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Brain morphology in first-episode schizophrenia: A meta-analysis of quantitative magnetic resonance imaging studies

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Abstract

Background: A number of meta-analytic reviews of structural brain imaging studies have shown that multiple subtle brain abnormalities are consistently found in schizophrenia. However, quantitative reviews till now published have included mainly studies performed on chronic schizophrenic patients but have failed to provide clear information on specific, possibly different, findings in first-episode schizophrenia.
Methods: We performed a systematic search for MRI studies that reported quantitative measurements of volumes of brain regions in first-episode schizophrenic patients and in healthy controls. Twelve meta-analyses were performed for 6 cerebral regions.
Results: Twenty-one studies were identified as suitable for analysis. Significant overall effect sizes were demonstrated for lateral and third ventricular volume increase, and for volume reduction of whole brain and hippocampus, but not for temporal lobe, amygdala and total intracranial volumes.
Conclusions: The available literature data strongly indicate that some brain abnormalities are already present in first-episode schizophrenic patients. However, unlike the results of published meta-analyses conducted primarily on samples of chronic schizophrenic patients, the present study did not confirm a significant reduction of temporal lobe or amygdala volumes in first-episode schizophrenia. These findings support the hypothesis of different patterns of involvement of various cerebral areas over the time course of schizophrenia.

Keywords: Schizophrenia; First-episode; Brain morphology; Magnetic resonance imaging; Meta-analysis

1. Introduction

In the last 20 years, several Magnetic Resonance Imaging (MRI) studies have enabled the identification

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of various structural brain abnormalities in schizophrenia. This has been confirmed also by a number of recent meta-analyses, which have shown the consistent occurrence of multiple subtle brain abnormalities in the disease. In particular, these meta-analytic reviews indicate that schizophrenic patients, compared to healthy controls, show reduced brain size (Ward et al., 1996; Wright et al., 2000), enlarged lateral and third ventricles (Lawrie and Abukmeil, 1998; Wright et al., 2000), reduced frontal lobe volume (Wright et al., 2000), reduced volumes of temporo-limbic structures (Ward et al., 1996; Nelson et al., 1998; Wright et al., 2000) and of corpus callosum (Woodruff et al., 1995), and increased volume of basal ganglia (Wright et al., 2000).

Despite the large body of studies on the issue and the strength of such meta-analytic studies results, the nature of brain abnormalities found in schizophrenia and their role in the pathophysiology of the disease are not yet completely understood. In this perspective, it becomes fundamental to establish the time course of such brain abnormalities, i.e. their epoch of onset and course over time. Many different approaches have been utilized to address this question: 1) cross sectional studies evaluating the correlation between brain morphological measures and duration of illness; 2) longitudinal studies of structural brain changes; and 3) patient–control comparison studies of intracranial volume decrease (that reflects early reduction in brain growth) and extracerebral volume increase (index of later loss of cerebral tissue). These studies have yielded controversial results. Cross sectional analyses of both recent onset and chronic schizophrenic patients did not show a strong correlation between brain pathomorphology and illness duration (Vita et al., 1991; Marsh et al., 1994), although some authors reported a relationship between longer duration of illness, earlier age of onset and magnitude of brain abnormalities in schizophrenia (Turetsky et al., 1995; Lim et al., 1996). Although most early Computerized Tomography (CT) longitudinal studies showed no significant change over time of ventricular dimensions (Nasrallah et al., 1986; Illowsky et al., 1988; Vita et al., 1988, 1994; Sponheim et al., 1991; Jaskiw et al., 1994), recent longitudinal MRI studies have more consistently found volume changes over time of cortical gray matter and ventricular system in schizophrenic patients as compared to healthy controls (Woods et al., 1990; DeLisi et al., 1995, 2004; Lieberman et al., 1996, 2001; Rapoport et al., 1997; Gur et al., 1998; Jacobsen et al., 1998; Mathalon et al., 2001; Ho et al., 2003; Kasai et al., 2003). Finally, the finding of both intracranial volume reduction and extracerebral volume increase in schizophrenic patients (Woods et al., 2005) supports the proposition of early volume reduction followed by a subsequent further later reduction of cerebral volume in the course of the disease.

If brain abnormalities in schizophrenia are not stable over time, then the investigation of brain morphology at the illness onset can lead to some more insight on the nature of brain abnormalities in schizophrenia and their role in the pathophysiology of the disease. In the last years, a large number of MRI studies have examined different cortical and subcortical regions in first-episode schizophrenic patients. Some have demonstrated a similar pattern of brain abnormalities to that reported in samples of chronic patients, with reduction of gray matter volume (Lim et al., 1996; Zipursky et al., 1998; Fannon et al., 2000; Cahn et al., 2002a; Kasai et al., 2003), lateral and third ventricular enlargement (Degreef et al., 1992; Lieberman et al., 2001; Lawrie et al., 2001; Chua et al., 2003), frontal lobe volume reduction (Nopoulos et al., 1995; Ohnuma et al., 1997; Gur et al., 1998, Hirayasu et al., 2001; Hietala et al., 2003; Bachmann et al., 2004) and temporo-limbic abnormalities (Gur et al., 1998; Hirayasu et al., 1998, 2000; McCarley et al., 2002; Sumich et al., 2002; Joyal et al., 2003; Kasai et al., 2003; Hietala et al., 2003). The results of these studies, however, have been somehow contrasted by others, that reported nonsignificant changes of different brain structures such as cerebral ventricles (DeLisi et al., 1992; Puri et al., 2001; Salokangas et al., 2002), frontal lobe (DeLisi et al., 1991; Bilder et al., 1994; Lawrie et al., 2001; Cahn et al., 2002a; Molina et al., 2004), temporal lobe (DeLisi et al., 1991; Bilder et al., 1994; Nopoulos et al., 1995; Ohnuma et al., 1997; Niemann et al., 2000; Salokangas et al., 2002) and temporo-limbic structures (Razi et al., 1999; Matsumoto et al., 2001; Cahn et al., 2002a,b; Smith et al., 2003) in similar samples of first-episode patients.

This is a prototypical situation where a traditional review provides little adjunctive information on the issue, whereas a meta-analytical approach makes possible more objective and certain conclusions (Hedges and Olkin, 1985).