Archival Report

Biological Psychiatry

Paradoxical Expectation: Oscillatory Brain Activity Reveals Social Interaction Impairment in Schizophrenia

Pablo Billeke, Alejandra Armijo, Daniel Castillo, Tamara López, Francisco Zamorano, Diego Cosmelli, and Francisco Aboitiz

ABSTRACT

BACKGROUND: People with schizophrenia show social impairments that are related to functional outcomes. We tested the hypothesis that social interaction impairments in people with schizophrenia are related to alterations in the predictions of others' behavior and explored their underlying neurobiological mechanisms.

METHODS: Electroencephalography was performed in 20 patients with schizophrenia and 25 well-matched control subjects. Participants played as proposers in the repeated version of the Ultimatum Game believing that they were playing with another human or with a computer. The power of oscillatory brain activity was obtained by means of the wavelet transform. We performed a trial-by-trial correlation between the oscillatory activity and the risk of the offer.

RESULTS: Control subjects adapted their offers when playing with computers and tended to maintain their offers when playing with humans, as such revealing learning and bargaining strategies, respectively. People with schizophrenia presented the opposite pattern of behavior in both games. During the anticipation of others' responses, the power of alpha oscillations correlated with the risk of the offers made, in a different way in both games. Patients with schizophrenia presented a greater correlation in computer games than in human games; control subjects showed the opposite pattern. The alpha activity correlated with positive symptoms.

CONCLUSIONS: Our results reveal an alteration in social interaction in patients with schizophrenia that is related to oscillatory brain activity, suggesting maladjustment of expectation when patients face social and nonsocial agents. This alteration is related to psychotic symptoms and could guide further therapies for improving social functioning in patients with schizophrenia.

Keywords: Alpha oscillation, EEG, Game theory, Schizophrenia, Social cognition, Theory of mind, Ultimatum game

http://dx.doi.org/10.1016/j.biopsych.2015.02.012

Schizophrenia is a disabling psychiatric disease that is associated with severe cognitive and social disabilities (1,2). Although antipsychotic medications have an important impact on reduction of symptoms, the social integration of patients with schizophrenia is still poorly addressed by current therapies (3). In this context, an important area of research in schizophrenia is the performance of patients in an ongoing social interaction and the underlying neurobiological mechanisms.

The most extensively studied social alterations of patients with schizophrenia are emotion recognition and mentalizing deficit. Failure to understand the intentions and emotions of others has been related to abnormal amygdala activation (4,5) and hypoactivation in the medial prefrontal cortex and temporoparietal junction (TPJ) (6–8). These alterations may be the basis for poor social functioning and psychotic symptoms such as paranoia (1,9–11). However, most studies did not examine social skills in real interactive settings, making it difficult to extrapolate these results to the daily life of these patients and possible therapeutic interventions.

Game theory is a source of ecological paradigms to study social skills (12). In one-shot games, people with schizophrenia or schizotypal traits proposed fairer money distribution than healthy people did; this occurred only when partners were able to reject this distribution (13–17). This finding may mean that patients' behaviors are guided by a negative bias related to the prediction of another's behavior. Following this line, in repetitive games that evaluated trust behaviors, patients with schizophrenia did not trust as much as healthy subjects did (18). In this context, the decision to trust was accompanied by exposure to the possibility that partners did not honor such behavior. Distrust can also be understood as a prediction problem. In these repeated interactions, patients with schizophrenia do not change this behavior according to feedback, which might also reflect insensitivity to social reward. Evidence showed that brain areas related to reward and mentalizing are hypoactive during social interaction in patients with schizophrenia (19). In nonsocial studies, patients with schizophrenia showed alterations in the anticipation of sensory consequences of their actions (20,21) and rewards (22). Current evidence cannot rule out the fact that the alterations in social behaviors are due to nonsocial reinforcement learning impairments.

ISSN: 0006-3223

In this study, we hypothesized that people with schizophrenia demonstrate an alteration in the anticipation of behaviors of other people when they participate in a social interaction compared with when they participate in a nonsocial interaction. To evaluate this hypothesis, we used a repeated version of the Ultimatum Game (UG) under social and nonsocial conditions (Figure 1) (23–25). This game involves two players, the proposer and the responder. First, the proposer makes an offer as to how to split a certain amount of money between the two players. Then the responder either accepts or rejects the offer. If the offer is accepted, the money is split as proposed; if it is rejected, neither player receives any money. During repeated interactions, proposers have to predict the most likely behavior of responders to estimate the risk of their actions and adapt their behavior accordingly (23,26). Crucially, we used a nonsocial condition in which participants know that they are playing against a computational algorithm to control for impairments in nonsocial reinforcement learning.

In healthy people, oscillatory brain activity has been related to sensory prediction. Suppressions of alpha oscillations in sensory cortices are related to the expectation of incoming stimuli (27,28), reflecting an increase of neuron excitability (29) via a release of the inhibition over these areas (30,31). Beta activity in frontal regions has been related to shift of task rules and attentional control required for adapting to a changing environment (32,33). These oscillatory brain activities play a key role in the pathophysiology of schizophrenia (34,35). Patients with schizophrenia failed to modulate oscillatory brain activity when predicting future events (36). Based on prior work that shows alpha and beta suppression related to the anticipation during the UG (24,26), we hypothesize that failure to anticipate behaviors of others in people with schizophrenia correlates with alpha and beta brain oscillations.

METHODS AND MATERIALS

Participants

Two groups of right-handed, Spanish-speaking subjects 18–40 years old participated in the study. The schizophrenia group consisted of 20 (7 women) patients with paranoid schizophrenia according to DSM-IV-R criteria (concordant structured diagnostic interview by two psychiatrists) with illness duration <10 years and currently receiving treatment with atypical antipsychotics (Table 1). All patients were recruited from their treating hospital (Instituto Psiquiátrico Dr. Horwitz Barak), managed their own money, and were not currently drug users. The control group consisted of 25 (10 women) healthy subjects without a personal history of psychiatric diseases or family history of psychosis. We used a database of healthy volunteers of the Cognitive Neuroscience Laboratory to select appropriate age-matched and education-matched control subjects. In this group, 15 subject recordings were taken from our prior work (23). These subjects were selected when their demographic features matched the patient group and their recordings were not >4 months old. All participants provided written informed consent to participate. Two ethics committees approved the experimental protocol (Pontificia Universidad Católica de Chile and Servicio de Salud Metropolitano Norte, Ministerio de Salud).

Assessment

Two psychiatrists used the Positive and Negative Syndrome Scale to assess the extent of psychotic symptoms (interrater agreement, $r = .91$; in the case of nonagreement, we used the mean value between the two scores). General cognition and social cognition of all participants were estimated using a battery of neuropsychological tests. The battery assesses speed of processing (Animal Naming and Symbol-Coding from the Wechsler Adult Intelligence Scale, third edition, and Trail Making Test Part A (37)), sustained attention (Continuous Performance Test, Identical Pairs version (38)), working memory (letter and number span and spatial span from the Wechsler Memory Scale, third edition), learning (free recall of Rey-Osterrieth Complex Figure and Wechsler Memory Scale, third edition, Word List1), planning and reasoning (copy of Rey-Osterrieth Complex Figure and Tower of London test (39)), and social cognition (Baron-Cohen *et al.* (40) face emotion recognition test). It took ≤3 weeks to carry out the

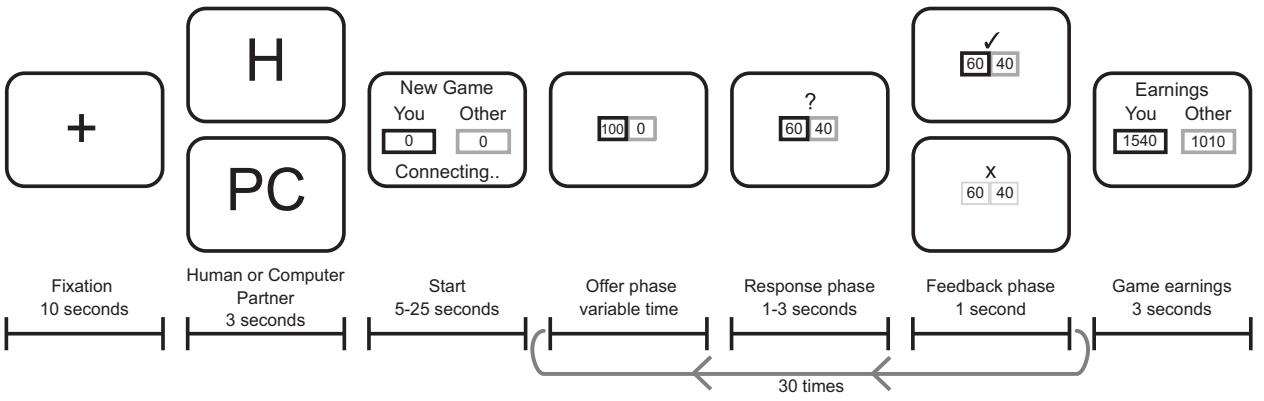

Figure 1. Timeline of a game. Proposers (black box) and responders (gray box, computational simulations; see Methods and Materials) played an iterated Ultimatum Game. The proposer makes an offer on how to split 100 Chilean pesos between the responder and himself or herself (offer phase). The responder decides either to accept or to reject it (response phase). If the responder accepts the offer, the money is split as proposed, and if the responder rejects it, the money is lost. The response is shown on the screen for 1 sec (feedback phase). Each game consists of 30 iterated offers. At the beginning of each game, the proposer sees a cue that indicates if his or her partner is a human (H) or computer (PC).

Table 1. Patient Characteristics

	Schizophrenic Patients (n = 20)	Control Subjects (n = 25)	p Value
Women, n (%)	7 (35%)	10 (40%)	.7
Age, Mean (SEM)	28.1 (.9)	27.9 (1.0)	.9
Socio-Educational Score, Mean (SEM)	18.65 (.7)	19.08 (.6)	.7
PANSS, Mean (SEM)			
Positive	21.3 (1.8)	—	—
Negative	24.2 (1.7)	—	—
General	46.6 (3.9)	—	—
Total	95.0 (8.8)	—	—
Medication, n (%)			
First-Generation Antipsychotic	4 (20%)	—	—
Second-Generation Antipsychotic	20 (100%)	—	—
Benzodiazepine	5 (25%)	—	—
Antidepressant	5 (25%)	—	—
Chlorpromazine Equivalent Doses, Mean (SEM)	625 (77.4)	—	—
Cognitive Evaluation, Mean (SEM)			
Speed of Processing	−.84 (.15)	.62 (.2)	<.001
Sustained Attention	−.56 (.19)	.75 (.14)	<.001
Working Memory	−.62 (.15)	.89 (.16)	<.001
Planning and Reasoning	.07 (.12)	1.05 (.11)	<.001
Learning	−.60 (.16)	.71 (.19)	<.001
Social Cognition	−.41 (0.19)	.59 (.23)	.002

PANSS, Positive and Negative Syndrome Scale.

psychiatric evaluation, the electroencephalography (EEG) recording, and the psychological evaluation.

Task

Participants played as proposers in a repeated version of the UG (Figure 1). Subjects believed they were playing with either a human partner or a computer partner, but they were actually always playing with a computational simulation (see further on). The experimenter explained the instructions describing the game verbally, and the participants read on-screen instructions at the beginning of the game. The participants played a probe game with the experimenter to get familiar with the setting. At the beginning of each game, participants watched a fixation cross (10 sec, fixation phase). Next, a signal on the screen indicated whether the game was against a computer partner ("PC") or a human partner ("H"). Each game consisted of 30 rounds, and each participant played as a proposer 16 times with different simulated responders (eight human games and eight computer games, randomly distributed). In the case of computer games, the experimenter explained that the computer simulation assigns a probability to accept the offer given the amount of money offered (a direct, positive relation) and that this probability could change between games but not during a game with the same computer partner. The simulation used in human games and computer games was the same. Each trial had three phases as follows: In the first (offer phase, variable duration), the proposer had to make the offer. In the second (anticipation phase, 1.5–4 sec), the proposer waited for the partner's response. In the last phase (feedback phase, 1 sec), the response was revealed. At the end of each game, the earnings each player had made were revealed. After the set of games concluded, the experimenter interviewed each participant to check whether they had understood the game correctly. The amount of money each participant received consisted of a fixed compensation and an incentive that depended on the participant's performance in 1 of the 16 games chosen randomly (the final compensation ranged from 6000 to 12,000 CLP [~12 to 24 USD]).

Simulation

The simulations used in the task were based on a modeling of real people playing as responders (Supplemental Methods and Materials in Supplement 1) (26). The simulation gives a probability of acceptance in direct relation to the money offered to the responder; the change of the money offered related to the preceding round and whether the responder had rejected or accepted the offer in the preceding round. Using this model, we were able to create different virtual players. All participants played with the same simulated partners. All participants indicated that they believed they had played against another human and that they felt the human games were different from the computer games. We used logit of the probability of acceptance (given by the simulation) to evaluate the risk per each offer made.

Electrophysiologic Recordings

Continuous EEG recordings were obtained with a 40-electrode NuAmps EEG system (Compumedics Neuroscan, Charlotte, North Carolina). All impedances were kept <5 kΩ. Electrode impedance was retested during pauses to ensure stable values throughout the experiment. All electrodes were referenced to averaged mastoids during acquisition, and the signal

was digitized at 1 kHz. Electro-oculography was performed using four electrodes with vertical and horizontal bipolar derivations. All recordings were acquired using Scan 4.3 (Compumedics Neuroscan) and stored for off-line treatment. At the end of each session, electrode position and head points were digitalized using a three-dimensional tracking system (Fastrack; Polhemus, Colchester, Vermont).

EEG Data Analysis

The EEG signals were preprocessed using a .1–100 Hz band-pass filter. Eye blinks were identified by a threshold criterion of $\pm$100 μV, and their contribution was removed from each dataset using principal component analysis by singular value decomposition and spatial filter transform (Supplemental Methods and Materials in Supplement 1). Other remaining artifacts (e.g., muscular artifacts) were detected by visual inspection of the row signal and the spectrogram. We obtained 425 $\pm$ 35 artifact-free trials per subject. All artifact-free trials were transformed into current source density (CSD) that was estimated using the spherical spline surface Laplacian algorithm suggested by Perrin *et al.* (41) and implemented by Kayser and Tenke (42,43). The CSD computes the second spatial derivative of voltage between nearby electrode sites, acting as a high-pass spatial filter. The CSD transformation highlights local electrical activities at the expense of diminishing the representation of distal activities (Supplemental Methods and Materials in Supplement 1). Induced power distribution was computed using wavelets transform, with a five-cycle Morlet wavelet, in -1.5 to 1.5-sec windows around the offer and feedback releases. We displayed the result only for -1 to 1 sec over the segmented signals to avoid edged artifact. For all analyses, we used the decibel of power related to the fixation phase as baseline (at the beginning of each game) (Figure 1), where we did not find any significant differences between groups (Figure S1 in Supplement 1). To estimate the source of the EEG signal, we applied a weighted minimum norm estimate inverse solution (44) with unconstrained dipole orientations in single trials per condition per subject (Supplemental Methods and Materials in Supplement 1). To calculate the current source distribution, we used individual head models based on default anatomy (Colin 27 from McConnell Brain Imaging Centre, Montreal Neurological Institute, McGill University, Montreal, Quebec) warped to the subject head shape.

Statistical Analysis

We used the Kolmogorov-Smirnoff test for normality. When the data did not meet the normal assumption, we used nonparametric tests. In the case of histogram of the frequency of each offer, we compared groups using the Wilcoxon test corrected with false discovery rate ($q < .05$). To test for interaction between diagnosis and type of game, we used analysis of variance to compare the mean of the offer, the variation of the offers, and the earnings per subject. Next, we re-evaluated pair comparisons using Wilcoxon test and false discovery rate. To analyze the evolution of the risk of the offers across the rounds during a game, we used the general linear model (GLM) and mixed linear model. For EEG statistical analysis, we first fitted a GLM of the power of the oscillatory activity per trial in each subject (first-level analysis). We obtained a three-dimensional matrix of t value (sensor, time, frequency) for each regressor and subject. We then explored for differences between groups and conditions using the Wilcoxon test (second-level analysis) (Supplemental Methods and Materials in Supplement 1). To correct for multiple comparisons in time-frequency charts and source, we used the cluster-based permutation test (reference 5 in Supplemental References in Supplement 1). For partial correlations between oscillatory brain activity and clinical parameters, we corrected by the chlorpromazine dose equivalent based on Andreasen *et al.* (45).

Software

All behavioral statistical analyses were performed in R (The R Project for Statistical Computing, available at http://www.r-project.org/). The EEG signal processing was implemented in MATLAB using the CSD toolbox (42), in-house scripts (available at http://lantoolbox.wikispaces.com/), BrainStorm (46) and OpenMEEG toolboxes (47).

RESULTS

Behavior

Patients made hyperfair offers (offers >50% of the money) more frequently at the expense of the frequency of fair offers (Figure 2A). During both conditions, patients made higher offers than the offers made by control subjects (mean offers, patients with schizophrenia, human games = 45.3, computer games = 46.6; control subjects, human games = 42.2, computer games = 42.3; analysis of variance, diagnosis [$F = 5.919$, $p = .0173$]; game [$F = .3$, $p = .5$]; diagnosis*game [$F = .11$, $p = .7$]) (Figure 2B). Patients also demonstrated a greater variation of their offers during a game, which was evaluated as the standard deviation (analysis of variance, diagnosis [$F = 26.841$, $p = 1.72e\text{-}06$]; game [$F = .2$, $p = .6$]; diagnosis*game [$F = .13$, $p = .7$]). This behavior results in patients obtaining fewer profits under both conditions (expressed by the mean of the money obtained normalized by the number of played rounds, patients with schizophrenia, human games = 31, computer games = 32; control subjects, human games = 34.4, computer games = 34.5; diagnosis [$F = 5.177$, $p = .0257$]; game [$F = .047$, $p = .8$]; diagnosis*game [$F = .13$, $p = .7$]).

We next evaluated whether patients elaborated a strategic evolution of their offers. For this, as in our prior work (23), we correlated the risk of the offer made during a game with the round number (i.e., the place of the offer during the game, range 1–30). The GLM estimated over the subjects' mean of the risk per condition indicated that there was a tendency to make safer offers during the last rounds (round [$t = 3.6$, $p = .0004$]) and that the patients made safer offers (diagnosis [$t = -3.016$, $p = .0031$]) (Table 2). The behavioral patterns in human games and computer games were different between the patients with schizophrenia and the control subjects (Figure 2D). Control subjects demonstrated a greater slope for computer games than for human games, whereas patients with schizophrenia presented a greater slope for human games. In the GLM, the interaction among round number, diagnosis, and games was significant (round*diagnosis*game [$t = 2.821$, $p = .005$]). Additionally, control subjects began

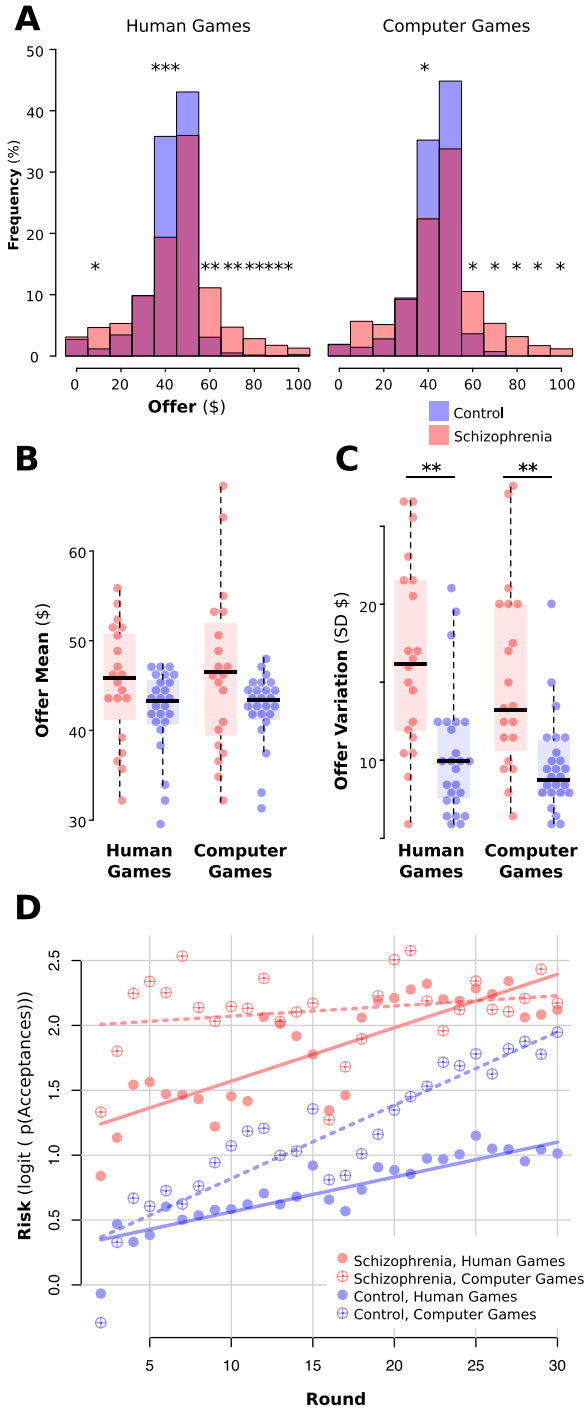

Figure 2. Behavioral results. **(A)** Histogram of the offers per conditions and groups. **(B)** Mean of the offer per subject separated by conditions and groups. **(C)** Variation of the offer per subjects separated by conditions and groups. **(B, C)** Circles represent subjects, broken lines represent the medians, and rectangles represent the interquartile segment. **(D)** Correlations between round number and risk per conditions and groups. Circles represent the mean of the risk across games and subjects per each round. The risk was estimated as the logit transform of the probability of acceptance (see Methods and Materials). **(A–D)** Blue represents healthy control subjects, and red represents patients with schizophrenia. $^{*}p < .05$, $^{**}p < .01$, $^{***}p < .001$ (Wilcoxon test and false discovery rate).

computer games and human games with comparable offers, whereas patients began computer games with safer offers (game*diagnosis [$t = -2.138$, $p = .034$]). We obtained similar results using a linear mixed model over single trials (Table S4 in Supplement 1). We did not find any correlation between either the offers or the variation of the offers and symptoms of schizophrenia.

EEG

Because the behavioral results indicated that patients with schizophrenia demonstrated an opposed strategy in human games and computer games compared with control subjects, we explored different modulations of oscillatory brain activity between both games. Per each subject, we modeled separately the power of the single-trial EEG signal in the anticipatory phase (using the risk of the offer as regressor; b2 in Figures 3A and 4A) and the feedback phase (using the response and the risk of the offer as regressors; b4 and b5 in Figures 3A and 4A). We calculated the mean of t values across subjects and compared them between conditions and groups (Methods in Supplement 1).

In the anticipatory phase, we found a modulation of medial prefrontal oscillations (Fz and FCz electrodes) in the alpha (9–12 Hz) and beta (15–30 Hz) ranges (Figure 3). In human games, control subjects demonstrated a positive correlation, which started .4 sec after they made the offer (Figure 3B), whereas patients with schizophrenia demonstrated a positive correlation mainly in computer games (Figure 3C). In the case of patients with schizophrenia, these patterns of activity led to a significant negative difference between human games and computer games (main effects, alpha, 10–15 Hz, .3–.6 sec; main probable sources in the superior frontal gyrus and left temporoparietal regions) (Figure 3D–F). When contrasting human games and computer games, we also found a significant difference between the groups (main effects, alpha, 10–15 Hz, .4–.6 sec; beta, 20–30 Hz, .5–.6 sec, main probable sources in the right temporoparietal region, right superior parietal lobule, and superior-middle frontal gyrus) (Figures 3D and 4F).

In the right posterior region (TP8 and T8 electrodes) (Figure 4), we found that control subjects demonstrated a specific modulation of alpha/beta oscillations during the anticipatory phase. These oscillations showed a correlation

Table 2. General Linear Model of the Mean of Risk Across Subjects per Round

	Slope	SE	t Value	p Value
Intercept	1.15787	.20642	5.609	1.53e-07[a]
Round	.04121	.01143	3.605	.000471[a]
Game (PC)	.83424	.29192	2.858	.005103[b]
Diagnosis (CON)	−.86406	.28651	−3.016	.003183[b]
Round*Game	−.03331	.01617	−2.060	.041728[c]
Round*Diagnosis	−.01433	.01542	−.930	.354505
Game*Diagnosis	−.87446	.40903	−2.138	.034738[c]
Round*Diagnosis*Game	.06302	.02234	2.821	.005686[b]

CON, control; PC, computer partner.
[a] $p < .001$.
[b] $p < .01$.
[c] $p < .05$.

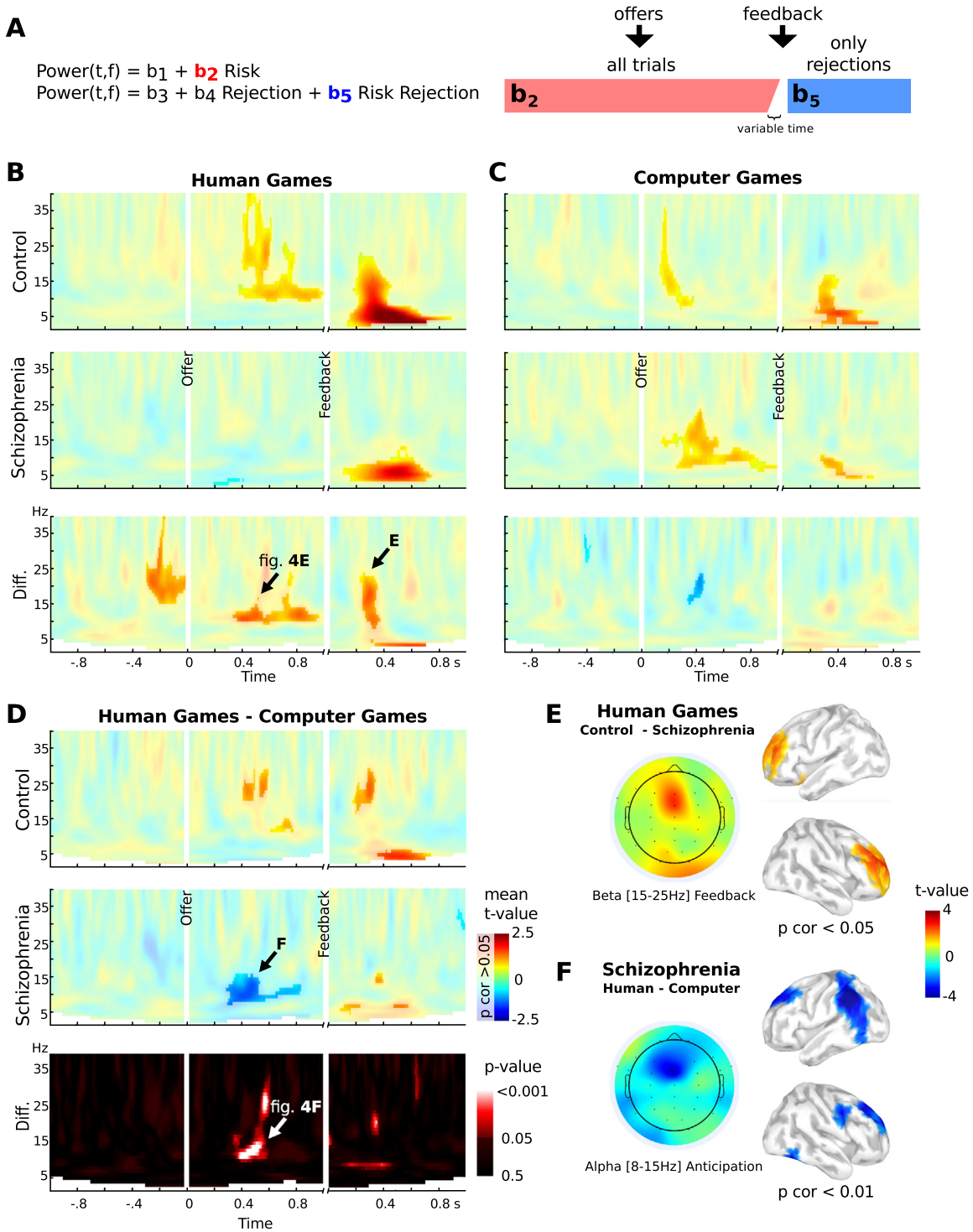

Figure 3. Oscillatory brain activity in the frontal region. **(A)** Model used to correlate the risk of the offer and the power of the oscillatory brain activity; b_2 and b_5 are the coefficients of the models plotted in **(B–D)**, for anticipatory and feedback phases, respectively. **(B)** Time-frequency chart during human games (frontocentral electrodes, Fz and FCz). **(C)** Time-frequency chart during computer games. **(D)** Time-frequency chart of the differences between human games and computer games. **(B–D)** Colors represent the mean across subjects of the *t* value of the individual correlation between the power of the oscillatory brain activity and the risk of the offer made (b_2 and b_5 in **(A)**). The clusters with significant effects are highlighted ($p < .01$ cluster-corrected). **(E)** Topographic distribution and estimated sources of the significant cluster of beta activity after the feedback (15–25 Hz, .2–.4 sec) in the contrast control − schizophrenia for human games, as indicated in **(B)**. **(F)** Topographic distribution and estimated source of the significant cluster of alpha activity after the offer (8–15 Hz, .3–.8 sec) in the contrast human games − computer games for control, as indicated in **(D)**.

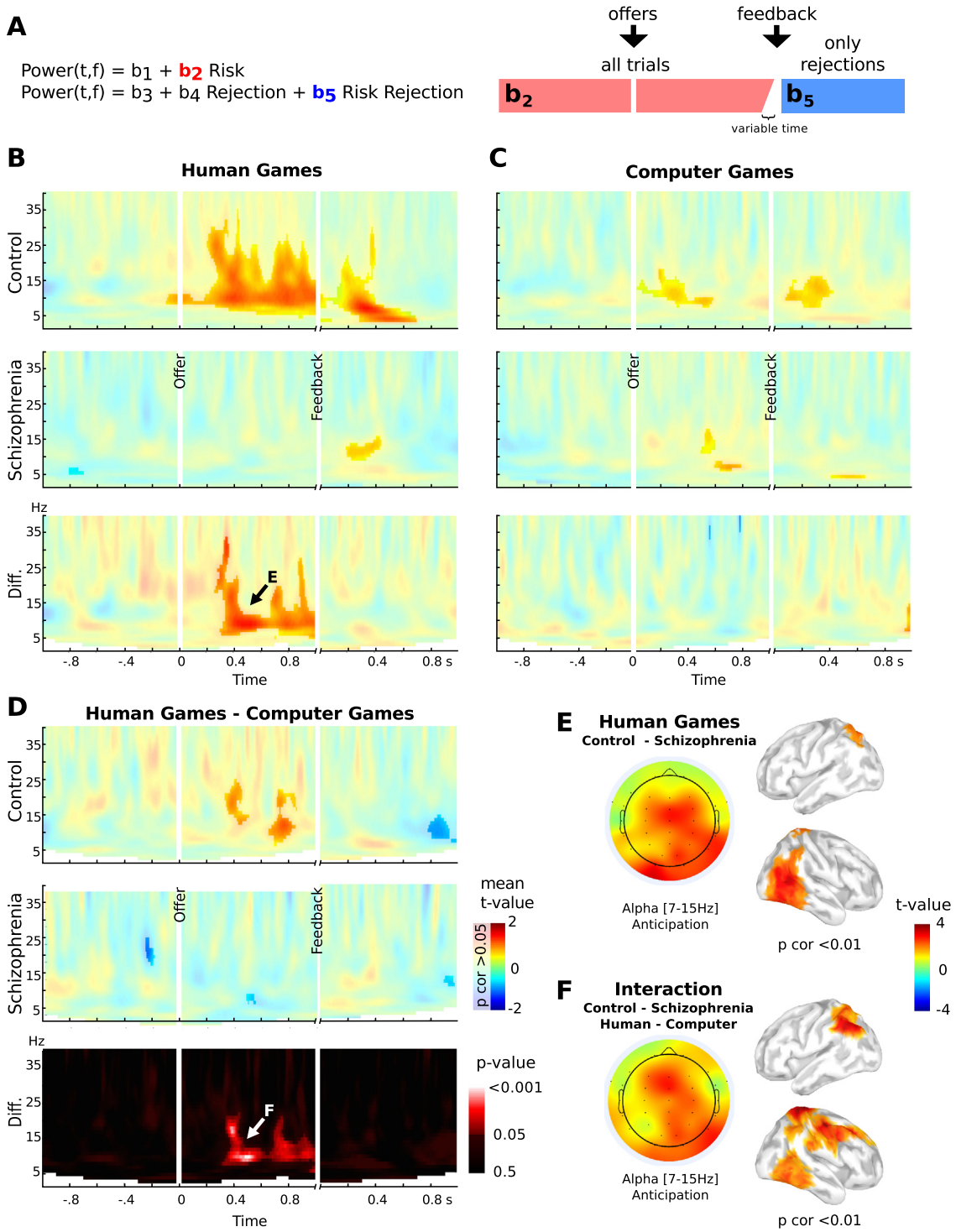

Figure 4. Oscillatory brain activity in the right temporoparietal region. **(A)** Model used to correlate the risk of the offer and the power of the oscillatory brain activity; b_2 and b_5 are the coefficient of the models plotted in **(B–D)**, for anticipatory and feedback phase, respectively. **(B)** Time-frequency chart during human games (temporoparietal electrodes, TP8 and T8). **(C)** Time-frequency chart during computer games. **(D)** Time-frequency chart of the differences between human games and computer games. **(B–D)** Colors represent the mean across subjects of the *t* value of the individual correlation between the power of the oscillatory brain activity and the risk of the offer made (b_2 and b_5 in **(A)**). The clusters with significant effects are highlighted ($p < .01$ cluster-corrected). **(E)** Topographic distribution and estimated sources of the significant cluster of alpha activity (differences between control subjects and patients with schizophrenia in human games) after the offer (8–15 Hz, .3–1 sec) as indicated in **(B)** and in Figure 3B. (F) Topographic distribution and estimated sources of the significant cluster of alpha activity (differences between control subjects and patients with schizophrenia in the contrast human games − computer games) after offer (8–15 Hz, .3–.8 sec) as indicated in **(D)** and in Figure 3D.

with the risk in human games only for control subjects, leading to a significant difference between the groups in the contrast human games − computer games (main effects, alpha, 8–13 Hz, .35–1 sec; beta, 15–20 Hz, .35–.45 sec, main probable sources in the right temporoparietal region, right superior parietal lobule, middle frontal gyrus, and left inferior parietal lobe) (Figure 4F). These results were consistent using risk as a categorical rather than a continuous variable (Figures S2–S4 in Supplement 1).

Finally, we assessed the behavioral meaning of the paradoxical patterns of alpha brain activity found in patients with schizophrenia when comparing human games versus computer games. Because antipsychotic medication may change the electrical brain activity, we used Spearman partial correlations correcting by chlorpromazine equivalent doses (CED). We found that the alpha frontal oscillations in the contrast human games − computer games correlated with the slope of the offer evolution in computer games ($\rho = .63$, $p = .006$, corrected by CED), although not in human games ($\rho = -.17$, $p = .5$, corrected by CED). Concerning symptoms, the alpha frontal oscillations correlated only with positive symptoms in the sense that patients with more severe symptoms demonstrated greater negative (paradoxical) alpha activity ($\rho = -.53$, $p = .031$, corrected by CED) (Table 3 and Supplementary Tables S4 and S6). In relation to cognitive tests, only the learning tests correlated with alpha activity ($\rho = -.56$, $p = .03$) (Table S5 in Supplement 1), although this correlation did not persist when we corrected by CED (Table 3 and Table S6 in Supplement 1).

DISCUSSION

A wealth of evidence indicates that patients with schizophrenia have stable social impairments that are highly related to functional deficits (1,48). However, the biological mechanisms underlying the social impairments remain elusive. Our findings provide evidence for the existence of a neural mechanism related to social interaction in patients with schizophrenia. To isolate the neuronal activity related to social processes, we used a well-known neuroeconomics paradigm and contrasted it with the same task framed in a nonsocial context. In healthy people, these different contexts generate a strategic switch to tackle the games (23). We used this contrast to identify the behavioral and neuronal alterations related to social decision making in people with schizophrenia. We found that patients with schizophrenia demonstrate an opposite pattern of offer evolution in human games versus computer games compared with control subjects. This behavioral pattern correlated with an opposite modulation of alpha activity in frontal and temporoparietal regions when subjects anticipated the behavior of their partners.

Table 3. Partial Correlations Among Alpha Power, Positive Symptoms, Learning Score, and Antipsychotic Doses

	Positive Symptoms	Learning Score	Antipsychotic Doses[a]
Alpha Power[b]	−.59[c]ρ	.17ρ	.57[c]ρ
p Value	.012	.49	.015
Positive Symptoms		−.19ρ	.74[d]ρ
p Value		.45	.0005
Learning Score			.26ρ
p Value			.31

[a]Chlorpromazine equivalent doses.

[b]Difference in the alpha power (8–12 Hz) between human games and computer games in frontal electrodes (Fz and FCz).

[c]$p < .05$.

[d]$p < .001$.

A possible interpretation is that these behaviors are due to nonsocial cognitive impairments. We found that most of the features of the behavior of the patients with schizophrenia described in one-shot UGs, such as making more hyperfair offers (13,14,16) and making more variable offers (13), were not different when comparing human games and computer games. Additionally, in a repeated version of the Trust Game, patients with schizophrenia do not modify their behavior in relation to either the knowledge of their partner's trustworthiness or their partner's behavior (18,19). This evidence could reflect a general mechanism related to either avoiding the possibility of negative feedback or learning impairments rather than a specific social alteration. However, patients with schizophrenia do not show risk aversion in nonsocial economic decision making (49). Our results also indicated that patients with schizophrenia demonstrated behavioral and electrophysiologic differences when comparing human games and computer games. It is unlikely that our results were due to nonsocial cognitive impairments per se. Our findings are compatible with two processes—impairments in the anticipation of behaviors of social agents and misattributions of intention to social and nonsocial agents.

There is evidence of a dysfunction in the ability to predict the sensory consequences of actions in patients with schizophrenia (20,21). It has been proposed that this sensory-prediction alteration may have a general role in the mechanism that leads to schizophrenic symptoms (50–52). This proposal may also be true for social skills because these skills may be understood as a prediction problem in the sense that they deal with the prediction of behaviors of other people (53). Suppression in alpha activity has been related to temporal prediction (27). Suppression in alpha activity can reflect the increase of local cortical excitability (29–31) and may have an active role in cortical processing, indicating an increase of information transmission (54,55). Alpha phase can coordinate pulses of information transmission that can coexist with power decrease (56,57). The location of the brain oscillatory activity is compatible with three brain regions that are related to social-decision mechanisms—medial prefrontal cortex, inferior parietal lobule, and TPJ. Hypoactivity in medial prefrontal cortex and TPJ is directly linked to the mentalizing deficits observed in patients with psychosis (6,58,59). In social games and in on-line mentalizing tasks, patients also showed reduced TPJ activity (19,60). In our experiments, one of the possible sources of the alpha activity was found in the left temporoparietal region, where other studies have found hypoactivation in patients with schizophrenia (6). The activation of this region in other games has also shown correlation with psychotic symptoms (61). A possible interpretation is that the failure of anticipating behaviors of other people is due to the lack of on-line mentalizing abilities, which is related to psychotic symptoms.

Another complementary interpretation is the existence of misattribution of intentions to social and nonsocial agents

secondary to an alteration of the evaluation of stimulus saliency. During reward anticipation tasks, patients show hypoactivation of the ventral striatum, which has been associated with the alteration of the processing of saliency (22,62). More recent evidence revealed a deregulation of the salience network activity, which includes insular and medial prefrontal cortex, and an alteration of its connectivity with dorsolateral prefrontal cortex (63,64). It has been proposed that alterations in the salience process generate erroneous attribution of stimuli relevance that could lead to the expression of psychotic symptoms. In the context of our experiment, misattribution of saliency to social and nonsocial partners can generate the opposite patterns of behavior and the electrophysiologic modulation in human games and computer games. The bias to attributing intentions to computer partners could generate the anticipatory oscillatory activity in frontal and parietal regions leading to an opposite strategy at the behavioral level. The oscillatory activity correlated mainly with the behavior during computer games. This correlation could reflect overinterpretation related to psychotic symptoms (65–67). A region in the inferior parietal lobule has been associated with impairments in agency attribution and self-other distinction in schizophrenia (68). Our results could also indicate an alteration in social saliency processes that can lead to an agency bias to nonhuman partners.

An important limitation of our results regards the existence of a correlation between alpha activity modulation and antipsychotic medication. However, this correlation had the opposite direction of the correlation between alpha activity and positive symptoms. The correlation between alpha activity and positive symptoms remains significant after statistical correction for antipsychotic doses. Despite these facts, it is impossible to rule out an effect of medication (69). It is important to carry out similar experiments in pharmacologically naïve patients or relatives to weigh the relative influence of medication and psychotic symptoms on these findings.

In conclusion, our results reveal an alteration in the anticipation of the behaviors of others in patients with schizophrenia. The patterns of social interaction and the underlying alpha oscillatory brain activity in the mentalizing network suggest an impairment of attribution of intentions in patients with schizophrenia that leads to maladjusted expectations for behaviors of social and nonsocial agents during an ongoing interaction. This impairment is related to psychotic symptoms and represents a potential target for the development of therapeutic interventions to improve social functioning in patients with schizophrenia.

ACKNOWLEDGMENTS AND DISCLOSURES

This work was supported by Comisión Nacional de Investigación Científica y Tecnológica Grant No. 791220014 (PB); Project "Anillo en Complejidad Social" Grant No. SOC-1101 (PB, FZ, and DC); and the Millennium Center for the Neuroscience of Memory, Chile, Grant No. NC10-001-F, which is developed with funds from the Innovation for Competitivity from the Ministry for Economics, Fomentation and Tourism, Chile.

We thank Rodrigo Henríquez and Sergio Ruiz for their supportive assistance, Gladys Bobadilla for mathematical assistance, and Marina Flores for proofreading the manuscript.

The authors report no biomedical financial interest or potential conflicts of interest.

ARTICLE INFORMATION

From the Centro de Investigación en Complejidad Social (PB, FZ), Facultad de Gobierno, Universidad del Desarrollo; Laboratorio de Neurociencias Cognitivas (PB, FZ, FA), Departamento de Psiquiatría, Facultad de Medicina, and Interdisciplinary Center for Neuroscience (PB, FZ, DCo, FA), and Escuela de Psicología (DCo), Facultad de Ciencias Sociales, Pontificia Universidad Católica de Chile; and Instituto Psiquiátrico Dr. Horwitz Barak (AA, DCa, TL), Servicio de Salud Metropolitano Norte, Santiago, Chile.

Address correspondence to Pablo Billeke, M.D., Ph.D., Centro de Investigación en Complejidad Social, Facultad de Gobierno, Universidad del Desarrollo. Av. La Plaza 680, Las Condes, Santiago, Chile; E-mail: pbilleke@udd.cl.

Received Aug 18, 2014; revised Dec 23, 2014; accepted Feb 6, 2015.

Supplementary material cited in this article is available online at http://dx.doi.org/10.1016/j.biopsych.2015.02.012.

REFERENCES

1. Billeke P, Aboitiz F (2013): Social cognition in schizophrenia: From social stimuli processing to social engagement. Front Psychiatry 4: 1–12.
2. Green MF, Penn DL, Bentall R, Carpenter WT, Gaebel W, Gur RC, *et al*. (2008): Social cognition in schizophrenia: An NIMH workshop on definitions, assessment, and research opportunities. Schizophr Bull 34:1211–1220.
3. Green MF, Horan WP (2010): Social cognition in schizophrenia. Curr Dir Psychol Sci 19:243–248.
4. Hall J, Whalley HC, McKirdy JW, Romaniuk L, McGonigle D, McIntosh AM, *et al*. (2008): Overactivation of fear systems to neutral faces in schizophrenia. Biol Psychiatry 64:70–73.
5. Holt DJ, Coombs G, Zeidan MA, Goff DC, Milad MR (2012): Failure of neural responses to safety cues in schizophrenia. Arch Gen Psychiatry 69:893–903.
6. Benedetti F, Bernasconi A, Bosia M, Cavallaro R, Dallaspezia S, Falini A, *et al*. (2009): Functional and structural brain correlates of theory of mind and empathy deficits in schizophrenia. Schizophr Res 114: 154–160.
7. Vistoli D, Brunet-Gouet E, Lemoalle A, Hardy-Baylé M-C, Passerieux C (2011): Abnormal temporal and parietal magnetic activations during the early stages of theory of mind in schizophrenic patients. Soc Neurosci 6:316–326.
8. Brunet-Gouet E, Achim AM, Vistoli D, Passerieux C, Hardy-Baylé M-C, Jackson PL (2011): The study of social cognition with neuroimaging methods as a means to explore future directions of deficit evaluation in schizophrenia? Psychiatry Res 190:23–31.
9. Frith CD (2004): Schizophrenia and theory of mind. Psychol Med 34: 385–389.
10. Sprong M, Schothorst P, Vos E, Hox J, van Engeland H (2007): Theory of mind in schizophrenia: Meta-analysis. Br J Psychiatry 191:5–13.
11. Smith MJ, Schroeder MP, Abram SV, Goldman MB, Parrish TB, Wang X, *et al*. (2014): Alterations in brain activation during cognitive empathy are related to social functioning in schizophrenia. Schizophr Bull 41: 211–222.
12. Fett AK, Shergill SS, Krabbendam L. (2015): Social neuroscience in psychiatry: Unravelling the neural mechanisms of social dysfunction. Psychol Med. 45:1145-65.
13. Agay N, Kron S, Carmel Z, Mendlovic S, Levkovitz Y (2008): Ultimatum bargaining behavior of people affected by schizophrenia. Psychiatry Res 157:39–46.
14. Wischniewski J, Brune M (2011): Moral reasoning in schizophrenia: An explorative study into economic decision making. Cogn Neuropsychiatry 16:348–363.
15. Wischniewski J, Windmann S, Juckel G, Brüne M (2009): Rules of social exchange: Game theory, individual differences and psychopathology. Neurosci Biobehav Rev 33:305–313.
16. Csukly G, Polgár P, Tombor L, Réthelyi J, Kéri S (2011): Are patients with schizophrenia rational maximizers? Evidence from an ultimatum game study. Psychiatry Res 187:11–17.

17. van't Wout M, Sanfey AG (2011): Interactive decision-making in people with schizotypal traits: A game theory approach. Psychiatry Res 185:92–96.
18. Fett AK, Shergill SS, Joyce DW, Riedl A, Strobel M, Gromann PM, Krabbendam L (2012): To trust or not to trust: The dynamics of social interaction in psychosis. Brain 135:976–984.
19. Gromann PM, Heslenfeld DJ, Fett AK, Joyce DW, Shergill SS, Krabbendam L (2013): Trust versus paranoia: Abnormal response to social reward in psychotic illness. Brain 136(Pt 6):1968–1975.
20. Shergill SS, Samson G, Bays PM, Frith CD, Wolpert DM (2005): Evidence for sensory prediction deficits in schizophrenia. Am J Psychiatry 162:2384–2386.
21. Voss M, Moore J, Hauser M, Gallinat J, Heinz A, Haggard P (2010): Altered awareness of action in schizophrenia: A specific deficit in predicting action consequences. Brain 133:3104–3112.
22. Grimm O, Heinz A, Walter H, Kirsch P, Erk S, Haddad L, *et al*. (2014): Striatal response to reward anticipation: Evidence for a systems-level intermediate phenotype for schizophrenia. JAMA Psychiatry 71:531–539.
23. Billeke P, Zamorano F, López T, Rodriguez C, Cosmelli D, Aboitiz F (2014): Someone has to give in: Theta oscillations correlate with adaptive behavior in social bargaining. Soc Cogn Affect Neurosci 9: 2041–2048.
24. Billeke P, Zamorano F, Chavez M, Cosmelli D, Aboitiz F (2014): Functional cortical network in alpha band correlates with social bargaining. PLoS One 9:e109829.
25. Slembeck T (1999): Reputations and fairness in bargaining: Experimental evidence from a repeated ultimatum game. Discussion paper 9904. St. Gallen, Switzerland: Forschungsgemeinschaft für Nationalökonomie an der Universität St. Gallen.
26. Billeke P, Zamorano F, Cosmelli D, Aboitiz F (2013): Oscillatory brain activity correlates with risk perception and predicts social decisions. Cereb Cortex 23:2872–2883.
27. Rohenkohl G, Nobre AC (2011): α oscillations related to anticipatory attention follow temporal expectations. J Neurosci 31:14076–14084.
28. Buchholz VN, Jensen O, Medendorp WP (2014): Different roles of alpha and beta band oscillations in anticipatory sensorimotor gating. Front Hum Neurosci 8:446.
29. Lange J, Oostenveld R, Fries P (2013): Reduced occipital alpha power indexes enhanced excitability rather than improved visual perception. J Neurosci 33:3212–3220.
30. Jensen O, Mazaheri A (2010): Shaping functional architecture by oscillatory alpha activity: Gating by inhibition. Front Hum Neurosci 4:186.
31. Klimesch W (2012): Alpha-band oscillations, attention, and controlled access to stored information. Trends Cogn Sci 16:606–617.
32. Miller EK, Buschman TJ (2013): Cortical circuits for the control of attention. Curr Opin Neurobiol 23:216–222.
33. Buschman TJ, Denovellis EL, Diogo C, Bullock D, Miller EK (2012): Synchronous oscillatory neural ensembles for rules in the prefrontal cortex. Neuron 76:838–846.
34. Uhlhaas PJ, Haenschel C, Nikolić D, Singer W (2008): The role of oscillations and synchrony in cortical networks and their putative relevance for the pathophysiology of schizophrenia. Schizophr Bull 34:927–943.
35. Uhlhaas PJ, Singer W (2010): Abnormal neural oscillations and synchrony in schizophrenia. Nat Rev Neurosci 11:100–113.
36. Lakatos P, Schroeder CE, Leitman DI, Javitt DC (2013): Predictive suppression of cortical excitability and its deficit in schizophrenia. J Neurosci 33:11692–11702.
37. Gaudino EA, Geisler MW, Squires NK (1995): Construct validity in the Trail Making Test: what makes Part B harder? J Clin Exp Neuropsychol 17:529–535.
38. Cornblatt BA, Risch NJ, Faris G, Friedman D, Erlenmeyer-Kimling L (1988): The Continuous Performance Test, Identical Pairs version (CPT-IP): I. New findings about sustained attention in normal families. Psychiatry Res 26:223–238.
39. Phillips LH, Wynn VE, McPherson S, Gilhooly KJ (2001): Mental planning and the Tower of London task. Q J Exp Psychol A 54:579–597.
40. Baron-Cohen S, Wheelwright S, Hill J, Raste Y, Plumb I (2001): The "Reading the Mind in the Eyes" Test revised version: A study with normal adults, and adults with Asperger syndrome or high-functioning autism. J Child Psychol Psychiatry 42:241–251.
41. Perrin F, Pernier J, Bertrand O, Echallier JF (1989): Spherical splines for scalp potential and current density mapping. Electroencephalogr Clin Neurophysiol 72:184–187.
42. Kayser J, Tenke CE (2006): Principal components analysis of Laplacian waveforms as a generic method for identifying ERP generator patterns: II. Adequacy of low-density estimates. Clin Neurophysiol 117:369–380.
43. Kayser J, Tenke CE (2006): Principal components analysis of Laplacian waveforms as a generic method for identifying ERP generator patterns: I. Evaluation with auditory oddball tasks. Clin Neurophysiol 117:348–368.
44. Baillet S, Mosher JC, Leahy RM (2001): Electromagnetic brain mapping. IEEE Signal Process Mag 18:14–30.
45. Andreasen NC, Pressler M, Nopoulos P, Miller D, Ho B-C (2010): Antipsychotic dose equivalents and dose-years: A standardized method for comparing exposure to different drugs. Biol Psychiatry 67:255–262.
46. Tadel F, Baillet S, Mosher JC, Pantazis D, Leahy RM (2011): Brainstorm: A user-friendly application for MEG/EEG analysis. Comput Intell Neurosci 2011(2011):879716.
47. Gramfort A, Papadopoulo T, Olivi E, Clerc M (2011): Forward field computation with OpenMEEG. Comput Intell Neurosci 2011(2011):923703.
48. Pinkham AE (2014): Social cognition in schizophrenia. J Clin Psychiatry 75(Suppl 2):14–19.
49. Trémeau F, Brady M, Saccente E, Moreno A, Epstein H, Citrome L, *et al*. (2008): Loss aversion in schizophrenia. Schizophr Res 103:121–128.
50. Fletcher PC, Frith CD (2009): Perceiving is believing: A Bayesian approach to explaining the positive symptoms of schizophrenia. Nat Rev Neurosci 10:48–58.
51. Synofzik M, Thier P, Leube DT, Schlotterbeck P, Lindner A (2010): Misattributions of agency in schizophrenia are based on imprecise predictions about the sensory consequences of one's actions. Brain 133:262–271.
52. Teufel C, Kingdon A, Ingram JN, Wolpert DM, Fletcher PC (2010): Deficits in sensory prediction are related to delusional ideation in healthy individuals. Neuropsychologia 48:4169–4172.
53. Koster-Hale J, Saxe R (2013): Theory of mind: A neural prediction problem. Neuron 79:836–848.
54. Hanslmayr S, Staudigl T, Fellner M-C (2012): Oscillatory power decreases and long-term memory: The information via desynchronization hypothesis. Front Hum Neurosci 6:74.
55. Jensen O, Gips B, Bergmann TO, Bonnefond M (2014): Temporal coding organized by coupled alpha and gamma oscillations prioritize visual processing. Trends Neurosci 37:357–369.
56. Palva S, Palva JM (2011): Functional roles of alpha-band phase synchronization in local and large-scale cortical networks. Front Psychol 2:204.
57. Hanslmayr S, Klimesch W, Sauseng P, Gruber W, Doppelmayr M, Freunberger R, Pecherstorfer T (2005): Visual discrimination performance is related to decreased alpha amplitude but increased phase locking. Neurosci Lett 375:64–68.
58. Hooker CI, Bruce L, Lincoln SH, Fisher M, Vinogradov S (2011): Theory of mind skills are related to gray matter volume in the ventromedial prefrontal cortex in schizophrenia. Biol Psychiatry 70:1169–1178.
59. Lee J, Quintana J, Nori P, Green MF (2011): Theory of mind in schizophrenia: Exploring neural mechanisms of belief attribution. Soc Neurosci 6:569–581.
60. Das P, Lagopoulos J, Coulston CM, Henderson AF, Malhi GS (2012): Mentalizing impairment in schizophrenia: A functional MRI study. Schizophr Res 134:158–164.
61. Gromann PM, Heslenfeld DJ, Fett AK, Joyce DW, Shergill SS, Krabbendam L (2013): Trust versus paranoia: Abnormal response to social reward in psychotic illness. Brain 136:1968–1975.
62. Juckel G, Schlagenhauf F, Koslowski M, Wüstenberg T, Villringer A, Knutson B, *et al*. (2006): Dysfunction of ventral striatal reward prediction in schizophrenia. Neuroimage 29:409–416.
63. White TP, Gilleen J, Shergill SS (2013): Dysregulated but not decreased salience network activity in schizophrenia. Front Hum Neurosci 7:65.

64. Palaniyappan L, Simmonite M, White TP, Liddle EB, Liddle PF (2013): Neural primacy of the salience processing system in schizophrenia. Neuron 79:814–828.
65. Peyroux E, Strickland B, Tapiero I, Franck N (2014): The intentionality bias in schizophrenia. Psychiatry Res 219:426–430.
66. Montag C, Dziobek I, Richter IS, Neuhaus K, Lehmann A, Sylla R, *et al*. (2011): Different aspects of theory of mind in paranoid schizophrenia: Evidence from a video-based assessment. Psychiatry Res 186: 203–209.
67. Abu-Akel A, Bailey AL (2000): The possibility of different forms of theory of mind impairment in psychiatric and developmental disorders. Psychol Med 30:735–738.
68. Brunet-Gouet E, Decety J (2006): Social brain dysfunctions in schizophrenia: A review of neuroimaging studies. Psychiatry Res 148: 75–92.
69. Blanchard J, Neale J (1992): Medication effects: Conceptual and methodological issues in schizophrenia research. Clin Psychol Rev 12:345–361.