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

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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.

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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...
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 I 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.
2.2.2. Implicit salience paradigm (ISP)

We developed the novel Implicit Salience Paradigm to assess aberrant salience implicitly during classical conditioning. In the ISP, one out of four conditioned cues (grey and colorful squares and triangles) were followed by an outcome (coin or circle) (see Fig. 1A). Similarly to the SAT, conditioned cues varied on relevant and irrelevant dimensions: color and shape (grey vs colorful and triangle vs square, see Fig. 1B). Differing from the SAT, participants were not instructed on the contingency between cues and outcomes. Instead, they were only told to perform target detections for the outcomes. The task structure also differed from the SAT since there were several reversals within the reinforced condition and one reversal within the extradimensional condition (e.g., first block shape, second block color relevant). As in the SAT, mean individual absolute RT differences for the irrelevant extradimensional (here, colorful cues – grey cues) for the first block) reflected aberrant salience and were collapsed across both blocks. They will be referred to as Implicit aberrant salience (ISP) in the following. For further description of the paradigm, please see Fig. 1.

2.2.3. Reversal learning task (Boehme et al., 2015)

This paradigm is a probabilistic reinforcement task that contained forced-choice trials in a dynamically changing environment. Participants chose one out of two different gaming cards and either won or lost ten Cents. The contingencies of the two stimuli were perfectly anti-correlated (80:20). There were 160 trials in total and the reversal of contingencies happened after trial 55, 70, 90, 110 and 125 anti-correlated (80:20). There were 160 trials in total and the reversal of contingencies happened after trial 55, 70, 90, 110 and 125 (positive, negative and general pathology) as predictors.

For short-term memory, we used the word list delayed recall (Morris et al., 1989) and the digit span backward test (Wechsler, 2008) for working memory. Speed of processing was operationalized with the Digit Symbol Substitution Test (DSST; Wechsler, 2008), visuomotor speed with the Trail Making Test-A and cognitive flexibility with the Trail Making Test-B (TMT; Reitan, 1955). For verbal intelligence, the verbal intelligence test (Schmidt and Metzler, 1992) was used.

2.3. Analysis

Statistical Analysis was carried out by using Statistical Program for Social Sciences, version 23 (SPSS; IBM Corp, 2013). For all tests, significance threshold was $p < 0.05$, two-tailed if not reported otherwise.

2.3.1. Group comparisons of task scores

To test for group differences on cognitive and salience measures between healthy controls and schizophrenia patients, $t$-tests for independent samples were applied.

2.3.2. Correlation analyses and PCA

In the patient group, Pearson's correlations were used in order to investigate associations between SAT and ISP performance as well between these salience and cognition measures. To further underpin this correlational analysis and in line with previous component analyses in healthy individuals (Schmidt and Roiser, 2009), we additionally attempted to identify potential underlying latent components using PCA with promax rotation ($kappa = 4$) in patients including all scores described in Table 2 (see Supplement Section 2). Nevertheless, we have to caution that due to limited sample size this analysis might overestimate the associations between measures. Therefore, we only interpreted these results with regard to the observed zero-order correlation scores. Based on the resulting pattern of correlations and underpinned by the PCA solution, we calculated a sum score for implicit aberrant salience. In a linear multiple regression, this aberrant salience score was used as dependent variable with the three PANSS scores (positive, negative and general pathology) as predictors.

### Table 1

Demographic measures.

|                      | Healthy controls ($n = 44$) | Schizophrenia patients ($n = 49$) | Statistics          |
|----------------------|-----------------------------|-----------------------------------|---------------------|
| Age (years)          | 33.7 (± 8.3)                | 35.10 (± 8.5)                     | $t(91) = 0.803$, $p = 0.424$ |
| Gender               | 19 females                  | 17 females                        | $\chi^2(1) = 0.704$, $p > 0.401$ |
| Duration of illness  |                             |                                   |                     |
| (years)              |                             |                                   |                     |
| Age of onset (years) |                             |                                   |                     |
| PANSS positive       |                             |                                   |                     |
| PANSS negative       |                             |                                   |                     |
| PANSS general        |                             |                                   |                     |
| PANSS total          |                             |                                   |                     |

**Fig. 1.** A) Implicit salience paradigm. Instructed like a target-detection task, participants saw one out of four cues (grey and colorful triangles and squares, see B)) that was followed by a coin (10 cents) representing reward or a blue circle representing a neutral outcome. The task was to respond to the outcome by pressing the assigned button. In a dynamic design, either the shape of the stimulus or the color probabilistically predicted the outcome (e.g., for extra-dimensional relevance of shape: 80% reinforcement for triangles and 20% for squares and this intra-dimensional association reversed every 20 trials). Whilst at the same time, the other extra-dimension (e.g., color) was irrelevant (50% reinforcement following colorful and grey cues). The extra-dimensional relevance reversed after the first half of trials (e.g., trial 1–80 shape relevant, trial 81–160 color relevant). The order of relevant features and reinforced manifestations was balanced across participants. They were told not to pay attention to the preceding cues. But in order to prime the implicit categorization of color and shape, participants were asked to verbally describe the cues before a training session (20 trials) that only used one cue not appearing in the main experiment.
3. Results

3.1. Task performance

Group comparisons for task performance are displayed in Table 2. Compared to healthy controls, schizophrenia patients showed increased implicit aberrant salience and decreased implicit as well as explicit adaptive salience on the SAT. In the novel ISP, patients also displayed increased implicit aberrant salience scores compared to healthy controls. In reversal learning, patients chose the correct option less often than healthy controls. In the neuropsychological test battery, patients performed worse than healthy controls. Explorative analysis found no consistency between the bias towards one of the two irrelevant stimulus features for implicit and explicit aberrant salience measures in the SAT (see Supplement Section 3).

3.2. Correlations between salience and cognitive measures

We investigated the relationships between task and cognition measures to reveal latent constructs of salience attribution. Regarding implicit aberrant salience, the respective measures from the SAT and ISP were positively correlated. Both also correlated negatively with reversal learning. Further, the ISP measure was negatively correlated with short-term memory, speed of processing and verbal intelligence. There was no significant correlation between implicit and explicit aberrant salience measures. Moreover, aberrant and adaptive salience measures were not correlated, but implicit and explicit adaptive salience were positively correlated. Both explicit salience measures revealed positive associations with cognition: aberrant salience with speed of processing, visuomotor speed and cognitive flexibility and adaptive salience with speed of processing and verbal intelligence. For associations regarding reversal learning and neuropsychology please see Table 3.

A very similar pattern appeared, when taking into account the four components that emerged from the PCA: Cognitive speed/aberrant report, general cognitive ability, implicit aberrant salience attribution and adaptive salience attribution (see Table 4).

3.3. Multiple regression of implicit aberrant salience to PANSS scales

Based on the zero-order correlations and underpinned by PCA solution, interindividual sum scores reflecting implicit aberrant salience (containing z-standardized implicit aberrant salience from SAT and ISP and reversal learning) were calculated and subjected to a multiple linear regression with the three PANSS scales as predictors. This model accounted for 17% of the variance ($R^2 = 0.431; t = 2.11; p = 0.046$), whereas only negative symptoms predicted implicit aberrant salience significantly ($F = 0.310; p = 0.002$).

4. Discussion

In this study, we provide first evidence for the construct validity of the Salience Attribution Test (Roiser et al., 2009) and the novel Implicit Salience Paradigm (ISP) in schizophrenia patients. Patients displayed increased implicit aberrant salience and decreased implicit and explicit adaptive salience compared to healthy controls. Focusing on correlations in the patient group, we found aberrant and adaptive salience attributions to be distinct processes. For aberrant salience,
implicit reaction time based and explicit self-report measures were not correlated. With regard to associations with psychopathology, implicit aberrant salience correlated with the severity of negative symptoms.

Implicit aberrant salience on both tasks was increased in patients and there were no associations between aberrant and adaptive salience. This suggests, that aberrant salience does not result from deficient salience attribution to relevant events as one could have expected. Instead, it should be treated as a distinct and rather automatic construct. Its implicit characteristic is illustrated by the absence of correlations with explicit salience and further by the fact that the ISP in which patients showed increased scores did not contain explicit instructions about contingencies between cues and outcomes. Here, several reversals inside the relevant and irrelevant dimensions may account for associations with cognition that were not present for the SAT measure where contingencies were kept constant. The negative correlation between implicit aberrant salience and reversal learning implies that patients with a stable bias towards one specific task-irrelevant cue feature were impaired in flexible behavior during instrumental reversal learning.

In line with findings in healthy individuals (Schmidt and Roiser, 2009), implicit and explicit aberrant salience measures were not correlated and loaded on different components in schizophrenia patients. This indicated that the conscious report of what patients thought to have learned during the task and their actual motivational behavior in terms of response speeding was not consistent. The same pattern emerged when taking into account directed aberrant salience measures from the SAT that reflect whether the same out of two irrelevant features was favored implicitly and explicitly. Thus, explicitly favoring one cue feature did not capture the implicit learning history and might rather reflect a momentary idiosyncratic report. The latter may rely on cognitive resources indicated by explicit aberrant salience correlating positively with cognitive speed and flexibility variables. This pattern may explain why - unlike in at-risk mental state subjects (Roiser et al., 2013) - explicit aberrant salience was not increased in our cognitively more impaired sample.

The SAT also probes adaptive salience to relevant events and this measure may be more closely transferrable to previously reported learning deficits in schizophrenia (Jensen et al., 2008; Murray et al., 2008; Romanik et al., 2010). In line with previous patient studies (Roiser et al., 2009; Schmidt et al., 2016; Smieskova et al., 2015), patients misjudged the reinforcement contingencies of the relevant cue features. Contrary to aberrant salience, salience attribution towards task relevant cue features may be consciously accessible as implied by strong correlations between implicit and explicit adaptive SAT scores.

Supporting its clinical relevance and in line with previous results (Roiser et al., 2009), a composite measure for implicit aberrant salience correlated with negative symptoms in our sample of chronic schizophrenia patients. However, in less chronic patients as well as in ultrahigh risk subjects implicit aberrant salience was not increased (Roiser et al., 2009, 2013; Smieskova et al., 2015). In these groups, the delusional mood presumably caused by aberrant salience experience (Heinz, 2002; Kapur, 2003) may be more prominent than in our sample. Here, effects of neuroleptic medication on negative symptoms and their neurobiological correlates remain to be further explored (Heinz et al., 1998; Heinz and Schlaughauf, 2010).

By task design, implicit aberrant salience as a mean RT difference reflects a stable bias towards one irrelevant cue feature. However, it does not capture continuous switching between features, even though this more dynamic kind of aberrant salience may rely on the proposed mechanism of chaotic dopaminergic prediction error activity related to psychosis (Heinz and Schlaughauf, 2010). In order to assess this process, dynamic trial-by-trial analyses are warranted using computational methods (Adams et al., 2016) and indeed, high switching was found in severely psychotic patients (Schlaughauf et al., 2014). In contrast, the stable irrelevance bias from the SAT may represent a secondary effect to chaotic aberrant salience by rigidly having to hold on to some strategy in a complex situation. Notably, this bias resembles perseveration errors in the Wisconsin Card Sorting Test that also correlated with negative symptoms (Nieuwenstein et al., 2001). Thus, perseveration towards cues that only randomly lead to reinforcement might contribute to decreased motivation and apathy.

Limitations of our study include that first our salience measures were narrowed down to motivational aspects and future studies might include salience in sensory processing and novelty (Winton-
Brown et al., 2014) as well as the phenomenological experience via self-reports (Cicero et al., 2010). Second, our PCA results should be interpreted with caution due to the limited sample size. Third, more fine-grained measure of negative symptoms should be considered by future studies on aberrant salience (Hartmann-Riemer et al., 2015). Fourth, our cross-sectional results require longitudinal data to explore parallel alterations in aberrant salience and symptoms as indicated by varying neurobiological deficits for different illness stages (Krystal and Anticevic, 2015).

To conclude, we provide first evidence for the construct validity of an automatic aberrant salience process in schizophrenia patients that does not rely on deficiencies in appropriate relevance attribution. In a stable environment as in the SAT, aberrant salience is also independent of cognitive impairment. Interestingly, aberrant salience correlated with negative rather than positive symptoms. We explain this by the perseveration-like characteristic of the SAT measure and its potential effect on motivation and the possible chronicization of the construct in our sample. To further explore these findings, studies are required for assessing illness phase-specific alterations using dynamic salience definitions.

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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.socg.2016.10.001.

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