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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 $\chi^2$ 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