Brain Imaging Correlates of Depressive Symptom Severity and Predictors of Symptom Improvement After Antidepressant Treatment

Chi-Hua Chen, Khanum Ridler, John Suckling, Steve Williams, Cynthia H.Y. Fu, Emilio Merlo-Pich, and Ed Bullmore

Background: It would be therapeutically useful to predict clinical response to antidepressant drugs. We evaluated structural magnetic resonance imaging (MRI) and functional MRI (fMRI) data as predictors of symptom change in people with depression.

Methods: Brain structure and function were measured with MRI in 17 patients with major depression immediately before 8 weeks treatment with fluoxetine 20 mg/day. For fMRI, patients were scanned during visual presentation of faces representing different intensities of sadness. Clinical response was measured by change in serial scores on the Hamilton Rating Scale for Depression. Symptom change scores (and baseline symptom severity) were regressed on structural and functional MRI data to map brain regions where grey matter volume, or activation by sad facial affect processing, was significantly associated with symptom change (or baseline severity).

Results: Faster rates of symptom improvement were strongly associated with greater grey matter volume in anterior cingulate cortex, insula, and right temporo-parietal cortex. Patients with greater than median grey matter volume in this system had faster rates of improvement and significantly lower residual symptom scores after 8 weeks' treatment. Faster improvement was also predicted by greater functional activation of anterior cingulate cortex. Baseline symptom severity was negatively correlated with greater grey matter volume in dorsal prefrontal and anterior midcingulate regions anatomically distinct from the pregenual and subgenual cingulate regions predicting treatment response.

Conclusions: Structural MRI measurements of anterior cingulate cortex could provide a useful predictor of antidepressant treatment response.

Key Words: Anterior cingulate cortex, antidepressant, Depression, magnetic resonance imaging, neuroimaging, treatment response

No more than one-half of the patients receiving antidepressant drugs will have full remission of symptoms (Brody *et al.* 1998). An ineffective period of pharmacological treatment exposes patients unnecessarily to risks of adverse events and delays consideration of possibly more effective treatments. Variability of treatment response among patients with depression enrolled in clinical trials of new drugs can also reduce the power of these trials to demonstrate drug efficacy. Our current lack of ability to predict heterogeneity of treatment response in depression is widely recognized as a challenging factor in the development of the next generation of antidepressant drugs (Berton and Nestler 2006).

For these reasons it would be therapeutically useful to have a widely accessible clinical predictor of antidepressant drug response. Several biological predictors have been explored previously, including greater pretreatment anterior cingulate activity measured with functional imaging (Brody *et al.* 1999; Davidson *et al.* 2003; Mayberg *et al.* 1997; Saxena *et al.* 2003) and electroencephalography (Pizzagalli *et al.* 2001); short pretreatment P300 latency indexing prefrontal function (Kalayam and Alexopoulos 1999); the dexamethasone/corticotrophin releasing hormone test (Holsboer 1983; Ising *et al.* 2005); higher pretreatment serotonin transporter availability (Kugaya *et al.* 2004); higher plasma or lower pretreatment platelet serotonin (5-HT) concentration (Castrogiovanni *et al.* 2003; Figueras *et al.* 1999); the long allele of the serotonin transporter promoter polymorphism (Smeraldi *et al.* 1998); and other genes implicated in serotonin signaling pathways (Serretti *et al.* 2005). Among these predictors, there is well-replicated evidence that variation in pregenual anterior cingulate cortical function is correlated with clinical response (Mayberg *et al.* 1997). However, many of the prognostic markers previously considered, like positron emission tomography (PET), have obvious limitations in terms of their availability and acceptability and are, therefore, unlikely to translate readily to clinical practice or clinical trial design.

In this context, we have addressed the following question: can we use structural (or functional) magnetic resonance imaging (MRI) as a predictor of clinical response to antidepressant drug treatment? We were particularly interested in the potential of structural MRI because it is a widely available neuroimaging technique for which we could find no prior data evaluating its utility either as a predictor of clinical response to antidepressant treatment or as a marker of baseline symptom severity. The motivation to use functional MRI (fMRI) was to replicate previous reports of functional imaging predictors of depressive symptom response and to compare directly the predictive power of structural and fMRI measures of anterior cingulate cortex.

We acquired structural and functional MRI data in a longitudinal study of 17 patients with major depressive disorder treated

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with fluoxetine 20 mg/day for 8 weeks. Symptom severity was serially rated with the Hamilton Rating Scale for Depression (HAM-D) at baseline and 2, 4, 6, and 8 weeks; structural and functional MR images were acquired at baseline (week 0). Baseline symptom severity (HAM-D score at start of treatment) and symptom improvement (linear change in symptom scores over 8 weeks, controlling for differences in baseline severity) were regressed on structural and functional MRI data at each voxel of the images, to construct whole brain maps highlighting regions associated with initial symptom severity or predictive of symptomatic improvement after antidepressant treatment. In many (though not all) previous relevant PET studies, greater severity of depressive symptoms and poor treatment response have been associated with decreased metabolism of the anterior cingulate cortex (Kimbrell *et al.* 2002; Mayberg *et al.* 1997). We hypothesized on this basis that baseline symptom severity and treatment response would both be associated with MRI measures of anterior cingulate function and structure, and that patients with reduced grey matter volume or task-related activation in anterior cingulate cortex would have more severe symptoms at baseline and/or slower rates of treatment response.

Methods and Materials

Participants

Seventeen participants (mean age ± SD = 44.06 ± 8.36 years; 12 women, 5 men) meeting DSM-IV (American Psychiatric Association 1994) criteria for major depressive disorder according to the Structured Clinical Interview for DSM-IV Axis 1 Disorders (First *et al.* 1995) were recruited from the general population by local newspaper advertisements. Inclusion criteria were an acute episode of major depressive disorder of the unipolar subtype and a score of at least 18 on the 17-item Hamilton Rating Scale for Depression (HAM-D) (Hamilton 1960). Exclusion criteria were a history of neurological trauma resulting in loss of consciousness; current neurological disorder; current comorbid Axis 1 disorder, including bipolar disorder and anxiety disorder; or a history of substance abuse within 2 months of study participation. Personality disorder was not formally assessed. All patients were free of psychotropic medication for a minimum of 4 weeks at recruitment. All participants provided written, informed consent. The project was approved by the Ethics Research Committee, Institute of Psychiatry, London, United Kingdom.

Fluoxetine Administration and Clinical Assessment Protocol

Participants received antidepressant treatment with oral fluoxetine hydrochloride, a selective serotonin reuptake inhibitor (SSRI), 20 mg/day in a single dose, starting as soon as possible after the baseline clinical, and MRI assessments and continuing until their completion of the study protocol 8 weeks later. For the duration of their participation in the study, the patients were assessed clinically every 2 weeks by a psychiatrist (CF) and

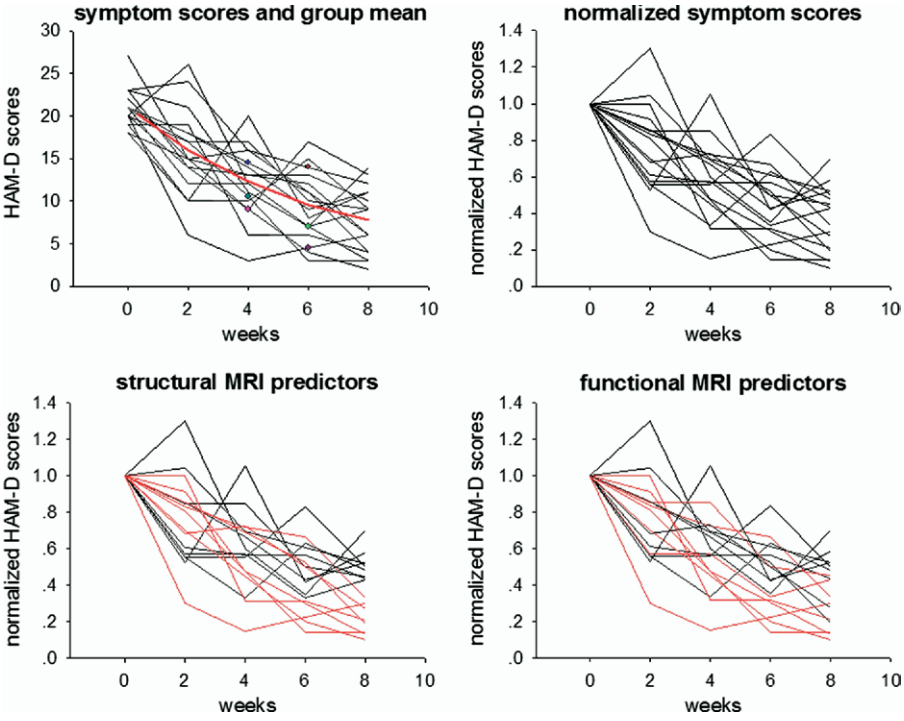

Figure 1. Serial ratings of depressive symptom severity (Hamilton Rating Scale for Depression [HAM-D] scores) in people with major depression treated for 8 weeks with fluoxetine. Top-left: raw scores and group mean; each line represents symptom change for an individual patient; the six discrete points highlight missing data on six patients who did not attend for clinical assessment at either week 4 or week 6; the red line is the group mean HAM-D score over time. Top-right: normalized symptom scores corrected for baseline severity; each line represents HAM-D(t)/HAM-D(0) {t = 0, 2, 4, 6, 8 weeks} for each patient over time. Bottom-left: differentiation of clinical outcome by median split on grey matter volume in anterior cingulate cortex. For anterior cingulate cortex, red lines represent the clinical trajectories of patients with greater than median grey matter volume, and black lines represent the trajectories of patients with smaller than median grey matter volume. The two groups are clearly distinguished in terms of clinical outcome after 8 weeks of treatment. Bottom-right: differentiation of clinical outcome by median split on functional activation in anterior cingulate cortex. For anterior cingulate cortex, red lines represent the clinical trajectories of patients with greater than median activation, and black lines represent the trajectories of patients with smaller than median activation. The two groups are not so clearly distinguished in terms of clinical outcome after 8 weeks of treatment. MRI, magnetic resonance imaging.

depressive symptoms were serially rated with the HAM-D. All patients recruited into the study were able to complete the protocol satisfactorily.

MRI Data Acquisition

Structural MRI data were acquired from all participants with a 1.5-T IGE LX System (General Electric, Milwaukee, Wisconsin) at the Maudsley Hospital, South London and Maudsley NHS Trust, London. A total of 120 dual echo, fast spin echo (T2-weighted and proton density [PD]-weighted) images of the whole brain were acquired in a coronal orientation with an in-plane spatial resolution of .8 mm and slice thickness = 3 mm, repetition time (TR) = 4000 msec, effective echo times (TE) = 15 msec and 105 msec, and echo train length (ETL) of 8.

For fMRI, gradient-echo single-shot echoplanar imaging (EPI) was used to acquire T2*-weighted MR image volumes with the same 1.5-T IGE LX System (General Electric). During an implicit facial affect processing task (detailed in the following text), we acquired 180 three-dimensional image volumes, each comprising 16 noncontiguous axial sections parallel to the intercommissural plane, with the following parameters: TR = 2000 msec; TE = 40 msec; section thickness = 7 mm; section skip = .7 mm; and in-plane resolution = 3 mm. To facilitate later co-registration of the fMRI data in standard space, a higher resolution EPI dataset comprising 43 sections of the whole brain in the intercommissural plane was acquired with the following parameters: TR = 16000 msec; TE = 73 msec; inversion time (TI) = 180 msec; and section thickness = 3 mm.

fMRI: Facial Affect Processing Experiment

We used an event-related fMRI paradigm with well-established stimuli from the Ekman series (Ekman and Friesen 1976) to activate brain systems implicated in incidental processing of affectively valent faces or emotional expressions. Ten faces (5 male, 5 female) from this standard series of facial expressions of sadness were computationally morphed (by interpolation between a highly sad and neutral face of the same identity) to represent low, medium, and high intensities of sadness. Each facial stimulus was presented twice at each intensity of sadness (60 faces in total) interspersed with 12 baseline trials (crosshair fixation) in random order. For each facial trial, subjects were asked to indicate the gender of the face by lateral movement of a joy-stick. Total duration of the experiment was 360 sec (Fu *et al.* 2004 for further details on paradigm design).

Clinical Data Analysis

Baseline severity of depressive symptoms was measured simply with the total HAM-D score at week 0, HAM-D(0). Linear change in depressive symptoms over time was estimated with the following regression model:

$$\text{HAM-D}(t)/\text{HAM-D}(0) = A + Bt + \varepsilon \quad (1)$$

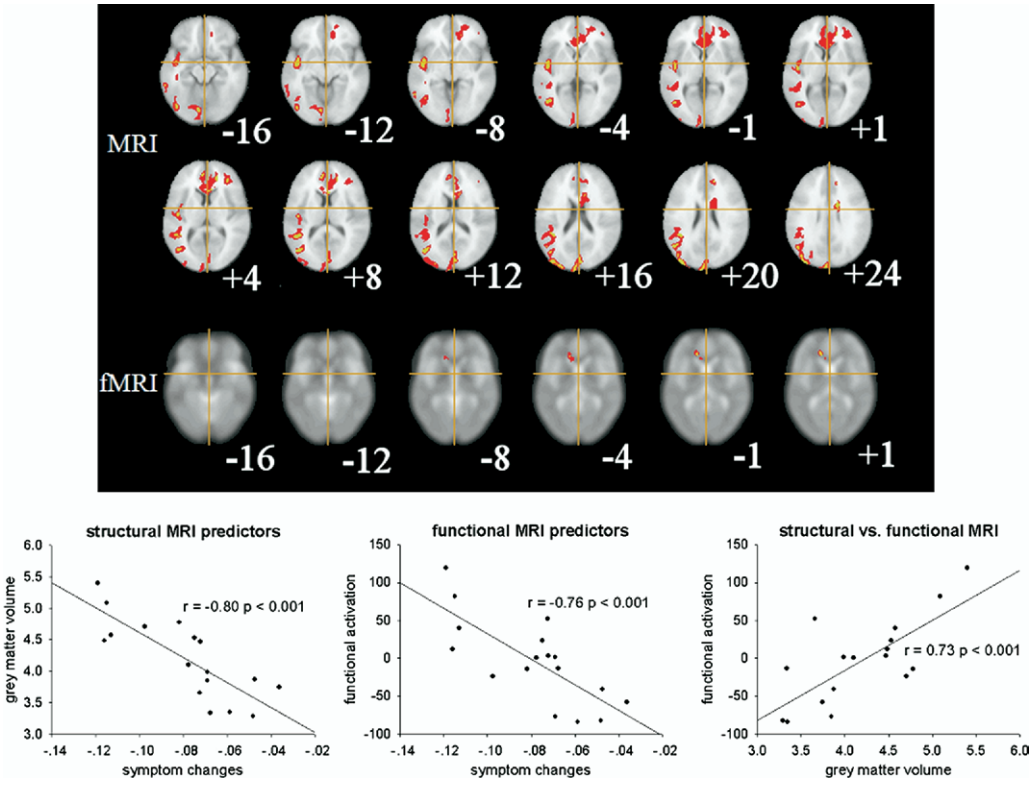

Figure 2. Structural magnetic resonance imaging (MRI) and functional MRI (fMRI) predictors of change in depressive symptoms over the course of 8 weeks' treatment with fluoxetine. Top panel: structural MRI predictors of depressive symptom change: red voxels in anterior cingulate and right temporo-parietal cortices indicate regions where faster rates of symptom improvement were predicted by greater grey matter volume. Functional MRI predictors of depressive symptom change: red voxels indicate where faster rates of symptom improvement were predicted by greater activation of anterior cingulate cortex. No areas were found when less grey matter volume or reduced activation predict treatment response. The right side of each section corresponds to the left side of the brain, and Talairach z-coordinates for each section are indicated numerically as millimeters above or below the intercommissural plane. Bottom panel: scatterplots, from left to right, illustrating the correlation between anterior cingulate grey matter volume and rates of symptom change; the correlation between functional activation of anterior cingulate cortex and rates of symptom change; and the correlation between anterior cingulate grey matter volume and functional activation of anterior cingulate cortex.

where the normalized symptom score HAM-D(t)/HAM-D(0) denotes the symptom score at time t = {0, 2, 4, 6, or 8 weeks} divided by the baseline severity, A is an intercept, B is the coefficient of linear change over time in normalized symptom scores, and ε is an error term. We used normalized symptom scores as the dependent variable in this model to control the confounding effect of baseline severity on linear symptom change. Clinical data were available at all five time points {0, 2, 4, 6, and 8 weeks} for 11 of 17 patients; 6 patients did not attend for clinical assessment at week 4 or week 6 (Figure 1).

Structural MRI Data Analysis

Structural MRI data were preprocessed by the following sequence of operations: removal of non-brain tissue, brain tissue partial-volume segmentation, affine registration with a template image in standard space. All preprocessing was implemented with FSL software (http://www.fmrib.ox.ac.uk/fsl). First, the non-brain tissues were removed with the automated brain extraction procedure (Smith 2002). These T2- and PD-weighted images were then segmented with a multichannel tissue classification algorithm, and the probabilistic maps of grey matter, white matter, cerebrospinal fluid, and dural tissues were created by estimating the partial volume coefficient for each voxel, which represents the probability of each voxel belonging to one of four tissue classes (Zhang *et al.* 2001). Segmented tissue maps were registered in standard space by an affine transformation (Jenkinson and Smith 2001; Jenkinson *et al.* 2002) and spatially smoothed by applying a Gaussian kernel with full width at half maximum (FWHM) = 3 mm.

For statistical analysis, the baseline severity score, HAM-D(0), and the symptom change coefficient, B, were separately regressed on the estimates of grey matter density at each voxel of the tissue-classified maps in standard space. Loci of significant association between grey matter density and HAM-D(0) or B were identified by a cluster-level permutation test. This involved applying a preliminary probability threshold ($p < .05$) to the corresponding voxel statistic maps and setting all subthreshold voxels to 0, thus creating a set of suprathreshold voxel clusters that were spatially contiguous in three dimensions. The sum of the suprathreshold voxel statistics, or cluster mass M, was tested by means of a permutation test with clusterwise probability of a type I error of $p < .005$. At this threshold controlled for multiple comparisons, we expect less than 1 false-positive cluster per map (Bullmore *et al.* 1999b; Suckling and Bullmore 2004).

fMRI Data Analysis

After correction of section-timing differences and head movement–related effects in the fMRI time series (Bullmore *et al.* 1999a), linear regression was used to estimate experimentally induced signal changes. Regression analysis modeled the difference in functional activation during crosshair fixation trials compared with all trials presenting a sad facial expression. Before model fitting, the regression matrix was convolved with a pair of Poisson kernels ($\lambda = 4$ or 8 sec) to model locally variable hemodynamic response functions. Statistic maps representing differential activation by face processing for each individual were registered in the standard space of Talairach and Tournoux (1988) by means of an affine transformation to a template image (Brammer *et al.* 1997). Significant associations between functional activation and both baseline severity, HAM-D(0), and symptom change, B, were then localized by second-level regression analysis and permutation testing as described earlier for whole brain mapping of structural MRI data. Additionally, we used the areas of association between severity or response and grey matter volume as a "mask" to restrict the search volume for mapping associations between severity or response and functional activation.

Results

Depressive Symptom Ratings

Mean baseline symptom score was in the moderate–severe range, HAM-D(0) = 20.9 ± 2.2 (SD), and was reduced by approximately 63% over the course of treatment, HAM-D(8) = 7.8 ± 3.8. The mean rate of normalized symptom change over time, $B \approx -.08$, indicates that symptom severity decreased linearly by 8% per week of treatment, with considerable between-subject variability in linear coefficients of symptom change, SD(B) = .025; Figure 1. There was no significant correlation between the coefficient of symptom change B and the baseline symptom severity HAM-D(0) [$r(15) = .063$, $p = .81$].

Structural and Functional MRI Predictors of Antidepressant Response Rate

Faster rates of symptom improvement (larger negative values of B) were predicted by greater grey matter volume in anterior cingulate cortex; left prefrontal and orbitofrontal cortices and caudate nucleus; right inferior parietal, temporal, and occipital cortices;

Table 1. Structural ($n = 17$) and Functional ($n = 17$) MRI Predictors of Symptom Changes After Antidepressant Treatment

	Regions	BA	Talairach Coordinates, mm X	Y	Z	Cluster Statistics[a] *R*	*t*
MRI							
	Middle frontal cortex	46	−35	44	3	−.80	−5.19
	Pregenual anterior cingulate	32	0	41	2	−.80	−5.19
	Subgenual anterior cingulate	25	0	31	−2	−.80	−5.19
	Orbitofrontal cortex	11	−15	41	−10	−.80	−5.19
	Insula	—	46	−4	−4	−.92	−9.24
	Middle temporal cortex	37	46	−61	2	−.92	−9.24
		21	47	−40	8	−.92	−9.24
	Temporal pole cortex	38	35	14	−21	−.92	−9.24
	Inferior temporal cortex	20	47	−15	−23	−.92	−9.24
	Angular cortex	39	47	−60	33	−.92	−9.24
	Cuneus	19	−3	−80	42	−.92	−9.24
	Middle occipital cortex	19	38	−83	22	−.92	−9.24
		19	39	−79	34	−.92	−9.24
	Lingual gyrus	17	10	−77	−4	−.92	−9.24
	Caudate	—	−15	9	21	−.80	−5.19
	Cerebellum	—	51	−51	−23	−.92	−9.24
	Brainstem	—	15	−37	−28	−.92	−9.24
fMRI							
	Anterior midcingulate	32	11	12	20	−.67	−3.49
	Pregenual anterior cingulate	32	15	37	2	−.76	−4.46
	Subgenual anterior cingulate	25	10	24	−3	−.76	−4.46
	Caudate	—	19	3	21	−.67	−3.49

MRI, magnetic resonance imaging; BA, Brodmann area; fMRI, functional MRI.

[a]Data are correlations [$df = 15$] between symptom change scores and grey matter density or functional activation, and corresponding t statistics, for two extended clusters in both structural and functional MRI maps.

insula; brainstem; and cerebellum [$r(15) = -.80$, $p < .001$; percentage of variance in treatment response explained by grey matter volume variation, $R^2 = 64\%$]; Figure 2 and Table 1. These results were not changed when gender and age were included as covariates in the regression analysis. The region of anterior cingulate cortex predictive of symptom improvement was located mainly in the pregenual anterior cingulate ($z > 0$ mm) and partly in the subgenual anterior cingulate ($z < 0$ mm) cortical regions as defined by (Vogt 2005).

Whole brain mapping identified no loci of significant association between functional activation and symptom change. However, an anatomically more restricted analysis, focused on the pregenual and subgenual anterior cingulate regions where grey matter density predicted treatment response, identified a small region of pregenual anterior cingulate cortex where greater functional activation predicted faster symptom response, although this association was not as strong as for the structural MRI predictor [$r(15) = -.76$, $p < .001$; $R^2 = 58\%$]; Figure 2 and Table 1.

Structural and Functional MRI Predictors of Clinical Outcome after 8 Week Treatment

To illustrate the predictive power of anatomical variation in the anterior cingulate/right temporo-parietal system, we used a median split on grey matter volume to divide the patient group in two subsets (large and small cingulate volume) and then compared their clinical trajectories over time; Figure 1. The subset with larger anterior cingulate volume had a faster rate of symptom improvement ($B = -.10$) and a lower final symptom score (HAM-D[8] = 4.25) than the subset with small anterior cingulate volume ($B = -.06$ and HAM-D[8] = 10.89). The difference between large and small volume groups in rates of symptom change was significant [$t(15) = 4.63$, $p < .001$], as was the difference in final symptom score [$t(15) = 7.94$, $p < .001$].

By a comparable analysis of the functional activation scores in anterior cingulate cortex we found the subset with more positive activation had faster rates of symptom improvement ($B = -.09$) and lower final symptom scores (HAM-D[8] = 5.25) than the subset with more negative cingulate activation ($B = -.06$ and HAM-D[8] = 10.00). The difference between subsets in rates of symptom change was significant [$t(15) = 2.80$, $p = .013$], as was the difference in final symptom score [$t(15) = 3.25$, $p = .005$]. However, the difference in clinical outcomes was less clear-cut by a median split on the fMRI predictors of symptom change, compared with the clearer outcome differentiation achieved by a median split on the structural MRI predictors, perhaps reflecting the generally greater variability of fMRI data in this experiment.

Structural and Functional MRI Correlates of Depressive Symptom Severity

Baseline symptom severity was negatively correlated with grey matter volume in bilateral dorsal prefrontal, bilateral medial frontal, left inferior frontal, left superior frontal, right orbitofrontal, and cingulate cortices; Figure 3 and Table 2. Greater grey matter volume in these regions was associated with lower baseline symptom scores [$r(15) = -.83$, $p < .001$]. In contrast, greater grey matter volume in regions of occipital cortex and cerebellum was associated with higher baseline symptom

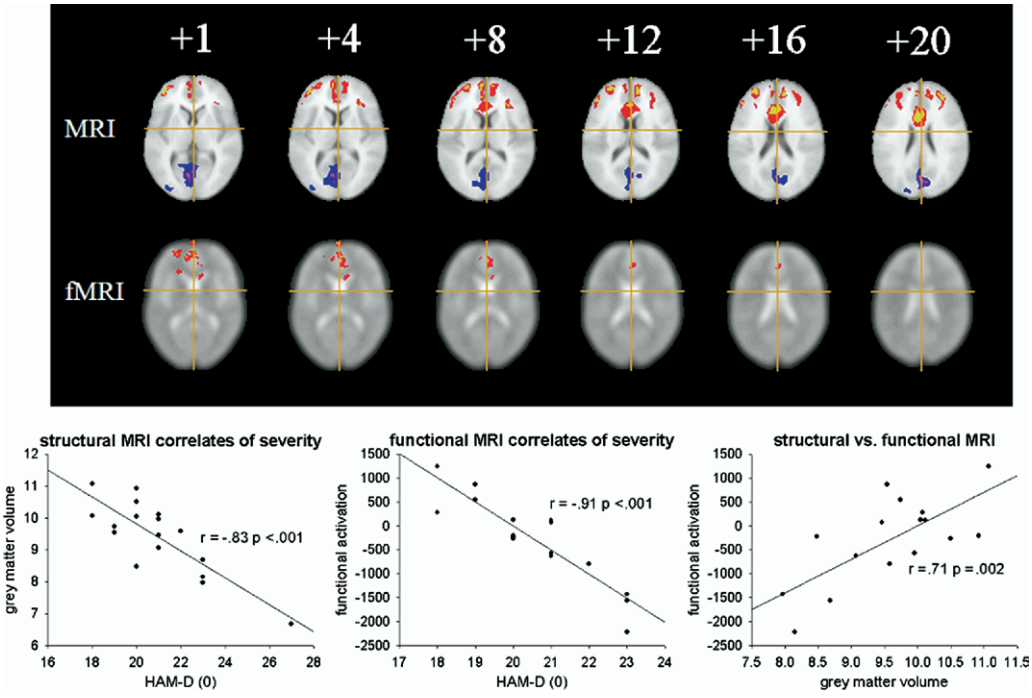

Figure 3. Structural and functional MRI correlates of depressive symptom severity. Top panel: structural MRI correlates of baseline symptom severity; red voxels in anterior midcingulate and dorsolateral prefrontal cortices indicate regions where increasing severity of symptoms was associated with smaller grey matter volume. Blue voxels in occipital cortex indicate regions where increasing symptom severity was associated with greater grey matter volume. Functional MRI correlates of baseline symptom severity: red voxels indicate where more negative functional activation (greater deactivation) by the facial affect processing task was associated with greater symptom severity. The right side of each section corresponds to the left side of the brain, and Talairach z-coordinates for each section are indicated numerically as millimeters above or below the intercommissural plane. Bottom panel: scatterplots, from left to right, illustrating the correlation between cingulate/prefrontal grey matter volume and baseline symptom severity; the correlation between functional activation of cingulate cortex and baseline symptom severity; and the correlation between cingulate/prefrontal grey matter volume and functional activation of cingulate cortex. Abbreviations as in Figure 2.

Table 2. Structural (n = 17) and Functional (n = 16) MRI Correlates of Depressive Symptom Severity at Baseline, HAM-D(0)

	Regions	BA	Talairach Coordinates, mm X	Y	Z	Cluster statistics[a] *R*	*t*
MRI							
	Middle frontal cortex	46	31	53	15	−.83	−5.65
		46	−32	45	17	−.83	−5.78
		9	32	34	30	−.83	−5.65
	Superior frontal cortex	9	−15	35	42	−.83	−5.78
	Medial frontal cortex	10	6	62	7	−.83	−5.65
		10	−11	59	9	−.83	−5.78
	Inferior frontal cortex	45	−32	35	8	−.83	−5.78
	Anterior midcingulate	24	2	22	19	−.83	−5.65
	Pregenual anterior cingulate	32	5	44	1	−.83	−5.65
	Orbitofrontal cortex	11	34	60	−6	−.83	−5.65
	Cuneus	18	−2	−73	29	.84	6.01
	Calcarine gyrus	17	1	−68	14	.84	6.01
	Lingual gyrus	18	−8	−70	−3	.84	6.01
		18	12	−60	1	.84	6.01
	Cerebellum	—	20	−74	−11	.84	6.01
fMRI							
	Medial frontal cortex	10	−1	53	4	−.91	−.85
	Pregenual anterior cingulate	32	−2	40	15	−.91	−.85
		32	−8	51	1	−.91	−.85
	Rectus gyrus	11	5	46	−14	−.91	−.85
	Orbitofrontal cortex	11	−20	46	−17	−.91	−.85
	Caudate	—	−11	25	1	−.91	−.85

[a]Data are correlations [df = 15] between symptom change scores and grey matter density or functional activation, and corresponding t statistics, for three extended clusters in the structural MRI map and one cluster in the fMRI map.

HAM-D, Hamilton Rating Scale for Depression; other abbreviations as in Table1.

scores [$r(15) = .84$, $p < .001$]; Figure 3, Table 2. The region of cingulate cortex negatively correlated with symptom severity was located mainly in the anterior midcingulate cortex and partly in the pregenual anterior cingulate. It was largely distinct from the more ventral region predictive of treatment response; Figure 4.

Baseline symptom scores were also negatively correlated with functional activation, by facial affect processing, in anterior cingulate cortex, right rectus gyrus, left medial frontal and orbitofrontal cortices, and caudate nucleus; see Figure 3, Table 2, Supplement 1, and Supplement 2 for detail. There was anatomical overlap in anterior cingulate cortex between structural and functional MRI correlates of symptom severity (Figure 3), and grey matter volume was significantly correlated with functional activation [$r(14) = .71$, $p = .002$]. In other words, less severe depressive symptom scores were associated with both stronger functional activation and greater grey matter volume of cingulate cortex before treatment.

Discussion

We have shown that severity of depressive symptoms and response to antidepressant treatment are strongly and independently associated with MRI markers of brain structure and function in people with major depression.

Neurobiological Predictors of Depressive Symptom Change

The most well-replicated neuroimaging predictor of depressive symptom improvement is baseline or pre-treatment activity of anterior cingulate cortex. Higher resting metabolic rates in pregenual anterior cingulate cortex (Talairach coordinates: $x = 1$, $y = 44$, $z = 10$ mm) differentiated eventual treatment responders from non-responders in a group of 18 depressed patients treated with different antidepressant agents (Mayberg *et al.* 1997). Here we have shown for the first time that faster rates of symptom improvement were predicted by greater grey matter volume in pregenual anterior cingulate cortex and regions of the right inferior parietal and temporal neocortex, right insula, and cerebellum. It is important to note that the pregenual anterior cingulate region predictive of symptom improvement was anatomically distinct in large part from the anterior midcingulate cortex correlated with symptom severity and that our measures of symptom improvement and severity were not correlated. These observations support the claim that structural variation in the pregenual and subgenual anterior cingulate is predictive of antidepressant treatment response.

In addition to the functional neuroimaging data reviewed earlier, there is additional support for the case that the affective subdivision of anterior cingulate cortex, including pregenual and subgenual regions, is a key target for antidepressant drugs and, therefore, a plausible predictive marker of treatment response. This subdivision of anterior cingulate is anatomically interconnected to multiple other limbic, paralimbic, and subcortical regions (amygdala, brainstem, ventral striatum, thalamus, insula, hippocampus, and orbitofrontal cortex), constituting an important network for mood regulation and related functions (Barbas

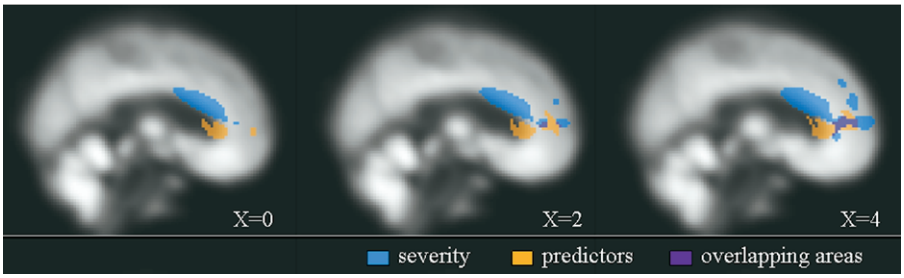

Figure 4. Structural magnetic resonance imaging (MRI) correlates of depressive symptom severity and predictors of treatment response are anatomically distinct. Blue voxels localize structural correlates of depressive symptom severity in anterior midcingulate and medial frontal areas; orange voxels localize structural predictors of symptom improvement in pregenual anterior cingulate; purple voxels indicate the relatively small area of anatomical overlap between these MRI markers. All sections represent sagittal orientations of the data (with Talairach x coordinate) overlaid on the mean image of structural MRI of all depressed subjects.

et al. 2003; Bush *et al.* 2000; Freedman *et al.* 2000; Hardy and Leichnetz 1981; Muller-Preuss and Jurgens 1976; Vogt and Pandya 1987). Mayberg *et al.* (2005) showed subgenual anterior cingulate was a key marker of therapeutic response in recent interventional studies, including pharmacotherapy and deep brain stimulation (Seminowicz *et al.* 2004). Pregenual anterior cingulate cortex, located between subgenual anterior cingulate and midcingulate components of the dorsal attentional network, has a regulatory role in integrating emotion and cognition information. Thus its candidacy as a predictive marker of treatment response also seems plausible in the context of prior literature. Most antidepressant drugs, including fluoxetine, have effects on serotonergic neurotransmission, and it is known that the affective subdivision of anterior cingulate receives a dense ascending projection from the raphé nuclei of the brainstem. The serotonin transporter, 5HTT, which is the molecular target of SSRIs, is concentrated in brain regions (including anterior cingulate cortex, brainstem, striatum, insula, and entorhinal cortex [Varnas *et al.* 2004]) similar to those regions that were predictive of treatment response in our data.

There are less extensive prior data in support of our observation that grey matter volume in right parietal and temporal cortices and cerebellum is predictive of treatment response. However, there are reports that abnormal functional activation of right parietal cortex and cerebellum is associated with depression and might be a substrate for the antidepressant effects of repetitive transcranial magnetic stimulation (Schutter and van Honk 2005).

Neural Correlates of Severity of Depression

Greater severity of depressive symptoms has previously been associated with decreased metabolism of the prefrontal and anterior cingulate cortices (Bremner *et al.* 1997; Davidson *et al.* 1999; Kimbrell *et al.* 2002). In contrast, severity of depression has also been associated with increased amygdala activity (Drevets 2003). There has been no clear evidence of structural MRI correlates of depressive symptom severity.

Here we have reported for the first time that grey matter volume was negatively correlated with depressive symptom severity in anterior midcingulate cortex and bilateral dorsolateral prefrontal cortex. These regions have previously been identified as abnormal in case-control neuroimaging studies of depression and are thought to represent an important network for effortful regulation of affective states (Bush *et al.* 2000; Phillips *et al.* 2003). Smaller grey matter volume in these regions was associated with greater baseline symptom severity and with reduced functional activation of anterior midcingulate cortex by a sad facial affect processing task. One hypothesis generated by these observations is that affective-attentional processes localized in anterior midcingulate and dorsolateral prefrontal cortex might play a protective role in the pathogenesis of depression such that people with reduced grey matter volume and functional activation of these regions, for whatever reason, might be predisposed to greater severity of depressive symptoms.

Therapeutic Implications

One possible implication of these results is that it might be possible to improve the design of a clinical trial to detect antidepressant efficacy of new compounds by selectively enriching the sample, on the basis of a screening MRI examination, for patients predicted to show rapid treatment response. Our post hoc analysis of these data suggests that this MRI-based sample enrichment strategy could be effective. People with pregenual anterior cingulate volume greater than the sample median had significantly faster symptom improvement ($B = -.10$) than the other half of the sample [$B = -.06$; $t(15) = 4.63$, $p < .001$] as well as significantly lower residual symptom scores at the end of treatment (HAM-D[8] = 4.25) compared with the group with smaller anterior cingulate volume [HAM-D(8) = 10.89; $t(15) = 7.95$, $p < .001$]. By the same analysis, we found that the fMRI predictors, although anatomically coincident with previously reported locations of brain functional predictors of antidepressant treatment response, were not as clearly predictive of clinical outcome as the structural MRI predictors in this sample.

A more speculative implication is that it might be conceivable, with a simple and widely available structural MRI protocol, to predict which patients with depression were most likely to respond quickly to antidepressant treatment. However, this application of predictive MRI markers to management of an individual patient, although imaginable on the basis of present data, would realistically demand much greater access by clinicians to quantitative morphometric analysis and appropriate (e.g., age-matched) structural MRI databases than is currently available.

Methodological Issues

The sample size is small, and although the pattern of results is plausible in the light of prior theory and data, it will be important to replicate and extend these findings in larger studies including greater patient heterogeneity in terms of age and severity of symptoms. These data cannot address the question of mechanism specificity (i.e., are structural MRI predictors also valid for other types of treatment—for example, psychotherapy—or antidepressant drugs that work by mechanisms of action other than inhibition of serotonin reuptake?). Likewise, the design of this study, which lacks a placebo-treated patient group, leaves open the possible interpretation that the symptomatic improvement predicted by greater anterior cingulate volume is mediated by a non-specific treatment (placebo) effect rather than by the specific effect of fluoxetine. This ambiguity could be resolved by future imaging studies including a placebo-treated patient group. One final issue is that our measure of brain function was the magnitude of local response to an affect processing task. Although this choice of paradigm and analysis strategy seemed reasonable, given prior reports of abnormalities of regional activation by similar tasks in patients with depression (Phillips *et al.* 2003; Surguladze *et al.* 2005), it is worth noting that there might also be treatment response–predictive value in fMRI data recorded during the no-task or resting state and/or in multivariate measures of functional connectivity between limbic and frontal regions.

Conclusions

We have reported new and anatomically distinct structural MRI markers of depressive symptom severity and symptom improvement in depressed patients treated with fluoxetine. The results further implicate the anterior cingulate cortex in the pathophysiology of depression and suggest that measures of cingulate structure (and perhaps function) could be useful predictors of clinical outcome in patients treated for depression.

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Supplementary material cited in this article is available online.

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