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Validating the construct of aberrant salience in schizophrenia — Behavioral evidence for an automatic process

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ABSTRACT

Suspecting significance behind ordinary events is a common feature in psychosis and it is assumed to occur due to aberrant salience attribution. The Salience Attribution Test (SAT; Roiser et al., 2009) measures aberrant salience as a bias towards one out of two equally reinforced cue features as opposed to adaptive salience towards features indicating high reinforcement. This is the first study to validate the latent constructs involved in salience attribution in patients. Forty-nine schizophrenia patients and forty-four healthy individuals completed the SAT, a novel implicit salience paradigm (ISP), a reversal learning task and a neuropsychological test battery. First, groups were compared on raw measures. Second and within patients, these were correlated and then used for a principal component analysis (PCA). Third, sum scores matching the correlation and component pattern were correlated with psychopathology. Compared to healthy individuals, patients exhibited more implicit aberrant salience in the SAT and ISP and less implicit and explicit adaptive salience attribution in the SAT. Implicit aberrant salience from the SAT and ISP positively correlated with each other and negatively with reversal learning. Whereas explicit aberrant salience was associated with cognition, implicit and explicit adaptive salience were positively correlated. A similar pattern emerged in the PCA and implicit aberrant salience was associated with negative symptoms. Taken together, implicit aberrant salience from the SAT and ISP seems to reflect an automatic process that is independent from deficient salience ascription to relevant events. Its positive correlation with negative symptoms might reflect motivational deficits present in chronic schizophrenia patients.

1. Introduction

The notion that psychosis is characterized by an increased focus on irrelevant stimuli is the common ground of prominent psychosis theories (Nelson et al., 2014), ranging from Kamin blocking (Jones et al., 1992) and latent inhibition (Gray et al., 1992) to aberrant incentive salience (Heinz, 2002; Kapur, 2003). The attribution of aberrant subjective meaningfulness to irrelevant events was linked with disturbances in striatal dopaminergic prediction error signals (Heinz and Schlagenhauf, 2010). Since a heightened dopaminergic state in the striatum is one of the most consistent neurobiological findings in schizophrenia (Howes et al., 2012), aberrant salience attribution as the mediating mechanism between neurobiology and symptoms has received a lot of attention in the field (Howes and Murray, 2014; Winton-Brown et al., 2014).

Despite the theoretical impact of the aberrant salience hypothesis on schizophrenia research, valid task measures of aberrant salience attribution to irrelevant events are still lacking. So far, most of the evidence for the aberrant salience hypothesis has been rather indirectly derived from reinforcement learning studies reporting blunted response patterns for cues associated with reward in patients (Jensen et al., 2008; Murray et al., 2008; Romaniuk et al., 2010). However, since task irrelevant aspects were not targeted in the respective studies blunted responses could reflect reinforcement learning deficits due to impaired encoding of reward-predicting cues and/or

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prediction errors in schizophrenia (Deserno et al., 2013; Juckel et al., 2006; Waltz and Gold, 2015) rather than aberrant salience. This crucial dissociation between deficient reinforcement learning and salience attribution to non-relevant events was addressed by the Salience Attribution Test (SAT; Roiser et al., 2009). In this learning paradigm, adaptive salience is reflected in the appropriate representation of reinforcement contingencies, whereas a bias towards one out of two equally reinforced cue features serves as the aberrant salience measure. Both salience scores are measured implicitly via reaction times and explicitly via rating scales. Schizophrenia patients failed in guiding their behavior by the relevant associations as reflected in decreased adaptive salience SAT scores (Pankow et al., 2015; Roiser et al., 2009; Schmidt et al., 2016; Smieskova et al., 2015). For aberrant salience SAT scores, the literature is less consistent. The original publication reported increased explicit salience ratings for irrelevant events in patients with delusions compared to those without delusions, but not on the implicit level (Roiser et al., 2009). However, in a previous study, we found increased implicit and no explicit aberrant salience differences in mostly chronic schizophrenia patients (Pankow et al., 2015). In addition, another recent study using the SAT in schizophrenia patients did not find any group differences for first-episode patients in aberrant salience (Smieskova et al., 2015). Even though this ambiguity in results might in parts be driven by heterogenic sample characteristics, it questions whether the SAT is a valid measure of the construct of aberrant salience in its target group of schizophrenia patients.

In our present study, we focused on the following research questions regarding behavioral measures of aberrant salience in schizophrenia patients. First, since previous results pointed towards unrelated latent constructs for implicit and explicit aberrant salience (Roiser et al., 2009; Schmidt and Roiser, 2009), we wanted to explore whether it is either a consciously accessible process driving explicit misjudgments or whether it is an unconscious process, implicitly guiding motivational behavior. Second, we probed whether aberrant salience interfered with appropriate salience attribution or has to be considered as an independent process. Neurobiological findings from studies investigating the role of dopamine pointed in both directions as dopamine agonists increased adaptive and aberrant salience attribution in Parkinson's disease patients (Nagy et al., 2012), but only implicit aberrant salience correlated positively with ventral striatal presynaptic dopamine release in healthy individuals (Boehme et al., 2015). Third, investigating the associations between salience attribution and learning and cognition in schizophrenia patients would help to disentangle salience attribution effects from deficits in various cognitive domains that may be required for performing the SAT as well as the newly introduced Implicit salience paradigm (ISP). While cognitive functions are known to be progressively impaired in schizophrenia (Green and Harvey, 2014; Meier et al., 2014) the SAT requires tracking the relevant reinforcement associations, quick response adaptations and verbalizing the contingencies in probability space, all of which certainly require reinforcement learning and memory abilities, visuomotor and processing speed, flexibility and intelligence. Lastly, the relationship between SAT aberrant salience and psychopathology remains unclear. In theory, aberrant salience is strongly related to psychosis but the SAT literature points towards a relation with negative symptoms possibly due to false negatives in prediction error signaling leading to stimulus devaluation (Roiser et al., 2009). In line with this idea, blunted ventral striatum activation elicited by reward-predicting cues hypothetically due to increased noise correlated with negative symptoms in unmedicated schizophrenia patients (Juckel et al., 2006).

This is the first study to investigate the construct validity of aberrant salience attribution using the SAT and a novel implicit salience paradigm (ISP) in schizophrenia patients. In a first step, we compared 49 schizophrenia patients to 44 healthy controls in their SAT and ISP performance. We then aimed to investigate construct validity of salience attribution from the SAT and ISP in schizophrenia by carrying out correlation analyses accompanied by PCA for salience and cognition measures. Based on the literature (Pankow et al., 2015; Roiser et al., 2009), we expected patients to show increased implicit aberrant and decreased implicit as well as explicit adaptive salience scores compared to healthy controls. We further predicted positive correlations between implicit aberrant salience from the SAT and ISP. Based on the component structure reported in healthy individuals (Schmidt and Roiser, 2009), we expected no correlations between implicit and explicit aberrant salience and none between aberrant and adaptive salience. We hypothesized that implicit aberrant salience would be associated with psychopathology.

2. Materials and methods

2.1. Participants

Forty-nine schizophrenia patients and 44 healthy controls participated in the present study. Patients met the criteria of the ICD-10 diagnosis for schizophrenia (First et al., 2002). Psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) (see Table 1). At the time of testing, fifteen patients were unmedicated, one was taking first-generation antipsychotics and 33 were taking second-generation antipsychotics (see section 1 in the Supplement). Healthy controls were recruited via mailing lists and online advertisement. They had no axis 1 diagnosis and did not report any past or present neurological or psychiatric illness, or past or current harmful substance use (assessed by the Structured Clinical Interview for DSM Disorders (First et al., 2002)). All participants gave written informed consent to the study and received monetary compensation for their study participation. The study was approved by the local Medical Ethics Committee. SAT scores for 24 healthy individuals and 16 schizophrenia patients overlapped with published data (Boehme et al., 2015; Pankow et al., 2015).

2.2. Cognitive assessment

2.2.1. Salience attribution test (Roiser et al., 2009)

In each trial of this computer-based learning paradigm, participants saw cues preceding a probe that they had to respond to by button press. Then, they received feedback about the amount of money gained. Participants were instructed that available reinforcement depended on the preceding cue features and that they could increase their wins by rapid reaction times (RT). The whole experiment consisted of two blocks of 84 trials. Following each block, explicit salience measures were assessed when participants were instructed to rate each cue feature's likelihood of reinforcement on a visual analogue scale (0–100%). Crucially in this design, the cues varied in color and type (red vs blue and animals vs household objects), whereas only one of these features (e.g., color) predicted the reward (e.g., 87.5% reinforcement of red cues vs 12.5% reinforcement of blue cues). The other feature (here, type) did not predict reinforcement since both manifestations were equally reinforced (50% for objects and animals). The difference in RT (implicit, in milliseconds) or VAS ratings (explicit, in mm) between high-reinforced and low-reinforced cue trials (here, red minus blue cues) reflected adaptive salience, whereas the absolute difference between RTs/VAS ratings of the irrelevant feature (here, |household objects − animals|) reflected aberrant salience. Both relevant and reinforced features were balanced across subjects. Aberrant salience scores were square root transformed in order to reduce skewness in distribution. All salience scores were collapsed across blocks.