

Decreased value-sensitivity in schizophrenia

Cristina Martinelli^{a*}, Francesco Rigoli^b, Ray J Dolan^{b,c}, Sukhwinder S Shergill^a

^aDepartment of Psychosis Studies, Institute of Psychiatry, Psychology & Neuroscience, King's College London, 16 De Crespigny Park, SE5 8AF, London

^bWellcome Trust Centre for Neuroimaging, University College London, 12 Queen's Square, WC1N 3BG, London

^cMax Planck UCL Centre for Computational Psychiatry and Ageing Research, University College London, WC1B 5EH, London.

Abstract

Pathophysiology in schizophrenia has been linked to aberrant incentive salience, namely the dysfunctional processing of value linked to abnormal dopaminergic activity. In line with this, recent studies showed impaired learning of value in schizophrenia. However, how value is used to guide behaviour independently from learning, as in risky choice, has rarely been examined in this disorder. We studied value-guided choice under risk in patients with schizophrenia and in controls using a task requiring a choice between a certain monetary reward, varying trial-by-trial, and a gamble offering an equal probability of getting double this certain amount or nothing. We observed that patients compared to controls exhibited reduced sensitivity to values, implying that their choices failed to flexibly adapt to the specific values on offer. Moreover, the degree of this value sensitivity inversely correlated with aberrant salience experience, suggesting that the inability to tune choice to value may be a key element of aberrant salience in the illness. Our results help clarify the cognitive mechanisms underlying improper attribution of value in schizophrenia and may thus inform cognitive interventions aimed at reinstating value sensitivity in patients.

Highlights

1. Pathophysiology in schizophrenia has been linked to aberrant value processing, but how value is used to guide behaviour in schizophrenia is unknown.
2. In the context of value guiding decision-making, we found reduced value sensitivity in patients with schizophrenia
3. Reduced value sensitivity was linked with aberrant experiences of value processing affecting patients in daily life
4. Our results clarify value processing deficits in schizophrenia and may thus inform cognitive interventions aimed at reinstating value sensitivity in patients.

1. Introduction

Schizophrenia is a severe mental health condition affecting approximately 1% of the general population worldwide and impacting on individuals, their carers and society (McGrath et al., 2008). It is characterized by a complex clinical profile comprising cognitive deficits, motivational impairments and aberrant perceptual and thought processes. However, its mechanisms remain unknown. One of the most influential accounts of schizophrenia posits that aberrant incentive salience, namely the dysfunctional attribution of value and salience to environmental stimuli underlies the pathophysiology of the illness (Kapur, 2003; Ziauddeen and Murray, 2010). The attraction of this framework is twofold. Firstly, it conceptualizes the saliency deficits connected with the pathology in terms of current psychological theories of motivation and value attribution (Berridge and Robinson, 1998). Secondly, given the well-documented link between value processing and dopamine (Schultz, 2010), it connects established molecular dopaminergic disturbances in schizophrenia to their functional role in reward and incentive salience thereby providing a bridge between the phenomenology and neurobiology of the disorder.

Incentive salience attribution involves assigning value to stimuli and depends on two interrelated aspects: how value is learnt and how it subsequently guides decision-making and behaviour. The former has been object of extensive investigation with evidence showing impaired reinforcement learning in schizophrenia. In particular, patients exhibited aberrant learning of cue-reward contingencies (e.g., Waltz and Gold, 2007; Gradin et al., 2011) and improper prediction-error processing (e.g., Waltz et al., 2011; Morris et al., 2012), namely the mismatch between expected and actual rewards that drives learning. Furthermore, studies showed that such dysfunctions are correlated with neural disturbances in regions with prominent dopaminergic innervation, including the ventral striatum and the substantia

nigra/ventral tegmental area (e.g., Murray et al., 2008; Nielsen et al., 2012; Schlagenhauf et al., 2009), providing support for the hypothesised link between aberrant incentive salience and dopaminergic unbalance.

However, salience attribution also involves how values are used to guide decision-making independently of how these values are learnt. Previous studies have focused on learning (e.g., Averbach et al., 2011), and do not dissociate this from value attribution, consisting in how much value is assigned to the different rewards. Hence the impact of value attribution independent of learning in schizophrenia is still poorly understood. Clarifying this is of particular importance so as to provide a proper quantification of the different facets of aberrant incentive salience in the disorder.

To investigate value-based decision-making in schizophrenia, independently of learning, we used a monetary gambling task (Rigoli et al., 2016a; 2016b; 2016c; 2016d) in which participants were explicitly informed regarding the values associated with different options, thus not requiring any ongoing learning of such values. Note that previous studies on risky decision-making in schizophrenia focused prominently on the Iowa Gambling Task (IGT; Bechara et al., 1994) or the Balloon Analogue Risk Task (BART; Lejuez et al., 2003), which however involve learning of values. Here, we were able to differentiate between three distinct factors underlying value attribution in the task: (i) an individual baseline gambling preference independent of the values at stake; (ii) a gambling preference which is sensitive to the values of the available choice; (iii) a tendency to adapt preference attribution with respect to the contextual availability of rewards (Rigoli et al., 2016a).

In line with proposals of aberrant value processing in schizophrenia, we predicted that patients would show altered value processing even in the absence of learning demands. We thus predicted that patients would show reduced ability to tune their preference attribution

both with respect to the current values at stake and to the contextual long-run availability of rewards. Furthermore, we predicted a likely association between such deficits and aberrant salience traits.

2. Methods and Materials

2.1. Participants

Twenty volunteers with a diagnosis of schizophrenia based on the DSM-IV-TR (American Psychiatry Association, 2000; 18 males; mean age: 41.2) treated with atypical antipsychotic medication and twenty-two healthy controls (19 males; mean age: 40.5) were recruited via local community referrals and advertisement. Individuals were excluded if they had substance abuse within the last 6 months, any significant neurological, physical or learning disability. Controls had no personal or family history of mental illness. All volunteers underwent cognitive assessment; working memory (Digit Span; Wechsler, 1981) and the vocabulary and matrix reasoning scales of the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999). Patients' symptoms severity was assessed using the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1988). Aberrant salience traits were measured using the Aberrant Salience Inventory (Cicero et al., 2010). The study was approved by an appropriate ethical committee, and informed consent was obtained from all participants.

2.2. Risk Task

The task (Figure 1), adapted from Rigoli and colleagues (Rigoli et al., 2016a), was programmed using Cogent 2000, developed by the Cogent 2000 team at the FIL and ICN. The task comprised of 480 trials; each trial consisted of participants selecting between two

monetary options: a fixed amount (i.e., safe option) and a gamble where the potential outcomes were either zero or double the fixed amount. Therefore, both options had equal average expected amount. Participants completed 2 blocks of 240 trials lasting 40 minutes in total; each block was interleaved by 3 breaks to allow for rest. In each block, the amount of the safe option was randomly drawn from a uniform distribution with increments of £0.10. Crucially, the two blocks had a different monetary range: £1-£5 for the safe option in the low-value context and £2-£6 for the safe option in the high-value context. Note that the range difference across the two blocks was minimal to enhance area of overlap and thus statistical power (analyses performed on overlapping amounts). At the start of each block, a panel reminded subjects of the upcoming monetary range. Block order was counterbalanced across all subjects. After a fixed inter-trial interval of 1.5 seconds, each monetary option was displayed on a different side of a 15 inches computer screen. Participants were requested to choose between the left and right option by pressing the corresponding arrow key. After the choice was made, only the selected option remained on the screen for 500 milliseconds. Next, the gained outcome was displayed in the centre of the screen for 1 second. Participants had 3 seconds to give their response; otherwise the words “too late” appeared and they got an outcome of zero. Gamble outcomes and positions of safe and gamble options were pseudorandomised. Before the experiment, all participants were given detailed instructions of task and their understanding was assessed. At the end of the task, one outcome was randomly selected and participants were paid accordingly.

3. Results

3.1. Task Analysis

Task analyses were conducted using the Statistical Package for the Social Sciences Version 21.0 (SPSS 21.0) and MATLAB (2013a). A two-tailed significance level of $\alpha = 0.05$ was adopted for all analyses. Demographic and clinical characteristics are shown in Table 1; significant group differences were found for WASI, Digit Span and Aberrant Salience Inventory.

On average, participants gambled less than 50% of the time (mean = 40.08; SD = 22.85; $t(41) = -2.81, p < 0.01$) with no evidence for group differences ($t(40) = -0.04, p = 0.97$), suggesting that both groups were mildly risk-averse. There was no difference in gambling propensity across the two different value range blocks ($t(41) = 0.85, p = 0.4$) and such difference did not vary across groups ($t(40) = -1.33, p = 0.19$).

Note that a single variable alone varied across trials, namely the trial average monetary amount. Indeed, the amount associated with the certain option was equal to the average amount of the gamble, given that the gamble had a 50/50 probability of obtaining zero or double the certain amount. We estimated the influence of the magnitude of trial monetary amount (i.e., predictor) on risky choice using logistic regression (i.e., dummy coding of 0 for certain option and 1 for gamble). Beta weights associated with the trial monetary amount indicated individuals' preference to gamble with high or low amounts, a tendency we refer to as gambling slope. This was not significantly different from zero across participants ($t(41) = -0.10, p = 0.92$) and was not significantly different across groups ($t(40) = -0.2, p = 0.84$).

We next computed the absolute value of the gambling slope (here referred to as value-sensitivity), indicating the impact of the trial amount on choice, independent of a preference

to gamble with small or large amounts. This quantity captures to the how much preferences are flexibly tuned to the value on offer, an aspect we predicted to be impaired in schizophrenia. In line with predictions, patients were significantly less influenced by reward amounts as they showed a smaller value-sensitivity index (Figure 2; $t(40) = 2.93, p < 0.01$).

In line with previous findings (Rigoli et al., 2016a; 2016b; 2016c; 2016d), a contextual influence was estimated by computing the difference in gambling percentage between low- and high-value contexts for overlapping amounts (i.e., in the £2-£5 range), multiplied by the gambling slope. Positive values for this index capture a propensity for subjects who preferred to gamble with large amounts (i.e., having a positive gambling slope) to gamble more when the same amounts were relatively larger (i.e., in the low-value context), whereas participants who preferred to gamble with small amounts (i.e., having a negative gambling slope) also to gamble more when the same amounts were relatively smaller (i.e., in the high-value context). Overall, participants demonstrated evidence of such a corrected context effect ($t(41) = 2.28, p = 0.03$), but contrary to expectations no group differences were found (Figure 3; $t(40) = 1.52, p = 0.14$), suggesting that patients could make use of long-run reward context to assign value to monetary stimuli. Considering SCZ patients, no correlations were found between value sensitivity and symptoms severity (PANSS negative scale: $r(20) = 0.20, p = 0.39$; PANSS positive scale: $r(20) = -0.22, p = 0.36$) or medication dosage ($r(20) = 0.08, p = 0.75$).

Overall these results indicate that patients show no difference from controls in the different dimensions of risky decision-making that we measured, except for value-sensitivity, which indicated that patients had an inability to tune their choice preference to reward amounts available on a trial.

3.2. Model-based Analysis

We adopted a computational modelling approach to further investigate the differences between groups reported before. We implemented the same computational model as in a previous study (Rigoli et al., 2016) to characterize the computational mechanisms underlying choice behaviour. The model takes the form of a standard mean-variance return account for which the value of an option x corresponds to $V(x) = \text{mean}(x) + \alpha \text{variance}(x)$. This model has three parameters: τ , which implements a (subtractive) normalization of the trial amount associated with the high-value context; α , which determines whether reward variance (i.e., risk) is attractive ($\alpha > 0$) or not ($\alpha < 0$), and which reflects the tendency to gamble dependent on the trial amount; and μ , which determines a baseline propensity to gamble. Taking A as the trial monetary amount (i.e., the certain reward) and χ as an indicator of the low-value ($\chi = 0$) or high-value context ($\chi = 1$), then the value of gambling is $V_{GAMB} = A - \chi\tau + \alpha(A - \chi\tau)^2 + \mu$, the value of the certain option is $V_{CERT} = A - \chi\tau$, with the probability of choosing the gamble given by a sigmoidal choice rule $\sigma(V_{GAMB} - V_{CERT}) = 1/(1 + \exp(-V_{GAMB} + V_{CERT}))$. Using the Bayesian Information Criterion (BIC) scores, we compared this model with simpler versions where one or two parameters were fixed. For both schizophrenia (SCZ) and healthy controls (HC), the full model had a lower BIC (HC: 9760.08; SCZ: 11113.79) than those with gambling slope only (HC: 10903.14; SCZ: 11466.31), average gambling percentage only (HC: 10970.86; SCZ: 11259.97), or the last two parameters together (HC: 9936.22; SCZ: 11165.57), suggesting that all three factors influence participants' behaviour. Based on this model, parameters of the winning model correlated with behavioural measures such that the average gambling percentage correlated with the baseline gambling coefficient μ ($r(42) = 0.57, p < 0.01$), the gambling slope correlated with the value function coefficient α ($r(42) = 0.8, p < 0.01$) and the context coefficient τ correlated with the corrected context effect ($\rho(32) = 0.33, p = 0.03$). No

significant group differences were found for the model parameters (μ : $t(40) = -0.46$, $p = 0.65$; α : $t(40) = -0.77$, $p = 0.45$; τ : $t(40) = 0.02$, $p = 0.98$). However, the absolute value of the coefficient α was significantly larger in HC compared to SCZ ($t(40) = 2.29$, $p = 0.03$). This is consistent with the results reported above given that the parameter α is tightly connected with the gambling slope.

To investigate the influence of previous trial outcome on participants' decision-making, we estimated a logistic regression model of choice including as predictor a dummy regressor whose values were set to one for wins and to zero otherwise. We found no group difference on the estimated betas ($t(40) = 3.36$; $p = 0.4$), suggesting that patients did not show any difference in this regard. To explore the influence on choice of expected value at preceding trial, we estimated a logistic regression with the expected value at the preceding trial as predictor. We found no group differences on the estimated betas ($t(40) = 0.4$, $p = 0.69$).

Overall, the model-based analysis confirms that controls and schizophrenia patients differ with regards to the strength of the influence of the trial monetary amount (here associated with the absolute value of the parameter α on choice), while all other aspects of choice mechanism did not differ.

3.3. Relationship with aberrant salience and cognitive measures

One of our main goals was to investigate the connection between the concept of aberrant salience and value attribution during decision-making under risk. Consistent with a link between these two domains, value-sensitivity was inversely correlated with the scoring on the Aberrant Salience Inventory (Figure 4A; $r(37) = -0.36$, $p = 0.03$). To test for non-linearity in this relationship, we performed a one-way ANOVA on the trait aberrant salience measure with the

quartiles of the value-sensitivity index as factor. This implies that participants (we considered only those who filled the ASI, $n = 37$) were ordered according to their value-sensitivity index and were grouped in four bins (bin one, two and three included 9 participants; bin four included 10 participants). We observed a difference in the aberrant salience levels across the quartile bins (Figure 4B; $F(3,33) = 3.46$, $p = 0.03$), a result driven by a larger aberrant salience score for the first quartile bin compared to the others (first vs second bin: $t(16) = 2.98$, $p < 0.01$; first vs third: $t(16) = 2.71$, $p = 0.02$; first vs fourth: $t(17) = 2.96$, $p < 0.01$; second vs third bin: $t(16) = -0.28$, $p = 0.78$; third vs fourth bin: $t(17) = 0.36$, $p = 0.73$). As both value-sensitivity and the aberrant salience score were significantly different across groups, we ran a mediation analysis using logistic regression with group as the dependent variable and value-sensitivity and the aberrant salience score as predictors. We found the beta weight associated with the aberrant salience score was not significant ($B = 0.09$; $SE = 0.06$; $p = 0.12$) while the beta weight associated with value-sensitivity was ($B = -0.07$; $SE = 0.03$; $p = 0.04$). This indicates that the relationship between group and aberrant salience was mediated by value-sensitivity.

We further observed that value-sensitivity (but not the Aberrant Salience Inventory) correlated with both IQ (Figure 4C; WASI; $r(42) = 0.29$, $p = 0.06$, trend) and working memory (Figure 4D; Digit Span; $r(38) = 0.41$, $p = 0.01$). As all these measures varied across groups (see Table 1), we investigated the contribution of the value-sensitivity index relative to the other measures in differentiating between patients and controls. We thus ran a mediation analysis using logistic regression with group as the dependent variable and value-sensitivity, IQ and working memory score as predictors. We found the beta weights associated with IQ ($B = -0.04$; $SE = 0.02$; $p = 0.12$) and working memory ($B = -0.11$; $SE = 0.1$; $p = 0.26$) were not significant, while the beta weight associated with value-sensitivity

was ($B = -0.07$; $SE = 0.03$; $p = 0.03$). This indicates that the relationship between group and cognitive measures was mediated by value-sensitivity.

Overall, these results indicate that value-sensitivity best discriminated patients from controls since it mediated the impact of aberrant salience score, working memory and IQ on group.

4. Discussion

Neurocognitive models of pathophysiology in schizophrenia emphasize the role of aberrant incentive salience in the illness. This framework has been fruitful in linking dopaminergic disturbance in schizophrenia to motivational and decision-making impairments in value-based learning. However, the mechanisms underlying improper value attribution independent of learning deficits in schizophrenia are still poorly understood. This is important because various facets of value processing need to be investigated in order to provide a composite understanding of when and how aberrant salience is impaired in schizophrenia; especially as the framework fails to delineate the cognitive mechanisms underpinning value misattribution.

Thus, we here investigated the mechanisms underlying value attribution free from learning by comparing the performance of schizophrenia patients and healthy control participants in a gamble task requiring repeated expressions of preference in the absence of learning. Importantly, our task enabled us to measure several components of value attribution under risk (i.e., a gambling tendency independent of the amounts at stake, a gambling preference dependent on the available amounts, a tendency to adapt decision-making to the different contextual availability of rewards) and thus to disentangle the specific mechanisms underlying aberrant incentive salience in the illness.

Patients demonstrated less influence of reward amount on their choices compared to healthy participants. The apparent insensitivity to this information reflects patients' inability to tune value attribution and concurrent decision-making to the variation of rewards in their environment. This finding may help clarifying significant impairments exhibited by patients in everyday life. Insensitivity to values and the inability to tune choices to those values may indeed account for several motivational aberrances, such as the inability to weight the risks associated with maladaptive behaviours, resulting in lack of medical compliance (Rettenbacher et al., 2004) and impulsive behaviour (Ouzir, 2013), or to engage in properly motivated behaviour (Strauss et al., 2014). In addition, a reduced sensitivity to value clarifies the mechanisms of aberrant incentive salience in schizophrenia, proposed as a key drive of both negative (Zauddeen and Murray, 2010) and positive (Kapur, 2003) symptoms. First, insensitivity to value can be potentially implicated in negative symptoms, as it might well result in reduced motivational drive with rewards and punishments. Second, reduced value sensitivity may play a role in the genesis of positive symptoms too, which according to the aberrant salience hypothesis arise from an attempt to cope with aberrant incentive salience (of which value sensitivity is a key aspect). Here, we found no association between value sensitivity and symptoms; however this may be due to our sample lacking sufficient variation on PANSS scores – future studies could explore this association further by performing stratified sampling.

We note that few studies investigated risky decision-making without learning in the context of schizophrenia. Heerey and colleagues (2008) asked participants to choose between two gambles differing for reward amounts, associated probabilities and potential outcomes (i.e., win, lose or nothing). They fitted a logistic regression model estimating the probability of choosing the more extreme gamble on the basis of outcome (wins or losses) and probability and reported reduced beta coefficients to losses in the patients compared to controls; however

as no tests on absolute betas were reported, it is not clear if this reflects increased tendency to gamble with low amounts (and probabilities) or reduced influence of losses on patients' decision-making. In a more recent study (Brown et al., 2013) subjects were asked to choose to either take, or not, a gamble with equal probability of either winning or losing an amount which could exceed, be less or equal than the amount of the concurrent potential outcome. In line with our results, patients showed reduced influence of the magnitude of their gains and losses on their behaviour. However, in this task, the participants were required to weigh the magnitude of differential gains and losses against each other. The ability to perform such mathematical comparisons relies heavily on executive functions and indeed authors report correlations between their task and both IQ and working-memory measures. On the contrary, our task avoids such complicated comparisons by only manipulating the gain amount set against the zero. As such, we could show that the absolute value of the gambling slope correlated with both cognitive (i.e., working memory and IQ) and motivational (i.e., aberrant salience) functions.

One of our main predictions was that dysfunctional value attribution during decision-making would be linked to aberrant salience experiences in the disorder. In support of this we found an inverse correlation between subjects' ability to tune to reward amounts' (i.e., our value-sensitivity index) and a measure of trait aberrant salience (i.e., Aberrant Salience Inventory). To our knowledge, this is the first report linking task behaviour to trait aberrant salience. The relevance of this finding is twofold. First, it connects an inability to take into account stimulus value to an expression of aberrant salience. Second, it further clarifies the nature of such construct by providing a specific and quantitative description of underlying computational mechanisms. To further investigate the relevance to the illness of such two indexes, we asked whether value-sensitivity index or the Aberrant Salience Inventory best differentiated between the two groups. Results revealed that while value-sensitivity fully

mediated the relation between group and trait aberrant salience, the latter did not mediate the relation between group and value-sensitivity. This suggests that our index might be a better predictor of illness compared to existent self-reports measures of aberrant salience.

An interesting aspect pertains to the role of intellectual level in motivational and value-based processing (Collins et al., 2012). In this regard, we found a correlation between value-sensitivity and measures of IQ (i.e., WASI) and working-memory (i.e., Digit Span). As the between-group differences were found for all these indexes, we first investigated whether these intellectual abilities could explain group differences on our value-sensitivity index, but this was not the case. We then found value-sensitivity to mediate the relation between cognitive measures and group. These findings suggest that the value-sensitivity index, namely subjects' ability to tune to reward amounts in our task, discriminated patients from controls better than the standard cognitive measures. In sum, value-sensitivity was a better predictor of whether a subject belonged to the patient or control group than aberrant salience, working memory and IQ. This might be explained by the fact that, the value-sensitivity index reflects both intellectual as well as motivational mechanisms, whereas aberrant salience taps into motivational mechanisms alone and working memory and IQ into intellectual mechanisms only. Contrary to our predictions, patients exhibited preserved ability to normalise values depending on the long run reward context. This was unexpected as patients have demonstrated contextual impairments in various domains, including perception (Robol et al., 2013) and socio-cognition (Fett et al., 2012). However, direct comparisons are difficult as these studies varied greatly in types of tasks used and domains investigated. One study investigated contextual effects in reward processing in the illness (Brown et al., 2013). This study employed a gambling task where participants could either gamble to achieve a greater gain, relative to a certain smaller one, or gamble to avoid a certain loss but with the risk of incurring a larger loss. As the expected values across the two trial types were identical, the

basis of the individuals' preference reflected the influence of the framing effect in the way the options were presented (Kahneman and Tversky, 1979; De Martino et al., 2006). Unlike healthy individuals, schizophrenia patients did not exhibit such framing effects. The discrepancy between this and our finding of absence of contextual deficits in patients might be attributable to the differential time-frame of the contextual adaptation required. Indeed, whereas in Brown and colleagues' study (2013) context was changing rapidly, our task allowed for a long-run adaptation to occur; thus suggesting that patients are able to incorporate contextual information if they have sufficient time to do so.

We observed no relationship between value sensitivity and medication dosage in patients, implying that it is unlikely that a lower value sensitivity observed in patients was a consequence of medication. This suggests that value sensitivity is unaffected by dopaminergic drugs, also in line with a recent study manipulating levodopa (a dopamine agonist) and adopting a task similar to the one employed here (Rigoli et al., 2016b). Hence, whether dopamine plays any role in value sensitivity (as one may predict based on the aberrant salience hypothesis) remains unclear, and available evidence suggests it does not. This leaves open the question on the neural determinants of value sensitivity.

There were no differences between the groups in the preference to gamble more with high or low amounts. This speaks against the possibility that schizophrenia patients, as a whole, are simply overly drawn to salient stimuli, in this case represented by larger monetary amounts. Furthermore, we also found no group differences for the baseline tendency to gamble. This contrasts with reports of gambling tendencies in patients (Potenza et al., 2001) and it suggests that more complex mechanisms of aberrant value attribution might underlie such gambling issues in patients. Our study has some limitations. First, it is possible that antipsychotic medication might account for some of the results on the behavioural task. However, the lack

of a correlation between performance and medication dosage suggests this is unlikely. Second, we found no correlation between symptoms and task performance; this might be due to an insufficient range of symptoms in our sample. Future studies should clarify the link between observed motivational dysfunctions and symptoms. Third, our task involved small monetary amounts and reward contexts with similar reward distributions. It remains to be clarified whether, when reward amounts are larger and contextual differences are greater, contextual effects and gambling propensities similar to those observed here emerge.

In conclusion we find that in keeping with a proposal of dysfunctional value attribution in schizophrenia, we observed a reduction in patients' ability to tune value attribution and concurrent decision-making to the reward magnitudes. This might underlie difficulties in making optimal choices in real life. Crucially, abnormal insensitivity to values in our task was linked to aberrant salience traits, suggesting that such mechanism might form the basis of aberrant salience attributions experienced daily in the disorder. The present study permitted analysis of several key components of choice behaviour, free from learning confounds; something necessary to better delineate the mechanisms underlying aberrant salience in the illness.

Acknowledgement

We wish to thank Tracy Collier for help with recruitment and all the participants who volunteered in the study. RJD is supported by the Wellcome Trust (Senior Investigator Award 098362/Z/12/Z) and the Max Planck Society. SSS is supported by a consolidator award from the European Research Council. CM is supported by the National Institute for

Health Research Biomedical Research Centre for Mental Health at South London and Maudsley NHS Foundation.

References

- American Psychiatric Association, 2000. Diagnostic and Statistical Manual of Mental Disorders, text revision (DSM-IV-TR). American Psychiatric Association, Washington, DC.
- Averbeck, B.B., Evans, S., Chouhan, V., Bristow, E., Shergill, S.S., 2011. Probabilistic learning and inference in schizophrenia. *Schizophr. Res.* 127 (1), 115-122.
- Bechara, A., Damasio, A.R., Damasio, H., Anderson, S.W., 1994. Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition* 50 (1), 7-15.
- Berridge, K.C., Robinson, T.E., 1998. What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience?. *Brain. Res. Rev.* 28 (3), 309-369.
- Berridge, K.C., 2007. The debate over dopamine's role in reward: the case for incentive salience. *Psychopharmacology* 191 (3), 391-431.
- Brown, J.K., Waltz, J.A., Strauss, G.P., McMahon, R.P., Frank, M.J., Gold, J.M., 2013. Hypothetical decision making in schizophrenia: the role of expected value computation and "irrational" biases. *Psychiatry Res.* 209 (2), 142-149.
- Cicero, D.C., Kerns, J.G., McCarthy, D.M., 2010. The Aberrant Salience Inventory: A new measure of psychosis proneness. *Psychol. Assessment* 22 (3), 688.
- Collins, A.G., Frank, M.J., 2012. How much of reinforcement learning is working memory, not reinforcement learning? A behavioral, computational, and neurogenetic analysis. *Eur. J. Neurosci.* 35 (7), 1024-1035.
- De Martino, B., Kumaran, D., Seymour, B., Dolan, R.J., 2006. Frames, biases, and rational decision-making in the human brain. *Science* 313 (5787), 684-687.
- Fett, A.K.J., Shergill, S.S., Joyce, D.W., Riedl, A., Strobel, M., Gromann, P.M., et al., 2012. To trust or not to trust: the dynamics of social interaction in psychosis. *Brain* 135 (3), 976-984.
- Gradin, V.B., Kumar, P., Waiter, G., Ahearn, T., Stickle, C., Milders, M., et al., 2011. Expected value and prediction error abnormalities in depression and schizophrenia. *Brain* 13 (6), 1751-1764.
- Heerey, E.A., Bell-Warren, K.R., Gold, J.M., 2008. Decision-making impairments in the context of intact reward sensitivity in schizophrenia. *Biol. Psychiatry* 64 (1), 62-69.
- Juckel, G., Schlagenhauf, F., Koslowski, M., Filonov, D., Wüstenberg, T., Villringer, A., et al., 2006. Dysfunction of ventral striatal reward prediction in schizophrenic patients treated with typical, not atypical, neuroleptics. *Psychopharmacology* 187 (2), 222-228.
- Kahneman, D., Tversky, A. 1979. Prospect theory: An analysis of decision under risk. *Econometrica*, 263-291.
- Kapur, S., 2003. Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. *Am. J. Psychiatry* 160 (1), 13-23.
- Kay, S.R., Opler, L.A., Lindenmayer, J.P., 1988. Reliability and validity of the positive and negative syndrome scale for schizophrenics. *Psychiatry Res.* 23 (1), 99-110.

- Lejuez, C.W., Aklin, W.M., Zvolensky, M.J., Pedulla, C.M., 2003. Evaluation of the Balloon Analogue Risk Task (BART) as a predictor of adolescent real-world risk-taking behaviours. *J. Adolesc.* 26 (4), 475-479.
- McGrath, J., Saha, S., Chant, D., Welham, J., 2008. Schizophrenia: a concise overview of incidence, prevalence, and mortality. *Epidemiol. Rev.* 30, 67.
- Morris, R.W., Vercammen, A., Lenroot, R., Moore, L., Langton, J.M., Short, B., et al., 2012. Disambiguating ventral striatum fMRI-related bold signal during reward prediction in schizophrenia. *Mol. Psychiatry* 17 (3), 280-289.
- Murray, G.K., Corlett, P.R., Clark, L., Pessiglione, M., Blackwell, A.D., Honey, G., et al., 2008. Substantia nigra/ventral tegmental reward prediction error disruption in psychosis. *Mol. Psychiatry* 13 (3), 267-276.
- Nielsen, M.Ø., Rostrup, E., Wulff, S., Bak, N., Lublin, H., Kapur, S., et al., 2012. Alterations of the brain reward system in antipsychotic naive schizophrenia patients. *Biol. Psychiatry* 71 (10), 898-905.
- Ouzir, M., 2013. Impulsivity in schizophrenia: a comprehensive update. *Aggress. Violent. Behav.* 18, 247-254.
- Potenza, M.N., Chambers, R.A., 2001. Schizophrenia and pathological gambling. *Am. J. Psychiatry* 158 (3), 497.
- Rettenbacher, M.A., Hofer, A., Eder, U., Hummer, M., Kemmler, G., et al., 2004. Compliance in schizophrenia: Psychopathology, side effects and patients' attitudes toward the illness and medication. *J. Clin. Psychiatry* 65 (9), 1211-1218.
- ^aRigoli, F., Rutledge, R.B., Dayan, P., Dolan, R.J., 2016. The influence of contextual reward statistics on risk preference. *NeuroImage* 128, 74-84.
- ^bRigoli, F., Rutledge, R.B., Chew, B., Ousdal, O.T., Dayan, P., Dolan, R.J., 2016. Dopamine increases a value-independent gambling propensity. *Neuropsychopharmacology* 41, 2658-2667.
- ^cRigoli, F., Friston, K. J., Martinelli, C., Selaković, M., Shergill, S.S., Dolan, R.J., 2016. A Bayesian model of context-sensitive value attribution. *eLife* 5, e16127.
- ^dRigoli, F., Friston, K.J., Dolan, R.J., 2016. Neural processes mediating contextual influences on human choice behaviour. *Nat. Commun.* 7, 12416.
- Robol, V., Tibber, M.S., Anderson, E.J., Bobin, T., Carlin, P., Shergill, S.S., et al., 2013. Reduced crowding and poor contour detection in schizophrenia are consistent with weak surround inhibition. *PloS one* 8 (4), e60951.
- Roiser, J.P., Stephan, K.E., Den Ouden, H.E.M., Barnes, T.R.E., Friston, K.J., Joyce, E.M., 2009. Do patients with schizophrenia exhibit aberrant salience?. *Psychol. Med.* 39 (02), 199-209.
- Schlagenhauf, F., Sterzer, P., Schmack, K., Ballmaier, M., Rapp, M., Wrase, J., et al., 2009. Reward feedback alterations in unmedicated schizophrenia patients: relevance for delusions. *Biol. Psychiatry* 65 (12), 1032-1039.
- Waltz, J.A., Gold, J.M., 2007. Probabilistic reversal learning impairments in schizophrenia: further evidence of orbitofrontal dysfunction. *Schizophr. Res.* 93 (1), 296-303.
- Waltz, J.A., Frank, M.J., Wiecki, T.V., Gold, J.M., 2011. Altered probabilistic learning and response biases in schizophrenia: behavioral evidence and neurocomputational modeling. *Neuropsychology* 25 (1), 86.
- Schultz, W., 2010. Dopamine signals for reward value and risk: basic and recent data. *Behav. Brain Funct.* 6 (1), 1.
- Wechsler, D., 1981. WAIS-R. Psychological Corporation.
- Wechsler, D., 1999. Wechsler abbreviated scale of intelligence. Psychological Corporation.

Table and Legends

Table 1. Demographic and clinical characteristics

Figure 1. Experimental Paradigm

Figure 2. Group differences in value sensitivity

Figure 3. Depiction of gambling percentages for each monetary bin (i.e., bin1 = £1-£2, bin2 = £2-£3, bin3 = £3-£4, bin4 = £4-£5 in the low value context and bin1 = £2-£3, bin2 = £3-£4, bin3 = £4-£5, bin4 = £5-£6 in the high value context) separately for gambling slope (i.e., positive and negative) and group. Red arrows connect bins with equal monetary amount and highlight the presence of context effect.

Figure 4. Depiction of relationship between value sensitivity and (A) aberrant salience (ASI), (C) IQ (WASI) and (D) working memory (Digit Span). HC and SCZ are represented by triangles and circles respectively. Figure (B) shows that the relationship between value sensitivity and aberrant salience is driven by those with higher aberrant salience scores.

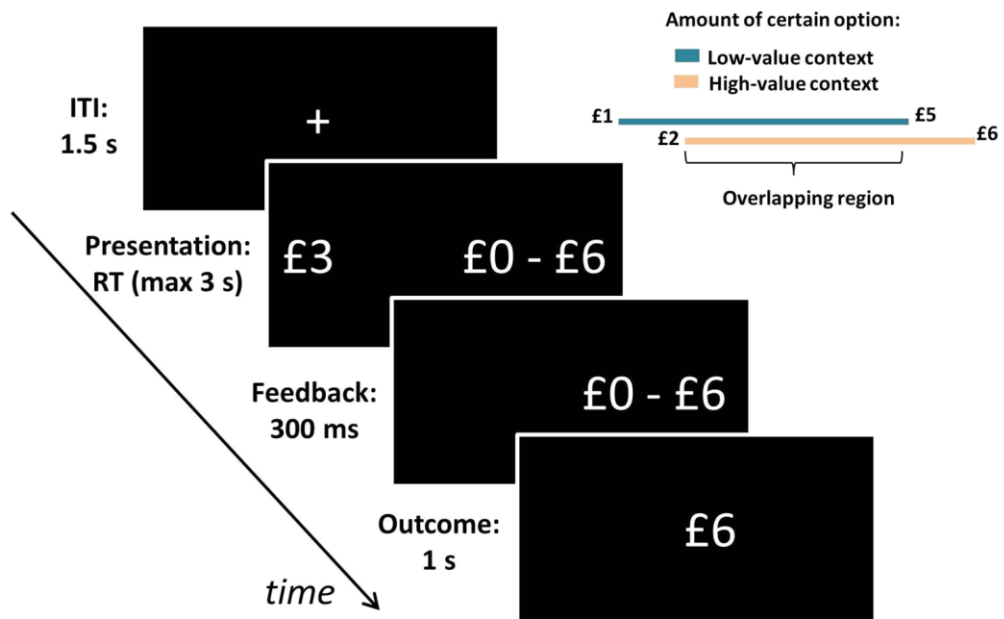
| Demographic and clinical characteristics | SCZ (<i>n</i> = 20) | HC (<i>n</i> = 22) | Test statistic | <i>P</i> value |
|---|----------------------|---------------------|-----------------------|----------------|
| Age: mean (SD) | 41.2 (1.64) | 40.5 (1.69) | <i>t</i> (40) = -0.3 | 0.77 |
| Gender/male: <i>n</i> (%) | 18 (90) | 19 (86.36) | FET | 1 |
| Handedness/right: <i>n</i> (%) | 19 (95.45) | 21 (95.45) | FET | 1 |
| WASI: mean (SD) | 99.75 (15.49) | 110.32 (14.75) | <i>t</i> (40) = 2.26 | 0.03 |
| Digit Span: mean (SD) ^a | 15.82 (3.58) | 18.38 (3.93) | <i>t</i> (36) = 2.08 | 0.05 |
| Aberrant Salience Inventory (SD) ^b | 15.73 (5.99) | 10.36 (6.9) | <i>t</i> (35) = -2.45 | 0.02 |
| PANSS Positive: mean (SD) | 18.75 (4.91) | -- | -- | -- |
| PANSS Negative: mean (SD) | 20.45 (4.15) | -- | -- | -- |
| PANSS General: mean (SD) | 37.05 (8.41) | -- | -- | -- |
| Medication: mean (SD) ^c | 561.65 (420.07) | -- | -- | -- |

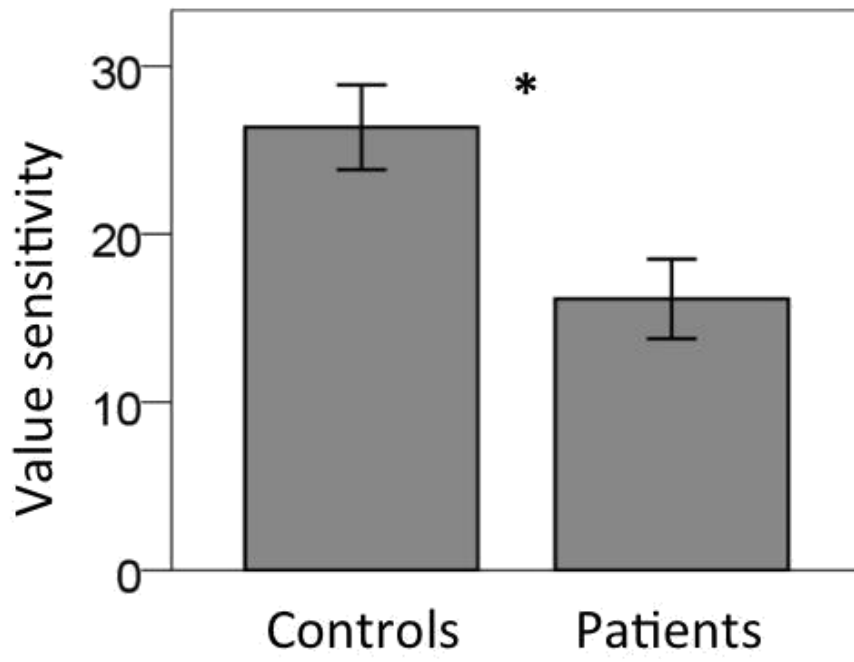
SCZ: volunteers diagnosed with schizophrenia, HC: healthy controls, SD: standard deviation, WASI: Wechsler Abbreviated Scale of Intelligence, PANSS: Positive and Negative Syndrome Scale, FET: Fisher's Exact Test.

^a Digit Span is missing in 3 SCZ and 1 HC.

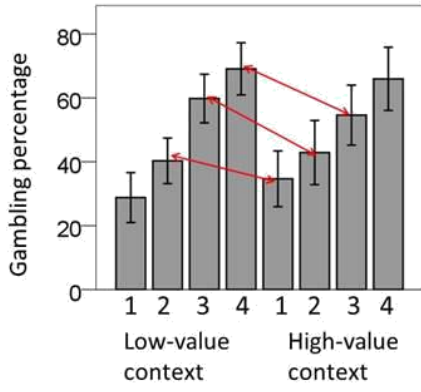
^b Chlorpromazine equivalent (mg per day).

^c ASI is missing in 5 SCZ.

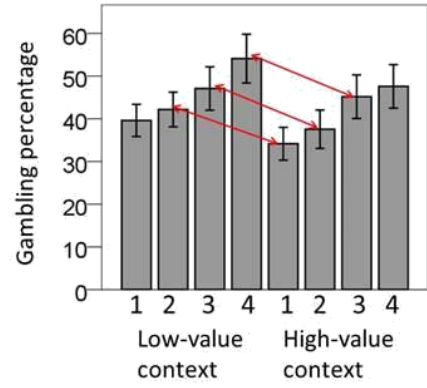




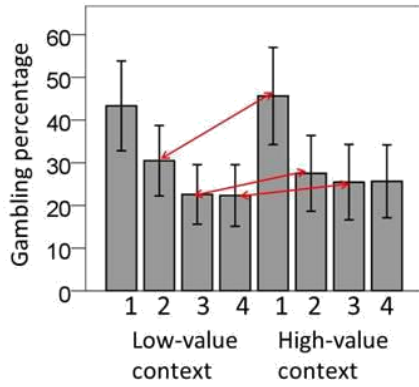
Positive gambling slope in controls



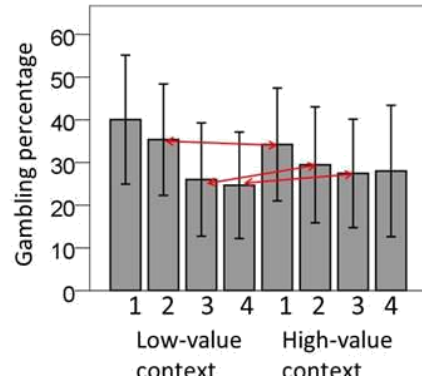
Positive gambling slope in patients



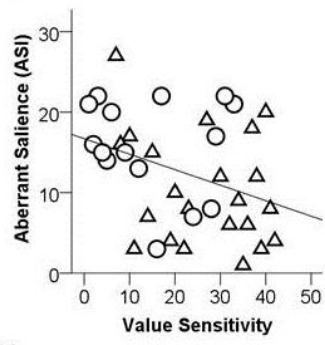
Negative gambling slope in controls



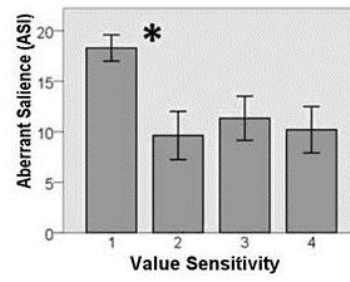
Negative gambling slope in patients



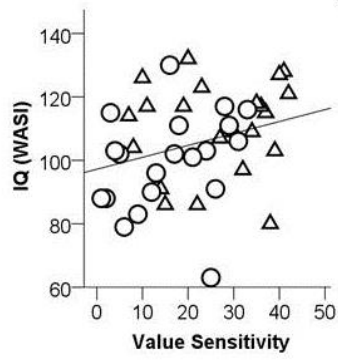
(A)



(B)



(C)



GROUP
△ Control
○ Patient

(D)

