Effect of a social defeat experience on prefrontal activity in schizophrenia

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Abstract

The social defeat (SD) hypothesis of schizophrenia posits that repeated experiences of SD may lead to sensitization of the mesolimbic dopaminergic system and to precipitation of psychosis. Based on previous definitions adapted to a human experimental paradigm, we prepared a computer simulation of SD to mimic this subjective experience. We measured prefrontal cortex (PFC) activity in subjects with schizophrenia and healthy controls during exposure to a single SD experience with functional near infrared spectroscopy. PFC activity declined in both groups. Compared with the control condition, SD exposure was associated with a broader decline in left ventromedial, right medial and right lateral PFC activity in healthy controls (n=25), and a sharper decline in right ventrolateral PFC activity in subjects with schizophrenia (n=25). The activity in the right ventrolateral PFC, was significantly lower in patients compared with controls. This may be due to a deficiency in emotion regulation or self-control, or it may be related to impaired empathy in schizophrenia. Different patterns of brain activity during the SD experience in subjects with schizophrenia versus healthy controls may provide indirect evidence regarding the SD hypothesis of schizophrenia.

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1. Introduction

Social defeat (SD) is a commonly used term that describes the physical defeat of one animal by another within-species conspecific member in a series of experiments conducted on social stress. These animal experiments are based on the resident-intruder paradigm: a male rodent (the intruder), put into the cage of another male, is attacked by the resident and prompted to display submissive behavior (Miczek and De Boer, 2005). Tidey and Miczek (1997) showed that, when exposed to social threat, the defeated rats have elevated levels of extracellular dopamine in the nucleus accumbens. Repeated experiences of SD lead to behavioral sensitization in the defeated intruder, who displays an enhanced behavioral response to dopamine agonists (Covington and Miczek, 2001).

Selten and Cantor-Graae (2005) proposed SD as a common unifying mechanism to explain the relationship of schizophrenia with migration, urbanicity, and lower IQ scores, since all these risk factors also involve high levels of SD. In an updated review, Selten et al. (2013) provide further evidence regarding the SD hypothesis of schizophrenia, expanding upon the association of the disorder with unemployment, childhood trauma, and a higher proportion of ethnic density. Selten et al. emphasized that indicators of social disadvantage that are associated with psychosis risk as such may act as proxies for SD, provided that the subject interprets the situation as defeating. Selten and Cantor-Graae (2007) also proposed that defeated animals in the resident-intruder paradigm resemble, in biological terms, subjects with schizophrenia who have increased amphetamine induced-dopamine release. If the results of the animal studies can be extended to humans, chronic exposure to SD may lead to sensitization of the mesolimbic dopamine system and/or overactivity of this system, and thus foster the development of psychosis (Selten and Cantor-Graae, 2005). The authors recommended future studies to investigate response patterns during stressful circumstances by functional neuroimaging tools such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET).

A large body of evidence from neuro-imaging studies, as well as related work from other methodologies, has suggested the lateral prefrontal cortex (PFC) as a central component related to cognitive dysfunction in schizophrenia (Goldman-Rakic and Selemon, 1997; Davidson and Heinrichs, 2003; Glahn et al., 2005; Barch and Ceasar, 2012). The PFC is also sensitive to stressful situations, particularly in the social context (Watt et al., 2009; Watt et al., 2014). In particular, medial PFC activity changes were associated with exposure to social stress both in animal and human studies (Nikulina et al., 2004; Burke et al., 2010) and, similar to defeated animals, patients with schizophrenia have functional abnormalities in the medial PFC during tasks that require social cognition (Benedetti et al., 2009; Das et al., 2012). In fact, social cognition is represented by a larger network that involves not only the PFC but also other brain regions such as the bilateral temporo-parietal junction, the precuneus, and the bilateral middle temporal gyrus (van Veluw and Chance, 2014). However, several animal studies suggest that the PFC seems to play a more prominent role in terms of

SD. In the rat PFC, SD exposure was shown to decrease dopaminergic activity (Watt et al., 2014), and interfere with the degree of PFC control over amygdala activity (Kumar et al., 2014).

Research on SD in humans is limited. Experiments in which human subjects are exposed to physical defeat would not be ethical. Besides, the subjective experience of SD is difficult to measure because individual self-assessments are sensitive to bias (Selten and Cantor-Graae, 2005). Absence of laboratory experiments in humans may also be a consequence of the difficulty in formulating an operational definition of the SD experience. Although the definition in animal research focused primarily on physical defeat, Selten and Cantor-Graae (2005) defined SD in humans as a subordinate position or an outsider status. In a similar attempt, Luhrmann (2007) described human SD as an actual social encounter in which one person physically or symbolically loses to another one. The encounter must be experienced by the individual losing a contest as in non-physical encounters. In that definitional context, SD paradigm can therefore be more readily adaptable to the experimental laboratory setting. In this light, an SD task would require the individual to experience a contested social encounter. However, in laboratory settings, fMRI and PET are physically restrictive procedures and may not provide ecologically valid measurement of brain activity during such a complex social experience. On the other hand, functional near infrared spectroscopy (fNIRS) is a non-invasive cortical imaging technology capable of measuring brain activity in a more naturalistic environment than is possible in fMRI experiments (Rolfe, 2000). Since fNIRS is relatively insensitive to motion artifacts, subjects can be examined in a natural sitting position, without any surrounding distraction (Takizawa et al., 2008). For example, fNIRS has been used in real-world situations (Dresler et al., 2009) such as face-to-face communication (Suda et al., 2010) and interpersonal cooperation (Cui et al., 2012).

The present study aims to investigate the PFC response to SD in schizophrenia. A differential activation pattern during a single experience of SD in subjects with schizophrenia versus healthy controls would be informative regarding the proposed association of SD exposure and schizophrenia. We hypothesize that subjects with schizophrenia and healthy controls have different activations in PFC during a computer simulation of a single SD experience. Based on the above-mentioned definitions of SD, the simulation was prepared to mimic this subjective experience as closely as possible to real-world settings, and for the same reason, fNIRS was used to measure brain activity.

2. Methods

2.1. Study groups

The index group comprised 26 consecutive outpatients [n=23 with DSM-IV (American Psychiatric Association, 1994) schizophrenia, n=3 with schizoaffective disorder] enrolled at a university hospital. All index subjects were in regular treatment with atypical antipsychotics, and none had a comorbid mood disorder, pervasive developmental disorder or intellectual disability. Symptom severity was assessed with the Scales for the Assessment of Positive (SAPS) and Negative Symptoms (SANS) (Andreasen, 1987). Hand preference was assessed by a Turkish version of Chapman and Chapman's Hand Preference Questionnaire (Nalcaci et al., 2002). The healthy controls (n=27) were evaluated by two

experienced psychiatrists to rule out any psychiatric disorder or a history of treatment with psychotropic medications. All participants had completed 8 years of compulsory education. Socio-demographic and clinical features of the two groups are presented in Table 1. The study was approved by the University Ethics Committee. All participants signed written informed consent. Regarding the index group, a family member also signed the informed consent and gave permission for his/her relative to be enrolled to the study. All the participants were right-handed and physically healthy at the time of recruitment; none had a history of intellectual disability, head trauma, serious medical or surgical illness, or alcohol/ substance abuse disorder.

2.2. The control and the social defeat conditions

The cognitive paradigm used in this study (the Box Filling Game) consisted of a control condition (CC) and a social defeat condition (SDC). In the CC task, subjects were informed that they were going to play a game called the Box Filling Game. They were instructed that the aim of the game was to fill in the boxes on the screen, and they were told to fill in as many boxes as they wished during the following 30 s. Next, subjects were presented 200 empty boxes, each of which could be "painted" red when clicked with the left mouse button. After filling in the boxes, they were allowed to rest for a minute in response to the '*please wait*' command on the screen. This was necessary in order to decrease the activity due to motor movements during the filling in of the boxes. After this rest period, subjects were prompted that the computer was ready to calculate how many boxes they filled in, and the '*hit the space-bar to proceed*' command appeared at the bottom of the screen. When the subject hit the space-bar, a sandglass appeared for 20 s in a box entitled '*the number of the boxes filled by the subject*' as if it was taking some time for the computer to make that calculation. Cortical activity during the sandglass was used as the pre-control baseline. Finally, the total number of boxes filled in by the subject replaced the sandglass and was presented to the subject for 30 s, during which the brain activity was recorded and used as the CC-task activation. The CC task was followed by the sandglass again for 20 s as the post-control baseline. Thus, the stimuli presented to the subject during the pre-control baseline, the CC task, and the post-control baseline were the same except that a number replaced the sandglass during the CC task.

In the SDC task, the subjects were informed that they were going to play the Box Filling Game against another human subject who was also a participant of the study, and the participant who filled in more boxes would win the game whereas the other participant would lose. In order to make this experience more realistic, we prepared two videos: one with a female and one with a male actor as if the actors were also participating in this study and were preparing in the next room to play the game against the participant. In these videos, the actors were in a sitting position and the NIRS probes were fixed on the scalp. They acted as if they were being instructed by a researcher to play the game against the participant. The video recorded with the male actor was shown to male participants and the one recorded with the female actor was presented to female subjects after the introduction screen of the SDC. Next, subjects were presented the same empty boxes as in the CC, and filled them in, but this time in order to win the game. After filling in the boxes, the subjects were allowed to rest for a minute facing the '*please wait*' command to reduce the brain

activity due to motor movements. After this rest period, subjects were prompted that the computer was going to calculate how many boxes the participant and the opponent had filled in. Two sandglasses appeared in two boxes for 20 s as the pre-task baseline followed by a screen that announced the results under the names of the participant and the virtual opponent. Regardless of the score of the participant, the task was designed to announce the score of the virtual opponent as being 1.4 times higher than the participant's score. This was done to expose all subjects to same magnitude of defeat during the SDC. The design of the results screen was the same as the CC task, except that the score of the opponent was also presented and a sentence announcing that the participant had lost the game. Similar to the CC task, the SDC task was followed by the sandglass for 20 s as the post-task baseline. The stimuli presented to the subject during the pre-task baseline, the SDC task and the post-task baseline were also the same except that numbers replaced the sandglasses. The steps of the task are presented in Fig. 1.

After the fNIRS procedure, participants were immediately invited to move to a different room where a post-task self-evaluation questionnaire (PTQ) was administered, followed by a semi-structured interview with a psychologist. The PTQ consisted of 10 questions, each of which could be answered '*yes*' or '*no*' in order to assess the subjective feelings of loss, defeat, disappointment and being in a subordinate status experienced after the game. These were applied to assess whether the subjects experienced the loss during the SDC as an SD or not. A participant was presumed to have experienced SD if he/she had answered '*yes*' to at least three of the questions. Two subjects among the control group and one subject among the patient group answered yes to fewer than three questions and they were excluded from further analyses. At the end of the semi-structured interview, participants joined a debriefing session and were informed that the opponent was in fact "virtual," and they in fact had had no chance to win.

2.3. fNIRS procedure

We used the 24-channel fNIRS device (ETG-4000; Hitachi Medical Co., Tokyo, Japan) located at the University Brain Research Center fNIRS Laboratory to measure cortical activity during the SD task. The fNIRS instrument measures relative changes in oxygenated (oxy-Hb) and deoxygenated (deoxy-Hb) hemoglobin through optodes (emittors and detectors) of two wavelengths (695 and 830 nm) of infrared light (indicated as mM/L) on the basis of the Beer–Lambert law. As a result, it is possible to noninvasively probe the human cerebral cortex using near-infrared light and monitor the cerebral concentration of hemoglobin, which is the dominant near-infrared absorbing species in the brain (Boas et al., 2004). The distance between emitter/detector optodes was set at 3.0 cm, and the channels were defined as the area between the emitter-detector pairs. The 3-cm space between the optodes allows the device to measure oxy-Hb and deoxy-Hb changes at a 2- to 3-cm depth from the scalp that corresponds to the surface of the cerebral cortex (Okada and Delpy, 2003; Toronov et al., 2001). The optodes were fixed to the scalp via two thermoplastic 3×3 shells, with the lowest optodes positioned along the Fp1–Fp2 line according to the international 10–20 system used in electroencephalography. Fig. 2 presents the arrangement of the optode placement and the measurement channels.

The time resolution of fNIRS was set at 0.1 s. The pre-task baseline was determined as the mean over the 10-s period just before the task period, and the post-task baseline was determined as the mean over the last 5 s of the post-task period; linear fitting was applied to the data between these two baselines. Fluctuations of fNIRS signals are known to be related to such physiological activities as the systemic arterial pulse oscillations (0.1 Hz) and respiration (0.2–0.3 Hz) (Hoshi, 2003). Thus, moving average methods were applied to correct such fluctuations in the analyzed data (moving average window: 5 s). Since oxy-Hb change (oxy-Hb) is assumed to more directly reflect cognitive activation than deoxy-Hb change as shown by a stronger correlation with blood-oxygenation level-dependent signal measured by fMRI (Strangman et al., 2002), we focused on the mean change in oxy-Hb during the task periods relative to the pre- and post-task baseline periods.

2.4. Statistical analysis

The number of boxes filled in by the participants in the two conditions was compared between the two groups with an independent samples t-test. PTQ scores were compared between the groups with the Mann–Whitney U-test. The number of boxes filled in the SDC and CC were compared within the groups with paired samples t-tests.

The effect of experimental manipulation on oxy-Hb levels was assessed in a 2 (Group) $\times$2 (Condition) $\times$24 (Channel) mixed design analysis of variance (ANOVA). The between-subject independent variable 'Group' had two levels as the control group and index group; the within-subject independent variable 'Condition' had two levels as the CC and the SDC; and the within-subject independent variable 'Channel' had 24 levels. Post hoc analyses were carried out with two-way ANOVA and the Bonferroni correction was applied to eliminate type-1 errors resulting from multiple comparisons.

Spearman correlation tests were carried out to examine the relationship of brain activity in each channel with the number of boxes filled in by the subject in each condition, as well as the relationship of these variables to SAPS and SANS scores.

3. Results

Both the index and control subjects filled in more boxes in the SDC (index: 57.9±12.3; control: 66.9±12.6) than the CC (index: 42.4±13.0; control: 49.5±14.7; index: t=−9.21, p<0.001; control: t=−10.36, p<0.001). In the CC task, index and control subjects filled in a similar number of boxes (index: 42.4±13.0; control: 49.5±14.7; t=−1.8, p=0.08). However, the mean number of boxes filled in by the controls was significantly higher than the corresponding number for index subjects in the SDC task (index: 57.9±12.3; control: 66.9±12.6; t=−2.57, p=0.013). The PTQ scores were not different between the two groups (index: 4.2±1.1; control: 4.0±1.1; t=0.66, p=0.516).

The mean overall prefrontal activity during the CC was 0.017±0.032 mMmm for the control group and 0.003±0.031 mMmm for the index group (t=−1.54, p=0.129). The mean overall prefrontal activity during the SDC was −0.005±0.024 mMmm for the control group and −0.012±0.039 mMmm for the index group (t=−0.72, p=0.48).

Mixed ANOVA revealed that the main effects of Channel [$F(8.86, 425.26)=1.99$, $p=0.039$, $\eta_p^2=0.04$, Greenhouse–Geisser $\varepsilon=0.39$] and Condition [$=F(1, 48)=12.15$, $p=0.001$, $\eta_p^2=0.20$] were significant. Post hoc tests revealed that the activity in the PFC was higher during the CC task than the SDC task for both groups ($X_{CC}=0.011 > X_{SDC}=-0.008$, $p<0.01$).

The Group Condition×Channel interaction was also significant [$F(9.12, 442.18)=3.21$, $p=0.001$, $\eta_p^2=0.063$, Greenhouse–Geisser $\varepsilon=0.40$]. In order to understand the origin of this interaction, we first performed two-way ANOVA tests for each channel separately. The Condition×Group interaction was significant only for channel 20 [$F(1, 49)=14.17$, $p<0.001$ (Bonferroni correction was applied for 24 comparisons), $\eta_p^2=0.23$]. oxy-Hb in channel 20 was higher in controls than index subjects during the SDC task (MD=0.065, $p<0.001$, 95% CI: 0.039–0.091). The waveform showing the course of activity at channel 20 in both conditions is presented in Fig. 3.

Next, we performed two-way ANOVA tests for each group separately. The condition×channel interaction was significant only for the control group [$F=(7.76, 186.2)=2.46$, $p=0.016$ (Bonferroni correction was applied for 24 comparisons), $\eta_p^2=0.09$]. Channels where oxy-Hb values were significantly different between the two conditions in both groups are presented in Table 2. The PFC activity in control and SD conditions for both groups is presented in Fig. 4.

We did not find any correlations between the number of the boxes filled in or PTQ scores with the brain activity. SAPS and SANS scores were not correlated with channel activations among the index subjects.

4. Discussion

Working from previous definitions of SD, we developed a SD paradigm and examined the effect of this experience on PFC activity assessed with fNIRS in subjects with schizophrenia and healthy controls. Both groups filled in more boxes in the SDC than in the CC tasks. This may either indicate that the participants had a realistic competition experience during the SDC, or it may be related to a learning effect, or both. The two groups filled a similar number of boxes for the CC, but healthy controls filled in more boxes than the index subjects for the SDC. This may imply that the psychomotor disturbance in schizophrenia becomes evident under stress.

The PTQ scores were not different between index and control subjects; therefore subjective feelings of defeat provoked by the paradigm were comparable in the two groups. The main effect of condition revealed by the mixed ANOVA indicates that regardless of the channels, the SD task, compared with the CC task, is associated with lower levels of prefrontal activity in patients and controls. In fact, the overall prefrontal activity during the SDC was below zero for both groups, which means that the activity during the SDC was not only smaller than during the CC, but was also smaller than the activity during the pre-task rest period, suggesting a pattern of deactivation during the SDC. In particular, the medial part of the PFC is a component of the default mode network and has been known to show deactivation

during goal-directed tasks (Buckner et al., 2008). Although the box-filling game is a goal-directed game, in the intervals during which we acquired measures of cortical activity, the participants were not expected to perform any motor or mental task; instead they were confronting results indicating that they had just been defeated by another participant. Furthermore, since we allowed the participants to rest for a minute after playing the box-filling game and before the announcement of the results, it is very unlikely that the deactivation is related to the goal-directed phase of the task; rather, the deactivation is probably intrinsic to the SD experience itself.

The significant Group × Condition × Channel interaction suggests that PFC activity was topographically different between the two conditions as well as the two groups. From the condition perspective, this significance stems from lower activity in the left ventromedial PFC (channels 8,9 and 11), the medial PFC (channels 3,16 and 17) and the right dorsolateral PFC (channel 13) in the SDC compared with the CC task in the control group. Similarly, in patients, the activity only in right ventrolateral PFC (VLPFC) (channel 20) was smaller during the SDC than the CC. This implies that although the SD experience is associated with a lower level of activity than that seen during the CC in both groups, individual channels that show an activity decline during the SDC are different in the index and control subjects. From the group membership perspective, the significant triple interaction stems only from channel 20 (right ventrolateral PFC) where the activity was higher in control than index subjects during the SDC. Taken together, these findings suggest that, compared with the CC, the SD experience leads to a broader decline in PFC activity in healthy controls, but a sharper decline in index subjects in the right ventrolateral PFC. The right ventrolateral PFC is involved in the ventral affective system, which is important for the regulation of negative affect as well as cognitive reappraisal of emotions (Dolcos et al., 2011; Buhle et al., 2014). Thus, smaller activity in the right ventrolateral PFC in the index group during the SDC may imply a dysregulation of emotions induced by the SD experience in psychotic subjects. In addition, simple motor response inhibition mostly assessed via go/no-go and stop-signal tasks consistently activate the right ventrolateral PFC (Aron et al., 2004), and this area may be critical for inhibiting responses (Aron et al., 2014). It has been proposed that the right ventrolateral PFC is well suited to serving a key role in exerting self-control over actions (Cohen and Lieberman, 2010). Thus, smaller activity in this area in patients compared with controls may also reflect a deficiency in response inhibition or self-control during the SD experience. Moreover, the ventrolateral PFC may also play a role in empathy. van der Heiden et al. (2013) investigated the effects of successfully adopting the first and third person perspectives on the neural correlates of pain perception using daily life situations and showed that the ventrolateral PFC is involved in successful perspective-taking, eliciting empathy for another person. Therefore, low activity in this area among the index subjects may also reflect an impairment in empathy for the virtual rival.

Studies that examined functional cerebral correlates of other negative social experiences in schizophrenia also suggest a prefrontal dysfunction associated with those negative experiences. In an fMRI experiment, Gradin et al. (2012) examined brain activity in schizophrenia and healthy controls during the cyber-ball paradigm, which involves passing a ball between the participant and two cartoon representations of other subjects. The authors found a blunted response in the medial PFC during social exclusion (ball not being passed to

the participant) in the patient group. In another fMRI experiment, Lee et al. (2014) examined brain activity in subjects with schizophrenia and healthy controls during a virtual handshake task, in which socially interacting contents such as acceptance and refusal of handshaking were implemented. During refusal, patients showed higher activity than control subjects in the prefrontal regions, including the lateral frontopolar cortex, which was interpreted as a signal of the inordinate mental load evoked by the salient social stimuli in the task. Similar to the findings in our study, the lateral frontopolar cortex was the only region that survived in the group comparison in that study. However, unlike Lee et al. (2014), we observed hypoactivity in that region. Given that prefrontal activity shows load-dependent pattern (i.e., overactive in low loads and underactive in high loads) (Johnson et al., 2006), the difference between the study of Lee et al. and our own study may be related to the higher social task load in the present study.

SD has been proposed to mediate the relationship of urbanicity and schizophrenia (Selten et al., 2013). Haddad et al. (2015) investigated possible morphological correlates of urbanicity in healthy human brains with voxel-based morphometry and detected a strong inverse correlation between early-life urbanicity and gray matter volume in the right dorsolateral PFC. In this study, a single SD experience was associated with deactivations in the PFC in both groups and with a lower level of activity in subjects with schizophrenia in the right ventrolateral PFC compared with healthy controls. This suggests that even a single experience of a computer-simulated SD experience is processed differently in index subjects and controls, providing further support for the toxic effect of social stress on the right PFC as a risk factor for the index condition and as a putative psychosis risk. Dopamine dysregulation involving striatal dopamine sensitization may represent a common mechanism, linking multiple environmental exposures to underlying biological mechanisms of psychosis (Yuii et al., 2007; Collip et al., 2008). Additionally, previous research suggests a reciprocal relationship between prefrontal and striatal dopaminergic dysfunction in schizophrenia. A number of researchers have suggested that prefrontal dopaminergic dysfunction may partly be the result of dysregulated input from the midbrain dopamine system (Braver et al., 1999; Braver and Cohen, 2000; Tanaka, 2006). On the other hand, according to the tonic-phasic dopamine theory introduced by Grace (1991), when the tonic activity is low, stressful stimuli are not optimally regulated by the PFC, resulting in increased phasic dopamine release in the striatum. The results of the present study also support this view by showing an altered response to SD in terms of right ventrolateral PFC activity in schizophrenia. This altered response may indeed represent inefficient processing of stressful experience such as SD.

This study has several limitations. The design of the SD task did not permit us to present the two conditions in a random order, and the CC always preceded the SDC. Therefore, it is possible that the main effect of condition is related to habituation of the PFC activity. However, unlike neurocognitive tasks examining mental sets of the same quality with varying task demands, the CC and the SDC were qualitatively different conditions designed to provoke different phenomenological experiences, thus reducing the possibility of habituation. Secondly, the sample size is small and the SD task has not been tested before. Nevertheless, the paradigm was designed to simulate the SD experience as realistically as possible, and the fNIRS technique allowed measures of brain activity in a relatively

naturalistic setting. Although we confirmed the SD experience just after the task, individual ratings of the defeat experience may have been sensitive to bias. Furthermore, antipsychotic use may interfere with cerebral perfusion (Miller et al., 1997) and lead to a different activity pattern in the index group. Another possibility is that several factors such as urban upbringing, migration and childhood trauma were not controlled in this study, and may theoretically confound the relationship of social defeat and cortical activity. Therefore, this study should better be regarded as a pilot experiment with positive results. Further studies may illuminate whether the different representation of SD experience in terms of PFC activity in brains of subjects with schizophrenia and healthy controls is indeed intrinsic to psychosis.

Acknowledgments

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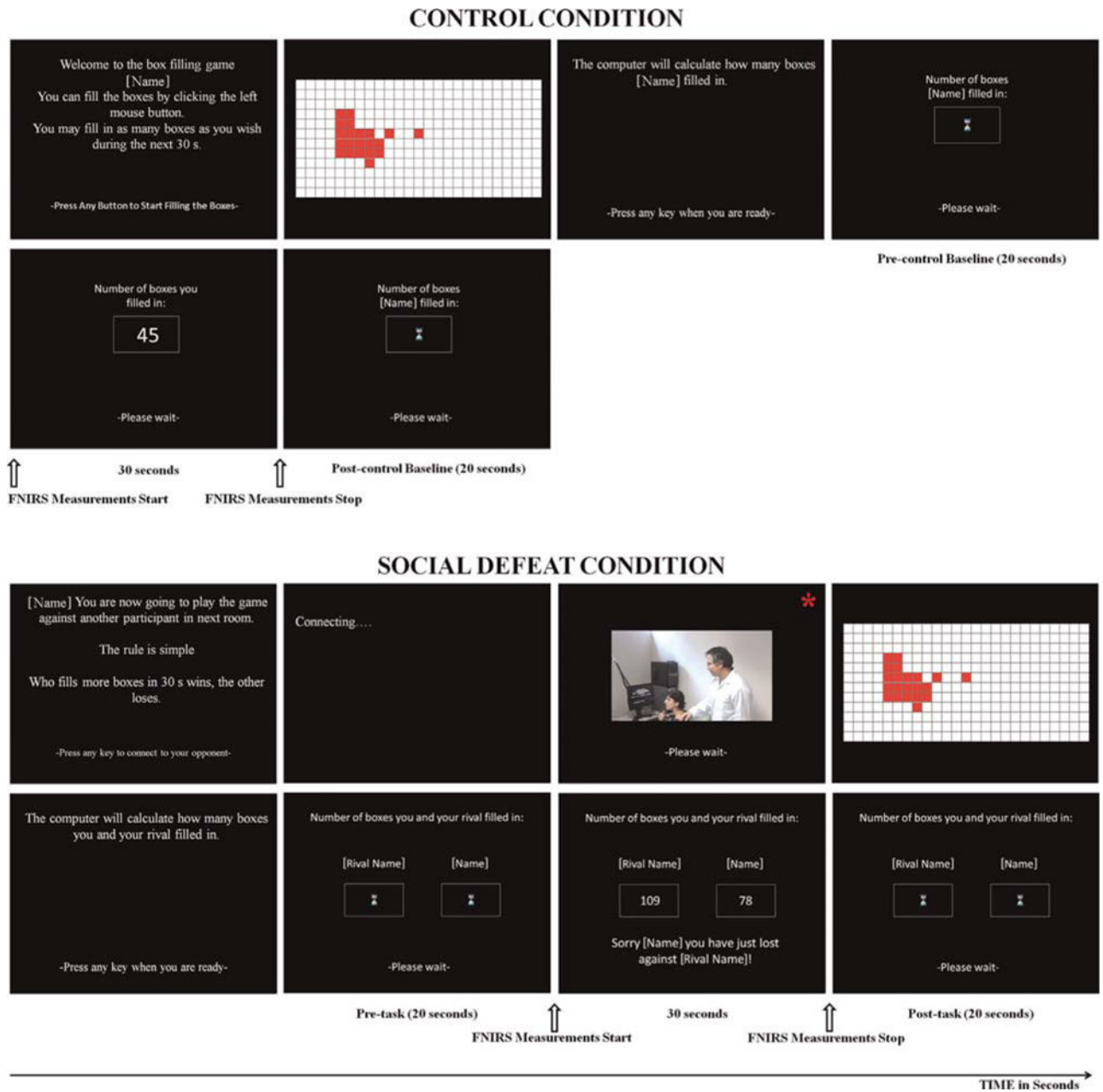
CONTROL CONDITION

SOCIAL DEFEAT CONDITION

Fig. 1.
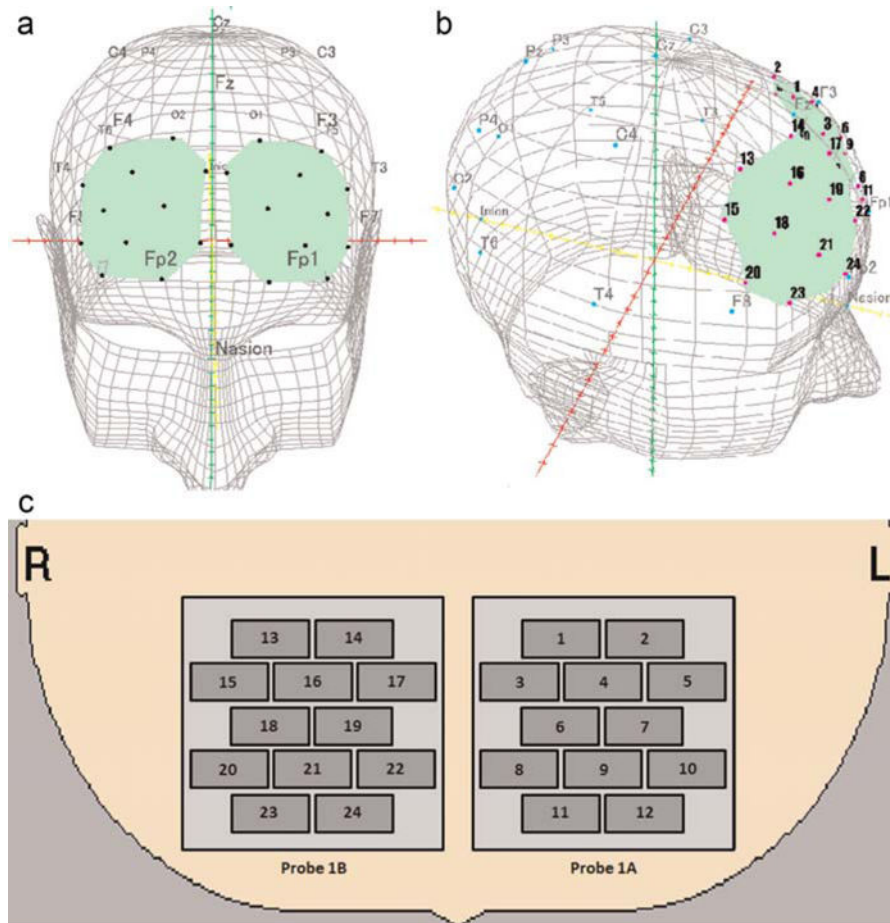The social defeat task and the control task.

Fig. 2.
3D representation of the measurement channels on the scalp according to the 10/20 system
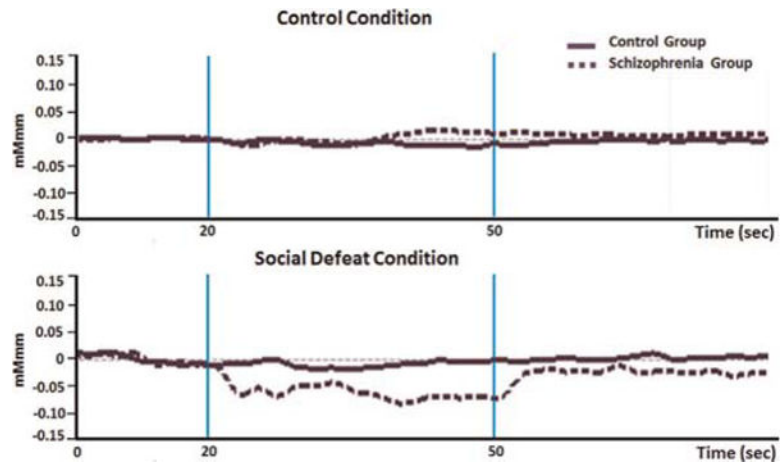((a) front view, (b) right-sided view, and (c) channel numbers).

Fig. 3.
The waveform graph of the prefrontal activity in channel 20 during the two conditions.
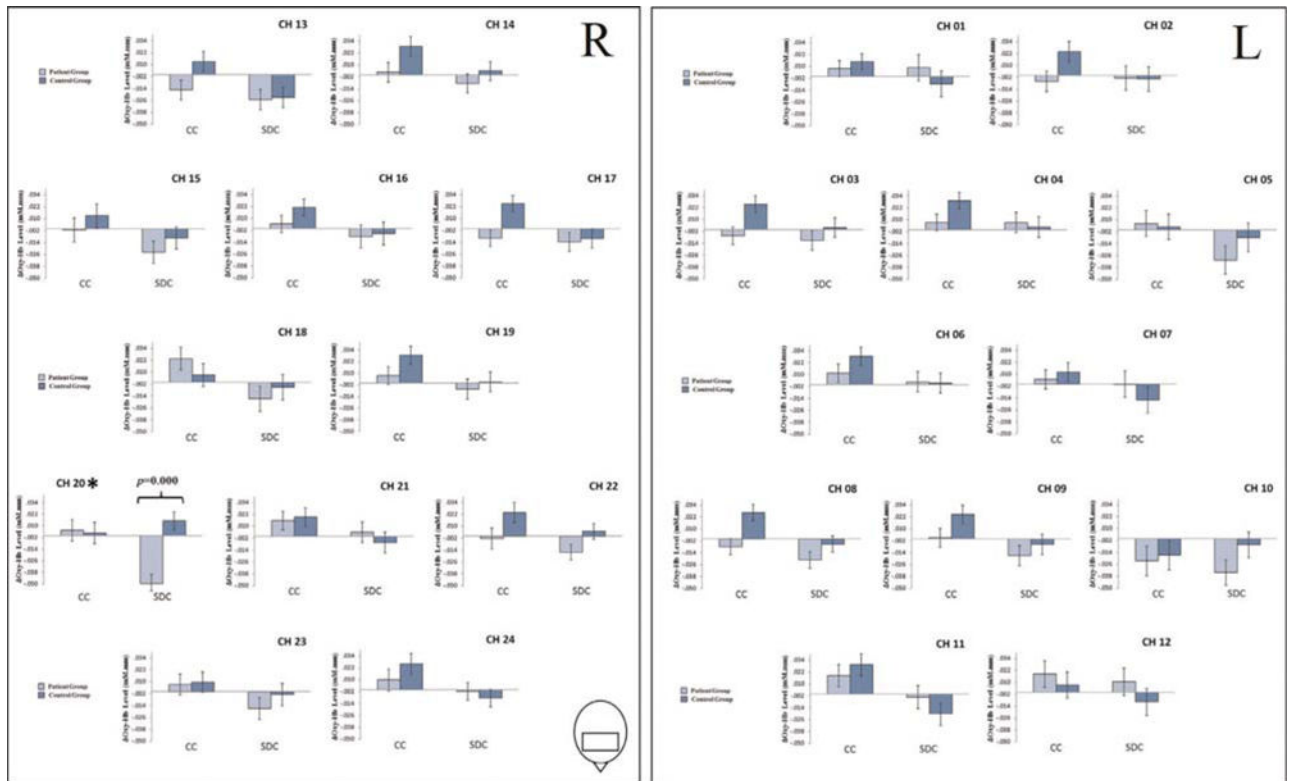
Fig. 4.
Mean prefrontal activity in all measurement channels during the two conditions in the index group and the control group.

Table 1

Socio-demographic and clinical characteristics of the groups.

	Patients (*n*=25)	Controls (*n*=25)	
Gender (F/M)	7/18	10/15	χ^2=0.8, *p*=0.55
Age (years±SD)	34.5±7.9	30.6±6.3	*t*=1.92, *p*=0.06
Education (years±SD)	12.2±2.6	12.6±1.8	*t*= 0.69, *p*=0.49
Mean duration of illness (years±SD)	11.6±5.5	–	–
SAPS score (mean±SD)	17.2±6.9	–	–
SANS score (mean±SD)	19.4±8.9	–	–
PTQ (median, range)	4, (3–7)	4, (3–7)	*z*= 0.74, *p*=0.45

F: female, M: male, SD: standard deviation, SAPS: Scale for the Assessment of Positive Symptoms, SANS: Scale for the Assessment of Negative Symptoms, PTQ: post-task self-evaluation questionnaire.

Table 2

Channel×condition interaction effect post hoc tests with Bonferroni adjustment.

Group	Channel/location	Mean difference (CC-SDC)	SE	p^a	95% Confidence interval for difference	
					Lower bound	Upper bound
CG	3/Left medial PFC	0.023	0.007	0.002	0.009	0.037
	8/Left ventromedial PFC	0.032	0.008	0.001	0.015	0.049
	9/Left ventromedial PFC	0.030	0.008	0.001	0.013	0.047
	11/Left ventromedial PFC	0.050	0.013	0.001	0.023	0.076
	13/Right dorsolateral PFC	0.036	0.008	0.000	0.021	0.052
	16/Right dorsolateral PFC	0.026	0.007	0.001	0.011	0.041
	17/Right medial PFC	0.035	0.008	0.000	0.019	0.051
SZ	20/Right ventrolateral PFC	0.055	0.012	0.000	0.030	0.079

SE: standard error, SZ: patient group, CG: control group, CC: control condition, and SDC: social defeat condition.

^{a}Bonferroni-corrected p threshold=0.05/24=0.00208.