatment response. In contrast, the persistence of the abnormal metabolic deficits in the dorsomedial/dorsal anterolateral PFC in MDD during treatment may conceivably relate to the histopathological changes reported in these regions in post mortem studies of MDD.

Keywords: Antidepressant drug treatment; Positron emission tomography; Regional glucose metabolism

1. Introduction

Neuroimaging studies of major depressive disorder (MDD) have provided invaluable information about the anatomical systems involved in depression. Positron emission tomography (PET) studies of cerebral blood flow (CBF) and glucose metabolism in depressed subjects demonstrate that neurophysiological activity is abnormal in several brain structures that have been shown by other types of evidence to participate in the modulation of emotional behavior. The relationships between metabolism and depression severity in these regions suggest that, in some structures, the abnormal neural activity is positively correlated with depressive symptoms, whereas, in others,
activity may instead comprise a compensatory response that modules such symptoms (reviewed in Drevets, 2001).

The neural circuits implicated by PET studies of depression involve anatomical loops between the medial and orbital prefrontal cortex (PFC) and anatomically related areas of the mesiotemporal cortex, striatum, and thalamus (reviewed in Drevets, 2000, 2001; Drevets et al., 2002; Öngür and Price, 2000). In the PFC, most studies comparing unmedicated depressed subjects with primary MDD have reported elevated CBF and metabolism in the lateral orbital/subgenual PFC, the anterior cingulate cortex (ACC) anterior to the genu of the corpus callosum (i.e., pregenual ACC) and the anterior insula during the eyes-closed, at-rest condition (reviewed in Drevets, 2000; Brody et al., 2002). These areas share extensive, reciprocal anatomical connections to the amygdala, which has also been shown to have abnormally increased activity in MDD (reviewed in Drevets et al., 2002; Öngür and Price, 2000). Elevated physiological activity has also been reported in the posterior cingulate cortex, which sends extensive projections to the pregenual ACC, the anteroventral striatum (Wilson et al., 2002), which encompasses the accumbens area and would receive projections from the amygdala, the orbital and medial PFC (Drevets et al., 2001; Öngür and Price, 2000; Russchen et al., 1985), and the medial thalamus, within which the mediodorsal nucleus also shares reciprocal projections with the amygdala and PFC (Drevets et al., 1992, 1995c; Price et al., 1996).

In addition to these areas of increased metabolic activity, areas of reduced CBF and metabolism were found in the ACC ventral to the genu of the corpus callosum (i.e., subgenual ACC; Drevets et al., 1997) and the dorsomedial/dorsal lateral PFC in depressives relative to controls (Bell et al., 1999, and replicating Baxter et al., 1989 and Bench et al., 1992). The subgenual ACC and the dorsal anterolateral PFC were subsequently shown to contain abnormal reductions in cortex volume and/or histopathological changes in MDD and BD by in vivo, morphometric MRI and post mortem neuropathological studies. The reductions in physiological activity seen in PET images from MDD and BD samples may thus be accounted for by structural abnormalities of the corresponding cortex.

The current study assessed metabolic effects of antidepressant drug treatment in regions-of-interest (ROI) where abnormalities of basal metabolism were reported in MDD by Drevets et al. (1992, 1997, 2002). The ROI selected for comparing metabolism between pre- and post-treatment scans were defined in a manner that would avoid biasing results toward deviations from the mean in the pre-treatment group. Some of the differences reported between depressed and control samples in previous studies were detected using voxel-by-voxel approaches which optimized the localization of peak, intergroup differences in mean CBF or metabolism relative to the variance by computing statistical parametric images consisting of t- or Z-scores (Drevets et al., 1992, 1997). These image data were thus sensitive to the noise distribution as well as to the mean intergroup differences in physiology (Drevets et al., 1992; Friston et al., 1991). The application of ROI defined based upon such peak differences between depressives versus controls could, therefore, introduce bias in the results of pre- versus post-treatment studies performed in the same subject sample (e.g., changes in the post-treatment scans obtained using such an approach could simply reflect regressions to the population mean).

The ROI of primary interest for brain structures studied herein were thus defined using either atlas-based, stereotaxic coordinates of peak differences between depressives and controls which had previously been identified in voxel-by-voxel analyses of image data from independent samples of depressives and controls (Drevets et al., 1992; Price et al., 1996; Talairach and Tournoux, 1988), or ROI defined on specific grey matter structures in MRI images that had been co-registered to the corresponding PET images (Drevets et al., 1997). The stereotaxic approach was used to assess treatment effects in the amygdala, while PET-MRI co-location was employed to investigate treatment-associated changes in the subgenual PFC (as described in Drevets et al., 1997) and lateral orbital cortex.

The lateral orbital ROI was positioned within the area of the left ventrolateral PFC where Drevets et al. (1992) demonstrated increased CBF in depressives versus controls (in samples independent from those studied herein). In this previous study a statistical parametric image (t-value image) was used to delimit an area where CBF inherently differed between one sample of depressives and controls, and the statistical significance of this difference between depressives and controls was then established by data obtained in the same ROI in a second, independent set of depressives and controls. This earlier study involved lower resolution PET images (PET VI measures of H$_2$O uptake) than those available for the current study, however, so the ventral PFC ROI delimited in Drevets et al. (1992) required modification in order to assess cortical glucose metabolism in the higher resolution images employed herein. This ventral PFC ROI where CBF had been abnormally elevated in depression in Drevets et al. (1992) included portions of the lateral orbital cortex, the ventrolateral PFC, the anterior insula, the pregenual ACC, and the frontal polar cortex (Drevets et al., 1992). An ROI defined to encompass this anatomical extent which also accommodated the higher spatial resolution FDG images acquired on the 953B scanner by narrowing its spatial extent was previously assessed in MDD by Drevets et al. (1995c). Metabolism was elevated in this area in depressives vs. controls, and decreased following antidepressant treatment (Δ=-5.4±10.0%, P<0.05) in a subsample of the subjects described herein. However, because of the marked anatomical variability of the orbital surface contour across humans (e.g., currently available spatial transformation algorithms have no ability to address the problem that the
Although several studies reported abnormalities of CBF or disorders prior to MDD onset, history of mania, treatment (Brody et al., 2001; Saxena et al., 2002). Similarly, and neurological disorders, history of other psychiatric correspond imaging abnormalities in the PFC in unmedicated depressives versus controls, and decreased during antidepressant drug treatment (−6.8±11%, P<0.02), with the reduction in metabolism and HDRS scores correlated at r=0.47 (P<0.05) in the MDD sample described herein. However, this ROI also extended beyond the brain edge in some subjects, leading to a high coefficient of variance across subjects.

Consequently, to more accurately and reliably measure cortical metabolism in a manner that addressed the variable contour of the orbital surface, the current study defined an orbital cortex ROI directly on each subject’s anatomical MRI image and extracted the corresponding metabolic data from coregistered PET images. This ROI sampled part of the lateral orbital area encompassed within the larger ROI from our original study (Drevets et al., 1992), and was more specifically defined to encompass the area where Rajkowska et al. (1999) reported abnormal reductions of grey matter volume and glial cells in a MDD sample studied post mortem. This histopathological pattern has also characterized the left subgenual PFC (Drevets et al., 1998; Öngür et al., 1998) and the amygdala (Bowley et al., 2002) in post mortem studies, and is hypothesized to be related to the hypermetabolic activity in these regions in PET studies (see Discussion).

An alternative approach was employed to address treatment effects in the dorsomedial/dorsal anterolateral PFC and the posterior cingulate cortex where abnormalities of regional CBF and metabolism had been reported in MDD, but where the specific localization of intergroup differences remained ambiguous. The spatial locations of reported differences between depressives and controls has varied so widely across studies in these areas that new studies performed in independent subject samples to assess treatment effects have had difficulty replicating the originally described abnormalities in ROI selected a priori. For example, using ROI predefined directly on PET images, Baxter et al. (1989) reported a reduction in the dorsal anterolateral PFC metabolism in depressives versus controls that reversed toward the normative baseline following antidepressant drug treatment. However, the same laboratory was unable to replicate the baseline abnormality in independent subject samples using ROI that were presumably positioned in the same area of the PFC in anatomical MRI images, and then transferred to the corresponding PET images to assess treatment effects (Brody et al., 2001; Saxena et al., 2002). Similarly, although several studies reported abnormalities of CBF or metabolism in the posterior cingulate cortex, the specific locations of these findings have differed widely across studies and have even differed in direction, being increased in most but reduced in some studies of depressives versus controls (reviewed in Drevets, 2000).

To assess treatment effects in such areas where the location of abnormalities in MDD remained unclear, a novel approach was applied in which the stereotaxic coordinates for areas implicated in interactions between emotional and cognitive processing were employed to guide ROI placement (Drevets and Raichle, 1998; Simpson et al., 2000). PET and fMRI studies of healthy humans have demonstrated several limbic and paralimbic cortical regions implicated in emotional behavior where hemodynamic activity consistently decreases as subjects perform attentionally demanding cognitive tasks (Shulman et al., 1997; Drevets and Raichle, 1998). In many of these regions, in contrast, hemodynamic activity increases during experimentally induced emotional states in healthy humans. The reciprocal patterns of the CBF changes in these limbic and paralimbic regions during attentionally demanding cognitive tasks were thus hypothesized to reflect interactions between cognitive and emotional processing (Drevets and Raichle, 1998).

Many of these regions closely correspond to areas where resting CBF and metabolism are abnormal during depression. Thus, the deactivation loci described by Shulman et al. (1997) in the amygdala, lateral orbital cortex, and subgenual PFC are encompassed within the ROI where we localized CBF and metabolism abnormalities in depression (Drevets et al., 1992, 1995c, 1997, 2002). Moreover, the deactivation loci in the dorsomedial/dorsal anterolateral PFC and posterior cingulate areas from Shulman et al. (1997) were situated in the vicinity of CBF and metabolic abnormalities reported in studies of depression (reviewed in Drevets, 2001). We thus hypothesized that the stereotaxic coordinates for the deactivation loci of Shulman et al. (1997), which were carefully localized and replicated in large, independent samples of healthy humans, might guide ROI placement to specific areas where metabolism is abnormal in depression.

2. Methods

2.1. Subjects

Currently depressed subjects aged 18 to 59 who met DSM-IV criteria for recurrent MDD (APA, 1994) were recruited from the clinical services affiliated with Washington University School of Medicine. Subjects provided informed consent, as approved by the Washington University School of Medicine Institutional Review Board. Exclusion criteria included the presence of major medical and neurological disorders, history of other psychiatric disorders prior to MDD onset, history of mania, treatment
with psychotropic or other medications likely to affect CBF or metabolism within the 3 weeks prior to scanning (except in the case of fluoxetine, where an 8 week medication-free period was required), substance abuse within the 1 year prior to scanning, lifetime history of substance dependence, and inability to provide informed consent. On the day of scanning, depression severity was rated by the Hamilton Depression Rating Scale (HDRS) scores (21 item; Hamilton, 1960), anxiety severity by the Spielberger State Anxiety Inventory (SSAI; Spielberger et al., 1970), and the frequency of depressive ideation by the Automatic Thoughts Questionnaire (ATQ; Hollon, 1980).

2.2. Antidepressant treatment

Depressed subjects were entered until a total of 20 subjects could be scanned both pre- and post-treatment. The target drug was the selective serotonin reuptake inhibitor, sertraline, initiated at 50 mg per day, and increased as needed at 2 to 4 week intervals. The post-treatment scan was performed once the subject received the optimized dose for ≥4 weeks. Because the goal of treatment was to produce as many responders as possible, subjects with a known history of nonresponse to sertraline were instead treated with other medications that were selected based upon either previous good responses to another antidepressant drug (generally a tricyclic antidepressant) or upon having a distinct, putative mechanism of action from sertraline. Treatment outcome was assessed by the change in the HDRS score and the Clinical Global Impression scale’s global improvement item (CGI).

2.3. Image acquisition and processing

PET scans of glucose utilization were acquired as subjects rested with eyes closed using a Siemens/CTI 953B (31 contiguous slices 3.375 mm thick; in-plane resolution 4.9 mm FWHM), 5–10 mCi of $^{18}$FDG (Phelps et al., 1979), and a 72 min dynamic emission scan (Fiorelli et al., 1992). The last 36 min consisted of nine 4 min frames which were aligned to each other to reduce the effects of movement using AIR (Woods et al., 1993). This PET-MRI alignment has a mean error of 2 mm for subcortical structures (Woods et al., 1993; Black et al., 1997). The precision of PET-MRI alignment was verified in three dimensions by visually comparing seven internal points/lines evident on both the PET and MRI images as described in Drevets et al. (2001).

The subgenual PFC ROI used to measure metabolic activity was the MRI-based ROI that had been defined in a previous study (Drevets et al., 1997) to measure this structure’s volume. This region encompassed the grey matter of the first full gyrus (anterior cingulate gyrus) situated immediately ventral to the floor of the corpus callosum through a range of slices beginning at the anterior-most point of the genu of the corpus callosum and extending caudally to the first slice where the internal capsule is first seen dividing the caudate and putamen. Although this cortex was significantly decreased in volume in familial unipolar and bipolar depressives relative to healthy controls in previous studies (Drevets et al., 1997; Öngür et al., 1998; Hirayasu et al., 1999), the abnormal reduction in subgenual PFC volume was unchanged following symptom remission and chronic antidepressant drug treatment (Drevets et al., 1997). The regional metabolic activity could thus be measured in the same ROI by aligning the pre- and post-treatment PET images to the same MRI image without biasing results toward either PET image set.

The lateral orbital cortex ROI was defined by segmenting the grey matter segment lateral to the orbital sulcus and extending laterally along the inferior frontal gyrus to the convexity to encompass the grey matter of the lateral orbital gyri and ventrolateral PFC through the same range.

2.4. Image analysis

The mean normalized metabolism was compared between the depressed and control groups using unpaired t-tests in two groups of ROI. The ROI of primary interest consisted of areas where we previously demonstrated abnormalities of CBF or metabolism in MDD in the amygdala, the subgenual PFC (Drevets et al., 1992, 1997), and the lateral orbital cortex (see Introduction). The secondary ROI were defined as described in Shulman et al. (1997; see Table 1 of this report) in the posterior cingulate cortex and areas of the medial and dorsomedial / dorsal anterolateral PFC.

In the ROI located in the subgenual PFC (ACC) and the lateral orbital cortex, ROI were defined using PET-MRI collocation. The PET images were co-registered to the corresponding MRI image using AIR (Woods et al., 1993). This PET-MRI alignment has a mean error of 2 mm for subcortical structures (Woods et al., 1993; Black et al., 1997). The precision of PET-MRI alignment was verified in three dimensions by visually comparing seven internal points/lines evident on both the PET and MRI images as described in Drevets et al. (2001).

MRI scans were acquired using a Siemens VISION 1.5 T scanner and a 3-D MPRAGE sequence (T1 = 300 ms, TR = 9.7, TE = 4, flip angle 12°, 1×1×1.25 mm voxels). Images were resliced so that horizontal sections were oriented parallel to the bicommissural line using ANALYZE™.
of slices in which the SGPFC measure was obtained (Fig. 1).

To assess the amygdala and the regions of secondary interest, ROI were positioned on PET images that had been stereotaxically transformed into a common spatial array (Talairach and Tournoux, 1988; Fox et al., 1985). The stereotaxic transformation employed was the same method as that previously employed by Shulman et al. (1997), allowing the identical ROI to be assessed across studies. To assess metabolic activity in the amygdala, a spherical ROI 1 cm in diameter was centered over the left amygdala at $x = -21$, $y = -7$, $z = -18$ as described in Drevets et al. (1992), after conversion of the coordinates from Talairach et al. (1967) to those of Talairach and Tournoux (1988; the former atlas sets the stereotaxic origin at the midpoint of the bicommissural segment, whereas the latter uses the anterior commissure as origin). The cortical ROI defined in the posterior cingulate cortex, the dorsomedial/ dorsal anterolateral PFC, and the medial PFC (frontal polar C, medial inferior PFC) were defined as described in Shulman et al. (1997) in larger volumes 14 mm in diameter centered over the stereotaxic loci listed in Table 2.

2.5. Assessment of antidepressant treatment on metabolism

In the ROI where significant differences were identified in the unmedicated depressives relative to the controls, image data were compared between the post- relative to the pre-treatment conditions using paired $t$-tests. A priori hypotheses regarding clinical correlations with the resulting metabolic changes were tested based upon previous findings: Because Drevets et al. (2002) previously found that glucose metabolism in the amygdala correlated with the stressed plasma cortisol measures obtained during PET scanning, a regression analysis was performed to assess whether the treatment-associated change in amygdala metabolism would also correlate with the corresponding change in stressed plasma cortisol levels. In addition, because physiological activity in the left amygdala appeared elevated in both the depressed and the unmedicated-remitted (i.e., between episodes, and pre-relapse) phase of FPDD, the relationship between the response to continuation treatment (judged by clinical status at 6 month follow-up) and treatment effects on amygdala metabolism were assessed. A positive and persistent treatment response to continuation therapy was declared if the HDRS scores decreased by at least 50% at the time of the post-treatment scan, and at 6 month follow-up on the drug regimen established at the time of the post-treatment scan the CGI remained ≤2 (i.e., much or very much improved) the subject did not meet DSM IV criteria for a major depressive episode. Because of the positive correlation reported between right subgenual ACC metabolism and depression severity (Drevets et al., 1999; Osuch et al., 2000), this ROI was subjected to the same analysis.

In post hoc analyses, relationships between the change in depression severity and the change in metabolism were assessed by linear regression analysis in all regions where significant treatment effects were identified.
3. Results

3.1. Subjects

The mean age, gender composition, HDRS score and handedness [Edinburgh Handedness Inventory (Raczkowski et al., 1974)] of the subject samples appear in Table 1. Fourteen of the MDD subjects met the Winokur (1982) criteria for familial pure depressive disease (FPDD). None of the depressed subjects had a history of psychosis. One subject could not undergo MRI due to metal inside the head, so this subject’s data was used in the stereotaxic ROI assessments but not in the MRI-based ROI assessments.

3.2. Antidepressant treatment effects

Twenty-one of the depressed subjects were reimaged following 6 to 16 weeks of antidepressant treatment (mean 9.1 ± 2.6 weeks, median 8 weeks, mode 8 weeks). Nineteen subjects received sertraline (dose range 50–150 mg; mean dose 75 ± 46 mg). One of these also required lorazepam (2 mg/d) and one concomitantly took nortriptyline (50 mg/d). In addition, one subject received desipramine (250 mg/d) and one received venlafaxine (225 mg/d). The subject treated with venlafaxine developed hypomania at the time of the post-treatment scan, however, and was dropped from further analyses (leaving n = 20).

The mean clinical ratings pre- and post-treatment are listed in Table 1. Sixteen of the subjects had a positive response to treatment [i.e., ≥50% reduction in HDRS score, and CGI ≤2 (much improved or very much improved)], with the post-treatment HDRS scores decreasing to the non-depressed range (≥7) in 15 subjects. At 6 months follow-up, three of the responders had relapsed during continued treatment, and had required alternative treatment regimens. Thus a total of 13 subjects both responded and remained well at follow-up (i.e., ‘good outcome group’).

The mean stressed plasma cortisol concentrations decreased 4.0 ± 11 μg/dl in the subset of subjects in whom this assay was performed (Drevets et al., 2002).

3.3. Baseline metabolic measures

3.3.1. Primary regions-of-interest

The mean subgenual ACC metabolism was significantly decreased in the depressives relative to the controls on the left (Table 2; t = −4.28, df 39, P < 0.001), but did not differ on the right (Table 2; t = −1.64, n.s.). The mean lateral orbital cortex metabolism was significantly elevated in the depressives relative to the controls on both the left (Table 2; t = 3.6, P < 0.001) and the right (Table 2; t = 2.8, P < 0.01). The mean left amygdala metabolism was also increased in the depressives versus the controls (0.852 ± 0.077 and 0.790 ± 0.082, respectively; t = 2.31, P < 0.05).

3.3.2. Secondary regions-of-interest

The mean metabolism was significantly decreased in the depressives relative to the controls in dorsomedial/dorsal anterolateral PFC on both the left (Table 2; t = −2.77, df 39, P < 0.01) and the right side (Table 2; t = −2.38, P < 0.05). The mean posterior cingulate cortex metabolism was significantly elevated in the depressives relative to the controls (Table 2; t = 2.11, P < 0.05). Metabolism did not differ between groups in the frontal polar cortex or the medial inferior PFC (Table 2).

3.4. Effects of antidepressant drug treatment on regional metabolism

Normalized regional glucose metabolism decreased 5.9% in the amygdala (t = −2.2, P < 0.05) and 3.7 ± 6.6% (t = 2.31, P < 0.05) in the left subgenual PFC. In the left lateral orbital cortex, the mean change in metabolism showed a nonsignificant trend toward decreasing in the post- relative to the pre-treatment condition (−1.9 ± 3.9%, 0.05 < P < 0.1). The corresponding change on the right side (−1.3 ± 3.3%) did not approach significance.

Of the regions of secondary interest assessed post-treatment, the mean metabolic changes in the posterior cingulate cortex and the two dorsomedial/dorsal anterolateral PFC ROI did not achieve statistical significance (Table 3).

### Table 1
Characteristics of the subject samples

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Depressed</th>
<th>Depressed Treatment subset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>14</td>
<td>27</td>
<td>20</td>
</tr>
<tr>
<td>Mean age±S.D.</td>
<td>34 ± 9.1</td>
<td>37 ± 9.1</td>
<td>36 ± 10</td>
</tr>
<tr>
<td>Percent females</td>
<td>64</td>
<td>67</td>
<td>70</td>
</tr>
<tr>
<td>Left-handed (n)</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Mean HDRS±S.D.</td>
<td>0.4 ± 0.7 (0–2)</td>
<td>24 ± 5.0 (17–37)</td>
<td>24 ± 4.8 (19–37)</td>
</tr>
<tr>
<td>Mean SAI±S.D.</td>
<td>7 ± 9 (0–32)</td>
<td>34 ± 12 (12–55)</td>
<td>34 ± 15 (14–55)</td>
</tr>
<tr>
<td>Mean ATQ±S.D.</td>
<td>3 ± 3 (0–9)</td>
<td>64 ± 21 (18–112)</td>
<td>67 ± 27 (21–112)</td>
</tr>
</tbody>
</table>

Abbreviations: ATQ, Automatic Thoughts Questionnaire; HDRS, Hamilton Depression Rating Scale; SAI, State Anxiety Inventory of Spielberger.
Table 2
Normalized (regional/global) metabolism in the primary and secondary regions-of-interest (ROI) in the control and depressed groups. A PET-MRI co-location method was used to define the first four primary ROI. A stereotaxic approach was instead used to define the remaining ROI, using spherical volumes centered on the coordinate set (x, y, z) listed in parentheses (x, left–right distance in mm from the midline; y, anterior–posterior distance from the anterior commissure; z, dorsal–ventral distance from the horizontal plane containing the anterior and posterior commissures, with positive values indicating right, anterior and dorsal, respectively).

<table>
<thead>
<tr>
<th>Region</th>
<th>Control (n = 14)</th>
<th>Depressed (n = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary regions-of-interest</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L subgenual PFC (PET-MRI co-location)</td>
<td>1.09±0.107</td>
<td>0.963±0.075 *</td>
</tr>
<tr>
<td>R subgenual PFC (PET-MRI co-location)</td>
<td>1.03±0.106</td>
<td>0.983±0.079</td>
</tr>
<tr>
<td>L lateral orbital C (PET-MRI co-location)</td>
<td>1.19±0.054</td>
<td>1.26±0.058 *</td>
</tr>
<tr>
<td>R lateral orbital C (PET-MRI co-location)</td>
<td>1.18±0.058</td>
<td>1.24±0.062 *</td>
</tr>
<tr>
<td>L amygdala (−21, −7, −18)</td>
<td>0.790±0.082</td>
<td>0.852±0.077 *</td>
</tr>
<tr>
<td>Secondary regions-of-interest</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L DM/DALPFC (−15, 55, 26)</td>
<td>1.14±0.120</td>
<td>1.02±0.151 *</td>
</tr>
<tr>
<td>R DM/DALPFC (5, 49, 36)</td>
<td>1.13±0.155</td>
<td>1.01±0.150 *</td>
</tr>
<tr>
<td>Medial inferior PFC (1, 47, −4)</td>
<td>1.37±0.084</td>
<td>1.36±0.077</td>
</tr>
<tr>
<td>L frontal polar C (−19, 57, 8)</td>
<td>1.22±0.092</td>
<td>1.20±0.099</td>
</tr>
<tr>
<td>Posterior cingulate (1, −35, 36)</td>
<td>1.39±0.119</td>
<td>1.47±0.109 *</td>
</tr>
</tbody>
</table>

Abbreviations: L, left; R, right; PFC, prefrontal cortex.
* P<0.05 relative to the control group.
† P<0.01 relative to the control group.
‡ P<0.001 relative to the control group.

3.4.1. Clinical correlations between treatment outcome and change in metabolism

In the amygdala, the magnitude of the treatment-associated, metabolic change correlated positively with the change in the stressed plasma cortisol levels measured during scanning (r = 0.66, t = 2.8, P<0.01). The correlation between the change in HDRS scores and the change in amygdala metabolism approached significance (r = 0.43, 0.05<P<0.1). When the subgroup who both responded and remained well at 6 months follow-up was examined separately, however, the amygdala metabolism decreased 6.6±12% (t = −2.8, P<0.01) at the medicated-remitted scan, and the decrement in HDRS scores was more tightly correlated with the decrement in amygdala metabolism (r = 0.76, P<0.01). The corresponding change in the subgroup (n = 7) who were nonresponsive or relapsed during 6 months follow-up on maintenance treatment was lower (mean ΔMRglu +3.5±12%, n.s.).

When the good outcome group was considered alone, the change in the left subgenual ACC metabolism was positively correlated with the change in HDRS scores (r = 0.67, P<0.01). Also, the reduction in the right subgenual ACC metabolism became significant when the good outcome group was considered alone (−4.4±5.0; t = 3.1, P<0.01). Metabolism did not significantly change (+1.4±3.4%, n.s.) in the subjects who failed to respond or relapsed.

Post hoc assessments showed that, in the lateral orbital cortex, the correlations between the treatment-associated metabolic changes and the corresponding HDRS score changes were not significant on either the left (r = 0.30) or the right side (r = 0.30). The corresponding correlation was also not significant in the left subgenual PFC (r = 0.24). In ROI other than the amygdala and the subgenual ACC, differences between the good and poor outcome groups were not significant.

Table 3
Change in metabolism in the post- relative to the pre-treatment scans in MDD

<table>
<thead>
<tr>
<th>Region</th>
<th>Mean (±S.D.) change post- vs. pre-treatment conditions (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L subgenual PFC</td>
<td>−3.7±6.6 *</td>
</tr>
<tr>
<td>R subgenual PFC</td>
<td>−2.7±5.5</td>
</tr>
<tr>
<td>L lateral orbital</td>
<td>−1.9±4.0</td>
</tr>
<tr>
<td>R lateral orbital</td>
<td>−1.3±3.3</td>
</tr>
<tr>
<td>L amygdala</td>
<td>−5.9±9.9 *</td>
</tr>
<tr>
<td>L DM/ALPFC (15, 55, 26)</td>
<td>+3.0±9.6</td>
</tr>
<tr>
<td>Dorsomedial PFC (5, 49, 36)</td>
<td>+4.3±10.5</td>
</tr>
<tr>
<td>Posterior cingulate (1, −35, 36)</td>
<td>−1.8±5.0</td>
</tr>
</tbody>
</table>

Abbreviations: L, left; R, right. Otherwise as in Table 1.
* P<0.05 in the post- relative to the pre-treatment group.

4. Discussion

In the unmedicated phase of MDD, metabolism was abnormally increased in the left lateral orbital cortex, left amygdala, and posterior cingulate cortex, and decreased in the subgenual ACC and dorsal medial/antrolateral prefrontal cortex (PFC) in the unmedicated depressed relative to the control samples, consistent with the results of previous studies (see below). Following treatment, metabolism significantly decreased in the left amygdala and left subgenual ACC, and corresponding changes in the orbital and posterior cingulate cortices approached significance.

The magnitude of the treatment-associated, metabolic
change in the amygdala correlated positively with the change in the stressed plasma cortisol levels measured during scanning, which is noteworthy because Drevets et al. (2002) reported that the left amygdala metabolism was positively correlated with the stressed plasma cortisol levels obtained during scanning. The reduction in amygdala metabolism was largely limited to those subjects who both responded to treatment and remained well at 6 months follow-up, in whom the reduction in amygdala metabolism tightly correlated with the reduction in HDRS scores ($r=0.76$).

4.1. Assessing baseline metabolic abnormalities and treatment-associated changes in MDD

4.1.1. Technical issues affecting sensitivity (type II error)

In considering the regional abnormalities in unmedicated depressives which are of interest for characterizing treatment effects, the psychiatric imaging literature implicates a large number of brain areas in the pathophysiology of MDD, but is in disagreement regarding the specific location and direction of these abnormalities (Drevets, 2000). The ability to detect and reproduce abnormalities of resting physiology in depression appears dependent upon several experimental design issues. First, sample selection criteria must exclude subjects who are currently medicated with psychotropic drugs, have depression secondary to other medical or psychiatric conditions, or have neuromorphological MRI evidence of cerebrovascular disease (i.e., the MR signal hyperintensities and lacunae which are prevalent in depressives who experience illness onset late in life). Entrance criteria which enrich the subject sample for the likelihood of having other psychobiological abnormalities (e.g., meeting melancholic or familial pure depressive disease criteria, or showing a beneficial response to somatic antidepressant treatments) can further increase sensitivity for identifying some of the abnormalities described above (Drevets et al., 2002; Wilson et al., 2002; Wu et al., 1992). Second, several technical aspects of the image acquisition and analysis exert a major impact on the sensitivity for detecting regional CBF or metabolic abnormalities in depression, especially those located in relatively small structures such as the amygdala, ventral striatum, or ventral ACC (reviewed in Drevets, 2000; Drevets et al., 2001, 2002). Third, the behavioral state in which the functional neuroimaging data are acquired influences metabolic activity in these structures, as described below.

The sensitivity of the PET data for detecting differences between conditions was enhanced in the current study by normalizing the regional data by whole brain metabolism in order to reduce variability associated with nonspecific global effects. Quantitative PET studies of depressed subjects with primary MDD in the age range studied herein have reported that whole brain CBF and glucose metabolism do not significantly differ between depressives and healthy controls (e.g., Baxter et al., 1985; Drevets et al., 1992, 1997; Kimbrell et al., 2002). Whole brain glucose metabolism is also not expected to differ between during chronic sertraline treatment. For example, Buchsbaum et al. (1997) measured absolute glucose metabolism in MDD subjects (who had received no psychotropic medications for ≥2 weeks prior to the baseline scan) before and following 10 weeks of sertraline treatment, and found that absolute metabolism did not change in any ROI on the cortical surface, and in only four of 126 ROI in the medial cortical wall and subcortex [at $P$(uncorrected)<0.05]. Of these four ROI, some showed increased activity and others decreased activity following sertraline, suggesting that these changes would not significantly alter whole brain metabolism. Thus, the assessment of normalized regional metabolic data in the current study was not expected to be confounded by systematic effects on whole brain metabolism.

An important limitation of this and all PET studies on the sensitivity and specificity for detecting differences between depressives and controls is the small physical size of brain structures of interest relative to the spatial resolution of PET. The cortex is 3 to 6 mm thick, and electrophysiological and high resolution fMRI studies show that functional units of the cortex activated by specific mental operations extend only a few millimeters along the transverse axis of the cortical sheet. Functionally relevant subregions within subcortical nuclei are also small relative to PET’s spatial resolution (Charney and Drevets, 2002). Nevertheless, quantitation using PET is optimally performed when the ROI is at least twice as large as the FWHM spatial resolution in all directions (Mazziotta et al., 1981). State-of-the-art PET scanners provide resolution of only about 6 mm FWHM before filtering (Drevets et al., 2001), so a structure-of-interest should ideally extend over ~12 mm in all dimensions. Unfortunately, the only cerebral grey matter structures which meet this criterion are the caudate and putamen (Talairach et al., 1967). Nevertheless, even these latter structures consist of a functional mosaic, so that the actual region size activated by separable mental operations extends a few millimeters at most. Consequently, the sensitivity and specificity of PET assessments of cortical and subcortical activation are limited by physical-anatomical effects, as reflected in the relatively subtle effect size of the differences reported herein.

4.2. Specificity of antidepressant drug effects on metabolism

The specificity of the effects shown in Table 3 to antidepressant drug treatment of MDD has not been established. Previous studies performed in healthy humans ($n=25$; Drevets and Raichle, unpublished data), scanned twice across a similar mean time interval as the treatment period assessed herein, showed that CBF (measured using PET VI and $H_2^{15}$O) did not significantly change between
4.3. Altered metabolism in depression in regions that normally deactivate during attentionally demanding tasks

As described in the Introduction, Shulman et al. (1997) characterized regions which showed consistent CBF decreases as humans engage in highly attentionally demanding tasks, relative to when they engage in control tasks requiring similar sensory and motor processing, but which place lower demands on attentional/cognitive processing. These ‘deactivations’ putatively reflect brain regions where neural transmission is specifically reduced in the experimental relative to the control condition (Drevets et al., 1995a; Drevets and Raichle, 1998). Some of these regional deactivations occurred in areas thought to subserve unattended sensory and spatial processes located in the parietal lobe, while others localized to areas implicated in emotional processing, such as the amygdala, posterior cingulate, and medial and orbital PFC (Shulman et al., 1997, 2000, 2002; Raichle et al., 2001; Simpson et al., 2001). The latter set of areas were assessed by the current study, in which the same stereotaxic imaging method employed by Shulman et al. (1997) was also applied to investigate both baseline differences between depressives and controls and antidepressant treatment-associated changes in metabolism in the medial and dorsal anterior PFC and the posterior cingulate cortex.

The regions selected from Table 1 of Shulman et al. (1997) to guide ROI placement for the current study were hypothesized to comprise areas where metabolism would differ between depressives and controls. The ROI from Shulman et al. in the amygdala, lateral orbital cortex, and subgenual PFC (i.e., \( x = 3, y = 31, z = -10 \)) were already encompassed within the corresponding primary ROI for the current study (Table 2). Although Shulman et al. (1997) identified CBF decreases in the amygdala bilaterally, our previous studies (Drevets et al., 1992, 2002) found elevations of CBF only in the left amygdala in MDD, so only the left amygdala was assessed herein. Moreover, additional ROI identified by Shulman et al. in more dorsal areas of the PFC were not assessed herein because not all of the subject’s PET images sampled the pixels encompassed by these ROI [the scanner gantry of the 953B (10 cm) was centered over more ventral slices to ensure optimal sampling of the amygdala and orbital surface]. The five areas assessed herein had all been implicated in emotional behavior by other types of evidence (Table 2). The medial inferior PFC defined by Shulman et al. (1997) was situated anterior to the subgenual PFC, and is an area where activity is normally modulated by anxiety (Simpson et al., 2000). The left frontal polar cortex was within the area implicated in MDD in Drevets et al. (1992). Evidence that the dorsomedial/dorsal anterolateral PFC and posterior cingulate cortex play roles in emotional behavior is reviewed below.

Although the mechanisms and nature of these regional deactivations have not been established, one hypothesis holds that they reflect shifts of attentional resources away from systems that monitor the environment for aversive stimuli (Raichle et al., 2001). If so, then activation of these regions during depressive episodes may reflect sustained evaluation of experiential stimuli for affective or behavioral significance (see below) (Drevets et al., 1992; Drevets and Raichle, 1998).

4.3.1. Implications for behavioral state in which depressives are imaged

These data imply that the behavioral state in which subjects are imaged may influence differences evident between depressives and controls. For example, the elevation of CBF and metabolism in left orbital/ventrolateral PFC and amygdala that has been reproducibly shown in subjects scanned while resting with eyes closed, has usually not been found in studies performed as subjects are engaged in attentionally demanding tasks during scanning. Thus, in PET images acquired in MDD subjects performing a continuous performance task, Kimbrell et al. (2002) did not detect abnormal elevations of physiological activity in the amygdala or orbital cortex. This observation suggests that depressives may successfully deactivate these regions during attentionally demanding tasks. Moreover, it might be hypothesized that because of their impairment in concentration, depressed subjects may actually exert greater effort during task performance in order to achieve a similar performance level as controls (Kimbrell et al., 2002), and may thus show a more robust decrement in metabolism in these areas than controls.

4.4. Comparison with previous studies of antidepressant treatment effects in MDD

The data presented herein are consistent with our findings (Drevets et al., in press) in an independent subject sample of 18 depressed MDD subjects in which glucose metabolism images were acquired before and following sertraline or citalopram treatment using a Siemens HR+ tomograph and \(^{18}\)FDG. These data were analyzed using a voxel-by-voxel approach (SPM99) which allowed assessment both of the ROI targeted herein and of regions outside these ROI. Antidepressant treatment was associ-
ated with significant reductions in metabolism in the left and right lateral orbital cortex, the left and right ventrolateral PFC, the subgenual and pregenual ACC, the left and right frontal polar cortex, the left and right anterior insula, the left posterior insula, the left amygdala, the left anterior ventral striatum, and the medial thalamus. No areas were identified in which metabolism significantly increased during treatment. These findings are reviewed in light of other literature below.

4.4.1. Amygdala

The treatment-associated reduction in amygdala metabolism may constitute a neurophysiological effect that is common to a variety of antidepressant treatments. Similar to the reduction in metabolism found in the current study during sertraline treatment, Drevets and Raichle (1992) previously reported that desipramine treatment reduced normalized CBF in the amygdala in MDD subjects imaged pre- and post-treatment. These data are compatible with preclinical evidence that chronic antidepressant drug treatments suppress amygdala function in experimental animals (Duncan et al., 1986; Gerber et al., 1983; Horovitz, 1966; Ordway et al., 1991).

In previous PET studies of MDD, CBF and glucose metabolism in the amygdala correlated positively with depression severity ratings (Drevets et al., 1992, 1995c; Abercrombie et al., 1996) and with stressed plasma cortisol secretion (Drevets et al., 2002). The amygdala plays an important role in organizing multiple emotional, behavioral, neuroendocrine, and autonomic aspects of emotional/stress responses, as reviewed in Drevets (2001). Electrical stimulation of the amygdala in humans increases cortisol secretion and can produce fear, anxiety, dysphoria, and vivid recall of emotionally provocative life events (Brothers, 1995; Gloor et al., 1982). The amygdala also facilitates stress-related corticotropin releasing hormone (CRH) release (Herman and Cullinan, 1997), suggesting a mechanism via which excessive amygdala activity could be involved in inducing the CRH hypersecretion reported in MDD (Musselman and Nemeroff, 1993; Feldman et al., 1994). Thus the tight correlation between the reduction in amygdala metabolism and clinical improvement (as measured by the decrease in HDRS scores) reported herein in subjects who both remitted and maintained remission ($r = 0.76$, $P < 0.01$), and between the change in amygdala metabolism and the change in stressed plasma cortisol concentrations ($r = 0.66$, $P < 0.01$), suggest that the ability of chronic antidepressant drug treatment to suppress amygdala activity plays a major role in attenuating the behavioral, endocrine, and autonomic manifestations associated with depressive episodes.

Furthermore, the left amygdala CBF also appeared abnormally increased (albeit to a lesser extent) in asymptomatic (i.e., between MDE), familial depressives who were not taking antidepressant drugs (Drevets et al., 1992). Bremner et al. (1997) reported that AD-medicated, relapsed MDD subjects who relapsed in response to serotonin depletion had a higher amygdala metabolism prior to depletion than similar subjects who did not relapse, suggesting that abnormal amygdala activity may be involved in the susceptibility to symptom recurrence, as well as to episode severity. In the current study, the reduction in amygdala metabolism during treatment appeared particularly prominent in subjects who both responded positively to treatment and maintained their response across 6 months follow-up. The 6.6% mean reduction in metabolism in these subjects was similar in magnitude to that of the abnormal increase in activity (ranging from 5 to 7%) found in five independent samples of depressives and controls in our previous studies (reviewed in Drevets, 2001). Thus, suppression of amygdala metabolism to normative levels may be necessary to both induce and maintain symptom remission during antidepressant drug (AD) treatment. The relationship between amygdala metabolism and stressed plasma cortisol concentrations is also noteworthy in this regard, because persistence of abnormal regulation of glucocorticoid secretion reportedly predicts an increased likelihood of relapse during antidepressant treatment (Ribeiro et al., 1993).

4.4.2. Subgenual ACC

Drevets et al. (1997) previously demonstrated that CBF and metabolism were reduced in the ACC ventral to the genu of the corpus callosum (i.e., subgenual ACC) in depressed subjects with BD and familial MDD. We initially found the reduction of CBF in BD subjects relative to controls using a voxel-by-voxel analysis approach (Drevets et al., 1997) and then established the significance of this finding ($P < 0.001$) using a stereotaxically placed ROI in an independent sample of BD and control subjects (Drevets et al., 1997). We then replicated this finding using both CBF and metabolic measures in a third, independent sample of BD and control subjects, and extended this finding to unipolar depressives with FPDD, also using a stereotaxic approach (Drevets et al., 1997). In the FPDD group, although the baseline metabolism was decreased in currently depressed versus healthy control subjects, activity correlated positively with depression severity during the unmedicated depressed condition, and decreased further during treatment. Finally, the current data show that, while the subgenual ACC metabolism appears decreased in unmedicated depressives relative to controls, activity fell further during sertraline treatment. Buchsbaum et al. (1997) also reported that, in the area corresponding to the subgenual PFC, metabolism was decreased in depressives versus controls at baseline and decreased further in the depressives following sertraline treatment [the area Buchsbaum et al. (1997) referred to as ‘rectal gyrus’ appeared to be the same region referred to by Drevets et al. (1997) as subgenual PFC based upon a comparison between the atlases used in each study—Matsui and Hirano (1974) and Talairach and Tournoux (1988), respectively].
To investigate this complex relationship between metabolism and illness severity, we measured the corresponding cortex in the MRI images from these subjects and found the cortex volume decreased on the left in both the MDD and BD samples relative to the control group \((P<0.0002;\) Drevets et al., 1997). The subgenual PFC volume did not change in MDD subjects \((n=20)\) rescanned following a mean treatment period of 3.2±3.5 months. In post mortem studies of MDD and BD, the abnormal reduction in cortex volume was confirmed \((\text{Drevets et al., 1998; Ongür et al., 1998})\). This decrement in cortex was associated with a reduction in glia, with no equivalent loss of neurons, in both the MDD and BD groups \((\text{Ongür et al., 1998})\).

In the current study, metabolism was measured using PET-MRI co-location in the subgenual ACC grey matter. Obtaining measures from ROI that emphasize grey matter reduces, but does not eliminate, the effects of partial volume averaging by reducing the contribution of radioactive counts from adjacent CSF and white matter. Thus, the magnitude of the reduction found in the unmedicated baseline condition in the current study was smaller than that found using the stereotaxic approach applied in our previous study \((\text{Drevets et al., 1997})\). Nevertheless, when the reduction in metabolism was more fully corrected for the corresponding reduction in grey matter volume using computer simulations, it appeared that the actual metabolic activity in the remaining cortex would be elevated, as opposed to reduced, relative to the normative level, and that antidepressant treatment decreased this elevated activity to normal \((\text{Drevets, 2000; Meltzer et al., 1999})\).

These results appear consistent with the positive correlation between metabolic activity in the subgenual ACC and depression severity \((\text{Drevets, 1999; Osuch et al., 2000})\) and with evidence that hemodynamic activity increases in the subgenual ACC in healthy humans during sadness induced via contemplation of internally generated sad memories and in PTSD subjects during internally generated imagery of past trauma \((\text{George et al., 1995; Damasio et al., 1998; Mayberg et al., 1999; Shin et al., 1999})\). The subgenual ACC consists of agranular cortex \((\text{principally Area 24b})\) on the pregenomic portion of the anterior cingulate gyrus. In rodents, nonhuman primates and/or humans this cortex has extensive reciprocal connections with areas implicated in the expression of behavioral, autonomic and endocrine responses to stressors, aversive stimuli, and rewarding stimuli, such as the lateral hypothalamus, amygdala, accumbens, subiculum, ventral tegmental area, raphe, locus ceruleus, periaqueductal grey \((\text{PAG})\), and nucleus tractus solitarius \((\text{NTS})\) \((\text{reviewed in Drevets et al., 1998; Ongür and Price, 2000})\). Humans with lesions that include subgenual PFC demonstrate abnormal autonomic responses to emotional experiences, inability to experience emotion related to concepts that ordinarily evoke emotion, and inability to use information regarding the likelihood of punishment and reward in guiding social behavior. Similarly, rats with experimental lesions of prelimbic C demonstrate altered autonomic, neuroendocrine, and behavioral responses to stress and fear conditioned stimuli \((\text{Morgan and LeDoux, 1995; Sullivan and Gratton, 1999})\). For example, Diorio et al. \((1993)\) demonstrated glucocorticoid receptors in these regions when stimulated by corticosterone \((\text{CORT})\), reduced stress-related HPA activity, and showed that lesions of the prelimbic and infralimbic cortex increased plasma ACTH and CORT responses to restraint stress. The observations of left-lateralized reduction of grey matter volume in the subgenual PFC in MDD and BD, and of PET data showing that, in rats, left sided lesions of the medial PFC strip that includes infralimbic, prelimbic and ACC cortices increase sympathetic arousal and CORT responses to restraint stress. Dysfunction of the ventral ACC in primary mood disorders may thus contribute to the altered emotional behavior and neuroendocrine function evident in depression.

4.4.3. Pregenual anterior cingulate cortex

In the ACC anterior to the genu of the corpus callosum \(\text{('pregenual')}\), Drevets et al. \((1992)\) initially found increased CBF in MDD. While other laboratories also reported abnormalities of CBF and metabolism in this area during depression, these data have been inconsistent \((\text{reviewed in Drevets, 1999})\). The preganual ACC more consistently shows areas of elevated hemodynamic activity during anxiety states elicited in healthy or anxiety disordered humans \((\text{reviewed in Drevets and Raichle, 1998; Charney and Drevets, 2002})\). Electrical stimulation of this region elicits fear, panic or a sense of foreboding in humans, and vocalization in experimental animals \((\text{reviewed in Price et al., 1996})\).

In our parallel study assessing the effects of chronic SSRI treatment in an independent MDD sample \((\text{Drevets et al., in press})\), metabolism significantly decreased in both the preganual ACC \((x=2, y=41, z=14)\) and subgenual ACC \((x=2, y=36, z=0)\). These data are consistent with data presented by other laboratories as well. For example, Buchsbaum et al. \((1997)\) also found that the ACC metabolism was increased in unmedicated depressives relative to controls, and decreased during sertraline treatment, with the treatment-associated metabolic reduction being correlated with the change in depression ratings \((r=0.76)\). Brody et al. \((2001)\) also found that in a voxel-by-voxel analysis of PET data from 38 depressed subjects scanned following either paroxetine treatment or interpersonal psychotherapy, both treatment groups showed metabolic reductions in the ACC, ventrolateral PFC, and medial PFC.

Several studies report relationships between preganual ACC activity and subsequent antidepressant treatment response. Wu et al. \((1992)\) reported that depressed subjects whose mood improved during sleep deprivation showed elevated metabolism in the preganual ACC and amygdala in the pretreatment baseline scans. Mayberg et al. \((1997)\) reported that while metabolism in the preganual ACC was abnormally increased in depressives who subsequently
proved responsive to AD, metabolism was decreased in depressives who later had poor treatment response. Finally, in a tomographic electroencephalographic analysis, Pizzagalli et al. (2001) reported that depressed subjects \( n = 9 \) who ultimately showed the best response to nortriptyline (based upon a median split of the post- vs. pre-treatment change in depression ratings) showed hyperactivity (higher theta activity) in the pregenual ACC at baseline, as compared to subjects showing the poorer response \( n = 9 \). In contrast to these data, Ketter et al. (2000) reported inverse correlations between pregenual ACC metabolism and subsequent antidepressant response in MDD, with lower basal metabolism predicting superior responsiveness to AD. The area assessed in this latter study appeared more rostral and ventral than those reported in the previously described studies, however. The current study did not assess treatment response in the pregenual ACC, as methods for sensitively assessing activity in this region in depression using PET-MRI co-location remain under development.

### 4.4.4. Lateral orbital/ventrolateral PFC

In the lateral orbital cortex, ventrolateral PFC, and anterior insula, CBF and metabolism are abnormally increased in unmedicated subjects with primary MDD scanned while resting with eyes closed (e.g., Baxter et al., 1987, Table 3; Biver et al., 1994; Brody et al., 2002; Cohen et al., 1992; Drevets et al., 1992, 1995c; Ebert et al., 1991), as replicated using PET-MRI co-location in the current study. The lateral orbital ROI defined herein using PET-MRI co-location largely corresponds to BA 47 in humans (Öngür and Price, 2000). This area receives projections from visual and somatosensory cortex, and shares reciprocal anatomical connections with the amygdala, ACC, ventral striatum, hypothalamus, and PAG, suggesting it participates in integrating experiential stimuli with emotional salience (Öngür and Price, 2000; Schultz, 1997).

The elevated activity in these areas in MDD appears mood-state dependent (Drevets et al., 1992). Flow and metabolism also increase in these areas during induced sadness and anxiety in healthy subjects and induced anxiety and obsessional states in subjects with anxiety disorders (reviewed in Drevets and Raichle, 1998; Charney and Drevets, 2002). Many studies report that flow or metabolism decrease during antidepressant treatment in the orbital cortex, ventrolateral PFC, and/or anterior insula (e.g., Drevets et al., 1992; Drevets, 1999; Brody et al., 2001; Mayberg et al., 1999; Nobler et al., 1994).

A complex relationship exists between depression severity and physiological activity in the orbital cortex and ventrolateral PFC. While CBF and metabolism increase in these areas in the depressed relative to the remitted phase of MDD, the magnitude of these measures correlates inversely with ratings of depressive ideation and severity (Drevets et al., 1992, 1995c). Moreover, while metabolic activity is abnormally increased in these areas in treatment-responsive, unipolar and bipolar depressives, more severely ill or treatment refractory BD samples show CBF and metabolic values that did not differ from those of control samples (e.g., Drevets, 1995; Mayberg et al., 1994). An inverse relationship between orbital cortex/ventrolateral PFC activity and the intensity of emotional behavior is also evident in other conditions. For example, posterior orbital cortex flow increases in OCD and animal phobic subjects during exposure to phobic stimuli and in healthy subjects during induced sadness (Rauch et al., 1994; Drevets et al., 1995b; Schneider et al., 1995), with the change in posterior orbital CBF being inversely correlated with changes in obsessive thinking, anxiety, and sadness, respectively. These data appear consistent with electrophysiological and lesion analysis data showing that parts of the orbital cortex participate in modulating behavioral and visceral responses associated with defensive, fear, and reward-directed behavior as reinforcement contingencies change (Rolls, 1995). These cells are thought to play roles in extinguishing unreinforced responses to aversive or appetitive stimuli, via their anatomical projections to neurons in the amygdala, striatum, hypothalamus, and other limbic and brainstem structures (Mogenson et al., 1993; Price et al., 1996; Rolls, 1995). The orbital cortex and amygdala send direct projections to each other and also have overlapping projections to the striatum, hypothalamus, and PAG through which these structures appear to modulate each other’s neural transmission (Fig. 4; Carmichael and Price, 1995; Garcia et al., 1999; Mogenson et al., 1993; Price, 1999; Timms, 1977). Activation of the orbital cortex during depression may reflect endogenous attempts to attenuate emotional expression or interrupt unreinforced aversive thought and emotion. Consistent with this hypothesis, cerebrovascular lesions and tumors involving the frontal lobe increase the risk for developing major depression (Mayeux, 1982; Starkstein and Robinson, 1989), and recent evidence more specifically implicates the orbital cortex in the pathogenesis of lesion-induced depression (MacFall et al., 2001). Finally, serotonin depletion (Rogers et al., 1999; Bremner et al., 1997) and Parkinson’s Disease appear to impair orbital cortex function (Mayberg et al., 1990; Ring et al., 1994), suggesting other mechanisms through which deficits in orbital cortex function may increase risk for depression.

Reducing CBF and metabolism in the orbital cortex and ventrolateral PFC during AD treatment may, therefore, not be a primary mechanism through which antidepressant drugs ameliorate depressive symptoms. Instead, direct inhibition of pathological limbic activity in areas such as the amygdala and right subgenual ACC may be more essential to correcting the pathophysiology associated with the production of mood symptoms. The orbital cortex neurons may thus be able to ‘relax’, as reflected by the reduction of metabolism to normal levels, as antidepressant drug therapy attenuates the pathological limbic activity to which these neurons respond (Garcia et al., 1999).
4.4.5. Dorsomedial/dorsal anterolateral prefrontal cortex

Dysfunction of the dorsomedial/dorsal anterolateral PFC may also impair the ability to modulate emotional responses in mood disorders. In a study aimed at replicating and more precisely localizing metabolic deficits reported in these areas by Baxter et al. (1989) and Bench et al. (1992), Bell et al. (1999) iteratively applied ROI and voxel-by-voxel analyses and demonstrated that metabolism was decreased in MDD in the dorsomedial PFC [vicinity of dorsal Brodmann areas (BA) 32 and rostral 9] and dorsal anterolateral PFC (rostral BA 9). The approach applied herein may more accurately localize the difference between depressives and controls, however, since the magnitude of the difference shown herein was substantially greater than that shown by Bell et al. (1999).

Flow increases in the dorsomedial/dorsal anterolateral PFC in healthy humans as they perform tasks that elicit emotional responses or require emotional evaluations (Dolan et al., 1996; Drevets et al., 1994; Reiman et al., 1997). In healthy humans scanned during anxious anticipation of an electrical shock, we observed CBF increases in this region which correlated inversely with changes in anxiety ratings and heart rate (Drevets et al., 1994), suggesting this region functions to attenuate emotional expression. In rats, lesions of the dorsomedial PFC result in exaggerated heart rate responses to fear-conditioned stimuli, and stimulation of these sites attenuate defensive behavior and cardiovascular responses evoked by amygdala stimulation (reviewed in Frysztak and Neafsey, 1994), although the homologue to these areas in primates has not been established. In primates the BA 9 cortex sends efferent projections to the lateral PAG and the dorsal hypothalamus through which it may modulate cardiovascular responses associated with emotional behavior (Price, 1999). It is thus conceivable that the metabolic deficits and histological abnormalities found in this area in MDD may disinhibit some emotional behaviors.

In post mortem studies of this portion of BA 9, Rajkowska et al. (1999) observed abnormal reductions in the density and size of neurons and glia in MDD. The reduction in metabolism in this region in the unmedicated depressed condition may reflect these histopathological changes, and account for the failure of antidepressant drug treatment to alter metabolism in these areas (Bell et al., 1999). Although other studies reported reductions in CBF or metabolism which did normalize with antidepressant treatment, it appears that the ROI in these studies were placed in different areas of the dorsolateral or medial PFC (e.g., Bench et al., 1995; Buchsbaum et al., 1997; Mayberg et al., 1999).

4.4.6. Posterior cingulate cortex

Several groups reported abnormally increased CBF in the posterior cingulate cortex in MDD (Drevets, 2000). Compatible with the findings presented herein, Buchsbaum et al. (1997) also reported that the PCC metabolism is elevated in depression and decreases during sertraline treatment. Bench et al. (1993) reported that the posterior cingulate flow was elevated in depressives relative to the controls and correlated positively with a factor that had high loadings for anxiety. Many functional imaging studies have reported that exposure to aversive stimuli of various types increases physiological activity in the posterior cingulate gyrus (reviewed in Maddock, 1999). Nevertheless, Mayberg et al. (1999) reported that script driven sadness resulted in decreased posterior cingulate activity in healthy subjects, and that flow was decreased in depressed relative to remitted subjects with MDD, raising the possibility that this large region is functionally heterogeneous with respect to emotional behavior.

The posterior cingulate cortex appears to serve as a sensory association cortex, and may participate in processing the affective salience of sensory stimuli. The posterior cingulate cortex sends a major anatomical projection to the ACC, through which it may relay such information into the limbic circuitry (Vogt, 1993).

4.4.7. Abnormalities in the striatum, thalamus and other brain areas

The orbital/ventrolateral PFC, ACC and amygdala have extensive anatomical connections with the mediodorsal nucleus of the thalamus (MD) and ventromedial striatum (Price et al., 1996; Öngür and Price, 2000). Flow and metabolism are abnormally increased in the depressed phase of FPDD in both the medial thalamus (Drevets et al., 1992, 1995c) and the anteroventral striatum (Wilson et al., 2002) which encompasses the accumbens area (Öngür and Price, 2000). The metabolic activity in these areas also decreases during antidepressant drug treatment (Drevets et al., in press; Wilson et al., 2002). Metabolism has also been reported to decrease in the more dorsal areas of the striatum during paroxetine treatment or interpersonal psychotherapy (Brody et al., 2001).

4.4.8. Anatomical circuits implicated in MDD

The abnormalities of structure and function in mood disorders implicate limbic–thalamo–cortical (LTC) circuits, involving the amygdala, medial thalamus, and orbital and medial PFC, and limbic–cortical–striatal–pallidal–thalamic (LCSPT) circuits, involving the components of the LTC circuit along with related areas of the striatum and pallidum (Drevets et al., 1992). The amygdala and PFC are connected by excitatory amino acid neurotransmitter projections with each other and with MD (Price et al., 1996; Carmichael and Price, 1995). Through these connections the amygdala is in a position to activate the PFC both directly and indirectly (through the striatum and pallidum), and to modulate the reciprocal interaction between the PFC and MD (reviewed in Drevets et al., 1992).

Post mortem studies of MDD and BD within the LCSPT circuitry have shown volumetric and/or histopathological
changes in the subgenual and pregenual ACC, the lateral orbital cortex, the hippocampal subiculum, the amygdala, and the ventral striatum. The histopathological correlates of these abnormalities include a reduction in glial cells without an equivalent loss of neurons, elevated neuronal density, reduced neuronal size, and loss of synaptic markers or proteins, findings which would be consistent with a reduction in neuropil (Baumann et al., 1999; Bowley et al., 2002; Cotter et al., 2000; Drevets et al., 1998; Eastwood and Harrison, 2000, in press; Öngür et al., 1998; Bowen et al., 1989; Rajkowska et al., 1997, 1999). While the pathogenesis of these changes has not been established, it is notable that the dendritic arborization which forms the neuropil can, in some structures, undergo atrophy or ‘reshaping’ in the adult brain by exposure to physiologically elevated concentrations of excitatory amino acid (EAA) neurotransmitters in the presence of elevated glucocorticoid secretion (McEwen, 1999). The targeted nature of the grey matter volume reductions to specific areas of the LTC and LCSPT circuits which show increased glucose metabolism is noteworthy, since the glucose metabolic signal is dominated by glutamatergic transmission (Magistretti et al., 1995). The reduction in metabolism in these regions during chronic antidepressant drug treatment may thus signal the attenuation of elevated metabolic activity occurring in this circuit in unmedicated depressed subjects (Nowak et al., 1995). Notably, chronic antidepressant drug administration and repeated electroconvulsive shocks desensitize NMDA-glutamatergic receptors in the rat frontal cortex (Paul et al., 1994) and increase expression of neurotrophic and neuroprotective factors that may influence neuroplasticity (Duman et al., 1997; Manji et al., 2001).

Consistent with the hypothesis that reducing excitatory transmission through the LTC/LCSPT circuitry plays a role in the mechanisms of antidepressant treatment is the observation that surgical lesions that interrupt projections within these circuits can reduce depressive symptoms. The neurosurgical interventions currently employed for intractable depression (e.g., subcaudate tractotomy, anterior capsulotomy, anterior cingulotomy, limbic leukectomy) (Corsellis and Jack, 1973; Nauta, 1973; Ballantine et al., 1987; Newcombe, 1975; Knight, 1965) would all be expected to interrupt amygdalar projections into the ventral striatum, orbital cortex and ACC. Malizia et al. (1994) examined cerebral perfusion before and following stereotactic subcaudate tractotomy using SPECT and [Tc]HMPAO in 10 mood disordered subjects, and showed that, in the six subjects who showed a positive treatment response, flow decreased in both the ‘anterior low frontal’ and ‘low cingulate’ cortex.

5. Conclusion

These results converge with those of other PET studies, lesion analyses and post mortem studies to support a neural model in which the signs and symptoms of the major depressive syndrome involve dysfunction of modulatory systems in the prefrontal cortex, striatum and brainstem. Antidepressant therapies may compensate for dysfunction by attenuating this disinhibited, pathological limbic activity by augmenting monoamine neurotransmission and altering neuropeptide sensitivity at various points in the pathways mediating abnormal emotional expression.

6. Uncited references

Bechara et al., 1998; Casey et al., 2002; Chimowitz et al., 1992; Damasio et al., 1990; Davis, 1992; DiRocco et al., 1989; Drevets and Button, 1997; Drevets et al., 1995a; Drevets and Todd, 1997; Eastwood and Harrison, 2002; Fazekas, 1989; Folstein et al., 1991; Francis et al., 1989; Iversen and Mishkin, 1970; Nofzinger et al., 1999; Rubin et al., 1966; Teneback et al., 1999; Wooten and Collins, 1981; Young et al., 1993

Acknowledgements

The authors thank Joseph L. Price and Gordon Shulman for scientific discussions related to the methods and the interpretation of the results. Supported by NIH grants MH00928 and MH51137.

References


Bell, K.A., Kupfer, D.J., Drevets, W.C., 1999. Decreased glucose metabo-
lism in the dorsomedial prefrontal cortex in depression. Biol. Psychiatry 45, 1185.
Damasio, A.R., Tranel, D., Damasio, H., 1990. Individuals with sociopathic behavior caused by frontal damage fail to respond autonomically to social stimuli. Behav. Brain Res. 41, 81–94.
Drevets, W.C., Raichle, M.E., 1998. Reciprocal suppression of regional cerebral blood flow during emotional versus higher cognitive pro-


tine circuitries involved in limbic-motor integration. In: Kalivas, P.W., Barnes, C.D. (Eds.), Limbic Motor Circuits and Neuro-


Musselman, D.L., Nemeroff, C.B., 1993. The role of corticotropin-


D-aspartate (NMDA) receptor complex in the frontal cortex of suicide victims. Brain Res. 675, 157–164.


Rolls, E.T., 1995. A theory of emotion and consciousness, and its application to understanding the neural basis of emotion. In: Gazza-


Schultz, W., 1997. Dopamine neurons and their role in reward mecha-


Shin, L.M., McNally, R.J., Kosslyn, S.M., Thompson, W.L., Rauch, S.L.,


