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The face and its emotion: Right N170 deficits in structural processing and early emotional discrimination in schizophrenic patients and relatives

Agustín Ibáñez [a,b,c,d,*], Rodrigo Riveros [d], Esteban Hurtado [f], Ezequiel Gleichgerrcht [a,b], Hugo Urquina [a,b], Eduar Herrera [g], Lucía Amoruso [a,b,c,h], Migdyrai Martin Reyes [e], Facundo Manes [a,b]

[a] Institute of Cognitive Neurology (INECO), Favaloro University, Buenos Aires, Argentina
[b] Institute of Neuroscience, Favaloro University, Buenos Aires, Argentina
[c] National Scientific and Technical Research Council (CONICET), Buenos Aires, Argentina
[d] Laboratory of Cognitive Neuroscience, Universidad Diego Portales, Santiago, Chile
[e] Unidad de Hospitalización Psiquiátrica, Hosp. Virgen del Camino, Pamplona, Spain
[f] Pontificia Universidad Católica de Chile, Chile
[g] Universidad Autónoma del Caribe, Barranquilla, Colombia
[h] IRICE — National Scientific and Technical Research Council (CONICET), Argentina

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ABSTRACT

Previous studies have reported facial emotion recognition impairments in schizophrenic patients, as well as abnormalities in the N170 component of the event-related potential. Current research on schizophrenia highlights the importance of complexly-inherited brain-based deficits. In order to examine the N170 markers of face structural and emotional processing, DSM-IV diagnosed schizophrenia probands ($n=13$), unaffected first-degree relatives from multiplex families ($n=13$), and control subjects ($n=13$) matched by age, gender and educational level, performed a categorization task which involved words and faces with positive and negative valence. The N170 component, while present in relatives and control subjects, was reduced in patients, not only for faces, but also for face–word differences, suggesting a deficit in structural processing of stimuli. Control subjects showed N170 modulation according to the valence of facial stimuli. However, this discrimination effect was found to be reduced both in patients and relatives. This is the first report showing N170 valence deficits in relatives. Our results suggest a generalized deficit affecting the structural encoding of faces in patients, as well as the emotion discrimination both in patients and relatives. Finally, these findings lend support to the notion that cortical markers of facial discrimination can be validly considered as vulnerability markers.

1. Introduction

The symptomatic description of schizophrenia has been well established ever since classic early research. Scientific literature on schizophrenia has been largely devoted to understanding the underlying neurobiological mechanisms that account for both positive and negative symptoms of this disorder (Andreasen et al., 1995). Research scientists have only recently begun to look at these symptoms in more detail (e.g. Tamminga, 2006), trying to draw more profound relationships between clinical features and their potential neural substrates. Hence, there is considerable interest in a possible neurodevelopmental hypothesis of schizophrenia, which has specifically led to the hypothesis that cognitive and social cognition impairments, typical of the disorder, are actually pre-morbid traits rather than state-dependent deficits (Rapoport et al., 2005). Accordingly, such impairments are clinically identifiable upon 'disease onset' and tend to remain stable once acute episodes have remitted (Heydebrand, 2006). Moreover, genetic research on schizophrenia has offered consistent evidence regarding the hereditary factors which contribute to this disorder. All of the aforementioned findings have revealed that patients with schizophrenia — *and* unaffected relatives — exhibit cognitive and social cognition impairments. Findings of this caliber have led to a growing interest in studying multiplex families, that is, families in which there are two or more schizophrenic patients. Naturally, studying these families in detail can help identify cognitive and behavioral impairments associated with genetic vulnerability in schizophrenia (Holden, 2003).

1.1. Emotional impairments in schizophrenia families and the role of N170

Emotional disturbances in schizophrenia, including flattened affect, inappropriate affect, and depression, have become the focus of much research effort. Indeed, one of the most consistent findings is that patients with schizophrenia have deficits in recognizing and

* Corresponding author at: Laboratory of Experimental Psychology and Neuroscience (LPEN), Institute of Cognitive Neurology (INECO) and CONICET, Pacheco de Melo 1860 (CP 1126) Buenos Aires, Argentina. Tel./fax: +54 11 4812 0010.
E-mail address: aibanez@ineco.org.ar (A. Ibáñez).
URL: http://www.ineco.org.ar/en/ (A. Ibáñez).

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discriminating facial emotions (Kohler et al., 2003). Recognizing the expression of facial emotion is a complex social cognition ability, which involves several stages for successful processing, including initial visual processing, structural encoding of a face and later association of the representation with cognitive, semantic, and affective information for distinguishing between the emotions (Balconi and Lucchiari, 2005; Jacques and Rossion, 2009). Despite extensive research in schizophrenia, there is an ongoing and yet unresolved debate regarding whether emotion identification deficits reflect a specific or generalized form of cognitive impairment in this disorder (Kerr and Neale, 1993; Whittaker et al., 2001); nonetheless, studies have shown that emotion processing deficits are uniquely related to clinical symptoms (Sachs et al., 2004).

The N170 is an event-related potential (ERP) with a negative waveform, achieving a peak amplitude approximately 150–180 ms post-stimulus (commonly detected at the occipito-temporal sites). It is commonly thought to reflect early perceptual processes involving the structural encoding of faces (Eimer, 2000). The N170 component is hypothesized to arise primarily from the fusiform gyrus and superior temporal sulcus (STS); it can be readily distinguished from the ERP response to other classes of stimuli (Herrmann et al., 2005). In addition, the N170 component has been reported to be lateralized, suggesting right-lateralized topography for face stimuli, whereas N170 for words tends to be more left-lateralized or bilateral (Rossion et al., 2003). Larger N170 waves have been shown for faces compared to words in the right scalp (Rossion et al., 2000, 2003), especially when faces and words are presented in the same block in an alternating fashion (Maurer et al., 2008).

N170 has also been described as a component modulated by emotional faces and emotions (Pizzagalli et al., 2002; Batty and Taylor, 2003; Ashley et al., 2004; Blau et al., 2007; but see Eimer and Holmes, 2002 and Eimer et al., 2003 for an absent emotional modulation). Specifically, when face and word categorization tasks are used, the N170 component has been reported to present increased amplitude for positive stimuli relative to negative stimuli (Schacht and Sommer, 2009). Overall, N170 is thought to be a neural marker of early face-selective processing modulated by emotional clues, but not influenced by processing of other objects.

In schizophrenia, despite limited ERP data, recent studies have documented an N170 deficit for visual encoding of faces. The N170 Amplitude difference of stimulus type discrimination (e.g., faces vs. objects) is reduced in schizophrenic patients (Herrmann et al., 2004). Abnormalities in N170 of emotional faces in patients have been reported, with larger responses to faces expressing emotions relative to neutral faces (Caharel et al., 2007). Moreover, an enhanced N170 amplitude in response to fearful faces has been reported (Ramos-Loyo et al., 2009). Probably, these effects suggest difficulties in encoding the structure of a face and subsequent familiarity and emotion evaluation. As well, the amplitude of the N170 responses to sad faces has been associated with the severity of positive symptoms in schizophrenic patients (Johnston et al., 2005; Turetsky et al., 2007). N170 deficits have been found more pronounced over the right scalp (Herrmann et al., 2004). In order to explore other ways in which ERPs of emotional processing could also be altered or affected, DSM-IV diagnosed schizophrenia probands, their unaffected first-degree relatives, and control subjects matched by age, gender, and educational level performed a classification task that involved the categorization of pleasant and unpleasant words, along with faces of anger and happiness.

1.2. The goal of this study

In the present study we propose that the N170 component (modulated by valence and stimulus type) has the potential to be a marker of vulnerability both in patients and relatives. This vulnerability should be more accentuated in multiplex families (families in which there are two or more schizophrenic patients). A subclinical impairment of emotional inference and stimulus type discrimination may be the basis for further studies of underlying risk and stable trait markers, or endophenotypes (Gottesman and Gould, 2003; Braff et al., 2007). Several reasons support such speculations. First, social cognition performance has been extensively studied in schizophrenic patients and their relatives (Brüne, 2005; Harrington et al., 2005; Beer and Ochsner, 2006; Irani et al., 2006; Green and Leitman, 2008; Bora et al., 2009). Second, recent reports suggest that complex social skills depend on basic emotional facial processing and emotional inference (Grossmann, 2010). Faces (especially eyes and gaze; Itier and Batty, 2009) constitute multi-dimensional stimuli that are directly related to important social incentives (Ohman and Mineka, 2001). Facial emotional expression can provide an automatic and rapid shortcut to alarm signals, mentalizing, and inter-subjective communication. Third, recent experimental data suggest that the key elements that evoke the N170 effect are the eyes of a face stimulus (Itier et al., 2007), thus constituting the most important area of the face as regards the inference of affective social cognition. Finally, as briefly reviewed above, in schizophrenia research, impairments in both stimulus type and emotional valence as captured by the N170 component have already been reported. Nevertheless, no previous report assessing such N170 modulations in first-degree relatives had been assessed until now.

In sum, cortical markers of facial-semantic valance (N170) could be a shortcut to basic subclinical impairments in schizophrenia families. One theoretical implication of this would be that emotional, as well as social cognition impairments in schizophrenia families may be connected to the early brain process involved in basic cognitive discrimination of stimulus type (face and words) and valence. In order to test this hypothesis, we chose an N170 paradigm that has been previously found to be affected by stimulus type and emotional valence.

2. Methods

2.1. Subjects

Thirteen schizophrenic patients, thirteen first-degree relatives, and thirteen controls were enrolled in this study. The three groups had the same distribution for age, level of education, and proportion of males to female. In the Supplementary data section, specific age comparisons between controls vs. patients, as well as controls vs. relatives can be found. In addition, our behavioral as well as ERP results were reanalyzed considering age as a covariate. All reported significant differences remained after introduce age as covariate (see Supplementary data). No difference between groups was observed with regards to either intellectual capabilities or speed processing, as assessed by the Raven Test (Raven et al., 2003) and Trail Making Test — Part A, respectively. No significant difference was observed in executive function performance, either, as assessed by the Trail Making Test — Part B (Bowie and Harvey, 2006). The Positive and Negative Symptoms Scale (PANNS; Kay et al., 1987) was evaluated in the patient group. A summary of demographic and clinical characteristics of the groups is presented in Table 1. Inclusion criteria for patients were: (1) the diagnosis of paranoid schizophrenia according to DSM-IV-TR criteria (First et al., 1996) and confirmed with the Schedules of Clinical Assessment in Neuropsychiatry (SCAN) (World Health Organization, 1992) applied by a trained physician; and (2) the presence of one or more relatives with the diagnosis of schizophrenia (no greater than a third-degree relative), evidenced by the Family Interview for Genetic Studies (FIGS) applied to the relative (NIMH, 1992). All patients were under antipsychotic medication (all except one, atypical). Healthy relatives had to be first-degree relatives and to have never been diagnosed with schizotypical disorder or any psychiatric disease. All relatives were family members of the patients. Participants recruited were aged 20–55 years. Written informed consent was obtained from all subjects, and they were paid for their participation.

2.2. Procedure

The task involved a valence categorization of stimuli with a positive or negative dimension valence: happy ($n=20$) and angry ($n=20$) faces along with pleasant words ($n=71$) and unpleasant words ($n=72$). Stimuli were controlled for frequency, content, valence, type of word, moderate levels arousal (for words), as well as physical features, valence, gender, moderate levels of and arousal (for faces). All stimuli were selected from a previously reported dataset (e.g., Hurtado et al., 2009; Ibáñez et al., 2010a,b, 2011a; Guex et al., 2011). A greater number of word stimuli relative to faces were selected in order to reduce repetition effect of words (see discussion, Section 4.5, for more details). Each block started with a brief explanation of which keys were assigned to each word/face category. Subsequently, the trials were presented one by one with strict alternation between words and faces (in order to enhance the stimulus type differences between faces and words in the right scalp previously reported by Maurer et al. (2008). Previous reports using stimuli strict alternation have been proved useful for the expected behavioral and N170 modulation specific to the task and independent of the alternation (e.g., Krombholz et al., 2007; Maurer et al., 2008; Hurtado et al., 2009; Ibáñez et al., 2010a, 2011c). The practice blocks involved

Table 1
Sample characteristics and mean performance for groups on cognitive tests.

	Schizophrenia probands	Relatives	Controls	Fisher Exact test, *F* Anova value or Chi-square value (d.f.)	*P* value
Gender (male/female)	13 (9/4)	13 (6/7)	13 (9/4)	4.18	0.144
Age (Mean ± S.D.)	38.62 (11.99)	47.31 (11.54)	39.46 (14.62)	$F_{(2,36)} = 1.82$	0.175
Level of education				$X^2_{(4)} = 7.5$	0.112
Secondary education	8	4	2		
Tertiary education uncompleted	2	6	5		
Tertiary education completed	3	3	6		
Age of onset (Mean ± S.D.)	26.15 (9.15)				
Illness duration (Mean ± S.D.)	12.46 (9.67)				
Antipsychotic medication (*N*)					
Typical	1				
Atypical	11				
Both	1				
PANSS Scores (Mean ± S.D.)					
Positive	16.92 (5.19)				
Negative	19.08 (6.3)				
General	28.62 (11.21)				
Raven's Coloured Progressive Matrices	30 (4.04)	28.85 (7.08)	32.92 (3.15)	$F_{(2,36)} = 2.25$	0.119
Trail Making Test — A	53.46 (26.39)	41.23 (20.86)	33.92 (10.52)	$F_{(2,36)} = 3.05$	0.059
Trail Making Test — B	129.1 (78.45)	97.23 (56.6)	79.69 (27.01)	$F_{(2,36)} = 2.42$	0.103

approximately 28 stimuli, consisting of 14 face and 14 word stimuli, while test blocks comprised 100 stimuli, that is, 50 face stimuli and 50 word stimuli. Practice block stimuli were not used in the actual experiment. In order to counterbalance the responses (positive vs. negative valence categorization), four blocks were included (400 stimuli). Based on previous reports (Hurtado et al., 2009; Ibáñez et al., 2010a, 2011c, stimulus duration was set to 100 ms and 300 ms in order to assure conscious perception of faces and words, respectively (see Section 4 for more details about this issue). Each test block lasted for approximately 4.6 min and the total time of the paradigm totaled to approximately 23 min.

In this forced-choice task, participants were instructed to categorize words or faces displayed on the computer screen into one of two response categories (positive or negative faces and words). Each trial began with a fixation point in the center of the screen ("+") during 200 ms, followed by a blank (200 ms), and a target (a face or a word for 100 ms and 300 ms respectively), which were in turn followed by another blank until the response was received (see Supplementary data for stimuli examples). Subsequent to the response, an intertrial interval was set at 400 ms. Incorrect responses were indicated with an 'X' in the centre of the screen immediately after the response. Following classical behavioral and ERPs assessment of the two-choice task (Greenwald et al., 1998; Brendan and Aidman, 2004; De Houwer et al., 2009; Hurtado et al., 2009; Ibáñez et al., 2010a, 2011c; Petroni et al., accepted for publication), the negative feedback was given immediately after incorrect categorization of a stimulus. Negative feedback increases the attention of the participants during two-choice tasks.

2.3. EEG recordings

EEG signals were sampled at 500 Hz from 129-channels system with HydroCel Sensors from an Electrical Geodesic amplifier. Data outside the frequency band that ranged from 0.1 Hz to 100 Hz were filtered out during the recording. Later, a band pass digital filter between 0.5 and 30 Hz was applied to remove unwanted frequency components. During recording, the reference was set by default to vertex but then was re-referenced off-line to average electrodes. Two bipolar derivations were designed to monitor vertical and horizontal ocular movements (EOG). Continuous EEG data were segmented from 200 ms prior to the stimulus to 800 ms after the stimulus. All segments with eye movement contamination and other artifacts were removed from further analysis using an automatic (Gratton, Coles, and Donchin method) and visual procedure. Artifact-free segments were averaged to obtain ERPs. All conditions yielded a percentage of trials without artifacts of 84% or more. No differences between groups regarding number of trials were observed ($F(1,36) = 1.42$, $p = 0.83$)

2.4. Data analysis

For behavioral (accuracy and RTs) and ERP data, Analysis of Variance (ANOVA) was performed. One between-subject factor with 3 levels was considered (GROUP: Controls, Relatives, and Probands). Two within-subject factors with two levels each one was considered too in the analysis (STIMULUS TYPE: Face vs. Word; and VALENCE: Positive vs. Negative). Univariate comparisons were performed whenever necessary. Results were corrected with the Tukey test to adjust the univariate output of repeated measure ANOVA for violations of the compound symmetry assumption. For ERP analysis, partial eta-squared (partial η^2) was analyzed in order to provide effects sizes (Cohen, 1992). T-BESP, Matlab software and EEGLab toolbox were used for off-line processing and analysis of EEG data.

Regions of interest (ROIs) were used to analyze the scalp topography of the ERP components, which is recommended for dense arrays since it improves statistical power. As stated in the introduction, the right N170 elicits the maximum amplitude for faces. When alternating faces and words are presented in the same block, larger N170 components for faces compared to words are found in the right scalp (Maurer et al., 2008). Moreover, compared to controls, N170 from schizophrenic patients are more reduced in the right scalp (Herrmann et al., 2004). Consequently, a region of interest (ROI) was chosen by visual inspection of the right N170 component comprising three electrodes around T6 (Herrmann et al., 2004; Rossion and Jacques, 2008): 83, 89, and 90 (see Supplementary data for a schematic location of the 129 electrodes). Hemisphere analysis (including individual electrode comparison) confirming the right dominance of the N170 effects and the absent group differences on left hemisphere is also available in the Supplementary data (refer to sections under *Electrode selection*, *N170 lateralization*, and *Separate electrode analysis of N170 left and right hemisphere*). For N170 analysis, a fixed time window (140–190 ms) was visually selected using difference waveforms from stimulus type conditions, and then means amplitude was obtained for the mean average of each category and each subject. Although signal plots showed the ERPs from T6, statistical tests were performed over the ROI average (three selected electrodes) using Matlab software.

3. Results

3.1. Behavioral results

In order to examine whether there were different performance scores in the discrimination of happy and angry faces, as well as pleasant and unpleasant words across the groups, both accuracy and reaction times were examined in detail. Table 2 shows these results.

Although non-significant, accuracy and RTs showed a poorer performance in relatives and patients compared to controls. Accuracy rates of discrimination of faces and words of positive and negative emotional valence were entered into a mixed ANOVA with stimulus type (that is, faces and words) and valence of stimuli (that is, positive and negative emotional valence) as within-subject factors, and group (proband, relative and control) as the between-subject factor. No main effect of stimulus type, valence or group was found (all $p > 0.05$). Only a stimulus type × valence interaction effect was observed ($F(2, 36) = 6.25$; $p < 0.05$). Post hoc comparison performed over this interaction (Honestly Significant Difference, HSD test, MS = 0.78, d.f. = 70.21) indicated better recognition rates benefiting word stimuli compared to face stimuli ($p < 0.05$) and words with negative emotional valence compared to positive ones ($p = 0.05$). No other interaction effects were observed (all $p > 0.05$).

The same effects were tested for reaction times. Only a main effect of stimulus type was found ($F(1, 36) = 7.28$; $p < 0.05$) benefiting the recognition of faces. Neither main effects of valence, group nor other interaction effects were observed (all $p > 0.05$).

3.2. ERP results

Fig. 1A (Top) shows the ERPs effects from the Right occipital ROI. First, we analyzed the N170 component related to faces and words. An ANOVA yielded an effect of stimulus type ($F(1,36) = 64.11$, $p < 0.001$, partial $\eta^2 = 0.64$) and an interaction of Stimulus type × Group ($F(2,36) = 5.35$, $p < 0.01$, partial $\eta^2 = 0.22$). Within the Control

group, as well as in the Relatives group, face category presented the most pronounced negativity, compared to control stimuli (words). Although not statistically significant, the N170 from Relatives presented smaller mean amplitude and a reduced difference between faces and words compared to controls. No other effects were significant. Table 3 summarizes the means and standard deviations (S.D. hereafter) of those effects and Figs. 1B and 2A shows the Stimulus type × Group interaction.

Post hoc comparisons following the Group × Stimulus type interaction ($F(2,36) = 5.35$, $p<0.01$) confirmed those effects (HSD test, MS = 0.37, d.f. = 71.94). Among controls, facial stimuli presented significant differences compared to word stimuli ($p<0.001$). Among relatives, the same comparison also yielded significant differences ($p<0.001$). Probands exhibited no differences between stimulus type ($p = 0.35$)

Face valence. In order to assess the emotional discrimination task, a 2 × 3 ANOVA design was performed: Valence (Positive or Negative Faces) × Group (Controls, Relatives and Probands). An effect of Group ($F(2,36) = 11.3$, $p<0.001$, partial $\eta^2 = 0.38$) and a Valence × Group interaction was observed ($F(2, 36) = 4.83$, $p<0.05$, partial $\eta^2 = 0.21$). As suggested by Fig. 1C, the positive category presented a more negative waveform in the control group than in relatives and probands (see also Fig. 2B). The ERPs of relatives and probands presented no differences between waveforms elicited by positive and negative valence faces. Post hoc comparisons confirmed said effects (Valence × Group; HSD test, MS = 0.49, d.f. = 69.21): only positive vs. negative differences yielded statistical significance in the Control groups ($p<0.01$). The same comparison in Relatives ($p = 0.98$) as well as in Probands ($p = 0.99$) showed no valence effects. Table 3 presents the mean and S.D. from each category and group.

Word valence. No main effects of Valence or Valence × Group interaction were observed.

4. Discussion

In the present study, an emotional word/face discrimination task was conducted in a sample comprising patients with schizophrenia, healthy first-degree relatives and controls. Subjects were asked to categorize happy and angry faces, as well as pleasant and unpleasant words presented on a screen. Behaviorally, better recognition of faces compared to words, and negative valence relative to positive emotional valence was observed. However, no difference in the intergroup evaluation was found, indicating similar performance across the types of stimuli used as well as across the groups. Participants from the three groups performed very accurately regarding emotional categorization both for faces and words. Even though subjects could have learned the face identity, they were paying attention to emotional clues, and the task was performed correctly.

N170 modulation of stimulus type discrimination was reduced in patients compared to controls (replicating the results by Herrmann et al., 2004). In addition, the N170 of structural and emotional processing was also reduced in patients compared to controls. The N170 elicited by facial valence discrimination, both for patients and relatives, showed no significant effects. For controls, the N170 was largest during the positive emotion identification task and smallest for the negative emotion identification task. However, the patients and relatives did not show N170 discrimination of emotional valence.

Our results therefore suggest that patients with schizophrenia as well as their relatives are less efficient at decoding facial affect features. Our results are also clearly relevant from a clinical point of view; as such abnormalities in the early stages of feature decoding could potentially underlie aspects of emotion identification deficits in schizophrenia (and hence, related vulnerability markers in first-degree relatives). An alternative hypothesis would be that our N170 results reflect only structural processing, and that the valence effects could be explained by automatic stimulus-driven attention. Whether N170 reflects exclusively a structural stage encoding or whether it also processes valence discrimination is certainly not out of controversy (but see Blau et al., 2007). Following this alternative hypothesis, patients and relatives would have an impaired stimulus-driven attention which should lead to non-significant differences in N170 amplitude valence modulation. Although we did not find any executive function differences between the groups, and our valence stimuli did not present different arousal levels between positive and negative categories (which would explain the valence differences in terms of early stimulus-driven attention), this alternative hypothesis calls for further research. It is possible that early N170 processing reflects stimulus-driven attention, so that the ERPs that follow (such as the N250 component) would be responsible for emotional discrimination (see Turetsky et al., 2007). Experiments combining early/automatic tasks (like the present paradigm) and late/controlled attention paradigms of facial stimuli in schizophrenic patients and their relatives would probably shed light on this alternative hypothesis.

4.1. N170 abnormalities in schizophrenia families

Our main finding is that cortical face processing is preserved in relatives but emotional face processing seems to be impaired within this group. Patients presented deficits both in face processing and emotional valence. This is relevant both for research on the N170 component per se, but also in term of vulnerability markers of schizophrenia domains. Theoretical models of emotion face perception (Vuilleumier and Pourtois, 2007) propose a parallel and interactive system indexing object recognition (e.g., triggered by the fusiform gyrus) and emotional discrimination (e.g., triggered by the amygdala, see too Busse et al., 2009). Our data suggest that patients have a deeper impairment, affecting both specific face recognition and emotional processing. In relatives, the more basic and structural face integration process seems to be preserved, yet more subtle processes, such as the emotional discrimination of the face, seem to be affected at early stages of processing. This is consistent with the model of vulnerability markers and the endophenotype agenda, as the possible endophenotype should exhibit family association and segregation: the impairments must be present both in patients and relatives, but more accentuated in the first group (Gottesman and Gould, 2003). Further research should determine whether structural and emotional pathways present in emotional face processing are affected differentially in patients and relatives in different contexts.

Table 2
Behavioral measures. Percentage of correct responses and Reaction times for each category and Group.

	Accuracy: % (S.D.)			Reaction times: ms (S.D.)		
	Controls	Relatives	Probands	Controls	Relatives	Probands
Positive face	83 (6.5)	78 (6.4)	74 (7.4)	852 (157)	990 (550)	1143 (794)
Negative face	80 (6.1)	74 (7.1)	70 (10.5)	948 (251)	1102 (260)	1085 (450)
Positive word	86 (4.1)	78 (3.8)	75 (4.5)	957 (222)	1157 (378)	1289 (842)
Negative word	87 (4.0)	79 (6.1)	79 (6.4)	975 (288)	1142 (415)	1437 (642)

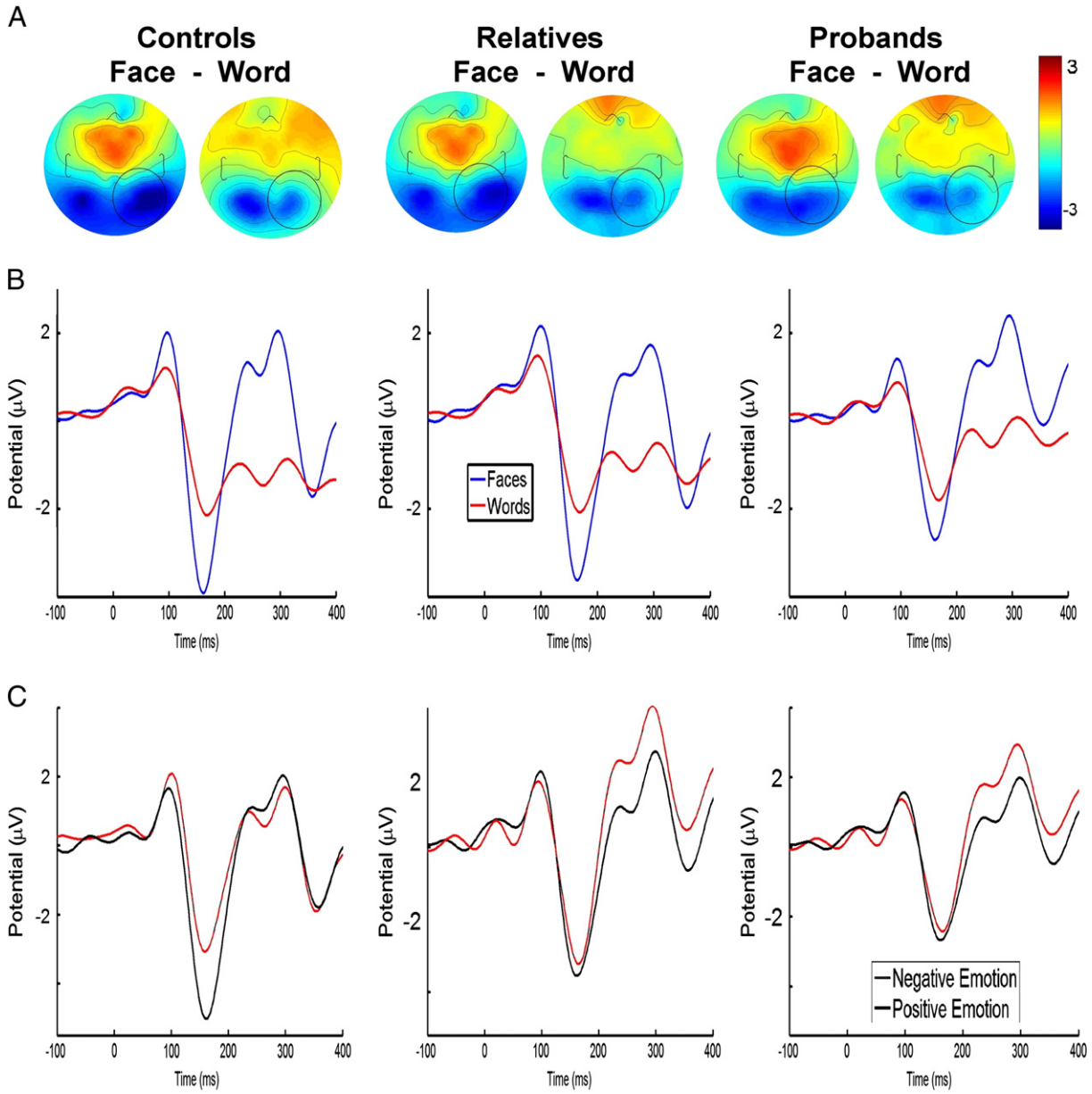

Fig. 1. ERPs results. A) Voltage maps for faces and word stimuli. Circles in the Topomaps highlight the right scalp where N170 effects were analyzed. B) Right N170 component from faces vs. words stimuli in the three groups at the T6 electrode. C) Emotional modulation of N170 component elicited by Faces in controls, relatives and probands at the T6 electrode.

A critical analysis of the literature in fact reveals that the electrophysiology of deficits in schizophrenia has been linked to altered N170 components (Herrmann et al., 2004). Specifically, patients with schizophrenia exhibit significantly lower differences in the face-specific N170 component between face vs. non-face (e.g. buildings) pictures, relative to healthy controls. Hall et al. (2004) further suggested that impaired frontotemporal activity in schizophrenic patients may account for their inability to process facial expressions properly, which, in turn, translates into marked impairments on social cognition. Interestingly, Gur et al. (2007) recently demonstrated that relatives of patients with schizophrenia also had a poorer performance on facial emotion processing relative to controls. The authors suggested that such impairment may be associated with decreased social adaptation. Moreover, facial emotion recognition was found to be significantly heritable in schizophrenia multiplex families (Greenwood et al., 2007; Gur et al., 2007); yet, there are no previous reports of N170 deficits in relatives. Our data seem to support an extended research background of face emotional processing in schizophrenia families.

In the current study, we focused on N170 (rather than on subsequent components such as P2, and N250), because we aimed at assessing the *early* stage of facial processing. N170 is a well characterized component of early face processing with neural sources related to face-specific areas (e.g., fusiform gyrus and, secondarily, superior temporal sulcus). The same cannot be said for P2 and N250. Both components seem to have different functional properties than N170 and their relation with N170 is yet to be established. In addition, all previous studies reporting N170 from paradigms including faces and words (e.g., Rossion et al., 2003; Krombholz et al., 2007; Maurer et al., 2008; Hurtado et al., 2009; Aranda et al., 2010; Ibáñez et al., 2010a, 2011a, 2011c; Zhu et al., 2010) had not reported P2. Moreover, just a few schizophrenia studies have reported the P2 component together with N170 (e.g., Ramos-Loyo et al., 2009). To our knowledge, the N170 is the best marker of early face processing. Nevertheless,

Table 3
a) Mean and S.D. for face and word mean amplitude in each group. b) Mean and S.D. for Positive and Negative Valence mean amplitude in each Group.

a)

Group	Effects	Mean	S.D.
Controls	Face	−2.62	0.18
Controls	Word	−1.06	0.35
Relatives	Face	−2.51	0.21
Relatives	Word	−1.18	0.27
Probands	Face	−1.44	0.23
Probands	Word	−0.95	0.36

b)

Group	Valence	Mean	S.D.
Controls	Positive	−2.88	0.43
Controls	Negative	−1.79	0.37
Relatives	Positive	−2.68	0.42
Relatives	Negative	−2.53	0.24
Probands	Positive	−1.69	0.34
Probands	Negative	−1.55	0.59

once the relation between N170 and subsequent components is better established, exploratory ERP analyses should include such later stages of face processing in schizophrenia families research studies.

Despite recent evidence of N170 deficits in relatives of other psychiatric populations and even with genetic associations (Dawson et al., 2005; Battaglia et al., 2007), the present work constitutes the first description of early electrophysiological impairments of face processing in relatives. Therefore, precise examination of the electrophysiological measures of early face processing in patients with schizophrenia and their relatives can shed light on the underlying neural substrate of abnormal social cognition, therefore contributing to the identification of potential endophenotypes useful for diagnosis.

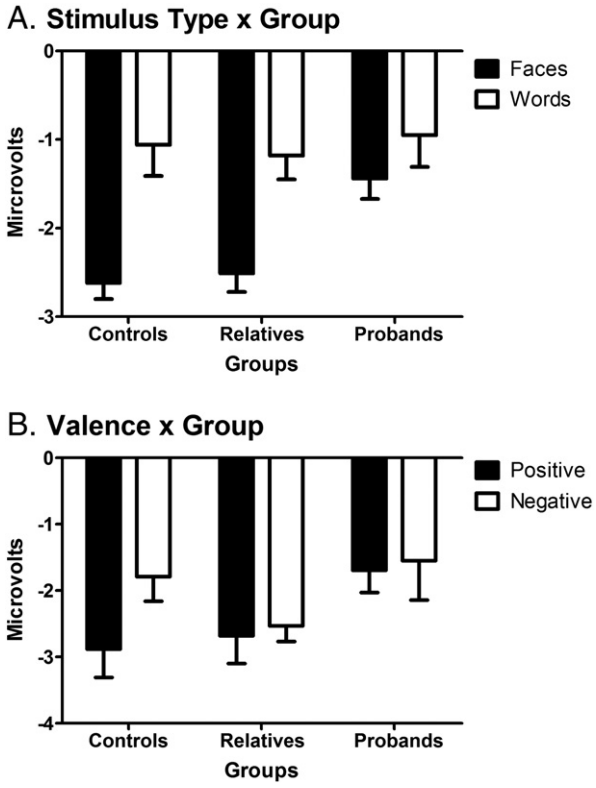

Fig. 2. Mean amplitude analysis. A) ERPs' mean amplitude values for stimulus type and group effects. ERPs from controls and relatives discriminate different type of stimulus. Probands showed no ERP differences between different types of stimuli. B) ERPs' mean amplitude values for valence and group effects. ERPs from controls discriminate different types of valence. Probands and Relatives showed no ERP differences between different types of valences. In A and B, bars are indicative of S.D.

4.2. Relevance for schizophrenia family research

Our findings are in line with the growing interest in targeting candidate endophenotypes by studying multiplex families in order to identify cognitive and behavioral impairments associated with hereditable vulnerability in schizophrenia (Gottesman and Gould, 2003; Holden, 2003; Braff et al., 2007). The neurophysiological basis of impaired perception of facial expressions by patients with schizophrenia has been consistently reported in the scientific literature across a wide variety of techniques including behavioral, neuroimaging, and neurophysiological variables (e.g. Streit et al., 2001; Edwards et al., 2002; Gur et al., 2002; Herrmann et al., 2004). Some authors have nevertheless argued that impaired processing of facial emotion in this population actually arises from a generalized deficit in facial processing (Salem et al., 1996; Doop and Park, 2009), rather than a specific disturbance of emotion perception (Kerr and Neale, 1993). Furthermore, facial processing deficits have been found to be associated with various cognitive abnormalities such as altered information processing, attention deficits, as well as global impairment (e.g. Schneider et al., 1995; Bryson et al., 1997; Addington and Addington, 1998; Kohler et al., 2000). Perhaps most strikingly, several studies have found a relationship between impaired face processing and clinical symptomatic profiles, including both positive (Schneider et al., 1995; Kohler et al., 2000; Baudouin et al., 2002) and negative symptoms (Mueser et al., 1996; Kohler et al., 2000; Suslow et al., 2003). Our study (by providing N170 deficits in emotional processing of schizophrenia families) calls for replicating the schizophrenia impaired face processing findings in the first-degree relatives in simplex and multiplex families.

4.3. ERPs as subclinical markers of impairments in schizophrenia research

The present study provided no behavioral evidence for a difference in facial processing as would have been manifested by different accuracy rates and reaction times on this task between the groups. Nevertheless, previous studies looking at N170 in schizophrenic patients did not report behavioral measures (Herrmann et al., 2004), while other similar paradigms on N170 had already reported no behavioral differences on performance accuracy or reaction times between emotional stimuli (Lee et al., 2010). In addition, further reports in patients did not find significant behavioral differences in the emotional inference of faces either (Kington et al., 2000; Kelemen et al., 2004; Riveros et al., 2010). As proposed by Bora et al. (2006), behavioral performance on emotional inference and social functioning should be preserved in functional patients. Our findings are in accordance with previous reports showing complex social cognition deficits despite of preserved performance in basic emotional inference (Riveros et al., 2010), suggesting that only complex emotional processing related to social cognition is abnormal in functional patients and relatives.

It is likely that behavioral differences were not found in this study because the positive and negative stimuli included encompass moderate levels of arousal, suggesting that emotional face processing among groups can be more readily detected at an electrophysiological level. As a matter of fact, reports of ERP changes without overt behavioral differences are frequently observed in ERP literature (i.e., Gray et al., 2004; Ibáñez et al., 2006; Kotchoubey, 2006; Ibáñez et al., 2008a, 2008b, 2010a), and even in schizophrenic patients and relatives (i.e., Guerra et al., 2009; Ibáñez et al., 2011b). This finding reveals that physiological responses may evidence subclinical aspects

of early facial discrimination that may not necessarily reach consciousness or manifest explicitly through behavior.

4.4. Right hemispheric dominance of N170

In our study, following preliminary analyses (see Supplementary data), we reported only right N170 effects. Right hemisphere dominance for face processing has been previously demonstrated. In contrast with other stimuli (words and objects), faces elicit an enhanced N170 amplitude discrimination to the right hemisphere (Bentin et al., 1999; Rossion et al., 2003; Joyce and Rossion, 2005). Source studies have shown right hemisphere dominance of facial N170 (Rossion and Gauthier, 2002; Rossion et al., 2003). Not only are stimulus type effects more accentuated to the right N170, but so are valence effects (Boucsein et al., 2001; Kolassa and Miltner, 2006; Ibáñez et al., 2011c; Petroni et al., accepted for publication; but see some reports of bilateral effects: Anes and Kruer, 2004). Moreover, compared to controls, N170 from schizophrenic patients are more reduced in the right scalp (Herrmann et al., 2004) and a significant association between reduced N170 to faces and the right posterior fusiform gyrus volume reduction in schizophrenia has been shown (Onitsuka et al., 2006). Given these previous findings, we have not included left N170 analysis.

4.5. Limitations and additional remarks

A key novel finding of our present study is that both patients with schizophrenia and their relatives showed no N170 discrimination of valence, which is highly suggestive of an underlying shared mechanism of altered facial affect processing. This abnormality occurred very early in face processing, which would be indeed consistent with a generalized deficit in the processing of facial features in schizophrenia (Salem et al., 1996; Doop and Park, 2009). These early impairments may impact upon patient performance in face recognition, therefore affecting the ability of patients to maintain successful social interactions. Consistent with this hypothesis, social cognition deficits have been reported both in patients and their relatives (Riveros et al., 2010). In addition to previous reports of N170 abnormalities related to highly arousing emotions (i.e., fear) in schizophrenia, we found similar discrimination deficits for happiness and anger. For relatives, it is likely that social withdrawal and awkwardness, which have been described in first-degree relatives of schizophrenic patients (Nuechterlein et al., 2002; Calkins et al., 2004), could be in part associated with the abnormal patterns observed for the N170. Previous reports had shown correlations between N170 and a social functioning scale (GAF — Global Assessment of Functioning — scores: Obayashi et al., 2009). Future studies will assess the possible relation between N170 impairments in relatives and social functioning.

Remarkably, the three groups in this study were not significantly different in terms of age, gender, IQ or educational level. Therefore, it is not at all likely that the differences found between them can be accounted for socio-demographic variability between the groups. No psychiatric disease was present in the relatives group, ruling out the possibility of an ERP abnormality secondary to other conditions. Although not statistically significant, differences were observed in cognitive tests assessing intellectual functioning, speed processing, and executive functions. As such, it is possible that the ERP differences found between the groups might be partially explained by patients' and relatives' subtle deficits in executive function and selective attention, both of which are required in order to quickly achieve an appropriate processing of facial features (Baudouin et al., 2000). Future studies relating behavioral and electrophysiological data with a more comprehensive neuropsychological battery are necessary to resolve this issue. In addition, further studies are also needed to examine the validity and reliability of N170 as a possible endophenotype, and a much wider appraisal of its role, perhaps in relation to subtle genetic abnormalities, could prove fruitful. In addition, the modest sample size of the present study is a main caveat, which should be addressed by future research studies attempting to reflect the remarkable heterogeneity of schizophrenia phenotypes more reliably.

Our study assesses emotional discrimination of positive and negative emotions. Although previous N170 reports of normal volunteers (Galli et al., 2006; Petroni et al., accepted for publication), as well as schizophrenia patients (i.e. Wynn et al., 2008), often times do not include neutral emotions, other studies with schizophrenic participants (e.g., Johnston et al., 2005; Caharel et al., 2007) have reported neutral stimuli. We did not include neutral faces in the present study, since the two-choice task uses two dimensions to be categorized for each side, left and right. Our study, by not including neutral stimuli, reduces the comparability to those previous studies regarding neutral emotions.

As well, the number of face stimuli in our study was different from that of words. Stimuli (faces and words) were repeated in order to obtain an enough number of trials for ERP estimation. Word stimuli present a classic repetition effect (e.g. Rugg, 1990; Rugg et al., 1994, 1997). On the contrary, facial ERP modulation can be found (in spite of any repetition effect) even with a smaller number of faces than the amount we presented (e.g. López et al., 2006; Maurer et al., 2008; Astikainen and Hietanen, 2009; Wong et al., 2009; Hurtado et al., 2009; Ibáñez et al., 2010b). Moreover, the habituation effects (e.g., attenuation of N170 amplitude and non-lateralization effects; Heisz et al., 2006), are more observable when only faces are considered as stimuli. When facial stimuli are presented together with other non facial stimulus (e.g., objects, words) habituation and repetition effects disappear (Maurer et al., 2008). Given the mixed and counterbalanced presentation of faces and words of our paradigm, we chose a small number of faces (40) because we did not expect habituation effects. In future studies, time-frequency analysis of oscillatory activity to assess habituation effects (as those reported in Busse et al., 2009) would be an interesting and complementary topic of N170 research in schizophrenia families.

5. Conclusion

In order to explore the ways in which early cortical processing of facial emotion could be affected in families with schizophrenia, DSM-IV diagnosed schizophrenia probands, their unaffected first-degree relatives, and control subjects, performed a face and words valence task that involved the categorization of pleasant and unpleasant words, along with faces of anger and happiness. The N170 component present in relatives and control subjects was largely reduced for faces in the patient population, suggesting a deficit in structural processing of stimuli. Consistent with previous reports of faces' and words' N170 elicited by positive and negative stimuli (Schacht and Sommer, 2009), control subjects showed N170 modulation by valence effects only for face stimuli. However, this discrimination effect appeared to be reduced both in patients and relatives. These results demonstrate an electrophysiological deficit in face processing and emotional discrimination in probands and clinically unaffected relatives, respectively, which provides evidence for abnormal processing. This indeed is an important first step in explaining significant subclinical abnormalities in face processing of schizophrenic patients' relatives.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.psychres.2011.07.027.

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