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Impaired social cognition in schizophrenia during the Ultimatum Game: An EEG study

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ABSTRACT

Background: Schizophrenia has a core feature of cognitive dysfunctions. Since these deficits are predictive for patients' functional outcome, understanding their origin is of great importance to improve their daily lives. A specific component of the deficit involves social decision-making, which can be studied using the Ultimatum Game (UG). In this task, a "proposer" proposes a share of money to a "responder", who can either accept or reject this offer. If the responder accepts the proposal, both win money. If the responder refuses, both players end up with nothing. Therefore, the UG evaluates decision-making strategies and social interaction.
Methods: We compared the neuronal bases of schizophrenic patients with healthy controls, while performing the UG. Electroencephalography (EEG) was used to find differences in the event-related potential (ERP) components typical for the UG, namely the P2 and feedback-related negativity (FRN). Source reconstruction was further used to define the origin of these differences.
Results: In the proposer condition, no differences were found in amplitude of the P2 and FRN components. In contrast, in the responder condition, significant differences were found for the amplitude of the FRN ($p = 0.009$). Using source reconstruction, a different activation in a border zone of the dorsolateral and the medial prefrontal cortex was revealed in schizophrenic patients to underlie this component.
Conclusions: We suggest that the difference found in the FRN amplitude is associated with difficulties of patients in interpreting another's behavior. Although schizophrenic patients correctly activate neuronal bases in the proposer condition, they were not able to activate the same networks in the responder condition, thereby exposing their difficulties in social interaction.

1. Introduction

Schizophrenia affects about 1% of the population worldwide and is considered to be a severe psychiatric disorder with a majority of patients experiencing poor outcomes. Schizophrenia symptoms include delusions, hallucinations and disorganized thinking (American Psychiatric Association, 2013). Impairments of various cognitive domains, such as executive functioning or social cognition, are also a core feature of the disorder. Social cognition describes mental processes underlying social interactions with other individuals (Tan et al., 2016). It was suggested that deficits in social cognition might already be present at the prodromal state of the disease and can be predictive of patients' functional outcomes (Brekke et al., 2005). Therefore, it is of high importance to understand the origin of cognitive and social cognitive dysfunctions, especially because the connection to functioning remains only partially understood.

In this context, the socioeconomic Ultimatum Game (UG) has been proposed as a tool to investigate social decision-making in schizophrenia patients (Csukly et al., 2011; Wischniewski and Brune, 2011). This game involves two players agreeing on a split of a defined amount of money. One player, the proposer, must offer a share to the second player, the responder. The responder must then decide whether he wants to accept the offer, and the money is shared according to the proposition, or refuse it, which leads to no gain for neither of the players. Despite the clear information that the goal of the game is the same for both players, i.e. to gain a maximal amount of money, participants have been found to react differently (Camerer, 2003; Fehr and Fischbacher,

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2003). Indeed, it has been demonstrated that UG players take social concepts of fairness and altruistic punishment into account (Sanfey et al., 2003). This means that one individual playing as responder would rather punish the proposer with a rejection if he or she considers an offer as unfair (i.e. low amounts), rather than acting as a rational maximizer by accepting even the smallest gain (Brethel-Haurwitz et al., 2016; Csukly et al., 2011). In this way, the UG evaluates decision-making strategies combined with social interactions.

To date, only few studies have been conducted in patients with schizophrenia using the UG, with inconsistent behavioral results being reported. The first study on this topic (Agay et al., 2008) found that patients tended to propose more hyperfair offers (i.e. high amounts) and fewer unfair offers than controls, whereas the number of fair offers remained similar. As shown by their offering style, patients did not fully exploit their strategic power when in the role of proposers. Interestingly, the acceptance pattern in the responder condition revealed no difference between groups. However, later studies (Csukly et al., 2011; de la Asuncion et al., 2015; Wischniewski and Brune, 2011) also reported a difference between patients and controls in the responder condition. From all these studies, the conclusion emerged that schizophrenia patients accepted more unfair offers and showed an increase in the rejection of fair offers (Csukly et al., 2011; de la Asuncion et al., 2015). Also, the behavior of increasingly accepting unfair offers has been shown to already exist in people with schizotypal traits (van 't Wout and Sanfey, 2011). Despite the higher acceptance rate of unfair offers of schizophrenic patients compared to controls, patients still showed a trend of refusing unfair offers as well. This suggests that patients have the ability to recognize deviations from social conventions. Patients thus seem to be unable to adapt their strategy quickly and anticipate or conceptualize their counterpart's intentions in order to maximize their own gain.

Functionally, social decision-making processes engage a neural network principally supported by several circuits in the prefrontal cortex (PFC). Consistent with this, neuroimaging studies have identified a set of regions implicated in the UG including the anterior insula, the medial prefrontal cortex (mPFC), the dorsolateral prefrontal cortex (dlPFC) and the anterior cingulate cortex (ACC) (for review: Gabay et al. (2014)). Importantly, relationships between the engagements of these brain regions and social cognition processes correlate well with an abnormal activation of the mPFC and the ACC reported in schizophrenia (Frascarelli et al., 2015; Glahn et al., 2005; Pomarol-Clotet et al., 2010).

Decision-making processes occur in the timeframe of several hundred milliseconds and are therefore better studied using a method with a high temporal resolution, such as the electroencephalography (EEG). EEG allows investigating fast changes in cognitive processing and has been used to study UG in healthy populations, but not in schizophrenic patients.

In the responder condition of the UG, several studies pointed to the presence of a major event-related potential (ERP) component located in the fronto-central region within 320–360 ms after stimulus onset (Boksem and De Cremer, 2010; Hewig et al., 2011; Polezzi et al., 2008; Qu et al., 2013). This component, the feedback-related negativity component (FRN) (also referred to as the medial frontal negativity), is modulated by the degree of fairness. More precisely, unfair offers have been found to elicit a more pronounced FRN, suggesting that this component strongly reflects the evaluation of the outcome events (Boksem and De Cremer, 2010). Further, the UG also involves workload and working memory processes, reflected by a positive component around 200 ms (P2) (Allison and Polich, 2008; Miller et al., 2011). However, only little importance has been attributed to the P2 component in the UG so far.

Despite the behavioral deficits previously reported in schizophrenia patients during the UG (Agay et al., 2008; Csukly et al., 2011; de la Asuncion et al., 2015), the underlying processing differences remain unclear and have not been investigated so far. Therefore, using ERP and supplementary source reconstruction analysis (LAURA), the primary purpose of this study was to compare the neuronal bases of patients with healthy controls during both conditions of the UG. We hypothesized to find a decrease of the FRN amplitude in the schizophrenic group. Secondarily, we also assumed to find changes in the P2 component between both groups, since patients present deficits in the cognitive functions underlying this component.

2. Materials and methods

2.1. Participants

PSixteen French-speaking patients were recruited while being hospitalized at the Mental Health Network Fribourg (RFSM) for a psychotic decompensation. Ten patients were diagnosed with paranoid schizophrenia (F20.0) and six with acute and transient psychotic disorders (F23). The diagnosis was made according to criteria of the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) (World Health Organization, 1992) by an experienced psychiatrist independent of the study. The patients were tested with the Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) to evaluate comorbidities. Three patients had a history of recreational cannabis use. All except three patients received antipsychotic medication. Drug intake was converted into chlorpromazine equivalents, according to Leucht et al. (2014).

Patients were clinically rated for symptom severity using items of the Brief Psychiatric Rating Scale (BPRS) (Ventura et al., 1993); clinical symptoms were evaluated with the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984) and the Peters et al. Delusions Inventory (PDI) (Peters et al., 2004). After careful assessment of their abilities to understand the proposed project, informed written consent was obtained from all patients before final inclusion.

PWe also included nineteen healthy adult controls closely matched in age, without history of sustained head injury or other neurological or psychiatric disorders in this study. Psychiatric disorders were excluded using the Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998).

Table 1
CogState neuropsychological performances for patients and healthy controls.

Tasks	Patients Mean (SD)	Controls Mean (SD)	p-Value
Executive function			
Set-shifting task - ER	28.69 (19.53)	15.89 (10.98)	0.034
Executive function/spatial problem solving			
Groton maze learning test - ER tot	59.00 (27.27)	39.47 (8.12)	0.016
Psychomotor function/speed of processing			
Detection task speed, $\log_{10}$(ms)	2.62 (0.16)	2.48 (0.08)[a]	0.005
Visual attention/vigilance			
Identification task speed, $\log_{10}$(ms)	2.75 (0.09)	2.68 (0.04)[b]	0.006
Visual learning and memory			
Groton maze learning test - DR	7.60 (5.33)[b]	4.58 (2.66)	0.067
Verbal learning and memory			
International shopping list			
- CR tot	25.75 (3.78)	29.79 (2.53)	0.002
- DR	8.63 (2.00)	10.53 (1.27)	0.004
Working memory			
One back task - AP	1.20 (0.17)	1.25 (0.18)	0.454
Social cognition			
Social-emotional cognition task - AP	1.00 (0.19)	1.18 (0.06)	0.003

Notes: Data are presented as mean (SD). AP, accuracy of performance (arcsine transformation of the square root of the proportion of correct responses); ER tot, total number of errors; DR, delayed recall (number of correct responses); CR tot, total number of correct responses. See text for details. Significant differences were found for each test except the one back task and only a tendency for the delayed recall of the Groton maze learning task.

[a] Two missing values: not included in the corresponding analysis.

[b] One missing value: not included in the corresponding analysis.

All subjects were tested with the extensive neuropsychological CogState Battery (see www.cogstate.com for details) (Table 1). General intelligence was evaluated using two subtests of the 3rd edition of the Wechsler Adult Intelligence Scale (Ringe et al., 2002) for matrix reasoning and vocabulary, to ensure that participants were not intellectually disabled (IQ score above 69). The clinical and socio-demographic data of patients and controls are summarized in Table 2.

All participants had normal or corrected-to-normal visual acuity and none of them suffered from a severe physical impairment. The study was approved by the Ethics Committee of the University of Fribourg, Switzerland, and the study protocol was in line with the Helsinki Declaration. All subjects provided written informed consent.

2.2. Task and procedure

The Ultimatum Game (UG) is a socioeconomic decision-making game. In this task the "proposer" has a certain sum of money (10 Swiss francs = 10 CHF) at his disposal and must propose a share of this money to the "responder", who can either accept or reject this offer. If the responder accepts the proposal, money is shared accordingly and both win money. However, if the responder refuses, both players end up with nothing. Classically, the game ends after the responder's decision (Guth et al., 1982). In the present version of the UG, each participant played both the role of the proposer (90 trials, Fig. 1A) and of the responder (90 trials, Fig. 1B) in three alternate blocks of 30 trials each (~180 s per block). Participants were also told to play the UG trying to maximize their gain as much as possible, and were instructed about the outcome of an "accept" or "reject" response. The overall experiment lasted about 70 min.

The participants were seated in a sound- and light-attenuated room and watched stimuli on a computer-controlled display screen at a distance of 110 cm. The size of the screen was 20.48″ × 12.95″ × 2.66″ with a resolution of 1280 × 1024. Stimuli presentation, trigger sending and response recording were implemented using the E-Prime software (Psychology Software Tools, Inc., Sharpsburg, PA 15215-2821, USA). The task was explained on a computer monitor at the beginning of the experiment, and specific instructions about the task condition were repeated before each block. Each trial started with a preparatory period of 2 s, where participants were focusing on a central fixation cross on the computer monitor. After, an Arial font message appeared to either make a proposition ("Please, make your offer") or respond to an offer ("Do you accept the offer of [1, …, 9] CHF?") according to the condition they were engaged in (proposer or responder, respectively). In the proposer condition, a smiling or frowning face (2° × 2.5° visual angle) showed the answer of the counterpart (a white smiling face, unicode character 0x263a, for "Accept" and a white frowning face, unicode character 0x2639, for "Reject"), while in the responder condition the smiley remained neutral to minimize the influence of positive or negative facial expressions, as has been shown by Mussel et al. (2013).

Table 2
Demographic and clinical data of schizophrenic patients and healthy controls.

Characteristics	Patients Mean (SD)	Controls Mean (SD)	p-Value
N[a]	16	19	
Age range	22–36	20–35	
Age (years)	26.38 (4.37)	26.37 (4.04)	0.997
Sex (male: female ratio)	12:4	10:9	0.177
Laterality (right: left ratio)	14:2	17:2	0.861
Education (years)	12.13 (3.46)	15.76 (2.85)	0.003
WAIS[b]	96.64 (9.93)	110.97 (12.62)	0.001
PDI[c] (total score)	96.94 (42.10)	55.68 (26.22)	0.003
BPRS[d]	52.31 (9.01)	28.53 (2.39)	0.000
SAPS[e]	7.20 (4.18)[f]	0.32 (0.57)	0.000
CPZ equivalents[g]	541.98 (582.65)	–	0.003

[a] Number of participants.
[b] Wechsler Adult Intelligence Scale: mean of matrix reasoning and vocabulary scales.
[c] Peters et al. Delusions Inventory.
[d] Brief Psychiatric Rating Scale.
[e] Scale for the Assessment of Positive Symptoms.
[f] One missing value: not included in the corresponding analysis.
[g] Chlorpromazine equivalents.

Participants were playing against a computer player, but they were not told explicitly (task instructions mentioned a "second player"). As responder, the computer program was implemented to simulate a human strategy, with increasing acceptance rates for higher offers. As proposer, each amount was programmed to be offered with the same probability in a random order, to remain neutral. All the recordings were done in the morning and no feedback on performance was provided.

2.3. Electrophysiological recordings

Continuous EEG was recorded using 128 active surface Ag/AgCl electrodes (ActiveTwo MARK II Biosemi EEG System, BioSemi B.V., Amsterdam, Netherlands) mounted on a head cap (NeuroSpec Quick Cap) and referenced to the common mode sense (CMS; active electrode). Linked right and left mastoid electrodes were used for a later re-referencing process. Additionally, right-, left-, supra-, and infra-orbital electrodes monitored horizontal and vertical eye movements. Electrode impedances were kept below 20 kΩ. Electrophysiological signals were sampled at 2048 Hz (DC amplifiers and software by Biosemi, USA). Markers corresponding to stimuli presentations and responses (proposer and responder offer types) were automatically documented with markers in the continuous EEG file. They were thereafter used off-line to segment the continuous EEG data into time-locked epochs.

2.4. Data processing

2.4.1. Reaction time

The reaction times (RT) for proposer and responder were systematically recorded and the averages are summarized in Table 3.

2.4.2. Electrophysiological processing

The continuous EEG was referenced to mastoid channels using the Brain Vision Analyzer 2.0 software (Brain Products GmbH, Munich, Germany). EEG signals were corrected for blinks and eye movement artifacts through an independent component analysis (Jung et al., 2000). The total analysis window was 700 ms, starting 200 ms before the appearance of the instruction to make a decision (i.e. stimulus onset (t = 0; Fig. 1): 'make an offer' or 'accept/reject the offer'). Next, the EEG trials were automatically scanned for contamination by muscular or electrode artifacts (criteria for rejection: voltage step > 70 μV/ms or peak to peak deflection within 200-ms intervals > 200 μV/ms). The remaining trials were inspected visually to control for residual minor artifacts. Finally, the EEG data were analyzed with two different types of electrophysiological analyses: event-related potentials (ERPs) and source reconstruction analysis.

2.4.3. Event-related potentials analysis

ERP analyses were performed by averaging the EEG signal over a window of 700 ms with a 200 ms pre-stimulus onset period. The epochs were band-pass filtered between 0.3 and 30 Hz (−48 dB/octave for a low-pass filter).

The ERP components of interest were the P2 and the Feedback-Related Negativity (FRN) components. These components were identified in the grand-average waveform.

The component analyses were restricted to a cluster of anterior midline electrode locations (FPz, AFz, Fz, FCz, Cz) as they are known to have a fronto-central maximum (Peterburs et al., 2013; Wu et al., 2012; Yang and Zhang, 2011).

The amplitude of the P2 did not show an easily detectable peak in the patients group and was a little larger in the responder condition. Therefore, for both conditions and each group we measured the mean

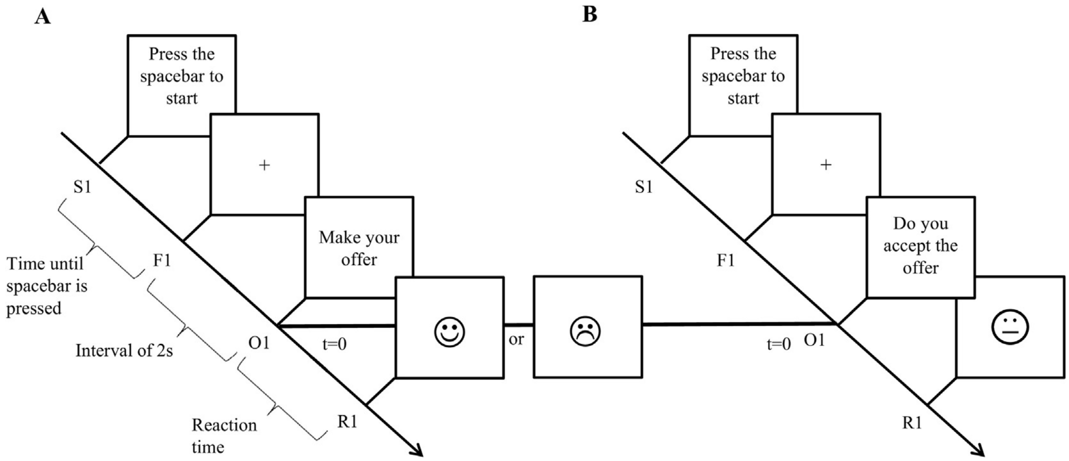

Fig. 1. Illustration of the Ultimatum Game. Tasks differed in the instructions given at the beginning of each run and in the response requirement. Each trial began with the instruction to press the spacebar (S1). As soon as participants did, they were instructed to maintain their gaze on a central fixation cross during an interval of 2 s (F1). Next, participants saw a message (O1) indicating to make an offer (1A - Proposer) or accept or reject an offer (1B - Responder). This time point was considered as our t = 0 for the ERP analyses, and is labeled with a horizontal black line. The response to the offer (R1) was displayed simultaneously when the participants pressed the button indicating their decision and presented as a smiling or frowning face in the proposer condition (representing acceptance or rejection of the offer by the responder, respectively), whereas the smiley was neutral in the responder condition.

amplitude (in μV) of the P2 based on the peak detected in responders ± 5%, i.e. using a time window of 220 ms to 240 ms.

The FRN is a large component with no detectable peak in either condition in the patient group. We determined the temporal limitations of the FRN as defined by the intersection of the ERP between both groups. Then, we measured the mean amplitude of the central 50% of the component, i.e. from 320 ms to 360 ms.

2.4.4. Electrical source localization

We estimated electric sources underlying scalp-recorded data using a distributed linear inverse solution based on a local autoregressive average (LAURA) regularization approach (Grave-de Peralta et al., 2004; Michel et al., 2004). The solution space is based on a realistic head model and includes 5010 solution points homogeneously distributed within the grey matter of the average brain of the Montreal Neurological Institute (courtesy of R. Grave-de Peralta Menendez and S. Gonzalez Andino, University Hospital of Geneva, Geneva, Switzerland). Intracranial source estimations were calculated for the time period of the FRN component (320–360 ms after stimulus onset) in the responder condition, which was defined as the period of interest. In order to do so, ERPs for each control and each patient in the responder condition were first averaged separately across the above-mentioned time period of interest to generate one time course per participant (patients and controls) in the responder condition. The distribution of source activities across groups was then statistically compared for each solution point using the difference in group means as a test statistic, a non-parametric permutation test with 10000 permutations, using a significance level of <0.05, uncorrected.

Table 3
Reaction times of controls and patients in both UG conditions (i.e. Proposer and Responder) by amount.

Amount	Proposer		Responder		
	Controls Mean (SD)	Patients Mean (SD)	Controls Mean (SD)	*	Patients Mean (SD)
1	1142 (777)	939 (424)	899 (301)		1127 (388)
2	1530 (2540)	1352 (1006)	961 (263)		1208 (587)
3	1162 (987)	1177 (688)	908 (291)		1300 (634)
4	1325 (1328)	1475 (1219)	1011 (335)		1303 (554)
5	1046 (403)	1149 (501)	908 (408)		1524 (1063)
6	1038 (519)	1323 (614)	847 (292)		1250 (611)
7	1369 (794)	1285 (1095)	844 (311)		1352 (892)
8	2000 (1441)	1087 (549)	809 (250)		1211 (551)
9	1444 (943)	1133 (554)	824 (295)		1253 (755)

Notes: Data are presented as Mean (SD) in milliseconds. A significantly longer reaction time was observed for the patient group in the responder condition. * $p < 0.05$.

2.5. Statistical analysis

Demographic and clinical characteristics as well as differences in cognitive performances (Cogstate tasks) between the two groups (patients and controls) were assessed using independent sample *t*-tests with unequal variances. For the offer distribution and acceptance rates between groups we conducted an Analysis of Variance (ANOVA) to check for global differences. If global differences were found, a linear regression model was used to identify the origin of the difference for each amount separately (1 to 9 CHF).

Statistical analyses of the ERP values were restricted to the mean amplitudes of the P2 and FRN components for five fronto-central electrodes (FPz, AFz, Fz, FCz, Cz). These five electrode locations and the participant groups (controls or patients) were included as independent variables in a repeated-measure linear regression model. Proposer and responder conditions were analyzed separately applying the same model.

Reaction times were assessed with ANOVA and a repeated measure linear regression model with group and offer as predictors for both conditions.

First, we performed a repeated measure linear regression model to predict Gain ((9-offer's value) ∗ nb of proposal) in the proposer condition with group and each of the IQ (WAIS, 3 items and total), PDI (8 items and total), BPRS (4 items and total) and Cogstate (9 items) variables with group ∗ items interaction term. In the responder condition, a repeated measure linear regression model was used to predict Acceptance Rates (for a given Amount proposed) with group, amount proposed and each of the IQ, PDI, BPRS and Cogstate variables with group ∗ items interaction term.

Second, we performed a repeated-measure linear regression model to predict the FRN amplitude with group, electrode, clinical (WAIS, PDI and BPRS) and Cogstate scores for each variable separately and with the group ∗ variables interaction term. Then, Pearson correlation coefficients were computed between FRN amplitude and variable scores with FPz as reference electrode.

Statistical analyses were performed using the Stata software package, version 14.2.

3. Results

3.1. Demographical data

There were no statistical differences between the two groups on age, sex, and laterality. In contrast, the years of education, the scores of the WAIS, the PDI, the BPRS, the SAPS and the amount of medication (CPZ equivalents) differed highly significantly. The clinical and demographic characteristics of the patients, including p-values, are summarized in Table 2. From a neuropsychological point of view, patients showed a significant deficit in their performance in all tasks of the Cogstate battery, except for the one-back task and the delayed recall of the Groton maze learning task. All values are displayed in Table 1.

3.2. Behavioral data

Behavioral data including proposition of offers and acceptance rates are presented in Fig. 2.

The ANOVA revealed a significant interaction between groups and amount of the offer ($p = 0.001$) in the proposer condition (Fig. 1A). Results showed that patients proposed a significantly higher amount of hyper fair offers (CHF 7, 8 and 9) compared to healthy controls (CHF 7: $p = 0.030$; CHF 8: $p = 0.005$; CHF 9: $p = 0.022$). Moreover, we found neither overall group effect, nor amount effect.

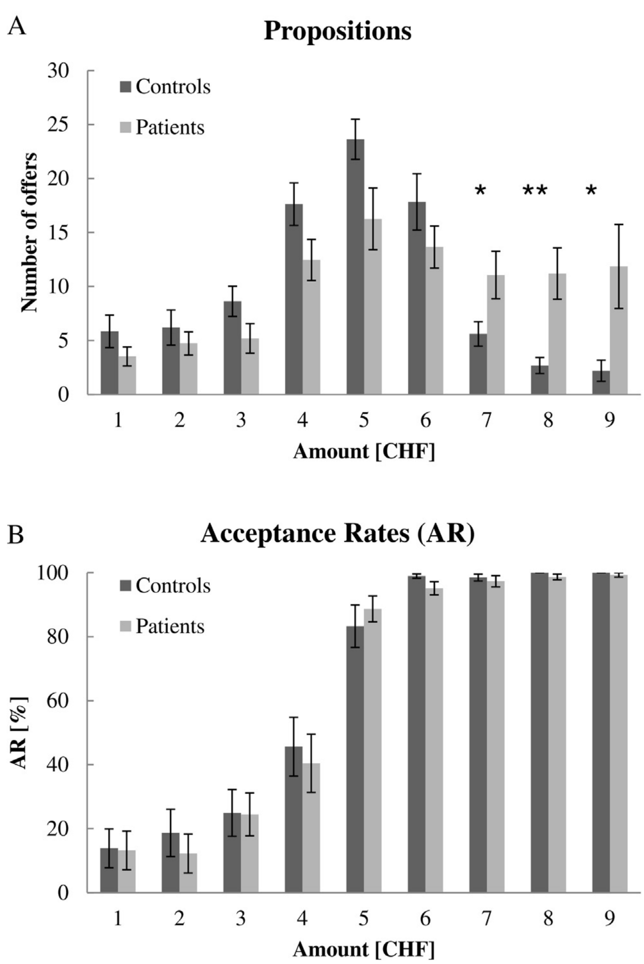

Fig. 2. A: Distribution of the propositions. Offers made by the controls (dark grey) or patients (light grey) groups when acting as proposers. The bars represent the number of times each offer (1 to 9 CHF) was made with standard errors (± SE). Note the significant difference found for the hyper fair offers: 7, 8 and 9 CHF. ** $p < 0.01$; * $p < 0.05$. B: Acceptance rates of each offer. Acceptance rates of the controls (dark grey) and patients (light grey) groups when acting as responders. The bars represent the percentage of accepted offers for each amount with standard errors (± SE). No significant differences were found for the acceptance rates between the two groups.

Regarding the acceptance rates (Fig. 1B), the ANOVA showed neither significant group effect, nor amount effect, nor interaction between both factors, thus indicating that acceptance rates of patients were similar to those of healthy controls whatever the amount proposed.

We used a repeated measure ANOVA and a linear regression model to predict reaction times with group and offers as predictors. We found no group effect in the proposer condition (β coefficient $= 102.8 \pm 163.2$ ms, $p = 0.533$), but a statistically longer reaction time in the patient group (β coefficient $= 391.0 \pm 168.3$ ms, $p = 0.026$) during the responder condition with no offer's effect and no offer vs group interaction.

3.3. Regression models to predict variable interactions

Among the clinical and neuropsychological variables (WAIS (3 items and total), PDI (8 items and total), BPRS (4 items and total), and Cogstate tasks (9 items)), only 3 were significantly associated with the FRN amplitude, independent of the presence of group ∗ electrode interactions. The set-shifting task (SETS) was positively associated with the FRN ($\beta = 0.07 \pm 0.01$ μV, $p < 0.001$), whereas the international shopping list (ISL) ($\beta = -0.24 \pm 0.11$ μV, $p = 0.040$) and the delayed recall (ISRL) ($\beta = -0.53 \pm 0.21$ μV, $p = 0.015$) were negatively associated.

When adding the social-emotional cognition scores (SEC) only, or SEC along with the group*SEC interaction term, the newly added variables and the group effect became non-significant. Looking further, we observed no correlation between FRN and SEC in the control group (Pearson $r = 0.1624$, $R^2 = 2.6\%$, $p = 0.507$), whereas there was a strong negative correlation between FRN and SEC in the patient group (Pearson $r = -0.618$, $R^2 = 38.2\%$, $p = 0.011$).

In the responder condition, only one test, the Cogstate detection task (DET), was significantly associated with Acceptance Rate, while also adjusting for group (no effect) and the amount proposed. The predictability of the model was quite high with a coefficient of determination $R^2 = 72.3\%$. It is worth noting that the acceptance rate was below 29% up to 4 CHF and increased sharply above this threshold ranging from 71% to 85%, with no significant differences among offers ranging from 5 to 9 CHF.

In contrast, the prediction of the model for Gains was very modest (coefficient of determination $R^2 = 2.8\%$) in the proposer condition.

3.4. Event-related potential analysis

Fig. 3 shows averaged ERP waveforms for controls (solid black line) and patients (dashed grey line) over anterior regions for each condition, including the 95% confidence interval (Fig. 3A: proposer; Fig. 3B: responder).

In the proposer condition, a late negative component (FRN) preceded by a P2 component was elicited in both groups. The mean amplitudes of the P2 and FRN components were free from significant group effects ($p = 0.88$ and $p = 0.08$, respectively).

In the responder condition, the FRN component was clearly distinguished in controls and its amplitude was significantly more pronounced compared to patients (β coefficient $= 1.91 \pm 0.68$ μV, $p = 0.009$, $R^2 = 18.2\%$) but not for the earlier P2 component ($p = 0.09$).

When adding the fairness of the offer (1–3 unfair (β coefficient $= 0.12 \pm 0.24$ μV, $p = 0.610$); 4–6 fair (reference β coefficient $= 1.0$ μV); 7–9 hyper fair (β coefficient $= -.15 \pm 0.23$ μV, $p = 0.529$)) during the responder condition alone or along with the group ∗ fairness interaction term, the newly added variables were non-significant with no changes in the group effect to predict the FRN amplitude (β coefficient group effect $= 1.92 \pm 0.68$ μV, $p = 0.008$) while adjusting for electrodes in the repeated measure linear regression model. The values without fairness adjustment for the β coefficient for group effect equal 1.91 ± 0.68 μV ($p = 0.009$).

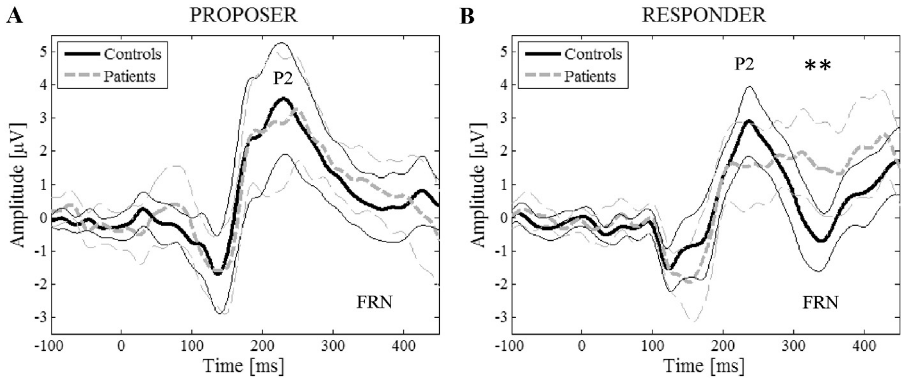

Fig. 3. Grand average waveforms. Grand average waveform for the electrode average of five electrodes (FPz, AFz, Fz, FCz and Cz) for controls (solid black line) and patients (dashed grey line), including the 95% confidence interval (thinner lines) following proposer (A) and responder (B) decision-making during the UG. The labels show the main components. Note the significant difference for the mean amplitude in the responder condition for the FRN component, while no differences were found for the proposer condition. ** $p < 0.01$.

3.5. Electrical source localization

We conducted the source localization to identify the differences in activity of the underlying brain regions of the FRN component in the responder condition. Fig. 4 displays the differences in grand mean source estimations for controls and patients over the 320–360 ms period. A significant difference between both groups ($p < 0.05$, uncorrected) was detected in a cluster bordering the medial and dorsolateral prefrontal cortex.

4. Discussion

The present study contributes to research on the electrophysiological bases of decision-making and social interactions in schizophrenia in the context of the Ultimatum Game.

Using ERPs, we demonstrated that the activity of neural bases involved in social decision-making was less pronounced in patients when they responded to the offered amount of money, as shown by a decrease of the amplitude of the FRN component in patients in the

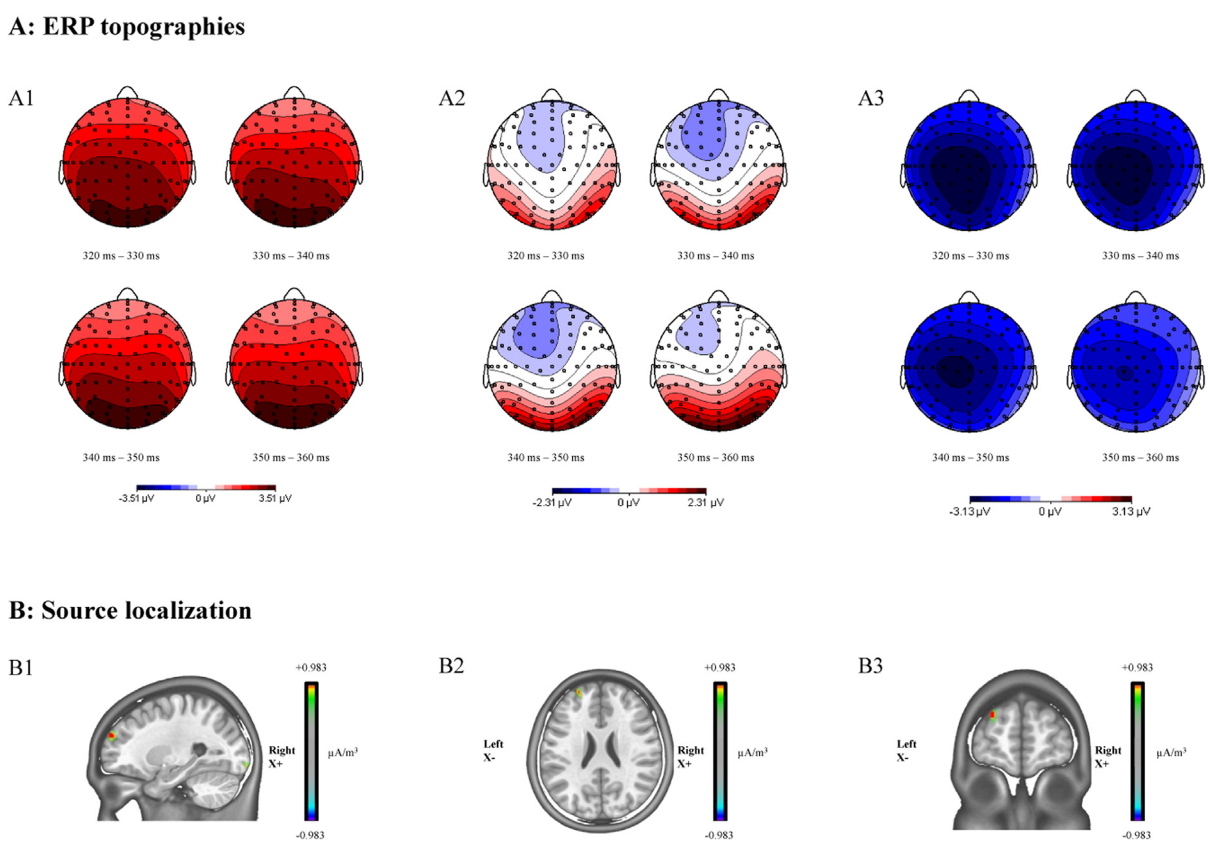

Fig. 4. A: ERP topographies. ERP topography maps for the time-window of the FRN component (320–360 ms) in the responder condition. A1 shows the topographies of the grand average waveform of the patients; A2 of the controls; and A3 of the difference wave. B: Source localization. Source localization for the time-window of the FRN component (320–360 ms) in the responder condition. A significantly different activation ($p < 0.05$) was found in a cluster bordering the left medial and dorsolateral prefrontal cortex. The unit of the color bars is in μA/m³. B1 shows a sagittal; B2 a horizontal; and B3 a frontal view.

responder condition. On the other hand, when the patients were in the proposer condition, no difference in the FRN amplitude between patients and controls was found, even though the goal of gaining a maximal amount of money was the same for both conditions. Source reconstruction analysis then revealed that this group discrepancy was the result of a differential activation of the medial and dorsolateral prefrontal cortex to underlie this ERP component. Finally, the P2 ERP parameters were free from group effects in both proposer and responder conditions.

As hypothesized, we found a less pronounced FRN component in patients in the responder condition. This component has previously been reported to be linked to the anterior cingulate cortex (Hewig et al., 2011). This region is functionally highly connected to the medial prefrontal cortex (Pomarol-Clotet et al., 2010), an area that has been identified to be altered in schizophrenia (Frascarelli et al., 2015). The mPFC was also found to be implicated in decision-making and reasoning (Talati and Hirsch, 2005), as well as social cognition and empathy (Nestler et al., 2015). Importantly, our source reconstruction analysis in the timeframe of the FRN component (320–360 ms) in the responder condition revealed a significant group-dependent modulation of the activity in an overlap zone between the mPFC and the medial part of the dorsolateral prefrontal cortex (mdlPFC). This second structure, which is anatomically interrelated to the mPFC, is involved in adaptive emotion regulation during cognitive control strategies. In various activation tasks, aberrant neural activation of the mdlPFC has been reported in individuals with schizophrenia (Billeke and Aboitiz, 2013; Green et al., 2015). Another visual ERP study furthermore reported an insufficient reflex processing of emotions in patients with schizophrenia (Csukly et al., 2013). This insufficiency was due to deficits in the recruitment of neural sources localized in the left mPFC, similarly to our findings. Our result could reflect changes in the recruitment of the neuronal generators for this ERP component in schizophrenic patients. Such changes may in turn impair cognitive functions that are originating in these cerebral areas. Indeed, we found an association of the FRN amplitude with the set-shifting task (SETS), which reflects executive functions.

From a cognitive point of view, the FRN component has previously been reported to increase with unfair offers in healthy responders (Polezzi et al., 2008). Therefore, its absence in patients suggests a lower interest in fairness considerations. However, since patients in our study rejected lower offers with a similar probability to the control group, a lower interest in the judgement of fairness cannot account for the whole difference. This interpretation is in line with findings of a recent study combining the UG paradigm with different emotional faces (de la Asuncion et al., 2015). The study concluded from behavioral data that schizophrenia patients differentiate between fair and unfair offers but seem to have difficulties with interpreting the emotional information of the second player. Thus, patients are able to understand and apply social reasoning but incorrectly integrate information from their counterpart. Even though our experiment did not include facial expressions, it seems highly plausible that the social interaction with the opposite player was also diminished in our patients. The significant difference found in the social-emotional recognition task further supports the interpretation of difficulties with understanding somebody else's emotions and intentions. In this context, the less pronounced FRN component could reflect this difficulty of interpreting the others behavior. The presence of a negative correlation between the FRN amplitude and social cognition scores in the patient group is in line with this hypothesis.

The theory describing the ability to take other people's viewpoints into account in order to understand the behavior and emotions of others in a social environment, is called Theory of Mind (ToM) or mentalizing (Green et al., 2015). It is well documented that schizophrenia patients show impairments in this domain (Billeke and Aboitiz, 2013; Green et al., 2015; Ventura et al., 2015). The mPFC has been associated with mentalizing abilities, while the dlPFC was activated by emotion regulation processes (Green et al., 2015). The present deficits of the electrophysiological sources in the mPFC and mdlPFC can reflect a mentalizing impairment of patients in the responder condition, further supporting these previous findings. Our results indicate that patients exhibit problems understanding the reasoning behind each offer made by the other player (responder condition), while they are able to anticipate and relate to the emotions of an accept or reject answer of the second player (proposer condition).

Another aspect playing a role in the aberrant social interaction is that schizophrenia patients generally show higher levels of suspicion and distrust to their environment (Fett et al., 2012). It has been suggested that patients' behaviors are guided by a negative bias when predicting a counterpart's behavior (Billeke et al., 2015). Thus, patients might expect little from the other participant and be positively surprised by the offers. In line with this hypothesis, the amplitude of the FRN has previously been reported in healthy participants to be smaller when outcomes were better than expected and larger when they were worse (Hewig et al., 2007; Holroyd et al., 2008).

On the other hand, no distinction in the brain processing of patients and controls could be seen in the proposer condition. This result partly disagrees with the findings of a recent study of Billeke et al. (2015), who investigated oscillatory brain activity. Their results suggested alterations in social interactions in schizophrenia patients in the proposer condition. More precisely, they found a modulation of medial prefrontal alpha and beta oscillations while anticipating the response of the other. However, their study observed effects after the propositions were made, while our study looked into the decision-making process before participants confirmed their offer by pressing a button. Button pressing occurred on average around 1180 ms after the instruction to either make an offer or react to one, over 800 ms after the appearance of the FRN component. While reaction times showed no difference between group and/or offer type in the proposer condition, the patient group displayed significantly higher global reaction times in the responder condition. These observations point to qualitative differences in the information processing according to the condition of the game. Supporting this interpretation, the acceptance rate was significantly associated with the processing speed in the detection task (DET) of the Cogstate battery. The results of our study thus suggest that while acting as proposers, the patients' brain response during the decision-making process is similar to that of controls, in contrast to the responder condition.

Similarly, the P2 amplitude was not affected by the psychiatric status in both proposer and responder conditions. From a neurophysiological viewpoint, this component reflects the active engagement of mental workload processes, working memory (McEvoy et al., 2001) and attention to the target stimulus (Horat et al., 2016). Although impairments in working memory have been reported in schizophrenic patients, it is possible that they only emerge when patients are engaged in tasks more difficult than it is the case in the present paradigm. This interpretation is further supported when looking at the one back working memory task of the CogState battery, which revealed no difference between patients and controls. Thus, our patient group seems to recruit the neuronal generators of these cognitive functions in both task conditions in an adapted manner.

Together, the preserved P2 amplitude in both conditions and the absence of a group difference in the FRN amplitude in the proposer condition strongly support the idea that schizophrenic patients are able to correctly activate neuronal networks involved in social decision-making in the proposer condition. In contrast, having the final say on the split in the responder condition seems to pose an additional conflict on the patients, which then reveals the deficits in the activation of the neuronal networks underlying the FRN component.

Despite the absence of a group-difference on the ERP components in the proposer condition, differences on the behavioral level were observed. Namely, significantly more hyper fair (7, 8, 9 CHF) offers were made by patients when acting as proposers, confirming the results of Agay et al. (2008). However, since segregating the offers according to the fairness level (unfair, fair, hyper fair) did not change the significance of our findings, we chose to report the ERP waveforms of all offers combined.

Finally, it should be specified that it cannot be excluded that the heterogeneity of the disease including differences in symptoms, severity and prescribed drug intake between participants, as well as the current state of the patient on the day of the recording, might slightly influence the data. However, the use of an extensive battery of neuropsychological exams allowed us to homogenize the patient group as much as possible.

To conclude, we found no differences in the processing of social decision-making in the proposer condition of the Ultimatum Game between healthy controls and schizophrenic patients, while the amplitude of the FRN component was lessened in the responder condition. These findings therefore suggest that schizophrenic patients are able to perform all steps involved in social decision-making correctly while they are engaged in the proposer condition. However, the responder condition seems to pose an additional conflict on the patients, hence revealing their difficulties in interpreting the other's behavior as part of deficits in social decision-making linked to the disease. Our EEG findings add to a better understanding of the underlying biological bases of the social deficits in psychotic patients and could therefore be of clinical importance, especially for the development of social cognition interventions.

Contributors

P. Missonnier, I. Gothuey and M. Merlo designed the study. S. Horat and G. Favre acquired the EEG and neuropsychological data, respectively. S. Horat and P. Missonnier analyzed the data. F. Herrmann and S. Horat conducted the statistical analyses. S. Horat, P. Missonnier and M. Merlo wrote the article. J. Ventura and A. Prévot critically reviewed the article.

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Conflict of interest

All authors declare that they have no conflict of interest.

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