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Abnormal brain activation during threatening face processing in schizophrenia: A meta-analysis of functional neuroimaging studies

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ABSTRACT

Impairment of face perception in schizophrenia is a core aspect of social cognitive dysfunction. This impairment is particularly marked in threatening face processing. Identifying reliable neural correlates of the impairment of threatening face processing is crucial for targeting more effective treatments. However, neuroimaging studies have not yet obtained robust conclusions. Through comprehensive literature search, twenty-one whole brain datasets were included in this meta-analysis. Using seed-based d-Mapping, in this voxel-based meta-analysis, we aimed to: 1) establish the most consistent brain dysfunctions related to threating face processing in schizophrenia; 2) address task-type heterogeneity in this impairment; 3) explore the effect of potential demographic or clinical moderator variables on this impairment. Main meta-analysis indicated that patients with chronic schizophrenia demonstrated attenuated activations in limbic emotional system along with compensatory over-activation in medial prefrontal cortex (MPFC) during threatening faces processing. Sub-task analyses revealed under-activations in right amygdala and left fusiform gyrus in both implicit and explicit tasks. The remaining clusters were found to be differently involved in different types of tasks. Moreover, meta-regression analyses showed brain abnormalities in schizophrenia were partly modulated by age, gender, medication and severity of symptoms. Our results highlighted breakdowns in limbic-MPFC circuit in schizophrenia, suggesting general inability to coordinate and contextualize salient threat stimuli. These findings provide potential targets for neurotherapeutic and pharmacological interventions for schizophrenia.

1. Introduction

Impaired facial expressions perception is a core domain of social cognitive dysfunction in schizophrenia. This impairment is strongly linked to psychopathology and is a reliable predictor of functional outcome in schizophrenia (Brüne, 2005; Couture et al., 2006). A growing number of studies show this to be particularly marked for processing threatening facial expressions such as fear and angry, i.e., evolutionary-determined facial expressions (Cao et al., 2016; Edwards et al., 2002; Edwards et al., 2001; Goghari et al., 2017; Green et al., 2001; Huang et al., 2011; Kohler et al., 2003; Leitman et al., 2008; Pinkham et al., 2011). Moreover, dysfunctional facial threat perception has been attributed a causal role in the development and maintenance of psychosis, such as positive symptoms, persecutory delusions (Freeman, 2007), the evolution of paranoia (Green and Phillips, 2004) as well as negative symptoms (Michalopoulou et al., 2008; van't Wout et al., 2007).

However, the neural mechanism underlying the impaired perception of threatening face remains unclear and inconsistent. A number of studies found reduced activation of limbic system, mainly including amygdala, hippocampus, fusiform and frontal areas in inferior frontal gyrus (Gur et al., 2007; Hall et al., 2008; Michalopoulou et al., 2008; Pinkham et al., 2011; Russell et al., 2007; Seiferth et al., 2009; Williams et al., 2004). Several other studies found decreased activation in putamen and thalamus (Fakra et al., 2008; Pinkham et al., 2011; Seiferth et al., 2009; Williams et al., 2004). Some other studies failed to observe group differences in limbic system (Mier et al., 2014; Spilka et al., 2015; Villalta-Gil et al., 2013). Importantly, taking a closer look at medial prefrontal cortex (MPFC), studies that investigated the hub region of threatening facial processing are not consistent in their results. Some studies supported a hyper-activation of the MPFC (Fakra et al., 2008; Habel et al., 2010; Mothersill et al., 2014; Salgado-Pineda et al.,

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2010; Surguladze et al., 2006) while several other studies found a decreased activation in MPFC (Williams et al., 2007; Williams et al., 2004). Possible explanations for these conflicting results could be: 1) small sample sizes in each study; 2) heterogeneous patient groups; 3) different task types, either implicit or explicit tasks. To clarify how such divergent activity patterns may arise, we present a voxel-based meta-analysis in this study.

Although two previous meta-analyses (Li et al., 2009; Taylor et al., 2012) have demonstrated decreased activation in schizophrenia when processing face emotion, including the limbic, visual, medial frontal, and subcortical regions, it should be noted that these two studies included all the diverse emotional face contrasts. Consequently, these findings do not encourage the knowledge of specific effect such as threatening facial expressions processing in schizophrenia. Surprisingly, no such a neuroimaging meta-analysis has been specially conducted to integrate heterogeneous activation findings of perceiving threatening face in schizophrenia. Furthermore, purifying the contrasts into threat-related face enables us to explore the possible moderating effect of demographic and clinical factors on brain activation in schizophrenia.

The primary aim of this meta-analysis study is to quantitatively characterize neural abnormalities in the processing of threatening facial expressions (fear and anger) in patients with schizophrenia using all published whole-brain fMRI studies. To reduce heterogeneity, subgroup meta-analyses were also conducted within either explicit or implicit tasks only, which would help to clarify whether schizophrenia would involve distinct alterations at different conscious levels of threatening facial expressions processing. We also conducted exploratory meta-regression analyses to explore the effects of demographic and certain clinical factors on abnormality of brain activation in schizophrenia.

2. Materials and methods

2.1. Literature search

We used PubMed and Web of Knowledge to identify functional neuroimaging studies of whole-brain approach comparisons between individuals with schizophrenia and healthy controls (HC) published up to February 1, 2017. The search terms were "emotion," "emotional," "affective," "affect," and "facial," with different combinations of "schizophrenia" or "psychosis" and "fMRI", or "functional magnetic resonance imaging". Next, additional studies were collected by reviewing the reference lists of the relevant papers and publications that cited those articles found in the first step, through the 'related article' function of the PubMed database and through two previously mentioned meta-analysis papers (Li et al., 2009; Taylor et al., 2012). Finally, the reference lists of those review articles were inspected for additional more relevant studies. Exclusion criteria for this meta-analysis were as follows: (1) non-peer-reviewed or non-English publications; (2) studies that did not compare differences in brain activation between schizophrenia participants and HCs; (3) studies where whole-brain results could not be obtained; (4) studies adopting the International Affective Picture System because not all the pictures contain facial emotion; (5) studies that did not report the comparison of threat-related VS. neutral baseline contrast. As suggested by previous studies (Loughead et al., 2008; Pinkham et al., 2011; Satterthwaite et al., 2010), faces displayed with an angry or fearful affect were modeled together as "threat". (6) Studies entirely overlapping samples and contrasts. Papers in which distinct schizophrenia groups were compared with a single HC group were coded as distinct studies (Dong et al., 2017b). This was relevant for two studies (Surguladze et al., 2011; Williams et al., 2007). The selection of papers for the meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009), as shown in Fig. 1. Our literature searches yielded 21 datasets of nineteen studies (Fakra et al., 2008; Gur et al., 2007; Habel et al., 2010; Hall et al., 2008; Li et al., 2012; Michalopoulou et al., 2008; Mier et al., 2014; Mothersill et al., 2014; Pinkham et al., 2011; Russell et al., 2007; Salgado-Pineda et al., 2010; Satterthwaite et al., 2010; Seiferth et al., 2009; Spilka et al., 2015; Surguladze et al., 2006; Surguladze et al., 2011; Villalta-Gil et al., 2013; Williams et al., 2007; Williams et al., 2004) for a total of 354 schizophrenia patients and 374 HC. The demographic and clinical characteristics of the participants are shown in Table 1.

2.2. Meta-analytic method

The present meta-analysis focuses particularly on the processing of threatening (fear and angry face) conditions in comparison with a neutral baseline condition. See Table 2 for a detailed description of tasks and supplementary material for contrasts selection.

Differences in activation of facial emotion perception during fMRI tasks were analyzed using the anisotropic effect-size version of SDM software (sdm_v4.31, Radua et al., 2012), which is a voxel-based meta-analytic approach. Based on given coordinates of under and over-activation, their respective statistical values and the sample size, SDM recreates maps of effect-sizes (Hedge's d) for each included study. Only effects that survived recommended thresholding with a voxel-level (height) threshold of $P < 0.005$ with peak $Z > 1$ and a cluster-level (extent) threshold of 20 voxels are reported (Radua et al., 2012).

To explore the extent of influence of the task type on the results, we classified tasks as explicit (12/21) or implicit (9/21), depending on whether attention is directed at the facial emotion or some other characteristic of the face (see Table 2 for details). For example, labeling emotional faces comprises explicit processing, whereas identifying the gender of emotional faces comprises implicit processing. In the present study, the former included viewing, matching emotion, emotion discrimination, labeling emotion; the latter included gender identification. Then, subgroup meta-analyses were conducted within each task design. To explore to what extent the patient type influenced the results, we also conducted additional meta-analysis of studies with chronic patients only (19 datasets for chronic excluding 2 datasets for first episode patients).

Systematic whole-brain voxel-based jackknife sensitivity analysis was performed to test the replicability of the main and subgroup meta-analytic results. Also, the possible existence of the publication bias for the brain regions was assessed by Egger's test (Egger et al., 1997) using Stata software (version12.0).

SDM also allows heterogeneity to be systematically quantified in a voxel-wise manner using the Q statistic. The overlap between significant areas of heterogeneity ($P < 0.005$, Radua et al., 2012) and areas of brain activation differences were systematically investigated with separate simple meta-regressions using available potential regressors, including sex (the ratio of female to male), mean age of participants, mean illness duration, the proportion of medicated patients, mean chlorpromazine equivalent and mean psychiatric symptoms scores (While for the sake of comparability, the scale for the assessment of positive symptoms (SAPS) and scale for the assessment of negative symptoms (SANS) were transformed into positive and negative syndrome scale (PANSS) values, using the formulas for total scale values of Van Erp et al. (2014)). Because patients showed distinctly abnormal activation patterns in explicit and implicit tasks (see Results section), meta-regression analyses were separately conducted within each task design. In addition, the main parameters of image acquisition (TR: repetition time, magnetic field strength), and preprocessing (the size of Gaussian smooth kernel) were also included in meta-regression analyses to investigate the potential moderator role. The voxel-level threshold of regression was decreased to $P < 0.0005$ to minimize the detection of spurious relationships (Radua et al., 2012).

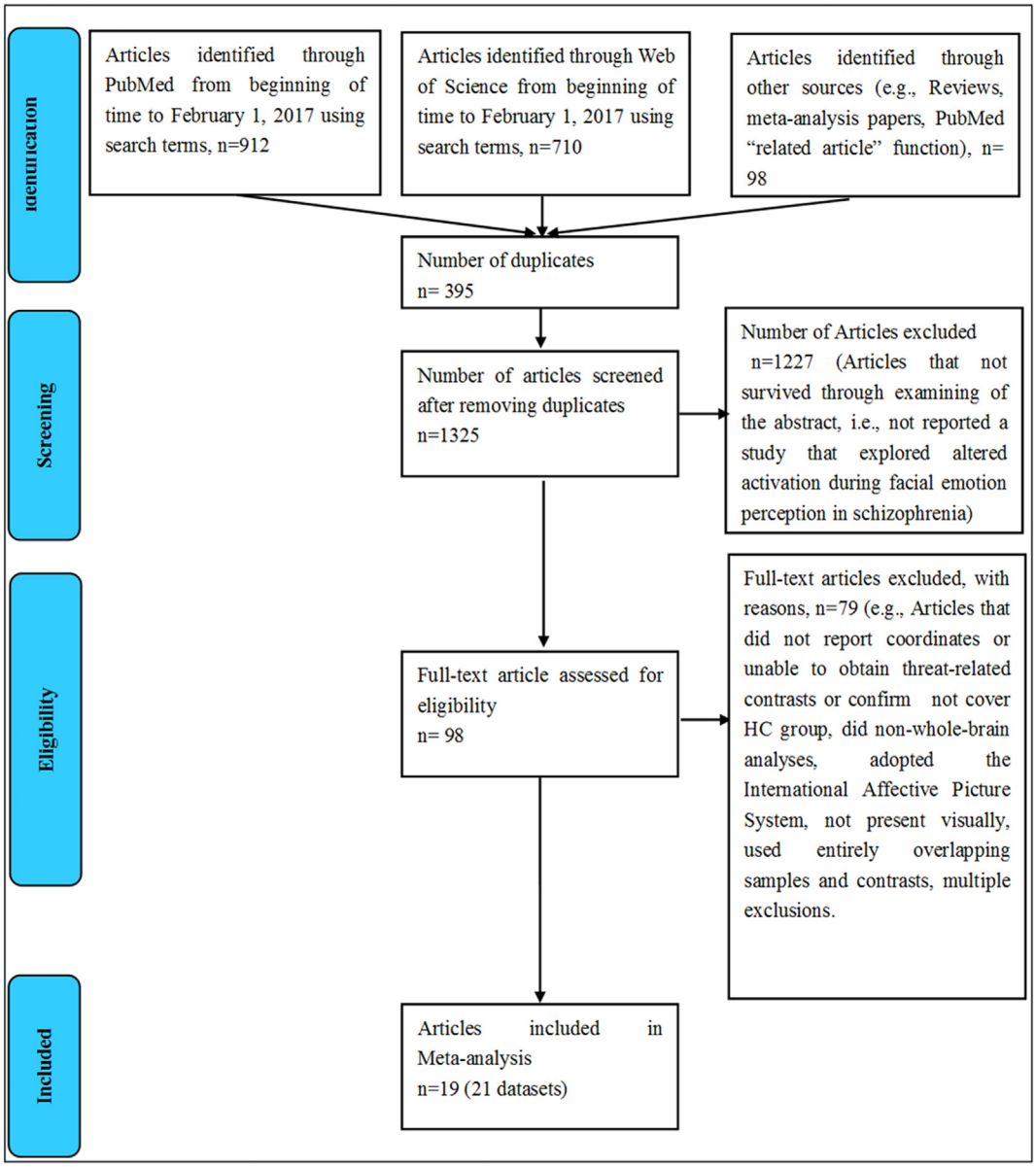

Fig. 1. The PRISMA flow chart of study selection.

3. Results

3.1. Overall meta-analysis

Taking all contrasts together, the meta-analysis identified seven clusters. It should be noted that only results that met the criteria for robustness are reported here. Our jackknife sensitivity analysis found these clusters showed high replicability. Under-activations in bilateral amygdala and left fusiform gyrus were the most robust findings (Table 3). Patients with schizophrenia relative to HCs showed convergent over-activation in a widespread ventral anterior cingulate and medial prefrontal cortex extending to superior prefrontal gyrus. Convergent under-activations for schizophrenia were found in six clusters. They are bilateral amygdala extending into putamen, hippocampus and para-hippocampal gyrus, fusiform gyrus extending into cerebellum lobule IV, VI, right inferior frontal gyrus (IFG), triangular part and right thalamus (Table 3 and Fig. 2a). These clusters were also significant when restricting the analysis in studies with chronic patients. We checked for publication bias by means of funnel plots and Egger test. No evidence for publication bias could be found in the current datasets.

3.2. Evaluation of different tasks

Only results that met the criteria for robustness were reported here. Our subgroup meta-analyses revealed that the over-activation in medial prefrontal gyrus to superior prefrontal gyrus (peak MNI = −8, 58, 12, Z = 1.636, $P < 0.001$, 990 voxels) was found during explicit threat processing in schizophrenia (Fig. 2b). During explicit processing, schizophrenia patients also showed under-activation in inferior frontal gyrus (peak MNI = 56, 16, 14, Z = −2.392, $P < 0.001$, 964 voxels), right cerebellum lobule VI (peak MNI = 32, −74, −24, Z = −1.878, $P < 0.001$, 200 voxels), left fusiform gyrus (peak MNI = −36, −52, −20, Z = −1.927, $P < 0.001$, 276 voxels) and thalamus extending into right amygdala (peak MNI = −4, −6, 2, Z = −2.381, $P < 0.001$, 819 voxels). We also found that patients showed convergent under-activation in bilateral amygdala extending into putamen, hippocampus and parahippocampal gyrus, fusiform gyrus extending into cerebellum lobule IV, VI (peak MNI = −30, −6, −8/26, 4, −8, Z = −4.082/−2.596, $P < 0.001$, 3953/2137 voxels) during implicit processing (Fig. 2b). Conjunction analysis found schizophrenia demonstrated under-activations of right amygdala and left fusiform gyrus across the task-types (Fig. 2b).

Table 1
Studies included in this meta-analysis.

Study	Schizophrenia patients											Health controls			
	N	M	F	Age	Type	Illness duration (y)	Meds	Mean PS	Mean NS	Mean GP	PANSS total	Chlorpromazine equivalent (mg)	N	M	F	Age
Fakra et al., 2008	14	9	5	37.29	Chronic	NA	100%	24.71	13.14	NA	NA	NA	14	9	5	34.64
Gur et al., 2007	16	12	4	30.1	Chronic	9.6	94%	1.4[a]	1.3[b]	NA	NA	NA	17	12	5	25
Habel et al., 2010	17	NA	NA	34.4	Chronic	9.9	94%	18	19.9	NA	76.5	NA	17	NA	NA	34.2
Hall et al., 2008	19	12	7	37.7	Chronic	NA	100%	12.3	11.8	22.7	46.8	496	24	16	8	35.1
Li et al., 2012	12	6	6	29.8	Chronic	5.42	100%	16.08	13.41	28.42	57.91	404.87	12	6	6	29.25
Michalopoulou et al., 2008	11	9	2	35	Chronic	12	100%	16	13.91	29	58.91	523	9	5	4	35.1
Mier et al., 2014	11	7	4	32.45	Chronic	10.18	100%	1.45[a]	6.59[b]	NA	NA	472.56	16	11	5	34.5
Mothersill et al., 2014	25	20	5	42.88	Chronic	NA	100%	9[a]	21[b]	NA	NA	377.52	21	16	5	38.24
Pinkham et al., 2011	35	17	18	36.46	Chronic	15.21	91%	11[a]	16.29[b]	NA	NA	378.19	37	18	19	35.59
Russell et al., 2007	15	15	0	44.7	Chronic	17.69	100%	24.11[a]	21.64[b]	NA	NA	NA	10	10	0	35.6
Salgado-Pineda et al., 2010	14	9	5	37.3	Chronic	14	100%	24.7	13.1	12.9	60.7	NA	14	9	5	34.6
Satterthwaite et al., 2010	12	NA	NA	37.6	Chronic	15.3	83.3%	NA	NA	NA	NA	290	21	10	11	39.0
Seiferth et al., 2009	12	12	0	17.8	FE	0.79	100%	16.2	13.3	26.8	56.3	231	12	12	0	17.9
Spilka et al., 2015	27	13	14	40.7	Chronic	NA	NA	14.5	12.43	26.75	53.68	NA	28	15	13	41.07
Surguladze et al., 2006	15	15	0	43.1	Chronic	19.9	100%	25.1[a]	27.9[b]	NA	NA	NA	11	11	0	36.8
Surguladze et al., 2011	16	10	6	43.7	Chronic (CONV)	18.6	100%	10.9	9.4	20.1	40.4	232	16	8	8	40.4
Surguladze et al., 2011	16	7	9	42.6	Chronic (RLAI)	15.3	100%	8.9	10.1	22.1	41.1	NA	16	8	8	40.4
Villalta-Gil et al., 2013	13	13	0	23.34	FE	0.5	100%	16.83	18.02	37.26	70	390.2	31	15	16	25.57
Williams et al., 2004	27	17	10	27.3	Chronic	4.1	100%	19.7	20.45	36.9	77.05	356.5	22	14	8	27.2
Williams et al., 2007	13	8	5	26.8	Chronic paranoid	5.6	100%	22.6	22.1	40.7	85.4	375.1	13	NA	NA	25.1
Williams et al., 2007	14	9	5	27.8	Chronic noparanoid	5.6	100%	13.5	18.8	33.1	65.4	339.3	13	NA	NA	25.1

Notes: [a] = Scale for the Assessment of positive Symptoms (SAPS); [b] = Scale for the Assessment of Negative Symptoms (SANS); [c] = Brief Psychiatric Rating Scale (BPRS); CONV = conventional antipsychotic depots; F = Female; FE = First episode; GP = General Psychopathology scale; M = Male; Meds = Proportion of medicated patient in the group; NA = not mentioned in the original study; NS = Negative syndrome; PANSS = Positive and negative syndrome scale; PS = Positive syndrome; RLAI = risperidone long-acting injections.

3.3. Meta-regressions

Significant between-study heterogeneities were found in amygdala for explicit task and in amygdala, fusiform gyrus and hippocampus for implicit task ($P < 0.005$). Significant between-study heterogeneities were explored with meta-regression analyses (Fig. 3 and Table 4). It should be noted that the significant effects were only reported when at least half of the studies drive the effects. In explicit task, meta-analyses indicated that studies with higher mean positive symptoms showed lower activation relative to HC in the right amygdala (Fig. 3a). In implicit task, studies with younger age or smaller proportion of female or shorter illness duration found lower activation relative to HC in the hippocampus (Fig. 3b,c,e), studies with smaller dosage of CPZ treatment found lower activation relative to HC in left amygdala (Fig. 3d), studies with higher mean negative or positive symptoms found lower activation relative to HC in the left fusiform gyrus (Fig. 3f, g). In addition, we found magnetic field strength, TR and size of Gaussian smooth kernel did not significantly modulate the results observed in sub-meta-analyses, although magnetic field strength showed a significant moderating effect on the right inferior frontal gyrus in the pooled tasks (MNI coordinate = 48, 22, 16; SDM-Z = −2.968; Voxels = 62).

4. Discussions

To our knowledge, this is the first meta-analysis of fMRI studies focusing on the threatening face perception in schizophrenia. The present meta-analysis identified the breakdowns in limbic-prefrontal circuits that underlie the impairment of threatening facial expression processing in schizophrenia. Specifically, overall meta-analysis found schizophrenia demonstrated attenuated activations of the amygdala, fusiform gyrus, hippocampus, putamen, inferior frontal gyrus, thalamus and cerebellum along with complementary over-activation of MPFC during the threatening face processing. Among these regions, under-activations in right amygdala and left fusiform gyrus were identified in both explicit and implicit tasks whereas altered activation in the remaining clusters varied with task types. Moreover, age, gender, medication and severity of symptoms were partly correlated with abnormalities of brain activation in schizophrenia.

Comparatively, this meta-analysis involves several improvements relative to previous activation meta-analyses (Li et al., 2009; Taylor et al., 2012). First, this meta-analysis is specifically focused on brain activation found from perceiving threatening face in schizophrenia. In this way, this meta-analysis also minimized the heterogeneity of included studies. Second, we went further than previous meta-analyses by conducting some exploratory meta-regression analyses to investigate the possible moderating effect of clinical and demographic factors. Third, the inclusion of negative findings in the current meta-analysis was built into the SDM methodology, which reduces the risk of false positives (Radua et al., 2014). Finally, our findings were robust and reliable by excluding any findings that failed to meet our criteria for reliability based on jackknife sensitivity analyses and visual inspection.

Our overall meta-analysis showed under-activation of limbic emotion areas in schizophrenia during the threatening facial expression processing. This indicates that disruption at systems level, rather than discrete loci, may best explain the pattern of activation abnormality in schizophrenia (Dong et al., 2017b). The 'limbic' emotion brain system is responsible for automatically orienting to emotionally salient (threat in this study) stimuli, conducting initial sensory processing of potential threat as well as modulating bodily responses (Das et al., 2005; Taylor et al., 2003; Williams et al., 2006). The decreased activation in the 'limbic' emotion brain system thus suggests that schizophrenia patients have a lesser engagement of these areas to automatically early orient to threat stimuli, which support rapid responses to danger (Liddell et al., 2005), leading to disrupted sensory processing of potential threat in schizophrenia (Das et al., 2007).

Interestingly, our under-activation in the 'limbic' emotion brain was in accordance with over-activation in the MPFC. This novel evidence for over-activation of the MPFC was inconsistent with the decreased activation of this region observed in previous two meta-analyses. This may be due to highly diverse emotional face contrasts in previous studies as well as the specificity of MPFC engaging in threat-face processing (Williams et al., 2001). The MPFC has been strongly linked to appraisal of the self-relevance of emotional stimuli (Buckner et al., 2008).

Table 2
Analyses of task types, contrasts in this meta-analysis.

Study	Task	Contrasts	Statistical threshold	Magnetic field strength, repetition time	Smooth kernel
Fakra et al., 2008	Match emotion [e]	Fear + angry vs. shapes	False discovery rate (FDR, $P < 0.05$)	3 T, 3 s	6 mm FWHM
Gur et al., 2007	Emotion identification [e]	Fear + angry vs. scrambled face	Height of $Z > 3.1$ and a cluster probability of $P < 0.05$	4 T, 1.5 s	8 mm FWHM
Habel et al., 2010	Emotion discrimination [e]	Fear/angry vs. black screen	Height of $P < 0.001$, uncorrected	1.5 T, 3 s	10 mm FWHM
Hall et al., 2008	Gender identification [i]	Fear vs. Neutral face	Height of $P < 0.001$, uncorrected and a cluster probability of $P < 0.05$	1.5 T, 2.5 s	8 mm FWHM
Li et al., 2012	Emotion discrimination [e]	Fear vs. Neutral face	Height of $P < 0.001$, uncorrected and cluster size > 10 voxels	3 T, 2 s	6 mm FWHM
Michalopoulou et al., 2008	Gender identification [i]	Fear vs. Neutral face	Non-parametric analysis ($P < 0.05$)	1.5 T, 2 s	NA
Mier et al., 2014	Label emotion [e]	Fear vs. Neutral face	Family-wise error (FWE) corrected ($P < 0.05$ at cluster level)	1.5 T, 3 s	10 mm FWHM
Mothersill et al., 2014	Viewing [e]	Angry vs. circles	FWE corrected ($P < 0.05$ at cluster level)	3 T, 2.2 s	10 mm FWHM
Pinkham et al., 2011	Label emotion [e]	Anger + fear vs. fixation	FWE corrected ($P < 0.01$ at cluster level)	3 T, 3 s	4 mm FWHM
Russell et al., 2007	Gender identification [i]	Fear vs. neutral face	Non-parametric analysis ($P < 0.05$)	1.5 T, 6 s	5 mm FWHM
Salgado-Pineda et al., 2010	Match emotion [e]	Angry + fear vs. shapes	FDR corrected($P < 0.05$)	3 T, 3 s	6 mm FWHM
Satterthwaite et al., 2010	Label emotion [e]	Angry + fear vs. neutral face	AlphaSim corrected ($Z > 2.33$, a cluster probability of $P < 0.05$)	3 T, 2 s	6 mm FWHM
Seiferth et al., 2009	Emotion discrimination [e]	Fear/angry vs. black screen	FWE corrected ($P < 0.05$, cluster size > 5 voxels)	1.5 T, 2.2 s	8 mm FWHM
Spilka et al., 2015	Viewing [e]	Fear/angry vs. neutral face	Gaussian Random Field theory ($Z > 2.3$, Cluster level $P < 0.05$)	3 T, 2.5 s	7 mm FWHM
Surguladze et al., 2006	Gender identification [i]	Fear vs. fixation	Non-parametric analysis ($P < 0.05$)	1.5 T, 2 s	7.2 mm FWHM
Surguladze et al., 2011	Gender identification [i]	Fear vs. neutral face	Non-parametric analysis ($P < 0.05$)	1.5 T, 2 s	7.2 mm FWHM
Surguladze et al., 2011	Gender identification [i]	Fear vs. neutral face	Non-parametric analysis ($P < 0.05$)	1.5 T, 2 s	7.2 mm FWHM
Villalta-Gil et al., 2013	Matching Emotion	Fear vs. neutral face	FWE corrected ($P < 0.05$, cluster size > 10 voxels)	1.5 T, 2 s	8 mm FWHM
Williams et al., 2004	Gender identification [i]	Fear vs. neutral face	Non-parametric analysis ($P < 0.01$)	1.5 T, 3 s	8 mm FWHM
Williams et al., 2007	Gender identification [i]	Fear/anger vs. neutral face	Non-parametric analysis ($P < 0.05$)	1.5 T, 3 s	8 mm FWHM
Williams et al., 2007	Gender identification [i]	Fear/anger vs. neutral face	Non-parametric analysis ($P < 0.05$)	1.5 T, 3 s	8 mm FWHM

Notes: [e] = explicit task; FDR = False discovery rate; FWE = Family-wise error; FWHM, full width at half maximum; [i] = implicit task.

Additionally, given that directed threatening facial expressions represents the clearest indication of self-relevant threat, hyper-activation of the MPFC may be closely related to compensatory process in schizophrenia (Hempel et al., 2003; Li et al., 2012; Spilka and Goghari, 2017). The more recruitment of the MPFC in schizophrenia, the more regulation and more self-related participation to counterbalance the deficits of early automatic orientation to salient threat signals and sensory processing. However, this compensatory process might still fail in schizophrenia. Meanwhile, studies have found reduced functional coordination between amygdala and the MPFC or within the affective network during fear or negative stimuli processing (Bjorkquist et al., 2016; Cao et al., 2016; Das et al., 2007; Goghari et al., 2017; Potvin et al., 2017), even when no stimuli were present, i.e., resting state (Dong et al., 2017b) in schizophrenia. Also, our previous study showed reduced structure connectivity of the uncinate fasciculus (Dong et al., 2017a), which connects the orbitofrontal cortex (including ventral MPFC) to the limbic system. Taken together, these finding may suggest that schizophrenia lack a general ability to coordinate and contextualize salient threat stimuli via limbic-MPFC circuits (Williams et al., 2004), which could lead to misattributions of potential threat to irrelevant stimuli in their interpretation (Das et al., 2007; Potvin et al., 2017).

Table 3
Brain regions showing abnormal activation during fear/angry face processing in schizophrenia.

Brain regions	MNI coordinate	SDM-Z	*P*	Voxels	Jackknife sensitivity
Over-activation					
Left ventral1 anterior cingulate/medial/superior prefrontal gyrus	−2, 36, −6	1.759	0.000018179	2573	20/21
Under-activation					
Left amygdala/putamen/hippocampus/parahippocampal gyrus	−14, −8, −12	−3.189	0.000000179	1615	21/21
Left fusiform gyrus/cerebellum lobule IV, VI	−32, −38, −28	−2.857	0.000000954	1811	21/21
Right amygdala/putamen/hippocampus/parahippocampal gyrus	22,−14, −8	−2.934	0.000000715	1408	21/21
Right inferior frontal gyrus, triangular part	54, 18, 16	−2.601	0.000019431	699	18/21
Right fusiform gyrus/cerebellum IV, VI	30, −40, −24	−2.148	0.000528455	514	18/21
Right thalamus	4, −8, −2	−2.205	0.000366092	393	19/21

Notes: Over-activation in right middle/inferior temporal gyrus was only supported by Pinkham et al. (2011), left superior parietal gyrus and left middle temporal gyrus were only supported by Fakra et al. (2008) and Salgado-Pineda et al. (2010). Therefore, these three regions were discarded in our following discussion.

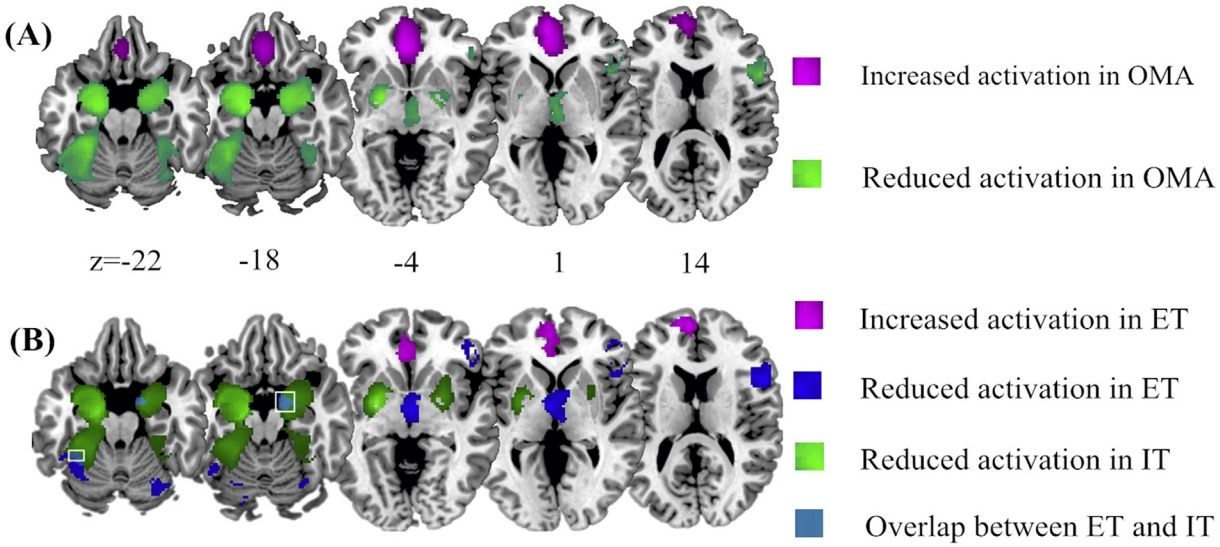

Fig. 2. (a) Results of overall meta-analysis in schizophrenia. (b) Results of sub-task meta-analyses in schizophrenia. ET, explicit tasks; IT, implicit tasks; OMA, overall meta-analysis.

It is well documented that threatening facial signals elicit amygdala activity when threat stimuli are presented during different levels of awareness (Liddell et al., 2005; Morris et al., 2001; Williams et al., 2006). In addition, fusiform gyrus, located in the extrastriate visual cortices, plays a specific role in processing faces (McCarthy et al., 1997) and in enhancing the signal to efficiently response to emotionally salient stimuli (Surguladze et al., 2003) in humans. Therefore, it is reasonable that the under-activation of amygdala and fusiform gyrus in the current meta-analysis represents a general abnormality across explicit and implicit processing in schizophrenia (Goghari et al., 2017; Johnston et al., 2005).

Our subgroup meta-analyses showed that under-activations of the IFG, thalamus and over-activation of MPFC are more pronounced in explicit tasks but not in implicit tasks. Previous studies showed the greater involvement of cognitive effort regions, e.g., the IFG and the MPFC, in explicit face processing (Fusar-Poli et al., 2009; Scheuerecker et al., 2007). Therefore, the impairment of explicit threatening face processing might tend to reflect a failure to appropriately launch top-down control to threat. In contrast, because participant's attention is directed toward some other characteristics of the face (e.g., gender) in implicit tasks, threatening face perception becomes less effort-demanding and more automatic driven. Thus, the observed limbic regions in implicit tasks might suggest the deficits of bottom-up processing in schizophrenia. However, it should be noted that, explicit and implicit processing are not mutually exclusive categories, but rather have porous boundaries over time or across situations (Gyurak et al., 2011).

For meta-regression analyses, studies including patients with more severe positive symptom showed lower activation in the amygdala during explicit threatening face processing. The amygdala has been proposed to play a key role in modulating the dopaminergic system (Fudge and Emiliano, 2003). Thus, this finding provided further evidence for strong relationships between the abnormalities of amygdala (response to aversive content or brain volume) and the severity of positive symptoms in schizophrenia (Koutsouleris et al., 2008; Rajarethinam et al., 2001; Satterthwaite et al., 2010; Taylor et al., 2002). On the other hand, studies including patients with more severe positive or negative symptoms showed lower activation in fusiform gyrus during implicit threat-related processing. Therefore, there may be different biological trajectories included in explicit and implicit threatening face processing in relation to psychiatric symptoms in schizophrenia. In addition, we found studies including smaller dosage of CPZ treatment exhibited lower activation in left amygdala in schizophrenia. This may reflect an amelioration effect of antipsychotic medication on pre-existing amygdala activation abnormalities in schizophrenia (Fudge and Emiliano, 2003), which needs to be clarified by future studies.

Our meta-regression analyses also showed that during implicit processing, studies including patients with younger age or shorter illness duration showed lower activation in the left hippocampus. These results further confirmed the critical role of hippocampus in pathological processes in schizophrenia (Harrison, 2004). Also, meta-regression analysis showed studies with a high ratio of female to male patients were associated with more decreased activation in the right hippocampus. Gender differences are apparent in emotion processing of schizophrenia (Mendrek et al., 2008; Mendrek and Mancini-Marïe, 2015). Studies in the literature about schizophrenia indicated, that females display more affective symptoms (Leung and Chue, 2000) and more impairment in facial emotion perception (Kohler et al., 2009). However, the above results of meta-regressions should be interpreted with caution as they do not directly test causal relations within samples.

Although significant, this study has several limitations, many of which are generally applicable to meta-analyses. First, peak-based meta-analyses are based on summarized (i.e., coordinates from published studies) rather than raw statistical brain maps, and this approach may result in less accurate results (Radua et al., 2014). Second, different studies employed different statistical thresholds. We ensure that the same statistical threshold in the whole brain is used in each study. Meanwhile, while thresholds of multiple comparisons are usually different and preferred, the inclusion of studies with more liberal thresholds is still statistically correct. Indeed, SDM preprocessing employs the coordinates of the peak voxels (highest differences) to approximately recreate the statistical parametric map for each study, but it does not make prior assumptions about whether or not these differences are significant in the final results (Radua et al., 2011). Third, the included studies varied in terms of the data acquisition and preprocessing of images. Although we found no significant modulating effects of the main parameters on the results within explicit or implicit tasks, we still cannot eliminate completely the potential confounding effects of these parameters. Fourth, recent study recommended the minimum number of studies for SDM meta-analysis is 10 (Carlisi et al., 2017), thus the relatively low number of studies (nine implicit studies) in this analysis would limit the generalizability of the results, especially in the sub-analyses with implicit task and meta-regressions. Further, while we found some significant results through meta-regression analyses, it should be noted, however, that meta-regressions are exploratory, that is, these analyses are limited by the fact that they depend on the summary

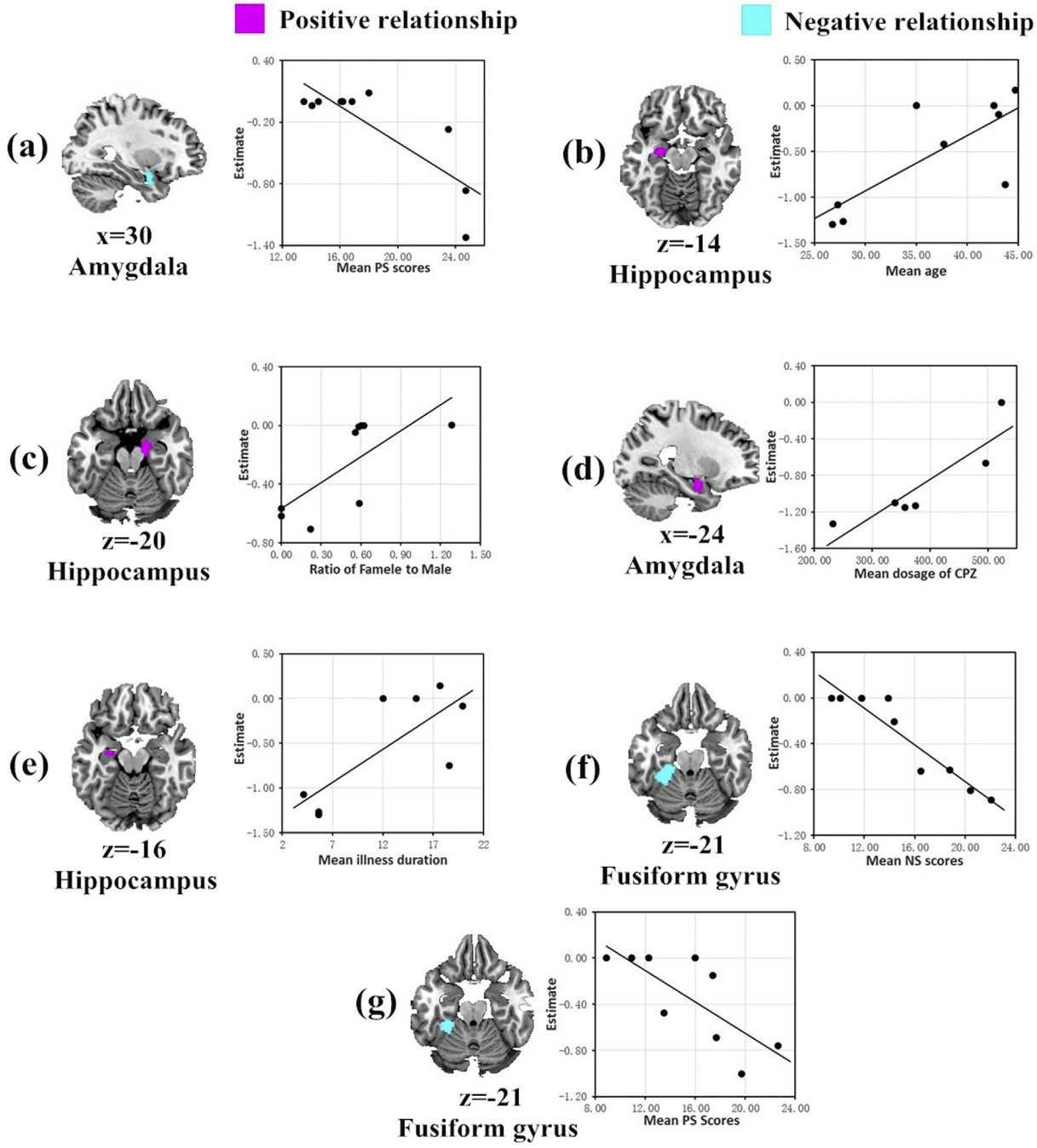

Fig. 3. (a) Results of meta-regression with severity of positive symptoms (PS) in schizophrenia during explicit tasks. (b) Result of meta-regression with patient age in schizophrenia during implicit tasks. (c) Result of meta-regression with sex in schizophrenia during implicit tasks. (d) Result of meta-regression with chlorpromazine (CPZ) equivalent in schizophrenia during implicit tasks. (e) Result of meta-regression with illness duration in schizophrenia during implicit tasks. (f, g) Results of meta-regression with severity of negative symptoms (NS) and PS in schizophrenia during implicit tasks. All images are shown in neurological convention; left on the image corresponds to left in the brain. Effect sizes represent effect sizes at the peak of the cluster.

mean scores of individual studies. They should thus be interpreted with caution, as they do not directly test relationships within samples. Fifth, another issue that should be taken into account is that many of the included studies used neutral faces as a baseline condition. Given that some studies showed excessive amygdala and hippocampal responses to neutral faces (Potvin et al., 2016), it was possible that the observed reduced activation in these two areas is due to the excessive activity to neutral faces. However, it was impossible for us to investigate this possibility because of the unavailable original statistical maps. Future studies are urgently needed to find out the best baseline condition. Additionally, while the present findings highlight alterations of activation in processing threatening faces across fear and anger emotions in schizophrenia, the specific alterations between two emotions in patients cannot be further explored due to insufficient data among the reported studies (6 datasets for angry emotional face) and this aspect therefore awaits future study. Finally, as all the studies included are medicated, we cannot eliminate the potential confounding effect of medication, and future studies of drug-naive first-episode patients are needed to replicate present findings. Thus, the findings in this meta-analysis would even more reflect the features in 'chronic state' of the patients.

Table 4
Factors moderating abnormal activation in studies of schizophrenia patients: meta-regression analyses.

	MNI Coordinates	SDM Z value	*P*	voxels
Effect of positive symptoms in explicit task				
Right amygdala	20, −2, −18	−4.169	0.000000119	125
Effect of age in implicit task				
Left hippocampus	−26, −12, −14	3.618	0.000006735	149
Effect of proportion of female in implicit task				
Right hippocampus	18, −12, −18	1.719	0.000058234	211
Effect of CPZ treatment in implicit task				
Left amygdala	−22, −8, −16	2.736	0.000003934	194
Effect of illness duration in implicit task				
Left hippocampus	−26, −14, −12	3.242	0.000018656	59
Effect of negative symptoms in implicit task				
Left fusiform gyrus	−30, −36, −24	−3.263	0.000017762	579
Effect of positive symptoms in implicit task				
Left fusiform gyrus	−32, −40, −22	−2.802	0.000099421	270

5. Conclusion

In summary, patients with chronic schizophrenia showed attenuated activations in the limbic emotional system along with compensatory over-activation in the MPFC during threatening faces processing. Our analysis suggested that the breakdowns in the limbic-MPFC circuits might represent a general inability to coordinate and contextualize salient threat face, which further lead to misattributions of potential threat to irrelevant stimuli in their interpretation. Thus, the limbic-MPFC circuit provided potential a target for neurotherapeutic and pharmacological interventions. Moreover, explicit and implicit threat processing tasks implied some common and distinct alterations of brain activity in schizophrenia. Importantly, abnormalities of brain activation in schizophrenia were partly modulated by age, gender, medication and severity of symptoms. Therefore, future studies should take these variables into account, which will be valuable to understanding the nature of deficits of threatening face processing in schizophrenia.

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Conflict of interest

None.

Author contributions

Debo Dong and Yulin Wang designed the study, searched the literature, and wrote the manuscript; Xiaoyan Jia and Yingjia Li searched the literature and checked the accuracy of data; Debo Dong and Xuebin Chang conducted the statistical analysis; Marie Vandekerckhove commented and revised the manuscript to improve the conciseness. Cheng Luo and Dezhong Yao, who contributed equally to playing the role of corresponding author, conceived, commented and worked on the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2017.11.013.

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