Chapter 5

Reduced brain reward response during cooperation in first-degree relatives of patients with psychosis: an fMRI study

Paula M. Gromann\textsuperscript{a,b}, Sukhi S. Shergill\textsuperscript{b}, Lieuwe de Haan\textsuperscript{c}, Dirk G.J. Meewis\textsuperscript{a}, Anne-Kathrin Fett\textsuperscript{a,b}, Nikie Korver-Nieberg\textsuperscript{c}, Lydia Krabbendam\textsuperscript{a}

\textsuperscript{a} Department of Educational Neuroscience, Faculty of Psychology and Education, VU University Amsterdam, The Netherlands; \textsuperscript{b} King’s College London, Institute of Psychiatry, Department of Psychosis Studies, CSI Lab, U.K; \textsuperscript{c} Department of Early Psychosis, AMC, Academic Psychiatric Centre, Amsterdam, The Netherlands

Chapter 5

ABSTRACT
The neural underpinnings of psychotic illness remain uncertain, confounded by changes secondary to the disease process, social isolation and antipsychotic medication effects. Recent data revealed analogous deficits across a range of neuropsychological measures, including social cognition tasks, in first-degree relatives of patients with psychosis. This study aimed to clarify the neural mechanisms underlying trust in siblings of patients during an interactive trust task. The hypotheses were: (i) siblings will invest less at the beginning of the trust game; and (ii) siblings will show reduced activation of the brain reward and mentalizing systems compared to controls.

Functional magnetic resonance imaging data was acquired on 50 healthy siblings of patients with psychosis and 33 healthy controls during a multiple-round trust game with a cooperative counterpart. An a priori region-of-interest (ROI) analysis of the caudate, temporo-parietal junction (TPJ), superior temporal sulcus (STS), insula and the medial prefrontal cortex (mPFC) was performed focusing on the investment and repayment phases. An exploratory whole-brain analysis was run to test for group-wise differences outside these ROIs.

The siblings’ behaviour during the trust game did not differ significantly from the behaviour of the controls. At the neural level, siblings showed reduced activation of the right caudate during investments, and the left insula during repayments. In addition, the whole-brain analysis revealed reduced putamen activation in siblings during investments. This suggests that siblings show aberrant functioning of regions traditionally involved in reward processing in response to cooperation, which may be associated with the social reward deficits observed in psychosis.

Keywords
functional MRI, schizophrenia, siblings, trust, caudate.
INTRODUCTION

Persecutory beliefs and hallucinations are characteristic features of psychotic illness; their functional implications are evident in the devastating impact on social functioning and levels of trust in others. Social interactions pose a major challenge to patients. The poor social functioning evident in psychosis has been linked to impaired mentalizing [1], i.e. the ability to understand the intentions of others. Mentalizing is highly relevant for engaging in social interactions, but the interactive nature of social encounters is difficult to probe experimentally. The recent development of neuro-economics now allows to investigate complex social interactions by means of interactive paradigms [2-6].

The classical trust game [7] is based on the interaction between two players. The first player (i.e. investor) decides how much money to invest out of a certain starting budget. The invested amount gets multiplied, and the second player (i.e. trustee) then chooses the amount of money to repay to the investor. Mutually beneficial outcomes are most likely if both players cooperate. However, investing involves a certain risk as the trustee gains the highest payoff by keeping all the money to himself. Hence, trust is required for the investor to make an investment. Previous research showed that healthy individuals invest at least some of their money, and that this sign of trust is strongly reinforced by the reciprocity of the interacting partner [8-11]. Recently, we demonstrated that patients with psychosis participate in fewer mutually trusting interactions than healthy individuals [12].

Interactive paradigms from the neuro-economics field have been linked to activation in mentalizing regions [13-14] and the brain reward circuit [4, 15-16]. Benevolent reciprocity (i.e. a higher than expected return) during trust game interactions was associated with significant activation of the caudate nucleus, with a change in the timing of the activation from the outcome to the decision phase indexing the development of trust between interacting persons [4]. Activation of the mPFC and TPJ was associated with mentalizing, and activation of the insula indicated reward and arousal [17]. We have recently shown that patients with psychosis had reduced levels of baseline trust, and reduced activation within the caudate nucleus and the TPJ in response to cooperative repayments [18]. Moreover, we found a negative correlation between the attenuated caudate signal and paranoia levels, but no other symptoms. In line with the King-Casas study [4], this suggests a prominent role of the caudate nucleus in processes related to trust and social reward.

However, imaging studies on psychosis are limited by the potentially confounding effects induced by the antipsychotic medication, which has been shown to act upon the brain reward response [19-20]. Investigating individuals with a familial risk to develop psychosis is a promising solution to this dilemma. Having a first-degree relative with psychosis has been proven to be a risk factor for developing the disorder [21-23]. Recent studies have revealed mentalizing deficits in unaffected relatives of patients with psychosis [24-28]. These impairments seem to be more severe in first-degree than in second-degree relatives [29]. Using a multi-round trust game, we found evidence for lower basic trust in first-degree relatives compared to controls [12]. Unlike patients, relatives increased their investments when receiving positive information about the trustworthiness of the trustee.
In a typical one-shot trust game, the investment phase involves mentalizing (i.e. trying to predict the trustee’s intentions), and the repayment phase involves social reward (or lack thereof, dependent on the magnitude of the repayment). In contrast, in a multi-round trust game, the mentalizing and social reward components become intermingled in both phases of the game. In the investment phase, anticipation of a positive repayment by the trustee may lead to activation of brain areas involved in social reward [4]. Likewise, in the repayment phase, mentalizing activity may occur when subjects start reflecting upon the intentions of the other player, as well as planning the optimal next investment choice. Thus, in the multi-round game used in the current study, reward and mentalizing-related activation can occur during both the investment and the repayment phases of the trust game.

The current study aimed to investigate the underlying neural mechanisms of the lack of trust linked to psychosis, without the typical confounders such as hospitalization, medication and symptoms. Functional magnetic resonance imaging (fMRI) data was acquired on 50 healthy siblings of patients with psychosis and 33 healthy controls while participating in a multi-round trust game with a preprogrammed cooperative counterpart. Based on previous research [4, 12, 18], we expected to find: (i) lower baseline trust in siblings than in controls; (ii) no group difference between overall trusting behavior (i.e. mean investments) throughout the trust game, in line with the previous behavioral finding in siblings of intact ability to adapt to the reciprocity of the trustee [12]; and (iii) reduced activation of the caudate, TPJ, STS, insula and the mPFC in siblings compared to controls.

**METHODS**

**Subjects**

Two groups of subjects were tested for this study: 50 healthy siblings of patients with psychosis, and 33 healthy control subjects. The subjects were recruited from the Dutch Genetic Risk and Outcome in Psychosis (GROUP) study [30] (https://www.group-project.nl). The age range was 18-60 years. The main exclusion criteria were: a personal and family history of any psychiatric or neurological disorders for the control group; and for the relatives: a personal history of psychosis or any psychiatric or neurological disorders, and a family history of any psychiatric disorder other than psychosis. Further exclusion criteria consisted of MRI contraindications such as metal implants, prostheses, pregnancy, history of claustrophobia or epilepsy. The study was approved by a local ethics committee and conducted with strict compliance to ethical standards.

**Experimental design**

We used a modified version of previously implemented multi-round trust games [4-5]. Subjects were scanned while playing one trust game against a computer. They received the information that they would play with an anonymous human partner in a different location. Subjects played the role of the investor throughout the whole game, and hence always made the first move. Each round started with the same starting budget consisting of €10. The main task of the subject
was to decide how much money he or she wanted to share with the anonymous partner. Any whole amount between zero and €10 could be shared. Shared money was tripled and the subject received an amount repaid by the partner.

The computer algorithm was programmed in a probabilistic way, reflecting a cooperative playing style. The amount of the repayments depended on the previous investments of the investor. The repayment of the first round was either 100% or 150% or 200% of the amount invested, each occurring with a probability of 33%. Subsequent repayment increased in a probabilistic way if the current investment reflected an increase in trust relative to the previous investment, but remained stable in all other situations. Hence, with each increase in trust from the side of the investor, the chance of a repayment of 200% increased with 10%.

The game consisted of 20 game trials and 20 null trials. The null trials were included as a baseline condition for the fMRI analysis. The design and duration of each event within the null trials was identical to the game trials. Participants were told that the null trials were not related to the investment decisions.

A single round was set up as follows. Every trial started with a short statement shown for two seconds asking the participant to make an investment choice. Next, the numbers zero to ten appeared on the screen for up to four seconds, requiring participants to make an investment choice. Responses were made with a MRI-compatible two-button box. The invested amount was shown as a histogram and in numbers. The participant waited between two to four seconds for the response of the partner, viewing a bar slowly filling itself with dots, followed by a fixation cross shown for 500 milliseconds. The partner’s response was displayed on the screen in both graphical and numerical form for three seconds. The totals were presented next, for three to five seconds (i.e. depending on the length of the partner’s response) by means of two bar graphs with the corresponding numbers. At the end of each trial, a fixation cross was shown for 500 milliseconds. In total, one trial lasted 18.5 seconds. At the beginning of a new trial, participants always received €10 again. The trials were independent of each other, thus there were no cumulative totals.

**Scanning parameters**

Imaging data were acquired using a 3.0 Tesla whole body scanner (Philips Intera, Best, NL) at the Academic Medical Centre in Amsterdam. A quadrature birdcage head coil was used for radio frequency transmission and reception. Foam padding was placed around the subject’s head in the coil to minimize head movement. The functional images were acquired by a T2-weighted echo producing 37 slices of 3.5 mm thick with no gap, providing complete brain coverage. The functional scans were made in the axial plane (TR = 2.00 s; TE = 30; FOV = 224.0, 129.5, 224.0; Voxel size: 3.5 x 3.5 x 3.5 mm). For anatomical reference, a T1-weighted image (170 slices; isotropic voxels of 1 mm; TR 9 ms; TE 3.54 ms; α 8°; FOV 256 mm) was acquired in the bicommissural plane, covering the whole brain. For safety reasons, ECG measurements were monitored to make sure the participant’s pulse remained stable throughout the entire scanning session.
Statistical Analyses

The SPSS software, version 19, was used to analyze the demographics and the behavioral data of the participants. The first investment made during the first trial of the game was used as an index for baseline trust, as in our earlier fMRI study [18]. Since this measure was based upon the investments from the very first round, subjects did not have any indication as to how the partner will respond. Hence, a higher first investment indicated higher baseline trust. This analysis was conducted by means of a standard one-way Analysis of Variance (ANOVA) with group as the independent variable and the first investment as the dependent variable. The average of all investments was calculated as an index for overall trusting behavior, and analyzed by a one-way ANOVA with group as the independent variable and mean investment as the dependent variable.

The imaging data was analyzed using Brainvoyager QX, version 2.3 (Brain Innovation, Maastricht, The Netherlands). The functional scans were coregistered to each individual anatomical scan and converted to Talairach space. Preprocessing consisted of slice scan-time correction, 3D motion correction, temporal highpass filtering (0.01 Hz), and modest temporal Gaussian smoothing (3 s). Finally, spatial smoothing using a 3D Gaussian kernel (FWHM = 6mm) was performed. The preprocessed functional data were then resampled in standard space, resulting in normalized 4D volume time-course data. For each subject, a protocol was created defining the onsets and offsets of the events (real vs. control investment with an onset of 0 seconds from trial onset and a duration until the last button press, with a maximum duration of 6 seconds; real vs. control repayments with an onset of 10.5-12.5 seconds after trial start -depending on the length of the waiting for partner’s response period- and a duration of 3 seconds). Using these protocols, design matrices were computed by convolving each event with a standard hemodynamic response function.

A priori ROIs were defined based on the Talairach coordinates from previous research, identifying robust activation in independent samples. The caudate (TAL 16, 17, 6) [31] and the insula (TAL -33, 14, -1) [6] were used as reward-related regions-of-interest. To tap mentalizing-related activation, the TPJ (TAL 51, -54, 27) [32], the STS (TAL 61, -56, 7) [33], and the mPFC (TAL -3, 64, 20) [33] were implemented. ROIs were created with a 5 mm sphere centered around the published coordinates. Random-effects General Linear Model analyses were run, based on the individual design matrices and 4D volume time-course data, but restricted to the voxels contained by the ROIs, after correction for serial correlations. The ROI analyses were conducted using Bonferroni adjusted alpha levels of .01 per test (.05/5).

An exploratory whole-brain, voxel-wise analysis focusing on the investment and repayment phase of the trust game was conducted to investigate if there were group wise differences in regions outside the a priori defined ROIs. To correct for multiple comparisons, a cluster extent threshold determined by Monte Carlo simulations was applied [34], which corresponded to a corrected threshold of $p < 0.05$ across the whole brain volume.
RESULTS

Demographics

The control group consisted of 19 men (57.6%) and 14 women (42.4%), with a mean age of 33.4 years (SD 10.17, range 23-55 years). The majority of the sample was right-handed (28 subjects, 84.8%), only 5 subjects were left-handed (15.2%). In total, 13 subjects had a university education level (39.4%), the remaining 20 subjects had lower educational degrees (60.6%).

The relatives group consisted of 21 men (42%) and 29 women (58%), with a mean age of 33.9 years (SD 8.74, range 20-59 years). The majority of the sample was right-handed (40 subjects, 80%), only 9 subjects were left-handed (18%) and one subject did not have a handedness preference (2%). In total, 13 subjects had a university education level (26%), the remaining 37 subjects had lower educational degrees (74%).

There were no significant differences between siblings and controls in terms of age ($F(1,81) = .06, n.s.$), gender ($F(1,81) = 1.93, n.s.$), education ($F(1,81) = .74, n.s.$), and handedness ($F(1,81) = .01, n.s.$).

Behavioural data

The investing behavior during the trust game was not different for the two groups. Siblings had a mean investment of 8.1 euros (SD 1.3) and a first investment of 6.3 euros (SD 2.5). For the controls, the mean investment was 8 euros (SD 1.5) and the first investment was 6.2 (SD 2.2). There were no significant differences between siblings and controls in terms of the mean investments ($F(1,81) = .25, n.s.$) or the first investment ($F(1,81) = .04, n.s.$).

fMRI data

ROI analyses

For the right caudate (Figure 1), there was a significant group effect ($t(81) = -2.93, p < .01$), with stronger activation in controls than siblings during the investment phase of the trust game.

During the repayment phase of the game, there was a significant group effect for the left insula ($t(81) = -3.83, p < .001$), with stronger activation in controls than in patients (Figure 2). There were no significant group differences for the right TPJ ($t(81) = -2.23, p > .01$), the right STS ($t(81) = -1.99, p > .01$) and the mPFC ($t(81) = -2.17, p > .01$) for both phases of the game.

Whole brain analysis

Making investments was associated with stronger activation of the right putamen, right caudate body and right superior frontal gyrus in controls compared to siblings (Table 1). Receiving repayments was associated with stronger activation of the left insula, the left superior frontal gyrus, and the left subcallosal gyrus in controls than siblings (Table 2).
Figure 1. Percent signal change and location of the right caudate, based on mean beta weights.

Figure 2. Percent signal change and location of the left insula, based on mean beta weights.

Table 1. Brain areas with stronger activation in controls vs. siblings during the investment phase

<table>
<thead>
<tr>
<th>Talairach coordinates (X, Y, Z)</th>
<th>Hemisphere</th>
<th>Brodmann's Area</th>
<th>Cerebral region</th>
</tr>
</thead>
<tbody>
<tr>
<td>21, 20, 5</td>
<td>R</td>
<td></td>
<td>Putamen*</td>
</tr>
<tr>
<td>10, 12, 10</td>
<td>R</td>
<td></td>
<td>Caudate*</td>
</tr>
<tr>
<td>12, 68, 6</td>
<td>R</td>
<td></td>
<td>Superior Frontal Gyrus*</td>
</tr>
</tbody>
</table>

* significant at p < 0.05 cluster extent corrected across the whole brain

Table 2. Brain areas with stronger activation in controls vs. siblings during the repayment phase

<table>
<thead>
<tr>
<th>Talairach coordinates (X, Y, Z)</th>
<th>Hemisphere</th>
<th>Brodmann's Area</th>
<th>Cerebral region</th>
</tr>
</thead>
<tbody>
<tr>
<td>-34, 10, 8</td>
<td>L</td>
<td>13</td>
<td>Insula*</td>
</tr>
<tr>
<td>-31, 44, 29</td>
<td>L</td>
<td>9</td>
<td>Superior Frontal Gyrus*</td>
</tr>
<tr>
<td>-22, 8, -12</td>
<td>L</td>
<td>34</td>
<td>Subcallosal Gyrus*</td>
</tr>
</tbody>
</table>

* significant at p < 0.05 cluster extent corrected across the whole brain
DISCUSSION
This study investigated the neural correlates of social reward processing during beneficial social interaction in healthy first-degree relatives of patients with psychosis using a neuro-economic game approach. We found no support for behavioral differences between relatives and controls in terms of initial and mean investments.

The imaging analyses revealed reduced caudate activation in siblings during investments, and reduced insula activation during repayments. The caudate has been linked to greater activation in the generous condition of the trust game in healthy controls [4], and might constitute a neural correlate of social reward processing. Our finding of reduced caudate activation in siblings is in line with our previous imaging study showing reduced caudate activation during trust game interactions in patients [18]. Just like patients, siblings showed a reduced brain reward response to beneficial social interactions, indicating an underlying familial substrate to this deficit.

Prior studies have linked the insular cortex to the processing of positive rewarding stimuli [35] and social cognition [16, 36-37], both processes assumed to be impaired in psychosis. Recently, insula activation during the trust game has been associated with reward and arousal [17]. Moreover, the anterior insula has been postulated to form part of the brain salience network [38-39]. Combined with our finding of reduced insula activation in siblings, this may suggest that reduced attention to social stimuli might be due to ineffective salience processing in the anterior insula.

Our results from the exploratory whole-brain analysis are in line with these ROI results: Controls showed stronger activation than siblings of the caudate during investments and stronger activation of the insula during repayments. Additionally, we found stronger activation of the putamen during investments, the superior frontal gyrus during investments and repayments, and the subcallosal gyrus during repayments. We did not have an explicit hypothesis regarding the subcallosal gyrus, but it has an established role in controlling hedonic tone and is observed to be impaired in depressive illness [40]. The putamen has been linked to reward processing [6], and may hence contribute to impaired reward–related activation in response to cooperation. This strengthens the caudate finding from the ROI analyses, suggesting that siblings show a reduced activation of regions of the brain reward circuit in response to beneficial social interactions. Our imaging data are in line with the findings of previous studies showing that reward-related brain activation is linked to engaging in economic exchange games in healthy controls [4, 15, 41], and further strengthens the hypothesis that aberrant social reward mechanisms may underlie disturbed social interactions in psychosis [18].

In spite of our expectations, we did not find any group differences in terms of TPJ, STS or mPFC activation. Considering that these are traditional mentalizing regions, this suggests that the neural basis for making inferences about the partner’s next moves and intentions might work equally well in siblings as in the control individuals during beneficial social interactions. This is also in line with the previous behavioral finding of intact feedback responsiveness in relatives during trust game interactions [12], implying that their ability to respond flexibly may be linked to a more intact mentalizing system. Abnormal mentalizing activation seems to occur
in patients during the trust game [18], but not in their healthy relatives. This may suggest that the observed mentalizing deficits during social encounters in patients are related to the illness itself, and may not constitute a potential risk factor for psychosis. In contrast, reduced basic trust was demonstrated in relatives previously [12], reflecting lower levels of reward during trusting behaviour, which can be related to our new finding of reduced neural reward processing. This implies that impaired reward-related activation seems to be present in both patients and healthy siblings, suggesting a potential role as a vulnerability marker for psychosis.

Our finding of no behavioral differences between the groups in terms of mean investments is in line with our hypothesis and our previous behavioral study, showing that first-degree relatives were able to adapt their trusting behavior when receiving feedback on the partner’s cooperativeness [12]. In general, this finding is also supported by previous studies, showing that investment behavior in healthy individuals is strongly reinforced by the reciprocity of the interacting partner [8-11]. Surprisingly, we did not find evidence for reduced basic trust in siblings. This is at odds with our previous studies showing lower basic trust in patients [18] and first-degree relatives [12]. However, the current study only included one round of initial investment, whereas the earlier study was set up with 10 rounds of initial investment, allowing for a more thorough investigation of basic trust. Future fMRI studies should focus on a more elaborated assessment of basic trust, by including a condition of subsequent non-feedback rounds, as described in our previous behavioural study [12]. Alternatively, there may be differences in characteristics associated with basic trust of the relatives tested in the current study compared to the relatives from our earlier study.

Finally, the extent to which the trust game indexes social reward as distinct from generic reward processing is unknown, as well as whether individual attitudes towards risk-taking may have an impact on the behavior during the trust game interaction. Although several authors have argued that attitudes towards risk influence behavior in a trust game [42-44], recent empirical studies point towards a fundamental distinction between those components. First, it has been shown that risk attitudes did not predict trust decisions [45]. Secondly, behaviour in a task not involving trust decisions was unrelated to behaviour in a standard trust game [46]. Moreover, social interactions measured by the trust game have been linked to mentalizing [47], and providing social information had an impact on traditional reward learning systems in the striatum [41], pointing towards a clear distinction between social learning and reward learning. However, recent data on healthy individuals playing the trust game during hyperscanning showed a clear shift in the trust signal from the repayment towards the investment phase, in line with traditional reinforcement learning [4]. Combined with the finding of aberrant reward prediction error in psychosis [48], this suggests a prominent role of neural reward processing in the mechanisms underlying social interactions. Our findings with regard to relatives may suggest that impaired reward processing might constitute a vulnerability factor for social deficits commonly observed in psychosis. However, the design of the study does not allow to differentiate social from generic reward. Further research is needed to disentangle the relationship between social learning, reward processing and risk sensitivity during social interactions.
Our findings are further limited by the use of a computer algorithm for the role of the trustee, rather than a real human partner. The manipulation check showed that there were individuals in both groups who had doubts as to whether they were playing with a real human partner. This might have affected the mentalizing operations during the game. However, we chose not to exclude these subjects from our sample, in order to avoid data loss. Future studies should focus on trust game fMRI paradigms with real human partners.

In conclusion, this study provides new evidence for diminished caudate, insula and putamen signals in response to beneficial social interaction in siblings of patients with psychosis. This may be related to the reward and salience deficits commonly observed in psychosis, and indicates that aberrant neural social reward processing reflects, at least in part, vulnerability for psychosis.
REFERENCES


Reduced brain reward response during cooperation in relatives


