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Neural correlates of aberrant emotional salience predict psychotic symptoms and global functioning in high-risk and first-episode psychosis

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Neurobiological and behavioral findings suggest that psychosis is associated with corticolimbic hyperactivity during the processing of emotional salience. This has not been widely studied in the early stages of psychosis, and the impact of these abnormalities on psychotic symptoms and global functioning is unknown. We sought to address this issue in 18 patients with first-episode psychosis (FEP), 18 individuals at ultra high risk of psychosis (UHR) and 22 healthy controls (HCs). Corticolimbic response and subjective ratings to emotional and neutral scenes were measured using functional magnetic resonance imaging. The clinical and functional impact of corticolimbic abnormalities was assessed with regression analyses. The FEP and UHR groups reported increased subjective emotional arousal to neutral scenes compared with HCs. Across groups, emotional *vs* neutral scenes elicited activation in the dorsomedial prefrontal cortex, inferior frontal gyrus/anterior insula and amygdala. Although FEP and UHR participants showed reduced activation in these regions when viewing emotional scenes compared with controls, this was driven by increased activation to neutral scenes. Corticolimbic hyperactivity to neutral scenes predicted higher levels of positive symptoms and poorer levels of functioning. These results indicate that disruption of emotional brain systems may represent an important biological substrate for the pathophysiology of early psychosis and UHR states.

Keywords: psychosis; at-risk mental state; emotional salience; fMRI; amygdala

INTRODUCTION

Impaired emotional processing has been proposed as a primary antecedent to the development of psychosis (Grace and Moore, 1998; Grace, 2000; Aleman and Kahn, 2005). Behavioral studies in patients with schizophrenia have shown that they are more likely to report greater subjective arousal to neutral stimuli than healthy controls (HCs) (Williams *et al.*, 2004; Dowd and Barch, 2010; Haralanova *et al.*, 2012; Llerena *et al.*, 2012). Moreover, perturbed processing of emotional salience has been associated with hyperactivity in corticolimbic brain regions in patients with schizophrenia (Aleman and Kahn, 2005; Taylor *et al.*, 2005, 2007; Anticevic *et al.*, 2012). This is important because corticolimbic abnormalities are associated with the psychotic features characteristic of psychosis and schizophrenia (Aleman and Kahn, 2005), for example with heightened activity in the amygdala involved in the generally increased tendencies to perceive threats in the environment (Ochsner, 2008). Notably, impaired emotional processing has severe consequences for the functional outcomes of patients and is not effectively treated by available therapies (Kee *et al.*, 2003; Baslet *et al.*, 2009; Kring and Caponigro, 2010). Understanding the neural basis of emotional dysfunction is thus critical to improving our knowledge of the pathophysiology of schizophrenia and to the development of new treatments.

A small number of studies have begun to investigate the role of aberrant emotional salience in psychosis risk cohorts (at genetic, clinical or psychometric risk). Similar to patients with schizophrenia, at-risk individuals report increased subjective emotionality and arousal (van 't Wout *et al.*, 2004; Phillips and Seidman, 2008), as well as deficits in emotional recognition (van Rijn *et al.*, 2011; Addington *et al.*, 2012; Amminger *et al.*, 2012; Comparelli *et al.*, 2013; Kohler *et al.*, 2014). Furthermore, a large body of evidence from retrospective and longitudinal studies implicates emotional dysfunction as a strong precursor to psychotic disorder (Walker *et al.*, 1993; Hafner *et al.*, 2003; Demjaha *et al.*, 2012; Alderman *et al.*, 2014; Allott *et al.*, 2014), thereby suggesting that psychosis vulnerability may manifest in emotional dysfunction prior to illness onset, feeding into the development of psychotic symptoms (Freeman and Garety, 2003).

The processing of emotional stimuli involves a corticolimbic network in which the medial prefrontal cortex (mPFC), anterior insula (aINS) and the amygdala are key components (Phan *et al.*, 2002; Kober *et al.*, 2008). Studies using functional magnetic resonance imaging (fMRI) in patients with schizophrenia show reduced activation in these regions in response to emotional *vs* neutral pictures compared with HCs (Taylor *et al.*, 2002; Paradiso *et al.*, 2003; Takahashi *et al.*, 2004; Mendrek *et al.*, 2007; Whalley *et al.*, 2009; Anticevic *et al.*, 2012). However, further investigation into the mechanisms underlying these differences suggests that corticolimbic reductions are in fact driven by an abnormally heightened response to innocuous or non-salient stimuli, that is, to the neutral comparator stimuli typically used in fMRI paradigms (Holt *et al.*, 2006; Hall *et al.*, 2008; Anticevic *et al.*, 2012). Abnormal corticolimbic response to emotional stimuli has also been documented in groups at high risk for psychosis (Habel *et al.*, 2004; Seiferth *et al.*, 2008; Modinos *et al.*, 2010, 2012; Li *et al.*, 2012) and patients with a first episode of psychosis (Bergé *et al.*, 2014), although responses to neutral stimuli have not been explicitly examined in these groups. Furthermore, the impact of these abnormalities on psychotic symptoms and global functioning in first-episode psychosis and individuals at high-risk is unknown.

In this study, we examined the neural correlates of emotional salience in people with an ultra high risk for psychosis (UHR), patients with a first-episode of psychosis (FEP) and healthy volunteers and the association with psychotic symptoms and levels of global functioning. We tested three hypotheses. On the basis of previous findings in

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schizophrenia, we hypothesized increased subjective emotional arousal to neutral stimuli in UHR and FEP subjects compared with HCs (Dowd and Barch, 2010; Haralanova *et al.*, 2012; Llerena *et al.*, 2012). Additionally, we predicted reduced corticolimbic response in UHR and FEP subjects to emotional stimuli, which would be driven by hyperactivation to neutral stimuli (Holt *et al.*, 2006; Hall *et al.*, 2008; Seiferth *et al.*, 2008; Anticevic *et al.*, 2012). Finally, we hypothesized that the degree of hyperactivation in corticolimbic regions to neutral stimuli would correlate with the severity of psychotic symptoms and the level of global functioning within the patient groups.

METHODS

Participants

Eighteen individuals at UHR were recruited from a UHR clinical service [Outreach and Support in South London service (OASIS)] (Fusar-Poli *et al.*, 2013a). Inclusion criteria required the presence of one or more of the following: (i) attenuated psychotic syndrome (APS), (ii) a brief psychotic episode of less than 1 week's duration that spontaneously remits without antipsychotic medication or hospitalization (Brief Limited Intermittent Psychotic episode) and (iii) trait vulnerability (schizotypal personality disorder or a first-degree relative with psychosis) plus a marked decline in psychosocial functioning (Global Assessment of Functioning, GAF) (American Psychiatric Association, 1994). UHR signs and symptoms were assessed with the Comprehensive Assessment of At-Risk Mental States (CAARMS) (Yung *et al.*, 2005), a semi-structured interview designed to assess prodromal psychopathology in people at clinical high risk for psychosis.

Eighteen patients aged 18–35 years (the same age range used for UHR and HCs) who presented with an FEP to the South London & Maudsley Mental Health National Health Service (SLaM NHS) Foundation Trust were invited to participate in the study. A first episode of psychosis was operationally defined as 'first treatment contact' plus an ICD-10 diagnosis of psychosis (codes F20-F29 and F30-F33) (World Health Organization, 1992a). The clinical diagnosis was validated by administering the Schedules for Clinical Assessment in Neuropsychiatry (World Health Organization, 1992b). Cases with a diagnosis of organic psychosis were excluded. Ten of the FEP participants were taking atypical antipsychotic medication. Potential effects of antipsychotics on the results were measured with correlational analyses and are reported in the Supplementary Material.

Twenty-two HCs were recruited by advertisement from the same geographical area. Absence of psychiatric illness history was confirmed with the Mini International Neuropsychiatric Inventory (Sheehan *et al.*, 1998). Table 1 summarizes the demographic and clinical characteristics of the three groups.

Exclusion criteria for all participants were other past/present diagnosis of axis I psychiatric illnesses, past/present/familiar history of neurological illness, intellectual impairments, medical illness, alcohol or other substance abuse or dependence [defined using DSM-IV criteria (American Psychiatric Association, 1994)] and pregnancy. Ethical approval for the study was obtained from the Research Ethics Committee of King's College London and SLaM NHS, and all participants provided informed consent.

Clinical and cognitive measures

Positive and negative symptoms were assessed using the CAARMS (Yung *et al.*, 2005) for UHR individuals and the Positive and Negative Syndrome Scale (PANSS) (Kay *et al.*, 1987) for FEP patients. Pre-morbid intelligence quotient (IQ) was assessed using the National Adult Reading Test (NART) (Nelson, 1982). Severity of symptoms of depression and anxiety were measured with the Depression Anxiety Stress Scale (DASS) (Lovibond and Lovibond, 1995). These measures were acquired during the same session in which the fMRI scanning was performed.

Table 1 Clinical and demographic characteristics

	Mean (s.d.)			F or χ^2	df	P
	HC	UHR	FEP			
Age	23.8 (4.6)	24.4 (4.1)	27.9 (5.0)	3.815	50	0.029[a]
Education	16.9 (2.1)	14.8 (1.8)	15.1 (3.9)	3.035	46	0.058
Gender (% male)	45.0	55.6	73.3	2.813	2	0.245
Pre-morbid IQ estimate (NART)	109.9 (10.3)	99.1 (15.6)	92.3 (15.3)	6.918	46	0.002[a]
GAF disability	91.75 (5.6)	60.6 (10.1)	59.4 (14.4)	25.678	32	0.000[a]
CAARMS positive	—	7.7 (4.9)	—	—	—	—
CAARMS negative	—	4.4 (3.7)	—	—	—	—
PANSS positive	—	13.4 (3.8)	13.9 (5.6)	.074	30	0.788
PANSS negative	—	13.5 (5.9)	13.3 (5.9)	.009	30	0.926
DASS depression	2.0 (4.5)	16.2 (10.9)	9.0 (9.8)	12.639	50	0.000
DASS anxiety	1.4 (2.0)	1.6 (10.0)	8.2 (7.2)	10.205	50	0.000
DASS stress	3.8 (6.9)	16.9 (10.5)	9.7 (9.0)	10.397	0	0.000
Medication (% taking)						
Average dose (CPZ equivalents)	—	—	124.4 (131.8)	—	—	—

Notes: CPZ, chlorpromazine. CAARMS-positive symptoms were the sum of severity scores for unusual thought content, non-bizarre ideas, perceptual abnormalities and disorganized speed; negative symptoms were the sum of severity scores for alogia, avolition/apathy and anhedonia.
[a]Bonferroni post-hoc tests: Age: HC *vs* UHR $P = 1$, HC *vs* FEP $P = 0.035$, UHR *vs* FEP $P = 0.099$; Pre-morbid IQ estimate (NART): HC *vs* UHR $P = 0.001$, HC *vs* FEP $P = 0.001$, UHR *vs* FEP $P = 1$; GAF disability: HC *vs* UHR $P = 0.081$, HC *vs* FEP $P = 0.002$, UHR *vs* FEP $P = 0.530$. DASS depression: HC *vs* UHR $P < 0.001$, HC *vs* FEP $P = 0.066$, UHR *vs* FEP $P = 0.066$; DASS anxiety: HC *vs* UHR $P < 0.001$, HC *vs* FEP $P = 0.022$, UHR *vs* FEP $P = 0.527$; DASS stress: HC *vs* UHR $P < 0.001$, HC *vs* FEP $P = 0.173$, UHR *vs* FEP $P = 0.070$.

fMRI task paradigm

The fMRI task was adapted from a previous study of emotional processing in patients with chronic schizophrenia (Dowd and Barch, 2010). The stimulus set consisted of 50 color pictures from the International Affective Picture System [IAPS (Lang *et al.*, 1997)], 10 in each of the following categories: negative high arousal (NHA), negative low arousal (NLA), positive high arousal (PHA), positive low arousal (PLA) and neutral (NEU), matched for social content (~50%). As done in Dowd and Barch (2010), NEU (mean valence ± s.d. = 5.1 ± 0.2; mean arousal ± s.d. = 2.9 ± 0.4), NHA (mean valence ± s.d. = 2.4 ± 0.8; mean arousal ± s.d. = 6.8 ± 0.2), NLA (mean valence ± s.d. = 3.4 ± 0.7; mean arousal ± s.d. = 4.1 ± 0.3), PHA (mean valence ± s.d. = 7.3 ± 0.5; mean arousal ± s.d. = 6.8 ± 0.4) and PLA pictures (mean valence ± s.d. = 6.7 ± 0.5; mean arousal ± s.d. = 3.1 ± 0.3) were chosen based on normative ratings, according to which 9 represents a high rating on each dimension (i.e. high arousal and positive valence) and 1 represents a low rating on each dimension (i.e. low arousal and negative valence) (Lang *et al.*, 1997, 2008). The final selection of images from the IAPS battery was based on a previous imaging study on schizophrenia reporting specific mean valence and arousal values (Ursu *et al.*, 2011). The IAPS pictures have been extensively used to reliably detect functional abnormalities within emotional regions in patients with schizophrenia (e.g. Taylor *et al.*, 2002, 2005; Paradiso *et al.*, 2003; Takahashi *et al.*, 2004; Mendrek *et al.*, 2007; Whalley *et al.*, 2009; Dowd and Barch, 2010; Ursu *et al.*, 2011) and in groups at heightened risk for developing psychosis (Modinos *et al.*, 2010, 2012).

Participants were scanned while rating their subjective emotional arousal response to each stimulus via button press (1 = not at all aroused, 2 = slightly aroused, 3 = highly aroused; see Supplementary Material for detailed study instructions). Each picture was presented

for 4000 ms, and a gray screen with a fixation cross serving as low-level baseline condition separated each trial (varying from 1000 to 10 000 ms). Order of trial presentation was pseudo-randomized based on simulations to optimize experimental power. Before scanning, all subjects were trained on a rating task of 10 IAPS images different from those used in the fMRI experiment.

Functional imaging parameters

Hemodynamic responses were measured with echo-planar images (EPIs) sensitive to blood oxygenation level–dependent contrast acquired on a 1.5-T General Electric Signa MR system (Milwaukee, WI) at the Institute of Psychiatry, Psychology & Neuroscience, King's College London. The EPI parameters were as follows: repetition time (TR): 3000 ms; echo time (TE), 40 ms; flip angle, 90°; 2.5 × 2.5 × 2.5-mm voxels; field of view, 240 and 46 axial sections collected with interleaved acquisition and 3-mm gap. Structural data were acquired by means of a three-dimensional T1-weighted FSPGR sequence (voxel size: 1 × 1 × 1 mm3, field of view: 280, 146 slices, TR = 11.092 ms, TE = 4.87 ms, inversion time (TI = 300 ms, $\alpha = 18°$).

Two FEP patients and two controls had to be excluded because of failure to complete the fMRI task. An additional FEP patient was excluded due to excessive head movement (>3 mm). Detailed examination of potential movement confounds on activation is reported in the Supplementary Material.

fMRI preprocessing

fMRI data were analyzed using SPM8 software (Wellcome Department of Cognitive Neurology, London, UK). After realignment, segmentation, co-registration and stereotaxic normalization ($2 \times 2 \times 2$ mm^3), images were spatially smoothed using an 8-mm full-width at half-maximum Gaussian filter and a high pass (128 s).

Data analysis

Sociodemographic, clinical and behavioral data.

Analysis of behavioral, demographic, neuropsychological and clinical data was performed in SPSS (SPSS Inc., Chicago, IL). Differences in demographic and clinical characteristics were examined using one-way analysis of variance (ANOVA) for parametric data and a Chi-square test (χ^2) for non-parametric data.

To investigate brain-behavior relationships, we used mean subjective ratings of arousal (to NHA, NLA, PHA, PLA and NEU trials) as a behavioral metric of emotional processing. A repeated-measures ANOVA with arousal ratings as a within-subjects variable and group (HC, FEP or UHR) as a between-subjects variable was computed to test our first hypothesis of increased subjective arousal ratings in the patient groups. The same procedure was used for analysis of reactions times (see Supplementary Material). Significant main effects are reported at $P < 0.05$ and trend effects at $P < 0.1$. Post-hoc tests are reported after Bonferroni correction.

fMRI analysis.

Statistical analyses of fMRI data were conducted using General Linear Model (GLM) implemented in SPM8 (http://www.fil.ion.ucl.ac.uk/spm). Separate regressors of interest were specified for each trial type: NHA, NLA, PHA, PLA and NEU. Additionally, realignment parameters (*x*, *y*, *z*, pitch, roll, yaw) were included in all first level models as covariates of no interest to account for variance associated with head movement. All regressors were convolved with a canonical hemodynamic response function.

Two contrast images were generated for each participant. The first one examined emotional-related activation by contrasting all emotional trials *vs* neutral trials. The second examined activation related to non-emotional stimuli by contrasting neutral trials *vs* fixation cross. Contrast images for each participant were submitted to second-level analyses, covarying for age, gender and IQ (NART). Complementary analyses of neural response to positive and negative emotion are reported in the Supplementary Material and Figure S2.

To identify regions involved in processing Emotional and Neutral stimuli, we performed whole-brain analyses collapsing across groups. Multiple comparison correction was performed using Monte Carlo simulation [AlphaSim (Forman *et al.*, 1995; McAvoy *et al.*, 2001) included in REST software 1.6 (Song *et al.*, 2011)], which incorporates the estimated smoothness of the data to establish the likelihood of false positives of different cluster sizes (i.e. cluster size thresholding). At an individual voxel threshold of $P < 0.001$, the cluster threshold was 74 voxels for the whole brain, resulting in a corrected $\alpha < 0.05$. On the basis of the role of the amygdala in emotional dysfunction in schizophrenia (Aleman and Kahn, 2005; Anticevic *et al.*, 2012), we additionally created a pre-defined anatomical mask for region of interest (ROI) analysis of the bilateral amygdala using the Automated Anatomical Labeling as implemented in the WFU_Pickatlas toolbox in SPM (results reported also at $P < 0.05$).

Corticolimbic areas demonstrating significant activation were subsequently tested for group differences in SPSS using a multifactorial GLM with group as between-subject factor, as done in previous fMRI studies in schizophrenia (Hall *et al.*, 2008; Eich *et al.*, 2014). These areas provide unbiased estimates for examining group differences because they were identified through analyses that collapsed across groups. Significant group effects were followed up using Bonferroni post-hoc correction for multiple comparisons.

Prediction of psychotic symptoms and functioning.

To test our third hypothesis that corticolimbic hyperactivation to neutral scenes would predict clinical symptomatology and global functioning, parameter estimates from corticolimbic regions showing significant task effects across groups as identified above were used as independent variables in separate regression models in SPSS with the following dependent variables: (i) CAARMS positive and negative dimensions (within UHR), (ii) PANSS-positive and -negative dimensions (within FEP) and (iii) GAF scores (within UHR and FEP). Significant effects are reported at $P < 0.05$ and trend effects at $P < 0.1$.

RESULTS

Full demographic and clinical results are presented in Table 1.

Behavioral performance

There was a significant main effect of condition ($F_{1,50} = 104.118$, $P < 0.001$) and a significant group × condition interaction ($F_{2,50} = 5.231$, $P = 0.009$), by which UHR and FEP groups rated NEU scenes as more emotionally arousing than HC did (UHR: $P = 0.038$; FEP: $P = 0.019$) and NHA scenes as less emotionally arousing than HC did (UHR: $P = 0.049$; FEP: $P = 0.037$). There were no differences in arousal ratings between FEP and UHR individuals (Figure 1).

Reaction time results are reported in the Supplementary Material and Figure S1.

fMRI results

Effect of task (emotional > neutral).

Across groups, emotional scenes were associated with greater activation in the dorsomedial prefrontal cortex (dmPFC), the right

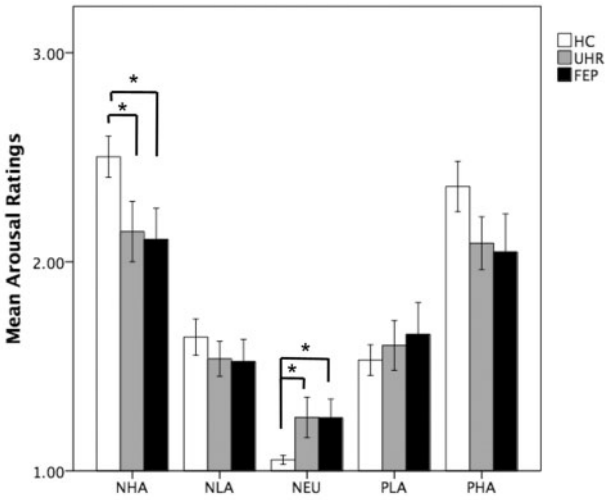

Fig. 1 Average arousal ratings (3 = highly aroused, 2 = slightly aroused, 1 = not at all aroused) for each emotional condition in individuals with an FEP, subjects at UHR and control subjects (HC). *Significant difference between groups at $P < 0.05$. Error bars represent standard error.

IFG, left IFG/aINS, bilateral occipital regions and the cerebellum (Table 2, Figure 2). ROI analysis revealed significant task effects also in the amygdala, bilaterally ($P < 0.05$ FWE corrected). Results of within-group analysis are reported in the Supplementary Material.

Effect of group for emotional vs *neutral scenes.*

There was a significant effect of group in the left IFG/aINS ($F_{2,50} = 11.897$, $P < 0.001$), with lower activation in UHR subjects than in HC and FEP ($P < 0.001$ and $P = 0.048$). There was also an effect of group in the right amygdala ($F_{2,50} = 4.623$, $P = 0.014$), with UHR and FEP subjects showing lower activation than HC ($P = 0.027$ and $P = 0.055$, respectively). Finally, there was an effect of group at trend level in the left amygdala ($F_{2,50} = 2.604$, $P = 0.084$), but pairwise comparisons results did not survive Bonferroni correction. No effect of group was observed for the dmPFC ($F_{2,50} < 1$, ns) (Figure 3).

Effect of group for neutral scenes vs *fixation.*

UHR and FEP subjects showed a significantly different response to neutral scenes in the left IFG/aINS (main effect of group: $F_{2,50} = 6.085$, $P = 0.004$), with greater activity than HC ($P = 0.004$ and $P = 0.071$, respectively). There was also an effect of group in the right ($F_{2,50} = 3.424$, $P = 0.040$) and left amygdala ($F_{2.50} = 3.739$, $P = 0.031$), with FEP patients showing more activation than HC (right, $P = 0.054$; left, $P = 0.026$). Finally, there was a trend toward an effect of group on the dmPFC ($F_{2,50} = 3.141$, $P = 0.052$), with greater activation in UHR individuals than in FEP ($P = 0.047$) (Figure 3).

Associations between subjective arousal ratings and activation to neutral pictures.

There was a positive correlation within the UHR group between activation in the left amygdala and arousal ratings to neutral pictures ($r = 0.531$, $P = 0.023$). In the FEP group, activation in the left IFG/aINS was associated with arousal ratings to neutral pictures ($r = 0.577$, $P = 0.024$). These correlations, however, did not survive Bonferroni correction ($P = 0.0125$ because of including four different regions). There were no significant correlations between neural response and subjective ratings to neutral stimuli in the HC group.

Table 2 Random effects analysis for emotional pictures *vs* neutral pictures across groups

Brain area	MNI coordinates			*k*	*Z*	Cluster-level corrected *P*
	x	*y*	*z*			
R superior frontal gyrus	18	46	30	2263	4.73	<0.001
L superior frontal gyrus	−12	48	36		4.45	
L medial frontal gyrus	−4	42	46		4.41	
L precuneus	−24	−82	26	330	3.87	<0.001
L cuneus	−22	−84	18		3.59	
R inferior frontal gyrus	52	36	6	111	3.90	0.053
R middle occipital gyrus	26	−82	14	319	3.70	<0.001
R cuneus	12	−80	18		3.64	
L inferior frontal gyrus/anterior insula	−40	36	2	154	3.64	0.012
R amygdala[a]	24	−6	−16	56	2.56	0.005
L amygdala[a]	−22	−6	−12	20	2.24	0.013

Notes: L, left; R, right.
[a]Within amygdala ROI (small volume correction).

Prediction of Psychotic Symptoms and Functioning

Within the UHR group, dmPFC activation to neutral scenes (*vs* fixation cross) predicted CAARMS positive symptoms ($\beta = 0.546$, $t = 2.232$, $P = 0.044$) and lower GAF scores ($\beta = -0.716$, $t = -2.712$, $P = 0.020$). Within the FEP group, activation of the left IFG/aINS and right amygdala to neutral scenes both predicted PANSS-positive symptoms ($\beta = 0.630$, $t = 2.393$, $P = 0.038$ and $\beta = 0.782$, $t = 3.353$, $P = 0.007$, respectively) (Figure 4).

DISCUSSION

Heightened levels of emotional arousal are widely reported in established schizophrenia, especially in patients presenting with positive psychotic symptoms such as paranoid beliefs (Williams *et al.*, 2004; Haralanova *et al.*, 2012; Llerena *et al.*, 2012). This has been linked to impaired processing of emotional salience (i.e. increased emotional response to non-emotional information) and corticolimbic hyperactivation (Holt *et al.*, 2006; Hall *et al.*, 2008; Seiferth *et al.*, 2008). In this study, we found similar abnormalities in early and prodromal psychosis. Behaviorally, both UHR and FEP groups reported increased subjective emotional arousal to stimuli that were otherwise neutral. At the neural level, across all participants, emotional relative to neutral scenes activated brain regions typically involved in emotional processing, including the dmPFC, left and right IFG/aINS and the amygdala (Kober *et al.*, 2008). For this contrast, in line with findings in patients with schizophrenia, we observed an effect of group by which UHR and FEP patients showed reduced activation in these regions compared with HC. Notably, further examination revealed that this was driven by an underlying hyperactivation of these regions to the neutral comparator condition. In UHR participants, hyperactivation was primarily located in prefrontal and paralimbic brain areas (IFG/aINS and dmPFC), whereas in FEP patients, hyperactivity involved predominantly core limbic regions (right and left amygdala). We speculate that qualitatively different parts of a corticolimbic circuit involved in aberrant emotional salience may be affected according to illness stage. Neuroimaging studies have demonstrated that the dmPFC plays a key role in the cognitive generation of emotional states, is particularly involved in the appraisal/identification of emotion (Drevets and Raichle, 1998; Phan *et al.*, 2002) and is functionally linked to core limbic areas such as the amygdala (Kober *et al.*, 2008). The anterior portion of the insula is involved in the evaluative, experiential or expressive aspects of 'internally generated' emotions (Reiman *et al.*, 1997; Craig, 2002) and is commonly activated in emotional tasks, particularly associated with negative or withdrawal-related emotions (Phan

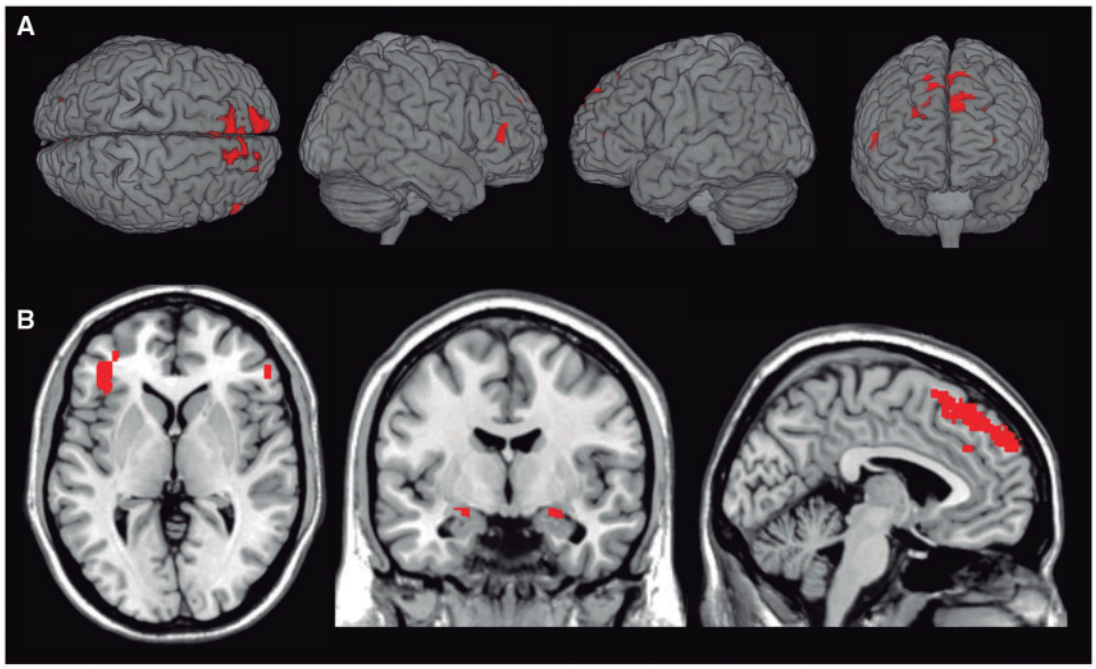

Fig. 2 Results of whole-brain analyses and amygdala ROI analysis of the main effect of Emotional *vs* Neutral contrast across the three groups (FEP, UHR and HCs). Regions are described in Table 2, **(A)** rendered views and **(B)** section views.

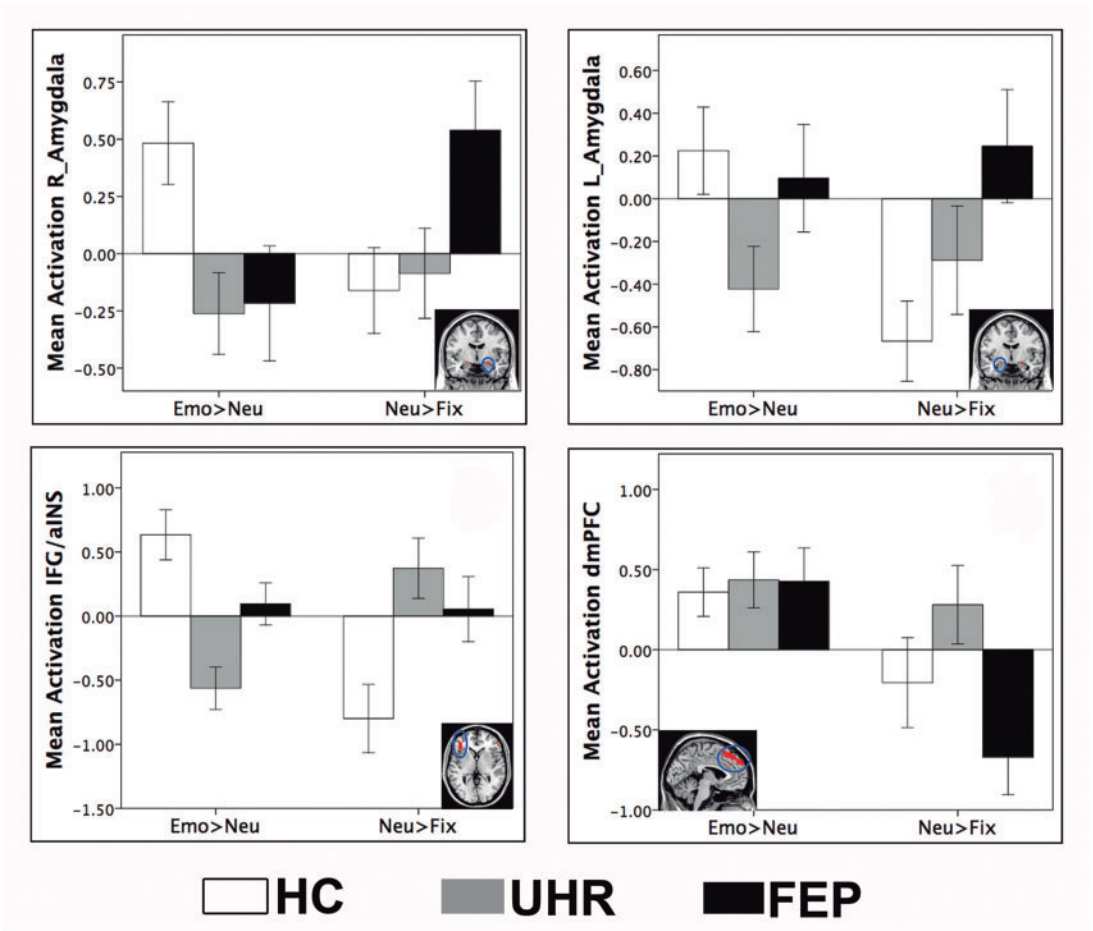

Fig. 3 Main activation clusters ($P < 0.05$ FWE) and parameter estimates (mean and standard error) for each emotional condition (emotional > neutral; neutral > fixation) and group in the voxel with max. *t* value. Mean parameter estimates are shown for voxel [−40 36 2] in the left inferior frontal gyrus/anterior insula, for voxel [18 46 30] in the dmPFC and voxels [24 −6 −16] and [−22 −6 −12], respectively, in the right and left amygdala. AMY, amygdala; IFG/aINS, inferior frontal gyrus/anterior insula; L, left; R, right.

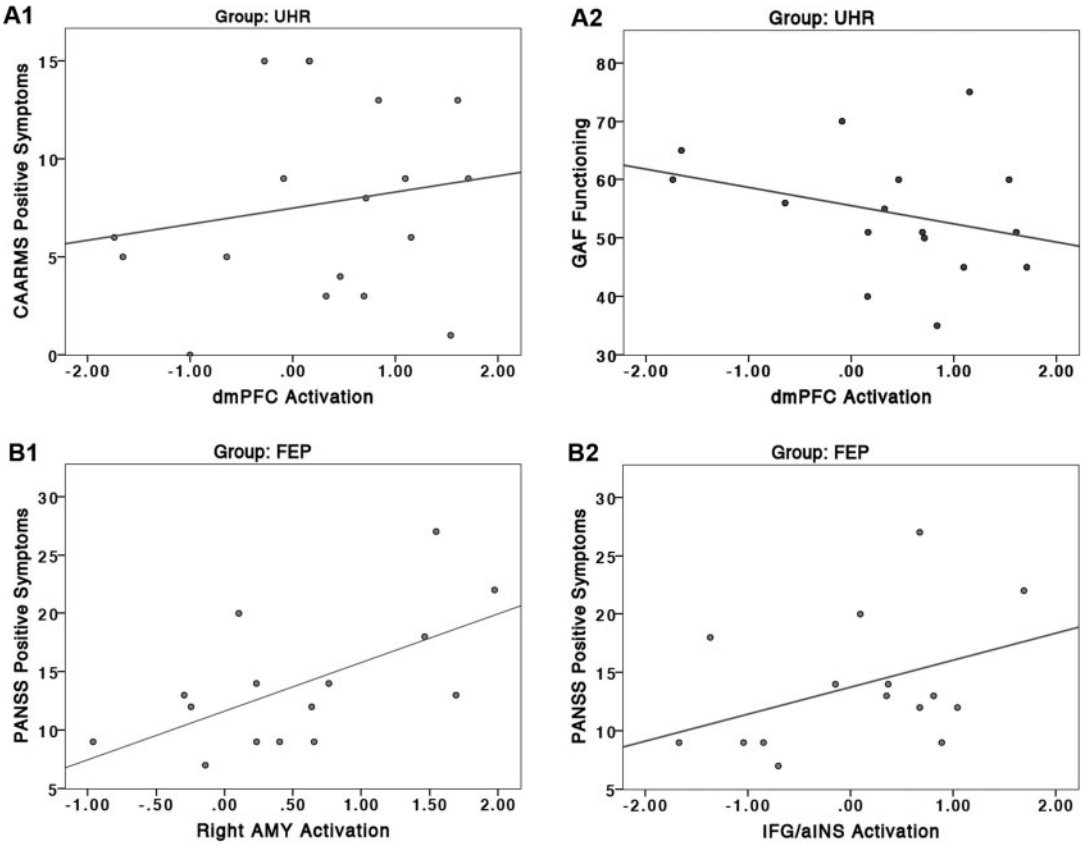

Fig. 4 Scatterplots of (A1) average CAARMS positive symptoms and (A2) average GAF levels of functioning as a function of dmPFC activation in UHR individuals; (B1) average PANSS positive symptoms as a function of right amygdala activation and (B2) as a function of IFG/aINS activation in FEP patients. AMY, amygdala. IFG/aINS, inferior frontal gyrus/anterior insula; L, left; R, right.

et al., 2002, 2004; Kober *et al.*, 2008). The amygdala has a more general role in the processing of emotional salience or attributes that make stimuli emotionally meaningful (Lang *et al.*, 1993; Davis and Whalen, 2001). Interactions between these corticolimbic regions are thus important for the experience, assignment and cognitive generation of emotional arousal (Augustine, 1996; Craig, 2002). In this study, aberrant emotional salience in UHR subjects engaged areas involved in more cognitive, evaluative and regulatory aspects of emotion. After a first episode of psychosis, our results indicate that aberrant emotional salience is associated with brain regions involved in more basic detection of emotionally relevant stimuli. Overall, we argue that our results suggest that the neural correlates of abnormal salience may involve different corticolimbic areas depending on illness stage. This needs to be systematically investigated with a longitudinal study paradigm, scanning UHR individuals before and after transition to psychosis, to inform changes in corticolimbic regions and how these are linked to psychosis onset and to remission of the UHR state.

Importantly, we observed an association between neural abnormalities during aberrant emotional salience and subjective experience, psychotic symptoms and global functioning, demonstrating a link with clinical features of the illness. Although widespread deficits in emotional processing (Phillips and Seidman, 2008; Green *et al.*, 2012) and social functioning (Horan *et al.*, 2012; Valmaggia *et al.*, 2013) have been documented in FEP and UHR cohorts, as well as corticolimbic hyperactivation to neutral stimuli has been reported in independent studies on chronic schizophrenia (Holt *et al.*, 2006; Surguladze *et al.*, 2006; Hall *et al.*, 2008), UHR (Seiferth *et al.*, 2008) and FEP cohorts (Bergé *et al.*, 2014), our results provide first evidence that corticolimbic dysfunction may be a key neurobiological mechanism associated with clinical manifestations in the early stages of psychosis. Establishing a link between hyperactivity in regions central to emotional processing and regulation (Phan *et al.*, 2003; Ochsner and Gross, 2005) and psychotic symptoms/functional levels may have important clinical implications. There are a number of training programs showing efficacy in remediating social cognitive deficits in schizophrenia (Wolwer *et al.*, 2005; Horan *et al.*, 2009; Roberts and Penn, 2009), and cognitive-behavioral therapy (CBT) can attenuate brain activation to threatening social stimuli in patients with schizophrenia (Kumari *et al.*, 2011). Such strategies may be beneficial to UHR subjects. UHR individuals and FEP patients may also benefit from future research into novel treatments aimed at down-regulating corticolimbic reactivity such as targeted real time fMRI neurofeedback (Linden *et al.*, 2012; Ruiz *et al.*, 2013, 2014).

Our sample was relatively small and future studies with larger samples are needed to expand these findings. We report statistically significant results from regression analyses testing the impact of neural abnormalities on levels of symptoms and functioning, although caution is warranted in interpreting these findings due to the limited sample sizes (Yarkoni, 2009; Button *et al.*, 2013). However, our results replicate corticolimbic abnormalities that converge with previous imaging studies in schizophrenia with both similar (Taylor *et al.*, 2005, 2007; Holt *et al.*, 2006; Surguladze *et al.*, 2006; Hall *et al.*, 2008) and larger samples (Dowd and Barch, 2010). The same applies to the correlation analysis of associations between antipsychotic drug use and activation. Ten of the 15 FEP patients were receiving antipsychotic medications. Although antipsychotic administration has been reported to contribute to alterations in brain volume and neural activation in patients with schizophrenia (Abbott *et al.*, 2013; Fusar-Poli *et al.*, 2013b),

the reported effects on fMRI activation referred to executive and mnemonic functions (Fusar-Poli *et al.*, 2007) and to resting-state activation (Lui *et al.*, 2010). Furthermore, dysfunctions in corticolimbic regions involved in emotional processing have been reported previously in antipsychotic-naïve UHR and FEP subjects (Seiferth *et al.*, 2008; Bergé *et al.*, 2014) and are unaffected by antipsychotic therapy (Reske *et al.*, 2007). In this study, neural activity in regions showing significant group effects did not correlate with antipsychotic dose (see Supplementary Material), and the group effect in these regions was also seen in the (medication naïve) UHR sample. In addition, we collected level of education and premorbid IQ from our participants and covaried for IQ in our fMRI analysis, but we did not have access to parental education or socio-economic status. To our knowledge, there is no evidence that these factors significantly affect emotional experience, and impairments in the ability to judge emotions (or the intensity of the emotions) depicted by visual stimuli are typically selective and present despite normal general intelligence, perception and language (Coan and Allen, 2007). Finally, it is interesting to consider the potential influence of comorbid affective disorders on imaging studies in the UHR (Fusar-Poli *et al.*, 2014; Modinos *et al.*, 2014). Although information on comorbid Axis I diagnoses was not collected as part of the study, higher severity of anxiety and depressive symptoms was found in the UHR and FEP using a dimensional measure (DASS), consistent with the notion that anxiety and depressive symptoms frequently mark the onset of the initial prodrome of psychosis (Hafner *et al.*, 1999). Future research with larger samples able to stratify the UHR group based on presence/absence of comorbidity should expand these findings.

In summary, we found increased emotional arousal to neutral stimuli and hyperactivity in several corticolimbic regions in UHR and FEP individuals. We also observed that these neural changes predict severity of positive symptoms and global functioning. Emotional dysfunction is an important determinant of clinical course and functional outcome in chronic schizophrenia. Our findings expand previous reports that emotional dysfunction and associated neural correlates are perturbed from the earliest manifestations of the disorder and contribute to abnormalities in behavior, functioning and psychotic symptomatology. Future studies are needed to establish whether corticolimbic dysfunction could be targeted as therapeutic focus of new treatments such as real-time fMRI neurofeedback (Linden et al., 2012; Ruiz et al., 2013, 2014), CBT (Kumari et al., 2011), social cognitive skills training (Wolwer et al., 2005; Horan et al., 2009; Roberts and Penn, 2009) or drugs that impact the GABAergic interneuron system to treat affective dysfunction as a complement to anti-psychotic medications (Benes, 2010).

SUPPLEMENTARY DATA

Supplementary data are available at *SCAN* online.

Conflict of Interest

None declared.

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