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Investigating the neuropsychological and neuroanatomical changes that occur over the first 2–3 years of illness in patients with first-episode schizophrenia

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Abstract

Objective: This study explored the concurrent courses of the neuroanatomical and neuropsychological changes that occurred over the first 2–3 years of illness in patients with first-episode schizophrenia (FES).
Methods: Fifty-two patients with FES underwent neuropsychological testing and a structural magnetic resonance imaging (sMRI) scan within three months of their first presentation to mental health services with psychotic symptoms (time1). Patients' cognitive performance was evaluated via an extensive neuropsychological test battery, which assessed 9 cognitive domains. Of the 52 patients at time1, 32 returned 2–3 years later (time2) for follow-up neuropsychological testing, and 20 of these also underwent follow-up sMRI. MR images were preprocessed in SPM99. Grey matter volumes of patients' whole-brain, frontal lobes and temporal lobes were calculated by convolving the preprocessed images with manually-drawn binary masks.
Results: Patients exhibited longitudinal improvements in full-scale IQ, performance IQ and visual memory. In contrast, concurrent reductions in grey matter were observed for the whole-brain (3% reduction) and the frontal lobe (3.65% reduction). Furthermore, the extent of patients' whole-brain and frontal-lobe grey matter changes were positively correlated with longitudinal changes in verbal learning and memory.
Discussion: The results of this study suggest that while the early stages of schizophrenia are associated with a mild improvement in patients' overall cognitive functioning, they are also associated with progressive grey matter atrophy.

Keywords: First-episode schizophrenia; Longitudinal; Neuroanatomy; Neuropsychology

1. Introduction

Prospective longitudinal studies of patients with first-episode schizophrenia have several potential benefits. They offer opportunities to better elucidate the etiology of schizophrenia, the core clinical and cognitive features of the disease, the risk factors associated with the development of the disease, and improved treatments.

Abbreviations: CPZ; chlorpromazine; DSM-IV; Diagnostic and Statistical Manual of Mental Disorders —4th edition; FES; first-episode schizophrenia; FWHM; full-width at half maximum; ICBM; International Consortium for Brain Mapping; sMRI; structural magnetic resonance imaging; PANSS; Positive and Negative Syndrome Scale; SPM; Statistical Parametric Mapping; SPSS; Statistical Package for the Social Sciences; VBM; voxel-based morphometry.

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Longitudinal studies in FES have consistently found evidence for improved cognitive performance in patients receiving treatment (e.g. Gold et al., 1999; Sweeney et al., 1991), but also for the persistence of cognitive deficits in the presence of symptom improvements (Censits et al., 1997; Hill et al., 2004; Hoff et al., 1999; Schuepbach et al., 2002). In contrast to this, studies that have explored brain structure in patients with FES have often provided evidence for progressive neurodegeneration (e.g. DeLisi et al., 2004; Lieberman et al., 2001; Pantelis et al., 2003; Puri et al., 2001; Whitford et al., 2006; Wood et al., 2001). However, other studies have found grey and white matter volumes in the prefrontal and temporal regions to be unrelated to the years of illness duration suggesting that any reductions in volume may not be progressive (Sanfilipo et al., 2000; Zipursky et al., 1998).

Few studies have explored the longitudinal relationship between structure and function in FES. Hoff et al. (1999) found no correlation between changes in cognitive function and brain structures. On the other hand, Ho et al. (2003) found that progressive decrements in frontal-lobe grey and white matter volumes correlated with poorer executive functioning.

The present study undertook a parallel exploration of neuropsychological and neuroanatomical changes in a group of participants with FES over a two to three year period after initial diagnosis. The specific aims were to:

1. Utilize longitudinal data to explore whether the neuropsychological deficits exhibited by the patients at the time of their first presentation changed over the first 2–3 years of their illness.
2. Undertake an analysis of grey matter volumes of the whole-brain, frontal lobes and temporal lobes to assess whether there were any changes in grey matter volumes between baseline and 2–3 year follow-up.
3. Determine if there was any relationship between changes in brain structure and changes in neuropsychological functioning from baseline to 2–3 year follow-up.

One of the primary aims of neuropsychological assessment is to identify and localize structural brain abnormalities on the basis of subjects' neuropsychological test performance. In the neuropsychological literature, damage to the frontal lobe has typically been associated with deficits in tests of attention and executive functioning, while damage to the temporal lobe has often been associated with deficits in verbal learning and memory (Lezak, 1995). Furthermore, global cerebral atrophy has been associated with deficits on tests of general intelligence (Loring and Larrabee, 2006). Thus on the basis of previous research which has indicated that patients with FES experience cerebral atrophy in the frontal and temporal cortices over their first few years of their illness (Ho et al., 2003; Thompson et al., 2001), we hypothesized that: a) decreases in frontal lobe volumes would be accompanied by decreases in performance on measures of attention and executive function, b) temporal lobe decreases would be accompanied by decline in performance on verbal learning and memory, and c) whole-brain decreases would be accompanied by decline in measures of general intelligence.

2. Method

2.1. Participants

This study was undertaken as part of the Western Sydney First Episode Psychosis Project, a multimodal project investigating the clinical, neuroanatomical, neuropsychological and psychophysiological profiles of young people in western Sydney experiencing their first episode of psychosis (Harris et al., 2005). Referrals to Western Sydney and Wentworth Area Mental Health Services were screened for individuals presenting with a first episode of psychosis. Psychotic symptoms were defined as hallucinations, delusions, formal thought disorder or prominent negative symptoms that persisted for a minimum of 3 days. Exclusion criteria included substance-dependence, exposure to electroconvulsive therapy in the last 6 months, mental retardation, a neurological disorder including epilepsy, or a history of head injury causing loss of consciousness for at least 1 hour. In addition to community based early intervention services, subjects were referred from an inpatient unit for adolescents with a significant mental illness at Westmead Hospital. Two referrals were received from private practitioners.

Fifty-two patients with first-episode schizophrenia (FES) (36M/16F, 45 righthanded/7 lefthanded, age = 19.2 years ± 3.3) underwent neuropsychological and MRI testing within three months of their first presentation to mental health services with psychotic symptoms (time1). Diagnosis of schizophrenia was made using DSM-IV criteria (American Psychiatric Association, 1994), by a consensus conference of at least three senior psychiatrists, at least two of whom were independent of the study. Of the 52 baseline participants, 32 participants (23M/9F, 27 righthanded/5 lefthanded, age-at-time1 = 18.8 years ± 3) also underwent neuropsychological testing 2–3 years later (34 months ± 5.8) (time2), and 20 of these (15M/5F, 16 righthanded/4 lefthanded, age-at-time1 = 18.9 years ± 3) also underwent MRI testing at time2.

Patients' clinical profile was rated on the basis of the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), by psychiatrists who had reached an acceptable level of inter-rater reliability ($r > 0.8$). Patients' comorbid symptoms of anxiety and depression were assessed on the basis of all available information, including a semi-structured interview between the patient and the treating psychiatrist (which incorporated the PANSS-General Scale and the Calgary Depression Rating Scale (Addington et al., 1990), hospital and/or community health centre records and interviews with parents/guardians. Patients' past and present substance use was also assessed on the basis of all available information, and patients who were judged to have a past or present substance-dependence were excluded from the study.

At time1, 27 individuals were receiving atypical antipsychotic medication. Mean dose for the total sample at time1 was 252 mg/day (±208) chlorpromazine (CPZ) equivalent. In addition to the antipsychotic medication, two patients were prescribed mood stabilizers, three were receiving anti-depressant medication and three were prescribed anticholinergic medication. At time2, 24 subjects were receiving atypical