Prefrontal Cortex Activity During Facial Affect Processing in Schizophrenia: Association with Clinical Symptoms and Social Cognitive Functions

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SUMMARY

Objectives: In the present study, we aimed to investigate the prefrontal cortex (PFC) activity during facial affect recognition in schizophrenia, as well as the association of this activity with symptom severity and with the higher order social cognitive functions, namely recognition of false beliefs, faux-pas and hinting.

Method: Functional near infrared spectroscopy (fNIRS) was used to measure frontal cortical activity during a neuroimaging task prepared with a standard set of pictures of facial affect. The data of the Index Group (IG) consisting of 27 subjects with DSM-IV based diagnoses of schizophrenia and schizophreniform disorder and control group (CG) (N=25) were compared. The control condition was to detect non-affective changes on a neutral face. Associations with frontal activity during affect recognition and clinical symptoms, false belief recognition, hinting and faux-pas were investigated.

Results: Prefrontal activity during both affective and non-affective conditions was higher in the IG than the CG. The IG performed worse than the CG in social cognitive tests. Social cognitive test performance was not correlated with cortical activity. There were no correlations between education status, age and PFC activity in both groups. In the IG, right ventral prefrontal cortex (VPFC) and right medial prefrontal cortex (mPFC) activities were associated with hallucination severity.

Conclusion: These results suggest the presence of hyperfrontality during face processing in schizophrenia. Results also suggest that schizophrenia patients require more frontal resources to achieve a performance comparable to that of healthy controls in order to detect both affective and non-affective changes on a face. There might be a relationship between facial processing and hallucinations.

Keywords: Schizophrenia, functional neuroimaging, theory of mind

INTRODUCTION

Recognition and identification of affective facial expressions are among the fundamental social cognitive abilities of humans. Inferring mental states and intentions of others is crucial to develop healthy social interactions (Baron-Cohen 1991). Problems in affect recognition have been shown in many psychiatric disorders such as schizophrenia, bipolar disorder and depression (Bora and Berk 2016, Boraand Pantelis 2016). Research suggests that facial affect recognition is impaired in schizophrenia and even clinically remitted patients with schizophrenia display a lower performance than healthy controls in affect recognition (Yalcin-Siedentopf et al. 2014). Impaired affect recognition is detectable in the first psychotic episode as well as during the following course of schizophrenia (Leung et al. 2011, Addington et al. 2006). Furthermore, individuals in the prodromal stage and those at risk for psychosis may also be impaired affect recognition

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(Addington et al. 2008). Patients with schizophrenia have impaired higher order social cognitive functions. Theory of mind (ToM) defects such as making simplistic or wrong inferences for mental states of others have been shown in schizophrenia (Bora et al. 2009). Lower performance in recognising faux-pas and empathy have also been reported (Bonfilis et al. 2016, Ozel-Kizil et al. 2012). Impaired perception of socio-emotional clues such as facial affect may indeed contribute to further impairment in higher order social cognitive functions and social functioning (Bora et al. 2009, Couture et al. 2006).

Hypofrontality refers to lower activity in the prefrontal cortex (PFC) and has been displayed in many neuroimaging studies in subjects with schizophrenia. Hypofrontality in schizophrenia has been detected during tasks that require executive functioning, creativity, working memory and even in resting state (Kühn and Gallinat 2013, Ragland et al. 2007, Hazlett et al. 2000, Andreasen et al. 1992). PFC is involved in processing both affective and non-affective facial information (Fusar-Poli et al. 2009).Nevertheless, lower activity particularly in frontal and medial parts of the PFC during social cognitive tasks has been shown in schizophrenia (Das et al. 2012, Bendetti et al. 2009). Thus, PFC is the common cortical area for facial processing and social cognition and activity changes in this area during facial processing may be associated with ToM performance in subjects with schizophrenia.

The aim of this study is to examine PFC activity in schizophrenia patients tested for recognition of elementary facial affects and to examine the relationship between PFC activities with social cognitive functions. We hypothesize that *(i)* schizophrenia subjects and healthy controls display different PFC activity during facial affect recognition, and *(ii)* there is a positive correlation between PFC activity during facial affect recognition and social cognitive performance, and *(iii)* a negative correlation between this activity and clinical symptoms in schizophrenia.

METHODS

Sample

The index group (IG) of this cross-sectional case control study consisted of consecutive outpatients with diagnoses of schizophrenia or schizophreniform disorder made on the DSM-IV-TR (American Psychiatric Association, 1994) who were admitted to Ankara University Faculty of Medicine Psychiatry Department and Psychiatric Rehabilitation Unit between July 2014 and April 2016. Inclusion criteria for the IG and the control group (CG) were; *(i)* having completed at least eight years of primary education, *(ii)* being at an age between 18-65 and *(iii)* being dominantly right-handed. Inclusion criteria for the IG also included *(iv)* meeting the DSM-IV-TR criteria (American Psychiatric Association, 1994) for schizophrenia or schizophreniform disorder, and *(v)* having a score equal to or lower than 3 on the Clinical Global Impressions Scale. Exclusion criteria for the IG were *(i)* alcohol or drug abuse, *(ii)* a history of head trauma with loss of consciousness longer than 30 minutes, *(iii)* application of electroconvulsive therapy within the previous 6 months, *(iv)* WAIS-R total IQ score lower than 75 and *(v)*a physical handicap (i.e. loss of hearing or sight) that interferes with the implementation of psychiatric scales and cognitive tests. The patients and one of their first degree relatives were initially informed verbally about the study protocol and written informed consents were obtained from those who agreed to participate in the study. The first degree relatives also signed a consent form. The CG comprised healthy volunteers without any psychiatric disorder history. The exclusion criteria for the CG were same as for the IG. Control participants were also verbally informed about the study protocol and signed a written informed consent (N=25). Two participants among the 27 subjects in the IG who agreed to participate dropped out on their own demand, and another participant was excluded due to change in diagnosis during the study period. Analyses were carried out with the remaining 24 participants among the IG. Similarly, one participant in the CG was also excluded due to inability to make contact in order to complete the data. Hence, data analyses were carried out with the remaining 24 control participants. Sociodemographic comparison of the two study groups revealed that participants in the IG were older than those in the CG (IG mean age: 39.9 (±9.4); CG mean age: 32.8 (±7.7); t=2.88, p=0.006). Further, education level was higher in the CG [the median (range) in years); IG: 12(8); CG: 15(6); Z=-2.4, p=0.02)]. The groups did not differ in terms of gender distribution (IG: 7 females/17 males; CG: 10 females/14 males; X2 =0.82, p=0.55). The study was approved by Ankara University Faculty of Medicine Ethics Board (08.22.2014; approval ID: 13-580-14).

Procedure

Measurements and evaluations were completed in two sessions. In the first session, socio-demographic and clinical data were obtained and cognitive tests were performed. The second session was carried out in Ankara University Brain Research Centre Functional Near Infrared Spectroscopy (fNIRS) Laboratory.

Socio-demographic, Clinical and Cognitive Tests and Evaluations

The participants first completed the socio-demographic data form that was prepared by the researchers. General severity of illness was evaluated by Clinical Global Impressions Scale (CGI) (Guy, 1976). Psychotic symptom severity was measured by Turkish versions of the Scales for the Assessment of Positive and Negative Symptoms in Schizophrenia (Erkoç et al. 1991a, Erkoç et al. 1991b). Social functioning was evaluated by Personal and Social Performance (PSP) Scale (Morosini et al. 2000). Total IQ score was measured by the Wechsler Adult Intelligence Scale- RevisedForm (Wechsler 1981).

Subsequently, Social Cognitive Assessment was made in the domains of (*i)* understanding false beliefs, *(ii)* hinting and *(iii)* understanding of faux pas. The ability to understand false beliefs were evaluated by two first degree and two second degree ToM tests (ToM-1 and ToM-2). The ability to understand social hints was evaluated by the Hinting Test (HT) and the ability to understand faux-pas was evaluated by the Faux-Pas Test (FT).

The first ToM-1 test used in this study was developed by Perner and Wimmer (1985) to assess thought process. In the second ToM-1 test, 2 out of the 6 stories developed by Frith and Corcoran (1996) were read out to participants. The test consists of a validity question, a memory question and a question that evaluates ToM-1 ability. The first ToM-2 test comprised adaptations of short stories that were developed by Bowler (1992). The second ToM-2 test comprised a story developed by Frith and Corcoran (1996). After reading the scenarios, the subjects were asked a naming question, prompt questions, a reality question, a memory question, and a belief question. The naming and prompt questions were expected to control the effect of memory. The scenarios were read again on participant request.

The HT was developed by Corcoran and colleagues (1995) and enables measuring the ability to understand underlying intentions beneath indirect verbal expressions. The stories were obtained from the authors. Two among the original ten stories were translated and adapted to the Turkish population. The participants were evaluated with questions for understanding the hints that passed within a dialogue between two characters in these stories.

FT evaluates the ability to comprehend that a person talks or acts inappropriately in a situation where he/she feels humiliated afterwards. The original scenarios developed by Baron Cohen (1999) consist of ten scenarios. Two out of these ten scenarios were translated and adapted to the Turkish population. The participant is evaluated for understanding the faux pas that was committed by a character within a dialogue in these scenarios.

Although there is not a validity and reliability study of this social cognitive test battery, the same battery was used in previous studies which revealed that this test battery is capable of distinguishing schizophrenia patients from healthy controls (Yucel et al. 2016, Ozguven et al. 2010).

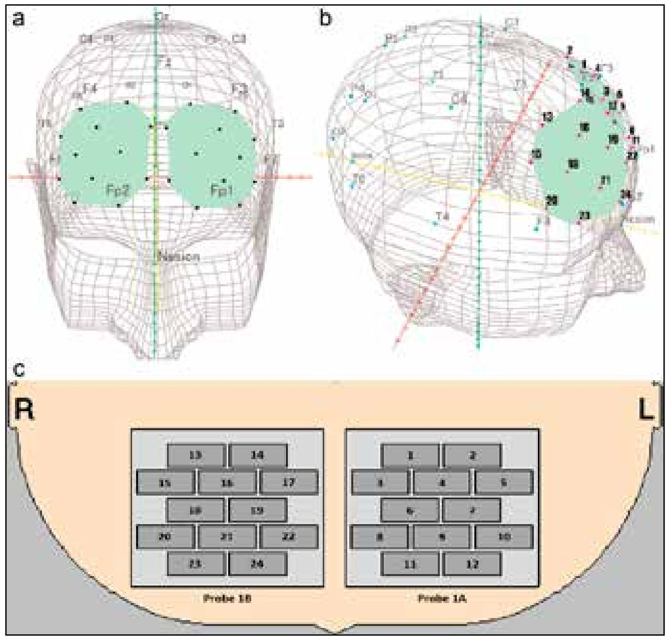

Figure 1. Placement of the channels in which the activity measurement was conducted according to International 10-20 EEG System

(a: front view, b: right side view, c: placement of the channels)

Neuroimaging

The non-invasive optical technique fNIRS enables measuring of in-vivo brain oxygenation. The method is based on different absorption of near infrared light by oxyhemoglobin (HbO2) and reduced deoxyhemoglobin (Hb) (Franceschini and Boas 2004). The measured values correspond to blood oxygen level dependent signal measured by functional magnetic resonance imaging and are equivalent to cortical activity in the cortical tissue 3-4 cm. beneath the scalp (Okada and Delpy 2003, Toronov et al. 2001). The distance between emitter/detector pairs was set at 3.0 cm, and the channels were defined as the area between these pairs. The optodes were fixed to 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 (Figure 1). This optode configuration has been used in previous studies and enables a valid measurement of PFC activity (Baskak et al. 2015a), (Baskak et al. 2015b). Hitachi ETG-4000 fNIRS device located at the Ankara University Brain Research Center was used in this study.

Facial Affect Identification Task

The Facial Affect Identification Task (FAIT) was developed by the researchers as the activation paradigm to be used during the fNIRS imaging. A set of photographs depicting affective adult faces (Pictures of Facial Affect) was purchased and used to develop the FAIT. POFA consists of validated affective facial expressions (Matsumoto and Ekman 1989, Ekman

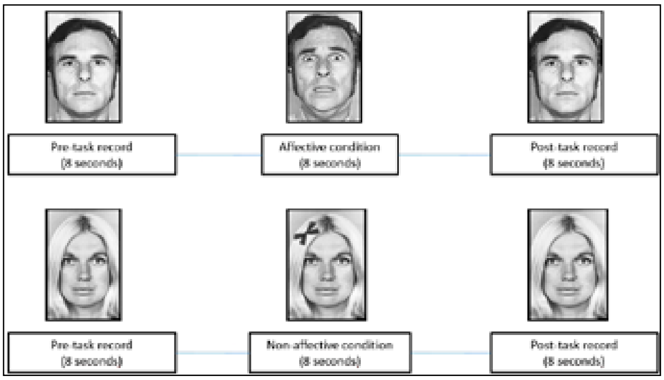

Figure 2. Task of Facial Affect Recognition (a: affective condition, b: non-affective condition)

and Freisen 1976). These photographs were transformed to a neuroimaging task by the E-Prime software. The FAIT consisted of 4 affective and a non-affective condition. In the affective conditions, the participants were required to identify expression of anger, happiness, sadness and surprise that appear on an affectively neutral face. Similarly in the non-affective condition, the participants were required to identify physical changes (i.e. eyeglasses/ribbons) that appear on an affectively neutral face. The sum of right answers was assigned as the FAIT-score and recorded as the behavioral output. The non-affective condition was employed to control effects of identifying non-affective changes on the face. The POFA set includes 110 face photographs and inter-rater reliability data is also available. The selection of the target stimuli among these 110 photographs were made by *(i)* sequencing the whole dataset from highest to lowest inter-rater reliability scores, *(ii)* choosing the photographs so as to ensure that the participants visualized equal number of photographs with female and male actors. Affectively neutral face photographs were already included in the dataset. The FAIT was built by juxtaposing affective faces with neutral ones by the E-Prime software. For the non-affective condition, eyeglasses and ribbons were positioned on neutral faces and those physically re-organized photographs were juxtaposed with neutral ones. Thus the activity changes during the fNIRS recordings were able to reflect identification of affective and physical changes on the faces during affective and non-affective test conditions, respectively (Figure 2).

Analyses

Neuroimaging data analyses

The analyses began by filtering and artefact rejection. The time resolution of fNIRS was set at 0.1 s. Fluctuations of fNIRS signals were known to be related to physiological activities such as the systemic arterial pulse oscillations (0.1 Hz) and respiration (0.2–0.3 Hz) (Hoshi, 2003). Thus, high-pass (0.5 Hz), low pass (0.001 Hz) and moving average methods were applied to remove short-term motion caused artefacts and to correct such fluctuations in the analyzed data (moving average window: 5 s). A sharp signal change over 0.4 mMmm in over twenty successive samples was labeled as a body movement artefact by the fNIRS device. A researcher blind to the study groups re-examined these artefacts in order to detect the individual channels responsible for body movement artefacts and these were removed from the data analyses and there after linear fitting was applied. Every measured value by the fNIRS device is relative to a baseline rather than being the absolute value of HBO2. The pre-task baseline was determined as the mean over an 8-s rest period just prior to the task period, and the post-task baseline was determined as the mean over the last 5s of the 8-s post-task rest period; and linear fitting was applied to the data between these two baselines. After this step, mean and grand average values were obtained by calculating the mean change in relative concentrations of HbO2 and Hb relative to the pre and post-task baselines during each task block for every channel and condition. Since oxy-Hb change is assumed to reflect cognitive activation more directly 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. Grand average values were obtained as the mean of each repeating condition. Grand average data were transferred to electronical environment. This was followed by outlier analysis. Any channel value that is smaller than X [X= 1^{st} quartile value – 1.5 x inter quartile range] and larger than Y [Y= 3^{rd} quartile value + 1.5 x interquartile range] was assigned as an outlier. Since outliers were regarded as valid measurements, they were winsorized. That is, outliers were replaced by the closest first and third quartile values. This was not applied to channels with body motion artefacts.

Statistical Analyses

Behavioral data analysis

Normality in the distribution of each variable was evaluated by the Kolmogorov-Smirnov test. Normally distributed continuous variables were compared between the study groups on the Independent Samples T-Test and variables that were non-normally distributed were compared using the Mann-Whitney U Test.

Neuroimaging data analyses

Neuroimaging data were analyzed by means of the multifactorial mixed variance analysis. Cortical activity evoked by the experimental paradigm in cortical regions of interests in both groups was analyzed with the 2 (Groups: Patients vs. Controls) × 5 (Conditions: angry, happy, sad, fearful, non-affective) × 24-Channel mixed ANOVA design.

In order to see the effect of affective and non-affective contrast, mixed ANOVA was repeated by grouping the four affective conditions together as the affective condition, compared with the non-affective condition. In this analysis, the 24-channel data were grouped to constitute 6 regions within the PFC (left and right dorsolateral PFC, left and right medial PFC and left and right ventral PFC). The relationship between neuroimaging data and behavioral outputs were examined with the Spearman Correlation Tests. To prevent Type-1 errors resulting from multiple testing we employed the False Discovery Rate (FDR) method (Benjaminive Hochberg 1995) (FDR alpha value=0.05).

RESULTS

Behavioral Results

CGI, SAPS, SANS and PSP scores of the IG are presented in Table 1. The IG consists of patients with mild severity of psychotic symptoms with slightly higher negative symptoms and with good functioning. The comparison of the results of the social cognitive battery test between the two groups revealed that the CG performed better than the IG in all tests except in the HT (Table 1). FAIT scores are presented in Table 2. Control subjects scored higher than the patients only in the FAIT-fearful condition, but the two groups displayed a comparable performance in other FAIT conditions.

Social cognitive test scores were not correlated with FAIT scores in both groups.

Table 1. Comparison of Index and Control Groups in Terms of Social Cognition with Severity and Functionality of Clinical Signs in the Index Group

	IG (N=24)	CG(N=24)	
ToM-1 Test Score (Median, range)	Median:3.5 Range: 4	Median: 4 Range: 0	Z=-3.91, p<0.0001*
ToM-2 Test Score (Median, range)	Median:2 Range:4	Median:3 Range: 4	Z=-3.16, p=0.002*
Faux-pas Test (Median, range)	Median: 4 Range: 11	Median: 10 Range: 7	Z=-4.33, p<0.0001*
Hinting Test (Median, range)	Median: 1.5 Range:2	Median:2 Range: 2	Z=-1.59, p=0.11
SAPS total score (mean±SD)	5.92±7.37	-	
SANS total score (mean±SD)	11.83±8.22	-	
PSP (mean ±SD)	75.8±8.59	-	
CGI (median, range)	2.29±0.81	-	

CG= Control Group CGI= Clinic Global Impressions Scale IG=Index Group PSP= Personal and Social Performance Scale SD=Standard Deviation ToM-1= Theory of Mind 1 ToM-2= Theory of Mind 2
*= Statistically Significant

Table 2. Comparison of two groups in terms of FAIT scores

	IG (N=24)	CG (N=24)	
FAIT-Anger	3 (3)	3 (1)	Z=-0.43, p=0.966
FAIT-Happiness	3 (0)	3 (0)	Z=0, p=1
FAIT-Sadness	3 (3)	3 (1)	Z=-0.918, p=0.359
FAIT-Fear	2 (3)	3 (2)	Z=-2.64, p= 0.008*
FAIT-Total	2.75 (2.25)	2.87 (0.5)	Z=-1.29, p=0.2

FAIT= Facial Affect Identification Task
The data in the table are given as median
*= Statistically significant

Neuroimaging Results

We first compared the two groups for activity difference in the 24 channels in 5 study conditions with 2 (Groups: Patients vs. Controls) × 5 (Conditions: angry, happy, sad, fearful, non-affective) × 24-Channels mixed ANOVA. The Group main effect was significant ($F=4.27$, $p<0.001$, partial eta square=0.21). Since the Condition main effect was insignificant, the 5 conditions were reduced to affective and non-affective conditions. In addition to this, the 24 channels were re-grouped to constitute 6 PFC areas (Figure 4). The 2 (Group: Patients vs. Controls) x 2 (Condition: affective vs. non-affective) x 6 (Area: right and left: DLPFC, MPFC, VPFC) ANOVA revealed that group main effect was significant ($F = 5.14$, $p = 0.028$, partial eta square = 0.10). Hence, patients with schizophrenia (0.013±0.006 mMmm) showed higher activity than healthy controls (-0.005±0.006 mMmm) in both conditions and six prefrontal areas. The Condition main effect was insignificant. However, the Area main effect was significant ($F = 11.1$, $p < 0.0001$, partial eta square= 0.57), meaning that in both groups and under the two conditions, the activity increases from back to front and left to right within the PFC. Condition x Area interaction was also significant ($F = 4.0$, $p = 0.005$, partial eta square= 0.32), indicating that in 5 out of the six areas the activity was higher during the affective condition than during the non-affective condition. The triple Group x Condition x Area interaction was not significant. The PFC activity in the two groups during different FAIT conditions is visualized in Figure 3. The prefrontal activity in the two groups during affective and non-affective conditions is presented in Figure 4.

Age and education levels were not correlated with the measured PFC activity. When we examined relationship between ToM abilities, clinical test scores and PFC activity in the IG, we found that SAPS-hallucinations items total score was positively correlated with right MPFC ($r = 0.45$, $p = 0.027$) and right VPFC ($r = 0.51$, $p = 0.01$) activity during the FAIT-Sad condition. This was preserved after the FDR correction. Social cognitive test scores were not correlated with PFC activity.

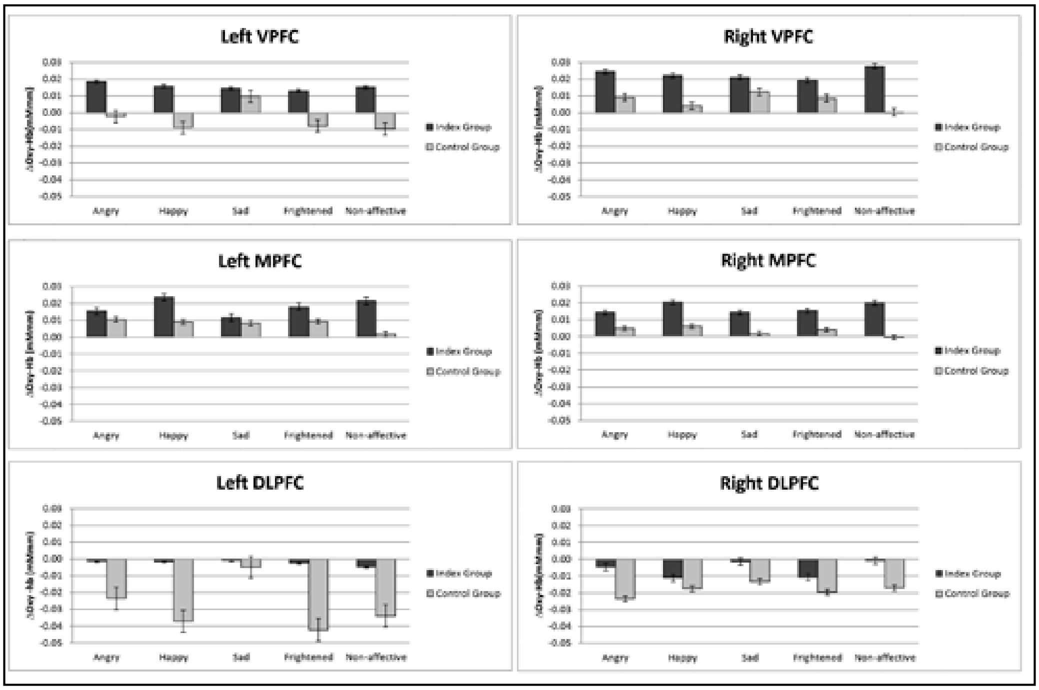

Figure 3. Comparison of activity occurring in prefrontal areas between two groups in all conditions of the experimental paradigm.

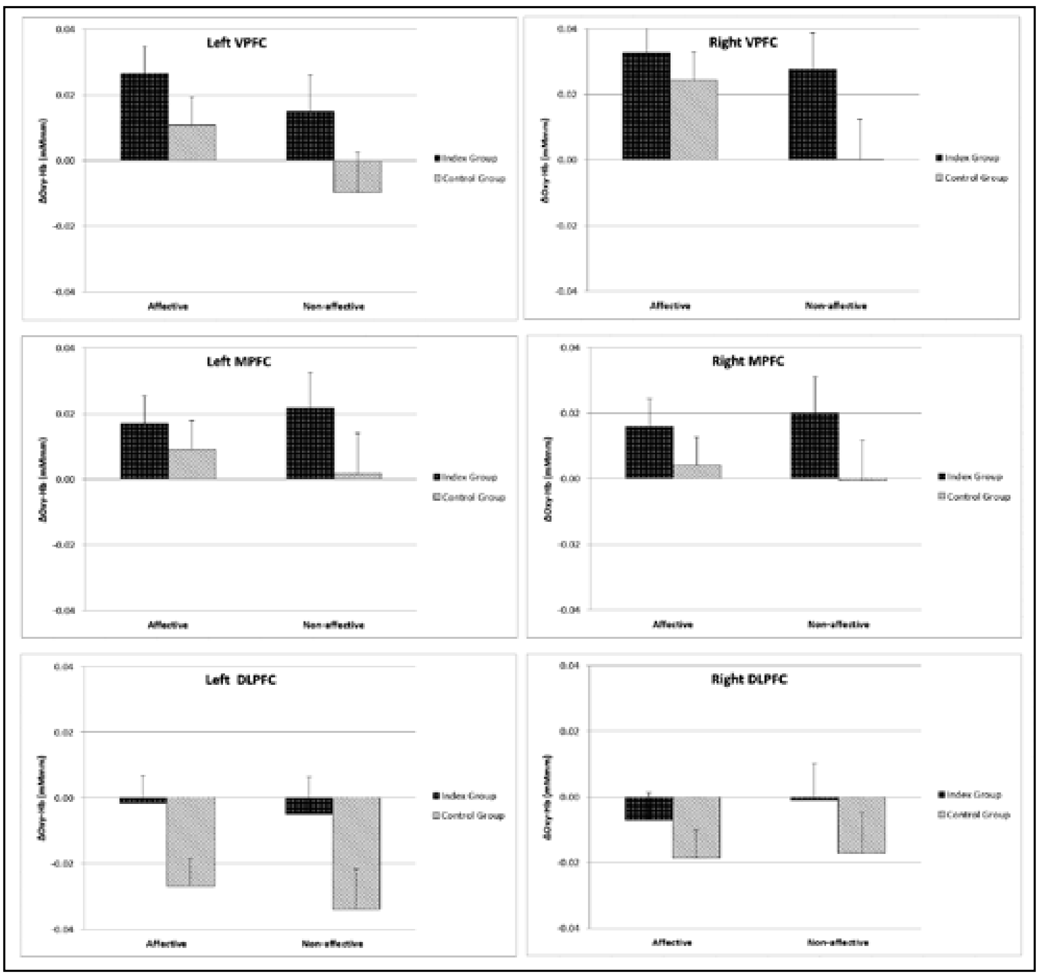

Figure 4. Comparison of the activity of the experimental paradigm in the affective and non-affective conditions of prefrontal areas between the two groups

DISCUSSION

When the results of neuroimaging were examined, activity was found to increase from back to forth and left to right within the PFC in both groups. Right VPFC was the most active area, the activity being higher during the affective condition as compared to the control condition. The highest activity during the affective condition was in the right ventral PFC, which was an expected finding since the right hemisphere is more involved in affect recognition than the left hemisphere (Adolps et al. 2000, Nakamura et al. 1999). We also observed that the affective conditions activate the ventral areas as compared to the dorsal areas. This was an expected finding. It has been shown that dorsal parts of the PFC are more sensitive to verbal memory tests (Dolcos and McCarthy 2006, Levy and Goldman-Rakic 2000), while ventral PFC is more sensitive to emotional stimuli (Phan et al. 2002). The discussed results and observations support the validity of the experimental paradigm on evoking cortical activity.

The Group x Condition interaction was found insignificant in the two ANOVAs. This implies that the two groups do not show different cortical activity in the affective vs. non affective conditions, thus rejecting the main hypothesis of this study. On the other hand, the Group main effect was significant in the two ANOVAs. This means that the IG displayed higher activity than healthy controls in all prefrontal regions during recognition of any change in the face whether it is affective or non-affective. Previous neuroimaging studies in schizophrenia consistently found hypofrontality, or lower activity in the PFC particularly in tasks requiring neurocognitive performance (Kühn and Gallinat 2013, Hazlett et al. 2000, Andreasen et al. 1992). The results of the present study contradict those findings. The discrepancy between the results may be associated with different task qualities. While hypofrontality is predominantly found in executive functioning tasks, FAIT is a social cognitive task.

When we compared social cognitive performance between the two groups, we found that the CG performed better than the IG in all domains except the Hinting Test. Lower social cognitive performance in schizophrenia is a well replicated finding (Brune 2005). However contrary to previous research (Schmidt et al. 2011) we did not find an association between social functioning and social cognitive performance in the IG. This may be associated with relatively high functioning level in the IG.

When the FAIT scores were compared between the two groups, we found that the IG displayed lower performance than the control group during recognition of fear. This is also in line with previous studies indicating that emotion recognition deficits in schizophrenia generally involve negative emotions (Caldiroli et al. 2016, Romero-Ferreiro et al. 2016). However, we did not find a difference in recognition of anger and sadness. This may be due to employing the FAIT was as a cortical activation paradigm rather than a performance measure which may have ended up with a type-2 error related to an observational bias. The same bias may also account for the lack of association between social cognitive task scores and the FAIT scores. However, FAIT scores were found to be associated with clinical symptoms which at least supports the validity in the IG.

When we examined the relationship between neuroimaging and behavioral findings, we found that right VPFC and MPFC activity were positively correlated with SAPS-hallucinations total item score. We also found that FAIT-total score was negatively correlated with SAPS–hallucinations item total score. Previous researchers suggested that social cognitive disorder may lie behind positive symptoms in schizophrenia (Kohler et al. 2003). Therefore our results support the view (Coy and Hutton 2012) that positive symptoms particularly hallucinations may be associated with emotion recognition deficits in schizophrenia.

Our conclusions must be evaluated in view of the limitations of this study. The most prominent limitation of this study involve the validity of the FAIT which was particularly developed as a cortical activation paradigm and this may have prevented valid measurement of facial affect recognition ability. Future studies that compare schizophrenia hsubjects with facial affect recognition deficits to those without these deficits in terms of other social cognitive domains may give valuable information. Another limitation is about the validity of the ToM tasks in the Turkish population. However, these tests were previously shown to distinguish psychotic subjects from healthy controls (Yucel et al. 2016, Ozguven et al. 2010). In addition to that, affect recognition involves a broader network including structures such as the amygdala and the precuneus. However, fNIRS does not allow us to examine deep brain structures and the difference between the groups may indeed be higher in those areas. Finally, the sample consists of remitted schizophrenia subjects followed at a university hospital and therefore the results may not be generalized to all subjects with schizophrenia.

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