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Social- and non-social reward learning reduced and related to a familial vulnerability in schizophrenia spectrum disorders

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Abstract

Patients with a disorder in the schizophrenia spectrum (SZ) demonstrate impairments in reward learning. A reduced sensitivity to social reward may impede social beyond non-social reward learning mechanisms. The aim of the current study was to investigate social- and non-social reward learning in SZ by means of two interactive game-theoretical investment paradigms. Unaffected first-degree relatives of patients were included to examine whether (social) reward-learning impairments are part of a familial vulnerability of SZ. We included 50 patients with a SZ disorder, 20 unaffected first-degree relatives of patients and 49 healthy controls. The trust game (social) and the lottery game (non-social) were used, consisting of 20 game trials each. The game paradigms were programmed to increase the likelihood of higher repayments in response to increased investments. Multilevel regression analyses were used to examine learning over trials in social- and non-social contexts. The results showed that controls learned equally well in social and non-social contexts, as reflected in an increase of investments over game rounds in both paradigms. In contrast, patients and relatives showed reduced reward learning, regardless of its social or non-social nature, reflected by flatter or decreasing slopes over game rounds in both paradigms. The findings suggest that patients and relatives have a general insensitivity to reward, which appears to reflect a familial vulnerability rather than illness related mechanisms. Results indicate that reward learning may be an important marker for the familial risk to SZ.

1.1 Introduction

Reward learning, i.e. increasing or decreasing behaviour as a function of the consequence that follows it, e.g. a reward (Berridge, 2000; Schultz, 2015), underlies motivated and goal-directed behaviour that plays a key role in almost all aspects of daily life. Previous studies have shown that patients with a disorder in the schizophrenia spectrum (SZ) demonstrate abnormalities in reward learning and that these abnormalities are related to dysfunctions in the dopaminergic system and suggested to be caused by aberrant salience attribution (Howes and Kapur, 2009; Murray et al., 2008; Schlagenhauf et al., 2014). Moreover, reward learning deficits seem to be related to positive symptoms, such as paranoia (Fett et al., 2012; Gromann et al., 2013), suggested to be caused by aberrant salience attribution (Fletcher and Frith, 2009) and negative symptoms, such as the lack of motivation (Lewandowski et al., 2016; Nestor et al., 2014; Strauss et al., 2011; Waltz et al., 2011).

Compared to non-social reward processing, processing social rewards is more complex, as it requires unique social information processing skills (e.g. processing of social cues and social valuation (Behrens et al., 2008) and mentalising abilities (Frith and Frith, 2006; Van Overwalle, 2009). It has been shown that patients with a SZ diagnosis direct less attention to social stimuli (Walsh-Messinger et al., 2014; Zivotofsky et al., 2008) and that they fail to show the same enhanced recognition for social stimuli as healthy controls (Harvey and Lepage, 2014). These impairments in social information processing may give rise to impairments in social reward learning and social decision making and may be independent from and go beyond abnormalities in more general reward-related processes. This is, for example, suggested by studies investigating the influence of neuropeptides, e.g. oxytocin, which plays a key role in

social behaviour, that demonstrate a specific effect on social rewards and not non-social rewards (Baumgartner et al., 2008; Skuse and Gallagher, 2009). Therefore, this study aims to explore the impact of social and non-social rewards on learning in SZ.

Research shows that healthy individuals perceive social interactions as rewarding (Krach et al., 2010), and that this in turn motivates social behaviour. An aberrant sensitivity to the rewarding nature of social interactions may underlie social dysfunctions in daily life in SZ patients, reflected in patients' difficulties maintaining interpersonal relationships with family and friends (Burns and Patrick, 2007; Pinkham and Penn, 2006). The social nature of the disorder is also reflected in some of the key characteristics of the disorder, e.g. social withdrawal (i.e. preference for being alone), distrust, and a lack of motivation to engage in social interactions (American Psychiatric Association, 2013; Penn et al., 2008). Social anhedonia, i.e. a lack of reward/lack of pleasure from social interaction, is not only seen once the disorder is developed, but is considered as a risk factor for the development of SZ (Kwapil, 1998). Understanding how social and non-social reward processing influence decision making and motivation in social and non-social situations will help unravel the underlying mechanisms of social dysfunction in SZ.

Many psychiatric disorders are associated with alterations or impairments in social-decision making, which can be measured with neuro-economic exchange paradigms (Hinterbuchinger et al., 2018). One way to measure social reward learning directly during social interactions is by means of the trust game (Berg et al., 1995; King-Casas et al., 2005). A multi-round trust game taps into social reward learning mechanisms, which is reflected in activation in reward related brain areas such as the caudate nucleus during cooperative interactions

(Delgado et al., 2005; King-Casas et al., 2005). Studies employing the trust game in SZ have shown that patients fail to use social feedback to adapt their trusting behaviour to the counterparts' behaviour over repeated interactions (Fett et al., 2012; Gromann et al., 2013). Research in first episode patients shows contrasting results. Intact learning in interactions with a cooperative and unfair partner (Lemmers-Jansen et al., 2019), decreased learning in interactions with a cooperative partner, but intact learning in unfair interactions (Campellone et al., 2018), and intact learning with a cooperative partner, but decreased learning in unfair interactions (Fett et al., 2016).

Studying unaffected first-degree relatives of patients with SZ provides the opportunity to study an endophenotype, i.e. indicator of risk or vulnerability, without possible interfering effects of medication or other illness-related factors, such as stigmatization. While individuals at familial risk often show intermediate impairments on social cognitive functions (Lavoie et al., 2013), literature on (social) reward learning does not point to alterations in learning. Reduced trust was found at baseline in a relatives sample, but trust levels normalized when social feedback was given, suggesting that social reward learning was intact (Fett et al., 2012). Other studies also demonstrate intact reward learning for non-social rewards (de Leeuw et al., 2014; Grimm et al., 2014; Hanssen et al., 2015) and social reward learning (Gromann et al., 2014) in individuals at familial risk for SZ. However, there are, to our best knowledge, no studies that compared social and non-social reward learning using real time investment games in SZ.

Therefore, the aim of this study was to investigate social and non-social reward learning in patients a SZ diagnosis, unaffected first-degree relatives and controls. The trust game was used to examine social reward learning and a lottery game (identical to the trust game, except

that it is played with a computer counterpart) was used to examine non-social reward learning. Both paradigms were programmed to reinforce increasing investments with a higher chance for repayment, so that learning is reflected by an increasing slope of investments over game rounds. We hypothesized that: 1) patients with SZ would show impairments in reward learning and social reward learning, reflected in flatter slopes in the trust and lottery game, whereas controls and relatives would show similar slopes of social and non-social reward learning; 2) in patients, social reward learning impairments would be more severe than non-social reward learning impairments 3) in patients, social and non-social reward learning impairments would be associated with positive and negative symptoms. We expected these associations to be stronger for social reward learning, in line with the strong social component of some of the key symptoms: paranoia, social anhedonia, social withdrawal, lack of (social) motivation.

2. Method

2.1 Subjects

Fifty patients with a SZ diagnosis, 20 unaffected first-degree relatives of patients and 49 controls without a personal or family history of SZ were included. Inclusion criteria for all participants were: 1) age between 18 and 65, 2) good understanding of the English language, 3) IQ > 70. An additional inclusion criterion for patients was: a SZ diagnosis according to the ICD-10 (WHO, 1992). Exclusion criteria for all participants were: 1) a history of neurological conditions, 2) a diagnosis of alcohol/drug dependence within six months of the study participation. The patient group was recruited via the South London and Maudsley National Health Service (SLaM

NHS), Oxleas NHS, North East London Foundation Trust (NELFT) and South Essex Partnership University NHS Foundation Trust (SEPT), the SLaM 'Consent for Consent c4c' initiative, with support of the Mental Health Research Network and via other research projects within the Psychosis Studies department at the Institute of Psychiatry, Psychology, Neuroscience (IoPPN), Kings College London. Relatives were recruited via patients and via the organisations Rethink and Mind. Controls were recruited through online announcements on local websites (e.g. Gumtree, Craigslist, Callforparticipants), via colleague researchers and circular emails for recruitment at the IoPPN. The study was approved by the London-Harrow Research Ethics Committee [14/LO/0071].

2.2 Measures

2.2.1 Estimated cognitive ability

To control for confounding by group differences in cognitive ability, an abbreviated two-test version of the Wechsler Abbreviated Scale of Intelligence (WASI) was used (Wechsler, 1999). The two-test version consisted of the vocabulary subtest, a verbal comprehension task consisting of 42 items and the matrix reasoning subtest, a perceptual reasoning task consisting of 35 incomplete grid patterns.

2.2.2 Symptoms

The Positive and Negative Syndrome Scale (PANSS) semi-structured interview was used to measure the symptom severity in patients (Kay et al., 1987), during a two week period prior to

testing. Thirty items are scored to evaluate the severity of psychopathology on a 7-point Likert scale.

2.2.3 Trust game

To measure social reward learning, a multi-round trust game was used (Berg et al., 1995; Gromann et al., 2013; King-Casas et al., 2005). In this neuro-economic computer based game consisting of 20 trials, participants played the role of the investor. Participants were instructed that they played with a human counterpart in another location via the Internet, and the partner was the in all 20 trials. In fact, they were playing against a computer that was pre-programmed to behave in a probabilistic manner. The opponent was programmed to be benevolent. The first repayment was either 1.0, 1.1, 1.2, 1.3, 1.4 or 1.5 times the first investment, with an equal chance for returns of each factor. After the first trial, the factors were updated depending on the amount being invested compared to the amount invested in the previous trial, i.e. whether this was an increase or decrease. When the investor's current investment reflected an increase of trust relative to the prior investment or when participants continued to invest the maximum amount (£10), then an increment of 0.05 was added to each of the randomly selected factors until each of the factors reached 1.6, thus reflecting higher repayments. Each factor decreased with the same increments (-0.05) when current investments reflected a decrease in trust from the previous investment or remained at the minimum (£0), with a minimum value of 1 for each factor, thus reflecting lower repayments. This way of programming ensured repayments that would resemble subtle changes in repayments in a probabilistic way.

At the start of each trust game trial the initials of the other player were displayed on the computer screen. Participants (investors) received an initial endowment of £10 and indicated, on a horizontal scale from zero to ten pounds, how much they wanted to share with the other player. The chosen amount was tripled during the transaction and after this the trustee gave the repayment. During the decision making of the trustee, participants saw the trustee's initials on the screen with the message that they had to wait for a response. At the end of the trial, they saw their own total investments (kept and given amount) and total earnings for both players. After this a new trial started.

2.2.4 Lottery game

Non-social reward learning was assessed by means of the lottery game, consisting of 20 trials. This game was identical to the trust game and the computer was pre-programmed in the same probabilistic way. The only difference with the trust game was that participants were told that they were playing a lottery game with a computer. There was no display of initials and during the decision making phase prior to the repayment participants saw the message 'waiting for the computer to respond'.

2.3 Procedure

All testing took place at the IOPPN. Participants gave written informed consent before start of the study. The study comprised of two visits, which were one week apart. The trust and lottery game were completed on the first and second visit to minimize cognitive load and carry-over effects. In the first session, participants first completed a demographic questionnaire. Second,

they completed several practice trials before playing the trust game to make sure that they understood how the game worked. All participants were told that they would receive the earnings from one randomly selected round in the trust game, in fact all participants received an extra payment of £5 for fairness reasons. After playing the trust game participants completed a brief evaluation questionnaire on whether they believed that they played with a real person. The question 'did you have the idea that the other person in the task was unreal?' was rated on a 7-point Likert scale (1 strongly disagree, 7 strongly agree) and used to control for credibility of the game. Last, they completed the PANSS interview, which was administered by a trained researcher.

The second session consisted of the participation in the lottery game, including practice trials, and the WASI vocabulary and matrix reasoning subtests. At the end of the study each participant received a payment for participation.

2.4 Statistical analysis

Statistical analyses were performed using STATA version 14 (StataCorp, 2015). We examined group differences in demographics using chi-square and regression analyses. Reward learning was analysed using mixed effects multilevel regression analyses to account for repeated measurements within persons, with investments as dependent variable and with group (patient, relative, control), task (trust vs. lottery game) and trial number (1-20) and their respective interactions as independent variables. Changes in investments over time, indicated by trial number, reflect (social) reward learning in the trust and lottery game. The analyses were controlled for gender and general cognitive ability. To investigate trial-to-trial investment

changes, we examined the distribution of change behaviours within each task using chi-square tests. Specifically, we were interested three types of investment changes: no change, increase or decrease in investment in relation the previous trial. Within the patient group we used mixed effects multilevel regression analyses to examine associations between reward learning in the trust and lottery game and symptoms.

3. Results

3.1 Demographics

Demographic information, clinical characteristics and task performance are shown in Table 1. The relatives group included significantly more females than the patient and control group. The estimated cognitive ability of patients was significantly lower compared to controls and relatives. Controls and relatives did not differ significantly. There were no group differences in age.

We examined whether credibility of the game, i.e. whether participants believed the other player in the trust game was real or not (21.85% expressed doubts about whether the other player was a real person, i.e. filled in 'strongly agree' on the question whether the other player was unreal), had an effect on investments. There was neither an effect of degree of belief on invested amounts ($p = .49$), nor was there an interaction between trial number and degree of belief ($p = .12$), i.e. no effect on learning. In addition, we examined whether trust and lottery game performance was correlated. For mean investments there was a significant correlation between the trust and the lottery game ($r(118) = 0.43$, $p < .001$). The slopes for

investments in the lottery and the trust game did not show a significant correlation ($r(118) = 0.08$, $p = .22$).

3.2 Social and non-social reward learning: investments over trials

Learning in the trust and lottery game is shown in Figure 1. There was a significant 3-way interaction between group, task and trial number ($b = -.02$, 95% CI [-.03, -.002], $p = .03$), showing that the association between task and learning over trials differed between groups. Post-hoc tests investigating the task and trial effect by group showed no significant interactions between task and trial number for any of the three groups (all $p > .24$), thus learning did not differ depending on the social or non-social nature of the rewarding stimulus.

Analyses of main effects by group showed that controls increased investments over trials ($b = .03$, 95% CI [.003, .05], $p = .03$) and invested significantly less in the trust game compared to the lottery game ($b = -.32$, 95% CI [-.51, -.12], $p = .001$). Patients did not demonstrate any reward learning ($p = .44$), and invested significantly less in the trust game than the lottery game ($b = -.31$, 95% CI [-.53, -.09], $p = .005$). Like patients, relatives did not show any main effect of trial number ($p = .86$). Relatives invested significantly more in the trust game than the lottery game ($b = .42$, 95% CI [.09, .74], $p = .01$).

3.3 Changes in investment behaviour from trial-to-trial

Within the lottery game, the distribution of changes in investment behaviour were different between groups [$\chi^2 (4) = 13.33$, $p = .01$]. Across the 3 types of investment changes (no change, increase or decrease) in relation to the investment in the previous trial, controls did not

significantly differ from relatives [χ^2 (2) = 3.16, p = .21]. Distribution of changes in investments in patients was marginally significantly different from controls [χ^2 (2) = 5.33, p = .07] and significantly different from relatives [χ^2 (2) = 11.76, p = .003], indicating significantly less investment increases and more equal investments compared to the preceding trial by patients.

In the trust game, the distribution of changes in behaviour was also different between groups [χ^2 (4) = 32.86, p < .001]. Controls did not differ significantly in investment changes from relatives [χ^2 (2) = 0.36, p = .84], but they did differ significantly from patients [χ^2 (2) = 29.53, p < .001]. Relatives also differed significantly from patients in the distribution of changes in investments [χ^2 (2) = 12.19, p = .002]. Patients increased investments less often and invested more equal amounts compared to controls and relatives. For percentages of changes in investments see Table 2.

3.4 Within patient analyses: associations between learning and symptoms

There was no significant 3-way interaction between negative symptoms, task and trial number on investments (p = .61). There were significant 2-way interactions between negative symptoms and trial number (b = .005, 95% CI [.001, .009], p = .02) and negative symptoms and task (b = -.13, 95% CI [-.18, -.09], p < .001). To examine these interactions we created two groups with lower and higher negative symptoms 1) PANSS score <= 14, representing absent and minimal symptoms, 2) higher symptom severity (PANSS score > 14), representing clinically significant symptoms. Individuals with lower symptoms made higher investments in the trust than lottery game (b = .37, 95% CI [.05, .69], p = .03). Individuals with higher symptoms showed the opposite pattern with higher investments in the lottery compared to the trust game (b = -

.98, 95% CI [-1.28, -.68], $p < .001$). The significant interaction between negative symptoms and trial number was caused by opposite effects, but was not reflected in a main effect of trial number in either symptom group (both $p > .13$). There were no significant effects of positive symptoms on investments (all $p > .49$).

4. Discussion

The current study set out to examine social and non-social reward learning in patients with a SZ diagnosis, unaffected first-degree relatives of patients and controls using social and non-social investment paradigms. Key findings indicate that healthy controls showed (social) reward learning, i.e. increase in investments over trials, but in patients and first-degree relatives learning was absent in both the social and non-social task, indicative of a generalized insensitivity to subtle reward cues in individuals with the familial liability to SZ. Contrary to our expectations, we did not find any difference in the degree of reward learning impairments between the social or non-social context within the patient group. These findings may suggest that the provided social context does not impair social reward learning beyond non-social reward learning, at least within social interactions that are devoid of complex social cues. While learning in the two paradigms did not differ within groups, it is interesting to note that trust game and lottery game performance was only correlated for mean investments, but not for the learning over trials, despite identical algorithms of the pre-programmed game partners in both paradigms. In line with previous evidence (Fulford et al., 2018b; Lee et al., 2018) this may suggest that individuals employ different underlying decision making processes in social and non-social situations (Houser et al., 2010).

4.1 Social and non-social reward learning

In the current study we expected to see similar learning mechanisms in healthy controls and unaffected first-degree relatives. However, surprisingly, relatives showed reduced reward learning compared to controls in both social and non-social contexts, which is in contrast to our hypothesis and results from previous studies investigating non-social reward learning (Hanssen et al., 2015; Li et al., 2018) and social reward learning (Fett et al., 2012; Gromann et al., 2014). Importantly, the reward cues in the current paradigm were subtler than the aforementioned studies, which could account for the contrasting findings. The current results suggest that the vulnerability for the disorder is associated with an altered sensitivity to subtle rewards in general regardless of their social or non-social character. Our findings are in line with several neuroimaging studies reporting brain abnormalities, albeit in absence of behavioural deficits, during non-social reward learning (de Leeuw et al., 2014; Grimm et al., 2014; Hanssen et al., 2015) and social reward learning (Gromann et al., 2014) in individuals at familial high risk. It has been suggested that neural measures are more sensitive to subtle reward processing and reward learning aberrancies, compared to most behavioural measures. Yet, there is also evidence for normal brain responses during normal reward learning in relatives (Kasanova et al., 2018).

Similar patterns of reduced learning were found in both social and non-social reward learning. This impairment in learning may be related to aberrant dopamine in brain reward circuits, causing an interference with processing rewards (Juckel et al., 2006b). This is suggested to be related with the aberrant salience model, where important stimuli are not

processed as such, and unimportant stimuli may be processed as being more important than they actually are (Kapur et al., 2005). Our findings could therefore suggest that aberrant dopaminergic mechanisms may play a role in patients and relatives. Importantly, 80% of the patients was on atypical antipsychotics. Antipsychotic medication is suggested to have a normalizing effect on reward processing (Juckel et al., 2006a; Nielsen et al., 2012). This may have dampened any illness related aggravating impairments in patients, which may be the reason that patients perform at similar levels as first-degree relatives. Thus, it is possible that differences between relatives and patients emerge during states of severe psychosis and dopamine deregulation.

Some previous research has shown that SZ patients are less sensitive to social rewards such as smiles as compared to non-social rewards (Catalano et al., 2018). The discrepancy with our findings might be explained by the less subtle nature of rewards, i.e. more obvious or bigger rewards in previous research.

Patients showed less consistent investment behaviour, i.e. a lower percentage of investment increases compared to the investment in the preceding trial than relatives and controls. A lower percentage of increases in investments as opposed to no change could reflect a lack of goal directed behaviour or lack of a clear strategy to achieve rewards. Previous research in SZ patients demonstrated impairments in distinguishing rewarding stimuli and difficulties in using rewards to initiate goal-directed behaviour (Barch, 2008; Strauss et al., 2014). Alternative explanations may lie in making choices without fully contemplating the best way to invest (Ventura et al., 2010).

Although we did not have specific hypotheses mean invested amounts, we found that controls and patients invested less in the trust game than the lottery game, while relatives showed a reversed pattern. This may be related to compensatory mechanisms, but this should be investigated further in future research.

4.2 Association with symptoms

Within the patient group we expected that reduced social and non-social reward learning would be associated with positive and negative symptoms, because of the social component of some key symptoms such as paranoia, social anhedonia, social withdrawal, lack of (social) motivation. However, neither negative nor positive symptoms showed a significant association with changes in investments over trials. The absence of any effect of symptoms on learning indicates that all patients, regardless of symptom severity, were unable to elicit or pick up on the subtle rewards. Thus, in contrast to our hypothesis, learning impairments cannot be explained by severity of symptoms.

While we did not find the hypothesised effect on learning, additional results did show an association between mean invested amounts and negative symptoms. Individuals with lower negative symptoms invested more in the social game compared to the non-social game, while the higher symptom group showed the opposite pattern. This may be related to higher social motivation in the social context (Robertson et al., 2014).

Symptom associations may be understated in this study and may not generalize to a wider SZ population, since the sample in the current study was very stable and had an overall low negative (and positive) symptom severity. Hence, it is important to examine this association

in future studies in samples with more acute psychosis, which would present with more severe symtpoms.

4.3 Limitations and directions for future research

First, the group of unaffected first-degree relatives was relatively small and the gender distribution was significantly different from the healthy control and patient group. Nevertheless, trust game studies do not show a strong gender effect; some studies did not find any gender effect (Croson and Buchan, 1999; Schwieren and Sutter, 2008), and other studies found that men are more trusting, i.e. invest more, than women (Chaudhuri and Gangadharan, 2007; Garbarino and Slonim, 2009). Second, for future studies it would also be interesting to include unaffected first-degree relatives and individuals who fit within the ultra-high risk (UHR) concept to investigate the psychometric risk. Thus far, both populations have only been studied in isolation (Lemmers-Jansen et al., 2019). A more detailed assessment in such a sample may provide useful information about the relation between reward learning and possible subclinical symptoms and the development of learning alterations. Third, we chose to have a basic representation of the other human counterpart to keep the social and non-social task condition as similar as possible (Houser et al., 2010), however, a basic trust game has been shown to tap into social nature of the task in previous literature before (Delgado et al., 2005; Gromann et al., 2013; King-Casas et al., 2005). Future studies should investigate whether more explicit social reward cues (e.g. for instance a smiling person, or social praise) are processed differently. Last, this study aimed to investigate (social) reward learning on a fundamental level, however, future research should investigate how these mechanisms relate to real life social functioning

measures, like monitoring functioning in daily life with the experience sampling method (ESM) or assessments with questionnaires.

4.4 Conclusion

In conclusion, our findings add to the growing body of literature in the field on the specificity of social reward learning (Fulford et al., 2018a) and point to a general insensitivity to reward learning in patients with no aggravating effect of social rewards. Given that the same pattern was observed in relatives, this insensitivity seems to reflect a familial vulnerability, which suggest that reward learning in general may be an important marker in SZ. It may be beneficial in future studies to focus on associations between reward sensitivity as indicated by experimental tasks and daily-life (social) motivation by means of experience sampling studies (ESM) and reward learning, to elucidate the role of reward learning in social- and daily-life functioning. In addition, functional neuroimaging studies directly comparing social and non-social reward learning may shed more light on the neural correlates involved in the processing of both social and non-social rewards.

References

American Psychiatric Association, 2013. Diagnostic and statistical manual of mental disorders 5th ed. American Psychiatric Association, Washington, DC.

Barch, D.M., 2008. Emotion, motivation, and reward processing in schizophrenia spectrum disorders: what we know and where we need to go. Schizophrenia bulletin 34(5), 816-818.

Baumgartner, T., Heinrichs, M., Vonlanthen, A., Fischbacher, U., Fehr, E., 2008. Oxytocin shapes the neural circuitry of trust and trust adaptation in humans. Neuron 58(4), 639-650.

Behrens, T.E., Hunt, L.T., Woolrich, M.W., Rushworth, M.F., 2008. Associative learning of social value. Nature 456(7219), 245.

Berg, J., Dickhaut, J., McCabe, K., 1995. Trust, reciprocity, and social history. Games and economic behavior 10(1), 122-142.

Berridge, K.C., 2000. Reward learning: Reinforcement, incentives, and expectations, Psychology of learning and motivation. Elsevier, pp. 223-278.

Burns, T., Patrick, D., 2007. Social functioning as an outcome measure in schizophrenia studies. Acta Psychiatrica Scandinavica 116(6), 403-418.

Campellone, T.R., Truong, B., Gard, D., Schlosser, D.A., 2018. Social motivation in people with recent-onset schizophrenia spectrum disorders. Journal of psychiatric research 99, 96-103.

Catalano, L., Heerey, E., Gold, J., 2018. The Valuation of Social Rewards in Schizophrenia. bioRxiv, 319095.

Chaudhuri, A., Gangadharan, L., 2007. An experimental analysis of trust and trustworthiness. Southern Economic Journal, 959-985.

Croson, R., Buchan, N., 1999. Gender and culture: International experimental evidence from trust games. American Economic Review 89(2), 386-391.

de Leeuw, M., Kahn, R.S., Vink, M., 2014. Fronto-striatal dysfunction during reward processing in unaffected siblings of schizophrenia patients. Schizophrenia bulletin 41(1), 94-103.

Delgado, M.R., Frank, R.H., Phelps, E.A., 2005. Perceptions of moral character modulate the neural systems of reward during the trust game. Nature neuroscience 8(11), 1611.

Fett, A.-K.J., Shergill, S., Korver-Nieberg, N., Yakub, F., Gromann, P., Krabbendam, L., 2016. Learning to trust: trust and attachment in early psychosis. Psychological medicine 46(7), 1437-1447.

Fett, A.-K.J., Shergill, S.S., Joyce, D.W., Riedl, A., Strobel, M., Gromann, P.M., Krabbendam, L., 2012. To trust or not to trust: the dynamics of social interaction in psychosis. Brain 135(3), 976-984.

Fletcher, P.C., Frith, C.D., 2009. Perceiving is believing: a Bayesian approach to explaining the positive symptoms of schizophrenia. Nature Reviews Neuroscience 10(1), 48.

Frith, C.D., Frith, U., 2006. The neural basis of mentalizing. Neuron 50(4), 531-534.

Fulford, D., Campellone, T., Gard, D.E., 2018a. Social motivation in schizophrenia: How research on basic reward processes informs and limits our understanding. Clinical psychology review.

Fulford, D., Campellone, T., Gard, D.E., 2018b. Social motivation in schizophrenia: How research on basic reward processes informs and limits our understanding. Clinical psychology review 63, 12-24.

Garbarino, E., Slonim, R., 2009. The robustness of trust and reciprocity across a heterogeneous US population. Journal of Economic Behavior & Organization 69(3), 226-240.

Grimm, O., Heinz, A., Walter, H., Kirsch, P., Erk, S., Haddad, L., Plichta, M.M., Romanczuk-Seiferth, N., Pöhland, L., Mohnke, S., 2014. Striatal response to reward anticipation: evidence for a systems-level intermediate phenotype for schizophrenia. JAMA psychiatry 71(5), 531-539.

Gromann, P., Heslenfeld, D.J., Fett, A.K., Joyce, D.W., Shergill, S.S., Krabbendam, L., 2013. Trust versus paranoia: abnormal response to social reward in psychotic illness. Brain 136(Pt 6), 1968-1975.

Gromann, P., Shergill, S., de Haan, L., Meewis, D., Fett, A.-K., Korver-Nieberg, N., Krabbendam, L., 2014. Reduced brain reward response during cooperation in first-degree relatives of patients with psychosis: an fMRI study. Psychological medicine 44(16), 3445-3454.
Hanssen, E., van der Velde, J., Gromann, P., Shergill, S., de Haan, L., Bruggeman, R., Krabbendam, L., Aleman, A., Atteveldt, V., 2015. Neural correlates of reward processing in healthy siblings of patients with schizophrenia. Frontiers in human neuroscience 9, 504.
Harvey, P.-O., Lepage, M., 2014. Neural correlates of recognition memory of social information in people with schizophrenia. Journal of psychiatry & neuroscience: JPN 39(2), 97.
Hinterbuchinger, B., Kaltenboeck, A., Baumgartner, J.S., Mossaheb, N., Friedrich, F., 2018. Do patients with different psychiatric disorders show altered social decision-making? A systematic review of ultimatum game experiments in clinical populations. Cognitive neuropsychiatry 23(3), 117-141.
Houser, D., Schunk, D., Winter, J., 2010. Distinguishing trust from risk: An anatomy of the investment game. Journal of economic behavior & organization 74(1-2), 72-81.
Howes, O.D., Kapur, S., 2009. The dopamine hypothesis of schizophrenia: version III—the final common pathway. Schizophrenia bulletin 35(3), 549-562.
Juckel, G., Schlagenhauf, F., Koslowski, M., Filonov, D., Wüstenberg, T., Villringer, A., Knutson, B., Kienast, T., Gallinat, J., Wrase, J., 2006a. Dysfunction of ventral striatal reward prediction in schizophrenic patients treated with typical, not atypical, neuroleptics. Psychopharmacology 187(2), 222-228.
Juckel, G., Schlagenhauf, F., Koslowski, M., Wüstenberg, T., Villringer, A., Knutson, B., Wrase, J., Heinz, A., 2006b. Dysfunction of ventral striatal reward prediction in schizophrenia. Neuroimage 29(2), 409-416.
Kapur, S., Mizrahi, R., Li, M., 2005. From dopamine to salience to psychosis—linking biology, pharmacology and phenomenology of psychosis. Schizophrenia research 79(1), 59-68.
Kasanova, Z., Ceccarini, J., Frank, M.J., van Amelsvoort, T., Booij, J., van Duin, E., Steinhart, H., Vaessen, T., Heinzel, A., Mottaghy, F., 2018. Intact striatal dopaminergic modulation of reward learning and daily-life reward-oriented behavior in first-degree relatives of individuals with psychotic disorder. Psychological medicine 48(11), 1909-1914.
Kay, S.R., Fiszbein, A., Opfer, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophrenia bulletin 13(2), 261.
King-Casas, B., Tomlin, D., Anen, C., Camerer, C.F., Quartz, S.R., Montague, P.R., 2005. Getting to know you: reputation and trust in a two-person economic exchange. Science 308(5718), 78-83.
Krach, S., Paulus, F.M., Bodden, M., Kircher, T., 2010. The Rewarding Nature of Social Interactions. Frontiers in Behavioral Neuroscience 4.
Kwapil, T.R., 1998. Social anhedonia as a predictor of the development of schizophrenia-spectrum disorders. Journal of abnormal psychology 107(4), 558.
Lee, J., Jimenez, A.M., Reavis, E.A., Horan, W.P., Wynn, J.K., Green, M.F., 2018. Reduced Neural Sensitivity to Social vs Nonsocial Reward in Schizophrenia. Schizophrenia bulletin.
Lemmers-Jansen, I.L., Fett, A.-K.J., Hanssen, E., Veltman, D.J., Krabbendam, L., 2019. Learning to trust: social feedback normalizes trust behavior in first-episode psychosis and clinical high risk. Psychological medicine 49(5), 780-790.
Lewandowski, K.E., Whitton, A.E., Pizzagalli, D.A., Norris, L.A., Ongur, D., Hall, M.-H., 2016. Reward learning, neurocognition, social cognition, and symptomatology in psychosis. Frontiers in psychiatry 7, 100.
Li, Z., Yan, C., Lv, Q.-y., Yi, Z.-h., Zhang, J.-y., Wang, J.-h., Lui, S.S., Xu, Y.-f., Cheung, E.F., Gur, R.E., 2018. Striatal dysfunction in patients with schizophrenia and their unaffected first-degree relatives. Schizophrenia Research 195, 215-221.

Murray, G., Corlett, P., Clark, L., Pessiglione, M., Blackwell, A., Honey, G., Jones, P., Bullmore, E., Robbins, T., Fletcher, P., 2008. Substantia nigra/ventral tegmental reward prediction error disruption in psychosis. Molecular psychiatry 13(3), 267.
Nestor, P.G., Choate, V., Niznikiewicz, M., Levitt, J.J., Shenton, M.E., McCarley, R.W., 2014. Neuropsychology of reward learning and negative symptoms in schizophrenia. Schizophrenia research 159(2), 506-508.
Nielsen, M.O., Rostrup, E., Wulff, S., Bak, N., Broberg, B.V., Lublin, H., Kapur, S., Glenthoj, B., 2012. Improvement of brain reward abnormalities by antipsychotic monotherapy in schizophrenia. Archives of general psychiatry 69(12), 1195-1204.
Penn, D.L., Sanna, L.J., Roberts, D.L., 2008. Social cognition in schizophrenia: an overview. Schizophrenia bulletin 34(3), 408-411.
Pinkham, A.E., Penn, D.L., 2006. Neurocognitive and social cognitive predictors of interpersonal skill in schizophrenia. Psychiatry research 143(2-3), 167-178.
Robertson, B.R., Prestia, D., Twamley, E.W., Patterson, T.L., Bowie, C.R., Harvey, P.D., 2014. Social competence versus negative symptoms as predictors of real world social functioning in schizophrenia. Schizophrenia research 160(1-3), 136-141.
Schlagenhauf, F., Huys, Q.J., Deserno, L., Rapp, M.A., Beck, A., Heinze, H.-J., Dolan, R., Heinz, A., 2014. Striatal dysfunction during reversal learning in unmedicated schizophrenia patients. Neuroimage 89, 171-180.
Schultz, W., 2015. Neuronal reward and decision signals: from theories to data. Physiological reviews 95(3), 853-951.
Schwieren, C., Sutter, M., 2008. Trust in cooperation or ability? An experimental study on gender differences. Economics Letters 99(3), 494-497.
Skuse, D.H., Gallagher, L., 2009. Dopaminergic-neuropeptide interactions in the social brain. Trends in cognitive sciences 13(1), 27-35.
StataCorp, 2015. Stata Statistical Software: Release 14. StataCorp LP, College Station, TX.
Strauss, G.P., Frank, M.J., Waltz, J.A., Kasanova, Z., Herbener, E.S., Gold, J.M., 2011. Deficits in positive reinforcement learning and uncertainty-driven exploration are associated with distinct aspects of negative symptoms in schizophrenia. Biological psychiatry 69(5), 424-431.
Strauss, G.P., Waltz, J.A., Gold, J.M., 2014. A review of reward processing and motivational impairment in schizophrenia. Schizophrenia bulletin 40(Suppl 2), S107-S116.
Van Overwalle, F., 2009. Social cognition and the brain: a meta-analysis. Human brain mapping 30(3), 829-858.
Ventura, J., Thames, A.D., Wood, R.C., Guzik, L.H., Hellemann, G.S., 2010. Disorganization and reality distortion in schizophrenia: a meta-analysis of the relationship between positive symptoms and neurocognitive deficits. Schizophrenia research 121(1-3), 1-14.
Walsh-Messinger, J., Ramirez, P.M., Wong, P., Antonius, D., Aujero, N., McMahon, K., Opler, L.A., Malaspina, D., 2014. Impairment in emotional modulation of attention and memory in schizophrenia. Schizophrenia research 157(1-3), 63-69.
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.
Wechsler, D., 1999. Wechsler Abbreviated Scale of Intelligence. The Psychological Corporation: Harcout Brace & Company, New York, NY.
WHO, 1992. The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines. World Health Organization.
Zivotofsky, A.Z., Oron, L., Hibsher-Jacobson, L., Weintraub, Y., Strous, R.D., 2008. Finding the hidden faces: schizophrenic patients fare worse than healthy subjects. Neuropsychologia 46(8), 2140-2144.

Figure 1 Trust and lottery game investments over trials shown for a) healthy controls, b) first-degree relatives of patients with schizophrenia, and c) patients with schizophrenia.