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Regional thinning of the cerebral cortex in schizophrenia: Effects of diagnosis, age and antipsychotic medication

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Abstract

Morphological abnormalities of the cerebral cortex have been reported in a number of MRI-studies in schizophrenia. Uncertainty remains regarding cause, mechanism and progression of the alterations. It has been suggested that antipsychotic medication reduces total gray matter volumes, but results are inconsistent. In the present study differences in regional cortical thickness between 96 patients with a DSM-IV diagnosis of schizophrenia ($n=81$) or schizoaffective disorder ($n=15$) and 107 healthy subjects (mean age 42 years, range 17–57 years) were investigated using MRI and computer image analysis. Cortical thickness was estimated as the shortest distance between the gray/white matter border and the pial surface at numerous points across the entire cortical mantle. The influence of age and antipsychotic medication on variation in global and regional cortical thickness was explored. Thinner cortex among patients than controls was found in prefrontal and temporal regions of both hemispheres, while parietal and occipital regions were relatively spared. Some hemispheric specificity was noted, as regions of the prefrontal cortex were more affected in the right hemisphere, and regions of the temporal cortex in the left hemisphere. No significant interaction effect of age and diagnostic group on variation in cortical thickness was demonstrated. Among patients, dose or type of antipsychotic medication did not affect variation in cortical thickness. The results from this hitherto largest study on the topic show that prefrontal and temporal cortical thinning in patients with schizophrenia compared to controls is as pronounced in older as in younger subjects. The lack of significant influence from antipsychotic medication supports that regional cortical thinning is an inherent feature of the neurobiological disease process in schizophrenia.

Keywords: Schizophrenia; Cortical thickness; Magnetic resonance imaging; Freesurfer; Antipsychotic medication

1. Introduction

The human cerebral cortex is an extensively folded ribbon consisting of discrete layers of neurons. Studies in macaque monkeys have shown that neurons migrate to their destination before birth (Rakic, 1988). Recent postmortem data suggest that new neurons are generated in the adult human hippocampus (Eriksson et al., 1998; Toro and Deakin, 2007), while there is conflicting evidence regarding adult neurogenesis in the neocortex (Abrous et al., 2005). Less than half of the cortical surface

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is visible as gyri, while the majority is buried in sulci (Griffin, 1994). This complex three-dimensional shape of the cortex renders it difficult to study both from a neuropathological and neuroimaging point of view. An automated procedure has been developed to estimate cortical thickness using magnetic resonance imaging (MRI) (Fischl and Dale, 2000).

The cerebral cortex constitutes the major part of gray matter tissue within the brain. Changes in gray matter volumes could therefore imply alterations in either cortical surface area or cortical thickness. Alternatively, variation in regional folding patterns of the cortex may explain alterations in gray matter volumes. MRI-studies have shown smaller volumes of global, frontal, and temporal gray matter as well as smaller volumes of hippocampus, cerebellum, thalamus, corpus callosum, and larger volumes of the lateral ventricles among patients with schizophrenia compared to controls (Honea et al., 2005; Shenton et al., 2001; Wright et al., 2000). A number of studies have also found thinner cortex in frontal and temporal regions both in childhood-onset (White et al., 2003), first-episode (Narr et al., 2005a,b) and chronic schizophrenia (Kuperberg et al., 2003) patients when compared to controls, though negative findings have been reported (Wiegand et al., 2004). Brain abnormalities have been shown to occur in persons with a high risk of developing schizophrenia (Job et al., 2003; Pantelis et al., 2003) and among patients with a first episode of schizophrenia (Keshavan et al., 2005; Steen et al., 2006). This indicates that at least some of the brain alterations in schizophrenia are present in the early phase of the illness. The underlying pathological process as well as the clinical importance of the gray matter loss is at present poorly understood (DeLisi et al., 2006). Postmortem studies have found lower brain weight (Harrison et al., 2003) and smaller gray matter volume (Pakkenberg, 1987) in patients relative to controls. The difference may represent reduction of neuropil (Selemon and Goldman-Rakic, 1999) or loss of glia cells (Stark et al., 2004), rather than loss of neuronal cells (Pakkenberg, 1992, 1993; Harrison, 1999a; Thune et al., 2001).

Longitudinal MRI-studies of normal aging have demonstrated a heterogeneous pattern of cortical maturation in the developing brain (Thompson et al., 2005) which at least partly is related to cognitive measures (Shaw et al., 2006). Frontal and occipital regions have thinner cortex with increasing age, while this has not been shown for temporal regions (Salat et al., 2004). In a longitudinal study of childhood-onset schizophrenia spanning over five years, the patients showed reduction of gray matter volume first in parietal, and later in temporal and prefrontal cortical areas compared to the healthy children (Thompson et al., 2001). Some cross-sectional studies of patients with schizophrenia have found an interaction effect of age and diagnosis on gray matter volumes (Hulshoff Pol et al., 2002; Velakoulis et al., 2002), indicating an accelerated loss of gray matter in schizophrenia with increasing age. With regard to cortical thickness, a negative correlation was found between age and prefrontal cortical thickness in patients with first-episode schizophrenia, but not in patients with first-episode affective psychosis or controls (Wiegand et al., 2004). In contrast, other cross-sectional studies have found no interaction effect of age and diagnostic group on variation in cortical thickness among patients with first-episode (Narr et al., 2005a,b) or chronic schizophrenia (Kuperberg et al., 2003). At present there is no published study assessing longitudinal data on cortical thickness in schizophrenia.

There is some evidence for an effect of antipsychotic medication on volumes of basal ganglia, particularly of the caudate nucleus, and total brain gray matter volume (Scherk and Falkai, 2006). The effect also appears to be influenced by gender (Heitmiller et al., 2004) and type of medication (Kopelman et al., 2005). A recent study reported reduction in frontal and total gray matter volumes among first-episode patients receiving haloperidol for two years, while no change was observed among patients receiving olanzapine (Lieberman et al., 2005). A smaller study of patients receiving treatment for an acute exacerbation of psychosis observed increase in gray matter volume in response to risperidone and ziprasidone, while no change was found in response to haloperidol treatment (Garver et al., 2005).

The aims of this hitherto largest study on the topic were to investigate differences in cortical thickness between patients with schizophrenia and healthy controls, and further investigate effects of antipsychotic medication and interaction effects between age and diagnostic group. A two-step analysis was performed: First, cortical thickness was measured at numerous points across the entire cortical mantle. Second, mean cortical thickness within selected regions of the prefrontal and temporal cortex in both hemispheres was calculated and compared between groups. Interactions between age and diagnostic group on variation in cortical thickness were also investigated in two steps: First, group differences in age regression slopes at numerous points across the cortical mantle were investigated. Second, group differences in age regression slopes of mean cortical thickness within regions where patients had thinner cortex than controls were explored. The potential effect of antipsychotic medication on variation in cortical thickness was investigated by including current and estimated lifetime exposure of medication as covariates in separate analyses among patients only.