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Grey matter reduction in the caudate nucleus in patients with persistent negative symptoms: An ALE meta-analysis

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ABSTRACT

Objectives: In the present study, we used Activation Likelihood Estimation (ALE) meta-analysis to quantitatively examine brain grey matter reduction in schizophrenia patients with persistent negative symptoms (PNS).
Method: A total of 12 voxel-based morphometry (VBM) studies were included in ALE meta-analysis using more stringent criterion of PNS.
Results: Significant grey matter reduction in the PNS group relative to controls was observed in the left caudate nucleus, the left precentral region, the left middle frontal region, the bilateral parahippocampal region, the left anterior cingulate region, the bilateral medial frontal gyrus, the thalamus and the insula.
Conclusion: Our results suggest that brain regions in the reward network may be specifically related to PNS, especially the left caudate nucleus. It is possible that abnormality in reward processing may constitute the neural basis of PNS.

1. Introduction

Negative symptoms are core clinical features of schizophrenia and contribute to deficits in cognitive and executive function (Bagney et al., 2013; Bow-Thomas et al., 1999; Capleton, 1996). They are often persistent in the whole course of schizophrenia in a large number of patients and are resistant to treatment (Kirkpatrick and Fischer, 2006; Stahl and Buckley, 2007; Tandon et al., 2010). Increasing evidence has suggested that negative symptoms include at least two dimensions, namely the motivational dimension (e.g., anhedonia, avolition and asociality) and the diminished expressivity dimension (e.g., restricted affect and alogia) (Blanchard and Cohen, 2006; Kirkpatrick and Fischer, 2006; Strauss et al., 2012). In particular, diminished pleasure and motivation, which contribute to poor outcome, have been suggested to be key aspects of negative symptoms (Barch and Dowd, 2010).

For research purposes, there are currently two main ways to conceptualize negative symptoms. The first way is the deficit syndrome (DS), which includes only primary and enduring negative symptoms (Carpenter et al., 1988). The second way is the concept of persistent negative symptoms (PNS), which requires at least moderate severity of negative symptoms for at least six months with defined threshold levels of positive symptoms, depression and extrapyramidal side effects during the stable phase of schizophrenia (Buchanan, 2007). The concept of PNS shares three features with the DS, namely persistence, resistance to treatment (Kalisz and Cechnicki, 2016), and the fact that both constructs include primary and enduring negative symptoms (Mucci et al., 2016). However, compared with the DS, the PNS concept is more inclusive and consequently patients with PNS are easier to identify for research purposes. Indeed, the PNS concept has been recognized by a National Institute of Mental Health consensus statement in 2006 (Kirkpatrick et al., 2006), and a large number of studies have examined the assessment, identification and treatment of PNS (Benoit et al., 2012; Bodnar et al., 2014; Buchanan et al., 2015; Chue and Lalonde, 2014; Hovington et al., 2015; Hovington et al., 2012; Mucci et al., 2016; Ucok and Ergul, 2014).

Although many previous studies have identified a correlation between negative symptoms and grey matter reduction (Andreasen, 1989; Berman et al., 1988; Bishop et al., 1983; Johnstone et al., 1994; Keilp et al., 1988; Luchins et al., 1984; Pfefferbaum et al., 1988; Saijo et al., 2001), few studies have been carried out in schizophrenia patients with PNS (Hovington and Lepage, 2012). Furthermore, results from the few neuroimaging studies using the PNS construct are inconsistent due to different imaging methods, terminologies, and under-powered samples. Until recently, only three imaging studies have used the PNS construct to investigate grey matter and white matter changes, but they are all limited by small sample sizes (Benoit et al., 2012; Bodnar

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et al., 2014; Hovington et al., 2015). A systematic narrative review on the neuroanatomical correlates of PNS reported that structural deficits of the frontal lobe and the temporal lobe may be specifically related to PNS (Hovington and Lepage, 2012). More research is clearly needed to explore the brain structural deficits of schizophrenia patients with PNS with a larger sample size.

In this study, we aimed to quantitatively examine grey matter reduction in schizophrenia patients with PNS using Activation Likelihood Estimation (ALE) meta-analysis.

2. Methods

2.1. Study selection

We used the following key words to search for relevant studies in online databases including PubMed, Web of Knowledge, Elsevier and PsycINFO: *schizophrenia*, *MRI*, *structural*, *negative symptoms*, *persistent negative symptoms*, *grey matter*. We included papers published in these databases up to August 31, 2016.

Before Buchanan developed the criteria of PNS, many researchers have used different criteria to identify patients with PNS (Bottlender et al., 2003; Edwards et al., 1999; Malla et al., 2004). As a result, the search was complicated by the use of different definitions, terminologies (e.g. "enduring negative symptoms", "residual negative symptoms" or "negative schizophrenia") and assessment instruments. To address this problem, we adopted the following inclusion and exclusion criteria developed by Hovington and Lepage (2012) to identify the relevant studies.

2.1.1. Inclusion criteria

(1) Negative symptoms must be measured by a validated negative symptom scale, such as the Positive and Negative Syndrome Scale (PANSS) and the Scale for the Assessment of Negative Symptoms (SANS) and must reach at least mild or moderate severity. Moreover, according to Buchanan's definition of PNS (Buchanan, 2007), he pointed that it should define the positive symptoms in low level. According to the criteria of PNS developed by Hovington and Lepage (2012), there were no criteria on positive symptoms. Thus, we added more criteria on presence of positive symptoms for the present study (see Fig. 1).

(2) The duration of illness (DOI) must be longer than or equal to six months. According to the criteria of PNS, negative symptoms must persist for a minimum of six months in a clinically stable period (Buchanan, 2007). However, when we identified studies on PNS, we found that most studies only reported the DOI rather than the duration of negative symptoms. The reason for defining a DOI of at least six months in this study was to ensure that first episode schizophrenia patients whose clinical symptoms (especially positive symptoms) have not been stabilized would not be inadvertently included.

2.1.2. Exclusion criteria

(1) Duplicated studies;
(2) Unrelated studies based on content and method;
(3) Studies investigating participants without at least mild to moderate levels of negative symptoms, and without using a validated negative symptom scale;
(4) DOI not reported or mean DOI of less than six months;
(5) Studies that did not use standardized space of Montreal Neurological Institute (MNI) or Talairach space, or contrast studies;
(6) A mean PANSS negative subscale score of <19, or a mean SANS total score of <20;
(7) A mean PANSS positive subscale score of >21, or a mean SAPS total score of >20;
(8) Studies in which the mean positive symptom scores of participants exceeded the mean negative symptom scores.

A total of 12 studies fulfilling the inclusion criterion of the PNS group were included (see Table 1). A total of 556 patients with schizophrenia and 765 normal controls were included in this meta-analysis. The lowest mean PANSS negative subscale score was 19.8. The mean levels of positive symptoms were all lower than negative symptoms in all 12 studies. Two of the studies reported grey matter concentration and 10 studies reported grey matter volume. Information on antipsychotic dosage of each study are also presented in Table 1.

2.2. Activation Likelihood Estimation

The Ginger ALE software was used for the present meta-analysis (Laird et al., 2005). The ALE analyses were conducted in Talairach space, and Lancaster transform was used if coordinates were reported in MNI space originally (Lancaster et al., 2007). The Lancaster's method was also used when Brett's formulation (Brett, 1999) was used for conversion from MNI space to Talairach space. The ALE analysis on patients with PNS included 12 studies (208 foci). We followed the recommendations of the Ginger ALE software (Laird et al., 2005) to obtain the final clusters identified in both meta-analyses by controlling for the false discovery rate (FDR) at $p < 0.05$ with a cluster extent threshold of 100 voxels.

3. Results

In the ALE analysis involving patients with PNS, the results showed that there was significantly reduced grey matter volume at the bilateral medial frontal gyrus (Brodmann area [BA] 11/10), the left precentral gyrus (BA44), the left middle frontal gyrus (BA9), the left caudate nucleus (caudate head), the bilateral parahippocampal gyri, the left anterior cingulate (BA32), the thalamus and the insula. More details see Table 2 and Fig. 2.

4. Discussion

The present meta-analysis demonstrated that schizophrenia patients with PNS had significant grey matter volume reduction at the left caudate nucleus, the left precentral region, the left middle frontal region, the bilateral parahippocampal region, the left anterior cingulate gyrus, the bilateral medial frontal gyri, the thalamus and the insula. This study is one of the few systematic reviews that quantitatively examines grey matter volume reduction in schizophrenia patients with PNS.

Numerous studies have reported the relationship between grey matter volume reduction and negative symptoms (Andreasen, 1989; Berman et al., 1988; Bishop et al., 1983; Johnstone et al., 1994; Keilp et al., 1988; Luchins et al., 1984; Pfefferbaum et al., 1988; Saijo et al., 2001). Grey matter volume reduction in the prefrontal cortex (including the orbitofrontal cortex and the medial and lateral prefrontal cortices) have been consistently correlated with the severity of negative symptoms in numerous imaging studies (Baare et al., 1999; Hazlett et al., 2008; Hirayasu et al., 2001; Koutsouleris et al., 2008). Taken together with our findings, grey matter volume reduction in the prefrontal cortex appears to be specifically correlated with PNS. Apart from the prefrontal cortex, subcortical regions such as the caudate nucleus (Young et al., 1991) and limbic regions (Koutsouleris et al., 2008), have also shown grey matter volume reduction in schizophrenia patients with negative symptoms. For example, consistent with our results, parahippocampal grey matter was found to be significantly correlated with the severity of negative symptoms in patients with PNS (Benoit et al., 2012; Bodnar et al., 2014). However, increased grey matter volume in the orbitofrontal cortex and the caudate nucleus has also been reported

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