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Ventricular enlargement and progressive reduction of cortical gray matter are linked in prodromal youth who develop psychosis

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ABSTRACT

In a recent prospective longitudinal neuroimaging study, clinical high-risk (CHR) individuals who later developed full-blown psychosis showed an accelerated rate of gray matter thinning in superior and medial prefrontal cortex (PFC) and expansion of the ventricular system after applying a stringent correction for multiple comparisons. Although cortical and subcortical volume loss and enlarged ventricles are well characterized structural brain abnormalities among patients with schizophrenia, no prior study has evaluated whether these progressive changes of neuroanatomical indicators are linked in time prior to onset of psychosis. Therefore, we investigated the relationship between the changes in cortical gray matter thickness and ventricular volume using the longitudinal neuroimaging data from the North American Prodrome Longitudinal Study at the whole-brain level. The results showed that ventricular expansion is linked in time to progressive reduction of gray matter, rather than to structural changes in proximal subcortical regions, in a broadly distributed set of cortical regions among CHR youth, including superior, medial, lateral, and inferior PFC, superior temporal gyrus, and parietal cortices. In contrast, healthy controls did not show the same pattern of associations. The main findings were further replicated using a third assessment wave of MRI scans in a subset of study participants who were followed for an additional year. These findings suggest that the gray matter regions exhibiting aberrant rates of thinning in relation to psychosis risk are not limited to the PFC regions that survived the statistical threshold in our primary study, but also extend to other cortical regions previously implicated in schizophrenia.

1. Introduction

A recent prospective longitudinal neuroimaging study of individuals at clinical high-risk (CHR) for psychosis revealed that those who converted to psychosis showed accelerated gray matter reduction in superior and medial prefrontal cortex (PFC) and expansion of the ventricular system compared with CHR subjects who did not convert and healthy controls (Cannon et al., 2015). These aberrant brain trajectories were predicted by initial prodromal symptom severity (Chung et al., 2015) and were not explained by exposure to antipsychotics (Cannon et al., 2015). However, two inter-related questions remain to be resolved: 1) Is the accelerated gray matter decline during the psychosis

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prodrome specific to the regions of PFC that survived vertex-wise correction for multiple comparisons?; and 2) Is ventricular expansion a consequence of this cortical thinning or of more proximal (i.e., subcortical) tissue loss?

As prefrontal cortical regions continue to mature via synaptic pruning and myelination throughout adolescence (Gogtay et al., 2004; Huttenlocher, 1979; Huttenlocher and Dabholkar, 1997), an accelerated rate of gray matter loss in this region observed during the psychosis prodrome may explain why onset of schizophrenia and related disorders commonly occurs during late adolescence (Cannon et al., 2015). If over-pruning is the mechanism for accelerated gray matter reduction, then the greatest rate of synaptic loss should be occurring in regions that are undergoing maximal pruning at the time. However, given that the pruning process occurs throughout the cortex to some degree during adolescence, the acceleration effects associated with onset of psychosis may be distributed more broadly.

Neuroimaging studies such as those referred to above rely on mass-univariate statistics to identify regions that show differential change linked to onset of psychosis. Given that tens of thousands of statistical comparisons are conducted (e.g., on each vertex in the cortical surface and each subcortical region), adjustment of the observed probabilities (e.g., by means of the False Discovery Rate or similar procedure) is required to guard against type I error. Although this approach is an effective strategy in elucidating brain areas that are likely to be affected by disease processes, it has been also criticized for biasing results toward highly localized regions that survive the statistical threshold employed (Davatzikos, 2004). This may help to explain why cortical regions that are generally reduced in thickness among patients with schizophrenia, including superior temporal gyrus, parietal cortex, and lateral and inferior aspects of prefrontal cortex, were not among those detected as showing a *significantly* steeper rate of decline among converters (Cannon et al., 2015). It is notable in this regard that these regions were associated with significantly differential reductions among converters when not correcting for multiple comparisons.

Previous studies have shown that cortical gray matter volumes are inversely related with ventricular volumes among patients with schizophrenia (DeLisi et al., 2004, 1997; Gaser et al., 2004; Symonds et al., 1999). However, no prior study has evaluated whether progressive changes in these two anatomical indicators are linked in time prior to onset of psychosis. Ventricular expansion could be a consequence of thinning of the cortical gray matter ribbon in regions that undergo accelerated loss in association with onset of psychosis, or it could reflect tissue loss in more proximal brain structures such as thalamus, basal ganglia, and hippocampus (Gaser et al., 2004). One reason to suspect that the ventricular changes are linked with cortical, rather than subcortical, reductions in gray matter prior to psychosis onset is that the subcortical structures do not appear to show differential change among CHR converters to psychosis (Cannon et al., 2015). If this interpretation is correct, the explanation would likely involve reductions in extraventricular mechanical pressures against the ventricular walls as the cortical ribbon thins (rather than CSF expanding to "invade" areas of adjacent tissue loss).

Based on the foregoing, we hypothesized that the rate of expansion of the ventricular system would be highly linked in time with the rate of cortical gray matter reduction among CHR patients. Although we expected this relationship to be maximal in superior and medial aspects of PFC (where converters showed the greatest differential reductions), we hypothesized that it would also be present in other cortical regions in which patients with schizophrenia have gray matter deficits, including lateral and inferior PFC, superior temporal gyrus, and parietal cortex (Cannon et al., 2015; Pantelis et al., 2003; Rimol et al., 2012; Shenton et al., 2001).

2. Methods

2.1. Participants

The study protocol and consent form was reviewed and approved by the Institutional Review Boards at each of the 8 data collection sites (UCLA, Emory, Beth Israel Deaconess Medical Center, Zucker Hillside Hospital, UNC, UCSD, Calgary, Yale). Participants were evaluated using the Structured Interview for Prodromal Syndromes (SIPS) (McGlashan et al., 2010) and the Structured Clinical Interview for Axis I DSM-IV Disorders (Addington et al., 2012; First et al., 1995). CHR cases were defined as those who met SIPS/SOPS criteria for a psychosis risk syndrome (McGlashan et al., 2010) excluding cases who had ever met DSM-IV criteria for a psychotic disorder. Summary of demographics are shown in Table 1 and in prior studies (Cannon et al., 2015; Chung et al., 2015)

2.2. MRI scans and image processing

Detailed information about MRI protocol, image processing, and test-retest reliability are described in previous studies (Cannon et al., 2015, 2013). Briefly, five sites operated Siemens scanners and three sites operated GE scanners, all at 3 T; optimized for each scanner manufacturer, software version and coil configuration according to the ADNI protocol (http://adni.loni.ucla.edu/research/protocols/mri-protocols/). MRI structural data were acquired at baseline (BL) and 12-month follow-up (12-FU), and follow-up scans for those who developed fully psychotic symptoms were assessed at the point of conversion.

Surface-based cortical reconstruction, estimation of cortical thickness and subcortical volumetric segmentation was performed using the automated Freesurfer pipeline (http://surfer.nmr.mgh.harvard.edu/) (Dale et al., 1999; Fischl and Dale, 2000; Fischl et al., 2002, 1999, 2004). The reconstructed baseline and follow-up scans were further processed using Freesurfer's longitudinal stream (Reuter and Fischl, 2011; Reuter et al., 2010, 2012).

2.3. Statistical analysis

Imaging measures were first transformed to annualized rates of percent change (ARCH) in each cortical vertex and subcortical region of interest (ROI), where ROI-ARCH = ((ROI-FU − ROI-BL) / ROI-BL) / Interval (years). Relationships between ARCH of total ventricle volume (i.e., sum of lateral and third ventricle volume) and ARCH of cortical gray matter values were tested vertex-wise using the general linear model. False Discovery Rate (FDR) correction was set to 1% (Genovese et al., 2002). Age, sex, and scanner were treated as nuisance covariates.

For additional ROI-based statistical tests, ARCH was calculated in particular cortical and subcortical ROIs using Freesurfer (Desikan et al., 2006). In particular, superior frontal cortex (SFC) from the Desikan atlas was chosen as an exemplary ROI as this region showed accelerated rate of gray matter decline among converters exhibiting high level of unusual thought content in our previous studies (Cannon et al., 2015; Chung et al., 2015). For all ROI-based analyses, Bonferroni correction was applied when appropriate. To protect correlation coefficients from being skewed by outliers, all analyses were run with statistical outliers excluded. An outlier was defined when Studentized deleted residuals exceeded ± 3.

For the purpose of testing the replicability of our main hypotheses, subset of CHR and control subjects were followed for an additional third time point for a 24-month (24-FU) MRI assessment. Parallel set of ROI-based statistical tests were performed as described above.

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