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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 threatening 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.

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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 (Loughhead 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).

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