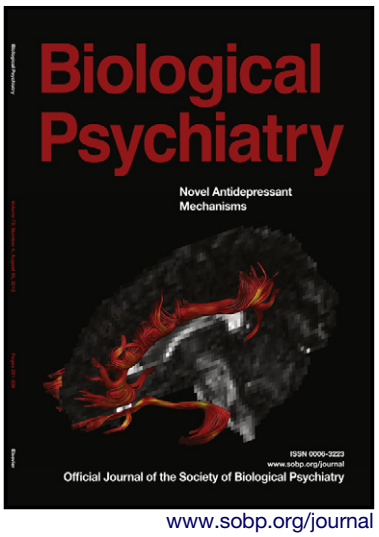

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Paradoxical expectation: Oscillatory brain activity reveals social interaction impairment in schizophrenia

Short Title: Social interaction impairment in schizophrenia

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Abstract

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

Methods: Twenty patients with schizophrenia and 25 well-matched controls underwent EEG recording. 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. Schizophrenia patients presented a greater correlation in computer games than that 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 schizophrenia that is related to oscillatory brain activity, suggesting maladjustment of expectation when patients face social and non-social agents. This alteration is related to psychotic symptoms and could guide further therapies addressed for improving social functioning.

Main Text

Introduction

Schizophrenia is a disabling psychiatric disease that is associated to severe cognitive and social disabilities (1; 2). In spite of the fact that antipsychotic remediation has an important impact on symptomatology reduction, the social integration of schizophrenia patients is still poorly addressed by current therapies (3). In this context, an important area of research in schizophrenia is the performance in an ongoing social interaction and its underlying neurobiological mechanisms.

The most extensively studied social alterations of these patients are emotion recognition and mentalizing deficit. Thus, failing to understand others' intentions and emotions has been related to abnormal amygdala activation (4; 5) and hypoactivation in both medial prefrontal cortex (mPFC) and temporo-pariental junction (TPJ) (6–8). These alterations may be the basis for poor social functioning and psychotic symptoms, like paranoia (1; 9–11). However, most of these works do not study social skills in real interactive settings, making it difficult to extrapolate these results to both the daily life of these patients and possible therapeutic interventions.

An interesting source of ecological paradigms to study social skills is Game Theory (12). In one-shot games, people with schizophrenia or schizotypal trails propose fairer money distribution than healthy people do. This occurs only when partners are able to reject this distribution (13–17). This may mean that patients' behaviors are guided by a negative bias related to the prediction of other's behavior. Following this line, in

repetitive games that evaluated trust behaviors, schizophrenia patients do not trust as much as healthy subjects do (18). In this context, the decision to trust is accompanied by exposure to the possibility that partners do not honor such behavior. Thus, distrust can also be understood as a prediction problem. Interestingly, in these repeated interactions, schizophrenia patients do not change this behavior according to feedback, which might also reflect insensitivity to social reward. Moreover, evidences show that both reward and mentalizing brain related areas are hypoactive during social interaction in schizophrenia (19). Indeed in non-social studies, schizophrenia patients show alterations in the anticipation of both sensory consequences of their actions (20; 21) and rewards (22). Thus, current evidence cannot rule out the fact that the alterations in social behaviors are due to non-social reinforcement learning impairments.

Here we test the hypothesis that people with schizophrenia present an alteration in the anticipation of other people's behaviors when they participate in a social interaction, in comparison to when they participate in a non-social interaction. In order to evaluate this, we used a repeated version of the Ultimatum Game (UG) under social and non-social conditions (Figure 1)(23–25). This game involves two players, namely 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 can either accept or reject 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 the responders in order to

estimate the risk of their actions and adapt their behavior accordingly (23; 26). Crucially, we used a non-social condition in which participants know that they are playing against a computational algorithm in order to control for impairments in non-social 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) by means of a release of the inhibition over these areas (30; 31). On the other hand, beta activity in frontal regions has been related to both 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). Indeed, schizophrenia patients failed to modulate oscillatory brain activity when predicting future events (36). Therefore, based on prior work that shows alpha and beta suppression related to the anticipation during the UG (24; 26), we finally hypothesize that failure to anticipate others' behaviors in schizophrenia correlates with alpha and beta brain oscillations.

Methods

Participants

Two groups of right-handed, Spanish speaking subjects, aged 18 to 40 years, participated in the study. The schizophrenia group consisted of 20 (7 women) patients

with paranoid schizophrenia according to DSM-IVr criteria (concordant structured diagnostic interview by two psychiatrists), with illness duration less than 10 years, and currently treated 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 personal history of psychiatric diseases or family history of psychosis. We used a database of healthy volunteers of the Cognitive Neuroscience Laboratory in order to select appropriate age-and-educational-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 older than 4 months. 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, Chile).

Assessment

Two psychiatrists used the Positive and Negative Syndromes Scale to assess the extent of psychotic symptoms (inter-rater agreement, r=0.91, in the case of non-agreement, we used the mean value between the two scores). Both general 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 WAIS-III, and Trail Making Test-A (37)), sustained attention (Continuum Performance Test – identical pairs (38)), working memory (letter and number span, and spatial span

from WMS-III), learning (free recall of Rey-Osterrieth Complex Figure and WMS-III Word List I), planning and reasoning (copy of Rey-Osterrieth Complex Figure and Tower of London Test, (39)), and social cognition (Baron-Cohen´s Face Emotion Recognition Test (40)). It did not take any longer than tree weeks to carry out the psychiatric evaluation, the 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 below). The experimenter explained verbally the instructions describing the game and the participants read on-screen the instructions at the beginning of the game. The participants then 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 seconds, 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 (8 human games and 8 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. Importantly, the simulation used in human 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 seconds), the proposer waited for the partner's response. In the last phase (feedback phase, 1 second), 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 in order 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 her performance in one of the 16 games chosen randomly (the final compensation ranged from 6,000 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 (see (26) and Supplementary Methods). Thus, 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 actually believed they had played against another human, and that they felt the human games 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.

Electrophysiological Recordings

Continuous EEG recordings were obtained with a 40-electrode NuAmps EEG System (Compumedics Neuroscan). All impedances were kept below 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-oculogram was obtained using four electrodes with both 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 3D tracking system (Polhemus Isotrak).

EEG Data Analysis

EEG signals were preprocessed using a 0.1-100 Hz band-pass filter. Eye blinks were identified by a threshold criterion of ±100μV, and their contribution was removed from each dataset using principal component analysis by singular value decomposition and spatial filter transform (see Supplementary Methods). Other remaining artifacts (e.g., muscular artifacts) were detected by visual inspection of both the row-signal and the spectrogram. Thus, we obtained 425±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 (41) and implemented by (42; 43). 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 (see Supplementary Method). Induced power distribution was computed using Wavelets transform, with a 5-cycle Morlet wavelet, in -1.5 to 1.5s windows around the offer and feedback releases. We displayed the result only for -1 to 1s over the segmented signals to avoid edged artifact. For all analyses, we used the dB of power related to the fixation phase as baseline (at the beginning of each game, see Figure 1), where we did not find any significant differences between groups (Supplementary Figure S1). 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 (see Supplementary Methods). To calculate the current source distribution, we used individual head models based on default anatomy (MNI/Colin27) 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 non-parametric tests. In the case of histogram of the frequency of each offer, we compared groups using the Wilcoxon test corrected with false discovery rate (FDR, $q<0.05$). 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 FDR. To analyze the evolution of the risk of the offers across the rounds during a game, we used both the General Linear Model (GLM) and the 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 thus obtained a 3D 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, see Supplementary Method). To correct for multiple comparisons in time-frequency charts and source, we used the Cluster-based permutation test (Maris and Oostenveld, 2007). For partial correlations between oscillatory brain activity and clinical parameters, we corrected by the chlorpromazine dose equivalent based on (45).

Software

All behavioral statistical analyses were performed in R. The EEG signal processing was implemented in MATLAB using CSD toolbox (42), in-house scripts (available online http://lantoolbox.wikispaces.com/), BrainStorm (46) and openMEEG toolboxes (47).

Results

Behavior

Patients made hyperfair offers (offers greater than 50% of the money) more frequently at the expense of the frequency of fair offers (Figure 2A). Thus, during both conditions, patients made higher offers than those made by control subjects. (Figure 2B; mean offers, SC: HG= 45.3, CG=46.6; CON: HG =42.2 CG= 42.3; ANOVA, Diagnosis F=5.919, p=0.0173; Game F=0.3, p=0.5; Diagnosis*Game F= 0.11, p=0.7). Patients also presented a greater variation of their offers during a game, which was evaluated as the standard deviation (ANOVA, Diagnosis, F=26.841, p=1.72e-06; Game, F=0.2, p=0.6; Diagnosis*Game F= 0.13, p=0.7). This behavior leads patients to obtaining fewer profits under both conditions (expressed by the mean of the money obtained normalized by the number of played rounds, SC: HG= 31, CG=32; CON: HG =34.4 CG= 34.5; Diagnosis F=5.177, p=0.0257; Game F=0.047, p=0.8; Diagnosis*Game F= 0.13, p=0.7).

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, ranging 1 to 30). The general linear model estimated over the subjects' mean of the risk per condition indicated that there was a tendency to make safer offers during the last rounds (Table 2, Round, T=3.6 p = 0.0004), and that the patients made safer offers (Diagnosis, T=-3.016, p=0.0031). Moreover, the behavioral patterns in both human and computer games were different between the patients and the controls (Figure

2D). Controls presented a greater slope for computer games than that for human games, whereas patients presented a greater slope for human games. Thus, in the general linear model, the interaction among round number, diagnosis, and games was significant (Round*Diagnosis*Game, T=2.821, p=0.005). Additionally, controls began both computer and human games with comparable offers, whereas patients began computer games with safer offers (Game*Diagnosis, T=-2.138, p=0.034). We obtained similar results using a linear mixed model over single trials (Supplementary Table S4). We did not find any correlation between either the offers or the variation of the offers and the symptomatology.

EEG

Since the behavioral results indicated that, compared to controls, patients presented an opposed strategy in both human and computer games, we explored different modulations of oscillatory brain activity between both games. For this, per each subject, we modeled separately the power of the single-trial EEG signal in both 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 (see Methods and Supplementary Figure X).

In the anticipatory phase, we found a modulation of medial prefrontal oscillations (Fz and FCz electrodes) in the alpha (9–12Hz) and beta (15–30Hz) ranges (Figure 3). In human games, controls presented a positive correlation which starts 0.4 seconds after they made the offer (Figure 3B), whereas patients presented a positive correlation mainly in computer games (Figure 3C). In the case of schizophrenia patients, these patterns of activity led to a significant negative difference between human and computer games (main effects, alpha: 10-15 Hz, 0.3-0.6s; main probable sources in superior frontal gyrus and in left temporo-parietal regions, Figure 3D-F). When contrasting human and computer games, we also found a significant difference between the groups (main effects, alpha: 10-15 Hz, 0.4-0.6 s; beta: 20 – 30 Hz, 0.5-0.6 s, main probable sources in the right temporo-parietal region, the right superior parietal lobule, and the superior–middle frontal gyrus, Figures 3D and 4F).

In the right posterior region (Figure 4, TP8 and T8 electrode), we found that controls presented a specific modulation of alpha/beta oscillations during the anticipatory phase. These oscillations presented a correlation with the risk in human games only for controls, leading to a significant difference between the groups in the contrast human – computer games (main effects, alpha: 8-13 Hz, 0.35-1 s; beta: 15 – 20 Hz, 0.35-0.45 s, main probable sources in the right temporo-parietal region, the right superior parietal lobule, the middle frontal gyrus, and the left inferior parietal lobe; Figure 4F). These results were consistent using risk as a categorial rather than a continuous variable (Supplementary Figures S2-S4).

Finally, we assessed the behavioral meaning of the paradoxical patterns of alpha brain activity found in schizophrenia when comparing human vs. computer games. Since the antipsychotic medication may change the electrical brain activity, we used Spearman partial correlations correcting by the chlorpromazine equivalent doses (CED). We found that the alpha frontal oscillations in the contrast human-computer games correlated with the slope of the offer evolution in computer games (ρ=0.63, p=0.006, corrected by CED), though not in human games (ρ=-0.17, p=0.5, corrected by CED). Concerning symptomatology, the alpha frontal oscillations correlated only with positive symptoms in the sense that more severe patients present greater negative (paradoxical) alpha activity (ρ= -0.53, p=0.031, corrected by CED, see Supplementary Table S4 and Table S6). In relation to cognitive tests, only the learning tests correlated with alpha activity (ρ= -0.56, p=0.03, see Supplementary Table S5), although this correlation does not persist when we corrected by CED (Table 3 and Supplementary Table S6).

Discussion

A wealth of evidence indicates that schizophrenic patients have stable social impairments which 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 schizophrenic patients. In order 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 non-social context. In healthy people, these different

contexts generate a strategic switch to tackle the games (23). Thus, we used this contrast to identify the behavioral and neuronal alterations related to social-decision making in schizophrenia people. We found that schizophrenia patients present an opposite pattern of offer evolution in human versus computer games when compared with controls. This behavioral pattern correlated with an opposite modulation of alpha activity in frontal and temporo-patiental regions when subjects anticipated their partners' behavior.

A possible interpretation is that these behaviors are due to non-social cognitive impairments. Interestingly, we found that most of the features of the schizophrenia patients' behavior described in one-shot UGs, like making more hyper-fair offers (13; 14; 16) and making more variable offers (13), were not different when comparing human and computer games. Additionally, in a repeated version of the Trust Game, schizophrenia patients do not modify their behavior in relation to either the knowledge of their partner`s trustworthiness or their partner`s behavior (18; 19). Thus, these evidences could reflect a general mechanism related to either avoiding the possibility of negative feedback or learning impairments rather than a specific social alteration. However, schizophrenia patients do not show risk aversion in non-social economic decision-making (49). Moreover, our results indicate that schizophrenia patients showed both behavioral and electrophysiological differences when comparing human and computer games. Therefore, it is unlikely that our results were due to non-social cognitive impairments per se. Thus, our findings are compatible

with two processes, namely impairments in the anticipation to social agents' behaviors and/or misattributions of intention to social and non-social agents.

There is evidence of a dysfunction in the ability to predict the sensory consequences of actions in schizophrenia (20; 21). It has been proposed that this sensory-prediction alteration may have a general role in the mechanism which leads to schizophrenic symptoms (50–52). This can also be true for social skills, since these skills may also be understood as a prediction problem in the sense that they deal with the prediction of other people's behaviors (53). Interestingly, 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). Thus, 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, namely mPFC, inferior parietal lobule, and TPJ. Hypoactivity in mPFC and TPJ is directly linked to the mentalizing deficits observed in psychosis (6; 58; 59). In social games and in on-line mentalizing tasks, patients also showed a reduced TPJ activity (19; 60). In our experiments, one of the possible sources of the alpha activity was found in the left temporo-parietal region where other studies have found hypo-activation in schizophrenia patients (6). Interestingly, the activation of this region in other games has also shown correlation with psychotic symptoms (61). Thus, a possible

interpretation is that the failure of anticipating others' human behaviors 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 non-social agents, due 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). In fact, recent evidence reveals both 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 non-social partners can generate the opposite patters of behavioral and the electrophysiological modulation in human and computer games. Thus, 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. Accordingly, the oscillatory activity correlated mainly with the behavior during computer games. This could reflect over-interpretation related to psychotic symptoms (65–67). Indeed, a region in the inferior parietal lobule has been associated with impairments in agency attribution and self-other distinction in schizophrenia (68). Therefore, our results could also indicate an alteration in social saliency processes which can lead to an agency bias to non-human partners.

An important limitation of our result regards the existence of a correlation between alpha modulation and antipsychotic medication. However, this correlation had the opposite direction of the correlation between alpha and positive symptoms. Indeed, the correlation between alpha and positive symptoms remains significant after statistical correction for antipsychotic doses. In spite of these facts, it is not possible to rule out an effect of medication (69). Thus, it is important to carry out similar experiments in pharmacologically-naïve patients or relatives to weigh the relative influence of medication and psychotic symptoms in these findings.

In summary, our results reveal an alteration in the anticipation of the others' behaviors in 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 schizophrenia that leads to maladjusted expectations for social and non-social agents' behaviors during an ongoing interaction. This impairment is related to psychotic symptoms and represents a potential target for the elaboration of therapeutic intervention addressed to improving the social function of schizophrenic patients.

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Figures

Figure 1. Timeline of a game. Proposers (black box) and responders (gray box, computational simulations, see Methods) played an iterated Ultimatum Game. The proposer makes an offer on how to split 100 Chilean pesos between the responder and himself/herself (offer phase). The responder decides to either accept or reject it (response phase). If the responder accepts the offer, the money is split as proposed, and if he/she rejects it, the money is lost. The response is shown on the screen during 1 s (feedback phase). Each game consists of 15 iterated offers. At the beginning of each game, the proposer sees a cue that indicates if his/her partner is a human ("H") or computer ("PC").

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** The variation of the offer per subjects separated by conditions and groups. **B-C** Circles represent subjects, lines are 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). **A-D** Blue represents healthy controls and red schizophrenic patients. *p<0.05, **p< 0.01, ***p<0.001 (Wilcoxon test and FDR)

Figure 3. Oscillatory Brain Activity in Frontal Region. A. Model used to correlate the risk of the offer and the power of the oscillatory brain activity; b2 and b5 are the coefficients of the models plotted in in B-D, for anticipatory and feedback phases respectively. **B.** Time-frequency chart during human games (fronto-central electrodes, Fz and FCz). **C.** Time-frequency chart during computer games. **D.** Time-frequency chart of the differences between human 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 (b2 and b5 in A). The clusters with significant effects are highlighted ($p<0.01$ cluster-corrected). **E**. Topographic distribution and estimated sources of the significant cluster of beta activity after the feedback (15-25Hz, 0.2-0.4s) 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 (8-15Hz, 0.3-0.8s) in the contrast Human – Computer Games for Control, as indicated in **D**.

Figure 4. Oscillatory brain activity in the right temporo-parietal region. A. Model used to correlate the risk of the offer and the power of the oscillatory brain activity; b2 and b5 are the coefficient of the models plotted in in B-D, for anticipatory and feedback phase respectively. **B.** Time-frequency chart during human games (temporo-parietal electrodes, TP8 and T8). **C.** Time-frequency chart during computer games. **D.** Time-frequency chart of the differences between human 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 (b2

and b5 in A). The clusters with significant effects are highlighted ($p<0.01$ cluster-corrected). **E**. Topographic distribution and estimated sources of the significant cluster of alpha activity (differences between controls and schizophrenics in human games) after the offer (8-15Hz, 0.3-1s) as indicated in **B** and in Figure **3B**. **F**. Topographic distribution and estimated sources of the significant cluster of alpha activity (differences between control and schizophrenic in the contrast human games – computer games) after offer (8-15Hz, 0.3-0.8s) as indicated in **D** and in Figure **3D**.

Tables

Table 1.

	Schizophrenics (n=20)	Controls (n=25)	p-value
Women n(%)	7 (35%)	10(40%)	0.7
Ages mean (s.e.m)	28.1 (0.9)	27.9 (1.0)	0.9
Socio-Educational Score mean (s.e.m)	18,65 (0.7)	19.08 (0.6)	0.7

PANS mean (s.e.m)			
Positive	21.3 (1.8)	-	-
Negative	24.2 (1.7)	-	-
General	46.6 (3.9)	-	-
Total	95.0 (8.8)	-	-
Medication n(%)			
Antipsychotic 1st Generation	4(20%)	-	-
Antipsychotic 2nd Generation	20(100%)	-	-
Benzodiazepine	5 (25%)	-	-
Antidepressive	5 (25%)	-	-
Chlorpromazine Equivalent Doses mean(s.e.m)	625 (77.4)	-	-
Cognitive Evaluation mean(s.e.m)			
Speed of Processing	-0.84 (0.15)	0.62 (0.2)	<0.001
Sustained Attention	-0.56 (0.19)	0.75 (0.14)	<0.001
Working Memory	-0.62 (0.15)	0.89 (0.16)	<0.001
Planning and Reasoning	0.07 (0.12)	1.05 (0.11)	<0.001

Learning	-0.60 (0.16)	0.71 (0.19)	<0.001
Social Cognition	-0.41 (0.19)	0.59 (0.23)	0.002

TABLE 2. General Linear Model of the Mean of Risk across Subjects per Round

	Slope	Std. Err.	t-value	p-value
(Intercept)	1.15787	0.20642	5.609	1.53e-07 ***
Round	0.04121	0.01143	3.605	0.000471***
Game (PC)	0.83424	0.29192	2.858	0.005103**
Diagnosis (CON)	-0.86406	0.28651	-3.016	0.003183**
Round*Game	-0.03331	0.01617	-2.060	0.041728*
Round* Diagnosis	-0.01433	0.01542	-0.930	0.354505
Game* Diagnosis	-0.87446	0.40903	-2.138	0.034738*
Round* Diagnosis*Game	0.06302	0.02234	2.821	0.005686**

Table 3. Partial correlations among alpha power, positive symptoms, learning score, and antipsychotic doses

Rho p-value	Positive Symptoms	Learning Score	Antipsychotic Doses[b]
Alpha Power[a]	**-0.59***	**0.17**	**0.57***
	0.012	0.49	0.015
Positive Symptoms		**-0.19**	**0.74*****
		0.45	0.0005
Learning Score			**0.26**
			0.31

[a] Difference in the alpha power (8-12 Hz) between human and computer games in frontal electrodes (Fz and FCz). [b]Chlorpromazine equivalent doses.

Fig 1

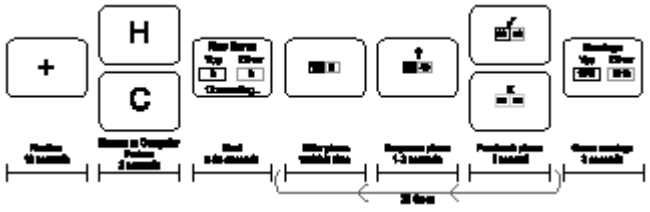


Fig 2

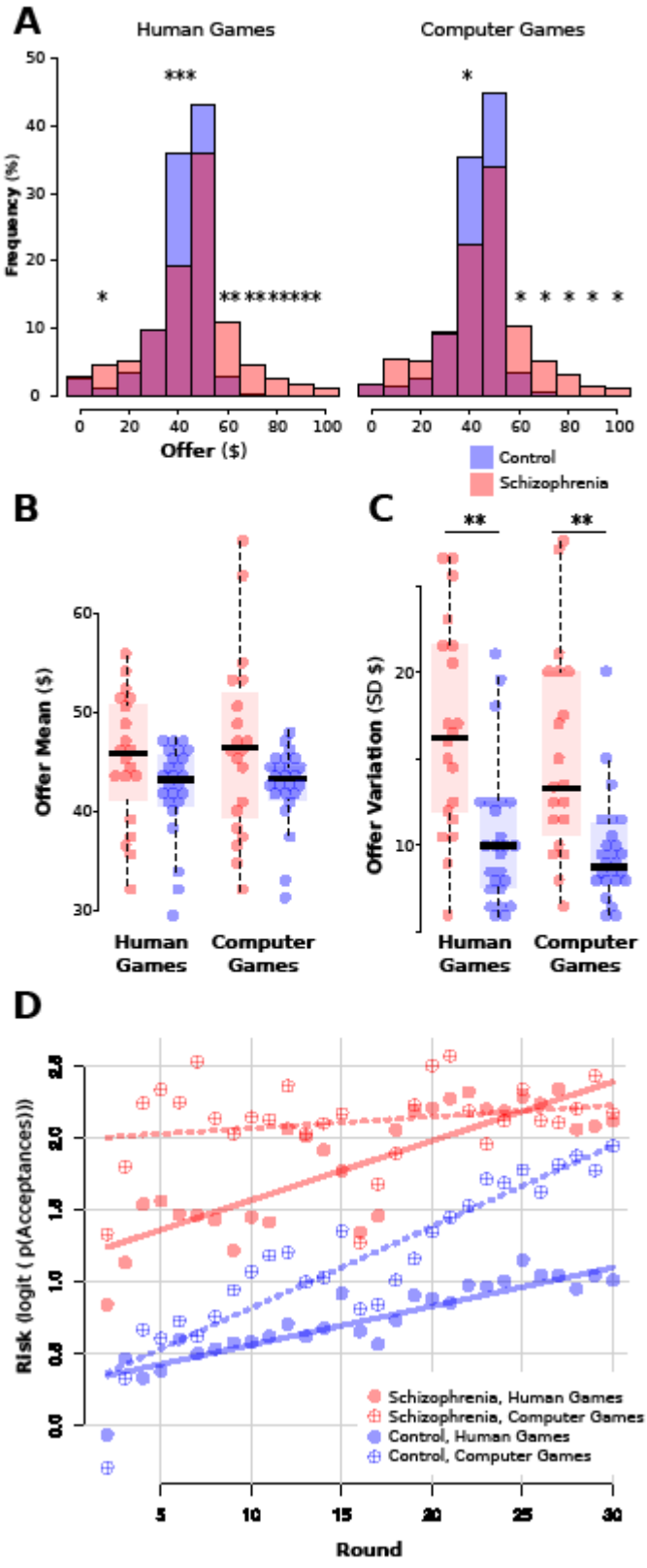


Fig 3

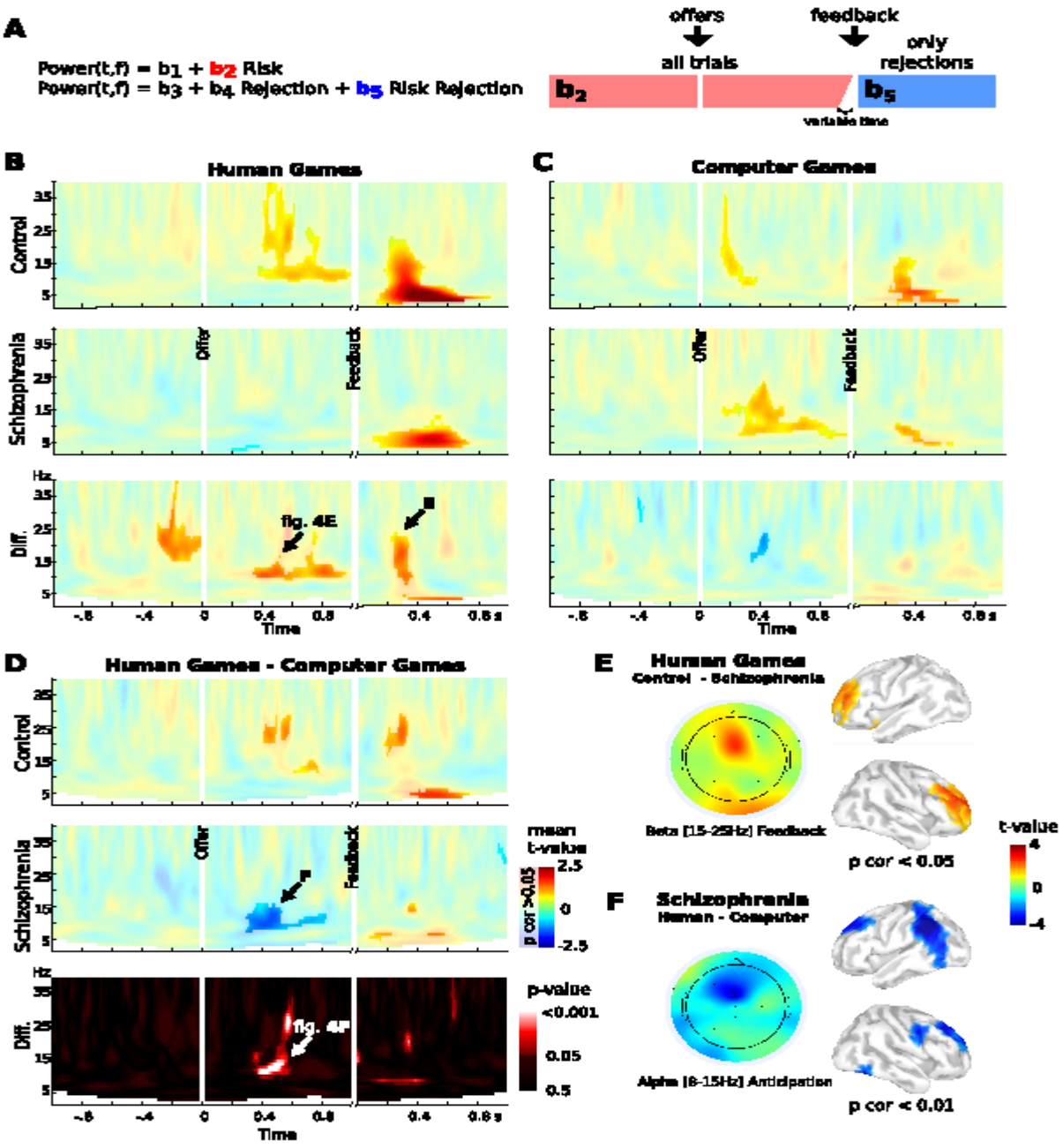
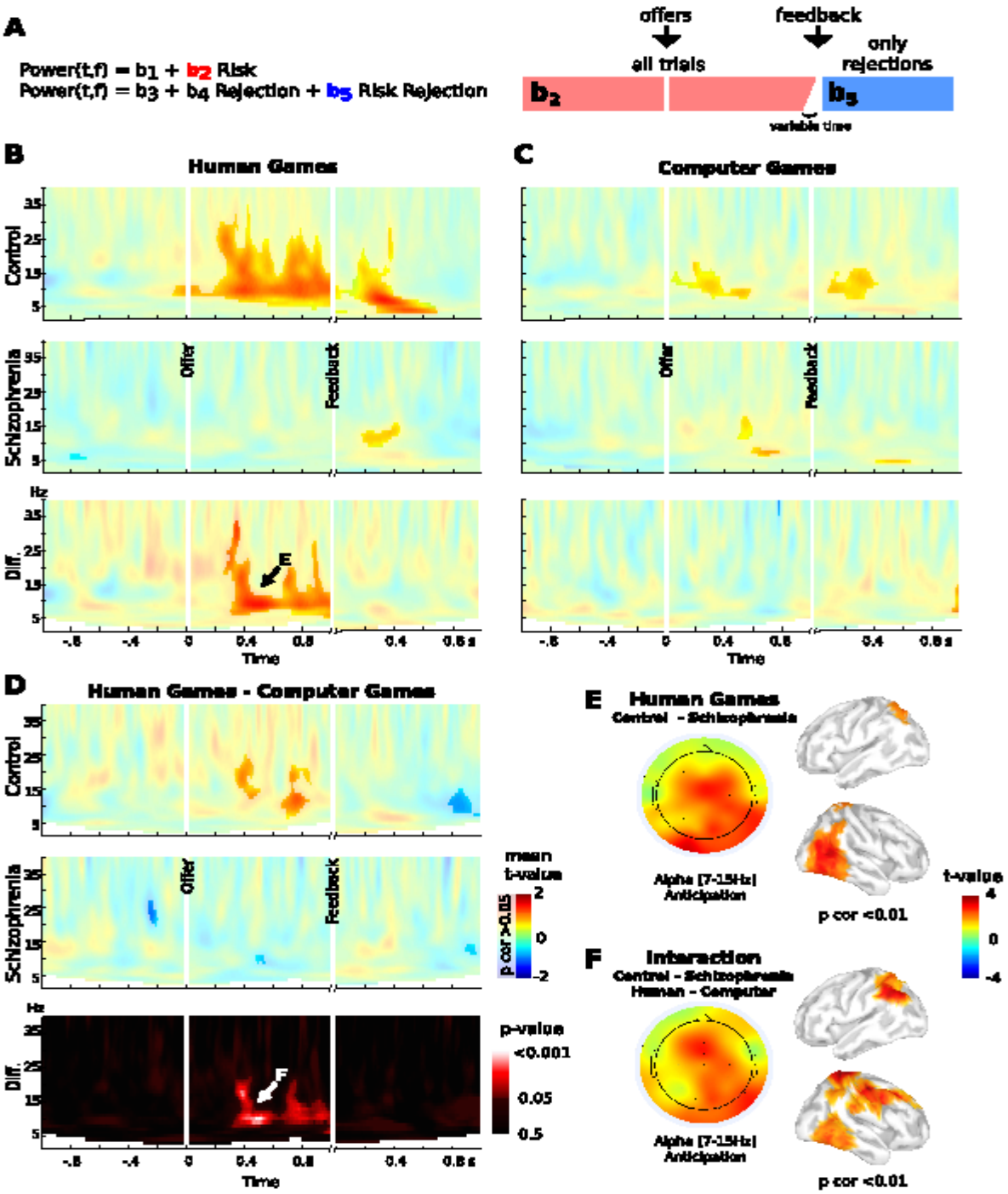

A
Power(t,f) = b1 + b2 Risk
Power(t,f) = b3 + b4 Rejection + b5 Risk Rejection
offers
all trials
feedback
only rejections
b2
b5
variable time
B
Human Games
C
Computer Games
Control
Schizophrenia
Diff.
Hz
Offer
Feedback
fig. 4E
fig. 4F
Time
D
Human Games - Computer Games
mean t-value
p cor >0.05
p-value
<0.001
0.05
0.5
E
Human Games
Control - Schizophrenia
Beta [15-25Hz] Feedback
p cor < 0.05
t-value
F
Schizophrenia
Human - Computer
Alpha [8-15Hz] Anticipation
p cor < 0.01

Fig 4


A
Power(t,f) = b1 + b2 Risk
Power(t,f) = b3 + b4 Rejection + b5 Risk Rejection
offers
all trials
feedback
only rejections
b2
b5
variable time
B
Human Games
C
Computer Games
Control
Schizophrenia
Diff.
Hz
Offer
Feedback
E
Time
D
Human Games - Computer Games
F
mean t-value
p cor >0.05
p-value
<0.001
0.05
0.5
E
Human Games
Control - Schizophrenia
Alpha [7-15Hz]
Anticipation
p cor <0.01
t-value
F
Interaction
Control - Schizophrenia
Human - Computer