Predicting treatment response in depression: the role of anterior cingulate cortex.

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Significance Statement

Most patients with depression do not respond to the first treatment they try and in many cases multiple attempts are necessary to relieve symptoms. The fact that depression affects about 20% of the population at least once in their lifetime means that this problem applies to a substantial number of individuals. The delay in finding effective treatment, often extending to months or years, translates into unnecessary personal suffering and burden. This burden could be lessened if there were tests indicating those patients who are unlikely to respond to first line treatment and require higher intensity treatment from outset. This study, using functional imaging, has added to the growing body of evidence pointing at the pregenual anterior cingulate cortex as a reliable predictor of subsequent treatment response in depression. Such studies bring us closer to the application of biological markers to predict therapeutic response in clinical practice.

Abstract

Background: Identification of biomarkers predicting therapeutic outcome to antidepressant treatment is one of the most important tasks in current research because it may transform the lengthy process of finding the right treatment for a given individual with depression. In the current study we explored the potential of pre-treatment pregenual anterior cingulate cortex (pgACC) activity as a putative biomarker of treatment response.

Methods: Thirty-two medication-free patients with depression were treated for 6 weeks with a selective serotonin reuptake inhibitor, escitalopram. Before treatment began, patients underwent an fMRI scan testing response to brief, masked, presentations of facial expression depicting sadness and happiness.

Results: After 6 weeks of treatment there were 20 SSRI responders and 12 non-responders. Increased pre-treatment pgACC activity to sad versus happy faces was observed in responders relative to non-responders. A leave one out analysis suggested that activity in the ACC was able to predict response status at the level of the individual participant..

Conclusions: The study supports the notion of pgACC as a promising predictor of antidepressant response.

Introduction

The search for biomarkers that can predict clinical response to the pharmacotherapy of depression is a task of substantial practical importance. Only 50% of patients respond to the first treatment they try, and remission rates are even lower (around 30%) (Rush et al. 2009). Many patients will take 2 or more different antidepressants before finding a drug that works for them (Warden et al. 2007). Identifying patients unlikely to respond to first line treatment may speed up the application of second line or adjunct treatments and improve overall time to remission.

Studies employing neuroimaging have led to the identification of a number of candidates for treatment response prediction biomarkers (eg. McGarth et al. 2013, Dunlop et al. 2017). One of the best established is increased pre-treatment activity in the pregenual anterior cingulate cortex (pgACC) which has been linked to a positive therapeutic response to antidepressant treatments. In a review of 23 imaging studies, Pizzagalli (2011) concluded that increased activity in the rostral ACC (rACC; equivalent to pgACC) both in the resting state, and in response to simple cognitive tasks, was associated with positive outcome to a variety of treatment modalities including pharmacotherapy, transcranial magnetic stimulation and sleep deprivation. This was also shown in a meta-analysis by Fu et al. (2013).

Of the studies reviewed by Pizzagalli (2011) and Fu (2013), five and fourteen, respectively, employed fMRI, the most widely available modality for imaging the ACC in depressed patients. Since these publications, a number of further fMRI studies have been conducted,

including a study by our group in which we reported that neural changes in response to an emotional processing task after one week of treatment with the selective serotonin re-uptake inhibitor (SSRI), escitalopram, predicted clinical outcome after six weeks of treatment in a group of 32 depressed patients (Godlewska et al. 2016). The present report concerns baseline (pre-treatment) neural responses of this patient group to a different emotional task that employed masked faces as 'implicit' (non-conscious) stimuli and their potential to act as predictors of subsequent response to escitalopram.

Interestingly a similar implicit task was employed in a recent fMRI investigation, which also found a correlation between pre-treatment activity in pgACC during the emotional processing task and the subsequent response to eight weeks of treatment with the selective serotonin re-uptake inhibitor (SSRI), sertraline, in ten unmedicated patients (Victor et al. 2013). This study was designed to assess whether the results can be replicated in a larger group, allowing for a categorical classification of patients into responders and non-responders. A similar task was used, based on the concept that structures involved in rapid, non-conscious stimulus processing may be particularly reactive to masked stimuli and sensitive to depression (Victor et al. 2010, 2013, 2017).

The aim of the present study was to test this hypothesis that increased pgACC to masked sad facial expressions at baseline would predict later treatment response and provide an initial estimate of the degree to which this effect was able to predict treatment response at the level of the individual patient, using a leave-one-out validation process.

Methods

Participants

Thirty nine patients with major depression consented to take part in the study. Thirty two (18F:14M) completed the fMRI scan and the six week period of escitalopram treatment (see Table 1 for demographic information). In the remaining seven patients relevant data were not available at the end of the treatment period (four patients dropped out before the six week assessment, and scanning data from a further three patients were not available due to technical issues). All participants were assessed with the Structured Clinical Interview for DSM-IV (Spitzer et al. 1995) for the presence of current and past psychiatric disorders. The depressed patients met criteria for a primary diagnosis of major depressive disorder; exclusion criteria were psychosis or substance dependence as defined by DSM-IV, a clinically significant risk of suicidal behaviour, contraindications to escitalopram treatment or treatment with psychotropic medication less than three weeks before the study (five weeks for fluoxetine), major somatic or neurological disorders, pregnancy or breast-feeding, any contra-indications to MR imaging or concurrent medication which could alter emotional processing. All participants were right-handed. The study was approved by the Oxford Research Ethics Committee and all participants gave written informed consent.

Study design and drug treatment

Following the baseline fMRI scan patients received 10mg escitalopram each morning for a period of 6 weeks without dose adjustment. Assessment of depressive severity and treatment response was made using the 17 items Hamilton Depression Rating Scale (HAM-D) (Hamilton 1960), with anxiety being measured with Spielberger's State-Trait Anxiety inventory (STAI) (Spielberger 1989) at baseline and week 6. The fMRI assessments were completed at the same time points. The current analysis focuses on how baseline differences in the function of pgACC were able to predict clinical response at week six of treatment.

After the 6 week duration of the study, all patients were offered treatment openly with escitalopram according to usual clinical practice. Clinical response to the SSRI was defined as a reduction in HAM-D of 50% or more from baseline after six weeks of treatment (Angst et al. 1993).

fMRI data acquisition

Functional MRI data were acquired on a 3T Siemens TIM TRIO (Siemens AG). Data were acquired with a voxel resolution of 3x3x3mm, TR/TE/FA =2000ms/28ms/89^{o}. A total of 256 volumes were acquired in an experiment lasting 6 minutes. T_1-weighted structural images were acquired using a magnetisation prepared rapid acquisition by gradient echo (MP-RAGE) sequence with a voxel resolution 1.0x1.0x1.0 mm on a 208 x 256 x 200 grid, TE/TI/TR= 4.68/900/2040ms. To monitor cardiac and respiratory processes subjects wore a pulse oximeter and respiratory bellows.

fMRI experimental task

During fMRI scanning, participants completed a backward masking task. This task consisted of viewing pairs of faces, paired in such a way that the first face, expressing sad, happy or neutral emotion, was shown for 30ms, and then immediately 'masked' by another face of neutral expression, shown for 70ms; this procedure has been shown to interfere with explicit perception of the first face (Victor et al. 2010). After each pair of faces was presented for 100ms in total, participants were asked to report the gender of the face via an MRI compatible key pad; the gender of both faces was the same. Each participant was shown 4 sad blocks, 4 happy blocks and 9 neutral blocks, which were interleaved with sad and happy blocks (N-S-N-H-N-S-N-H-N or N-H-N-S-N-H-N-S-N). Between each block, there was a 10-s block of a baseline fixation cross.

fMRI preprocessing and statistical analysis

Functional MRI data were preprocessed and analysed using FSL (Jenkinson et al. 2012). Briefly, motion correction was applied using a rigid body registration to the central volume; brain matter was segmented from non-brain using a mesh deformation approach. Gaussian spatial smoothing was applied with a full width half maximum of 5mm; high pass temporal filtering was applied using a Gaussian-weighted running lines filter, with a 3dB cut-off of 120s.

A general linear model was fitted in pre-whitened data space. Three explanatory variables (plus their temporal derivatives) were modelled: 'sad faces', 'happy faces' and 'neutral faces'. All explanatory variables were convolved with a default haemodynamic response function (Gamma function, delay=6s, standard deviation =3s), and filtered by the same high pass filter as the data. The impact of physiological noise on the BOLD signal was reduced using the Physiological Noise Modelling (PNM) tool of FSL. Pulse oximetry and respiratory bellows data were processed by PNM to create 33 nuisance regressors which were added to the first level fMRI model. The full model was simultaneously regressed against the BOLD data, giving the best-fitting amplitudes for each explanatory variable while accounting for the physiological noise.

The task contrast of interest in this study was the relative activation of sad vs. happy faces. The degree to which the change in neural activity in this contrast predicted participants' clinical response on the HAM-D to medication over six weeks, was tested using a two level analysis. The first level consisted of the sad vs. happy contrast maps, as described above, calculated for each depressed subject. Second level, between subject, random effects analysis assessed whether this change in neural activity differed between depressed patients who went on to respond to the medication and those who did not. Baseline HAM-D score was included

as a regressor in the second level analysis to account for the potential influence of initial depression severity effects on overall clinical response (NB baseline HAM-D score did not differ between the two groups, responders and non-responders, Table 1, and equivalent results were obtained when the analysis was run without this covariate, Sup Table 4).

The mask for the ACC as *a priori* region of interest was derived from the Harvard–Oxford Cortical anatomical atlas and used in small volume correction analysis SVC (clusters determined by Z>2.3 and a (corrected) cluster significance threshold of P=0.05). The mask included 1531 voxels. The results of group level the whole brain analyses were corrected using cluster-based thresholding with a height threshold of Z > 2·3 and a (whole-brain corrected) spatial extent threshold of P = 0.05.

Additional analysis was performed with randomise, FSL's non-parametric tool using Threshold-Free Cluster Enhancement (TFCE) thresholding approach, with baseline HAMD as a nuisance variable. This allowed for non-parametric permutation-based inference without a pre-defined arbitrary threshold, reducing the likelihood of false positive results Five thousand permutations were performed

Predictive analysis

In addition to the analysis described above, in which participant groups were defined based on future response to treatment, we were also interested in whether activity of the ACC could be used to predict response for individual patients. This was done using a leave-one-out approach in which training and testing data were kept completely separate. This analysis involved: firstly defining a cluster of voxels in which activity was greater for responders than non-responders to the sad-happy contrast within the ACC (NB the cluster was defined using Z>2.3 and p<0.05 with a structural ROI based on the Harvard-Oxford Cortical Atlas) using

just the training data (i.e. data from all but one participant). Secondly, extracting mean activity within this cluster for all participants, with the data from the training sample being used to generate a receiver operator characteristic (ROC) curve. Lastly, defining a cut-off from the ROC curve of the training data as the point furthest from the leading diagonal and classifying the held out participant as a responder or non-responder based on this cut-off. Note, this analysis was repeated for every participant and resulted in different clusters of voxels used in each classification as well as different cut-offs for the classification. This analysis provides an initial estimate of the ability of activity within the ACC to predict response at the level of the individual patient.

Results

Clinical and demographic data

After six weeks' escitalopram treatment, 20 out of 32 patients (62%) were classified as responders. There were no differences between responders and non-responders in terms of gender, age, baseline depression severity, baseline trait anxiety or duration of current episode (See Table 1).

fMRI data

ROI analysis. We performed SVC-corrected analysis of pgACC. In line with our hypothesis, we found an increased fMRI response to sad vs. happy faces in the group of patients who after 6 weeks responded to treatment, as compared to those who did not, both with and without controlling for baseline depression HAMD severity (family wise error (FWE)-corrected $P<0.05$, SVC; 248 voxels, Z-value of the peak voxel 3.48, $p=0.005$). Exploring each emotion separately vs baseline showed that non-responders had numerically greater pgACC responses to both sad and happy faces, with the majority of the difference between the two groups apparently being due to altered responses to happy faces (Figure 1).

While we used an ACC mask based on the commonly used Harvard–Oxford Cortical anatomical atlas, the part of the cluster identified can be described as located in the anterior midcingulate cortex (aMCC). An additional analysis with a 600 voxel mask consisting only of volumes anterior to the genu of corpus callosum was run, and a similar response to reported above was observed in a cluster of 123 voxels, the part of the original cluster corresponding to strictly defined anterior cingulate cortex (results not reported).

Whole-brain analysis. The exploratory analysis at the whole brain level using a parametric approach revealed a greater activation to sad vs happy faces in treatment responders as

compared to non-responders across a network of structures including ACC, paracingulate, right and left caudate, right thalamus and a small part of left thalamus, left putamen, and a small portion of fronto-occipital cortex, both when controlling for baseline depression HAMD severity, and not (P<·05, FWE corrected); see Figure 2. For details on functional clusters, see Table 2. The TFCE (Threshold-Free Cluster Enhancement) non-parametric method revealed a similar increased activation in response to sad vs happy faces in treatment responders vs non-responders across a network of structures, with the peak in the ACC, and inclusing paracingulate gyrus, bilateral middle frontal gyrus, bilateral frontal orbital cortex, frontal pole, bilateral thalamus, and left insula.

Prospective analysis allowed predicting classification into responders and non-responders with moderate accuracy of 71.875%. The centre of mass of the clusters is shown in Figure 2. A histogram of cut off scores and confusion matrix are shown in Figure 3 and 4, respectively.

Discussion

Our study showed that pretreatment neural activation of pgACC in response to subliminal emotional information was predictive of short-term (6 weeks) therapeutic response to an SSRI escitalopram in patients with depression. A similar pattern was observed in a network of cortical and limbic areas associated with depression. Our findings support the body of evidence pointing to the ACC as currently the most reliable marker of response to various modes of treatment for depression and show its role in response to emotional information presented below the level of conscious awareness.

Our findings are consistent with meta-analyses by Pizzagalli (2011) and Fu et al. (2013), and other more recent studies implicating the pgACC as the region in which baseline function is linked to future response to antidepressant treatment (eg. Klumpp 2017, Crane 2017, Cullen 2016, Vai 2016, Dichter 2015, Victor 2013, Miller 2013, Kozel 2011, Roy 2010). Of recent investigations, the study by Victor et al. (2013) was of particular relevance to our investigation because it also employed an implicit emotional task based on presentation of masked sad and happy faces. Victor et al. (2013) found a decrease in the haemodynamic response in the pgACC to the contrast of masked sad vs happy faces after 8 weeks of treatment with another SSRI, sertraline, in 10 participants with depression. They also found a positive correlation between symptomatic improvement in depression ratings and baseline pgACC activation to masked sad vs happy faces, implicating pgACC in antidepressant response and its prediction. Studying a larger group of participants, and using a similar task based on masked presentation of emotions, we were also able to show differential baseline pre-treatment activity of the pgACC in treatment responders and non-responders.

The pgACC is a part of an extended medial prefrontal network, uniquely positioned with connections both to the amygdala and PFC (Drevets 2001, Mayberg 2003). It plays an important role in emotion appraisal and regulation, evaluation of the salience of emotional stimuli and emotion-related learning (Stevens et al. 2011), the processes that are dysregulated in depression and improve with successful treatment. Since the seminal publication by Mayberg et al. (1997), a wide range of research has consistently implicated pgACC as a brain region linked to treatment response.

Increased activity in the pgACC was typically found to be predictive of better treatment outcomes regardless of the modality used to measure ACC activity (fMRI, PET, MEG and EEG), design (ie. resting state or task-based) and form of treatment employed (pharmacotherapy, transcranial magnetic stimulation, CBT and sleep deprivation), as reviewed by Pizzagalli in 2011. Although only five out of 23 studies included in this review were fMRI studies, other fMRI studies have since been published, including a meta-analysis by Fu et al. (2013) of 20 functional neuroimaging papers (14 fMRI studies, 10 using various emotional processing tasks, and 4 using non-emotional tasks, and 6 PET studies in resting state conditions). Similar to Pizzagalli's paper (2011), this meta-analysis showed a higher likelihood of improvement in response both to pharmacotherapy (14 included studies) or CBT (6 included papers) in patients with increased pre-treatment activation in the pgACC, as well as in subgenual and medial prefrontal cortices.

Since the publication of these meta-analyses other studies, including ours (Godlewska et al., 2016), have added to the relatively consistent body of evidence suggesting increased ACC activation during emotional processing and resting state as a putative marker of good clinical response to treatment. Although the results are not unequivocal (Fu et al. 2013) and are still some way off routine clinical application, currently the pgACC is considered to be one of the

most – if not the most – promising pre-treatment imaging biomarkers of antidepressant response, both because of its postulated role in the pathophysiology of depression and the consistency of reports on its role in treatment response prediction.

In addition to the pgACC, our exploratory whole-brain analysis revealed a number of other regions showing a similar neural response to the employed task, ie. increased activity in response to sad vs happy facial expressions allowed differentiation between future treatment responders and non-responders. These regions included paracingulate cortex, thalamus, caudate, putamen, nucleus accumbens and orbitofrontal cortex (OFC) (Figure 2). These structures are a part of networks involved in the processing of emotionally valenced information and reward, and their disruption has been hypothesized to contribute to low mood and anhedonia, core symptoms of depression (Graham et al. 2013, Fettes et al. 2017).

The basal ganglia regions identified in this study: the caudate nucleus, the putamen and the nucleus accumbens, are involved in reward processing and form connections with the ACC and thalamus, with the ACC-basal ganglia-thalamus loop suggested to monitor unexpected events and to recruit adaptive mechanisms as required (Maia and Frank, 2011). Our results suggest that the pgACC is clearly a node in a distributed network of regions involved in processing of emotionally salient information. It is likely that differences in the function of this network, rather than solely in the pgACC function, are associated with antidepressant response.

The period of time when response to antidepressants was assessed, six weeks into treatment, was chosen to be consistent with common clinical practice. Six weeks is around the time when clinicians often make decisions as to whether to continue treatment unchanged, adjust the dose or switch to a different medication, and is in line with current treatment guidelines (NICE Pathways, 2017). A reliable marker of this early response could potentially save a

patient from unnecessary weeks of delay in finding treatment they respond to. Treatment response was defined as baseline at least 50% decrease in HAMD scores as this definition, although somehow arbitrary, is a commonly used measure (Angst et al., 1993).

To be clinically useful, a biomarker of treatment response needs to classify patients into responders and non-responders with reasonable accuracy; so far no known biomarker has been consistently replicated in subsequent studies with accuracy high enough to be deemed useful in clinical practice (Fu and Costafreda 2013). Predictive analysis performed in this study allowed classification of participants into responders and non-responders with an accuracy of 71.9%, which differs from a probability of 0.5 with a p of 0.02. However, caution is required with this estimate of accuracy as leave-one-out (LOO) approaches to validation, as used in the current study, will tend to overestimate classifier accuracy when compared to validation in a fully held out sample (Hastie et al., 2009). This limitation is related to a number of statistical and methodological aspects of LOO procedures. First, clinically relevant classification requires between-dataset generalisation of classification performance (predictions need to be made on completely unseen data) which are not accounted for by LOO procedures which are based only on within dataset performance. Second, individual data points in LOO procedures will be used in all but one training sets, meaning that influential (e.g. outlying) data points can have exaggerated effects on classifier performance across training sets, which can skew estimates of classifier performance. As a result it will be essential to test whether pgACC activity is able to meaningfully predict treatment response in a fully held out sample of patients.

A number of studies have used machine learning approaches to derive classifiers from fMRI data. These approaches tend to have many more predictors (i.e. voxels) than data points (patients) and are also difficult to interpret from a mechanistic perspective as they incorporate

complex interactions between predictors. In our study we used a very simple, univariate outcome from a pre-specified region which provides a mechanistically transparent predictor. Clearly however, it may be possible to improve on the predictive performance reported here by employing a multivariate approach to combine different features in the classifier. Additionally, there may well be alternative methods for deriving the predictive features from the fMRI data. In the current study we used mean signal change from clusters, defined in the training set. The clusters were defined on the basis of anatomical location (within the ACC) and statistical significance. It may be that using alternative methods for cluster/feature definition (e.g. changing the level of statistical significance for the cluster, or relaxing the anatomical specification) would increase the information contained in the cluster and improve classification performance.

The ACC response seems to predict positive therapeutic outcome to many different kinds of treatment (Pizzagalli 2011, Fu et al. 2013). Therefore it does not currently point to selection of a particular antidepressant treatment modality or psychotherapy in preference to pharmacotherapy. Equally it does not suggest an alternative treatment regime for patients with low ACC responsivity who, at the moment, are predicted to do less well with various kinds of antidepressant therapies. At the same time it may play an important role in identifying people with poor prognosis who can be given more intensive treatment from the start, leading to improving overall time to remission. It might also serve as a marker of efficacy when testing new drugs for antidepressant properties.

Our study has some limitations. The main limitation is the small size of the group. The group itself was composed of carefully chosen drug free patients, yet increasing the number would increase the power and allow for more complex analyses combining different putative markers, an approach aiming at increasing accuracy of classification. The lack of a control

group may be considered as another limitation, however, the aim of the current study was to explore markers of treatment response prediction, for which a group of healthy volunteers or placebo treated patients is not strictly necessary. One limitation reflects a general question of feasibility of using imaging biomarkers in clinical settings, as scanning is not yet widely available and the procedure is still relatively costly. However, if the prediction using imaging biomarkers becomes sufficiently accurate, benefits including a decrease of depression burden on both individuals and society achieved through more efficient therapeutic processes could make it cost-effective.

In summary, our study has shown that pre-treatment pgACC activity is predictive of response to antidepressant treatment after 6 weeks. It has also identified other brain regions where differential activity in response to an implicit emotional task had a similar predictive value. Our study adds to the growing body of evidence pointing at the pgACC as a reliable predictor of subsequent treatment response to a variety of therapeutic approaches to depression. Although the accuracy of classification in our study was moderate, it was higher than by chance and given that the pgACC pre-treatment function as response prediction marker has been the most consistently replicated neuroimaging finding, it makes it the most promising putative fMRI-based treatment response biomarker. To understand better the potential of pgACC imaging in this context, future studies are needed, on large groups and in patients at different stages of depression, employing machine learning approaches to combine pgACC effect with other neuroimaging and/or behavioural measures to increase classification accuracy.

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Statement of Interest

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Table 1. Demographic information for responders and non-responders to 6 weeks treatment with escitalopram. Presented as mean ± standard error (SE).

	Responder s (n=20)	Non-Responders (n=12)	
Gender	10F/10M	8F/4M	p=0.358, $\chi 2$=0.847
Age at the time of the scan (years)	28.25 ± 2.64	28.75 ± 9.28	p=0.886, t=0.144
Baseline depression severity (HAM-D)	23.0 ± 1.1	23.67 ± 0.9	p=0.687, t=0.407
Baseline depression severity (BDI-I)	31.2 ± 1.5	33.1 ± 1.5	p=0.420, t=0.818
Baseline trait anxiety (STAI-T)	59.5 ± 1.9	63.2 ± 10.8	p=0.298, t=1.059
Duration of current	4.5 ± 0.6	8.8 ± 2.6	p=0.06, t=1.992

episode (months)			

Table 2. Prediction of clinical response after 6 weeks of escitalopram treatment from baseline differences in pre-treatment neural response to sad compared with happy facial expressions. The table shows functional clusters identified by the exploratory analysis at the whole brain level. Please refer to Figure 1 for more details.

Cluster content	Peak voxel MNI Coordinates			Cluster size, voxels	Z-value	P-value
	x	y	z			
Parametric approach (Gaussian Random Field Theory)						
Cluster A: L middle frontal gyrus, ACC, paracingulate gyrus, R caudate, R thalamus leaking into L thalamus	-28	32	28	2173	3.66	0.000000238

Cluster A: local maxima	22	12	16		3.59	
	24	-28	26		3.59	
	22	16	22		3.54	
	30	26	24		3.53	
	-6	30	20		3.48	
Cluster B: Frontal Orbital Cortex, L Putamen, L Caudate, L Accumbens	-32	34	-4	544	3.68	0.0276
Cluster B: local maxima	-18	22	-4		3.37	
	-28	40	-4		3.24	
	-22	48	-8		3.04	
	-24	12	-18		3.03	
	-22	44	-8		3.00	
Cluster C: ACC, paracingulate gyrus	26	36	0	523	3.7	0.0336
Cluster C: local maxima	16	36	-4		3.37	

	18	42	2		3.27	
	34	42	-2		3.04	
	20	26	10		3.03	
	20	42	-8		2.89	
Non-parametric approach (Threshold-Free Cluster Enhancement)						
Cluster: ACC, paracingulate gyrus, bilateral Middle Frontal Gyrus, bilateral Frontal Orbital Cortex, Frontal pole, bilateral Thalamus, left Insula	-4	30	16	6617	4.99	<0.05

Figure 1. Baseline differences in neural response (percent signal change) in the pgACC region of interest in response to sad vs happy facial expressions differentiated between responders and non-responders to 6 weeks treatment with escitalopram. The figure represents (a) results of SVC-corrected analysis in the anterior cingulate cortex using a parametric approach (Gaussian Random Field Theory); (b) extracted signal change in the identified cluster (mean and standard error); c) results of SVC-corrected analysis in the anterior cingulate cortex using a non-parametric approach (Threshold-Free Cluster Enhancement). Analysis was thresholded at Z=2.3 and cluster-corrected with a FWE P<0.05. ACC, anterior cingulate cortex; FWE, family wise error; SVC, small volume correction. Baseline HAM-D scores were entered as a covariate.

Figure 2. Baseline differences in neural response (percent signal change) at the whole brain level in response to sad vs happy facial expressions differentiated between responders and non-responders to 6 weeks treatment with escitalopram. The figure represents (a) results of the exploratory analysis at the whole brain level using a parametric approach (Gaussian

Random Field Theory); (b) extracted signal change in the identified clusters (mean and standard error); c) results of the exploratory analysis at the whole brain level using a non-parametric approach (Threshold-Free Cluster Enhancement). Details of the clusters can be found in Table 2. Analysis was thresholded at Z=2.3 and cluster-corrected with a FWE P<0.05. ACC, anterior cingulate cortex; FOC fronto-orbital cortex; FWE, family wise error. Baseline HAM-D scores were entered as a covariate.

Figure 3. Confusion plot. Green squares represent correctly classified cases: TP – true positives, TN – true negatives, the number of correct classifications by the trained network, percentage of all cases they represent. Red squares represent incorrectly classified cases: FP – false positives, FN – false negatives, the number of correct classifications by the trained network, percentage of all cases they represent. The blue square represents the percentage of correct and incorrect classifications.

The first row represents predicted non-responders, of whom 61.5% were classified correctly, and 38.5% incorrectly. The second row represents predicted responders, of whom 78.9% were classified correctly, and 21.1% incorrectly. Out of 12 non-responders, 66.7% were correctly predicted as non-responders and 33.3% were predicted as responders. Out of 20 responders, 75% were correctly classified as responders and 25% were classified as non-responders. Overall, 71.9% of the predictions were correct and 28.1% cases were classified incorrectly.

Figure 4. Histogram of the cut off scores used in the classifier.

Figure 1.

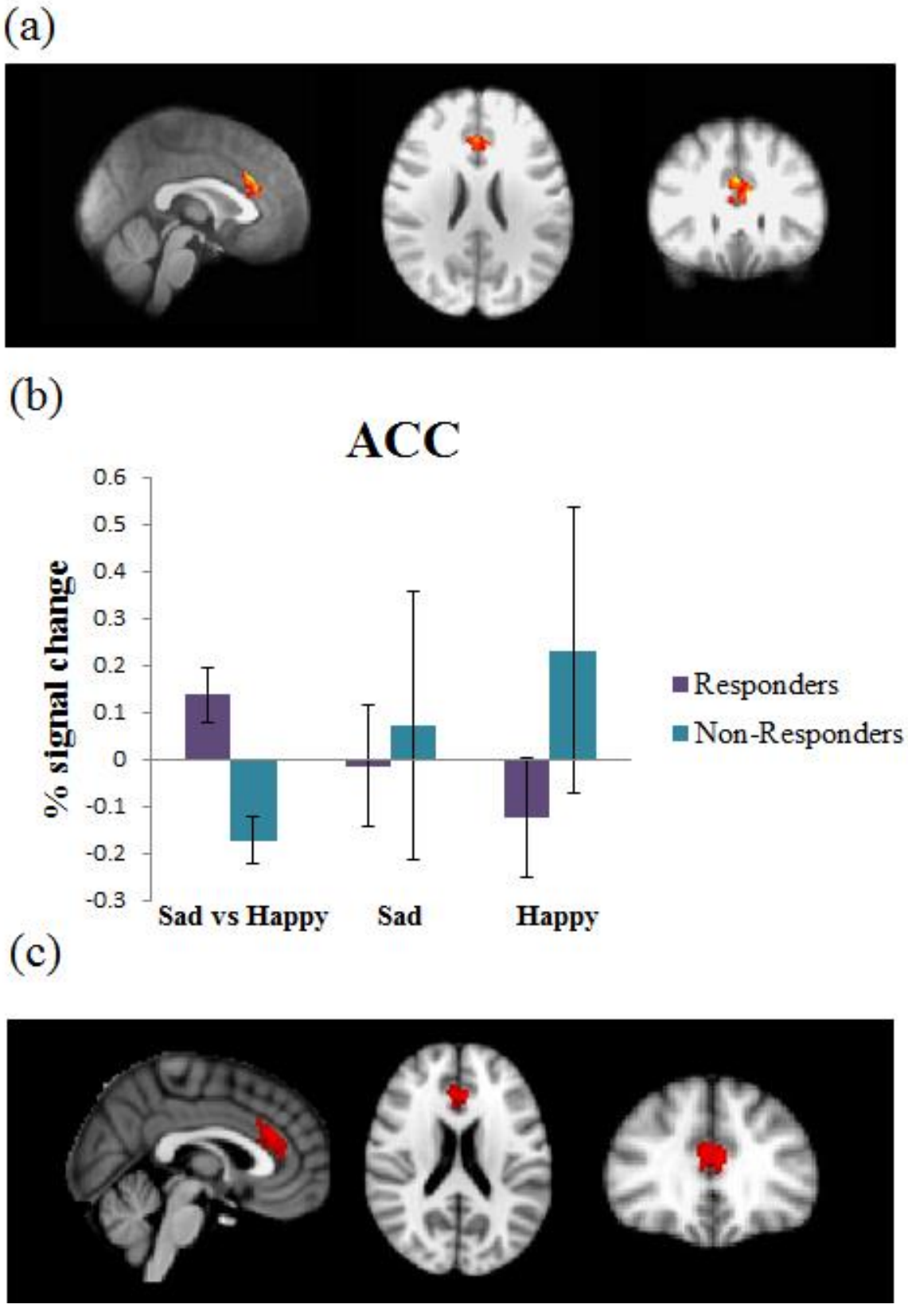

Figure 2.

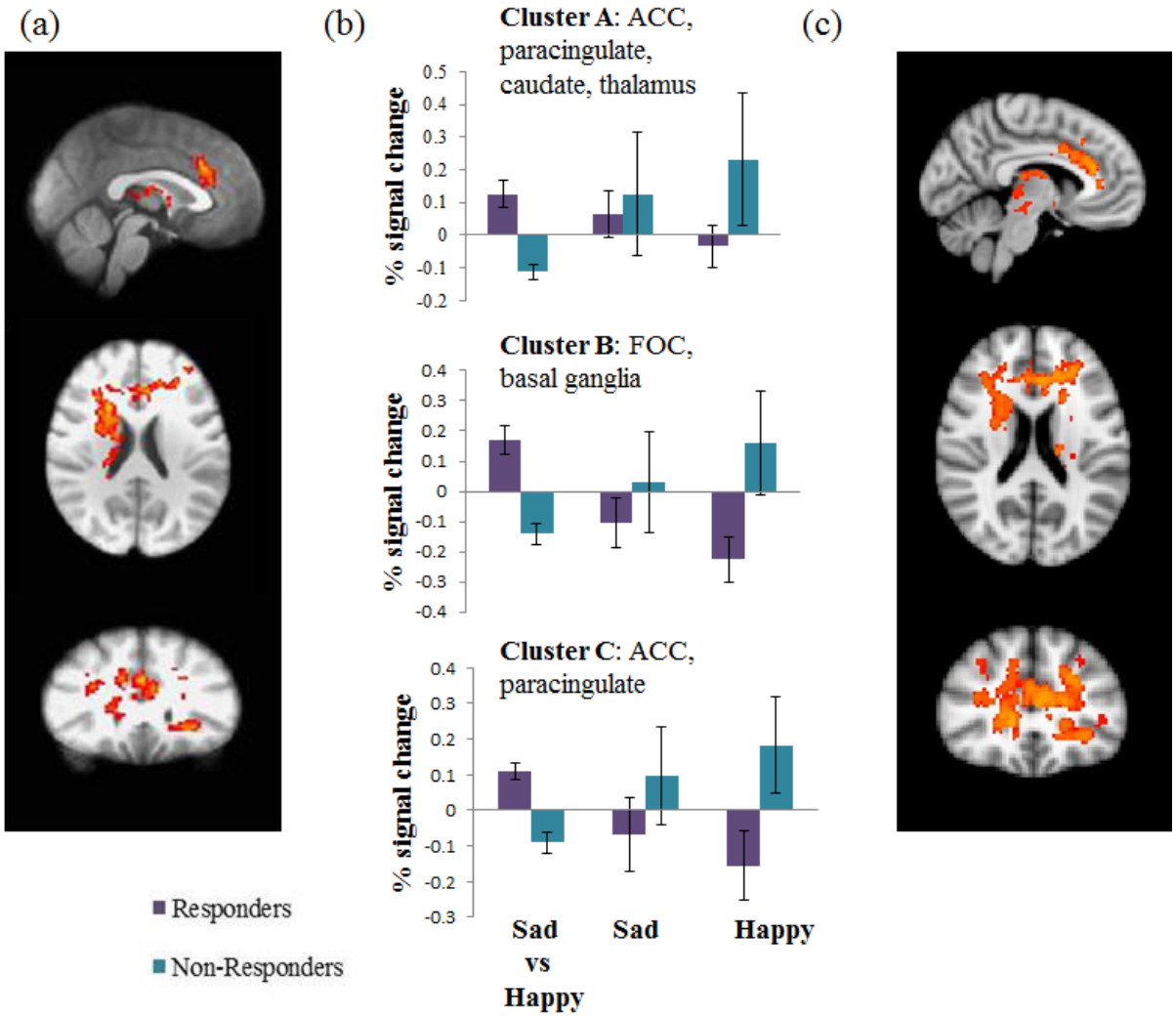

Figure 3.

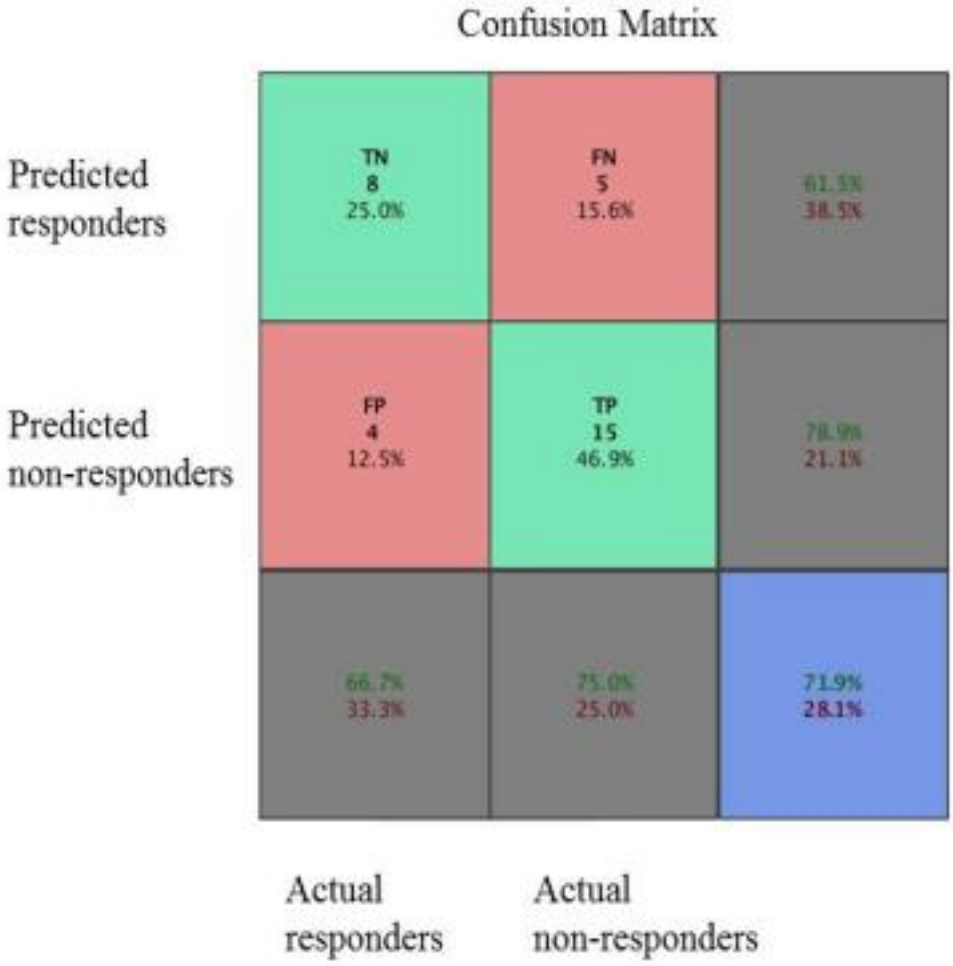

Figure 4.