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Regional specificity of cerebrospinal fluid abnormalities in first episode schizophrenia

Katherine L. Narr [a], Robert M. Bilder [b,c], Roger P. Woods [b], Paul M. Thompson [a], Philip Szeszko [d], Delbert Robinson [d], Martina Ballmaier [a], Bradley Messenger [a], YungPing Wang [a], Arthur W. Toga [a,b,*]

[a] *Laboratory of NeuroImaging, Division of Brain Mapping, UCLA School of Medicine, 710 Westwood Plaza, Los Angeles, CA 90095-1769, USA*
[b] *Ahmanson-Lovelace Brain Mapping Center, Department of Neurology, UCLA School of Medicine, Los Angeles, CA, USA*
[c] *Department of Psychiatry and Biobehavioral Sciences, Geffen School of Medicine at UCLA, Los Angeles, CA, USA*
[d] *Department of Psychiatry Research, The Zucker Hillside Hospital, North-Shore Long Island Jewish Health Systems, Glen Oaks, NY, USA*

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Abstract

The timing and regional specificity of cerebrospinal fluid (CSF) enlargements have not been well described in schizophrenia. High-resolution magnetic resonance images and computational image analysis methods were used to localize cross-sectional changes in lateral ventricle and sulcal and subarachnoid CSF in first episode schizophrenia patients (51 males/21 females) and healthy subjects (37 males/41 females). Volumes were obtained for each lateral ventricle horn and regional differences identified by comparing the distances from the ventricular surfaces to the central core at anatomically matched locations. Extra-cortical CSF differences were compared by measuring the proportion of CSF voxels sampled from spatially homologous cortical surface points. Significant extra-cortical CSF enlargements were observed in first episode patients, where regional differences surrounded the temporal, anterior frontal and parietal cortices. Volume and ventricular surface analyses failed to show significant effects of diagnosis. However, interactions indicated dorsal superior horn expansions in female patients compared with same-sex controls. Since ventricular enlargements are widely reported in chronic patients, our observations at first episode suggest ventricular enlargement may progress after disease onset with early changes occurring around the dorsal superior horn. In contrast, sulcal and subarachnoid CSF increases may be manifest near or before the first episode but after brain development is complete, reflecting pronounced reductions in proximal brain tissue.

Keywords: MRI; Ventricles; Sulcal; Morphology; Temporal lobe; Cortex

1. Introduction

Larger cerebrospinal fluid (CSF) to brain tissue ratios, sulcal widening and ventricular enlargements observed in prior computed tomography (CT) studies (Johnstone et al., 1976; Raz and Raz, 1990) have been replicated in the majority of magnetic resonance imag-

* Corresponding author. Laboratory of NeuroImaging, Department of Neurology, Division of Brain Mapping, UCLA School of Medicine, 710 Westwood Plaza, Los Angeles, CA 90095-1769, USA. Tel.: +1 310 206 2101; fax: +1 310 206 5518.
E-mail address: toga@loni.ucla.edu (A.W. Toga).

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ing (MRI) studies of schizophrenia in recent decades (Lawrie and Abukmeil, 1998; DeLisi, 1999; Harrison, 1999; Wright et al., 2000; Shenton et al., 2001). Extra-cortical (sulcal and subarachnoid) and/or subcortical CSF enlargements have also been observed in patients experiencing their first episode of schizophrenia (DeLisi et al., 1991; Degreef et al., 1992; Nopoulos et al., 1995), where enlargements may relate to clinical outcome (Lieberman et al., 2001; Ho et al., 2003b), and have been reported in patients with no prior antipsychotic medication exposure (Fannon et al., 2000). Several studies, however, have failed to detect significant ventricular or sulcal CSF enlargements at the time of first episode (DeLisi et al., 1995, 1997; Niemann et al., 2000; Puri et al., 2001; Ho et al., 2003b), although some of these same studies report accelerated enlargements in patients during the initial years following diagnosis (DeLisi et al., 1997; Ho et al., 2003b).

Although CSF enlargements are among the most widely reported structural abnormalities observed in schizophrenia, sulcal and ventricular volume increases occur in other neuropsychiatric (Parashos et al., 1998; Salokangas et al., 2002; Strakowski et al., 2002) and degenerative disorders (Silbert et al., 2003). Sensitive image analysis techniques are thus necessary to characterize changes in CSF that may be specific to schizophrenia. Increases in CSF generally are thought to imply a corresponding loss of brain tissue once brain size has peaked during neurodevelopment (notwithstanding lack of certainty about the causes for CSF increases in schizophrenia and the field's failure so far to rule out possible causes involving more complex changes in cellular or interstitial fluid compartments). Therefore, identifying local changes in extra-cortical CSF may index regional brain tissue reductions that more closely relate to the underlying pathophysiology of the illness. Relatively few studies have investigated the regional specificity of CSF enlargements in the sulcal and subarachnoid space in schizophrenia. Measuring extra-cortical CSF volumes in lobar regions, some investigators report enlargements in all brain regions in chronic (Andreasen et al., 1994; Woods et al., 1996) and first episode schizophrenia (Nopoulos et al., 1995), while others show increases in temporal and frontal regions specifically (Zipursky et al., 1994; Cannon et al., 1998b; Sullivan et al., 1998), or no significant enlargements early in the disease course (Ho et al., 2003b; Molina et al., 2004). Only one prior study of chronic schizophrenia has examined regional CSF increases in the sulcal and subarachnoid space surrounding the entire cerebral cortex at high spatial resolution. Patients showed pronounced CSF increases surrounding perisylvian cortices, including the superior temporal gyrus bilaterally, compared with healthy subjects (Narr et al., 2003).

Regional changes in ventricular size have been the focus of several prior investigations, where enlargements of the superior and temporal horns, particularly in the left hemisphere, appear to be the most frequently observed findings (Crow et al., 1989; DeLisi, 1991; Lawrie and Abukmeil, 1998; Wright et al., 2000; Shenton et al., 2001). The proximity of the hippocampus to the temporal horn of the lateral ventricles suggests relationships between CSF enlargements and the hippocampal volume reductions that are widely documented in the illness (Nelson et al., 1998; Heckers, 2001; Harrison, 2004), and at least one study has demonstrated these relationships empirically (Suddath et al., 1989), although others have not (Degreef et al., 1992). With the use of novel computational image analysis methods, significant relationships between lateral ventricle enlargement and thalamic shrinkage and structural changes in the putamen, left superior temporal gyrus and insula have been reported (Gaser et al., 2004). To our knowledge, no prior study has focused on identifying highly localized changes in lateral ventricular morphology in first episode schizophrenia.

Investigating patients at the time of first episode can provide baseline information about structural brain abnormalities present near or before disease onset that are not affected by prolonged antipsychotic medication exposure and/or other clinical factors associated with ongoing disease processes. In this study, we thus set out to characterize regional changes in extra-cortical and subcortical CSF in a large sample of first episode schizophrenia patients, who had little or no prior antipsychotic medication exposure, compared with demographically similar healthy subjects. We employed standard volumetric methods to compare changes in whole brain tissue volumes and the volumes of each lateral ventricular horn. To isolate regional changes in sulcal and subarachnoid CSF and ventricular surface morphology, we used more sensitive computational image analysis approaches. Changes in extra-cortical CSF were measured by comparing the proportion of CSF voxels in the sulcal and subarachnoid space across the cortex at high spatial resolution after using cortical pattern-matching methods to align homologous anatomical regions between subjects (Narr et al., 2003; Thompson et al., 2004a). Local changes in ventricular morphology were estimated by comparing radial distances measured from homologous ventricular surface points to the central core