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Anterior Cingulate Volumes in Never-Treated Patients with Major Depressive Disorder

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The anterior cingulate cortex (ACC) is implicated in the cognitive and affective abnormalities observed in mood disorders. Bilateral ACC volume reductions have been reported in patients with major depressive disorder (MDD) when compared to healthy controls. We compared regional brain volumes in the subgenual prefrontal cortex (SGPFC; Brodmann area (BA) 24_{sg}), subcallosal gyrus (BA25), and paracingulate gyrus (BA32) in 65 patients receiving a first course of treatment for MDD and 93 healthy control subjects. Patients with more than three episodes of untreated MDD had smaller subcallosal gyrus volumes than healthy controls, while those with three or fewer past untreated episodes did not differ from controls. We also found preliminary evidence that medication-exposed patients had smaller SGPFC volumes than patients with no exposure to medication and healthy controls. There was no evidence that these effects related to mood state, duration of untreated illness, or to patient age. No differences were apparent in paracingulate gyrus volumes between patients and controls. These findings confirm the presence of ACC volume reductions in untreated patients with MDD and suggest that illness burden and short-term medication exposure mediate this change.
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INTRODUCTION

The anterior cingulate cortex (ACC) is important in cognitive and affective regulation, serving diverse functions in attention, problem solving, error detection, motivation, decision making, and social behavior (see reviews by Rushworth *et al,* 2007; Allman *et al,* 2001; Bush *et al,* 2000). The ACC comprises of two subdivisions that differ in their neural connectivity and cytoarchitectonic features (Bush *et al*, 2000; Yucel *et al*, 2003). Together, the subgenual prefrontal cortex (SGPFC; Broadmann area (BA) 24_{sg}), subcallosal gyrus (BA25), and paracingulate gyrus (BA32), along with BA24 a–c and BA33, form the rostral–ventral affective subdivision of the ACC, thought to be involved in assessing emotional and motivational information and in the regulation of emotional responses (Bush *et al*, 2000). Accordingly, this division has extensive reciprocal connections to regions involved in affective responding (eg, amygdala, orbitofrontal cortex). By contrast, the dorsal cognitive subdivision (BA24 a′–c′, BA32′) lies superior to the corpus callosum and is involved in cognitive processing through response selection and the processing of cognitively demanding information (Yucel *et al*, 2003). Regions comprising these divisions are thought to have related, but functionally distinct, roles in the pathophysiology of major depressive disorder (MDD) (Mayberg, 1997; Ressler and Mayberg, 2007).

Several studies have reported gray matter reductions in the subgenual gyrus ($BA24_{sg}$) in patients with MDD when compared to age- and sex-matched controls (Botteron *et al*, 2002; Drevets *et al*, 1997; Hastings *et al*, 2004; but see, Brambilla *et al*, 2002; Bremner *et al*, 2002 for negative findings). In contrast to Bremner *et al* (2002) and Pizzagalli *et al* (2004), who found no differences in BA25 or in BA32 (Bremner *et al*, 2002) volume between MDD patients and healthy controls, Coryell *et al* (2005) subsequently reported a reduction in left subcallosal gyrus volume in patients with MDD relative to controls. Finally, a number of studies demonstrate smaller gray (Lavretsky *et al*, 2007; Caetano *et al*, 2006; Ballmaier *et al*, 2004) and white (Ballmaier *et al*, 2004) matter volume in 'total' and in ventral (Tang *et al*, 2007) ACC in patients with MDD relative to controls; however, the cingulate regions assayed in these studies varied widely. A small number of studies have relied upon voxel-based morphometry (Pizzagalli *et al*, 2004; Chen *et al*, 2007; Tang *et al*, 2007) as opposed to manual delineation, as is common across the majority of studies. Further confounding these issues is the inclusion of mixed samples of patients with MDD and bipolar disorder (eg, Hirayasu

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et al, 1999) in studies reporting volumetric reductions in SGPFC.

ACC volume in MDD has been further examined in relation to clinical and demographic variables, including age (Lavretsky et al, 2007), family history of illness (Drevets et al, 1997), treatment response (Coryell et al, 2005), and current mood state (Caetano et al, 2006). Patients included in these studies were heterogeneous with respect to illness history and medication status, however; rendering the conclusions of these reports equivocal. Here, we examine ACC volume in a sample of patients who had never been treated for psychiatric illness. As pharmacological treatment was initiated shortly before MRI scanning in a subgroup of these patients, we were able to compare ACC volume in patients who had not been exposed to medication at the time of scanning to those of patients with preliminary exposure to medication. Examination of these patients allowed us to evaluate the early effects of antidepressant therapy, as well as of key clinical variables, on ACC volume without the confounding factor of heterogeneous treatment histories. Our focus was on alterations in the rostral–ventral affective subdivision of the ACC where we examined volume in BA25, $BA24_{sg}$, and BA32.

MATERIALS AND METHODS

Subjects

Sixty-five patients with a primary diagnosis of MDD (mean age = 28.8; SD = 10.3; 30 women) were recruited from the mood disorders inpatient and outpatient clinics at St Joseph's Healthcare Hamilton. The diagnosis of MDD was confirmed by the Structured Clinical Interview for DSM-IV (SCID; First et al, 2001). All patients were treatment naive, having never received prior treatment for psychiatric illness at the point of entry into our clinical service. An average of 8.2 (8.7) years had elapsed between patients' first symptoms and evaluation. The healthy comparison group (HC) comprised of 93 healthy subjects matched to the patients in terms of age (mean age = 28.4, SD = 10.7) and gender distribution (56 women).

Symptom severity in these patients was assessed using the 17-item Hamilton Depression Rating Scale (Ham-D), Young Mania Rating Scale (YMRS), and the Global Assessment of Functioning Scale (GAF). Healthy controls also received these measures to rule out the presence of subthreshold psychiatric illness.

Exclusion criteria for patients and healthy controls were: (i) substance use-related disorder within the past 6 months as determined by the SCID; (ii) lifetime history of substance dependence as measured by the SCID; (iii) Post-traumatic stress disorder (PTSD) as determined by the SCID; (iv) use of alcohol or illicit psychoactive substance within 48 h of testing; (v) untreated medical illness such as uncontrolled diabetes or other endocrine disorders; (vi) history of head injury with loss of consciousness; (vii) history of neurological disease; and (viii) past treatment with pharmacotherapy (greater than 5 days lifetime with any psychotropic medication including stimulants in childhood), electroconvulsive therapy, transcranial magnetic stimulation or psychotherapy.

The MRI scan was completed prior to or shortly after medication was initiated. Nineteen of our patients received no medication prior to scanning. Twenty-six patients received citalopram at doses ranging from 10 to 50 mg ($x = 18.6(4.5)$ mg) for an average of 31.9(27.1) days prior to scanning. One of the citalopram-treated patients received adjunctive therapy with 0.5 mg of risperdal for 2 days and another received 2.5 mg of olanzapine for 2 days. Five patients received a mean dosage of 46.9(25.6) mg of sertraline for an average of 22.2(18.8) days prior to scanning. Three patients received venlafaxine at a mean dosage of 65.1(8.8) mg for an average of 63.3(55.1) days prior to scanning; one of these patients received adjunctive therapy with quetiapine (mean dosage = 129.4 mg) for 96 days. Two of our patients received a mean dosage of 129.3(29.3) mg of bupropion for an average of 41(8.5) days prior to scanning. Finally, three patients received treatment with fluvoxamine (mean dosage = 69.6 days), mirtazapine (30 mg), and paroxetine (10 mg), for 23, 70, and 54 days duration, respectively. The demographic and clinical characteristics of the study sample are further described in Table 1.

Demographic and Clinical Subgroups

A review of the literature identified several demographic and clinical variables that may impact ACC volumes and for which sufficient data were available to conduct analyses. Participants were divided into subgroups based on the criteria below. In cases where we were unable to confirm key clinical information from history, chart review, and consultation with treating clinicians, we excluded those

Table 1 Demographic and Clinical Characteristics of Study Sample

	Controls ($n = 93$)	**MDD patients ($n = 65$)**
Characteristic		
	n	*n*
Sex		
Male	37	35
Female	56	30
	Mean	*Mean*
Age	28.4 (10.7)	28.8 (10.3)
Number of affective episodes		4.5 (7.6)
Onset of illness (in years)		20.9 (10.3)
Duration of illness (in years)		8.2 (8.7)
Duration of medication (in days)		22.0 (28.0)
Ham-D score at baseline	1.8 (1.7)	16.2 (7.6)
YMRS score at baseline	0.2 (0.6)	0.4 (1.1)
GAF score at baseline	83.1 (3.7)	53.1 (13.8)
Ham-D score at scanning	1.8 (1.7)	13.3 (7.1)
YMRS score at scanning	0.2 (0.6)	0.1 (0.7)
GAF score at scanning	83.1 (3.7)	60.4 (8.8)

Abbreviations: GAF, Global Assessment of Function Scale; HAM-D, 17-item Hamilton Rating Scale for Depression; YMRS, Young Mania Rating Scale.

participants from the subgroup analyses that required this information.

To examine the effect of number of untreated illness episodes, MDD patients were divided into two groups and compared to healthy controls: (i) those patients with three or fewer previous episodes of untreated illness ($n = 37$) and; (ii) those patients with more than three previous episodes of untreated illness ($n = 17$). Recent reports suggest that rates of recurrence are three times higher at a fourth episode of MDD than recurrence rates following a single episode of illness (Keller and Boland, 1998). Moreover, this effect appears exponential, where recurrence risk is increased and length of time to recurrence shortened with each subsequent episode of illness (Keller and Boland, 1998; Kendler *et al*, 2001). To examine the effects of medication exposure, MDD patients were divided into two additional groups and compared to healthy controls: (i) patients who received five or fewer days of medication administration prior to baseline scanning and who therefore could be considered medication-unexposed based on conventional estimates of drug uptake ($n = 28$; mean = 0.4(1.2) days); and (ii) medication exposed patients who received more than 5 days but less than six months of medication administration prior to scanning ($n = 37$; mean = 38.3(27.5) days). Finally, MDD patients were divided based on the basis of family history of illness and compared to healthy controls. This division resulted in three subgroups of MDD patients: (i) those with no family history of illness ($n = 26$); (ii) those with one first-degree family member with a confirmed diagnosis of a mood disorder (MDD or bipolar illness) and/or multiple second-degree relatives with a confirmed history of mood disorders ($n = 26$); and (iii) those with an enriched family history of mood disorder involving two or more first-degree relatives with a confirmed diagnosis of a mood disorder ($n = 10$).

All subjects provided a written informed consent in accordance with the Declaration of Helsinki. The study was approved by the Research Ethics Boards of St Joseph's Healthcare (Ontario, ON, Canada) and Hamilton Health Sciences Corporation (Ontario, ON, Canada).

MRI Image Acquisition and Analysis

One hundred twenty two of the MRI scans were obtained on a 1.5-T. Sigma GE Genesis-based Echo-Speed scanner (General Electric Medical Systems, Milwaukee, WI) running version 5.7 software and using a standard 30-cm circularly polarized head coil. Sagittal anatomic images were acquired by using a 3D/FSPGR/20 sequence (flip angle = 20; echo delay time in-phase (TE), minimum repetition time (TR) = 300 ms; inversion recovery = 300 ms; matrix = 512×256; field of view (FOV) = 24 cm; scan thickness = 1.2 mm). The remaining 36 subjects were scanned on a 3-T MRI Sigma GE Genesis (General Electric Medical Systems, Milwaukee, WI). Here, sagittal T-1 weighted images were acquired using a 3D FSPGR-IR sequence, (TR/TE = 10.3/2.1 ms; flip angle = 20; inversion time = 300; matrix = 512×256; FOV = 24; and slice thickness = 1.2 mm. Seventy-four percent ($n = 69$) of control subjects were scanned at 1.5T and 26 percent ($n = 24$) at 3T. Eighty one percent of the MDD patients ($n = 53$) were scanned at 1.5T and 19 percent ($n = 12$) at 3 T.

The AFNI software package (National Institute of Mental Health, Bethesda, Maryland, MD, USA; http://afni.nimh.nih.gov/afni/) was used to analyze these data.

Ventral–Rostral ACC Measurement

All the three subdivisions were measured on the coronal plane, although the sagittal plane was also used simultaneously. The axial plane was used primarily to delineate BA25 from the nucleus accumbens. For the volumetric measurements of BA24sg (SGPFC), we relied primarily on the protocol of Drevets *et al* (1997), but also benefited from the studies of McCormick *et al* (2006) and Fornito *et al* (2008) as well as the human brain atlas of Mai *et al* (1997). We used previously published studies (Bremner *et al*, 2002; McCormick *et al*, 2006) and the human brain atlas of Mai *et al* (1997) to measure the volume of BA25. The most posterior border on the coronal plane was set as the slice anterior to the slice where putamen was first visible and the most anterior border was the anterior most point of the corpus callosum (rostral tip of the genu). The inferior border was the cingulate sulcus. We used previously published studies (Bremner *et al*, 2002; McCormick *et al*, 2006) and the human brain atlas of Mai *et al* (1997) to measure the volume of BA25 (subcallosal gyrus). We set our anterior border coronally as the last slice in which internal capsule was visible, separating the caudate from the putamen; in other words the first slice in which putamen was visible. The posterior border was set to be the slice anterior to anterior commissure. The inferior border of the BA25 was defined by the medial border of the gyrus rectus (straight gyrus). In more posterior slices, care must be given to avoid including the forebrain basal nuclei, so the superior limit of the prepyriform cortex which lies laterally was followed to set the inferior border of BA25. Simultaneous with coronal tracings, besides sagittal plane, axial plane was used to delineate the lateral borders. BA32 (paracingulate gyrus) was defined as the gyrus that lies beneath BA24sg. The cingulate sulcus formed the superior border, whereas the inferior border was formed by the superior rostral sulcus or paracingulate sulcus whenever existed. We used previous studies by McCormick *et al* (2006), Fornito *et al* (2006), and Bremner *et al* (2002) to delineate the borders of BA32 (see Figure 1).

The volumes were measured by one rater (KY) who was unaware of group designation. The intraclass correlation coefficient (ICC) values for intra-rater reliability in 10 brains were 0.99, 0.995, and 0.981 for BA24sg, BA25, and BA32, respectively.

Total Cerebral Volume Measurement

Total cerebral volume (TCV) was defined as the gray and white matter of both hemispheres spanning the midbrain superior to the pons, a border chosen for its easy identification. Here, the inter-rater reliability (intraclass correlation coefficient (ICC)) between two raters was 0.99.

Statistical Analyses

We compared overall volume in the subgenual gyrus, subcallosal gyrus, and paracingulate cortex and TCV in MDD patients and healthy controls using independent

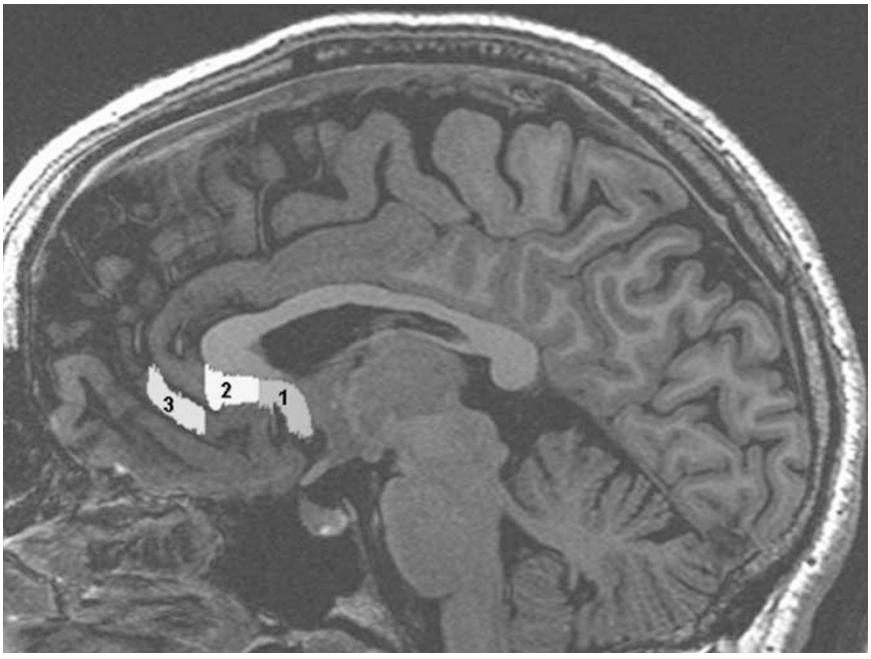

Figure 1 Rostral-ventral anterior cingulate subdivisions. 1 = BA25 (subcallosal gyrus), 2 = BA24sg (SGPFC), and 3 = BA32 (paracingulate gyrus).

sample *t*-tests with α set at 0.05. Subgroup volumes were compared using one-way ANOVAs where subgroup was treated as a between-subjects variable and Tukey's Honestly Significant Difference *post hoc* test with α set at 0.05 was used for follow-up of pairwise comparisons.

To determine whether ACC volume change varied with symptom severity and age at onset, we performed correlational analyses (Pearson's r; two tailed). Given the large number of correlations to be computed, we applied a conservative cutoff of $\alpha = 0.01$ for these analyses.

RESULTS

Subcallosal Gyrus (BA25) Volume

BA25 volumes were smaller in the MDD patients compared to healthy controls, $t(151) = 1.99$, $p = 0.049$ (mean volume = 643.4 (136.4) mm^3 and 598.6 (138.1) mm^3, for controls and patients, respectively). Patients' history of untreated illness, however, mediated this effect, $F(2, 139) = 4.25$, $p = 0.02$ (see Table 2). Whereas MDD patients with more than three episodes of untreated illness had smaller subcallosal gyrus volumes than did healthy controls ($p = 0.02$), patients with three or fewer episodes did not differ from control subjects, $p > 0.05$. We found no evidence, however, that subcallosal gyrus volume was influenced by medication status or by family history of illness (p's > 0.05). Moreover, volume in this region did not relate to Ham-D, YMRS and GAF scores at baseline assessment and at time of scanning nor was there any relation between age at time of scanning or time since first illness symptoms and subcallosal gyrus volume (p's > 0.01).

SGPFC ($BA24_{sg}$) Volume

There was no overall difference in $BA24_{sg}$ volume between MDD patients and healthy controls, $p > 0.05$ (mean volume = 511.5 (215.7) mm^3 and 462.0 (166.2) mm^3 for controls and patients, respectively). When we compared patients with and without medication exposure to healthy controls, however, we found a trend towards volume loss in this region, $F(2, 155) = 2.86$, $p = 0.06$ (see Table 2). Given the provocative nature of this finding, we compared SGPFC volume in each of the patient groups to that of healthy controls. Patients with medication exposure had smaller $BA24_{sg}$ volumes than healthy controls, $t(128) = 2.26$, $p = 0.03$ and patients without medication exposure, $t(63) = 2.19$, $p = 0.03$. However, $BA24_{sg}$ volumes did not differ between patients with no medication exposure and healthy controls ($p > 0.05$). There were no differences in age at scanning, age at disease onset, duration of untreated illness, mean number of episodes of untreated illness, and scores on the Ham-D, YMRS and GAF (p's > 0.05) between the medication exposed and medication unexposed groups, suggesting that this difference in volume may be related to the effects of antidepressant onset on $BA24_{sg}$ volume, rather than from clinical or demographic differences in these subgroups.

We found no evidence that $BA24_{sg}$ volume was influenced by number of untreated illness episodes or by family history of illness (p's > 0.05). Furthermore, volume in this region did not relate to Ham-D, YMRS and GAF scores at baseline assessment and at time of scanning nor was there any relation between age at time of scanning or duration of untreated illness and $BA24_{sg}$ volume (p's > 0.01).

Paracingulate Gyrus (BA32)

There was no overall difference in BA32 volumes between MDD patients and healthy controls, $p > 0.05$ (1331.0 (321.3) mm^3 and 1432.4 (359.2) mm^3 for controls and patients, respectively). We also found no evidence for volume change when we examined the influence of number of untreated illness episodes, medication exposure, and family history of

Table 2 Mean Volume (mm^3) in Anterior Cingulate Sub-divisions

	Controls ($n=93$)	MDD patients ($n=65$)	
	Mean (mm^3)	*Mean (mm^3)*	
Subcallosal gyrus (BA25)	643.4 (136.4)	598.6 (138.1)	
Subgenual PFC ($BA24_{sg}$)	511.5 (215.7)	462.0 (166.2)	
Paracingulate gyrus	1331.0 (321.3)	1432.4 (359.2)	
	Controls	MDD patients with $\leqslant 3$ episodes	MDD patients with >3 episodes
	($n=93$)	($n=37$)	($n=17$)
	Mean (mm^3)	*Mean (mm^3)*	*Mean (mm^3)*
Subcallosal gyrus (BA25)	643.4 (136.4)	604.8 (109.5)	548.5 (132.1)
	Controls	Medication-unexposed MDD patients	Medication-exposed MDD patients
	($n=93$)	($n=28$)	($n=37$)
	Mean (mm^3)	*Mean (mm^3)*	*Mean (mm^3)*
Subgenual PFC ($BA24_{sg}$)	511.5 (215.7)	512.3 (175.4)	423.9 (150.2)

Abbreviation: PFC, Prefrontal gyrus.

illness on volume in this region ($p>0.05$). Finally, BA32 volumes did not relate to Ham-D, YMRS, and GAF scores at baseline assessment and at time of scanning nor was there any relation to age at time of scanning or duration of untreated illness (p's >0.01).

Total Cerebral Volume

There were no differences in TCV between patients and controls ($p>0.05$).

DISCUSSION

The key finding of this study was that patients presenting for first treatment of depression had subcallosal gyrus volumes smaller than those of age- and sex-matched healthy subjects. Critically, this difference was apparent only in patients with more than three episodes of untreated illness, suggesting that volume loss in this region is apparent only after an extended course of untreated illness. We also found preliminary evidence that SGPFC volumes decreased immediately following medication exposure; there was a trend towards smaller SGPFC volumes in medication-exposed patients compared to patients with no exposure and to healthy controls. There was no evidence that any of these effects related to mood state at baseline or at the time of scanning, duration of untreated illness or to patient age; there were no correlations found between these variables and volume in the ACC regions examined here. Finally, we found no difference in paracingulate gyrus volumes between patients and controls. To our knowledge, this is the first study to examine ACC volume in an entire sample of treatment naive MDD patients, the number of whom exceeds that of any patient group reported previously in the ACC volumetric literature.

Coryell *et al* (2005) also reported smaller left BA25 (posterior SGPFC) volume in patients with MDD when compared to healthy controls. No data were provided regarding the medication status of these participants. By contrast, Bremner *et al* (2002) found no evidence for smaller BA25 volumes in a group of MDD patients receiving antidepressant treatment, a finding analogous to that reported by Pizzagalli *et al* (2004). Patients in the Bremner *et al* (2002) study had an extended history of severe illness, having an average of three previous inpatient hospitalizations; it is possible that long-term treatment with antidepressant medication may have normalized ACC volumes in these patients, as an extensive preclinical literature suggests that antidepressant medication may have neuroprotective and perhaps even neurotrophic effects (for a review see Tanis *et al*, 2007).

Interestingly, follow-up analyses indicated that small subcallosal gyrus volumes were apparent only in patients with more than three previous episodes of untreated illness; no such finding emerged for patients with three or fewer untreated episodes. The hypercortisolemia theory of MDD (see Sapolsky, 2001) suggests gradual decreases in tissue volume in MDD stemming from hyperactivity/disinhibition of the hypothalamic–pituitary–adrenal (HPA) axis. Indeed, BA25 has extensive connections with structures within, and regulating, this axis (eg, hypothalamus, amygdala, hippocampus). In the absence of effective treatment interventions, this may result in volume change following repeated illness episodes. There was no evidence that additional clinical or demographic factors contributed to ACC volume differences in our patients. We found no evidence that family history of mood disorders differentiated patients' ACC volumes, although it is possible that these effects might be apparent in a larger sample of patients with an enriched family history of illness. Similarly, we found no relation between mood symptoms and volume in any of the ACC subregions. This finding contrasts with an earlier report by

Caetano *et al* (2006) who found a relation between total ACC volume and mood symptoms; however, the SGPFC region was not included in that measurement protocol. Chen *et al* (2007) reported a relation between dorsal (anterior midcingulate region) ACC volume and mood symptoms; however, we did not measure this subdivision.

In the present study, we found a trend towards smaller $BA24_{sg}$ volume in patients with minimal durations of treatment with antidepressant medications relative to healthy controls; no such effect was apparent in patients without medication exposure. Mayberg *et al* (2000) found no change in glucose metabolism in BA25 following 1 week of treatment with fluoxetine; however, differences in metabolism emerged at 6 weeks duration. In another PET study, the metabolic reduction in the SGPFC was reported as related to antidepressant treatment (Drevets *et al*, 2002). There were no significant differences in clinical or demographic variables in our patients with and without medication exposure, suggesting that this preliminary finding may relate to the effects of antidepressant administration on tissue volume. Further studies are required to confirm whether this pattern achieves significance in larger samples of patients.

Two studies have demonstrated a positive relation between ACC volume and treatment response in MDD (Coryell *et al*, 2005; Chen *et al*, 2007), although an earlier study was negative in this respect (Drevets *et al*, 1997). PET and functional MRI studies show that treatment with antidepressants is associated with increased cerebral metabolism (Vlassenko *et al*, 2004) and greater activation in the ACC in patients with MDD (Chen *et al*, 2007; Davidson *et al*, 2003). Despite positive findings in other limbic regions in patients with MDD (eg, hippocampus; (Sheline *et al*, 1999)), the relation between treatment with antidepressants and ACC volume has not been systematically examined. While it is notable that in several studies reporting small ACC volumes, patients with MDD were free of medication for periods ranging between 2 and 4 weeks (Drevets *et al*, 1997; Lavretsky *et al*, 2007; Caetano *et al*, 2006; Ballmaier *et al*, 2004); it is unknown whether the withdrawal of antidepressants influenced the pattern of findings reported. Medication history is an important factor in studies of patients with MDD (Dickstein *et al*, 2005; Strasser *et al*, 2005; Frazier *et al*, 2005; Rajkowska, 2002) and our data further support the notion that even relatively short-term treatment may exert a measurable effect on the volumes of key brain regions.

A limitation of this study is that patients and controls were scanned in one of two scanners; we could find no evidence of systematic differences between these groups and the proportion of patients compared to controls scanned in each scanner was similar. In common with many studies, this investigation was cross-sectional and therefore provides limited information on the possible changes in ACC volume over the course of illness. Following the approach of Bremner *et al* (2002) we measured total volumes of ACC subregions, and did not examine volume by hemisphere (eg, Coryell *et al*, 2005; Drevets *et al*, 1997) leaving us unable to comment on lateral effects with respect to these data. A strength of the study compared to many, however, is that patients had minimal lifetime exposure to psychotropic medication prior to scanning. Most other studies examining ACC volume in MDD have been conducted in patients with variable and unknown exposure to past treatment. Longitudinal studies that track patients over disease onset and through follow-up, in particular those involving systematic reporting of medication status and illness burden are urgently needed. Careful collection and reporting of these data will be essential if future studies are to advance our understanding of the factors that mediate ACC volume in patients with MDD.

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DISCLOSURE/CONFLICT OF INTEREST

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