



EEG correlates of face recognition in patients with schizophrenia spectrum disorders: A systematic review



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HIGHLIGHTS

- Schizophrenia patients exhibit an impaired face processing outside an emotional context.
- Specific conditions of tasks make the differences between patient and control groups more prominent.
- The N170 may have a role as a diagnostic and treatment monitoring biomarker.

ABSTRACT

Objective: To systematically assess EEG studies and evaluate neuropsychological changes of face recognition in the context of neutral face stimuli in individuals with schizophrenia spectrum disorders.

Methods: A literature search was conducted using the PubMed database from inception to March 2018. Studies included in the review measured any event-related potentials, neural oscillations, or phase synchrony.

Results: A total of 113 articles were identified. Twenty-nine studies were included for the review. The majority of the studies focused on the N170 component. Smaller N170 amplitudes were consistently reported in schizophrenia patients compared to the healthy control group. Significant correlations between N170 amplitudes and social functioning scales were reported. Other results were quite inconsistent; however, group differences were more prominent for tasks with specific conditions.

Conclusions: Older patients with longer disease duration show more consistent neuropsychological correlations. Alterations of event-related potentials are likely to be linked to higher severity of symptoms. The N170 component seems to be the most promising event-related potential to be used for evaluation of present status and for dynamic control of cognitive impairments, social functioning, and rehabilitation effectiveness.

Significance: This systematic review provides evidence of (1) neuropsychological alterations of face processing outside an emotional context, and (2) a potential role of N170 as a diagnostic and treatment monitoring biomarker.

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1. Introduction

Schizophrenia is a chronic psychiatric disorder characterized by a wide variety of clinical symptoms, including positive symptoms, negative symptoms, cognitive impairments, and social dysfunction. The latter is mostly due to a deficit in social cognition, which means an impaired ability to perceive the intentions and disposition of others and to maintain social interactions (Brothers,

1990). Face processing is a key component of this deficit (Marwick and Hall, 2008).

The dominant theory by Bruce and Young divides face processing into two independent processes: facial recognition and facial emotion processing (Bruce and Young, 1986). Regarding individuals with schizophrenia, research has been conducted in both directions; however, most studies have focused on emotion perception (Kohler et al., 2010) and relatively few have systematically assessed non-emotional aspects of face processing (Darke et al., 2013). Still, debate continues regarding the relationship between face perception and facial emotion recognition deficit in patients with schizophrenia (Rocca et al., 2009). Some authors hypothesize

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a “generalized deficit” based on the observations of impaired recognition of both emotional and non-emotional stimuli (Kohler et al., 2003; Kucharska-Pietura et al., 2005). Other authors found intact facial recognition with impaired facial emotion recognition, and support the hypothesis of a specific deficit of emotion perception (Poole et al., 2000; Kosmidis et al., 2007). The third point of view is that each kind of facial information affects the processing of the others (e.g., participants could not selectively pay attention to emotions regardless of the identity) (Bediou et al., 2005; Martin et al., 2005).

The literature on face perception and facial emotion recognition can be divided into behavioural and neuroimaging studies (typically two types of studies: functional magnetic resonance imaging (fMRI) and electroencephalography (EEG)). Darke et al. (2013) noted that neuroimaging studies can explore the underlying face perception abnormalities that may go undetected through commonly used behavioural measures. The millisecond-level temporal resolution of event-related potentials (ERPs), which are waveforms measured by means of EEG, are well-suited to investigate the processes of face perception.

McCleery et al. (2015) used meta-analysis to show that the N170 and N250 ERP amplitudes in reaction to face stimuli among schizophrenia patients were smaller than in controls. However, the majority of studies included both neutral and emotional faces, so reduced amplitudes of these ERPs might reflect impairments in face processing as well as in facial affect processing. Likewise, Feuerriegel et al. (2015) in their systematic review reported reduced N170 amplitudes among schizophrenia patients. Studies included in their review also involved both emotional and non-emotional face stimuli. The authors noted that revealed abnormalities were specific to facial expressions, but there was also some evidence for impaired configural processing of faces in patients with schizophrenia, such as N170 insensitivity in response to face inversion. Moreover, some psychopathological symptoms contribute to the impairment of various cognitive functions, which can bias the results of testing emotional and non-emotional face processing (Kontaxaki et al., 2014; Gur et al., 2017).

It is worth noting that abnormalities in facial identity and expression recognition are also documented in other psychiatric and neurological disorders, including Autism Spectrum Disorder (ASD). Feuerriegel et al. (2015) supposed that N170 differences in ASD were specific to certain types of facial information, as there were no consistent abnormalities in response to upright faces. Recently Kang et al. (2018) conducted meta-analysis and reported delayed N170 latencies in response to face stimuli in ASD. The authors assumed that attenuation of N170 amplitude and relative lag in N170 latency may also increase with age.

Findings from research on other disorders (alcohol dependence, bipolar disorder, attention deficit hyperactivity disorder, bulimia nervosa, mild cognitive decline, Huntington’s disease) showed that people suffering from these disorders almost always had smaller amplitudes or slower latencies in reaction to emotional faces compared to controls, regardless of diagnosis (Feuerriegel et al., 2015).

The aim of our review was to systematically assess EEG studies of face perception outside an emotional context in individuals with schizophrenia spectrum disorders.

2. Methods

2.1. Search strategy

We conducted an electronic search of the Pubmed/Medline database from inception to March 27, 2018. The search string used was “(eeg[Title/Abstract] OR electroencephalography[Title/Abstract] OR erp[Title/Abstract] OR N170[Title/Abstract] OR P100[Title/

Abstract] OR erp[Title/Abstract] OR event-related[Title/Abstract] OR (evoked[Title/Abstract] AND potential[Title/Abstract]) OR evoked-response[Title/Abstract]) AND (psychosis[Title/Abstract] OR schizophrenia[Title/Abstract] OR schizoaffective[Title/Abstract]) AND (face[Title/Abstract] OR facial[Title/Abstract])”.

2.2. Eligibility criteria

Only English-language articles were included. Articles were retained if they measured any ERPs or other EEG data in response to visual presentation of photographs or schematic face stimuli with neutral face expression, in the context of various conditions, in patients with schizophrenia spectrum disorders. Studies were excluded if there was no data analysis about neutral face expression, or if these data were not presented, or if they contained only data based on emotional faces.

All titles and abstracts identified in the search were screened to exclude obviously irrelevant articles. Full-text versions of all remaining articles were read and assessed for eligibility. The remaining articles were included in the review. The reference lists of all included studies were hand-searched for additional relevant reports.

2.3. Data extraction

The following data were extracted onto a customized sheet: participants (sample size, mean age, gender distribution, diagnosis, mean illness duration, scales used and inclusion/exclusion criteria), task (description of experimental task, stimuli used), and results regarding neutral face stimuli (ERPs and reported correlations between ERP measures and behavioural performance, scores of scales for ERP studies, and event-related changes reported for EEG studies). Furthermore, the Newcastle-Ottawa Scale (NOS) was applied to assess the quality of all included studies (Wells et al., 2000). Studies were evaluated by selection with a maximum of four points and comparability with a maximum of two points.

3. Results

A total of 113 articles were identified. After screening titles and abstracts 82 articles remained, of which 29 met the eligibility criteria. The article inclusion/exclusion process is shown in Fig. 1. Characteristics of patient samples, study characteristics and results are shown in Tables 1 and 2, respectively.

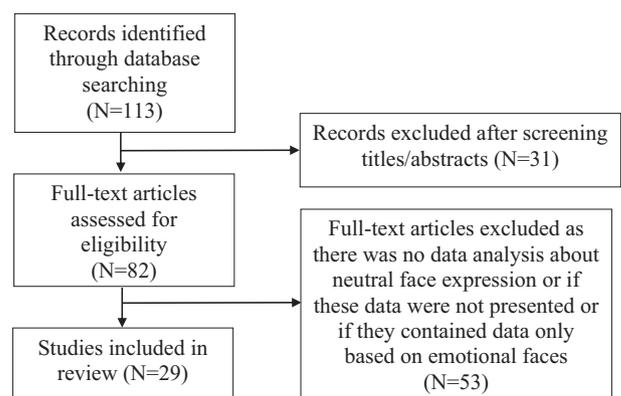


Fig. 1. Article screening and selection process.

Table 1
Characteristics of patient samples.

Study	Patient sample				
	N; gender	Mean age (years (SD))	Diagnosis	Mean illness duration (years (SD))	Symptom and social functioning scales
Batty et al. (2014)	“Low” group: 13 (f = 7) “High” group: 14 (f = 6)	“Low” group: 30.16 (9.69) “High” group: 24.45 (3.54)	Schizotypy	NR	O-LIFE scales *Groups were divided according to the O-LIFE Cognitive Disorganization dimension
Bediou et al. (2007)	10 (f = 4)	27.8 (8.4)	Schizophrenia	5.6 (6.4)	PANSS
Brennan et al. (2014)	108 (f = 38)	20.71 (2.91)	First onset psychosis: schizophrenia, schizophreniform disorder, psychosis not otherwise specified, schizoaffective disorder, bipolar disorder with psychosis, substance induced psychosis, major depressive disorder with psychosis, delusional disorder	NR	PANSS, CDSS
Caharel et al. (2007)	18 (f = 8)	37.7 (8.29)	Schizophrenia	13.6 (9.97)	NR
Campanella et al. (2006)	14 (f = 5)	47.7 (11.9)	Schizophrenia	NR	PANSS, Beck depression inventory *Groups were divided into 2 subgroups by total PANSS score
Csukly et al. (2014)	24 (f = 11)	34.2 (10.3)	Schizophrenia	9.7 (7)	PANSS, Symptom checklist 90
Dima et al. (2011)	20 (f = 4)	33.45 (10.2)	Schizophrenia	NR	PANSS
Guillaume et al. (2012)	20 (f = 3)	27.9 (6.5)	Schizophrenia	6.4 (4.9)	SAPS, SANS, STAI
Guillem et al. (2003)	RD + group: 17 (f = 6); RD– group: 21 (f = 5)	RD + group: 36.0 (11.7); RD– group: 40.4 (7.8)	Schizophrenia	RD + group: 9.3 (6.4); RD– group: 12.9 (7.6)	SAPS, SANS, BPRS *Groups were divided by their reality distortion score (hallucination and delusion SAPS subscales)
Herrmann et al. (2004)	24 (f = 5)	32.2 (10.0)	Schizophrenia	NR	PANSS
Johnston et al. (2005)	11 (f = 2)	30.4 (8.3)	Schizophrenia	NR	NR
Jung et al. (2012)	23 (f = 11)	32.2 (10.1)	Schizophrenia	5.2 (4.9)	PANSS
Kim et al. (2013)	23 (f = 11)	32.2 (10.1)	Schizophrenia	5.2 (4.9)	PANSS
Kim et al. (2015)	21 (f = 10)	37.57 (11.37)	Schizophrenia	NR	PANSS
Kirihara et al. (2012)	15	34.5 (6.8)	Schizophrenia	12.5 (5.6)	PANSS, NEO-FFI, GAF scale
Lee et al. (2010a)	25 (f = 13)	34.6 (12.6)	Schizophrenia	6.1 (5.6)	PANSS
Lee et al. (2016)	24 (f = 14)	34.67 (12.72)	Schizophrenia	8.7 (8.15)	PANSS
Liu et al. (2016)	17 (f = 1)	46.9 (9.66)	Schizophrenia	16.7 (9.19)	PANSS
Liu et al. (2018)	21 (f = 21)	34.48 (10.15)	Schizophrenia	8.47 (4.93)	PANSS
Maher et al. (2016)	20 (f = 9)	47.75 (12.38)	Schizophrenia, schizoaffective disorder	23.9 (8.5)	PANSS
Obayashi et al. (2009)	16 (f = 0)	32.9 (10)	Schizophrenia	9.9 (7.3)	SAPS, SANS, GAF scale
Onitsuka et al. (2006)	20 (f = 0)	Range: 20–55	Schizophrenia	NR	PANSS
Onitsuka et al. (2009)	17 (f = 0)	42.4 (10.8)	Schizophrenia	20.2 (11.8)	PANSS
Ramos-Loyo et al. (2009)	10 (f = 0)	30.2 (7.27)	Schizophrenia	NR	PANSS, BPRS
Tso et al. (2015)	28	Range: 18–60	Schizophrenia, schizoaffective disorder	NR	SAPS, SANS, BACS, WRAT3-R
Tsunoda et al. (2012)	15 (f = 7)	30.4 (3.2)	Schizophrenia	0.53 (0.3)	SAPS, SANS, SFS

Table 1 (continued)

Study	Patient sample N; gender	Mean age (years (SD))	Diagnosis	Mean illness duration (years (SD))	Symptom and social functioning scales
Turetsky et al. (2007)	16 (f = 4)	30.5 (6.0)	Schizophrenia	Male: 7.5 (5.5); female: 10.5 (8.3)	SAPS, SANS, BPRS
Yan et al. (2017)	25 (f = 10)	31.1 (10.8)	Schizophrenia	NR	PANSS, PSP
Zheng et al. (2016)	24 (f = 12)	32.3 (11.2)	Schizophrenia	8.7 (6.3)	PANSS

Comment: NR - not reported, SD - standard deviation, RD - reality distortion. PANSS - Positive and Negative Syndrome Scale, SAPS - Scale for the Assessment of Positive Symptoms, SANS - Scale for the Assessment of Negative Symptoms, BPRS - Brief Psychiatric Rating Scale, O-LIFE - Oxford-Liverpool Inventory of Feelings and Experiences, CDSS - Calgary Depression Scale for Schizophrenia, STAI - State-Trait Anxiety Inventory, WRAT3 - Wide Range Achievement Test 3, BACS - Brief Assessment of Cognition for Schizophrenia, NEO-FFI - NEO Five-Factor Inventory, GAF - Global Assessment of Functioning, PSP - Personal and Social Performance Scale, SFS - Social Functioning Scale.

3.1. Study characteristics

Twenty-seven studies compared one or more clinical groups against a control group, one compared two schizotypy groups (high vs. low, measured by O-Life scores) (Batty et al., 2014), and one assessed only a clinical group (Kim et al., 2013). All control groups were age- and sex-matched to clinical groups. The size of clinical groups varied between 10 and 25 participants, except one study which had 108 participants in control group and which had taken data from the Brain Resource International Database (Brennan et al., 2014). Mean age varied from 20.71 to 47.75 years. As for the diagnoses, 26 studies assessed only schizophrenia, others included schizophrenia and schizoaffective disorder (Tso et al., 2015; Maher et al., 2016), schizotypy (Batty et al., 2014) and first onset psychosis (Brennan et al., 2014). The main exclusion criteria were any history of neurological disease and substance abuse.

A variety of rating scales were used to assess symptoms and social functioning. The most widely used scale was the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) (21 studies). Other assessment tools included the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984) and the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983) (n = 6), the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962) (n = 3), the Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE) (Mason et al., 1995) (n = 1), the Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1990) (n = 1), the State-Trait Anxiety Inventory (STAI) (Spielberger and Sydeman, 1994) (n = 1), the Wide Range Achievement Test 3 (WRAT3-R) (Wilkinson, 1993) (n = 1), Brief Assessment of Cognition for Schizophrenia (BACS) (Keefe et al., 2004) (n = 1), NEO Five-Factor Inventory (NEO-FFI) (Costa and McCrae, 1992) (n = 1), the Global Assessment of Functioning (GAF) (American Psychiatric Association, 1994) (n = 2), the Personal and Social Performance Scale (PSP) (Morosini et al., 2000) (n = 1), and the Social Functioning Scale (SFS) (Birchwood et al., 1990) (n = 1).

Most of the studies focused on the ERP component N170 (n = 20). Other ERPs assessed in the studies were P100 (n = 12), N100 (n = 3), P200 (n = 3), N250 (n = 4), P300 (n = 8), P400 (n = 2), N400 (n = 3). Alterations in EEG bands were studied in 7 articles. Many studies probed more than one component; that explains why the sum of the number of studies is larger than the total number of papers reviewed.

Most of the studies did not find any significant correlations between medication dose and ERP amplitudes and latencies. Some studies did not analyse these correlations (Johnston et al., 2005; Bediou et al., 2007; Ramos-Loyo et al., 2009; Lee et al., 2010a; Dima et al., 2011; Brennan et al., 2014; Zheng et al., 2016; Yan et al., 2017; Liu et al., 2018).

The NOS scores of the included studies are presented in Table 3. Selection scores ranged from 0 to 3, and most of the studies were controlled at least for the most important factor.

We first grouped studies together by each component and reported the differences. Then we separated these studies by features. Data reported once were not included as incomparable.

3.2. Electrophysiological data

3.2.1. P100

Twelve studies assessed the P100 component (Herrmann et al., 2004; Johnston et al., 2005; Campanella et al., 2006; Bediou et al., 2007; Caharel et al., 2007; Turetsky et al., 2007; Obayashi et al., 2009; Jung et al., 2012; Kim et al., 2013, 2015; Batty et al., 2014; Liu et al., 2016). Regarding amplitudes, 9 studies revealed no differences (mainly measured at occipital electrodes) (Herrmann et al., 2004; Johnston et al., 2005; Bediou et al., 2007; Turetsky et al.,

Table 2
Study characteristics and results.

Study	Behavioural task	Stimuli	Results (patient group vs. healthy controls measured in response to neutral face stimuli unless otherwise specified)
Batty et al. (2014)	Button press to either an intact or disorganized face.	Mooney faces and neutral photographic faces (upright, inverted, upright disorganized, and inverted disorganized)	No significant differences between groups in P100 amplitudes and latencies and N170 latencies to upright faces. Significantly reduced N170 amplitudes to inverted photographic faces in “high” vs. “low” schizotypy groups. Attenuated face inversion effect both to photographic and Mooney faces in “high” group.
Bediou et al. (2007)	Count either male or female faces	Emotional and neutral faces	No significant differences in P100 and N170 amplitudes.
Brennan et al. (2014)	Passive viewing task	Emotional and neutral faces	Reduced N100 amplitude. Greater absolute magnitude of P300 amplitude.
Caharel et al. (2007)	Button press to either familiar or not face	Photographs of the subject’s own face, a face personally known to the subject, totally unknown faces (neutral and emotional)	Reduced P100 amplitudes and increased latencies. N170 amplitude reduction. Delayed N170 latencies.
Campanella et al. (2006)	Button press to target image (deviant face)	Emotional and neutral faces	Reduced P100, N170, P300 and N400 amplitudes in “high” vs. “low” group or HC. No significant differences in P100 and N170 latencies between groups.
Csukly et al. (2014)	Button press to categorize emotional expression on face	Neutral and fearful faces	No difference in N170 amplitudes and latencies.
Dima et al. (2011)	Make a decision whether the current stimulus was concave or convex	Ordinary objects (e.g. a chair), a mask, and faces of men and women	The decreased amplitude of P300 for 3D inverted faces compared to 3D normal faces in the patient group, while there was no difference in P300 amplitudes in HC.
Guillaume et al. (2012)	Indicate whether any face had been previously presented (old) or not (new)	Neutral faces against natural landscape	Weaker old-new effect modulation during the FN400 time window in the patient group.
Guillem et al. (2003)	Indicate whether any face had been previously presented (old) or not (new)	Unfamiliar faces	Less positive fronto-polar component of N300 in both patient groups; increased posterior lateral component in RD+, but reduced in RD– group. Reduced old-new effect modulation during the N400 time window in both clinical groups compared to controls.
Herrmann et al. (2004)	Silently classify images as a face or a building	Faces and buildings	No difference in P100 amplitudes. N170 amplitude reduction to faces, but not to buildings. Higher amplitudes of P200 regardless of used stimuli.
Johnston et al. (2005)	Count either male or female faces	Emotional and neutral faces	No significant differences in P100 and P300 amplitudes and latencies.
Jung et al. (2012)	Button press to an emotional face	Emotional and neutral faces	No significant differences in P100, N170, N250 and P300 amplitudes and latencies. No significant differences in source activation of these components using sLORETA.
Kim et al. (2013)	Button press to target image (happy or fearful face)	Emotional and neutral faces	Source localization using sLORETA: PANSS positive scores were negatively correlated with P100 source activation in the left temporo-parietal regions and with N170 and N250 source clusters in the middle or medial frontal gyrus for neutral face stimuli. The left fusiform gyrus showed negative correlation with PANSS negative scores in the P100 components regardless of emotion type.
Kim et al. (2015)	Button press to target image (chair)	BSF, LSF, and HSF pictures of fearful and neutral faces and chairs	No difference between groups in P100, N170, N250 and P300 amplitudes and latencies. Reduced P100 amplitude for HSF faces compared to BSF and LSF. Source localization using sLORETA: enhanced P100 activation of the medial frontal gyrus in the HSF neutral condition in the patient group. Significantly enhanced N170 activation for LSF faces compared to HSF faces in the right hemisphere in the patient group, while HC did not show these differences.
Kirihara et al. (2012)	Button press to target image (butterflies)	Emotional faces, neutral faces, cars, and butterflies	Not significant reduction of the N170 amplitude.
Lee et al. (2010a)	Button press to an emotional face	Emotional and neutral faces	Significantly lower gamma band activity in the 700 to 800 ms time window. Weak patterns of significant synchrony lines in schizophrenia patients.
Lee et al. (2016)	Button press to target image (butterflies)	Faces, chairs, nature scenes, and butterflies	Absence of the early-stage GBA preferential pattern for facial stimuli vs. non-facial stimuli and aberrantly increased early-stage GBA for all types of stimuli in the patient group. No significant intergroup differences in phase synchrony for either face or non-face stimuli.
Liu et al. (2016)	Button press to target image (monkey face)	Neutral human and primate faces	No difference between groups in P100 and P200 amplitudes and latencies. Reduced N170 amplitudes to face stimuli. Reduced P400 amplitudes.
Liu et al. (2018)	Mental count of the number of flowers	Faces (upright and inverted), tables (upright and inverted), flowers	No difference in the evoked power of the low-frequency β wave and the induced power of the γ wave under face and non-face conditions.
Maher et al. (2016)	Indicate on which side of the display the line drawing was present	Faces and trees line drawings of 0% contrast, perceptual threshold, two times perceptual threshold, and 100% contrast	N170 amplitude reduction.

Table 2 (continued)

Study	Behavioural task	Stimuli	Results (patient group vs. healthy controls measured in response to neutral face stimuli unless otherwise specified)
Obayashi et al. (2009)	1. Button press to target image (shoes) 2. Identify emotions using the BSF, HSF, and LSF pictures	BSF, LSF, and HSF pictures of happy, angry, fearful, and neutral faces and houses	No difference between groups in N170 latencies and P100 amplitudes or latencies. Bilateral face-specific N170 amplitude reduction. Lack of P100 and N170 amplitude enhancement in response to face stimuli of different spatial frequency in the patient group.
Onitsuka et al. (2006)	Button press to target image (butterflies)	Neutral faces, hands, cars, butterflies	Bilateral N170 amplitude reduction in response to faces, but not to cars.
Onitsuka et al. (2009)	Button press to target image (the female face).	Neutral male faces (unrepeated faces), one neutral male face (repeated face), and one neutral female face (target stimulus)	N170 amplitude reduction. No significant correlations between PANSS scores and N170 amplitudes. Reversed pattern of lateralization in schizophrenia patients.
Ramos-Loyo et al. (2009)	Button press to target image	Emotional and neutral faces	N100 amplitude reduction in prefrontal and inferior frontal regions. Not significant N170 amplitude increase in occipital regions. Significantly larger P200 component over the occipital areas in all of the tasks performed. Lower P300 amplitude in identity tasks. In the alpha band, the amplitude of oscillations was higher in occipital regions. No difference in the theta band between groups.
Tso et al. (2015)	Indicate whether the face was “looking at me” or “looking away from me,” and press corresponding button	Neutral and fearful faces with different head orientation (forward, 30° deviated), and gaze direction (direct, averted)	No significant differences in N170 amplitudes and latencies. A reduction of the normal N170 amplitude modulation by head orientation.
Tsunoda et al. (2012)	Button press to target image (butterflies)	Neutral faces (upright and inverted), cars, butterfly	Bilateral N170 amplitude reduction to images of faces. A reduced FIE of the N170 amplitude. Trend-level delayed N170 latencies to inverted objects.
Turetsky et al. (2007)	Button press to categorize emotional expression on face	Emotional and neutral faces	No difference in P100 amplitudes between groups. N170 and P300 amplitude reduction. Non-significant N250 amplitude reduction.
Yan et al. (2017)	Mental count of the number of flowers	Unfamiliar faces (upright and inverted), tables (upright and inverted), flowers	Reduced synchrony patterns in the gamma-frequency range in patients in the 150–300 ms interval during upright face perception.
Zheng et al. (2016)	Mental count of the images of flowers	Faces (upright and inverted), tables (upright and inverted), flowers	Reduced N170 amplitudes for all stimuli. Delayed N170 latencies in the patient group only under face-evoked conditions (both upright and inverted). A reduced FIE of the N170 amplitude.

Comment: LSF - low spatial frequency, HSF - high spatial frequency, BSF - broad spatial frequency, FIE - face inversion effect, RD - reality distortion, GBA - gamma band activity, PANSS - Positive and Negative Syndrome Scale, SAPS - Scale for the Assessment of Positive Symptoms, SANS - Scale for the Assessment of Negative Symptoms, GAF - Global Assessment of Functioning.

2007; Obayashi et al., 2009; Jung et al., 2012; Batty et al., 2014; Kim et al., 2015; Liu et al., 2016), two reported significant reduction (at P7, P8 (Caharel et al., 2007) and at O1, O2 electrodes (Campanella et al., 2006)), and one did not assess P100 amplitudes (Kim et al., 2013). Six studies reported no differences in P100 latencies (Johnston et al., 2005; Campanella et al., 2006; Obayashi et al., 2009; Batty et al., 2014; Kim et al., 2015; Liu et al., 2016), Caharel et al. (2007) reported increased latencies in the clinical group, and four studies did not assess the P100 latencies at all. Two studies assessed the effect of spatial frequency on P100 and found scattered differences in both groups (Obayashi et al., 2009; Kim et al., 2015). Three studies assessed and found no correlations with any social or symptom scales (Obayashi et al., 2009; Caharel et al., 2007; Batty et al., 2014). Three studies used a source localization tool (sLORETA). Among them, Kim et al. (2015) reported enhanced activation of the medial frontal gyrus in clinical groups compared to healthy controls (HC), Kim et al. (2013) found significant correlations between positive and negative PANSS and some source clusters, while Jung et al. (2012) did not find any link between PANSS and ERP sources.

3.2.2. N100

Three studies evaluated the N100 component (Ramos-Loyo et al., 2009; Brennan et al., 2014; Liu et al., 2016). Two of them revealed N100 amplitude reduction in frontal (Brennan et al., 2014), prefrontal, inferior frontal regions (Ramos-Loyo et al., 2009), and one study found more negative N100 in frontal than in fronto-central or central regions in patients with schizophrenia, with no difference between regions found in HC (Liu et al., 2016).

3.2.3. N170

Nineteen studies measured N170 amplitudes in response to upright faces, of which ten reported significant reduction compared to HC (Herrmann et al., 2004; Onitsuka et al., 2006, 2009; Caharel et al., 2007; Obayashi et al., 2009; Turetsky et al., 2007; Tsunoda et al., 2012; Maher et al., 2016; Liu et al., 2016; Zheng et al., 2016). Campanella et al. (2006) showed significant reduction in high-score vs. low-score schizophrenia patients' group (separated on the basis of their total PANSS score) or control group, two reported non-significant reduction (Kirihara et al., 2012; Batty et al., 2014), five did not reach significant differences between groups (Bediou et al., 2007; Jung et al., 2012; Csukly et al., 2014; Kim et al., 2015; Tso et al., 2015), and one reported a non-significant enhancement of N170 amplitude in patients with schizophrenia vs. HC (Ramos-Loyo et al., 2009). It is worth noting that all studies that included patient groups with mean age ≥ 37.7 years and with mean illness duration ≥ 13.6 years found N170 amplitude reduction in the patient group compared to HC (Campanella et al., 2006; Caharel et al., 2007; Onitsuka et al., 2009; Maher et al., 2016; Liu et al., 2016). Other studies included patient groups with mean age ≤ 37.57 years and with mean illness duration ≤ 12.5 years, and their results were not entirely consistent.

Nine studies examined correlations between N170 amplitudes and symptom or social scales. Six of these studies did not find any correlations between symptom scales (PANSS (Herrmann et al., 2004; Onitsuka et al., 2009; Kim et al., 2013; Zheng et al., 2016), SAPS/SANS (Kirihara et al., 2012; Tsunoda et al., 2012)). Maher et al. (2016) reported marginal correlation with negative

Table 3
Newcastle-Ottawa scale scores for included studies.

Newcastle-Ottawa scale scores for included studies	Newcastle-Ottawa scale scores for included studies	
	Selection	Comparability
Batty et al. (2014)	–	+ (IQ)
Bediou et al. (2007)	+	+ (age)
Brennan et al. (2014)	+++	++ (age, gender)
Caharel et al. (2007)	++	++ (age, gender)
Campanella et al. (2006)	++	+ (age)
Csukly et al. (2014)	++	++ (age, gender, education)
Dima et al. (2011)	+	++ (age, gender)
Guillaume et al. (2012)	++	++ (age, gender, SES)
Guillem et al. (2003)	++	++ (age, gender, parental SES)
Herrmann et al. (2004)	+	+ (education)
Johnston et al. (2005)	+++	++ (age, gender)
Jung et al. (2012)	+++	++ (age, gender, education)
Kim et al. (2013)	–	–
Kim et al. (2015)	++	++ (age, gender, education)
Kirihara et al. (2012)	++	++ (age, personality traits (NEO-FFI))
Lee et al. (2010a)	+++	++ (age, gender, education)
Lee et al. (2016)	++	++ (age, gender, education)
Liu et al. (2016)	++	++ (age, parental SES)
Liu et al. (2018)	+++	++ (age, gender, education)
Maher et al. (2016)	++	++ (age, gender, verbal IQ)
Obayashi et al. (2009)	++	++ (age, parental SES)
Onitsuka et al. (2006)	+++	++ (age, parental SES)
Onitsuka et al. (2009)	+++	–
Ramos-Loyo et al. (2009)	++	++ (age, education)
Tso et al. (2015)	+	++ (age, gender)
Tsunoda et al. (2012)	++	++ (age, parental SES)
Turetsky et al. (2007)	+	+ (age)
Yan et al. (2017)	+	–
Zheng et al. (2016)	+	+ (age)

Comment: SES - socioeconomic status.

PANSS, Campanella et al. (2006) showed positive correlation with positive PANSS, and Kim et al. (2013) revealed correlation between N170 source clusters and positive PANSS. In addition, three of the nine studies assessed correlations between N170 amplitudes and rating scales of social functioning. Tsunoda et al. (2012), Kirihara et al. (2012), and Obayashi et al. (2009) found negative correlation with SFS scores, NEO scores for extraversion, and GAF scale scores, respectively.

Eight studies assessed N170 latencies, of which six studies reported no significant interactions between groups (Campanella et al., 2006; Obayashi et al., 2009; Tsunoda et al., 2012; Batty et al., 2014; Kim et al., 2015; Tso et al., 2015) and two found delayed latencies (Caharel et al., 2007; Zheng et al., 2016).

Zheng et al. (2016) assessed correlations between N170 latencies and symptom scales and found positive correlations with positive and general PANSS.

Three studies assessed face inversion effect. All of them reported reduced N170 amplitudes in response to inverted faces in the clinical group compared to HC (Tsunoda et al., 2012; Zheng et al., 2016), or in high-score vs. low-score schizotypal group, where low-score schizotypal group showed a classic increase in amplitude to inverted relative to upright photographs (Batty et al., 2014). Zheng et al. (2016) found significantly delayed N170 latencies in response to inverted and upright faces, Tsunoda et al. (2012) revealed trend-level delayed latencies only to inverted faces, and Batty et al. (2014) did not find differences in response to inverted faces. Batty et al. (2014) also assessed the response to upright and inverted Mooney faces in high-score vs. low-score schizotypal groups. The low-score schizotypal group showed an increase in amplitude to upright relative to inverted Mooney faces, whereas high-score patients showed comparable N170 amplitude to Mooney faces in both orientations. Moreover, the authors found negative correlation between O-LIFE scores and the latency of the N170 for inverted Mooney faces.

Two studies assessed N170 abnormalities for spatial frequency (SF)-filtered neutral faces and found diverse significant interactions for both groups (Obayashi et al., 2009; Kim et al., 2015).

Tso et al. (2015) revealed decreased modulation of N170 amplitude by head orientation in patients with schizophrenia compared with HC.

Onitsuka et al. (2009) found a reversed pattern of lateralization of N170 repetition effect in schizophrenia patients (over the left hemisphere in schizophrenia patients and over the right in HC).

3.2.4. P200

Only three studies evaluated the P200 component, two of which found significantly larger amplitudes over occipital electrodes in the clinical group compared to HC (Herrmann et al., 2004; Ramos-Loyo et al., 2009), and Liu et al. (2016) reported no significant differences of P200 amplitudes between groups in visual condition; however, in the latter study P200 was measured over the fronto-central region.

3.2.5. N250

None of the four studies assessing N250 waveform found significant interactions of N250 amplitude or latency with the group types (Jung et al., 2012; Kim et al., 2013, 2015), and only Turetsky et al. (2007) reported a non-significant trend towards patients having reduced N250 amplitudes. However, Kim et al. (2013) found that PANSS positive scores were significantly correlated with source clusters in the middle or medial frontal gyrus.

3.2.6. P300

For the P300 component, two studies found significantly reduced amplitudes in the clinical group compared to controls (Turetsky et al., 2007; Ramos-Loyo et al., 2009) and one study in high-score vs. low-score schizophrenia patients' group/control group (Campanella et al., 2006). Three studies did not find any significant correlations (Johnston et al., 2005; Jung et al., 2012; Kim et al., 2015). Moreover, Brennan et al. (2014) observed greater P300 amplitudes in the first onset psychosis group compared to HC. Dima et al. (2011) investigated hollow mask illusion in patients and reported a decreased amplitude of P300 for the 3D inverted faces compared to 3D normal faces in the patient group, however, in the control group there was no difference between results for the 3D normal faces and 3D inverted faces.

3.2.7. P400

Liu et al. (2016) found reduced P400 amplitude in visual condition in fronto-central region in the clinical group. Guillem et al. (2003) assessed a control group and two clinical groups divided by reality distortion (RD) scores into RD+ and RD–, and found that a fronto-polar component was less positive in both patient groups; and a posterior lateral component was increased in RD+, but reduced in the RD– group. The former study included a patient group with mean age of 46.9 years and mean illness duration of 16.7 years. For the latter study these values were 36.0 and 9.3 for the RD+ group and 40.4 and 12.9 for the RD– group respectively.

3.2.8. N400

Campanella et al. (2006) evaluated the N400 component in their study. The task included one frequently repeated stimulus (face) and a number of deviant faces. The authors reported that low-score patients tended to display decreased N400 (measured at occipito-temporal sites (T5, Oz, T6)) in response to deviant faces as compared to controls, while in high-score patients this decrease was more significant. Guillem et al. (2003) reported a modulation of the old-new effect (i.e., when a subject makes old/new recognition judgements on presented stimuli) over posterior sites during the N400 time window, which was similarly reduced in both RD

+ and RD– groups compared to controls. [Guillaume et al. \(2012\)](#) assessed FN400 and revealed that the mid-frontal FN400 old-new effect was weaker and limited to a small topographic area (fronto-central) among patients as compared to controls, whereas there was no difference between groups at posterior sites (Cz and Pz). Mean age (27.9 years) and mean illness duration (6.4 years) in this study were the lowest among those that assessed N400.

3.2.9. Neural oscillations and phase synchrony

[Lee et al. \(2016\)](#) and [Liu et al. \(2018\)](#) found that the power of gamma band in schizophrenia patients was not modulated by the stimulus (i.e. face or non-face stimulus) in early-stage processing, however the “face effect” was still presented in schizophrenia patients in alpha band ([Liu et al., 2018](#)). In addition, [Lee et al. \(2016\)](#) reported aberrantly increased early-stage gamma band activity (GBA) either for face or non-face stimuli, significant correlation between negative symptoms and frontal GBA for non-face stimuli, and a lack of deactivation of GBA in the middle stage of visual processing (400–700 ms) in schizophrenia patients. [Liu et al. \(2018\)](#) also found that both control and clinical groups presented an inversion effect in gamma band, but the occipital area was deficient in schizophrenia patients. [Lee et al. \(2010a\)](#) reported significant differences in GBA in the 700 to 800 ms time window only, whereas it was lower in the clinical group. In addition, the gamma band activity measures of frontal, central and parietal areas were negatively correlated with the score for negative symptoms on the PANSS, and the number of hospitalizations in schizophrenia patients.

[Yan et al. \(2017\)](#) and [Lee et al. \(2010a\)](#) revealed that patients with schizophrenia exhibited reduced synchrony patterns in the gamma-frequency range in the early stage processing, while [Lee et al. \(2016\)](#) found no significant intergroup differences in phase synchrony for either face or non-face stimuli.

4. Discussion

In the last few decades it was shown that patients with schizophrenia can demonstrate cognitive deficit, in particular impairments in face recognition. In our review we assessed neuropsychological changes in the context of neutral face stimuli in schizophrenia spectrum disorders.

Unfortunately, many studies assess face stimuli of various emotional valence, and thus the results on face perception and emotion recognition cannot always be differentiated. Data are quite non-conclusive; however, results appeared more consistent and the difference between the patient group and HC were more pronounced among the studies that assessed older participants with longer disease duration (mean age >37.7 years old and illness duration >12.9 years) ([Guillem et al., 2003](#); [Campanella et al., 2006](#); [Caharel et al., 2007](#); [Onitsuka et al., 2009](#); [Liu et al., 2016](#); [Maher et al., 2016](#)). This conforms with the results of behavioral studies, although the latter assessed emotion recognition. For example, [Bortolon et al. \(2015\)](#) in their review reported deficits in patients with the mean disease duration varying from 11.40 to 18.80 years, while most other studies that included individuals at ultra-high risk for psychosis and early onset schizophrenia patients did not present deficits in face processing at the behavioural level ([Kucharska-Pietura et al., 2005](#)). More generally, [Silverstein et al. \(2014\)](#) showed that the group of patients with schizophrenia demonstrated more significant impairments in processing images of different spatial frequency than the first episode psychosis group at discharge from hospital.

A possible mechanism of the relationship between face perception impairments and illness progression could be assumed. Infe-

rior temporal gyrus has been shown to be important in the representation of visual shapes. The fusiform gyrus has been shown to be involved in face recognition. Significant reductions in grey matter density of the fusiform area occur even in patients with first episode schizophrenia ([Bangalore et al., 2009](#)). More generally, among treatment-naïve schizophrenia patients temporal and occipitotemporal grey matter volume decrease has been reported ([Guo et al., 2013](#)). In addition, grey matter volume atrophy progressed with illness duration, showing more reductions in temporal and occipital areas in later stages of the disorder ([van Haren et al., 2007](#); [Jiang et al., 2018](#)). According to source localization studies among healthy individuals, N170 elicited in response to face stimuli reflects activity of the fusiform gyrus and occipital cortex ([Herrmann et al., 2005](#); [Deffke et al., 2007](#)). Similarly, correlations of attenuated N170 amplitudes with decreased grey matter volume in the right fusiform gyrus among schizophrenia patients have been shown ([Johnston et al., 2005](#); [Onitsuka et al., 2006](#)).

Thus, it can be speculated that increasing impairments in face perception during illness progression are associated with progressive grey matter loss in the relevant brain areas and can be objectively assessed by neuropsychological methods. Future studies should recruit older participants with longer illness duration to clarify the precise changes in the neuropsychological picture.

Secondly, despite no consistent correlations with symptom scales, the studies that separated patient groups into two subgroups by severity (assessed by symptom scales) showed significant results for groups with more severe schizophrenia symptoms, while patients with mild disease more likely had no differences from HC ([Guillem et al., 2003](#); [Campanella et al., 2006](#); [Batty et al., 2014](#)), so it can be suggested that significant correlations appear just in more severe cases. Behavioural studies also show a tendency of the severity of schizophrenia symptoms to be linked to more pronounced face processing impairments ([Soria Bauser et al., 2012](#)), for instance, patients with higher severity of symptoms showed a weaker inversion effect ([Joshua and Rossell, 2009](#)). Moreover, the review of research on perceptual organization impairment showed a link to disorganized symptoms ([Silverstein and Keane, 2011](#)). However, we do have insufficient data to confirm or deny these results in our study. We conclude that future research should recognize this gap and investigate correlations with subscales in two or more patient groups separated by symptom severity.

Current neuropsychological results present within the context of neutral face stimuli, which supports the hypothesis of generalized deficit rather than only emotion recognition deficits. The most convincing data are shown for the N170 component. Our results are consistent with previous reviews ([Feuerriegel et al., 2015](#); [McCleery et al., 2015](#)) and confirm the reduction of N170 amplitude in patients. In two cases the N170 amplitude reduction was constantly reported. Reduction was clearly expressed while using tasks that compared responses to face and non-face stimuli (the HCs' response to face stimuli differed from other stimuli, while patients mostly had similar patterns for both kinds of stimuli). Likewise, face inversion effect in HC was characterized by higher amplitudes to inverted face stimuli than to upright ([Rossion and Gauthier, 2002](#)), but patients showed smaller amplitudes and delayed latencies. This is also supported by event-related EEG data such as phase synchrony and neural oscillations ([Yan et al., 2017](#); [Liu et al., 2018](#)). Accordingly, such tasks can be used in assessing face recognition deficit more effectively than just passive viewing tasks. However, there are still 9 out of 19 tasks that were not reported to correlate with significant reduction of N170 in schizophrenia patients. It can be attributed to the difference between experimental conditions that were not always well reported. For instance, some authors argued that N170 could be

modulated by the quality of attention in healthy participants (Jacques and Rossion, 2007; Feng et al., 2012), while Asgharpour et al. (2015) found that schizophrenia patients had decreased visual attention to neutral and emotional face stimuli. It was shown that in autism spectrum disorder N170 was affected by reference electrode location (Joyce and Rossion, 2005). Maurer et al. (2008) showed that N170 was affected by habituation. Moreover, Sel et al. (2015) stated that one's own facial expression of happiness can significantly modulate the N170 in response to neutral faces.

Facial emotions are also supposed to modulate N170 (Blau et al., 2007; Schacht and Sommer, 2009). Turetsky et al. (2007) showed that emotional faces elicited larger responses than the neutral faces. Caharel et al. (2007) reported that N170 amplitudes among schizophrenia patients were smaller for disgusted relative to smiling and neutral expressions, implying inadequate emotional reactions to negative emotions. Lee et al. (2010b) found that the N170 amplitude for happy and fearful emotions was significantly lower among schizophrenia patients than in normal control groups. Hence, the assessment of neutral face stimuli was aimed to exclude this factor.

ERP N170 is usually called “face-specific” potential (Yovel, 2016), while face recognition is one of the basic skills needed for effective social communication (Tsunoda et al., 2012). Thus, a link between N170 and social functioning can be supposed (Kucharska-Pietura et al., 2005; Earls et al., 2016), and this is supported by our results of significant correlations between N170 amplitude and social functioning scales. Therefore, future studies should assess the viability of using N170 as a neuropsychological index of social functioning. Moreover, social cognition training, even if aimed ultimately at teaching higher order social cognitive skills, should begin by addressing facial recognition deficits, modelling the bottom-up nature of social cognition (Ventura et al., 2013). It could be speculated that the N170 component may be tested as a neuropsychological assessment tool for evaluating the effectiveness of social cognition training methods.

The other component, N400 ERP, was originally used in language experiments and refers to “contextual expectancy”, where it has increased amplitudes for incongruent endings of sentences in healthy people (Olivares et al., 2015). When N400 ERP was used in the context of face stimuli, it was studied within the old-new effect (participants should decide whether the stimulus was presented before or not). Significant difference between patients and HC was seen in such tasks (Danker et al., 2008), where N400 amplitude was reduced in patients. Taking into account that abnormal N400 ERP component in schizophrenia is reported in language studies that rely on priming paradigms (Mohammad and DeLisi, 2013), this component cannot be interpreted as specific to face abnormality, but rather point to memory associated deficit (Kutas and Federmeier, 2011).

Our data on P100 in response to neutral face stimuli are inconsistent with the results of a recent meta-analysis of P100 in schizophrenia by Earls et al. (2016). These authors concluded that P100 amplitude while viewing neutral faces was greater in healthy controls than in patients. On the one hand, this meta-analysis had strict limitations on inclusion criteria, so fewer studies could be assessed, and such small samples can produce biased results. On the other hand, we cannot affirm the opposite point of view based on our data, therefore this should be studied in the future on larger samples.

Regarding other ERPs, there were too few studies for us to arrive at any definite conclusion on their usefulness; in addition, ERPs did not show consistent associations to neutral face stimuli in various studies. Further research should analyse them in view of other paradigms.

Our review was limited to neutral face stimuli with no limits to experimental tasks. Also, sample sizes in the majority of the included studies were very small. There was a lack of data about the disease: not all the studies provided information about the duration of illness, age at onset, severity of positive, negative and disorganized symptoms, and some studies even had no healthy controls (instead, patient groups with more severe vs. less severe symptoms were compared). Furthermore, antipsychotic medication could influence the amplitude of ERPs (Korostenskaja and Kähkönen, 2009; Su et al., 2012; Du et al., 2015). We cannot exclude this potential influence of medication, even though no significant correlations between medication dose and ERPs' amplitudes and latencies were reported in the included studies. The findings of this systematic review should be interpreted with caution owing to these limitations and to the heterogeneity of the studies' design that could have affected the results of the review. According to NOS scores we cannot exclude selection bias as well as a potential publication bias due to the fact that studies are more likely to be published if they produce positive findings, as well as selective reporting bias, as non-significant differences are less likely to be reported than significant ones.

5. Conclusions

The main findings of our review: (1) neuropsychological correlations of face recognition impairments are often revealed in older patients with schizophrenia spectrum disorders with longer disease duration; (2) neuropsychological studies show a tendency for association between ERPs and higher severity of symptoms; (3) among ERPs, N170 seems to be the most significant component with the potential to be used for evaluation of patients' present status, as well as for dynamic control of cognitive impairments, social functioning, and rehabilitation effectiveness.

Future research is needed with respect to age, illness duration, and division by disease type and symptom severity, to assess the neuropsychological changes in dynamics.

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Conflict of interest

None.

Contributors

Murashko: searching for articles, their primary screening, analysis of abstracts and full-text versions of articles, drafting the article. Shmukler: idea, analysis of the abstracts and full-text versions of articles, article editing.

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