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

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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.

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

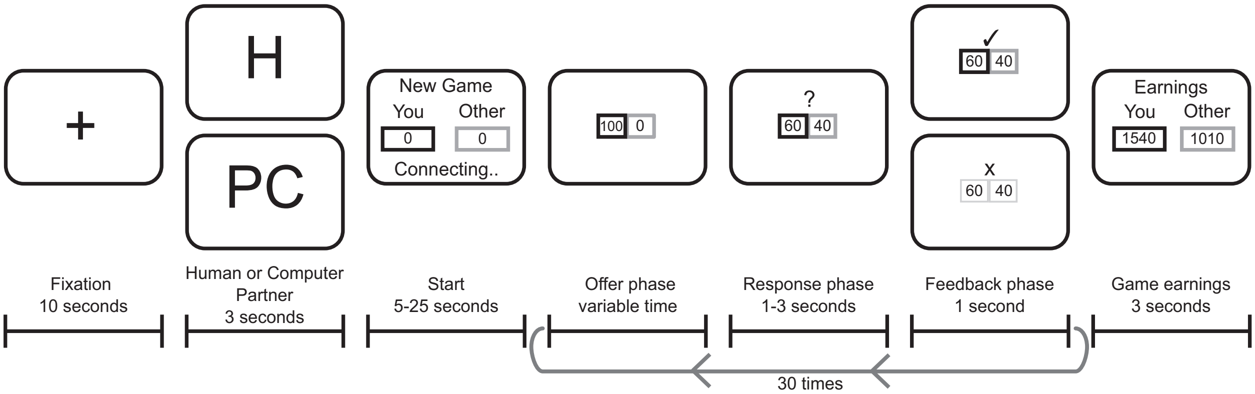

Figure 1. Timeline of a game. Proposers (black box) and responders (gray box, computational simulations; see Methods and Materials) played an iterated Ultimatum Game. The proposer makes an offer on how to split 100 Chilean pesos between the responder and himself or herself (offer phase). The responder 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).