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Late Electrophysiological Potentials and Emotion in Schizophrenia: A Meta-Analytic Review

THESIS

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by

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ABSTRACT OF THE THESIS

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Master of Arts in Social Ecology

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Introduction: There is mixed evidence about emotional processing abnormalities in schizophrenia and schizoaffective disorder, with trait self-reports and clinician ratings indicating significant differences between patients and controls, but studies of in-the-moment, self-reported emotional experience finding only small differences between these groups. The current meta-analysis synthesizes statistics from studies measuring the P3 and LPP, two event-related potential (ERP) components sensitive to attentional allocation, to examine whether patients exhibit ERP response abnormalities to neutral and valenced visual stimuli.

Methods: Standardized mean amplitudes and standard errors of P3 and/or LPP waveforms (300-2000 ms) in response to neutral and valenced images were calculated for 13 studies (total n=339 individuals with schizophrenia, 331 healthy controls).

Results: In response to neutral images, there were very small, non-significant differences in ERP amplitudes between patient and control groups (k=9; Hedges' g=-0.06, 95% CI: -055, 0.43, p=0.81). In contrast, patients showed a small, significant reduction in ERP amplitudes compared to controls in response to negative images (k=13; Hedges' g=-0.32, 95% CI: -0.59, -0.05,

p=0.02), and a small, but nonsignificant, reduction in amplitudes in response to positive images (*k*=7; Hedges' *g*=-0.27, 95% CI: -0.71, 0.18, *p*=0.24).

Conclusions and implications: The current review indicates that compared to controls, patients have slightly diminished P3 and LPP amplitudes in response to positive and negative stimuli. This small reduction may reflect decreased attention allocation, possibly indicating an abnormality during a distinct stage of early processing related to evaluating the motivational salience of a stimulus.

1. Introduction

It is widely reported that individuals with schizophrenia and schizoaffective disorder have emotional abnormalities compared to controls (Kring and Elis, 2013; Trémeau, 2006). These abnormalities can have a profound negative impact on the psychosocial functioning, wellbeing, and overall quality of life of patients (Kohler and Martin, 2006). However, there are mixed reports about the nature of emotional abnormalities in schizophrenia. Some comparisons indicate a similar response to valenced stimuli in patients relative to controls, whereas others report a decreased or increased response (Cohen and Minor, 2010; Kring, 1999; Trémeau, 2006). Clarifying the nature of emotional abnormalities in schizophrenia is a crucial step towards developing targeted and effective treatments that may lead to improved emotional functioning for individuals with schizophrenia.

The current meta-analytic review presents a comprehensive quantitative synthesis of studies that have applied the event-related potential (ERP) technique, an objective and direct measure of brain activity in response to stimuli, to elucidate the nature of emotional abnormalities in schizophrenia. Two specific ERP components, the P3 and late positive potential (LPP), are particularly valuable in the study of emotional functioning, as they reflect neural correlates of attentional allocation to emotional information (Hajcak et al., 2011) – a critical step in emotional regulation and emotional memory development (Gross, 2002; Talmi et al., 2007).

1.1. Emotion in schizophrenia

Emotional dysfunction in patients has been assessed in multiple ways, including in self-reports of trait affect and clinician ratings, where the differences between patients and controls are largest. However, recently, it has been suggested that people with schizophrenia have intact in-the-moment, self-reported experience of positive emotion compared to control participants

(Kring & Moran, 2008, but see Strauss, Visser, Lee, & Gold, 2017). In a meta-analysis of 26 studies that presented emotional stimuli, Cohen and Minor (2010) reported small differences between schizophrenia patients and controls in self-reported positive emotion (Hedges' D = -0.16). Importantly, this does not appear to be the result of insensitive measures for self-reported positive emotion, as other disorders associated with emotional abnormalities (e.g., major depressive disorder) do show significantly diminished positive responding compared to controls (Dunn et al., 2004; Sloan et al., 1997). At the same time, individuals with schizophrenia report high levels of trait negative emotion (Cohen et al., 2011), but it has also been suggested that patients show similar in-the-moment responses to negative stimuli as control participants (mean weighted effect size Hedges D' = 0.24; Cohen & Minor, 2010). Further, "ambivalent" emotional responses, characterized by some as the co-activation of both positive and negative emotion and by others as reports of feelings inconsistent with stimulus valence, have also been widely reported in schizophrenia (Bleuler, 1950; Docherty et al., 2015; Trémeau et al., 2009). These various findings have not yet led to a clear and unifying account of the extent to which people with schizophrenia experience emotion differently from healthy individuals. However, objective and direct measures of brain activity, such as event-related potentials (ERPs), could help reconcile these findings and identify mechanisms that contribute to aberrant emotional functioning in people with psychotic disorders.

The ERP technique offers a method of examining emotion processing that is complementary to self-report, clinician ratings, and behavioral methods. By synthesizing data across ERP studies of emotion processing in schizophrenia, we can elucidate one of the apparent conflicts in the literature: the finding that differences between patients and controls are greatest in self-reports of trait affect and clinician ratings of emotional dysfunction, whereas self-reports

of in-the-moment emotion experience show much smaller differences. ERP studies of emotional functioning employ mixed methodologies, including passive viewing tasks and tasks wherein participants must respond verbally or by pressing a button. Additionally, the majority of these studies have small samples, making it difficult to determine whether findings support the large effects observed in self-reports of trait affect and clinician ratings or whether they fall more in line with measures of in-the-moment emotional experience. Currently, there is no comprehensive review of this literature, and the present article is the first quantitative analysis to examine studies of ERP responses to visual emotional stimuli in individuals with schizophrenia and healthy controls. By systematically examining objective measures of emotional experience in individuals with schizophrenia, this work will lead to a better understanding of patients' emotional abnormalities. This can contribute to targeted interventions that improve emotional functioning and, consequently, improve quality of life for individuals with schizophrenia.

The purpose of the current review is to determine whether patients and controls differ in magnitude in response to neutral, positive, or negative stimuli on late ERP components (P3 and LPP). Late ERP components are typically associated with sustained increase in attention to emotional information in healthy individuals (Hajcak et al., 2010). Additionally, though several studies have examined responses to neutral and emotional stimuli, the actual size of the difference between patients and controls using more objective measures remains unclear. We therefore seek to clarify the effect of valence by investigating potential differences between responses to neutral, positively, and negatively valenced emotional images, as measured by late ERP components.

1.2. ERP associated with motivational salience: P3

The P3 component can be divided into the P3a and P3b, with the P3a typically signifying the orienting of attention to a novel stimulus, even among a stream of unattended stimuli (Näätänen and Kreegipuu, 2011). The P3b, on the other hand, is associated with the motivational salience of a stimulus, whether from intrinsic or extrinsic sources. The current review will focus on the P3b component (hereafter referred to as 'P3'), which generally appears as a positive deflection over Pz starting from 250-500 ms following stimulus presentation (Hajcak et al., 2011).

P3 studies have traditionally used nonemotional stimuli (e.g., *X*s and *O*s) in an oddball design comparing responses to infrequent 'targets' and frequent 'standard' stimuli (Polich, 2007). Research indicates that the amplitude of the P3 is modulated by motivation, such that task demands and proportion of targets to standards impact the magnitude of the response to target stimuli (Duncan-Johnson and Donchin, 1977; Hillyard et al., 1973). More recently, researchers have used the P3 to examine responses to emotional stimuli in similar oddball paradigms. The reason the P3 lends itself well to use in emotion studies is that emotional stimuli may serve as "natural targets," automatically capturing attention and requiring additional processing resources because of their emotional content (Hajcak et al., 2011). The inherent motivational salience of emotional stimuli allows researchers to include positive and negative images in P3 studies as an index of emotional responding.[1]

[1] Although the neural origins of the P3 are a subject of continued debate, evidence from functional magnetic resonance imaging (fMRI), electroencephalography (EEG) source localization techniques, and intracranial recordings have pointed to areas in the cerebral cortex, particularly the parietal and temporal lobes, as likely sources of the P3 (Polich, 2007). It is plausible that the P3 is generated from a neural circuit linking these parietal and temporal areas, reflecting the activation of attentional and working memory systems.

1.3. ERP associated with sustained emotional information processing: LPP

Another ERP component closely related to attentional allocation to emotional stimuli is the late positive potential (LPP). Appearing maximally over centro-parietal sites, the LPP is a positive-going waveform starting from 300-2000 ms post-stimulus and continuing for up to several seconds (Hajcak et al., 2011). Both pleasant and unpleasant stimuli elicit increased amplitudes of the LPP waveform compared to neutral stimuli in healthy individuals, especially in cases where the emotional stimuli are related to survival, injury, or death (e.g., images depicting erotica or mutilation; Briggs & Martin, 2009). The LPP appears to track with subjective arousal ratings, such that images rated as more arousing also elicit greater LPP amplitudes (Martin, Li, & Castro, under review; Weinberg & Hajcak, 2010). Because the LPP is considered to reflect the sustained attentional processing of motivationally relevant emotional stimuli, it may play an important role in the emotion deficits observed in schizophrenia.[2]

1.4. The current study

The goal of the current meta-analytic review was to establish whether there are significant differences in responses to neutral, positively, or negatively valenced visual stimuli in individuals with schizophrenia and schizoaffective disorder compared to healthy controls using the P3 and LPP waveform amplitudes. In addition, the current review investigated the role of other variables across studies and samples that may potentially moderate these effects, such as measurement approach, time window examined, task procedures, and image content (see Appendix C). These variables were chosen for moderator analyses, as they represent the task and participant characteristics often controlled in patient studies.

[2] Efforts to localize the origins of the LPP in the brain using fMRI and EEG techniques have led to the understanding that brain areas involved in emotional processing (i.e., ventrolateral prefrontal cortex, insula, and prefrontal cortex) may serve as potential LPP generators (Liu et al., 2012; Sabatinelli et al., 2013).

2. Materials and method

The current meta-analysis followed PRISMA guidelines (Moher et al., 2009) for transparent and replicable methods and findings. Please see Appendix A, Supplementary Table 1 for the PRISMA checklist.

2.1. Eligibility criteria for meta-analysis

Inclusion criteria for the current analyses were as follows: 1) the study included a sample of patients meeting DSM-III-R (American Psychiatric Association, 1987) or DSM-IV-TR (American Psychiatric Association, 2000) criteria for schizophrenia or schizoaffective disorder; 2) the study included a nonpsychiatric control sample (i.e., individuals with no history of psychopathology determined by a screening or diagnostic interview); 3) the stimuli used in the study included positively or negatively valenced visual images (e.g., faces, scenes, objects); 4) at least one of the ERP components of interest (P3 and LPP, from 300-2000 ms) was measured; 5) mean amplitudes or peak amplitudes were reported for the P3/LPP waveforms for patients and control subjects; 6) statistics were reported that allowed for calculation of effect size (standardized mean difference between groups) of P3/LPP ERP waveform amplitude (or the authors provided us with this information, upon request); and 7) study findings were reported in a peer-reviewed journal article in English. Studies were excluded if they did not meet inclusion criteria. There were no other exclusion criteria. The literature search took place between October 19, 2015 and August 3, 2017.[3]

[3] We used the Risk of Bias Assessment Tool for Nonrandomized Studies (RoBANS) (Kim et al., 2013) to evaluate risk of bias in individual studies. Two raters (M. Castro and E. Martin) completed independent ratings of each study with good inter-rater agreement (87% agreement, Cohen's kappa=0.66). Scoring discrepancies were resolved by consensus ratings (M. Castro and E. Martin). For the majority of studies, risk of potential bias was low. A summary of the RoBANS data can be found in Appendix A, Supplementary Table 2.

In response to the variability in ERP nomenclature across studies, we distinguished the P3 and LPP ERP components by time course and topography.[4]

2.2. Information sources, search terms, and study selection

We searched the online databases PubMed, PsycINFO, and Google Scholar for relevant studies using the following search terms: schiz* AND (EEG OR ERP) AND (P3 OR LPP OR late positive complex OR late positive component OR LPC OR late positivity) AND (emotion* OR affect*). The articles resulting from this search were examined for eligibility, and articles referenced by or referencing each article resulting from the computer search were also examined for eligibility for the meta-analysis. Furthermore, we contacted experts in the field with more than two articles identified in the keyword searches for any additional articles meeting our criteria. We contacted the corresponding author of the study when the information needed to calculate effect size was not reported in the article.[5] Figure 1 shows a PRISMA flow diagram of systematic search and study selection (Moher et al., 2009).

[4] The P3 was categorized as a positive-going waveform, recorded at midline parietal sites, that peaks approximately 300-500 ms following the presentation of a visual stimulus. Likewise, the LPP was categorized as a positive deflection, recorded at midline centroparietal sites, that is evident after 300 ms following the onset of a visual stimulus and that may continue for 2000 ms or more following stimulus presentation.

[5] All articles were examined for overlapping samples. When multiple articles were written by the same research group, samples were examined to ensure they were not overlapping. When articles reported responses to more than one image type (k = 11), the samples used were the same for all image types.

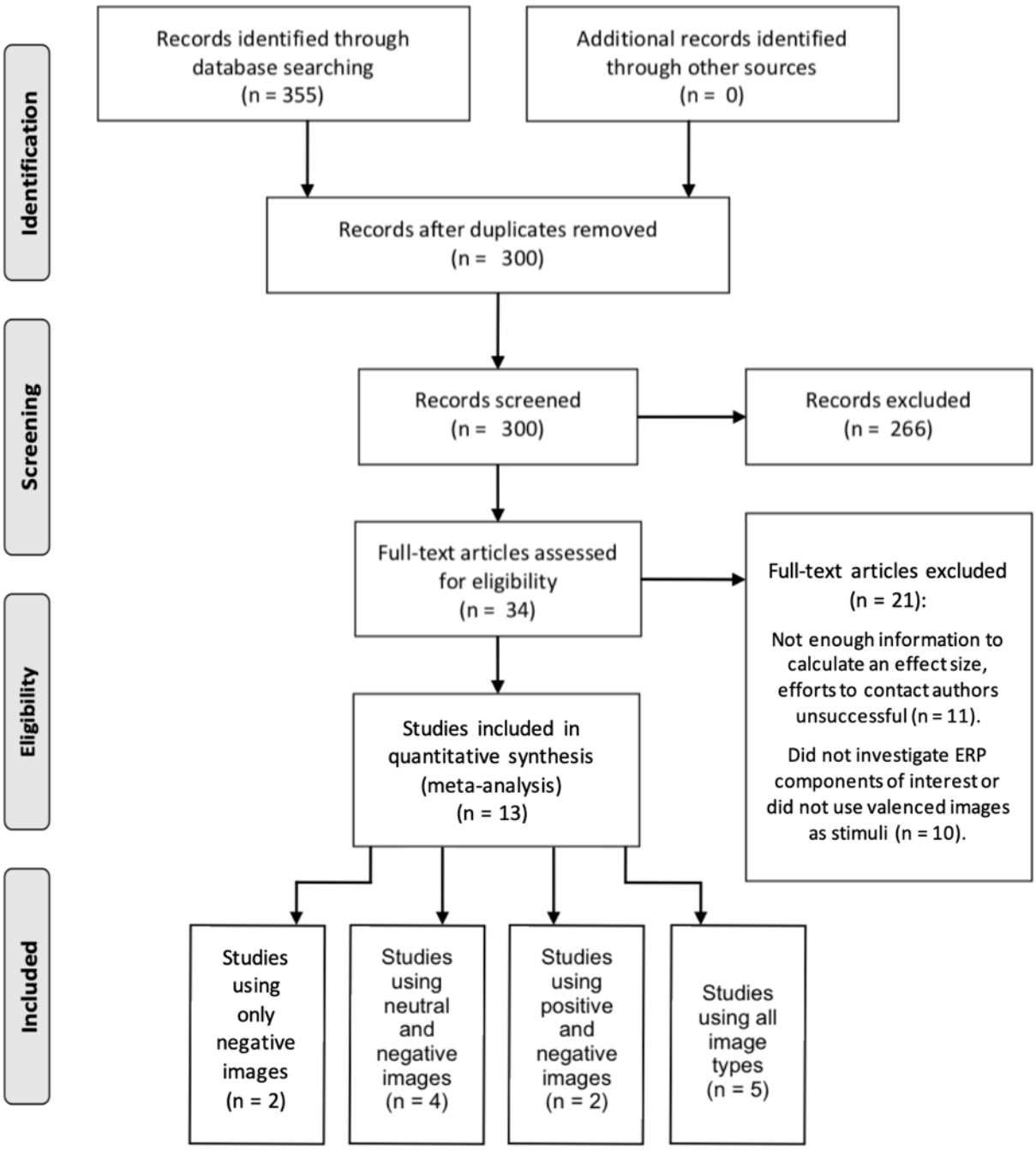

Figure 1. PRISMA flow diagram of systematic search and study selection (Moher et al., 2009).

2.3. Data analysis plan

The primary variables of interest were mean amplitudes of P3 and/or LPP waveforms to neutral, positive, or negative visual stimuli in individuals with schizophrenia compared to healthy controls. Standardized mean amplitudes, standard error, and 95% confidence interval (CI) of P3 and/or LPP waveforms were calculated for each study. All analyses were conducted in the statistical software program R (R Development Core Team, 2011), using the *metafor* package for meta-analysis (Viechtbauer, 2010).

Estimates were calculated using a random-effects model and the *Q* statistic was used to test for heterogeneity of the effect size distributions. Funnel plots graphing the effect sizes of each study against the study's sample size were created and Egger's regression test of funnel plot asymmetry was used to assess publication bias. Bias is unlikely in this analysis, as the contrast examined here is not the primary effect of interest in most of the included studies. For example, one study examined ERPs and empathic responses in patients (Corbera et al., 2014). The partitioned *Q* statistic was used to examine the effects of potential moderators.

3. Results

3.1. Characteristics of included studies and samples

Information about the characteristics of included studies is shown in Table 1 and Appendix C, Supplementary Table 3.[6]

[6] Information on medication dosing was reported in six studies, and symptom ratings were reported in seven studies. Patients were excluded based on history of neurological conditions (11 studies), head injury (five studies), current substance abuse (seven studies), or intellectual disability (six studies). Inclusion criteria for nonpsychiatric control samples included screening for DSM-IV-TR (American Psychiatric Association, 2000) Axis I psychotic conditions using a structured or semi-structured clinical interview (seven studies) and/or screening for DSM-IV-TR Axis II conditions (nine studies). Control participants were also excluded for recent history of substance abuse (seven studies), family history of psychotic disorder (five studies), history of neurological disorder (nine studies), or history of head injury (five studies).

Table 1
*Study Characteristics (*K = *13)*

	Demographic Data							
	Patients				Controls			
Study	*n*	Mean age (years)	Sex (% male)	Mean education (years)	*n*	Mean age (years)	Sex (% male)	Mean education (years)
An *et al.* (2003)	20	31.4 (8.8)	60	14.0 (2.1)	20	27.3 (7.1)	55	14.7 (2.1)
Andersen *et al.* (2015)	31	24.8 (5.2)	83.9	4.2 (1.6)	47	26.8 (7.0)	53.2	3.2 (1.4)
Corbera *et al.* (2014)	19	46.05 (9.37)	42	13.42 (2.12)	18	39.78 (8.61)	67	15.61 (2.59)
Herrmann *et al.* (2006)	22	31.7 (8.4)	77	10.3	22	31.9 (11.0)	77	9.9
Horan *et al.* (2010)	38	44.5 (10.6)	81.6	12.8 (1.5)	36	38.5 (10.3)	74.3	14.7 (1.5)
Horan *et al.* (2012)	35	48.3 (7.6)	74.3	13.2 (1.6)	26	44.9 (8.5)	73.1	14.5 (1.7)
Horan *et al.* (2013)	31	47.8 (9.8)	75	12.5 (1.9)	27	45.5 (6.7)	77.4	14.9 (1.3)
Jung *et al.* (2012)	23	32.2 (10.1)	52.2	12.8 (2.1)	24	38.0 (11.9)	50	13.0 (2.9)
Kim *et al.* (2015)	21	37.57 (11.37)	52.4	12.44 (2.33)	18	40.83 (12.07)	44.4	14.17 (4.13)
Lee *et al.* (2010)	38	30.2 (10.3)	42.1	13.0 (2.3)	38	34.2 (11.9)	47.4	14.1 (2.9)
Okruszek *et al.* (2016)	26	28.2 (6.4)	69.2	NR	21	24.7 (6.0)	71.4	NR
Turetsky *et al.* (2007)	16	30.5 (6.0)	75	12.5 (1.8)	16	28.1 (5.4)	75	17.1 (2.5)
Wexler *et al.* (2014)	19	46.05 (2.1)	42.1	13.4 (0.5)	18	39.7 (2.0)	66.7	15.6 (0.6)
Total	339	36.9 (8.5)	63.6	12.0 (2.6)	331	35.4 (7.0)	64.0	13.4 (3.7)

Note: Means are presented with accompanying standard deviations in parentheses. Totals are unweighted by sample size. NR: not reported.

3.2. Results for responses to neutral visual stimuli

The results for responses to neutral visual stimuli for the patient and control groups are summarized in Table 2, and a corresponding forest plot of the effect size and 95% confidence interval (CI) for each study is presented in Figure 2.

Table 2
*Effect Sizes for Differences Between Groups (*K = *13)*

			Responses to Neutral Images			*Responses to Positive Images*			*Responses to Negative Images*		
Study	SZ *n*	HC *n*	Hedges' *g*	Standard error	95% CI	Hedges' *g*	Standard error	95% CI	Hedges' *g*	Standard error	95% CI
An *et al.* (2003)	20	20	NA	NA	NA	-0.26	0.58	-1.40, 0.88	-0.92	0.50	-1.89, 0.05
Andersen *et al.* (2015)	31	47	-0.82	0.30	-1.41, -0.22	-1.42	0.49	-2.37, -0.46	-0.78	0.39	-1.54, -0.01
Corbera *et al.* (2014)	19	18	NA	NA	NA	NA	NA	NA	-0.23	0.60	-1.40, 0.95
Herrmann *et al.* (2006)	22	22	1.02	0.17	0.69, 1.35	NA	NA	NA	0.23	0.16	-0.09, 0.55
Horan *et al.* (2010)	38	36	-1.45	0.66	-2.75, -0.15	1.44	0.54	0.39, 2.50	-0.74	0.64	-2.01, 0.52
Horan *et al.* (2012)	35	26	-0.38	0.16	-0.70, -0.07	-0.24	0.19	-0.61, 0.14	-0.34	0.20	-0.73, 0.05
Horan *et al.* (2013)	31	27	-0.05	0.55	-1.13, 1.02	NA	NA	NA	-0.53	0.51	-1.54, 0.48
Jung *et al.* (2012)	23	24	-0.14	0.14	-0.42, 0.14	-0.51	0.15	-0.81, -0.22	-0.28	0.18	-0.63, 0.07
Kim *et al.* (2015)	21	18	1.59	0.63	0.35, 2.84	NA	NA	NA	1.12	0.52	0.10, 2.13
Lee *et al.* (2010)	38	38	NA	NA	NA	-0.10	0.12	-0.33, 0.14	-0.02	0.12	-0.25, 0.21
Okruszek *et al.* (2016)	26	21	NA	NA	NA	NA	NA	NA	-0.21	0.53	-1.26, 0.84
Turetsky *et al.* (2007)	16	16	-0.37	0.12	-0.61, -0.13	-0.45	0.13	-0.71, -0.20	-0.50	0.11	-0.73, -0.28
Wexler *et al.* (2014)	19	18	0.05	0.16	-0.26, 0.36	NA	NA	NA	-0.98	0.17	-1.32, -0.65
Total	339	331	-0.06; p = 0.8070	0.25	-0.55, 0.43	-0.27; p = 0.2425	0.23	-0.71, 0.18	**-0.32**; p = 0.0196	0.14	-0.59, -0.05

Note: SZ: individuals with schizophrenia. HC: healthy controls. CI: confidence interval. NA: not applicable. Positive Hedges' *g* values indicate studies wherein SZ responses were greater than HC responses. Bold value represents a statistically significant mean effect size across studies.

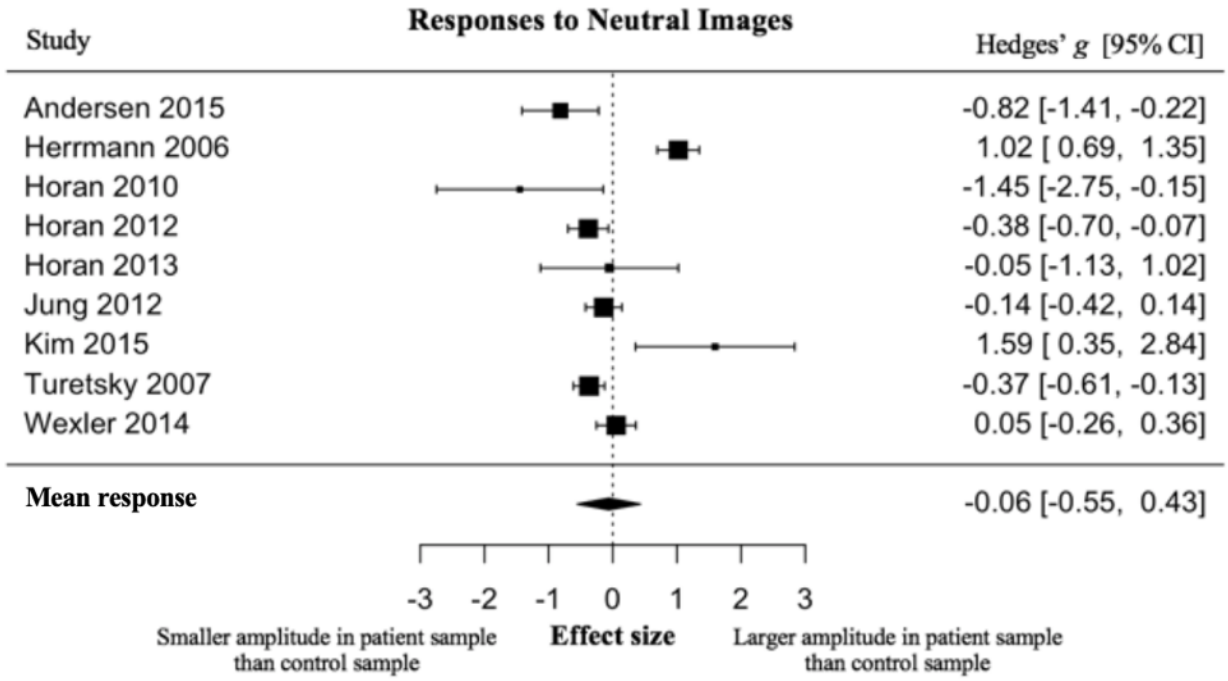

Figure 2. Forest plot of the effect size and 95% confidence interval (CI) for each study using neutral images.

As shown in Table 2, the weighted mean Hedges' *g* effect size of the nine studies examining responses to neutral images was not significant (Hedges' g = -0.06, p=0.807), and the distribution of effect sizes was significantly heterogeneous ($Q_{total}(8) = 70.45$, $p < 0.001$; $I^2 = 91.99\%$). The funnel plot appeared symmetrical (see Appendix B, Supplementary Figure 1), and Egger's test of funnel plot asymmetry was not statistically significant (z = -0.02, p = 0.98), suggesting limited influence of publication bias.

3.3. Results for responses to positive visual stimuli

The results for studies using positive images are shown in Table 2. A forest plot of the effect size and 95% CI for each study is presented in Figure 3.

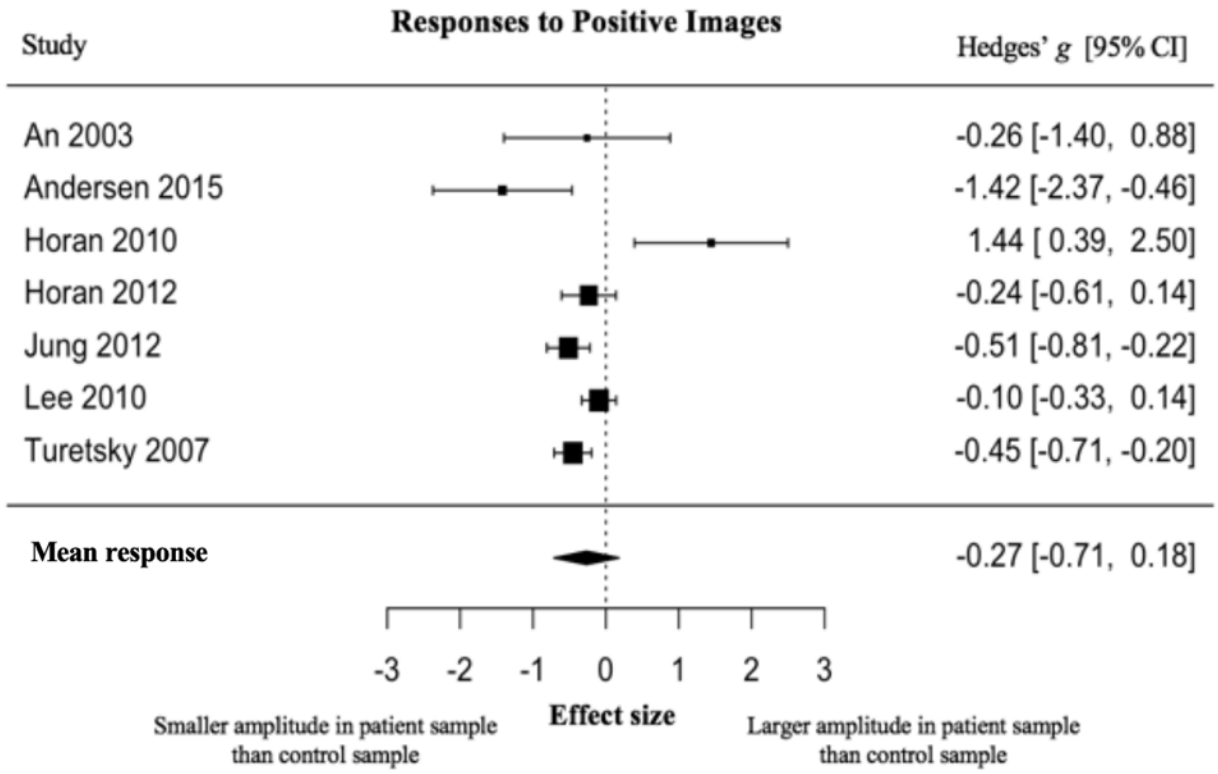

Figure 3. Forest plot of the effect size and 95% confidence interval (CI) for each study using positive images.

As can be seen in Table 2, the weighted mean Hedges' *g* effect size of the seven positive-image studies was not significant (Hedges' $g = -0.27$, $p = 0.242$), and the distribution of effect sizes was significantly heterogeneous ($Q_{total}(6) = 22.24$, $p = 0.0011$; $I^2 = 87.53\%$). The funnel plot appeared asymmetrical (see Appendix B, Supplementary Figure 1), but Egger's test of funnel plot asymmetry was not statistically significant ($z = 0.51$, $p = 0.61$), indicating that publication bias was unlikely to influence effect size.

3.4. Results for responses to negative visual stimuli

Table 2 shows the results for responses to negatively valenced visual stimuli for the patient and control groups. A forest plot of the effect size and 95% CI for each study is presented in Figure 4.

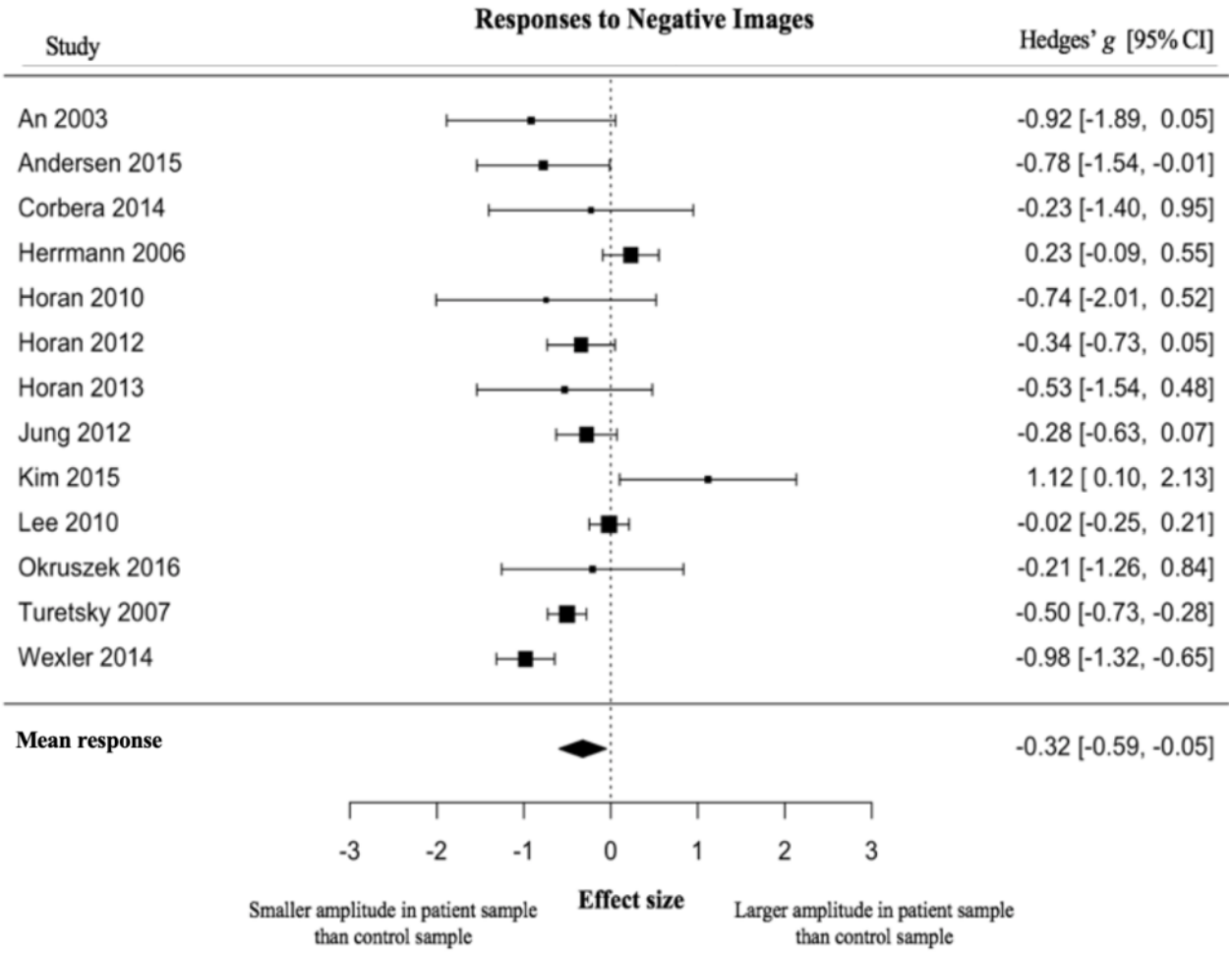

Figure 4. Forest plot of the effect size and 95% confidence interval (CI) for each study using negative images.

As seen in Table 2, there was a small weighted mean Hedges' *g* effect size of the 13 studies examining responses to negative images. The amplitude of the patient group was smaller than that of the control group, and the effect size was significantly different from zero (Hedges' $g = -0.32$, $p = 0.0196$). There was significant heterogeneity in the distribution of effect sizes ($Q_{total}(12) = 46.60$, $p < 0.001$; $I^2 = 75.47\%$). The funnel plot appeared mostly symmetrical (see Appendix B, Supplementary Figure 1). There was no evidence of a significant influence of publication bias, analyzed using Egger's test of funnel plot asymmetry ($z = -0.02$, $p = 0.98$).

For negative image studies, we conducted additional analyses of measurement approach, time window examined, task procedures, and image content as possible moderators. Though these results should be interpreted with caution given the small number of available studies, analyses indicated that measurement approach, time window examined, and task procedures did not account for proportion of heterogeneity of effect sizes. Image content did appear to be a significant moderator, with studies using other (non-face) images having smaller mean effect sizes than studies using images of faces, on average. More information regarding moderator analyses can be found in Appendix C and Table 3.

Table 3
Moderator Analyses

	*Studies Using Negative Images (*K = *13)*		
Moderator	*Q*	*p*	Effect size (SE)
Measurement approach	0.02	0.88	Mean: **-0.33 (0.18)** Peak: -0.20 (0.16)
Time window examined	1.64	0.20	Extended P3: **-0.58 (0.18)** Conventional P3: -0.18 (0.18)
Task procedures	0.40	0.53	Passive: -0.61 (0.40) Response: -0.30 (0.15)
Image content	**3.99**	0.04	Faces: -0.11 (0.19) Other: **-0.62 (0.16)**

Note: SE: Standard error. Measurement approach: whether the study used mean or peak ERP amplitudes. Time window examined: "extended P3," wherein the time window measured had minimal overlap (< 32%) with the conventional P3 time window (i.e., the majority of time measured was after 500 ms) or "conventional P3", wherein more than 32% of the total time window measured fell within the conventional P3 time window. Task procedures: whether study used a passive viewing or response required paradigm during ERP recording. Image content: whether study used images of faces only or used "other" images including people, objects, and scenes. Bold values represent statistically significant moderators.

4. Discussion

The results of this meta-analysis suggest a small possible disruption in attentional allocation to valenced visual stimuli in schizophrenia and schizoaffective disorder. At the same time, patients and controls responded almost identically to neutral stimuli, indicating a potential abnormality in early attentional allocation may be specific to valenced visual information. Based on the available information, the current findings have implications for how we conceptualize dysfunction in schizophrenia spectrum disorders.

4.1. Small, nonsignificant differences between patients and controls to neutral visual stimuli

The present analyses found a very small, nonsignificant difference between the P3 and LPP responses of patients with schizophrenia or schizoaffective disorder and healthy controls in response to neutral visual stimuli. Thus, as opposed to evidence of increased amygdala activation to neutral stimuli in individuals with schizophrenia (Kring and Barch, 2014; Kring and Elis, 2013) or self-reports of higher positive and negative emotion coactivation in response to neutral stimuli compared to controls (Cohen and Minor, 2010), the results from this meta-analysis suggest similar early attentional allocation to neutral stimuli between the groups. Given that some techniques (i.e., functional magnetic resonance imaging, self-report) assess functioning at different stages of emotion processing (Berkman et al., 2014), they may allow for biases and beliefs about emotion to influence responses. This is in contrast to ERP measurement, which is a more direct assessment of early attention (Hajcak et al., 2010) that is less likely to be influenced by beliefs. These findings taken together suggest that there may be a distinct time course of emotion abnormities in schizophrenia.

In general, it would be important for researchers to incorporate a neutral condition that is methodologically consistent with other conditions when investigating responses to emotional

stimuli in future studies. Studies examined for this review were not always consistent in their conceptualization and measurement of responses to neutral and emotional stimuli. As a result, only studies with neutral conditions that were procedurally similar to emotion conditions were included in the analyses (k = 9). Differences between task procedures for neutral and emotional stimuli may complicate efforts to distinguish results related specifically to the emotional nature of stimuli. Including neutral stimuli and maintaining consistent task procedures across stimulus types makes it possible to draw more robust conclusions about whether differences between patients and controls actually reflect a deficit specific to emotion processing, or whether patients show an overall blunting of ERPs in response to visual stimuli. However, the current finding that both groups show similar responses to neutral images suggests that individuals with schizophrenia have relatively intact processing through the first several thousand milliseconds of viewing for neutral stimuli, and that any abnormalities found in response to emotional images (i.e., positive or negative images) may be attributable to the specifically emotional nature of those images.

4.2. Small, nonsignificant reduction in response to positive visual stimuli in patients

The current meta-analysis found a small, nonsignificant reduction in response to positively valenced visual stimuli for individuals with schizophrenia or schizoaffective disorder compared to healthy controls. Although nonsignificant, the effect size was of similar magnitude as the size of the difference between patients and controls in response to negative image studies. It is possible that, while the effect sizes were similar for positive and negative image studies, the current analysis had insufficient power to detect significant differences in the case of positive image studies because there were fewer available studies to include in the analysis (Gelman and Stern, 2006). Thus, the fact that positive and negative image studies had similar effect sizes may

be more meaningful than the fact that only responses to negative images were statistically significant.

The finding of a small reduction in response to positively valenced images for individuals with schizophrenia is largely consistent with literature indicating no differences between patients and controls in self-reported positive affect in response to positive stimuli (Cohen and Minor, 2010), and also supports the theory that in-the-moment positive emotion is largely intact in people with schizophrenia (Cohen et al., 2011; Gard et al., 2007; Kring and Moran, 2008; Strauss et al., 2017).

Although current findings suggest only a small abnormality with respect to attentional allocation to positive stimuli, differences regarding positive emotions between individuals with schizophrenia spectrum disorders and healthy controls may emerge at later stages of processing. For example, a deficit in sustained (as opposed to initial) attention to positive information may be related to findings that schizophrenia is associated with memory impairment for emotional experiences, particularly over long time periods (Herbener, 2008). This is because sustained attentional allocation involves "embellishing" stimuli and linking them to other information (Anderson, 2005), deepens encoding of to-be-remembered information (Anderson and Reder, 1979). This process, sometimes referred to as elaborative processing, persists for a minimum of several seconds (e.g., Martin, Siegle, Steinhauer, & Condray, 2018; Siegle, Condray, Thase, Keshavan, & Steinhauer, 2010) and results in more durable and easily recalled memories than non-elaborated material (Anderson, 2005; Craik and Lockhart, 1972). Thus, impaired sustained attention to positive information could contribute to a downstream deficit in memory for emotional information in schizophrenia. Relatedly, deficits in memory encoding and retrieval (Strauss and Gold, 2012), as well as abnormal elaborative processing (Martin et al., 2018), have

been linked to low-pleasure beliefs, or beliefs that one does not generally experience pleasure or that certain activities and events are not pleasurable. Low pleasure beliefs have been associated with anhedonia (Yang et al., 2018) and may partially account for the findings that individuals with schizophrenia report diminished experience of positive affect compared to healthy individuals (Kring and Moran, 2008). Self-reported desires to attend to or ignore emotions also show large differences between patients and controls (Martin et al., 2013), which supports the theory that subjective awareness of attentional allocation (to a sufficient extent such as to allow self-report) may become most apparent later in processing, when these downstream differences arise.

4.3. Small reduction in response to negative visual stimuli in patients

The findings of the current analysis indicate that patients showed a small, significant reduction in attention allocation to negative images compared to controls. At the same time, individuals with schizophrenia or schizoaffective disorder consistently report higher levels of negative emotion compared to control participants (Horan et al., 2008; Trémeau, 2006). Considering these results together, it is possible that because patients have significantly higher trait negative affect, they allocate less attention to negative information because it is their "norm." That is, given that their baseline level of negative affect is already high, negative stimuli do not capture their attention in the same way as they do for control participants. Consistent with this theory, it is widely reported that individuals show diminished responses to familiar stimuli across a variety of biological systems (Bradley et al., 1993). Thus, it is possible that patients do not allocate attention to negative stimuli to the same extent as control participants, because the stimuli lack the same novelty.

Consistent with the current findings for schizophrenia, blunted P3 and LPP waveforms to negative stimuli have been reported in groups at risk for psychopathology as well as in individuals already diagnosed with a disorder. For example, Strauss and colleagues (2018) found diminished LLP amplitudes in individuals who are at ultra high-risk for psychosis. A similar finding has also been reported for individuals at risk for depression (Kayser et al., 2017) and those with psychopathic traits (Medina et al., 2016). Additionally, individuals with major depression (Foti et al., 2010) or non-psychotic bipolar I disorder during an episode of mania (Ryu et al., 2010) show reductions in these later ERP components in response to unpleasant stimuli. Thus, measures of attentional allocation to negative stimuli may indicate risk for or current psychopathology.

4.4. Limitations and conclusions

Despite adherence to the PRISMA guidelines (Moher et al., 2009) for transparent and replicable methods and findings, there are some limitations to the current review. Unpublished manuscripts were solicited, but no manuscripts eligible for inclusion were found, and information required for inclusion was not available for all eligible studies. Additionally, there were insufficient details regarding sample characteristics, such as symptom levels, duration of illness, functional impairment, and medication dosage information, to test these as potential moderators across all studies. These may be potential sources of the significant heterogeneity of the effect size distribution detected in response to all image types. Additionally, the results generalize only to adult populations, as none of the included studies involved participants under the age of 18.

Despite these limitations, the current review is the first to show that initial attention allocation to positive and negative images is slightly diminished in schizophrenia and

schizoaffective disorder. The size of the difference between patients and controls for valenced stimuli was small, with patients showing slightly blunted ERP waveforms. The disruption of attention allocation to valenced stimuli, coupled with the finding of intact early-stage responding to neutral images, suggests that impaired initial allocation of attention may be specific to valenced stimuli in schizophrenia. Thus, the analysis presented here contributes to furthering the current understanding of abnormal emotional processing in schizophrenia spectrum disorders.

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Appendix A

PRISMA Checklist and Risk of Bias Assessment

Supplementary Table 1. PRISMA checklist for transparent and replicable methods and findings.

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5, 7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	9
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	9
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	9, Figure 1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	9-10
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8, Supple-mentary Table 2
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9-10
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	11-12
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	10-12
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Supple-mentary material (moderator analyses)
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10, Tables 1, 2, 4
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Supple-mentary Table 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 2, Figure 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10-12, Table 2, Figure 2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10-12
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Supple-mentary material (moderator analyses); Table 3
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12-17

Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12-17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	NA

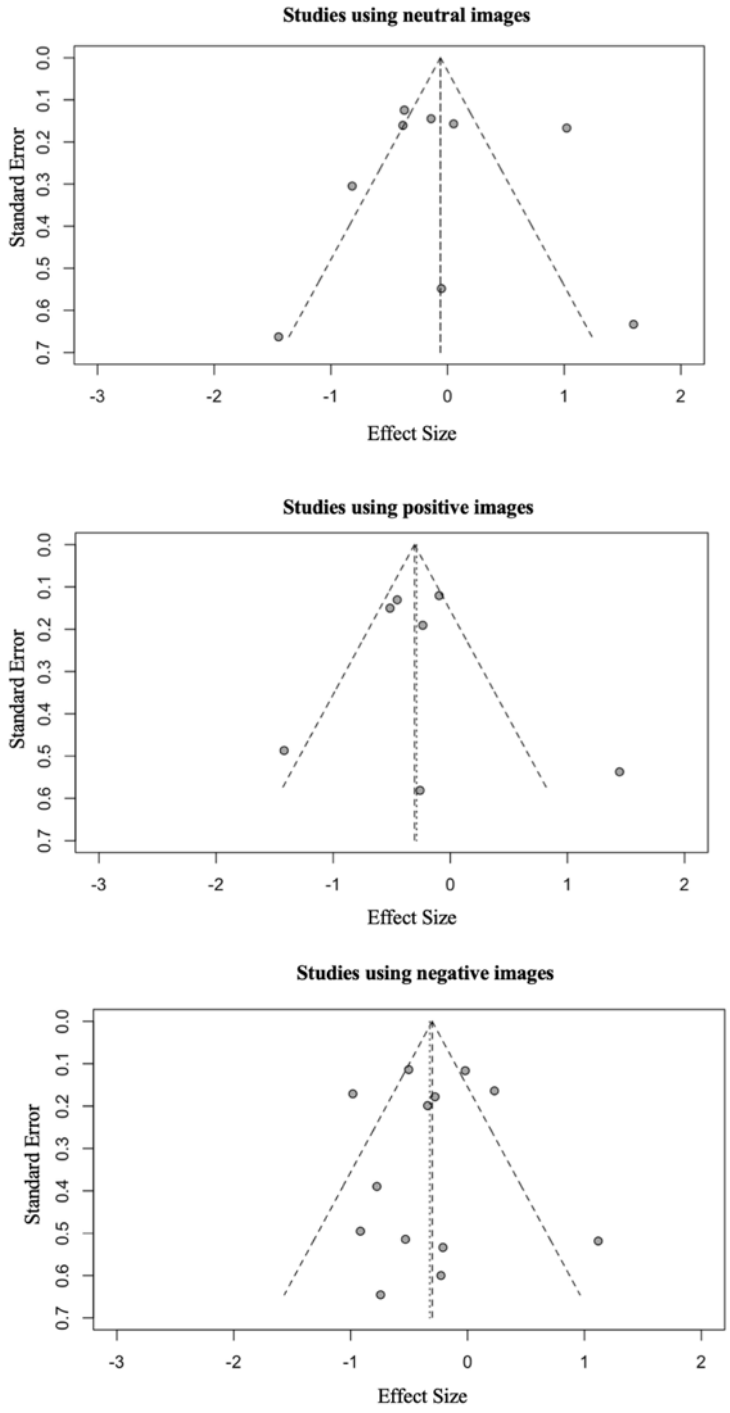
Supplementary Table 2. Risk of Bias Assessment Tool for Nonrandomized Studies (RoBANS; Kim et al., 2013) ratings of potential for bias within studies.

Study	1. Selection of participants	2. Confounding variables	3. Measurement of exposure	4. Blinding of outcome assessment	5. Incomplete outcome data	6. Selective outcome reporting
An et al. (2003)	LR	LR	LR	UR	LR	LR
Andersen et al. (2015)	UR	LR	LR	UR	LR	LR
Corbera et al. (2014)	LR	LR	LR	UR	UR	LR
Herrmann et al. (2006)	UR	LR	LR	UR	UR	LR
Horan et al. (2012)	LR	LR	LR	UR	LR	LR
Horan et al. (2013)	LR	LR	LR	UR	UR	LR
Horan et al. (2010)	LR	LR	LR	UR	LR	LR
Jung et al. (2012)	LR	LR	LR	UR	UR	LR
Kim et al. (2015)	LR	LR	UR	UR	UR	LR
Lee et al. (2010)	LR	LR	LR	UR	UR	LR
Okruszek et al. (2016)	UR	LR	LR	UR	LR	LR
Turetsky et al. (2007)	LR	LR	LR	UR	UR	LR
Wexler et al. (2014)	LR	LR	LR	UR	LR	LR

Note: LR: low risk. UR: unclear risk. Inter-rater reliability of RoBANS ratings: 87% agreement; Cohen's kappa=0.66; SE of kappa=0.10; 95% CI: 0.475, 0.855; strength of agreement considered 'good.'

Appendix B

Funnel Plots for All Included Studies



Supplementary Figure 1. Funnel plots of effect sizes.

Appendix C

Moderator Information and Analyses

1. Moderators examined

Each article was coded for several experimental and sample-level variables that could serve as potential moderators (coding workbook available from the corresponding author upon request). Based on the information accessible from the articles (or from the authors directly, when the information was not presented in the article), the following variables were tested as moderators: ERP extraction method (mean vs. peak amplitude); time window measured in the study (300-500 ms vs. 300-2000 ms and beyond, corresponding to conventional definitions of the P3 and LPP components, respectively); type of task (passive viewing vs. response required); and stimulus image content type (faces only vs. other images, including people, objects, and scenes). There were insufficient data to test symptomatology, duration of illness, or parental education level as potential moderators. Importantly, none of the included studies examined ERP responses in individuals under the age of 18. For this reason, the current findings apply only to adult populations.

2. Results of moderation analyses

To test for the effects of potential moderators on effect size, we conducted several subsequent analyses. However, all moderator analyses should be interpreted with caution, given the small number of included studies. We examined moderators only for responses to negatively valenced stimuli, as there were not enough studies examining responses to neutral or positive stimuli to conduct moderation analyses (The Cochrane Collaboration, 2011).

As seen in Table 3, measurement approach used in the study, examined as mean amplitude (k = 10) vs. peak amplitude (k = 3), was not a significant moderator. Additionally,

time window measured in the study, calculated as percentage of overall time window falling within the conventional P3 time window (300-500 ms), did not account for a significant proportion of the heterogeneity of effect sizes. Similarly, task procedures, calculated as passive viewing (k = 2) vs. response required (k = 11), was not a significant moderator for studies using negative stimuli

Lastly, the content of stimulus images used in the study, comparing studies that used images of faces only (k = 6) with studies using any other types of images (e.g., International Affective Picture System (Lang et al., 2008) slides of people, objects, and scenes; k = 7) did account for a significant proportion of the heterogeneity of effect sizes (see Table 3; amount of heterogeneity accounted for, R^2 = 34.98%; $Q_{\text{Content}}(1) = 3.99$, $p = 0.046$). Studies using other (non-face) images accounted for this moderation effect, as they had smaller mean effect sizes than studies using images of faces, on average.

3. Discussion of moderation effects

Measurement approach was not a significant moderator in studies using negative images. Twelve studies measured mean amplitude, while only three measured peak amplitude. As a result, there may not have been enough studies measuring peak amplitude to detect a potential moderating effect of measurement approach. Percentage of overall time window falling within the conventional P3 time window also did not account for a significant proportion of the heterogeneity of effect sizes. Task procedures, defined by whether studies used passive viewing or response required tasks, similarly was not a significant moderator for studies using negative images.

The final moderator examined was the content of stimulus images used in the study. For studies that used images of faces only, the mean effect size was larger than for studies using

other types of images (i.e., pictures of people, objects, and scenes). This finding supports an earlier meta-analysis of studies examining ERPs to emotional images of faces (McCleery et al., 2015), which found that individuals with schizophrenia show a significant disruption of ERPs associated with early sensory processing of emotional face images compared to healthy controls. This impairment has been identified at the behavioral level, as well (Kohler et al., 2010; Savla et al., 2013), and may be related to the marked deficit in social cognition associated with schizophrenia.

Of note, a number of other patient characteristic factors that might be related to ERP component amplitude were not able to be tested in the current meta-analysis because too few studies that reported this information. In particular, data regarding duration of illness and level of functional impairment would be informative, as these variables have been previously linked to emotional experience, emotional expression, and social functioning in schizophrenia and schizoaffective disorder (Martin et al., 2015; Mueser et al., 1996; Shtasel et al., 1992). Thus, future research should aim to report this information in order to test for such moderation effects.

Table 4
*Additional Study Details (*K = *13)*

	Procedures, Stimuli, and Patient Characteristics							*EEG Recording and Processing*			
Study	Task type	Task details	Image content type	Image details	Mean image ratings: valence	Mean image ratings: arousal	Mean symptom ratings	Measure-ment approach and electrodes	Time windows (ms)	Offline reference electrodes	Filtering
An *et al.* (2003)	Response required	Button press for targets	Faces only	Negative and positive faces	NR	NR	PANSS pos 18.4 PANSS neg 16.3 PANSS gen 35.4	Peak amplitudes; Pz	250-500	NR	Online: Bandpass 0.16-30 Hz
Andersen *et al.* (2015)	Response required	Button press for targets and other stimuli	Other	Neutral, negative, and positive IAPS: Objects, activities, violence, mutilation, disease, animals	Neutral: 5.24 Negative: 2.32 Positive: 7.01	Neutral: 3.28 Negative: 6.44 Positive: 4.21	SOPS gen 5.4	Mean amplitudes; Pz	350-500 500-650 650-800	NR	Online: Bandpass 0.15-70 Hz, Notch 60 Hz Offline: Low-pass 15 Hz
Corbera *et al.* (2014)	Response required	Button press for "pain" versus "neutral" images	Other	Painful hands (accident or injury) and neutral hands (matched situation without injury)	Neutral: <1.25 Negative: >2.5	NR	PANSS pos 11 PANSS neg 10.9 PANSS gen 18.9	Mean amplitudes; Cz Pz	350-550 550-700 700-900	Average mastoids	Online: Bandpass 0.1-40 Hz
Herrmann *et al.* (2006)	Response required	Verbalize judgment of emotional expression	Faces only	Neutral faces and negative (anger, disgust, fear) faces	NR	NR	PANSS pos 10.7 PANSS neg 24.1 PANSS gen 17.1	Mean amplitudes; Fz Cz Pz	301-648	Average	Online: Bandpass 0.1-70 Hz

Table 4 (Continued)
*Additional Study Details (*K *= 13)*

	Procedures, Stimuli, and Patient Characteristics							*EEG Recording and Processing*			
Study	Task type	Task details	Image content type	Image details	Mean image ratings: valence	Mean image ratings: arousal	Mean symptom ratings	Measure-ment approach and electrodes	Time windows (ms)	Offline reference electrodes	Filtering
Horan *et al.* (2010)	Passive viewing	Simply viewing images	Other	Neutral, negative, and positive IAPS: People, scenes, animals, injuries, crime, erotica	Neutral: 4.92 Negative: 2.95 Positive: 7.65	Neutral: 3.07 Negative: 5.83 Positive: 5.09	SANS aff 2.2 SANS alog 1.0 SANS avol 3.1 SANS anhe 2.9	Mean amplitudes; Fz Cz Pz	250-500 500-1000	Left and right mastoids	Online: Bandpass 0-100 Hz Offline: Low-pass 20 Hz
Horan *et al.* (2012)	Response required	Silent counting targets among standards and affective pictures	Other	Neutral, negative, and positive IAPS	NR	NR	BPRS total 41.4	Mean amplitudes; CPz C1 Cz C2 FCz	400-1000	Average	Offline: Bandpass 0.1-30 Hz
Horan *et al.* (2013)	Passive viewing	Audio description of each image followed by passive viewing	Other	Neutral and negative IAPS: People, scenes, animals, accidents, injuries, crime, insects	Neutral: 5.05 Negative: 2.82	Neutral: 2.91 Negative: 5.71	BPRS total 36.7	Mean amplitudes; C1 C2 Cz CPz CP1 CP2	300-600 600-1000 1000-1500 1500-2000	Average	Online: Bandpass 0-100 Hz Offline: Bandpass 0.1-30 Hz

Table 4 (Continued)
Additional Study Details (K = 13)

	Procedures, Stimuli, and Patient Characteristics							*EEG Recording and Processing*			
Study	Task type	Task details	Image content type	Image details	Mean image ratings: valence	Mean image ratings: arousal	Mean symptom ratings	Measure-ment approach and electrodes	Time windows (ms)	Offline reference electrodes	Filtering
Jung *et al.* (2012)	Response required	Button press for emotional images	Faces only	Neutral, fearful, and happy faces	NR	NR	PANSS pos 20.2 PANSS neg 18.7	Peak amplitudes; NR	300-450	Average	Online: Bandpass 1-100 Hz Offline: Bandpass 1-30 Hz
Kim *et al.* (2015)	Response required	Button press for irrelevant stimulus (chair image)	Faces only	Neutral and fearful faces	NR	NR	PANSS pos 15.7 PANSS neg 20.2 PANSS gen 39.6	Mean amplitudes; F1 FC1 F2 FC2	300-450	Average	Online: Bandpass 0.1-100 Hz, Notch 60 Hz Offline: Bandpass 0.1-30 Hz
Lee *et al.* (2010)	Response required	Button press for emotional images	Faces only	Neutral, fearful, and happy faces	NR	NR	PANSS pos 21.2 PANSS neg 18.9	Peak amplitudes; F1 FC1 F2 FC2	300-450	Average	Online: Bandpass 1-100 Hz Offline: Bandpass 1-30 Hz

Table 4 (Continued)
*Additional Study Details (*K *= 13)*

	Procedures, Stimuli, and Patient Characteristics							*EEG Recording and Processing*			
Study	Task type	Task details	Image content type	Image details	Mean image ratings: valence	Mean image ratings: arousal	Mean symptom ratings	Measure-ment approach and electrodes	Time windows (ms)	Offline reference electrodes	Filtering
Okruszek *et al.* (2016)	Response required	Button press for targets	Other	Neutral and negative social and nonsocial NAPS images	Neutral: ≧ 4 Negative: 1-4	Neutral: ≦ 6 Negative: ≧ 6	PANSS pos 14.9 PANSS neg 19.6	Mean amplitudes; Fc Cz Pz	250-450 450-1000	Linked mastoids	Online: Bandpass 0.1-200 Hz Offline: Low-pass 30 Hz
Turetsky *et al.* (2007)	Response required	Button press for happy, sad, and neutral images	Faces only	Very sad, neutral, and very happy faces	NR	NR	BPRS female 27 BPRS male 33.1	Mean amplitudes; GFP (broad midline positivity and parietal maximum)	350-450	"Mathematical average of all scalp potentials at each time point"	Online: Bandpass 0.1-50 Hz Offline: Bandpass 0.5-20 Hz
Wexler *et al.* (2014)	Response required	Button press for "pain" versus "neutral" images	Other	Painful hands (accident or injury) and neutral hands (matched situation without injury)	Neutral: <1.25 Negative: >2.5	NR	NR	Mean amplitudes; Cz Pz	350-900	Average mastoids	Offline: bandpass 0.1-40 Hz
Total	Response required: 11; Passive viewing: 2		Faces only: 6; Other: 7					Peak: 3; Mean: 10			

Note: NA: not applicable. NR: not reported. PANSS: Positive and Negative Syndrome Scale; Kay, Fiszbein, & Opler, 1987. PANSS gen, pos, neg: general, positive, negative scores, respectively. SOPS: Scale of Prodromal Symptoms; McGlashan *et al.*, 2001. SOPS gen: total general score. SANS: Scale for the Assessment of Negative Symptoms; Andreasen, 1984. SANS aff, alog, avol, anhe: affective flattening, alogia, avolition, anhedonia scores, respectively. BPRS: Brief Psychiatric Rating Scale; Overall & Gorham, 1962. IAPS: International Affective Picture System; Lang, Bradley, & Cuthbert, 2008. NAPS: Nencki Affective Picture System; Marchewka *et al.*, 2014. All image ratings for IAPS images except Corbera *et al.* and Wexler *et al.*, which used the Wong-Baker scale (Hockenberry, 2005) and Okruszek *et al.*, which used the NAPS scale.