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Modulation of motivational salience processing during the early stages of psychosis

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ABSTRACT

Background: Deficits in motivational salience processing have been related to psychotic symptoms and disturbances in dopaminergic neurotransmission. We aimed at exploring changes in salience processing and brain activity during different stages of psychosis and antipsychotic medication effect.
Methods: We used fMRI during the Salience Attribution Task to investigate hemodynamic differences between 19 healthy controls (HCs), 34 at-risk mental state (ARMS) individuals and 29 individuals with first-episode psychosis (FEP), including a subgroup of 17 FEP without antipsychotic medication (FEP-UM) and 12 FEP with antipsychotic medication (FEP-M). Motivational salience processing was operationalized by brain activity in response to high-probability rewarding cues (adaptive salience) and in response to low-probability rewarding cues (aberrant salience).
Results: Behaviorally, *adaptive* salience response was not accelerated in FEP, although they correctly distinguished between trials with low and high reward probability. In comparison to HC, ARMS exhibited a lower hemodynamic response during *adaptive* salience in the right inferior parietal lobule and FEP-UM in the left dorsal cingulate gyrus. The FEP-M group exhibited a lower *adaptive* salience response than HC in the right insula and than ARMS in the anterior cingulate gyrus. In unmedicated individuals, the severity of hallucinations and delusions correlated negatively with the insular- and anterior cingulate hemodynamic response during *adaptive* salience. We found no differences in *aberrant* salience processing associated with behavior or medication.
Conclusion: The changes in *adaptive* motivational salience processing during psychosis development reveal neurofunctional abnormalities in the somatosensory and premotor cortex. Antipsychotic medication seems to modify hemodynamic responses in the anterior cingulate and insula.

1. Introduction

Aberrant salience processing has been proposed as a pathophysiological hallmark of psychosis (Kapur, 2003). Positive psychotic symptoms (hallucinations and delusions) result from inappropriate attribution of motivational properties to stimuli, thoughts and percepts (Kapur, 2003). Motivational salience transforms the brain's neutral representations of conditioned stimuli into attractive representations and 'grabs attention' (Berridge and Robinson, 1998). Adaptive motivational salience refers to stimuli with a reliable association with reinforcement and which can therefore influence behavior and attract attention (Roiser et al., 2009). In contrast, aberrant salience refers to stimuli that have no reliable association with reinforcement but come to be attention-grabbing and which inappropriately capture thought- and goal-directed behavior (Jensen and Kapur, 2009). Adaptive and aberrant motivational saliences have been operationalized using a probabilistic reward-learning task, the Salience Attribution Task (SAT) (Roiser et al., 2009). This task can distinguish between the use of relevant cues (*adaptive* salience) and irrelevant cues (*aberrant* salience). In the SAT, *adaptive* motivational salience is defined as the increase in probability ratings (the explicit measure) or acceleration of responses (the implicit measure) to stimuli strongly associated with reward, relative to those weakly associated with reward (Roiser et al., 2009). *Aberrant* motivational salience is defined as the absolute difference in acceleration or probability ratings between the two levels of the task-irrelevant stimulus dimension (Roiser et al., 2009).

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Neuroimaging studies using the SAT have revealed that *adaptive* salience processing and *aberrant* salience processing occur in partially overlapping (Roiser et al., 2010) or even in identical neurocircuits (Roiser et al., 2013). In healthy controls (HCs), cues associated with *adaptive* salience elicited greater activation in the midbrain, thalamus, superior temporal gyrus, insula, ventral striatum and cerebellum (Roiser et al., 2010), with similar effects in individuals with an at-risk mental state (ARMS) (Roiser et al., 2013). Chronic schizophrenia patients exhibited (a) increased *aberrant* salience responses in the striatum, hippocampus and prefrontal regions than with HC (Diaconescu et al., 2011) and (b) lower *adaptive* salience responses in the striatum (Gradin et al., 2013; Grimm et al., 2012), amygdala, hippocampus, and midbrain (Gradin et al., 2013). The only fMRI study on salience processing with ARMS demonstrated elicited *adaptive* salience brain responses in the ventral striatum but did not find differences from HC (Roiser et al., 2013).

Psychotic patients treated with antipsychotics showed behavioral impairments in *adaptive* salience (Roiser et al., 2009), consistent with reinforcement-associated abnormal brain responses in medicated schizophrenia patients (Murray et al., 2008; Waltz et al., 2009). Dopaminergic agonists facilitate (Nagy et al., 2012; Pessiglione et al., 2006), while antipsychotics attenuate motivational salience (Kapur, 2003), leading to undesired effects, e.g. loss of motivation, apathy and anhedonia (Roiser et al., 2009).

In the present study, we focused on hemodynamic responses during motivational salience processing and their relationship to hallucinations and delusions in emerging psychosis. We firstly hypothesized that there were differences in whole-brain activity in ARMS and unmedicated FEP patients (FEP-UM) relative to HCs. Secondly, we expected that antipsychotic-medicated FEP patients (FEP-M) would exhibit lower responses in salience-related brain regions than did patients without current antipsychotic medication (FEP-UM). Thirdly, given the relation between salience processing and positive symptoms (Roiser et al., 2013), we further tested whether salience-related brain activity was related to positive symptoms (hallucinations and delusions) in ARMS and FEP patients.

2. Materials and methods

2.1. Study population

The Early Detection of Psychosis (FePsy), Psychiatric University Clinics in Basel, Switzerland, recruited and followed up ARMS and FEP individuals (Riecher-Rossler et al., 2009). This is an ongoing prospective naturalistic study and all individuals included were assessed for current symptoms at the time of the MRI scan (for details see supplement).

The ARMS (N = 34) individuals were characterized using the Basel Screening Instrument for Psychosis (Riecher-Rössler et al., 2007), identical with the Comprehensive Assessment of ARMS (CAARMS) criteria (Yung et al., 2005): a) "attenuated" psychotic symptoms; b) brief limited intermittent psychotic symptoms; or c) a first-degree relative with a psychotic disorder plus a marked decline in social or occupational functioning. After 33.3 months of clinical follow-up, 6 ARMS individuals transited to psychosis. All but one ARMS individual were antipsychotic-naïve. Eleven of the ARMS individuals were receiving antidepressants.

The FEP patients (N = 29) fulfilled the criteria for acute psychotic disorder according to the ICD-10 or DSM-IV, but not yet for schizophrenia (Yung et al., 1998). The transition to psychosis in ARMS individuals was defined by the CAARMS criteria (Yung et al., 1998). The mean duration of psychosis was 7.76 months (SD = 15.77 months), with an upper limit of 5 years. We divided FEP according to their current status of antipsychotic medication: 17 FEP-UM were without current antipsychotic medication and 12 FEP-M were receiving atypical antipsychotics. Ten of the FEP group (N = 5 in FEP-M) were taking antidepressants.

The 19 HCs, from the same geographical area, had no history of psychiatric or neurological disorder, head trauma, serious illness, or substance abuse, assessed by an experienced psychiatrist.

General exclusion criteria were: history of previous psychotic disorder, psychotic symptomatology secondary to an 'organic' disorder, recent substance abuse according to ICD-10 research criteria, psychotic symptomatology associated with an affective psychosis or a borderline personality disorder, age under 18 years, inadequate German knowledge, and IQ < 70 (measured using the multiple choice vocabulary-intelligence test (MWT-B)). All participants provided written informed consent and received compensation for participating. The local ethics committee approved the study.

2.2. Salience Attribution Task (SAT)

Neural and behavioral responses during motivational salience processing were assessed with the SAT (Roiser et al., 2009, 2010). Participants had to respond quickly to the presentation of a square. Money was available in 50% of trials, with the likelihood of reward in a given trial signaled by one of four categories of cues. The cues varied in two different visual dimensions, with one of these cue dimensions being task-relevant. Participants estimated reward probabilities for each cue-category using visual analogue scales in %.

2.3. Statistical analysis of demographic and behavioral data

Data were analyzed using the Statistical Package for the Social Sciences version 20.0 (SPSS Inc., Chicago, IL, USA). We used one-way analysis of variance (ANOVA) and χ^2 tests for demographic, clinical and behavioral analyses. The Bonferroni correction (at $P < 0.05$) was applied for all post-hoc tests.

2.4. Magnetic resonance imaging acquisition

Participants were scanned using a whole-body 3 T MRI system (Magnetom Verio, Siemens Healthcare, Erlangen, Germany). During the SAT, we acquired T_2^*-weighted echo-planar images (EPIs) with the following parameters: 38 axial slices of 3 mm thickness, 0.5 mm interslice gap, field of view 228 × 228 cm^2 and an in-plane resolution of 3 × 3 mm^2. The repetition time was 2.5 s and the echo time 28 ms.

2.5. fMRI analysis

EPIs were analyzed using Statistical Parametric Mapping (SPM8, www.fil.ion.ucl.ac.uk/spm). Maximum likelihood parameter estimates were calculated at the first level at each voxel using the general linear model. Our design matrix included an autoregressive AR(1) model of serial correlations and a high-pass filter with a cutoff of 128 s. The onsets of each event were convolved with the SPM synthetic hemodynamic response function and its temporal and dispersion derivatives. The first level design matrix included four cue regressors, an outcome regressor and its parametric modulation by magnitude of reward (in Swiss Francs); for more details see Roiser et al. (2010). Only *adaptive* and *aberrant* reward prediction contrasts entered the second-level analyses to identify the main effect of motivational salience and between-group differences, using the summary statistics approach to random-effects analysis.

We used a full factorial ANOVA to compare FEP-M and FEP-UM, ARMS, and HC on the *adaptive* and *aberrant* reward prediction contrasts. For between-group differences, significance was assessed at a cluster-level threshold of $P < 0.05$ FWE corrected across the whole brain, using a cluster-forming threshold of $P < 0.005$ (uncorrected) (Petersson et al., 1999). Effects were visualized in the FMRIB Software Library Viewer and labeled using the incorporated atlas tools. Based on the previously described essential roles of the insula and the anterior cingulate cortex (ACC) in salience processing, along with their

association with positive psychotic symptoms (Palaniyappan and Liddle, 2012), we tested the correlation of the BPRS hallucination and delusion score with activation in the right ACG and the right insula during *adaptive* salience, using Spearman's ρ.

3. Results

3.1. Demographic and clinical characteristics

The groups were well matched for gender, age, handedness, and verbal IQ. There was a significant main effect of group on positive and negative symptoms and global functioning ($P < 0.0001$). FEP-UM, FEP-M and ARMS had more positive, negative psychotic symptoms and worse global functioning than HC ($P < 0.005$). FEP-UM had significantly more positive symptoms ($P < 0.0001$) and worse global functioning ($P = 0.027$) than ARMS (Table 1).

3.2. Behavioral characteristics

There was no main effect of group in the overall ANOVA for *adaptive* (explicit $F(3,78) = 1.478$, $P = 0.227$; implicit $F(3,78) = 1.104$, $P = 0.353$) or *aberrant* (explicit $F(3,78) = 2.186$, $P = 0.096$; implicit $F(3,78) = 1.115$, $P = 0.348$) salience. Each group exhibited significant explicit *adaptive*, and explicit and implicit *aberrant* salience (one sample t tests, $P < 0.0001$). The ARMS ($t(33) = 4.63$, $P < 0.001$) and HC groups ($t(18) = 4.63$, $P < 0.001$) responded significantly more quickly to *adaptive* salience. However, neither the FEP-M group ($t(11) = 0.67$, $P = 0.52$) nor FEP-UM ($t(16) = 1.31$, $P = 0.21$) showed any significant implicit *adaptive* salience (Supplementary Table 6).

3.3. fMRI data

3.3.1. Within-group analyses

Hemodynamic responses of *adaptive*, reverse *adaptive*, *aberrant*, and reverse *aberrant* reward prediction in separate groups are presented in Supplementary Tables 2, 3, 4, and 5.

3.3.2. Between-group analyses

Compared to HC, ARMS had significantly lower hemodynamic responses during *adaptive* salience in the right inferior parietal lobule. FEP-UM exhibited lower responses in the left dorsal cingulate gyrus than HC (Fig. 1, Table 2). Compared to HC, there was less activation in the whole FEP group in the right precentral gyrus and insula.

FEP-M exhibited lower hemodynamic responses than ARMS in the bilateral cingulate gyri and than HC in the right insula (Fig. 2, Table 2). We found hemodynamic responses in the ventral striatum and prefrontal cortex in all included groups. Nevertheless, there was no between-group difference in these motivationally relevant regions.

The FEP-UM group exhibited higher *aberrant* salience responses than HC in the right cuneus. HC exhibited a higher *aberrant* salience response than ARMS and FEP in the left inferior parietal lobule (Supplementary Table 1).

3.3.3. Correlation analyses of positive psychotic symptoms and insular and anterior cingulate activation

The FEP-UM group showed negative correlation between insular activation and hallucinations ($r = -0.643$, $P = 0.005$; survived correction for multiple comparison). If ARMS and FEP-UM were pooled, there was a negative correlation between ACG activation and delusions ($r = -0.245$, $P = 0.013$), but this did not survive the correction for multiple comparison; Fig. 3.

4. Discussion

We explored the neural correlates of motivational salience processing in subjects with an ARMS for psychosis and in FEP patients. Attenuated *adaptive* salience-related responses in the dorsal cingulate cortex were found in unmedicated FEP patients, reflecting psychosis-associated deficits independent of antipsychotic medication. Surprisingly, currently medicated FEP patients showed intact explicit *adaptive* salience in behavior, but attenuated *adaptive* salience-related activation in the right ACC and insular cortex.

Table 1
Demographic and clinical data.

	FEP-M (n = 12)	FEP-UM (n = 17)	ARMS (n = 34)	HC (n = 19)	Statistics	Post hoc
Gender M/F	6/6	13/4	26/8	10/9	$\chi^2(3) = 5.417$ $P = 0.144$	
Mean age in year (SD)	27.42 (7.9)	24.82 (5.7)	24.35 (5.5)	26.42 (4.1)	$F(3,78) = 1.155$ $P = 0.332$	
Handedness non-left/non-left	11/3	16/1	32/2	18/1	$\chi^2(3) = 0.988$ $P = 0.988$	
MWT-B IQ (SD)	105 (20)	103 (12)	113 (15)	113 (10)	$F(3,41) = 1.786$ $P = 0.165$	
BPRS total (SD)	42.75 (14.8)	51.71 (15.5)	39.67 (9.5)	24.53 (1.2)	$F(3,77) = 19.920$ $P < 0.0001$	M > H, U > H, A > H, U > A
BPRS 9	3.00 (1.7)	3.47 (1.4)	2.27 (1.2)	1.00 (0.0)	$F(3,77) = 14.184$ $P < 0.0001$	M > H, U > H, A > H, U > A
BPRS 10	2.50 (2.1)	3.53 (2.0)	1.55 (1.0)	1.00 (0.0)	$F(3,77) = 12.439$ $P < 0.0001$	M > H, U > H, U > A
BPRS 11	3.25 (1.9)	3.71 (1.9)	1.97 (1.3)	1.00 (0.0)	$F(3,77) = 13.645$ $P < 0.0001$	M > H, U > H, M > A, U > A
SusHalDel	8.75 (4.7)	10.71 (4.4)	5.79 (2.4)	3.00 (0.0)	$F(3,77) = 21.238$ $P < 0.0001$	M > H, U > H, M > A, U > A, A > H
SANS total (SD)	17.08 (16.2)	21.82 (14.9)	23.03 (15.2)	0.00 (0.0)	$F(3,75) = 13.036$ $P < 0.0001$	M > H, U > H, A > H
GAF total (SD)	63.50 (10.0)	53.06 (17.94)	64.13 (13.3)	88.63 (4.5)	$F(3,76) = 24.496$ $P < 0.0001$	M < H, U < H, A < H, U < A
Antipsychotic n AN/AF/Med	0/0/12	11/6/0	34/0/0	19/0/0	$\chi^2(6) = 105.967$ $P < 0.0001$	
Antidepressants n (%)	5 (29%)	5 (24%)	11 (31%)	0	$\chi^2(3) = 7.323$ $P = 0.062$	
Alcohol n No/Mod/Uncon	2/6/4	7/9/1	8/17/9	1/14/4	$\chi^2(6) = 9.878$ $P = 0.130$	
Cannabis currently (%)	1 (8%)	7 (41%)	11 (32%)	4 (21%)	$\chi^2(3) = 4.641$ $P = 0.200$	
Smoking (cig/day)	9.42 (18.42)	10.88 (11.5)	7.19 (9.8)	2.47 (5.8)	$F(3,78) = 2.799$ $P = 0.045$	U > H

Bonferroni correction (at $P = 0.05$) was calculated for post-hoc analysis in SPSS 20.0. Abbreviations: Alcohol n, number of subjects consuming alcohol: No, no alcohol; Mod, moderate intake of alcohol; Uncon, uncontrolled drinking; Antipsychotic, antipsychotic medication on the date of MRI: AF, antipsychotic free; AN, antipsychotic naïve; Med, antipsychotic medicated; ARMS, at-risk mental state individuals = A in the Post hoc column; BPRS, brief psychiatric rating scale; BPRS 9, suspiciousness; BPRS 10, hallucinations; BPRS 11, delusions; FEP-M, FEP individuals who were medicated with antipsychotics at the time of testing = M in the Post hoc column; FEP-UM, FEP who were without antipsychotic medication at the time of testing = U in the Post hoc column; GAF, Global Assessment of Functioning; HC, healthy control = H in the Post hoc column; MWT, intelligence quotient test (multiple choice-vocabulary-intelligence test); SANS; SusHalDel, BPRS 9 + BPRS 10 + BPRS 11, sum of suspiciousness, hallucinations, and delusions.

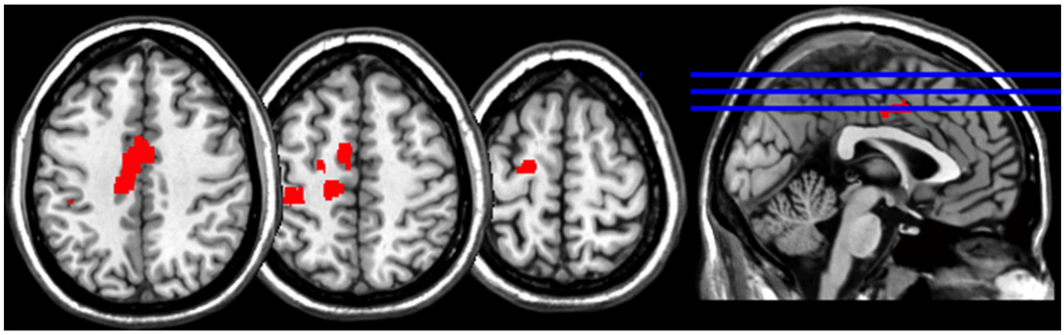

Fig. 1. Brain activation during adaptive salience associated with psychosis. Compared to HC, FEP-UM showed lower reward-related responses in the left dorsal cingulate gyrus (P = 0.005 FWE corrected at cluster level). The image is displayed at a threshold of P = 0.005 uncorrected across the whole brain, and the right side of the brain is displayed on the right side of the figure.

As expected, highly rewarding stimuli elicited responses in a cortico–striatal–thalamic circuit (Ongür and Price, 2000), including the prefrontal cortex, striatum, and thalamus (Roiser et al., 2010). Compared to HC, reduced *adaptive* salience neural activity in ARMS was found in the secondary somatosensory cortex and in FEP-UM in the premotor cortex, and this may contribute to cognitive deficits in early psychosis (Fusar-Poli et al., 2012). The differences in prefrontal and insular activity between the FEP and HC during *adaptive* salience processing correspond with a recent theory proposing that abnormalities in these regions are a key pathophysiological hallmark of psychosis (Palaniyappan and Liddle, 2012). The precentral and insular gyri deficit seen in the whole FEP group was driven primary by the FEP-M subgroup.

Behaviorally, FEP-M and FEP-UM did not respond significantly more quickly to *adaptive* salience, although they correctly distinguished between high-probability-reward trials and low-probability-reward trials. Nevertheless, FEP-M showed additional neural deficits in the insula and ACC during *adaptive* salience, which could be related to the modulatory antipsychotic effect. We did not succeed in confirming *aberrant* salience deficits.

Contrary to previous evidence (Roiser et al., 2009, 2010, 2013) and the reported psychosis-associated neurocognitive impairments (Fusar-Poli et al., 2012), we found no behavioral differences between FEP, ARMS and HC during the SAT. Our negative results might be associated with high within-group variability in motivational salience processing and dopaminergic dysregulation (Howes and Kapur, 2009), as well as with possible schizotypy characteristics (Roiser et al., 2010). Additionally, our HC exhibited higher explicit *aberrant* salience than the previously tested HC (Roiser et al., 2009). Furthermore, in contrast to schizophrenia patients under long-term medication (Roiser et al., 2009), our briefly medicated FEP patients did not perform significantly worse on explicit *adaptive* salience.

Table 2
Between group differences in regional brain activations identified by adaptive reward prediction contrast.

Contrast	Cluster level		Voxel level		Z-score	Hemisphere and region
	$P_{FWE-corr.}$	kE	$P_{FWE-corr.}$	MNI		
ARMS < HC	0.021	710	0.387	56 −32 44	4.05	R supramarginal G
			0.480	36 −40 38	3.96	R supramarginal G
			0.742	56 −24 34	3.74	R IPL
FEP-UM < HC	0.005	935	0.511	−8 −14 42	3.93	L dorsal ACG
			0.849	−22 −10 56	3.63	L MFG
			0.975	−14 −24 50	3.40	L precentral G
FEP < HC	0.034	635	0.863	48 6 20	3.61	R precentral G, IFG
			0.958	54 6 10	3.45	R precentral G
			0.995	32 16 8	3.27	R insula
FEP-M < HC	0.007	881	0.539	38 24 −4	3.91	R insula
			0.807	48 6 20	4.04	R precentral G
			0.918	36 18 8	3.54	R insula
	0.072	527	0.466	18 38 22	3.97	R paracingulate G
			0.581	6 22 32	3.88	R ACG
			0.750	0 32 26	3.73	R ACG
FEP-M < ARMS	0.025	684	0.200	8 40 24	4.26	R paracingulate G
			0.319	−2 32 26	4.11	L paracingulate G, ACG
			0.957	4 50 4	3.46	R paracingulate G

FEP-M < FEP-UM: R insula, kE = 125; MNI 38 26 0; P = 0.072 uncorrected at cluster level.
The data presented here are from ANOVA of 4 included groups (FEP-M, FEP-UM, ARMS, HC) at a threshold of P = 0.005 uncorrected across the whole brain, where whole FEP was FEP-M + FEP-UM. All results with cluster size bigger than 20 voxels are reported.
There were no significant differences in the following contrasts: FEP > HC, FEP-UM > HC, FEP-M > HC, FEP-M vs. FEP-UM, FEP vs. ARMS, FEP-UM vs. ARMS, FEP-M > ARMS, and ARMS > HC.
Abbreviations: CG, cingulate gyrus; G, gyrus; ACG, anterior cingulate gyrus; FEP-M, with current antipsychotic medication FEP; FEP-UM, without current antipsychotic medication; FG, frontal gyrus; IFG, inferior frontal gyrus; IPL, inferior parietal lobule; ITG, inferior temporal gyrus; MFG, middle frontal gyrus; MNI, coordinates x y z according to the Montreal Neurological Institute; MOG, middle occipital gyrus; SFG, superior frontal gyrus; vs., the contrast was made in both directions (> as well as <).

4.1. Adaptive-salience-processing deficits associated with psychosis

The reduced activity in the somatosensory and premotor cortices in ARMS and FEP-UM compared to HC is interesting considering recent research on cognition. The SAT, designed to assess the learning of stimulus–reinforcement associations, comprises multiple cognitive tasks, including tests of sustained attention, maintaining stimulus information, and decision making (Roiser et al., 2010). Finally, these cognitive processes determine participants' motor responses, which are probably mediated by premotor regions (Hanakawa et al., 2008; Radua et al., 2014). Both structural (Exner et al., 2006) and functional changes in the pre-supplementary and supplementary motor areas or premotor cortex have been reported in schizophrenia and linked to deficits in attention, executive function and time perception (Ojeda et al., 2002; Ortuño et al., 2002). These neural deficits may be a part of a dysfunctional cognitive network in early schizophrenia, rather than being specifically related to motivational salience dysfunction (Roiser et al., 2013).

Insular neural responses correlated negatively with the severity of hallucinations in unmedicated FEP patients. These prefrontal neural alterations, together with the known striatal and hippocampal alterations (Roiser et al., 2013), may explain deficits during motivational salience processing. Ventral striatal neural responses were attenuated in chronic schizophrenia patients (Juckel et al., 2006b) and deregulated but not decreased in unmedicated FEP patients (Esslinger et al., 2012). Furthermore, schizophrenia patients exhibited dysregulated but not decreased activation in the frontal insular and anterior cingulate network

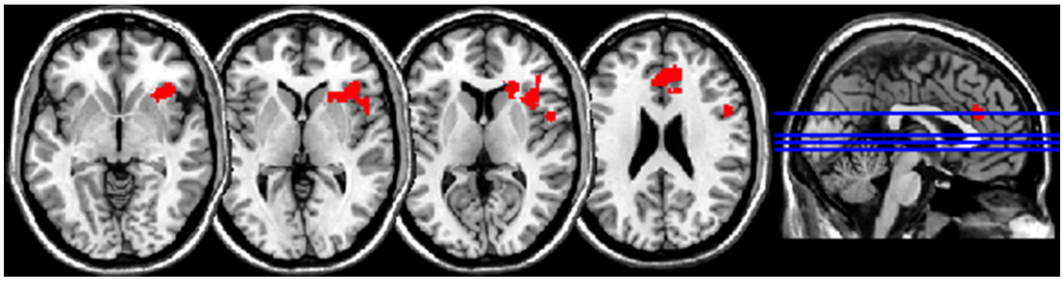

Fig. 2. Brain activation during adaptive salience associated with antipsychotic medication. The FEP-M group compared to the HC, showed attenuated reward-related responses in the right insula (P = 0.007 FWE corrected at cluster level) and the right anterior cingulate (P = 0.072 FWE corrected at cluster level). The image is displayed at a threshold of P = 0.005 uncorrected across the whole brain, and the right side of the brain is displayed on the right side of the figure.

compared to HC (White et al., 2013). In accordance with these differences, our FEP group did not exhibit a lower striatal neural response on whole brain analysis.

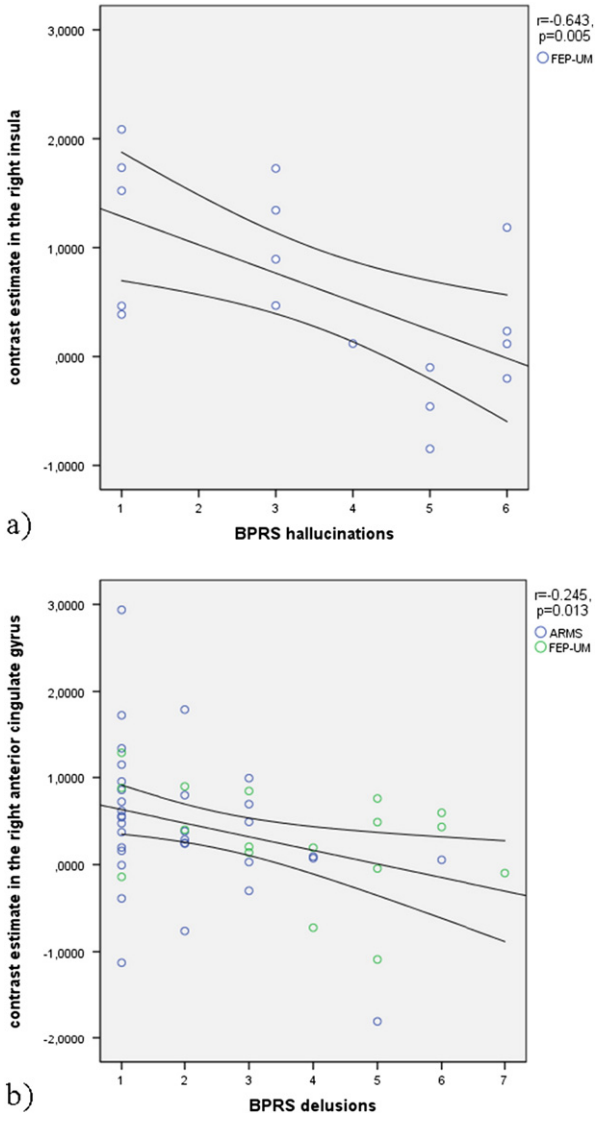

Fig. 3. Relationship between adaptive salience hemodynamic responses and positive psychotic symptoms in unmedicated first-episode of psychosis and at-risk mental state individuals. (a) The adaptive salience hemodynamic response in the right insula (peak voxel 38 24 −4, a 15-mm-radius sphere) correlated negatively with hallucination severity in the unmedicated first-episode of psychosis group. (b) The adaptive salience hemodynamic response in the right anterior cingulate gyrus (peak voxel 10 38 22, a 15-mm-radius sphere) correlated negatively with delusion severity in the unmedicated first-episode of psychosis and at-risk mental state groups.

4.2. Adaptive-salience-processing deficits associated with current antipsychotic medication

In contrast to schizophrenia patients on long-term antipsychotic treatment (Roiser et al., 2009), our briefly medicated FEP patients did not perform significantly worse than HC. However, impaired neural anterior cingulate- and insular-responses were associated with antipsychotic medication. The anterior cingulate seems to be especially sensitive to the antipsychotic effects (Radua et al., 2012; Snitz et al., 2005). Antipsychotic exposure can affect structure and function even in the early phases of psychosis (Ho et al., 2011; Nielsen et al., 2012; Smieskova et al., 2009). Short-term antipsychotic treatment can alter the neurophysiological cortical response during cognitive functioning (Fusar-Poli et al., 2007). These results correlate with 'the final common pathway' hypothesis of psychosis (Howes and Kapur, 2009): both acute antipsychotic administration in HC and chronic antipsychotic medication in schizophrenia patients increase the striatal presynaptic dopamine synthesis capacity (McGowan et al., 2004). Additionally, extracellular dopaminergic levels can be elevated in the striatum (Abi-Dargham et al., 2000) and decreased in the prefrontal cortex in unmedicated schizophrenia patients (Abi-Dargham et al., 2012). Antipsychotics may interfere with salience attribution (Schlagenhauf et al., 2008), although this effect should not be intense, as atypical antipsychotics also influence other neurotransmitters (Juckel et al., 2006a). Furthermore, dopamine dysfunction may be particularly prominent during the very early stages of psychosis (Heinz and Schlagenhauf, 2010). Thus, both of our subgroups, FEP-UM and FEP-M, may have dysregulated prefrontal cortical dopamine levels. However, this conclusion requires testing in longitudinal studies.

Overall, our findings support a model in which antipsychotics target brain areas related to pathophysiology in early psychosis, but do not necessarily suggest that drug treatment causes these alterations (Fusar-Poli et al., 2013; Radua et al., 2012).

4.3. Limitations and future directions

The main limitation of our study is the cross-sectional design. Various factors may have influenced our results, such as different neurocognitive characterizations (Rausch et al., 2013) and profiles of psychotic symptoms in the FEP subgroups; underlying gray matter deficits (Pujol et al., 2013); lack of assessment of the affective state and antidepressants used (Eshel and Roiser, 2010), alcohol (Sullivan et al., 2013), nicotine or cannabis (Charboneau et al., 2013). We acknowledge that different interview measures for prodromal symptoms have been developed that assess either attenuated and/or brief limited psychotic symptoms, or cognitive basic symptoms. Early prodromal states, mainly driven by cognitive basic symptoms, may be insufficiently represented when ARMS is defined as in the present study (Rausch et al., 2013). Additionally, the differences we studied using SAT may also be related to stress and motor learning associated with dopamine release (Winton-Brown et al., 2014). The ARMS group may still contain some individuals

with a later transition to psychosis or those who will fully remit (Simon et al., 2013; Smieskova et al., 2012).

Recent studies have examined task-related integration among motivational salience-related regions and have found aberrant functional and effective connectivity in schizophrenia patients (Diaconescu et al., 2011; Palaniyappan et al., 2013; White et al., 2010). The differences in focal brain activity found here were probably derived from dysfunctional connections to other task-related regions, and this should be addressed in connectivity studies (Ham et al., 2013; Moran et al., 2013; Orliac et al., 2013; Schmidt et al., 2013; Wotruba et al., 2014). Additionally, salience network activity also plays an important role in other psychiatric diagnoses (Balthazar et al., 2014; Connolly et al., 2013; Day et al., 2013; Doll et al., 2013; Pannekoek et al., 2013a,b; Uddin et al., 2013).

4.4. Conclusion

We examined motivational salience processing in ARMS and both medicated and unmedicated FEP individuals, in comparison to healthy controls. Our findings revealed reduced *adaptive* salience-related hemodynamic responses in the anterior cingulate and insular cortex in relation to psychosis, collaterally with modulation in these regions by antipsychotic treatment. To disentangle whether abnormal functional activity during salience processing is disease- or treatment-related, longitudinal studies are needed — both before and after transition to psychosis and before and after treatment with antipsychotics.

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Contributors

Authors contributed to the manuscript as follows:

Renata Smieskova undertook the literature searches, MRI measurements and statistical analyses, and wrote the first draft of the manuscript.

Jonathan Roiser designed and programmed the paradigm and scripts to extract data, and supervised the writing of the manuscript.

Christopher Chaddock contributed to the extraction and statistical analysis of the data.

André Schmidt revised the manuscript, commented on statistical analysis, and improved the writing.

Fabienne Harrisberger provided MRI measurements and helped with pre-processing of the data.

Kerstin Bendfeldt contributed to the neuroimaging analysis and to the presentation of the results.

Andor Simon and Anna Walter provided clinical and demographic tests and recruited the patients.

Paolo Fusar-Poli critically reviewed and extensively commented on the first draft of the manuscript.

Anita Riecher-Rössler supervised the FePsy study and recruitment of included patients, and critically revised the manuscript.

Stefan Borgwardt managed the study and supervised writing of the manuscript.

All authors contributed to and have approved the final manuscript.

Conflict of interest

All authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.schres.2015.04.036.

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