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Progressive brain changes in children and adolescents with early-onset psychosis: A meta-analysis of longitudinal MRI studies

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ABSTRACT

Background: Studies on longitudinal brain volume changes in patients with early-onset psychosis (EOP) are particularly valuable for understanding the neurobiological basis of brain abnormalities associated with psychosis. However, findings have not been consistent across studies in this population. We aimed to conduct a meta-analysis on progressive brain volume changes in children and adolescents with EOP.
Methods: A systematic literature search of magnetic resonance imaging (MRI) studies comparing longitudinal brain volume changes in children and adolescents with EOP and healthy controls was conducted. The annualized rates of relative change in brain volume by region of interest (ROI) were used as raw data for the meta-analysis. The effect of age, sex, duration of illness, and specific diagnosis on volume change was also evaluated.
Results: Five original studies with 156 EOP patients (mean age at baseline MRI in the five studies ranged from 13.3 to 16.6 years, 67.31% males) and 163 age- and sex-matched healthy controls, with a mean duration of follow-up of 2.46 years (range 2.02–3.40), were included. Frontal gray matter (GM) was the only region in which significant differences in volume change over time were found between patients and controls (Hedges' g −0.435, 95% confidence interval (CI): −0.678 to −0.193, $p < 0.001$). Younger age at baseline MRI was associated with greater loss of temporal GM volume over time in patients as compared with controls ($p = 0.005$). Within patients, a diagnosis of schizophrenia was related to greater occipital GM volume loss over time ($p = 0.001$).
Conclusions: Compared with healthy individuals, EOP patients show greater progressive frontal GM loss over the first few years after illness onset. Age at baseline MRI and diagnosis of schizophrenia appear to be significant moderators of particular specific brain volume changes.

1. Introduction

Recent meta-analyses assessing longitudinal brain changes over a 2- to 10-year follow-up period in patients with adult-onset schizophrenia suggest progressive decreases over time in cortical gray matter (GM) volume compared with healthy controls (Olabi et al., 2011; Vita et al., 2012; Fusar-Poli et al., 2013; Haijma et al., 2013). These changes seem to be even greater in patients with early-onset psychosis (EOP, i.e., patients with psychotic symptoms appearing before the age of 18 years and diagnosed with psychotic disorder) (Gogate et al., 2001; Vita et al., 2012), especially during the first 1–3 years after the onset of psychotic symptoms (Arango et al., 2012; Brent et al., 2013).

In particular, compared with healthy controls, patients with EOP – both those with first-episode psychosis (FEP) and non-FEP patients – show greater progressive GM volume decreases over time in total GM volume (TGV), and frontal GM and parietal GM volumes (Jacobsen et al., 1998; Rapoport et al., 1999; Thompson et al., 2001; Gogtay et al., 2004b; Reig et al., 2009a; Arango et al., 2012). EOP patients also show greater decreases in cerebellar (Keller et al., 2003a; Greenstein et al., 2011), hippocampal (Jacobsen et al., 1998; Giedd et al., 1999; Nugent et al., 2007; Mattai et al., 2011a; Johnson et al., 2013b), and thalamic volumes (Rapoport et al., 1997; James et al., 2002; Janssen et al., 2012), and greater increases in lateral ventricle volume (Rapoport et al., 1997; Giedd et al., 1999; James et al., 2004).

However, findings in EOP patients have not been consistent across longitudinal studies. One study reported loss of corpus callosum (CC) volume over time (Keller et al., 2003b), which was not reported in Johnson et al. (2013a). Several studies showed greater progressive loss of temporal GM volume over time compared with healthy controls (Jacobsen et al., 1998; Rapoport et al., 1999; Gogtay et al., 2004b;

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James et al., 2004), but see Arango et al. (2012). There were even two studies reporting an absence of progressive brain changes in patients over the first 2–3 years of follow-up (James et al., 2002; James et al., 2004).

Discrepant volumetric findings in young people may be at least partly attributable to different factors and conditions that moderate the detected pattern of structural brain changes, i.e., 1) differences in sex proportion (Lenroot et al., 2007; Janssen et al., 2012), 2) age at onset (Vita et al., 2012), 3) duration of illness (Haijma et al., 2013), 4) duration of follow-up (Vita et al., 2012; Haijma et al., 2013), 5) brain regions of interest (ROIs) under study (Arango et al., 2008), 6) use of voxel-based morphometry (VBM) versus ROI-based approaches (Giuliani et al., 2005), 7) exposure to lithium or antipsychotic treatment (Navari and Dazzan, 2009; Ho et al., 2011; Hafeman et al., 2012; Fusar-Poli et al., 2013; Haijma et al., 2013), 8) symptom presentation and severity (DeLisi et al., 1998; Strakowski et al., 2002; Nery et al., 2009; Arango et al., 2012), and 9) diagnostic heterogeneity (Arango et al., 2008; Arango et al., 2012).

Childhood-onset schizophrenia (COS) is defined as schizophrenia with onset prior to age 13 years. Individuals with COS are reported to show a higher rate of pre-psychotic neurodevelopmental problems as compared with adolescent-onset cases (Hollis, 1995; Arango et al., 2008). Cross-sectional and longitudinal studies report GM volume deficits in COS that could be considered an *exaggeration* of GM development reported in typically developing subjects (Thompson et al., 2001; Greenstein et al., 2006; Burke et al., 2008), while studies in patients with late-adolescent-onset and adult-onset forms of the disease (adult-onset schizophrenia — AOS) report less marked differences in parietal GM volume and more marked differences in the later maturing prefrontal and temporal cortices as compared with their childhood-onset counterparts (Rimol et al., 2010; Rimol et al., 2012; Janssen et al., 2014a). This is also true for first-episode non-schizophrenia patients (e.g., patients with early-onset bipolar disorder) who are reported to show similar, albeit less marked and widespread, age-related GM volume abnormalities and trajectories than SSD patients (Farrow et al., 2005; Janssen et al., 2008; El-Sayed et al., 2010; Janssen et al., 2014b). This suggests a neurobiological continuum between EOP and adult-onset psychosis (AOP) (Arango et al., 2008), with the former following a more severe clinical and functional course (Driver et al., 2013; Bernardo and Bioque, 2014).

In typically developing individuals, maturation of TGV includes an increase during childhood with a peak around puberty, followed by a sustained decrease during adolescence (Gogtay et al., 2004a). However, rate and amount of GM loss varies by region and age, supposedly starting in the dorsal parietal cortices around puberty and then spreading rostrally over the frontal cortex (after reaching peak volume at 11–12 years old) and caudally and laterally over the occipital, parietal, and finally the temporal cortices (after reaching peak volume at 16–17 years old) (Gogtay et al., 2004a) and the dorsolateral prefrontal cortex, which does not reach adult dimensions until the early 20s (Lenroot et al., 2007). In fact, longitudinal trajectories suggest that the rate of cortical and hippocampal GM loss plateaus during adolescence (Giedd et al., 1999; Sporn et al., 2003). The pattern of morphological brain changes in EOP patients may thus be modulated by age (and thus stage of brain development) at illness onset.

Studies on brain volume changes in children and adolescents with psychosis seem to be particularly valuable for understanding the neurobiological basis of the illness overall (Brent et al., 2013). However, to date, a meta-analysis on progressive brain volume changes in children and adolescents with EOP has never been conducted.

The primary goal of the current meta-analysis was to examine to what extent EOP patients undergo progressive brain volume changes compared with healthy controls. We also aimed to assess the effect of factors potentially affecting brain volume change, such as age, male to female ratio, duration of illness, and specific diagnosis.

2. Methods

2.1. Selection procedures

2.1.1. Search strategies

Using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for literature search, a systematic two-step literature search was conducted to identify appropriate studies (Moher et al., 2009). First, a PubMed, Web of Science, and Embase search was performed to detect putative longitudinal MRI studies in EOP. The search was conducted from inception through May 2014. The following search terms were used: "magnetic resonance imaging" (MRI) (OR "MRI" OR "neuroimaging") AND "psychosis" (OR "schizophrenia") AND adolescent (OR "child") AND "longitudinal" (OR "progressive" OR "follow-up") NOT review, and combinations of the above terms. Second, the reference list of the selected articles was manually checked for any studies not identified by the computerized literature search. There was no language restriction.

2.1.2. Selection criteria

Studies were considered for review if they met the following hierarchical criteria: 1) they were published as original peer-reviewed articles; 2) they compared patients with a diagnosis of psychotic disorder (according to DSM-IV, DSM-III-R, or ICD-10) with age- and sex-matched healthy controls; 3) patients were younger than 18 years old at the beginning of the psychotic illness; 4) the studies had a longitudinal design (i.e., patients and controls were followed over a time period and underwent two or more MRI assessments); and 5) they used ROI volumetric analysis of structural MRI data (studies providing information on areas, volume estimation by means of an inadequate number of slices, VBM, cortical pattern matching, diffusion tensor imaging, tractography, or other techniques that do not provide brain volumetric data for a priori defined anatomical regions of interest were not included).

Studies were excluded if 1) there were fewer than five subjects in the EOP group and/or the control group; 2) the data overlapped with those of another publication assessing the same ROIs, in which case the publication with the largest group size was selected; 3) the data did not contribute to an ROI included in the meta-analyses (meta-analyses were conducted when at least 3 independent studies reported the volume of the specific ROI); and 4) the means and standard deviations (SDs) of the baseline and follow-up volumes of the included ROIs were not reported (or could not be extracted from the reported data or retrieved from the authors).

Supplementary Table 1 provides a summary of longitudinal MRI studies in EOP and the reason for exclusion from this meta-analysis as appropriate.

2.1.3. ROI selection and data abstraction

The following ROIs were included in the meta-analysis: total brain volume (TBV), TGV, frontal GM volume, parietal GM volume, temporal GM volume, and occipital GM volume. For each of the ROIs, brain volume changes were extracted as the primary outcome. Specifically, volume was extracted in mL, and the mean and SD of the percentage change in volume were computed as follows: [(volume at follow-up − volume at baseline) / volume at baseline] * 100. Annualized rates of loss of brain volume were then estimated by dividing the percentage volume change over time in each study by the mean inter-scan interval (all included studies had a mean interval >1 year). These were the raw data used for meta-analysis (see Supplementary Table 2 for details).

When articles provided data for defined subgroups (for example, by sex or by left/right hemisphere), the data were combined (weighted by the sample size of each group) so that each study contributed only one datapoint per ROI to the meta-analysis. This was done in order to make the data from the different studies comparable.