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Changes in prefrontal and amygdala activity during olanzapine treatment in schizophrenia

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Abstract

Earlier imaging studies in schizophrenia have reported abnormal amygdala and prefrontal cortex activity during emotion processing. We investigated with functional magnetic resonance imaging (fMRI) during emotion processing changes in activity of the amygdala and of prefrontal cortex in patients with schizophrenia during 8 weeks of olanzapine treatment. Twelve previously drug-free/naïve patients with schizophrenia were treated with olanzapine for 8 weeks and underwent two fMRI scans after 4 and 8 weeks of treatment during implicit and explicit emotional processing. Twelve healthy subjects were also scanned twice to control for potential repetition effects. Results showed a diagnosis by time interaction in left amygdala and a diagnosis by time by task interaction in right ventrolateral prefrontal cortex. In particular, activity in left amygdala was greater in patients than in controls at the first scan during both explicit and implicit processing, while it was lower in patients at the second relative to the first scan. Furthermore, during implicit processing, right ventrolateral prefrontal cortex activity was lower in patients than controls at the first scan, while it was greater in patients at the second relative to the first scan. These results suggest that longitudinal treatment with olanzapine may be associated with specific changes in activity of the amygdala and prefrontal cortex during emotional processing in schizophrenia.

Keywords

Amygdala; Antipsychotic drugs; Emotions; Functional magnetic resonance imaging; Schizophrenia

1. Introduction

Processing of threatening emotional stimuli provides a powerful means to guide behavior when danger and hostility have to be faced. The central role played by the amygdala in processing fearful stimuli has long been established in animal studies (LeDoux, 1998). Studies in humans

have been largely consistent. Activity of the amygdala has been associated with automatic and intuitive processing of emotional stimuli (Hariri et al., 2000) and it increases with greater fear intensity (Hariri et al., 2000; Morris et al., 1998). Moreover, other studies in patients with bilateral amygdala lesions showed that these subjects lose the ability to judge approachability and trustworthiness in social stimuli such as human faces, especially when these faces are rated most unapproachable and untrustworthy by healthy subjects (Adolphs et al., 1998). These data suggest that the amygdala is an important component of the neural systems associated with different aspects of processing of hostile signals.

Activity in amygdala is modulated by serotonin (LeDoux, 1998) and dopamine (Rosenkranz and Grace, 2001) projections from the brain stem. Other evidence also suggests that the amygdala is part of a more extended neuronal network involved in emotional processing including other brain regions, such as areas of prefrontal cortex. This brain region has also been associated with higher order emotional processes (Hariri et al., 2003; Rubino et al., 2007; Tessitore et al., 2005; Wang et al., 2004). In particular, several studies have indicated that the ventrolateral prefrontal cortex is deeply involved in the modulation of emotional responses (Ochsner and Gross, 2005; Ochsner et al., 2004; Williams et al., 2006). For example, this brain region may be implicated in evaluating the emotional value of stimuli in a context-specific manner for further action selection (Ochsner and Gross, 2005). On the other hand, other studies have associated ventral prefrontal areas with more cognitive processes, like inhibition of interfering stimuli or memories (Aron et al., 2004).

Schizophrenia is characterized by important emotional and social deficits, including abnormal emotion perception (Edwards et al., 2002) and deficits in social cognition (Brunet-Gouet and Decety, 2006), the latter involving high order cognitive and emotional processes. However, relatively little attention has been devoted to emotional aspects of psychotic symptoms. Distress and anxiety have been reported in several phenomenological surveys of patients suffering from threatening hallucinations and delusions (Freeman et al., 2001). Psychophysiological data support these clinical observations. Several studies have shown higher levels of skin conductance reactivity in patients with schizophrenia (Kring and Neale, 1996). In particular, an earlier study (Kring and Neale, 1996) has investigated facial expressions and skin conductance reactivity during presentation of emotional video clips in unmedicated patients with schizophrenia and healthy subjects. Results indicated reduced facial expression modulation in patients in spite of greater skin conductance reactivity (Kring and Neale, 1996). These data suggest that, consistent with other studies (Edwards et al., 2002), patients with schizophrenia may be characterized by abnormal activity of the amygdala as implicated by reduced emotion perception and expression, but greater emotional arousal and reactivity, particularly associated with psychotic symptoms such as hallucinations and delusions (Aleman and Kahn, 2005; Glascher and Adolphs, 2003; LeDoux et al., 1988; Ohira et al., 2006). This hypothesis is also consistent with theoretical models postulating amygdala hyperreactivity in schizophrenia associated with subcortical dopamine imbalance (Grace, 2000). Importantly, this view is paralleled and integrated by others in which the prefrontal cortex is crucially associated with emotional symptoms in this disorder, possibly due to altered dopaminergic signaling (Grace, 2000; Laviolette, 2007). Consistently, several studies with functional imaging during emotion processing in schizophrenia have reported abnormal neuronal activity in nodes of the emotion network, including amygdala (Aleman and Kahn, 2005) and prefrontal cortex (Paradiso et al., 2003; Takahashi et al., 2004). However, findings have not always been consistent, showing increases, decreases, or no differences in activity in different nodes of the emotional network (Streit et al., 2001; Kosaka et al., 2002; Williams et al., 2004; Holt et al., 2006; Surguladze et al., 2006; Das et al., 2007; Russell et al., 2007; Williams et al., 2007; for review, see Aleman and Kahn, 2005). Among other factors like age, gender, severity of symptoms, as well as the nature of the stimuli used, pharmacological treatment may be associated with these inconsistencies.

The purpose of the present study in patients with schizophrenia with recent acute exacerbation of psychotic symptomatology was to evaluate putative changes in brain activity during implicit and explicit processing of facial threatening stimuli during longitudinal treatment with olanzapine. With this aim, we have employed a paradigm repeatedly used in previous reports investigating aspects of physiology (Bertolino et al., 2005; Hariri et al., 2000; Hariri et al., 2003; Meyer-Lindenberg et al., 2006b; Rubino et al., 2007) and pathophysiology (Fakra et al., 2008; Tessitore et al., 2002; Wang et al., 2004) during automatic and intuitive (implicit processing) or higher order (explicit processing) emotional processes.

We chose to use only one antipsychotic to avoid confounds associated with multiple drug administration. To also control for potential repetition effects, we included in the study a group of healthy subjects studied twice over a time interval similar to that of patients. Given the crucial involvement of amygdala and prefrontal cortex in different aspects of emotion processing, their dopaminergic modulation, as well as the well-known action of olanzapine on dopamine receptors, we hypothesized that changes of activity in these brain regions may be present during longitudinal olanzapine treatment while implicit or explicit processing of emotional stimuli is required.

2. Materials and methods

2.1. Subjects

Twelve patients with current exacerbation of psychotic symptoms requiring hospitalization as judged by the attending physician were enrolled in the study (Table 1). Diagnosis of schizophrenia was made with the Structured Clinical Interview for DSM-IV (SCID), which was administered by a trained psychiatrist (GC). Twelve healthy subjects with similar demographics were also enrolled in the study (Table 1) after exclusion of any psychiatric diagnosis with SCID. No subject in this study had a history of significant drug or alcohol abuse, head trauma with loss of consciousness, or any significant medical condition.

The present experimental protocol was approved by the local institutional review board. Moreover, after complete description of the study to the subjects, written informed consent was obtained. The study was carried out in accordance with the Declaration of Helsinki.

2.2. Experimental procedures

Before enrollment three patients were drug-naïve and nine drug-free for at least 2 weeks from oral antipsychotics or from at least two cycles of depot antipsychotic treatment because they had voluntarily withdrawn from pharmacological treatment. After inclusion in the study, all patients were treated with olanzapine in monotherapy. Titration was allowed during the first 2 weeks, and then the dose was kept constant until 8 weeks of treatment (Table 1). Symptom scores were assessed by one of the investigators using the Positive and Negative Syndrome Scale (PANSS) at baseline and then at 4 and 8 weeks of treatment.

All subjects underwent two functional magnetic resonance (fMRI) studies while performing a task eliciting emotional processing (Bertolino et al., 2005). Patients were scanned at 4 and 8 weeks of treatment and healthy subjects 4 weeks apart. We scanned patients after 4 and 8 weeks of treatment consistent with clinical studies indicating that olanzapine is associated with statistically significant beneficial effects on brain function only after 6 weeks of treatment (Purdon et al., 2000) and with molecular studies suggesting long-term regulatory effects of second generation antipsychotics on long-lasting structural and functional changes of synaptic efficacy (Dwivedi et al., 2002; Fumagalli et al., 2003; Pozzi et al., 2003).

2.3. Emotion task

The fMRI paradigm was identical to those utilized in previously published studies (Bertolino et al., 2005; Hariri et al., 2002). Briefly, we used a block-design paradigm with four emotion blocks interleaved with five sensorimotor control blocks. In two of the emotion blocks, which were identical, subjects had to match one of two simultaneously presented faces (angry or afraid) at the bottom of the screen with an identical target image at the top (implicit processing). In this condition, subjects tend to match the faces based on perceptual characteristics, such as wide eyes, furrowed brow or clenched teeth, but need not judge or interpret the emotion. This condition requires automatic and intuitive processing, as also strongly suggested by previous findings of significant limbic activation (especially amygdala) in healthy subjects performing this task (Altshuler et al., 2005; Tessitore et al., 2005; Wang et al., 2004; Wright et al., 2006). In the other two blocks of the emotion task, subjects had to label a target face by selecting one of two words (angry or afraid) simultaneously presented at the bottom of the screen (explicit processing). This condition required subjects to perceive and interpret the displayed emotions based on acquired knowledge of social standards and definitions for specific emotions. In general, this condition also engages higher emotional and cognitive processes, as strongly suggested by previous studies (Tessitore et al., 2005; Wang et al., 2004). During the sensorimotor control, subjects had to select one of two geometric shapes (bottom) identical to the target shape (top). Each block consisted of six different images (faces or geometric shapes) presented sequentially for 5 s and lasting for 32 s. Total task duration was 4 min 48 s. Behavioral performance was measured as accuracy (percent correct responses) and reaction time (milliseconds).

2.4. fMRI data acquisition

Each subject was scanned using a GE Signa 3 Tscanner (Milwaukee, Wisconsin). Blood oxygenation-level dependent (BOLD) functional images were acquired with a gradient-echo echo planar imaging (EPI) sequence, with 24 axial contiguous slices (5 mm thick, no gap) encompassing the entire cerebrum and the majority of the cerebellum (repetition time/echo time [TR/TE]=3000/30 ms, field of view [FOV]=24 cm, matrix=64×64) (Bertolino et al., 2005; Hariri et al., 2000).

2.5. Data analysis

2.5.1. Demographics and behavioral data—Analyses of variance (ANOVAs) were used to compare demographic and behavioral data. The Fisher LSD test was used for post hoc analyses.

2.5.2. fMRI data—Whole-brain image analysis was completed using Statistical Parametric Mapping 5 (SPM5-<http://www.fil.ion.ucl.ac.uk/spm>; Wellcome Department of Imaging Neuroscience, London, UK). Images for each subject were realigned, spatially normalized into the Montreal Neurological Institute (MNI) template (12-parameter affine model), and spatially smoothed (10-mm Gaussian filter). After realignment, data sets were also screened for high quality (scan stability) as demonstrated by small motion correction (2.5 mm translation, 2° rotation). Residual movement was modeled as regressor of no interest.

Predetermined condition effects at each voxel were calculated using a *t* statistic, producing a statistical image for the contrast of each emotion condition (implicit and explicit) versus the sensorimotor control for each subject. These individual contrast images were then used in second level random effects models for group analyses. In particular, a full factorial design ANOVA was performed to evaluate the main effect of diagnosis, of time, of task, and of their interactions for each contrast. Furthermore, contrasts were then performed to better characterize differential BOLD responses between groups at each time point and within groups at the two time points in brain regions showing a diagnosis by time interaction. Moreover,

further contrasts were also performed to investigate differential BOLD responses between groups at each time point and within groups at the two time points for each task in the brain regions showing a diagnosis by time by task interaction. All these comparisons were constrained by masks obtained combining brain activity of both groups during the task ($P < 0.05$).

Because of the strong *a priori* evidence of the involvement of the amygdala and of the prefrontal cortex in emotional processing and our use of a rigorous random effects statistical model, we used for the fMRI interaction analyses a statistical threshold of $P < 0.005$, $k=4$, followed by familywise error (FWE) small volume correction at $P < 0.05$ within a 10-mm-radius sphere centered around the coordinates in amygdala ($x -16$, $y 1$, $z -13$) (Williams et al., 2006) and in prefrontal cortex ($x 50$, $y 17$, $z -6$; $x 34$, $y 23$, $z -15$) (Ochsner et al., 2004) published in previous studies (Ochsner et al., 2004; Williams et al., 2006). Because we did not have *a priori* hypotheses regarding the activity of brain regions outside of the amygdala and the prefrontal cortex, we used a statistical threshold of $P = 0.05$, FWE corrected for multiple comparisons across all voxels, for these whole-brain comparisons.

Finally, Spearman's correlations were performed between behavioral measures or symptom scores and signal changes extracted within relevant brain regions.

3. Results

3.1. Demographics and behavioral data

Groups were well matched in terms of age, gender, handedness, and parental socio-economical status (all $P > 0.3$). Accuracy data (Table 1) during the emotion task showed an effect of diagnosis ($F_{1, 22} = 6.58$, $P = 0.02$), while there was no effect of time or task condition, and no interaction (all $P > 0.1$). Post hoc analysis showed greater accuracy for controls. Reaction time data (Table 1) showed an effect of diagnosis ($F_{1, 22} = 6.1239$, $P = 0.02$), while there was no effect of time or task condition (all $P > 0.7$). Furthermore, there was a significant interaction between time and diagnosis ($F_{1, 22} = 5.5397$, $P = 0.03$). Post hoc analysis showed slower responses for patients relative to controls at the second time point during explicit processing ($P = 0.01$). No other significant interactions were found.

3.2. Imaging data

Consistent with studies using the same paradigm (Bertolino et al., 2005; Hariri et al., 2000), analysis of BOLD response during both emotion conditions showed activity in a network of brain regions including bilateral amygdala, dorsolateral, ventrolateral and medial prefrontal cortices, as well as fusiform gyrus.

ANOVA performed to investigate putative effects of diagnosis, time, task, and their interactions indicated the following (Table 2): a main effect of diagnosis in right dorsolateral prefrontal cortex ($x 45$, $y 34$, $z 16$; BA 46); a main effect of time in right dorsolateral prefrontal cortex ($x 45$, $y 26$, $z 26$; BA 9); a main effect of task in bilateral medial and lateral prefrontal cortex; an interaction between time and task in left ventrolateral prefrontal cortex ($x -27$, $y 14$, $z -17$; BA 47); no interaction between diagnosis and task; an interaction between diagnosis and time in left amygdala ($x -11$, $y -5$, $z -16$) (Fig. 1); an interaction between diagnosis, time and task in right ventrolateral prefrontal cortex ($x 45$, $y 15$, $z -1$; BA 47), ($x 41$, $y 32$, $z -18$; BA 47) (Fig. 2 and Table 2). To exclude the possibility that behavioral changes over time might account for these results, we covaried imaging data for both accuracy and reaction time in SPM. This analysis did not modify the findings, in that there was an interaction between time and diagnosis in the same amygdala cluster ($x -11$, $y -5$, $z -16$; $z = 3.0$, $k = 5$) and between time, task and diagnosis in the same ventrolateral prefrontal clusters ($x 45$, $y 15$, $z -1$; $z = 3.25$; $k = 30$;

$x 41 y 32 z -18$; $z=3.1$, $k=10$), suggesting that it is unlikely that behavioral changes may affect these results. Further contrasts were performed to better characterize BOLD responses in the regions showing the described interactions between diagnosis and time (left amygdala) and between diagnosis, time and task (right ventrolateral prefrontal cortex). Analysis of left amygdala response showed that patients with schizophrenia had greater activity compared with healthy subjects at the first time point ($x -11 y -5 z -16$; $Z=2.75$; $K=6$) and with their own amygdala activity at the second time point ($x -11 y -3 z -16$; $Z=3.12$; $K=4$). No differential activity was found at the second time point between groups or between time points in healthy subjects in this brain region. Investigation of ventrolateral prefrontal cortex responses showed that, during implicit processing, healthy subjects had greater activity than patients with schizophrenia at the first time point ($x 41 y 32 z -17$; BA 47; $Z=3.14$; $K=8$). No differential activity was present between groups at the second time point. Furthermore, patients with schizophrenia showed greater BOLD responses at the second relative to the first time point ($x 41 y 32 z -17$; BA47; $Z=3.14$; $K=4$). On the other hand, during explicit processing, patients showed lower ventrolateral prefrontal activity than healthy subjects at the second time point ($x 45 y 22 z -14$; BA 47; $Z=3.09$; $K=11$). Within-group analyses indicated that healthy subjects increased activity in ventrolateral prefrontal cortex over time ($x 48 y 15 z 4$; $z 4$; BA 45; $Z=3.65$; $K=14$), while the opposite tended to be true in patients (Fig. 2).

3.2.1. Correlation analyses—To investigate if changes in symptom severity might be associated with changes in brain activity, Spearman's correlation were performed between change in symptom severity (PANSS positive symptoms, negative symptoms, general psychopathology, total score) between scan 1 and scan 2, and changes in activation of the left amygdala and right ventrolateral prefrontal cortex. No significant correlations were found between these variables (all $\rho < 0.21$; all $P > 0.51$), suggesting no significant relationship between symptom effects and changes in brain activity.

Moreover, to explore the possibility that increased activity of the amygdala at 4 weeks is a concomitant of the therapeutic effect taking place, we reasoned that, if this hypothesis was true, we would have expected to find a correlation between partial symptomatic improvement and activity of the amygdala at 4 weeks of treatment. In fact, we did not find any statistically significant correlation between symptom change between baseline and 4 weeks of treatment (as rated with the PANSS sub-scores) and activity of the amygdala at 4 weeks of treatment in the patients (PANSS positive symptoms: $\rho = -0.2$, PANSS negative symptoms, $\rho = 0.1$; PANSS general psychopathology $\rho = -0.2$; PANSS total score $\rho = -0.3$; all $P > 0.3$), suggesting that these variables do not strongly covary.

4. Discussion

The present results suggest that changes of brain activity during implicit and explicit processing of threatening stimuli in patients with schizophrenia recovering from acute exacerbation of psychotic symptoms are present during longitudinal olanzapine treatment. In particular, an interaction between diagnosis and time was found in left amygdala. In this brain region, patients had higher activity than controls after 4 weeks of treatment with olanzapine. On the other hand, activity of the amygdala in patients was reduced after 8 weeks of treatment when compared with their own activity in amygdala at 4 weeks. No statistical difference was evident in healthy subjects in amygdala between the two time points. Furthermore, an interaction between diagnosis, time and task was found in right ventrolateral prefrontal cortex. Here, patients had lower activity than controls only at the first time point during implicit processing, and only at the second time point during explicit processing. Within-subject analyses indicated that patients had greater activity in ventrolateral prefrontal cortex during implicit processing at 8 weeks of treatment, whereas healthy subjects had the opposite pattern during explicit processing. All these data suggest that 8 weeks of treatment with olanzapine in patients with

schizophrenia may be associated with changes of activity in nodes crucially involved in emotion processing, including the amygdala and the ventrolateral prefrontal cortex. It seems unlikely that these effects in patients are associated with repetition or practice effects. In fact, no effect of time was present on behavioral measures of task performance in healthy subjects. Furthermore, no effect of time was present on accuracy in patients, while they showed slower responses at the second time point. Since practice effects are generally associated with faster reaction times, we believe that the changes we have measured for reaction time in patients are not likely attributable to practice effects. At the physiological level, within-group comparisons in healthy subjects showed no difference at all or differences which were opposite in sign compared with those in patients. Moreover, covarying accuracy and reaction time did not affect the findings. Finally, our differences are more evident during implicit processing, when subjects have to simply match facial features independent of any significant cognitive evaluation. These further findings are also consistent with the idea that the effects we have measured in patients are unlikely to be associated with practice.

The data of the present study also suggest that changes in brain activity may be relatively independent from changes in symptoms. In particular, lack of correlations between changes in amygdala and ventrolateral prefrontal cortex activity and changes in symptom scores may indicate that the task used in this study and the associated brain activity do not strongly correlate with behavioral phenotypes and symptoms as measured with the PANSS. Given the conceptual and biological distance between these phenotypes, it is not surprising that the different measures do not correlate with each other.

Increased amygdala activity at 4 weeks of olanzapine treatment suggests that patients with schizophrenia recovering from acute exacerbation of psychotic symptoms have abnormal activity in brain regions implicated in the physiology of emotions. This result is consistent with previous studies showing abnormal amygdala response during processing of emotional stimuli (Streit et al., 2001; Holt et al., 2006; Surguladze et al., 2006; Das et al., 2007; Gur et al., 2007; Russell et al., 2007; Williams et al., 2007; for review, see Aleman and Kahn, 2005). After 8 weeks of treatment, patients had lower BOLD responses compared with their own activity at 4 weeks. These effects may be associated with effects of longitudinal treatment with olanzapine (see below).

We also found a diagnosis by time by task interaction in right ventrolateral prefrontal cortex. In general, this result is consistent with previous studies showing that different paradigms may differentially modulate changes in brain activity during emotion processing. For example, studies using visual paradigms (emotional faces) have found a decrease in prefrontal activity in patients compared with controls (e.g., see Gur et al., 2007), while others using auditory emotional paradigms (emotional words) have shown enhanced prefrontal activity treatment-resistant patients (Sanjuan et al., 2007). Our results further support the view that the paradigm used is relevant in determining how antipsychotic treatment may modulate brain activity during emotion processing. In fact, the diagnosis by time by task interaction found in right ventrolateral prefrontal cortex suggests that different emotional processes may lead to different antipsychotic effects in the brain. In particular, we found that patients showed greater activity in ventrolateral prefrontal cortex during implicit processing after 8 weeks of olanzapine treatment compared with 4 weeks of treatment. Previous studies have associated activity in this brain region with emotional regulation (Ochsner and Gross, 2005). Therefore, an interpretation of these data in the patients may be that an 8-week course of treatment with olanzapine was associated with an increase in activity of the prefrontal region involved in regulation of emotional responses during implicit processing. This interpretation is consistent with the fact that no such effect was found during explicit processing, when different cognitive processes may be used to regulate responses. On the other hand, differential activity in healthy subjects between the two time points during explicit processing was found. These results are

difficult to interpret at present and might be associated with repetition effects and with slightly faster reaction times. Previous studies have associated activity in this brain region with inhibition from interfering stimuli or memories (Aron et al., 2004). A more specific interpretation of these data requires further study.

Changes of activity in amygdala and prefrontal cortex during longitudinal treatment with olanzapine may be explained by cortical and/or subcortical effects. At the subcortical level, the effect of antipsychotics on dopamine D2 receptors may be taken into account to explain our results. As proposed previously (Grace, 2000), the amygdala may be involved in a functional loop with prefrontal cortex. In particular, outputs from prefrontal cortex providing plans for goal-directed behavior may direct the most appropriate response according to contextual factors. On the other hand, environmental inputs immediately relevant for survival, such as dangerous stimuli, lead to increased amygdala reactivity, which in turn competes with prefrontal inputs to drive behavioral responses. In vivo electrophysiological evidence in rodents indicates that dopamine potentiates reactivity of the amygdala by augmenting excitation from sensory inputs (Rosenkranz and Grace, 1999). Furthermore, functional imaging studies in healthy humans (Hariri et al., 2002) and in patients with Parkinson's Disease (Tessitore et al., 2002) have indicated that administration of dopamine agonists increases reactivity of the amygdala to implicit threatening stimuli. Therefore, increased dopaminergic signaling in the amygdala in schizophrenia may abnormally increase amygdala reactivity to environmental stimuli, overriding prefrontal planning for contextual adherence. Consistently, dopamine signaling in amygdala may be increased *in vivo* in untreated patients with schizophrenia (Kumakura et al., 2007). Within this context, olanzapine blockade of D2 receptors may contribute to attenuate subcortical dopamine signaling and amygdala reactivity (Grace, 2000). This hypothesis is consistent with previous models (Kapur, 2003) postulating psychosis as a state of aberrant salience. In particular, altered dopaminergic signaling may be associated with abnormal attribution of salience to environmental inputs. Antipsychotic treatment may act by 'dampening' salience of external stimuli leading to subsequent symptom improvement (Kapur, 2003). The amygdala has been implicated in salience attribution in human studies (Liberzon et al., 2003). Therefore, a decrease in amygdala activity after antipsychotic treatment may be predicted within this conceptual framework and is consistent with our data.

At the cortical level, studies in rodents have demonstrated that dopamine release in prefrontal cortex is involved in fear extinction (Pezze and Feldon, 2004) and that optimal dopamine signaling in prefrontal cortex increases neuronal signal-to-noise by modulating glutamatergic release (Seamans and Yang, 2004). Dopamine signaling in the prefrontal cortex of patients with schizophrenia may be reduced (Akil et al., 1999). Second generation antipsychotics increase dopamine release in prefrontal cortex (Gessa et al., 2000) and improve neuronal signal-to-noise during cognition (Bertolino et al., 2004b; Blasi and Bertolino, 2006). Thus, it is possible that improved prefrontal dopamine signaling related to olanzapine treatment may contribute to modulate prefrontal function during emotional processing.

Several studies have investigated the functional correlates of emotion processing in patients with schizophrenia. These studies have reported decreases, increases, or no difference in amygdala activity relative to healthy subjects during processing of emotionally salient stimuli (Streit et al., 2001; Holt et al., 2006; Surguladze et al., 2006; Das et al., 2007; Russell et al., 2007; Williams et al., 2007; for review, see Aleman and Kahn, 2005). Some of these discrepancies may be related to the different cognitive demands of tasks probing emotion processing, which may differentially affecting activity within the emotion network. Other inconsistencies may be related to clinical state and pharmacological treatment of the patients. With regard to the latter, few studies have investigated the effect of antipsychotic treatment on BOLD responses during motor, cognitive and emotional processes. In particular, some of these

studies have shown increased activity in motor areas (Bertolino et al., 2004a) or changes in functional connectivity (Stephan et al., 2001) in the motor network during motor tasks after second generation antipsychotic treatment. Other studies have found increased efficiency (Bertolino et al., 2004b), increased activity (Honey et al., 1999; Meisenzahl et al., 2006; Wolf et al., 2007), or altered BOLD response (Fusar-Poli et al., 2007) in prefrontal cortex during cognitive processes after treatment with second generation antipsychotics. On the other hand, only two studies in patients with schizophrenia with blunted affect (Fahim et al., 2005; Stip et al., 2005) have assessed the effect of longitudinal treatment with quetiapine on brain activity during emotion processing. These studies, which did not include a control group and did not control for potential repetition effects, reported that longitudinal treatment with quetiapine increases activity in prefrontal cortex during passive viewing of sad films (Stip et al., 2005) and in amygdala during passive viewing of pictures with negative affective valence (Fahim et al., 2005). Inconsistencies between our data and these earlier studies may arise from different factors. Clinical characteristics of the patients included (acute vs. stable and with flat affect), different cognitive demands during the different emotion-processing tasks (passive viewing vs. behavioral response required), and pharmacological treatment may contribute to determine these inconsistencies. Taken together, these inconsistencies along with our present data may also be viewed as suggesting that different activity of the emotion-processing network in patients with schizophrenia may be influenced by state variables.

A limitation of our study is that, due to ethical and clinical reasons, we did not acquire fMRI data when patients were free of pharmacological treatment. In fact, during acute exacerbations requiring hospitalization, it is extremely difficult to obtain co-operation from patients to undergo complicated research experiments. Therefore, we cannot rule out the possibility that increased activity of the amygdala at 4 weeks is a concomitant of the therapeutic effect taking place. However, lack of significant correlation in patients between changes in PANSS scores between baseline and 4 weeks of treatment and activity of the amygdala at 4 weeks of treatment does not support this view. Moreover, consistent with the hypothesis of greater sub-cortical dopamine signaling in schizophrenia, in vivo evidence from positron emission tomography (PET) evidence indicates greater dopamine synthesis and reduced trapping of dopamine in synaptic vesicles in amygdala of unmedicated patients with schizophrenia (Kumakura et al., 2007). Given that dopamine dampens prefrontal inhibition on amygdala neurons (Grace and Rosenkranz, 2002), our results are consistent with these latter PET data suggesting that greater dopamine signaling in amygdala may be associated with increased response to threatening stimuli. Moreover, consistent with molecular studies suggesting long-term regulatory effects of second generation antipsychotics on long-lasting structural and functional changes of synaptic efficacy (Dwivedi et al., 2002; Fumagalli et al., 2003; Pozzi et al., 2003), clinical studies (Purdon et al., 2000) have indicated that olanzapine is associated with statistically significant beneficial effects on cognition only after 6 weeks of treatment. Therefore, it is possible to argue that 8 weeks of olanzapine treatment may be associated with changes in activity of the emotion network in patients with schizophrenia when compared with 4 weeks.

Another limitation of our study is that we have used only one antipsychotic treatment in order to avoid confounding effects associated with use of different drugs. However, it is indeed possible that similar effects could be found with other second generation antipsychotics.

It may be argued that because the sensorimotor control task was not matched to the other two tasks with respect to the visual features of the stimuli, it is possible that the activity measured is mostly related to the visual object features (faces relative to geometrical shapes) rather than to the emotional content of the facial expressions. However, the same task used in several previous studies (Altshuler et al., 2005; Hariri et al., 2003; Meyer-Lindenberg et al., 2006a; Tessitore et al., 2005; Wang et al., 2004; Wright et al., 2006) was associated with activity in brain regions tightly linked with emotion processing, such as the amygdala, the ventrolateral

and the medial prefrontal cortex. Furthermore, our study also shows that the effect of olanzapine was specifically found in the amygdala and ventrolateral prefrontal cortex, but not in other regions like the fusiform gyrus that is more directly associated with face processing. Therefore, we believe that our data may have a more direct relationship with emotion processing rather than face processing *per se*.

In conclusion, our data suggest that changes in activity of brain areas implicated in emotion processing are associated with longitudinal treatment with olanzapine in patients with schizophrenia.

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References

- Adolphs R, Tranel D, Damasio AR. The human amygdala in social judgment. *Nature* 1998;393:470–474. [PubMed: 9624002]
- Akil M, Pierri JN, Whitehead RE, Edgar CL, Mohila C, Sampson AR, Lewis DA. Lamina-specific alterations in the dopamine innervation of the prefrontal cortex in schizophrenic subjects. *American Journal of Psychiatry* 1999;156:1580–1589. [PubMed: 10518170]
- Aleman A, Kahn RS. Strange feelings: do amygdala abnormalities dysregulate the emotional brain in schizophrenia? *Progress in Neurobiology* 2005;77:283–298. [PubMed: 16352388]
- Altshuler L, Bookheimer S, Proenza MA, Townsend J, Sabb F, Firestone A, Bartzokis G, Mintz J, Mazziotta J, Cohen MS. Increased amygdala activation during mania: a functional magnetic resonance imaging study. *American Journal of Psychiatry* 2005;162:1211–1213. [PubMed: 15930074]
- Aron AR, Robbins TW, Poldrack RA. Inhibition and the right inferior frontal cortex. *Trends in Cognitive Sciences* 2004;8:170–177. [PubMed: 15050513]
- Bertolino A, Blasi G, Caforio G, Latorre V, De Candia M, Rubino V, Callicott JH, Mattay VS, Bellomo A, Scarabino T, Weinberger DR, Nardini M. Functional lateralization of the sensorimotor cortex in patients with schizophrenia: effects of treatment with olanzapine. *Biological Psychiatry* 2004a; 56:190–197. [PubMed: 15271588]
- Bertolino A, Caforio G, Blasi G, De Candia M, Latorre V, Petruzzella V, Altamura M, Nappi G, Papa S, Callicott JH, Mattay VS, Bellomo A, Scarabino T, Weinberger DR, Nardini M. Interaction of COMT Val108/158 Met genotype and olanzapine treatment on prefrontal cortical function in patients with schizophrenia. *American Journal of Psychiatry* 2004b;161:1798–1805. [PubMed: 15465976]
- Bertolino A, Arciero G, Rubino V, Latorre V, De Candia M, Mazzola V, Blasi G, Caforio G, Hariri A, Kolachana B, Nardini M, Weinberger DR, Scarabino T. Variation of human amygdala response during threatening stimuli as a function of 5-HTTLPR genotype and personality style. *Biological Psychiatry* 2005;57:1517–1525. [PubMed: 15953488]
- Blasi G, Bertolino A. Imaging genomics and response to treatment with antipsychotics in schizophrenia. *NeuroRx* 2006;3:117–130. [PubMed: 16490418]
- Brunet-Gouet E, Decety J. Social brain dysfunctions in schizophrenia: a review of neuroimaging studies. *Psychiatry Research. Neuroimaging* 2006;148:75–92.
- Das P, Kemp AH, Flynn G, Harris AW, Liddell BJ, Whitford TJ, Peduto A, Gordon E, Williams LM. Functional disconnections in the direct and indirect amygdala pathways for fear processing in schizophrenia. *Schizophrenia Research* 2007;90:284–294. [PubMed: 17222539]
- Dwivedi Y, Rizavi HS, Pandey GN. Differential effects of haloperidol and clozapine on [(3)H]cAMP binding, protein kinase A (PKA) activity, and mRNA and protein expression of selective regulatory and catalytic subunit isoforms of PKA in rat brain. *The Journal of Pharmacology and Experimental Therapeutics* 2002;301:197–209. [PubMed: 11907174]

- Edwards J, Jackson HJ, Pattison PE. Emotion recognition via facial expression and affective prosody in schizophrenia: a methodological review. *Clinical Psychology Review* 2002;22:789–832. [PubMed: 12214327]
- Fahim C, Stip E, Mancini-Marie A, Gendron A, Mensour B, Beauregard M. Differential hemodynamic brain activity in schizophrenia patients with blunted affect during quetiapine treatment. *Journal of Clinical Psychopharmacology* 2005;25:367–371. [PubMed: 16012281]
- Fakra E, Salgado-Pineda P, Delaveau P, Hariri AR, Blin O. Neural bases of different cognitive strategies for facial affect processing in schizophrenia. *Schizophrenia Research* 2008;100:191–205. [PubMed: 18234477]
- Freeman D, Garety PA, Kuipers E. Persecutory delusions: developing the understanding of belief maintenance and emotional distress. *Psychological Medicine* 2001;31:1293–1306. [PubMed: 11681555]
- Fumagalli F, Bedogni F, Maragnoli ME, Gennarelli M, Perez J, Racagni G, Riva MA. Dopaminergic D2 receptor activation modulates FGF-2 gene expression in rat prefrontal cortex and hippocampus. *Journal of Neuroscience Research* 2003;74:74–80. [PubMed: 13130508]
- Fusar-Poli P, Broome MR, Matthiasson P, Williams SC, Brammer M, McGuire PK. Effects of acute antipsychotic treatment on brain activation in first episode psychosis: an fMRI study. *European Neuropsychopharmacology* 2007;17:492–500. [PubMed: 17337340]
- Gessa GL, Devoto P, Diana M, Flore G, Melis M, Pistis M. Dissociation of haloperidol, clozapine, and olanzapine effects on electrical activity of mesocortical dopamine neurons and dopamine release in the prefrontal cortex. *Neuropsychopharmacology* 2000;22:642–649.
- Glascher J, Adolphs R. Processing of the arousal of subliminal and supraliminal emotional stimuli by the human amygdala. *Journal of Neuroscience* 2003;23:10274–10282. [PubMed: 14614086]
- Grace AA. Gating of information flow within the limbic system and the pathophysiology of schizophrenia. *Brain Research. Brain Research Reviews* 2000;31:330–341. [PubMed: 10719160]
- Grace AA, Rosenkranz JA. Regulation of conditioned responses of basolateral amygdala neurons. *Physiology & Behavior* 2002;77:489–493. [PubMed: 12526988]
- Gur RE, Loughhead J, Kohler CG, Elliott MA, Lesko K, Ruparel K, Wolf DH, Bilker WB, Gur RC. Limbic activation associated with misidentification of fearful faces and flat affect in schizophrenia. *Archives of General Psychiatry* 2007;64:1356–1366. [PubMed: 18056543]
- Hariri AR, Bookheimer SY, Mazziotta JC. Modulating emotional responses: effects of a neocortical network on the limbic system. *Neuroreport* 2000;11:43–48. [PubMed: 10683827]
- Hariri AR, Mattay VS, Tessitore A, Fera F, Weinberger DR. Neocortical modulation of the amygdala response to fearful stimuli. *Biological Psychiatry* 2003;53:494–501. [PubMed: 12644354]
- Hariri AR, Mattay VS, Tessitore A, Fera F, Smith WG, Weinberger DR. Dextroamphetamine modulates the response of the human amygdala. *Neuropsychopharmacology* 2002;27:1036–1040. [PubMed: 12464460]
- Holt DJ, Kunkel L, Weiss AP, Goff DC, Wright CI, Shin LM, Rauch SL, Hootnick J, Heckers S. Increased medial temporal lobe activation during the passive viewing of emotional and neutral facial expressions in schizophrenia. *Schizophrenia Research* 2006;82:153–162. [PubMed: 16377154]
- Honey GD, Bullmore ET, Soni W, Varatheesan M, Williams SC, Sharma T. Differences in frontal cortical activation by a working memory task after substitution of risperidone for typical antipsychotic drugs in patients with schizophrenia. *Proceedings of the National Academy of Sciences of the United States of America* 1999;96:13432–13437. [PubMed: 10557338]
- Kapur S. Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. *American Journal of Psychiatry* 2003;160:13–23. [PubMed: 12505794]
- Kosaka H, Omori M, Murata T, Iidaka T, Yamada H, Okada T, Takahashi T, Sadato N, Itoh H, Yonekura Y, Wada Y. Differential amygdala response during facial recognition in patients with schizophrenia: an fMRI study. *Schizophrenia Research* 2002;57:87–95. [PubMed: 12165379]
- Kring AM, Neale JM. Do schizophrenic patients show a disjunctive relationship among expressive, experiential, and psychophysiological components of emotion? *Journal of Abnormal Psychology* 1996;105:249–257. [PubMed: 8723006]

- Kumakura Y, Cumming P, Vernaleken I, Buchholz HG, Siessmeier T, Heinz A, Kienast T, Bartenstein P, Grunder G. Elevated [18F]fluorodopamine turnover in brain of patients with schizophrenia: an [18F]fluorodopa/positron emission tomography study. *Journal of Neuroscience* 2007;27:8080–8087. [PubMed: 17652599]
- Laviolette SR. Dopamine modulation of emotional processing in cortical and subcortical neural circuits: evidence for a final common pathway in schizophrenia? *Schizophrenia Bulletin* 2007;33:971–981. [PubMed: 17519393]
- LeDoux J. Fear and the brain: where have we been, and where are we going? *Biological Psychiatry* 1998;44:1229–1238. [PubMed: 9861466]
- LeDoux JE, Iwata J, Cicchetti P, Reis DJ. Different projections of the central amygdaloid nucleus mediate autonomic and behavioral correlates of conditioned fear. *Journal of Neuroscience* 1988;8:2517–2529. [PubMed: 2854842]
- Liberzon I, Phan KL, Decker LR, Taylor SF. Extended amygdala and emotional salience: a PET activation study of positive and negative affect. *Neuropsychopharmacology* 2003;28:726–733. [PubMed: 12655318]
- Meisenzahl EM, Scheuerecker J, Zipse M, Ufer S, Wiesmann M, Frodl T, Koutsouleris N, Zetzsche T, Schmitt G, Riedel M, Spellmann I, Dehning S, Linn J, Bruckmann H, Moller HJ. Effects of treatment with the atypical neuroleptic quetiapine on working memory function: a functional MRI follow-up investigation. *European Archives of Psychiatry and Clinical Neuroscience* 2006;256:522–531. [PubMed: 17151834]
- Meyer-Lindenberg A, Mervis CB, Berman KF. Neural mechanisms in Williams syndrome: a unique window to genetic influences on cognition and behaviour. *Nature Reviews. Neuroscience* 2006a; 7:380–393.
- Meyer-Lindenberg, A.; Buckholtz, JW.; Kolachana, BARH.; Pezawas, L.; Blasi, G.; Wabnitz, A.; Honea, R.; Verchinski, B.; Callicott, JH.; Egan, M.; Mattay, V.; Weinberger, DR. Neural mechanisms of genetic risk for impulsivity and violence in humans; *Proceedings of the National Academy of Sciences of the United States of America*; 2006b. p. 6269–6274.
- Morris JS, Ohman A, Dolan RJ. Conscious and unconscious emotional learning in the human amygdala. *Nature* 1998;393:467–470. [PubMed: 9624001]
- Ochsner KN, Gross JJ. The cognitive control of emotion. *Trends in Cognitive Sciences* 2005;9:242–249. [PubMed: 15866151]
- Ochsner KN, Ray RD, Cooper JC, Robertson ER, Chopra S, Gabrieli JD, Gross JJ. For better or for worse: neural systems supporting the cognitive down- and up-regulation of negative emotion. *Neuroimage* 2004;23:483–499. [PubMed: 15488398]
- Ohira H, Nomura M, Ichikawa N, Isowa T, Iidaka T, Sato A, Fukuyama S, Nakajima T, Yamada J. Association of neural and physiological responses during voluntary emotion suppression. *Neuroimage* 2006;29:721–733. [PubMed: 16249100]
- Paradiso S, Andreasen NC, Crespo-Facorro B, O'Leary DS, Watkins GL, Boles Ponto LL, Hichwa RD. Emotions in unmedicated patients with schizophrenia during evaluation with positron emission tomography. *American Journal of Psychiatry* 2003;160:1775–1783. [PubMed: 14514490]
- Pezze MA, Feldon J. Mesolimbic dopaminergic pathways in fear conditioning. *Progress in Neurobiology* 2004;74:301–320. [PubMed: 15582224]
- Pozzi L, Hakansson K, Usiello A, Borgkvist A, Lindskog M, Greengard P, Fisone G. Opposite regulation by typical and atypical anti-psychotics of ERK1/2, CREB and Elk-1 phosphorylation in mouse dorsal striatum. *Journal of Neurochemistry* 2003;86:451–459. [PubMed: 12871586]
- Purdon SE, Jones BD, Stip E, Labelle A, Addington D, David SR, Breier A, Tollefson GD. The Canadian Collaborative Group for research in schizophrenia. Neuropsychological change in early phase schizophrenia during 12 months of treatment with olanzapine, risperidone, or haloperidol. *Archives of General Psychiatry* 2000;57:249–258. [PubMed: 10711911]
- Rosenkranz JA, Grace AA. Modulation of basolateral amygdala neuronal firing and afferent drive by dopamine receptor activation in vivo. *Journal of Neuroscience* 1999;19:11027–11039. [PubMed: 10594083]
- Rosenkranz JA, Grace AA. Dopamine attenuates prefrontal cortical suppression of sensory inputs to the basolateral amygdala of rats. *Journal of Neuroscience* 2001;21:4090–4103. [PubMed: 11356897]

- Rubino V, Blasi G, Latorre V, Fazio L, d'Errico I, Mazzola V, Caforio G, Nardini M, Popolizio T, Hariri A, Arciero G, Bertolino A. Activity in medial prefrontal cortex during cognitive evaluation of threatening stimuli as a function of personality style. *Brain Research Bulletin* 2007;74:250–257. [PubMed: 17720547]
- Russell TA, Reynaud E, Kucharska-Pietura K, Ecker C, Benson PJ, Zelaya F, Giampietro V, Brammer M, David A, Phillips ML. Neural responses to dynamic expressions of fear in schizophrenia. *Neuropsychologia* 2007;45:107–123. [PubMed: 16814818]
- Sanjuan J, Lull JJ, Aguilar EJ, Marti-Bonmati L, Moratal D, Gonzalez JC, Robles M, Keshavan MS. Emotional words induce enhanced brain activity in schizophrenic patients with auditory hallucinations. *Psychiatry Research. Neuroimaging* 2007;154:21–29.
- Seamans JK, Yang CR. The principal features and mechanisms of dopamine modulation in the prefrontal cortex. *Progress in Neurobiology* 2004;74:1–58. [PubMed: 15381316]
- Stephan KE, Magnotta VA, White T, Arndt S, Flaum M, O'Leary DS, Andreasen NC. Effects of olanzapine on cerebellar functional connectivity in schizophrenia measured by fMRI during a simple motor task. *Psychological Medicine* 2001;31:1065–1078. [PubMed: 11513374]
- Stip E, Fahim C, Mancini-Marie A, Bentaleb LA, Mensour B, Mendrek A, Beauregard M. Restoration of frontal activation during a treatment with quetiapine: an fMRI study of blunted affect in schizophrenia. *Progress in Neuropsychopharmacology and Biological Psychiatry* 2005;29:21–26.
- Streit M, Ioannides A, Sinnemann T, Wolwer W, Dammers J, Zilles K, Gaebel W. Disturbed facial affect recognition in patients with schizophrenia associated with hypoactivity in distributed brain regions: a magnetoencephalographic study. *American Journal of Psychiatry* 2001;158:1429–1436. [PubMed: 11532727]
- Surguladze S, Russell T, Kucharska-Pietura K, Travis MJ, Giampietro V, David AS, Phillips ML. A reversal of the normal pattern of parahippocampal response to neutral and fearful faces is associated with reality distortion in schizophrenia. *Biological Psychiatry* 2006;60:423–431. [PubMed: 16487943]
- Takahashi H, Koeda M, Oda K, Matsuda T, Matsushima E, Matsuura M, Asai K, Okubo Y. An fMRI study of differential neural response to affective pictures in schizophrenia. *Neuroimage* 2004;22:1247–1254. [PubMed: 15219596]
- Tessitore A, Hariri AR, Fera F, Smith WG, Das S, Weinberger DR, Mattay VS. Functional changes in the activity of brain regions underlying emotion processing in the elderly. *Psychiatry Research. Neuroimaging* 2005;139:9–18.
- Tessitore A, Hariri AR, Fera F, Smith WG, Chase TN, Hyde TM, Weinberger DR, Mattay VS. Dopamine modulates the response of the human amygdala: a study in Parkinson's disease. *Journal of Neuroscience* 2002;22:9099–9103. [PubMed: 12388617]
- Wang AT, Dapretto M, Hariri AR, Sigman M, Bookheimer SY. Neural correlates of facial affect processing in children and adolescents with autism spectrum disorder. *Journal of the American Academy of Child and Adolescent Psychiatry* 2004;43:481–490. [PubMed: 15187809]
- Williams LM, Das P, Liddell BJ, Kemp AH, Rennie CJ, Gordon E. Mode of functional connectivity in amygdala pathways dissociates level of awareness for signals of fear. *Journal of Neuroscience* 2006;26:9264–9271. [PubMed: 16957082]
- Williams LM, Das P, Harris AW, Liddell BB, Brammer MJ, Olivieri G, Skerrett D, Phillips ML, David AS, Peduto A, Gordon E. Dysregulation of arousal and amygdala-prefrontal systems in paranoid schizophrenia. *American Journal of Psychiatry* 2004;161:480–489. [PubMed: 14992974]
- Williams LM, Das P, Liddell BJ, Olivieri G, Peduto AS, David AS, Gordon E, Harris AW. Fronto-limbic and autonomic disjunctions to negative emotion distinguish schizophrenia subtypes. *Psychiatry Research. Neuroimaging* 2007;155:29–44.
- Wolf RC, Vasic N, Hose A, Spitzer M, Walter H. Changes over time in frontotemporal activation during a working memory task in patients with schizophrenia. *Schizophrenia Research* 2007;91:141–150. [PubMed: 17258892]
- Wright CI, Wedig MM, Williams D, Rauch SL, Albert MS. Novel fearful faces activate the amygdala in healthy young and elderly adults. *Neurobiology of Aging* 2006;27:361–374. [PubMed: 16399218]

Fig. 1.

A. Coronal section of the brain with the region in left amygdala showing diagnosis by time interaction (local maxima in $x = -11$ $y = -5$ $z = -16$) during processing of threatening stimuli. B. Plots of signal change extracted from the cluster depicted in A. Error bars represent standard error of the means.

Fig. 2.

A. Rendered image showing regions in right ventrolateral prefrontal cortex in which a diagnosis by time by task interaction was found (local maxima in x 45 y 15 z -1; BA 47; and x 41 y 32 z -18; BA 47). B. Plots of signal change extracted from one of the clusters depicted in A (x 45 y 15 z -1; BA 47). Error bars represent standard error of the means.

Table 1
Demographics and behavioral data of the two groups, and symptom scores in patients.

	Patients		Normal controls	
	M	F	M	F
Gender	10	2	10	2
Age	Mean	S.D.	Mean	DS
Handedness (Edinburgh Inventory)	28.2	±6.3	27.0	±4.8
Parental socio-economical status (Hollingshead Scale)	0.7	±0.60	0.8	±0.2
Mean length of illness (months)	36.0	±19.7	41.9	±21.8
Olanzapine daily dose (mg)	81.1	±67.5		
16.0	±7.0			
Symptoms				
PANSS positive week 0	22.8			±5.4
PANSS positive week 4	17.5			±4.1
PANSS positive week 8	15.2			±4.6
PANSS negative week 0	25.7			±9.1
PANSS negative week 4	20.7			±6.6
PANSS negative week 8	17.8			±7.6
PANSS general week 0	56.1			±11.1
PANSS general week 4	42.8			±11.3
PANSS general week 8	36.1			±10.6
PANSS total week 0	105.4			±20.0
PANSS total week 4	80.5			±17.8
PANSS total week 8	70.0			±20.2
Behavioral data				
Accuracy implicit processing week 4	82.6	±17.2	93.1	±7.8
Accuracy implicit processing week 8	91.7	±14.2	93.1	±11.1

	Patients		Normal controls	
	M	F	M	F
Accuracy explicit processing week 4	75.7		93.8	±9.5
Accuracy explicit processing week 8	85.4		94.4	±8.2
RT implicit processing week 4	1835.4		1765.0	±367.2
RT implicit processing week 8	1925.3		1645.2	±484.8
RT explicit processing week 4	1814.7		1739.3	±420.5
RT explicit processing week 8	2137.6		1530.3	±240.5

Local maxima of brain regions showing effects of diagnosis, time, task, and their significant interactions during processing of threatening stimuli.

Brain region	BA	Coordinates			
		x	y	z	k
Main effect of diagnosis					
Right middle frontal gyrus	46	45	34	16	12
Main effect of time					
Right middle frontal gyrus	9	45	26	26	13
Main effect of task					
Left cingulate gyrus; superior frontal gyrus; medial frontal gyrus	32, 6, 8	-4	14	38	495
Left precentral gyrus; medial frontal gyrus; inferior frontal gyrus	44, 8, 46	-53	15	9	460
Right inferior frontal gyrus; middle frontal gyrus; precentral gyrus	47, 6, 44	45	23	9	328
Interaction: diagnosis × time					
Left amygdala		-11	-5	-16	8
Interaction: time × task					
Left inferior frontal gyrus	47	-27	14	-17	13
Interaction: diagnosis × time × task					
Right inferior frontal gyrus	47	45	15	-1	15
Right inferior frontal gyrus	47	41	32	-18	11