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Facial, vocal and cross-modal emotion processing in early-onset schizophrenia spectrum disorders

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ABSTRACT

Recognition of emotional expressions plays an essential role in children's healthy development. Anomalies in these skills may result in empathy deficits, social interaction difficulties and premorbid emotional problems in children and adolescents with schizophrenia.
Twenty-six subjects with early onset schizophrenia spectrum (EOSS) disorders and twenty-eight matched healthy controls (HC) were instructed to identify five basic emotions and a neutral expression. The assessment entailed presenting visual, auditory and congruent cross-modal stimuli. Using a generalized linear mixed model, we found no significant association for handedness, age or gender. However, significant associations emerged for emotion type, perception modality, and group. EOSS patients performed worse than HC in uni- and cross-modal emotional tasks with a specific negative emotion processing impairment pattern. There was no relationship between emotion identification scores and positive or negative symptoms, self-reported empathy traits or a positive history of developmental disorders. However, we found a significant association between emotional identification scores and nonverbal communication impairments. We conclude that cumulative dysfunctions in both nonverbal communication and emotion processing contribute to the social vulnerability and morbidity found in youths who display EOSS disorder.

1. Introduction

Early onset schizophrenia (EOS) is a severe but rare neurodevelopmental disorder (Driver et al., 2013) that dramatically impacts the healthy development of children and adolescents. Definitions of schizophrenia in children and adolescents are based on chronology: onset before 18 years constitutes early onset schizophrenia (EOS), and before 13 is very early onset (VEOS) (Russel, 1994). Despite the continuity with its adult counterpart, the disorder in youths is characterized by higher rates of premorbid abnormalities in motor, language, academic and affective development (Vyas et al., 2011; Schimmelmann et al., 2007; Hollis, 2003); uni-, bi- or multimodal hallucinations; disorganized behaviors; negative symptoms; and a more insidious onset (McClellan et al., 2013; David et al., 2011; Reichert et al., 2008; Fleischhaker et al., 2005; Hollis, 2000).

A number of investigations have focused on emotional identification deficits in adult-onset schizophrenia (AOS), supporting the idea that evaluating affect expression in everyday life is an essential social cognitive process required for efficient understanding and behavior (Green et al., 2013). Social cognition impairment in schizophrenia (for a review, see Green et al., 2008) is an independent domain that interplays in the disease course with other clinical dimensions. Notably, social cognition is thought to be an essential mediator between cognitive impairment and functional disease outcomes (for a review, see Schmidt et al., 2011). Other studies showed that well-established deficits in emotion identification (Simpson et al., 2013; Tseng et al., 2013) were correlated with clinical features such as negative symptoms (Chan et al., 2010; Addington and Addington, 1998; Schneider et al., 1995), illness duration (Savla et al., 2013; Hooker and Park, 2002; Ihnen et al., 1998), social abilities (Hooker and Park, 2002; Ihnen et al., 1998) and functional outcomes (Irani et al., 2012).

Only three studies have assessed facial emotion identification in EOS (Habel et al., 2006; Seiferth et al., 2009; Barkl et al., 2014). They reported deficits in facial emotion identification in children and adolescents with EOSS that were characterized by misidentifying negative emotions and the tendency to misattribute other emotional expressions (Barkl et al., 2014). They found no correlation with psychotic symptoms and/or functioning, as opposed to the established correlations with negative

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symptoms in adult schizophrenia (Chan et al., 2010; Addington and Addington, 1998; Schneider et al., 1995). Amminger et al. (2012, 2014) focused on ultra-high-risk (UHR) subjects and their transition to psychosis. Although UHR subjects showed less accuracy in emotion identification (face and prosody) tasks compared with healthy controls, this finding was not correlated with the prediction of psychosis.

In EOS, no study has examined vocal emotion identification, defined as assessing auditory emotion stimuli. Vocal emotion identification stimuli are characterized by their prosody. Stimuli are either semantically neutral words, meaningless pseudo-language or direct rhythm patterns of vocal utterance such as screams, and laughter (Klasen et al., 2012). Investigations in adult-onset schizophrenia (AOS) showed a less well-established impairment pattern in the ability to identify vocal emotions (Leitman et al., 2010; Kucharska-Pietura et al., 2005; Edwards et al., 2001) than that for facial emotions. The mixed results are based on different assessment tools and on multiple open questions (generalized or specific impairment, characterized by different features such as pitch, intensity, frequency, etc.). Most works (Strous et al., 1995; Rabinowicz et al., 2000) found deficits in basic pitch perception in schizophrenic subjects. In a study that compared vocal emotion identification based on pitch and intensity features (Gold et al., 2012), schizophrenia patients presented evident pitch perception impairment relative to intensity features.

Although real-life emotion recognition is based on perceiving, integrating and understanding emotion cues from different sources (e.g., visual/posture; audio/vocal; visual/face), to our knowledge, no study has evaluated impairment patterns in facial and vocal emotion identification matched with cross-modal (facial and vocal) congruent identification in EOSS. Multisensory integration is crucial for social interactions (Dolan et al., 2001; de Gelder and Vroomen, 2000; Chaby et al., 2012). In daily situations, humans perceive co-occurring and merging audiovisual signals as coherent information for understanding and attributing social cues to other people. This synergistic process is necessary for reducing ambiguous stimuli (Ernst and Bülthoff, 2004) and for optimizing behavioral reactions and cognitive understanding. The few studies that have investigated multisensory integration in adults with schizophrenia (de Gelder et al., 2005; de Jong et al., 2009, 2009; Ross et al., 2007) showed that cross-modal emotion recognition was also impaired. Another factor in multisensory integration is selective attention ability (de Jong et al., 2009), which could have a regulatory role in the daily integration of convergent information from multiple modalities. Dysfunctions in selective attention could result in an exaggerated focus on vocal cues and/or auditory negative emotion stimuli.

Based on a neurodevelopmental perspective of schizophrenia (Weinberger, 1987; Rapoport et al., 2012), we propose that early anomalies in processing nonverbal (facial mimicry, gestures, postures and prosody) emotion recognition cues provide a central contribution to social cognition skill impairment across the premorbid pathways that lead to schizophrenia onset. Early in children's development, emotions enhance their sensory processing of faces and voices (Grossmann, 2010). Notably, infants reliably match and recognize emotion information across faces (e.g., Vaillant-Molina et al., 2013) and voices (e.g., Cohen et al., 2013). This first ability in children to be active, tuned in and "connected" to emotion information is a fundamental skill for understanding people's intentions and for attributing emotions to others in real life. The everyday challenge to discard useless, redundant or excessive stimuli results in efficient multisensory identification, but only if one's filter for selecting pertinent social cues is well activated (i.e., by emotion information and/or modalities). These non-verbal communication competences are essential for building the bases of empathic responses in children. According to Gonzalez-Liencres et al.'s (2013) model of empathy, we propose that the set of developmental empathy-related abilities (mimicry, emotional contagion, imitation) could be dysfunctional in youths with schizophrenia. Indeed, some form of empathic deficits in adult schizophrenia has been reported using Interpersonal Reactivity Index and Questionnaire of Cognitive and Affective Empathy (Achim et al., 2011; Corbera et al., 2013; Michaels et al., 2014).

In this study, we suppose that difficulties in nonverbal communication abilities as well as uni- and multimodal emotion recognition could play a role in the development of empathic feelings and social behaviors in EOSS subjects. The aim of our study was to explore: (1) emotion identification of facial, auditory and cross-modal stimuli compared with healthy controls and (2) specific or shared patterns in emotion misidentification and misattribution in children and adolescents with schizophrenia. We also assessed associations between emotion identification scores and (3) history of premorbid developmental anomalies or (4) EOSS clinical features and self-reported empathy traits.

2. Methods

2.1. Participants

A group of 26 patients (80.7% boys) was enrolled in the Child and Adolescent Psychiatric Department, Pitié-Salpêtrière Hospital in Paris (France) between October 2012 and April 2014. Age-matched healthy control (HC) volunteers participated in the study (N = 28; 50% boys). Only patients who met criteria A for schizophrenia, schizophreniform disorder, schizoaffective disorder, and brief psychotic disorder and psychotic disorder NOS in the DSM IV-TR (APA, 2000) were included. Given the diagnostic instability of major depressive disorder with psychotic features (Castro-Fornieles et al., 2011), we chose to enroll also patients at first-episode psychosis (FEP) in the context of major depression. The diagnosis of EOSS was made by consensus of C.L. and M.G. based on interviews of the child and the parents with the Diagnostic Interview for Genetic Studies version 2 (DIGS, Nurnberger et al., 1994) and medical records. The DIGS was translated into French by a French–Swiss collaboration which demonstrated good inter-rater reliability (Preisig et al., 1999). Subsequently, minor modifications were made by M.F. Poirier and M.O. Krebs and then by C.L. and D.F. Levinson. C.L. adapted the DIGS for administration to children and parents. Exclusion criteria were: i) known neurological condition or sensory dysfunction (i.e., cerebral palsy; hypoacousia), ii) moderate or severe intellectual disabilities; and iii) insufficient French language skills to understand tasks. Given the comorbidity between EOSS-VEOSS and intellectual disabilities (ID) (Doody et al., 1998; Lee et al., 2003), we chose to enroll patients with mild intellectual disability (N = 4). The study was a part of a more extensive work on EOSS and VEOSS in our department that is focusing on dimensional assessment in schizophrenia. All participants and their parents gave written informed consent before participation in the research, which was approved by the local ethics committee. Self-report questionnaires, history and emotional testing were conducted in stabilized EOSS patients.

2.2. Clinical evaluation and history of developmental anomalies

Patients with EOSS were assessed to delineate: i) age at onset; ii) history of developmental anomalies; iii) DSM-IV TR axis I psychiatric diagnosis; iv) positive symptoms; v) negative symptoms; vi) history of and current difficulties in social interactions, communication, and repetitive behaviors; and vii) empathy traits. The included patients were interviewed with the Diagnostic Interview for Genetic Studies-2 (DIGS-2; Preisig et al., 1999) to specify diagnostic phenotypes (i.e., premorbid features, disease course, psychiatric diagnosis). Psychotic symptoms were also evaluated with the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984) and the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1983). Patients were also instructed to answer the Eysenck's self-rated empathy questionnaire. This 23-item questionnaire is a part of the 77-item Eysenck Impulsivity Junior questionnaire to measure impulsivity, venturesomeness and empathy in youths (Eysenck et al., 1984). The French translation and validation was conducted in the context of the Montreal

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longitudinal study on aggression (Carrasco et al., 2006). All patients received antipsychotic drugs, and we converted their prescriptions into chlorpromazine (CPZ) equivalent doses.

Developmental anomalies or disorders were evaluated for every patient. Their parents were interviewed by two child psychiatrists (C.L.; M.G.) to check developmental milestones, history of motor, language and social anomalies, and corresponding remediation therapies. We collected ages and related deviances at developmental milestones from national child health records and/or from other psychomotor assessments. With the particular goal of evaluating social disabilities and other autistic developmental features, we interviewed parents using the autism diagnostic interview-revised (ADI-R; Lord et al., 1994).

2.3. Emotional recognition task

2.3.1. Stimuli

For the visual stimuli, participants were instructed to identify emotions from a set of photographs of human facial emotions, taken from the Karolinska Directed Emotional Faces Database (Lundqvist et al., 1998). For every basic emotion (happiness, sadness, disgust, anger, and fear, and a neutral expression), eight full frontal view pictures (4 males and 4 females) were presented in slide form on a screen for a total of 48 trials for every participant. For the auditory stimuli, we used a set of eight affect vocalizations (4 males and 4 females) for the six basic emotions. This set was obtained from the Montreal Affective Voices, a standardized presentation of vocal emotion expressions developed for research in auditory affective processing (Belin et al., 2008). The avoidance of potential confounds from linguistic content is an essential characteristic of this set. Fig. 1 shows a sample of set of stimuli. For the cross-modal stimuli, the set was composed from the same 48 faces and voice emotions congruently and simultaneously presented.

2.3.2. Procedure

All stimuli were presented on a 17 in. monitor (resolution set to 1200 Â 800 pixels). Each participant performed 144 trials, which were divided into 3 blocks (visual, auditory, and cross-modality). Two sets of 48 items in pseudorandom order were constructed for each block. The visual and auditory conditions were randomly presented, and the cross-modal condition was always presented last. In the three emotion recognition tasks, the participants were instructed to carefully consider all six alternatives before responding. The verbal labels for the six emotion expressions were printed under each picture on the computer screen throughout the test, and the subjects were asked to select the word that best described the emotion presented in each slide. The responses were recorded with mouse clicks. There was no time limit for analyzing each stimulus or for responding. The patients were not given feedback on their performance. Eight practice trials were conducted prior to each block.

2.4. Statistical analyses

Statistical analyses were implemented using R, version 2.12.2 (R Foundation for Statistical Computing), with two-tailed tests and a 95% confidence level. Because of the forced-choice paradigm (six possible answers) that was used in our experiment, we used a generalized linear mixed model (GLMM; lme4 package) to explore the data. A binomial family was specified in the GLMM to estimate the log-odds ratio for the corresponding factors in the model. For the primary analysis, those factors were group (EOSS vs. HC), emotion (joy, neutral, anger, disgust,

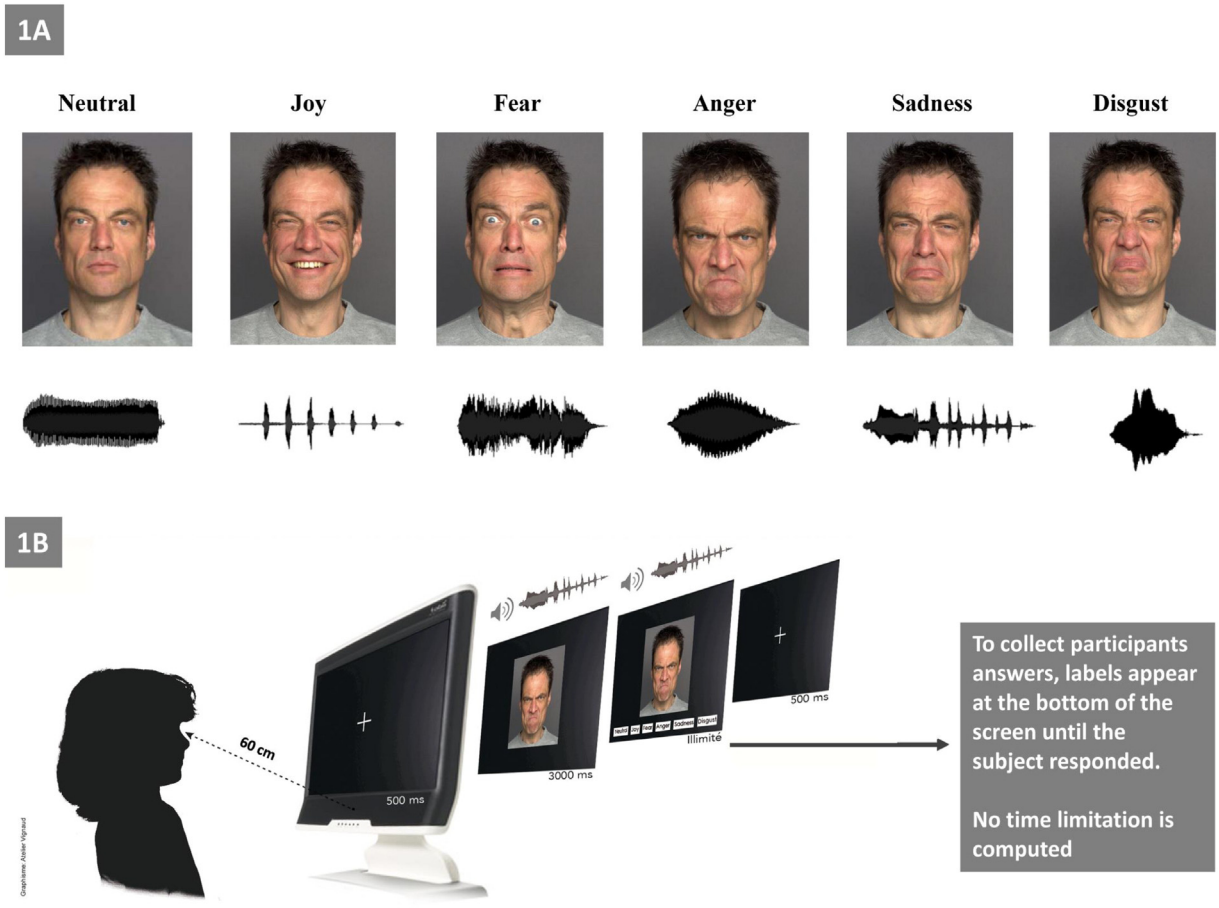

Fig. 1. Experimental setting. 1A. Examples of facial and vocal emotion stimulus presentations for each of the six primary emotions (e.g., "Joy" with the outline of a prosodic laugh). 1B. Experimental procedure.

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fear, or sadness), task (visual, auditory, or cross-modal), age, handedness and sex (model formulation: number of successes ~ Task + Emotion + Group + fixation duration + age + handedness + sex + random participant factor). To avoid false alarm bias (corresponding to the tendency to preferentially use one class of answer in cases of doubt), we used the unbiased hit rate (Hu) (Wagner, 1993) rather than the percentage of correct responses for each emotion and task. Unbiased hit rate can vary between 0 and 1, where a hit rate of 1 indicates not only that an emotion was always identified correctly but also that the corresponding response was always used correctly (e.g., the response "anger" was only given for anger stimuli). Hu index is defined as follows:

$$Hu = (N_{hits} \times N_{hits})/(N_{responses} \times N_{stimuli}).$$

Secondary analyses were separately performed for each task (i.e., visual, auditory, and cross-modal). Then, for the EOSS subgroup, the following factors were considered as possible predictors: age of onset, history of developmental anomalies, total SANS and SAPS scores, ADI-R total and domain scores, and Eysenck score. Moreover, we also distinguished two subgroups relative to severity of developmental anomalies (absent or mild vs. severe) as covariate. Interactions between group and other factors were also investigated to determine whether the effect of the predictor would be higher for EOSS children than HC children.

3. Results

3.1. Description of participants

In total, 54 participants were enrolled in this study, as shown in Table 1. The EOSS and HC groups were matched for age, handedness and language. As detailed in Table 2, mean age at onset was 12.5 years (median: 13 years; SD: 2.24 years; range: 7–16 years), with 50% of the patients showing very early onset. In the EOSS group, 77% of subjects presented developmental deviances. Based on severity of developmental deviances, we preferred to distinguish patients with typical development or with mild specific developmental disorders [(oral and written specific language impairment; developmental coordination disorder, N = 13)] from patients with serious developmental anomalies [(multi-specific impairments, intellectual disabilities and ASD), N = 13]. Clinical characteristics are shown in Table 2.

3.2. Emotional identification task

The assessment results for emotion labeling from visual, vocal and cross-modal stimuli are summarized in Fig. 2. An ANOVA with four factors (emotion, group, modality, handedness, and gender) for correct responses revealed: an important effect of emotion type ($\chi^2 = 300.15$; Df = 5; $p < 0.001$), perception modality ($\chi^2 = 295.04$; Df = 2; $p < 0.001$), and group ($\chi^2 = 23.05$; Df = 1; $p < 0.001$). There was a significant interaction between group and perception modality ($\chi^2 = 8.76$; Df = 2; $p = 0.01$). No significant association was found for gender. In our sample, there is indeed a discrepancy in gender matching between the groups. We carried out a supplementary analysis on the male subgroup and the results remain still significant for the interaction between group and perception modality ($\chi^2 = 6.21$; Df = 2; $p = 0.01$).

Using happiness as the reference for emotion and visual facial stimuli as the reference for modality, the GLMM found that all participants were less efficient at recognizing negative emotions and neutral expressions compared with happiness [in descending order: anger (estimate value = −0.34; $p < 0.001$), disgust (estimate value = −0.28; $p < 0.001$), fear (estimate value = −0.28; $p < 0.001$), sadness (estimate value = −0.11; $p < 0.001$), neutral (estimate value = −0.08; $p < 0.001$)]. Facial and vocal emotion identification were more difficult for all subjects than was cross-modal emotion identification (for visual stimuli, estimate value = −0.18; $p < 0.001$; for vocal stimuli, estimate value = −0.27; $p < 0.001$). EOSS patients showed greater probability of succeeding at the cross-modal task than the visual-only task (estimate value = −1.38; $p < 0.001$), relative to the performances of the

Table 1
Demographic characteristics.

Group	EOSS	HC
N	26	28
Mean age (range)	15.2 (10–18)	14.4 (11–18)
Gender (M/F)	21/5	14/14
Maternal language (% French)	25 (96.2%)	28 (100%)
Handedness (% right)	23 (88.5%)	23 (82.2%)

Table 2
Clinical characteristics of EOSS group.

	Mean (range)
Age at psychotic onset	12.5 (7–16)
Age groups	N (%)
EOS	13 (50%)
VEOS	13 (50%)
History of developmental disorders	N (%)
Typical development	6 (23%)
Specific language impairment	2 (8%)
Developmental coordination disorder	5 (19%)
Multi-specific developmental impairment	5 (19%)
Mild intellectual disabilities	4 (15%)
Autism spectrum disorder	4 (15%)
Diagnosis (DIGS-2)	N (%)
Schizophrenia	20 (76.9%)
Schizophreniform disorder	0
Psycosis not otherwise specified	3 (11.5%)
Major depressive disorder with psychotic symptoms	3 (11.5%)
Medication (N)	Mean CPZ mg (range)
Risperidone (10)	261 (120–470)
Aripiprazole (11)	249 (60–500)
Clozapine (3)	223.3 (120–300)
Quetiapine (1)	500
Amisulpride (1)	NA
Haloperidol (1)	30
SAPS	Mean score (range)
Hallucinations	8.1 (7–16)
Delusions	16.4 (1–30)
Bizarre behavior	6.1 (0–12)
Positive formal thought disorder	10.5 (0–25)
Total of sub-scores	41.1 (13–73)
Total of global assessments	10.5 (5–17)
Total	51.6 (18–88)
SANS	Mean score (range)
Affective flattening	15 (7–16)
Alogia	9.2 (0–16)
Avolition-apathy	6.5 (0–12)
Anhedonia-asociality	4.7 (1–20)
Attention	3.9 (0–7)
Total of sub-scores	46.1 (9–81)
Total of global assessments	13.4 (2–22)
Total	59.5 (11–101)
ADI-R	Mean score (range)
Qualities abnormalities of reciprocal social interactions	9.92 (1–20)
Verbal communication	3.40 (0–9)
Nonverbal communication	2.84 (0–12)
Restricted and repetitive behaviors	3.04 (0–8)
Eysenck's self-rating questionnaire	Mean Score (range)
Total score	14.32 (11–19)

EOS: Early-onset schizophrenia.
VEOS: Very-early onset schizophrenia.
EOP: Early-onset psychosis.
DIGS-2: Diagnostic interview for genetic studies.
CPZ: Chlorpromazine.
ND: Not available.
SAPS: Scale for the assessment of positive symptoms.
SANS: Scale for the assessment of negative symptoms.
ADI-R: Autism diagnostic interview — revised.

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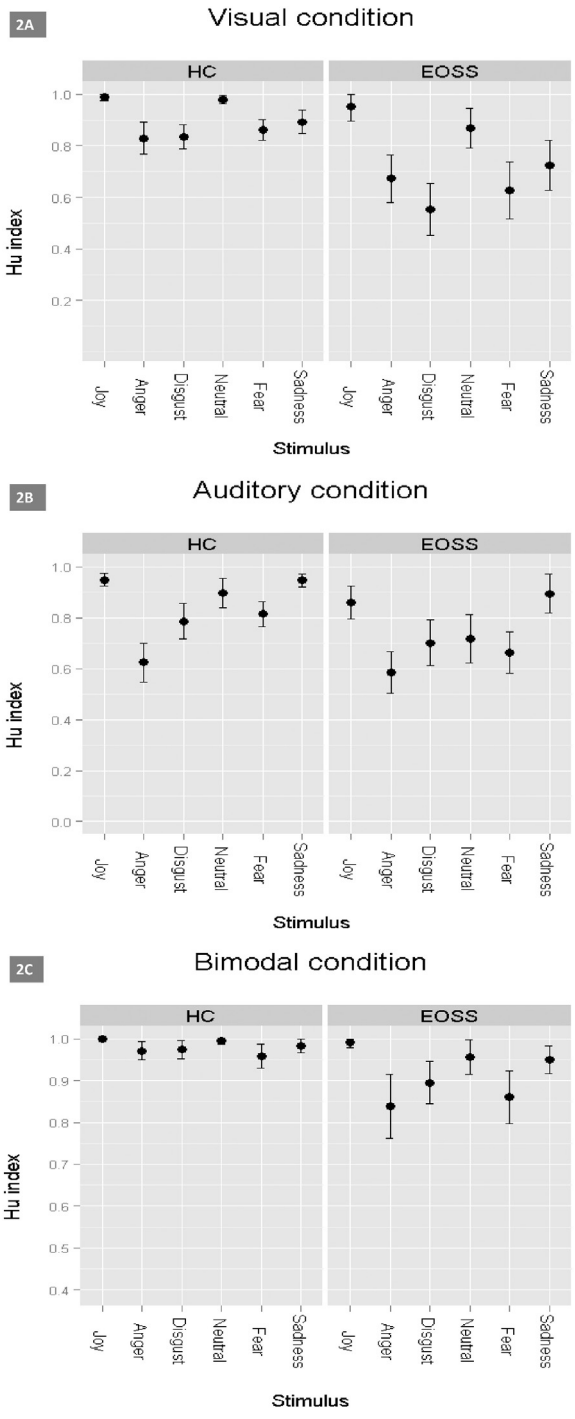

Fig. 2. Probability of correct emotion recognition as a function of the emotions and tasks in EOSS (2a.) and HC (2b.) children. EOSS = Early Onset Schizophrenia Spectrum; and HC = Healthy Control.

HC, as shown in Fig. 3. Additionally, for the HC, the probability of succeeding at the audio task was greater that for the visual-only task (Estimate value = 0.07; p = 0.04). A confusion matrix (Table 3) shows that EOSS subjects had more misclassified answers for (1) disgust (12.6%), which was confused for anger, and for neutral expressions and sadness; (2) fear (11.1%), which was confused for anger, and for disgust and sadness; and (3) anger (10.9%), which was confused for fear, and for disgust and neutral expressions.

In addition, we focused on the time latency for correct responses in all participants. The EOSS group showed slower responses than did the HC (estimate value = 0.41; $p < 0.001$). We also found that

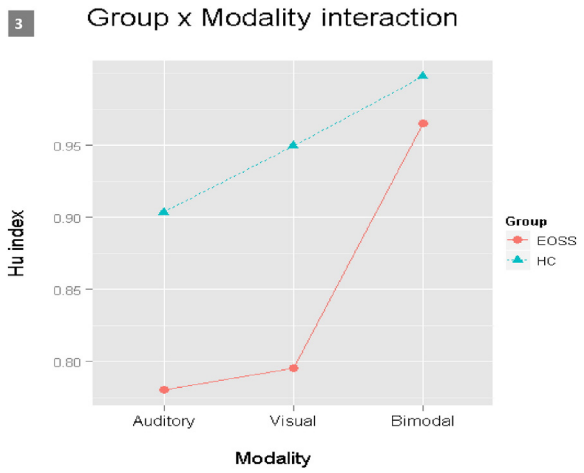

Fig. 3. Interaction plot between group (HC vs. EOSS) and modality (auditory vs. visual vs. bimodal) for emotion recognition score (Hu index). EOSS = Early Onset Schizophrenia Spectrum; and HC = Healthy Control.

individuals (both HC and EOSS) showed slower responses for negative emotions [fear (estimate value = 0.22; $p < 0.001$); anger (estimate value = 0.19; $p < 0.001$); disgust (estimate value = 0.16; $p < 0.001$); sadness (estimate value = 0.14; $p < 0.001$)] and neutral expressions (estimate value = 0.04; $p < 0.05$) compared with happiness. Finally, time latency for one modality (visual or vocal) was slower compared with that for cross-modal identification (for facial emotion identification: estimate value = 0.20; $p < 0.001$; for vocal emotion identification: estimate value = 0.08; $p < 0.001$). In addition, EOSS patients performed more quickly at cross-modal than at vocal emotion identification (estimate value = 0.06; $p < 0.05$) (Fig. 4).

3.3. Association with clinical variables

We also ran other GLMMs with the additional scores obtained on clinical scales, age of onset and history of developmental anomalies as explicative variables. As described in Section 3.1, we distinguished two groups relative to developmental deviances, a first group with no developmental anomalies or with mild specific difficulties (i.e., dyslexia) and a second characterized by different severe difficulties (multi-specific impairments) or pervasive and serious developmental disorders such as ID and ASD. There was no relationship between emotion identification accuracy and scores obtained on the SAPS (estimate value = 0.004; p = 0.47) or the SANS (estimate value = 0.01; p = 0.20) or empathy traits on Eysenck's self-rating questionnaire (estimate value = 0.01; p = 0.76). Similarly, no associations were found between history of developmental disorders and performances on emotion identification tasks (estimate value = 0.10; p = 0.54). However, the analysis revealed that the probability of succeeding at the emotion identification tasks was lower in the EOSS subjects, who showed higher scores on the ADI-R nonverbal communication domain (estimate value = 0.15; $p < 3.60 \times 10 - 5$) and lower with older age at onset (estimate value = 0.14; $p < 0.05$). Finally, when investigating time latency, we found that patients with later onset of schizophrenia presented more

Table 3
Confusion matrix.

	Joy	Anger	Disgust	Neutral	Fear	Sadness
Joy	1277	4	7	5	11	19
Anger	1	1060	47	22	54	7
Disgust	6	85	1142	14	44	16
Neutral	4	36	38	1242	20	4
Fear	1	96	14	12	1129	18
Sadness	6	14	47	0	35	1230

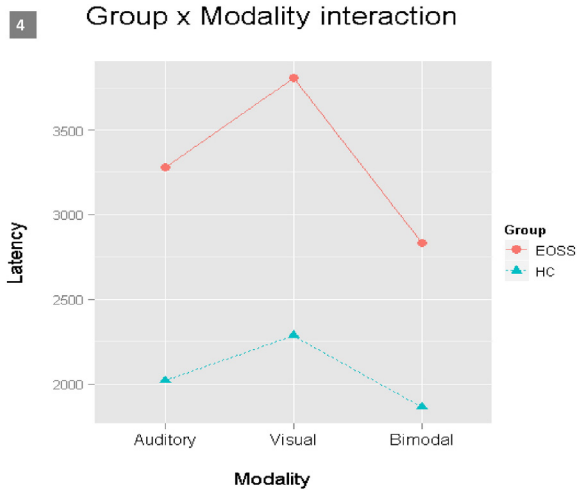

Fig. 4. Interaction plot between group (HC vs. EOSS) and modality (auditory vs. visual vs. bimodal) for time latency. EOSS = Early Onset Schizophrenia Spectrum; and HC = Healthy Control.

rapid time latency than did patients with earlier onset (estimate value = −0.07; $p < 0.001$).

4. Discussion

The current study aimed to investigate facial, vocal and cross-modal emotion identification patterns in individuals who were diagnosed with early onset schizophrenia and correlated disorders (EOSS). We also focused on the relationship between emotion recognition and history of developmental anomalies, based on the hypothesis that impaired emotion identification may be involved in the premorbid pathways that lead to schizophrenia onset. To our knowledge, this is the first study that has explored uni- (facial; vocal) and cross-modal (facial + vocal) emotional recognition in a sample composed only of EOSS individuals, with a high rate of VEOSS patients (N = 13; 50%) and a low rate of affective psychosis (major depressive disorder with psychotic signs: N = 3; 11.5%). The closest studies on clinical high-risk subjects (Amminger et al., 2012; Addington et al., 2008) either had higher ages at onset and/or did not report the rate of first-episode schizophrenia that had occurred earlier than age 18 years.

In our study, EOSS subjects showed significantly worse performances on facial, vocal and cross-modal emotion identification compared with the HC. Consistent with facial emotion recognition findings in other EOSS works (Barkl et al., 2014; Seiferth et al., 2009; Habel et al., 2006), labeling negative emotions was more difficult than was recognizing happiness or neutral expressions. EOSS patients also showed a tendency to misattribute disgust, fear, and anger to other negative emotions (above all with pictures representing anger). Thus, negative emotion processing is an everyday problem for juveniles with schizophrenia and relative disorders. Regarding facial emotion identification, works on EOSS explained this tendency to misattribute negative emotions based on functional neuroimaging correlates such as (1) hypoactivation of both fusiform gyri (especially for sadness) and in the left inferior occipital gyrus, (2) hyperactivation of the right cuneus (Seiferth et al., 2009), and (3) impaired amygdala activation patterns (Williams et al., 2009).

More extensive studies are needed to elucidate the relationship between neuroimaging anomalies (structural and functional) and negative emotion processing, especially from a neurodevelopmental perspective that includes the well-established neuroimaging patterns in EOS and VEOSS (increased lateral ventricular volume combined with a total and regional gray matter volume loss; Giedd et al., 1999; Greenstein et al., 2006; Rapoport et al., 1999; Sporn et al., 2003) and, in a secondary view, the contribution of the primary emotional system across the trajectory of normal cerebral ontogeny (for an overview, see Toronchuk and Ellis, 2013; Tamietto and de Gelder, 2010; Tottenham, 2014).

In patients with EOSS, we found that vocal emotion recognition was more difficult than cross-modal and (though to a lesser degree) than facial emotion identifications. This essential lag was found also in the analysis of time latency. Although sound waves arrive to ears more quickly than light does to the retina (King and Palmer, 1985), EOSS subjects performed more slowly with vocal stimuli (compared with facial, visual and cross-modal stimuli). A number of speculations may be proposed here. One hypothesis relates to the auditory stimulus set in our study. In essence, vocal tokens were repeated (with an interval of 250 ms), and participants could listen multiple times to the same stimulus. For the facial, visual and cross-modal tasks, the emotion materials were presented at stable time intervals. Another explanation is that the observed finding could be related to a pattern of "auditory hypoemotionality" (as described by de Gelder et al. (2005)) compared with the more dominant visual modality.

Regarding multisensory integration, the results for cross-modal stimuli deserve specific comments. Although the EOSS group showed better abilities at cross-modal emotion identification compared with other unimodal emotional tasks, their performances were significantly poorer than those of the HC for the congruent bimodal task. This observed pattern is congruent with the recent advances in the field of multisensory integration and schizophrenia. Studies on adult forms reported deficits in cross-modal emotion identification (de Jong et al., 2009; de Gelder et al., 2005) using a different method for exploring multisensory integration. The disintegrated pattern in cross-modal emotion synthesis in EOSS could be explained in different ways: i) a mixed pattern of audiovisual integration characterized by the reduced effect of the voice in identifying facial emotions and an exaggerated effect of the faces in the opposite task (de Gelder et al., 2005); ii) impaired cross-modal sensory modulation and interaction in the multimodal convergence areas (i.e., the superior colliculus) (Driver and Spence, 2000; Vroomen and de Gelder, 2000; Macaluso et al., 2000); iii) an anomalous filter of modality-specific selective attention that might preclude the efficient synthesis of different emotional cues, emphasizing irrelevant, "noisy" stimuli or ignoring essential emotion information (de Jong et al., 2010). Taken together, these hypotheses lend strong support to the evidence for multisensory emotion integration impairments in youths who have schizophrenia and related disorders. Additional studies are necessary for investigating the role of selective attention skills (Tamietto and de Gelder, 2010; de Jong et al., 2010) in negative emotion recognition difficulties and schizophrenia. In daily life, we know that vocal emotion information influences how listeners explore faces and facial information (Paulmann et al., 2012; Rigoulot et al., 2014), confirming the essential interaction between audio and visual sources in multisensory integration. A fascinating hypothesis is that anomalies or difficulties in a number of the steps in perceiving and processing emotions (i.e., cross-modal perception of emotion information; filtering out irrelevant cues; convergent synthesis of emotion stimuli) could result in fragmented, disintegrated perception and understanding of human social interactions in children and adolescents who are affected by schizophrenia and correlated disorders.

Regarding time latency, we found that the EOSS group gave correct responses more slowly than did the HC, as reported by Barkl et al. (2014) and Seiferth et al. (2009) for facial emotion labeling. Our analysis showed that patients with later disease onset gave correct responses more quickly than did those whose schizophrenia had earlier onset. This finding can be explained in accord with neurophysiological correlates for facial emotion recognition in adolescents (Tottenham et al., 2011), resulting in more rapid responses compared with those of children and adults. Another interpretation may be that later illness onset is associated with a minor impact on neural performance.

In contrast to studies on adult schizophrenia (Addington and Addington, 1998; Schneider et al., 1995; Chan et al., 2010) that support

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a relationship between emotion recognition and negative symptoms, we found no association between either SAPS or SANS scores and emotion identification scores. This lack of association may reflect (1) a more important heterogeneity in EOSS (Bonnot et al., 2012) or the lack of specific tools for patients with early onset schizophrenia, which could hamper the assessment of negative symptoms in youths. However, the current finding may be valid *per se* in its showing emotion identification to be independent of EOSS clinical dimensions. This view is in line with the absence of positive correlations between positive or negative symptoms in EOS and specific neuroimaging structural anomalies or neuropsychological impairment (Banaschewski et al., 2000; Cervellione et al., 2007; Frangou et al., 2008; Jepsen et al., 2010; Greenstein et al., 2012).

Although no association was found between a positive history of developmental disorders and emotion identification scores, we found (1) a significant association between ADI-R nonverbal communication and emotion recognition scores and (2) longer time to label emotions in patients with EOSS. Nonverbal communication explores anomalies and/or lack of ability in the area of pointing and other gestures, spontaneous imitation and imaginative social play (Lord et al., 1994). A child, who is less suited to nonverbal social communication, is likely less able to process and understand emotion-related stimuli. These cumulative dysfunctions in both nonverbal communication and emotion processing, and the age-related time latency, contribute to the social vulnerability and morbidity found in youths who display EOSS (Nicolson et al., 2000).

We are aware that this study has a number of limitations. First, there are no specific tools for assessing EOS, VEOS and correlated disorders. We used scales that had used and validated for children and adolescents with schizophrenia, but specific scales and interviews are suited for specifically characterizing the phenomenology and its relationship with emotional identification impairment. A second methodological issue is the sample size. To have a larger sample size, we included disorders that resembled schizophrenia (schizophreniform disorder, brief psychotic disorder, psychosis not otherwise specified, etc.), which could have introduced bias in our analyses. However, our excluding those patients did not dramatically change the results found here (data not shown). Another methodological issue is the large discrepancy in gender matching between the groups. Although gender didn't come out as a significant covariable, we cannot totally exclude its effect due to the absence of gender matching in our sample. Finally, the study was transversal, meaning that we did not collect developmental history prospectively, that we cannot exclude issues about understanding of the empathy questionnaire, and that emotion identification impairment was assessed in stabilized patients who were taking psychotropic medications. This could have biased our results.

We conclude that cumulative dysfunctions in both nonverbal communication and emotion processing contribute to the social vulnerability and morbidity found in youths with EOSS. Early detection of emotion correlates and focused social interventions may be crucial for better outcomes.

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The sponsor had no involvement in the study design, data analysis, or interpretation of results.

Contributors

Authors M.G., J.X., D.C., L.C. designed the study. C.L. wrote the full protocol for assessing EOSS. L.C. M.G. and D.C. computed the emotional task. M.G. and L.C. managed the literature searches and the data collection. M.G. and C.L. interviewed all patients using the DIGS-2. M.G. and J.X. assessed all patients using the SAPS, SANS and ADI-R. M.G. and A.F. recruited and evaluated healthy controls. N.B. and D.C. undertook the statistical analysis. M.G. wrote the first draft of the manuscript, and D.C. and L.C. revised this draft. All authors contributed to and have approved the final manuscript.

Conflict of interest

The authors report no biomedical financial interests or potential conflicts of interest.

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