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Progressive Reduction in Cortical Thickness as Psychosis Develops: A Multisite Longitudinal Neuroimaging Study of Youth at Elevated Clinical Risk

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ABSTRACT

BACKGROUND: Individuals at clinical high risk (CHR) who progress to fully psychotic symptoms have been observed to show a steeper rate of cortical gray matter reduction compared with individuals without symptomatic progression and with healthy control subjects. Whether such changes reflect processes associated with the pathophysiology of schizophrenia or exposure to antipsychotic drugs is unknown.

METHODS: In this multisite study, 274 CHR cases, including 35 individuals who converted to psychosis, and 135 healthy comparison subjects were scanned with magnetic resonance imaging at baseline, 12-month follow-up, or the point of conversion for the subjects who developed fully psychotic symptoms.

RESULTS: In a traveling subjects substudy, excellent reliability was observed for measures of cortical thickness and subcortical volumes. Controlling for multiple comparisons throughout the brain, CHR subjects who converted to psychosis showed a steeper rate of gray matter loss in the right superior frontal, middle frontal, and medial orbitofrontal cortical regions as well as a greater rate of expansion of the third ventricle compared with CHR subjects who did not convert to psychosis and healthy control subjects. Differential tissue loss was present in subjects who had not received antipsychotic medications during the interscan interval and was predicted by baseline levels of an aggregate measure of proinflammatory cytokines in plasma.

CONCLUSIONS: These findings demonstrate that the brain changes are not explained by exposure to antipsychotic drugs but likely play a role in psychosis pathophysiology. Given that the cortical changes were more pronounced in subjects with briefer durations of prodromal symptoms, contributing factors may predominantly play a role in acute-onset forms of psychosis.

Keywords: Inflammation, MRI, Prefrontal cortex, Prodromal, Psychosis, Schizophrenia

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Evidence of progressive loss of gray matter in individuals at clinical high risk (CHR) who convert to psychosis (1–7) suggests that disturbances in neuromaturational processes during the transition from adolescence to early adulthood (8–12) may play a role in onset of psychosis. However, numerous questions remain to be answered before such an interpretation would be warranted. First, this effect may be a secondary phenomenon. Antipsychotic drugs are associated with gray matter decline in animal models (13) and in patients with schizophrenia (14,15), including patients with a first episode (16). Because follow-up (FU) scans for converting CHR cases in all longitudinal magnetic resonance imaging (MRI) studies were performed after conversion, most of the converters (and relatively fewer of the nonconverters) received antipsychotic drug treatment during the interscan interval. In the only prior study to examine this question, converters who had not received antipsychotics during the interscan interval ($n = 5$) did not differ in rate of tissue loss from converters who did receive antipsychotics before the FU scan ($n = 5$) (5). However, this comparison was almost certainly underpowered to detect a difference if one exists; a more conclusive result would emerge from comparing the rate of loss among converters not exposed to antipsychotics during the interscan interval with nonconverters and control subjects.

If the accelerated gray matter loss associated with psychosis onset is not a secondary phenomenon, it could be due to factors related to the pathophysiology of schizophrenia and related disorders, such as neuroinflammation (17). Neuroinflammatory

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markers are elevated in postmortem neural tissue from patients with schizophrenia (18), and these same markers are associated with microglial-mediated synaptic pruning and dendritic retraction in animal models (19), providing a potential mechanistic basis for the reduced neuropil seen in patients (10). Although neuroinflammatory processes initiated during prenatal stress exposures could play a role (21), activation of such processes in association with the synaptic pruning characteristic of adolescent brain development represents an influence more proximal to psychosis onset (10,12,17,20). Recently, an elevation in plasma-based markers of inflammation and oxidative stress was found to precede and predict onset of psychosis among CHR cases (21). It remains to be determined whether such markers also predict the acceleration in gray matter loss around the time of psychosis onset.

Given that CHR cases are ascertained at different ages and at various points along the putative trajectory toward overt illness, such variability could obscure different subgroups of future converters with different profiles of change in brain structure over time. In particular, accelerated gray matter decline would be expected especially among cases with shorter durations from onset of prodromal symptoms to conversion (because the underlying pathology among cases with longer durations would likely be relatively more slowly progressing). In addition, although studies of patients with early psychosis are generally consistent in showing lower volumes in dorsolateral prefrontal, superior temporal, and parahippocampal cortex (22,23), prior longitudinal MRI studies are conflicting as to whether the steeper rate of loss in CHR converters is general or specific to these regions (1–7). However, these discrepancies may merely reflect regional differences in measurement reliability or between-study differences in statistical power.

In this multisite study, 274 CHR cases, including 35 individuals who converted to psychosis, and 135 demographically comparable healthy comparison subjects underwent MRI at baseline (BL) and at 12-month FU or the point of conversion for individuals who developed fully psychotic symptoms (24). We hypothesized that converters would show steeper rates of gray matter reduction in prefrontal, superior temporal, and parahippocampal regions compared with nonconverters and control subjects and that these effects would be present in cases without exposure to antipsychotic medications during the interscan interval. We further hypothesized that the cortical changes would be greatest among cases with a more recent onset of prodromal symptoms and that BL levels of proinflammatory cytokines would predict the rate of gray matter loss especially among converters. We also evaluated statistical power to detect differential change across brain regions by incorporating information on reliability from a traveling subjects substudy.

METHODS AND MATERIALS

Subjects

The study protocol and consent form were reviewed and approved by the institutional review boards at each of the eight data collection sites (University of California, Los Angeles, Emory, Beth Israel Deaconess Medical Center, Zucker Hillside Hospital, University of North Carolina, University of California, San Diego, University of Calgary, and Yale University). Participants were evaluated using the Structured Interview for Prodromal Syndromes (25) and the Structured Clinical Interview for Axis I (DSM-IV) (26) at each assessment by trained interviewers who met high reliability standards (intraclass correlations [ICCs] = .92–.96) (24). The CHR cases met Structured Interview for Prodromal Syndromes/Scale of Prodromal Symptoms criteria for a psychosis risk syndrome (25), excluding individuals who had ever met DSM-IV criteria for a psychotic disorder. Control participants were excluded if they met criteria for a psychotic disorder, had a first-degree relative with a current or past psychotic disorder, or met prodromal criteria. General exclusions included substance dependence, neurologic disorder, or full scale IQ <70.

Subjects included in this report are those with MRI scans at BL and at 12-month FU or at the point of conversion to psychosis. Given that nearly all (37 of 41) of the converters with both BL and FU scans available had converted before the scheduled 12-month FU, few converting subjects had FU scans before conversion. To avoid mixing cases whose FU scans occurred before and after conversion, the four converters whose FU scans were obtained before conversion were excluded from the primary analyses (but included in secondary analysis). In total, 35 CHR cases who converted to psychosis, 239 CHR cases who did not convert, and 135 healthy comparison subjects had usable data and were included. These subjects were drawn from the larger pools of subjects (n = 62 converters, n = 491 nonconverters, and n = 224 control subjects) who had BL scans. Subjects with both BL and FU scans available did not differ from subjects with BL scans only in age, sex, education, parental education, or socioeconomic class overall or in any group separately (all p values $>$ .30).[1] Demographic characteristics of the three groups are shown in Table 1. There were no significant differences in age, sex, site of origin, or socioeconomic class by group. Nonconverters had lower parental education than converters and control subjects, who did not differ. Converters and nonconverters had a higher rate of substance use disorders than the control subjects but did not differ from each other. The interscan interval was significantly briefer among converters compared with nonconverters and control subjects, who did not differ. Dividing at the median duration from onset of prodromal symptoms to FU scan among converters (26 months; range, 2–149 months) produced subgroups of 18 cases with short durations and 17 with long durations. For nonconverters, applying the same cutoff resulted in 140 cases with short durations and 76 with long durations (information on age at onset of symptoms was unavailable for the remaining 23 nonconverters).

Because this was a naturalistic study, subjects were treated in their respective communities according to prevailing standards and the judgment of the treating clinicians, who were often primary care physicians rather than psychiatrists. We

[1]Subjects who were not scanned had a slightly lower level of education (11.1 years vs. 11.9 years) and included a greater proportion of females (49% vs. 42%) compared with subjects who were scanned but did not differ on other demographic characteristics.