Schizophrenia Research 173 (2016) 152–158

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Baseline grey matter volume of non-transitioned "ultra high risk" for psychosis individuals with and without attenuated psychotic symptoms at long-term follow-up

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ARTICLE INFO

Article history:
Received 20 January 2015
Received in revised form 4 May 2015
Accepted 7 May 2015
Available online 29 May 2015

Keywords:
Ultra-high risk
Psychosis
Attenuated psychotic symptoms
Non-transition
Imaging
Grey matter volume

ABSTRACT

Introduction: Two thirds of individuals identified as ultra-high risk (UHR) for psychosis do not transition to psychosis over the medium to long-term (non-transition; UHR-NT). Nevertheless, many of these individuals have persistent attenuated psychotic symptoms (APS). The current study examined whether there were differences in baseline grey matter volume (i.e. at initial identification as UHR) in UHR-NT individuals whom had APS compared to those without APS (No-APS) at medium to long-term follow-up.
Methods: Participants were help-seeking individuals who were identified as being at UHR for psychosis between 2 and 12 years previously (mean = 7.5). The sample consisted of 109 participants who underwent a Magnetic Resonance Imaging scan at baseline and who had not been observed to develop a psychotic disorder over the follow-up period (UHR-NT). Using voxel-based morphometry, baseline grey matter volume (GMV) was compared between participants with (N = 30) and without (N = 79) APS at follow-up.
Results: At baseline, the APS and No-APS groups were clinically indistinguishable. At follow-up, the APS group had significantly worse symptoms and impaired functioning. Individuals with APS had reduced baseline GMV in frontal, temporal, posterior and cingulate regions compared to those without APS at follow-up. Reduced GMV was associated with more severe positive, negative and depressive symptoms and lower global functioning in the combined UHR-NT cohort. These associations were independent of later APS outcome.
Discussion: This study found that differences in regional GMV are discernible at an early stage of UHR and may be specific to individuals who have APS and psychopathology at follow-up. Our findings suggest that lower GMV at baseline may confer neurobiological risk for later APS and/or increased psychopathology while the absence of these structural abnormalities might be protective.

1. Introduction

A large body of research has examined the neuroanatomical characteristics of clinical help-seeking samples identified as being at ultra high-risk (UHR) for psychosis. Both cross-sectional and longitudinal studies have typically focused on identifying differences between individuals with clinical UHR in comparison to healthy controls, as well as individuals categorized either as having transitioned (UHR-T) or not transitioned (UHR-NT) to psychosis in order to identify vulnerability predictors for transition to psychotic illness. Research employing structural magnetic resonance imaging (MRI) has reported subtle but widespread neuroanatomical abnormalities in temporo-parietal, prefrontal and limbic regions in UHR, with evidence for more pronounced abnormalities in UHR-T (for reviews see Bois et al., 2015; Fusar-Poli et al., 2011; Smieskova et al., 2010). However, about two-thirds of help-seeking individuals identified as at risk for developing psychosis do not transition to frank psychotic disorder over the medium term (Fusar-Poli et al., 2012). This suggests that neuroanatomical alterations

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http://dx.doi.org/10.1016/j.schres.2015.05.014
0920-9964/

in UHR may represent markers other than, or in addition to, vulnerability to psychosis, such as outcomes related to non-transition or other non-psychotic disorders. Despite the large proportion of UHR individuals who do not develop psychosis there is little research examining the clinical and biological correlates of this cohort followed over the long-term.

There is a paucity of imaging studies in UHR that have specifically assessed the morphological characteristics of individuals who did not develop psychosis. Of studies that compared UHR-NT individuals to controls, increases (Fornito et al., 2008), decreases (Phillips et al., 2002; Garner et al., 2005) and no change (Takahashi et al., 2009; McIntosh et al., 2011; Ziermans et al., 2012) in brain structure have been identified in UHR-NT. Even fewer studies have examined neuroimaging indices in relation to clinical outcomes of UHR-NT. To our knowledge, only one brain structural study has defined subgroups of UHR-NT according to their long-term clinical outcome; those who remained 'well' (no symptoms) and those who reported one or more psychotic symptoms throughout the follow-up period (McIntosh et al., 2011). Although no differences in brain structure (either at baseline or over time) were detected between the two UHR-NT subgroups, this study raises the possibility that other outcomes of the UHR-NT group might be associated with discrete neurobiological changes. In addition, as this study consisted of relatives who were at risk for schizophrenia (genetic at-risk paradigm) it is possible that individuals with an elevated risk for psychosis based on clinical or help-seeking factors might show a different neuroanatomical profile (see Nenadic et al., 2015).

Recent studies have demonstrated that UHR-NT individuals have a wide range of outcomes with respect to symptomatic, functional and non-psychotic disability (Schlosser et al., 2012). At follow-up, many individuals present with significant non-psychotic mental health problems, poor psychosocial functioning and negative symptoms (e.g. Addington et al., 2011; Lin et al., 2011; Salokangas et al., 2013). A proportion (23–50%) of UHR-NT individuals also experience attenuated psychotic symptoms (APS) (Haroun et al., 2006; Lemos-Giraldez et al., 2009; Simon and Umbricht, 2010; Addington et al., 2011; Velthorst et al., 2011; Ziermans et al., 2011), which often co-occur with functional impairment and comorbidity. The presence of APS in UHR-NT individuals provides the opportunity to assess the impact of subthreshold intensity or frequency of psychotic symptoms on biological indices. This is highly relevant given recent discussions concerning the arbitrary nature of the cut-off for psychosis that may not be optimal for measuring associated functional and neurobiological changes (see Lin et al., 2012). As the UHR literature has primarily examined neurobiological correlates of threshold psychotic symptoms (i.e. symptoms exceeding the threshold for frank psychotic disorder), the neurobiological associations of attenuated (subthreshold) psychotic symptoms remain unknown.

We have recently examined the course and outcomes of UHR individuals who did not develop a psychotic disorder over a period of 2 to 14 years (the PACE 400 sample) (Lin et al., 2015). This work identified that 28% of individuals reported APS at follow-up. The current study aimed to assess the brain structural predictors of the APS outcome in this UHR-NT cohort. We sought to examine whether there were differences in baseline grey matter volume (GMV) in UHR-NT individuals whom had APS compared to those who did not experience such symptoms at follow-up (No-APS). Based on structural imaging studies in UHR-T, and given the arbitrary nature of the 'psychosis threshold' (Yung et al., 2010), we predicted that individuals with APS at follow-up would have reduced GMV at baseline in prefrontal, temporal and limbic regions compared to UHR-NT individuals with No-APS.

2. Methods

2.1. Participants and design

PACE is a specialist clinic for young people at UHR for psychosis in Melbourne, Australia. Data for the current study was taken from a larger sample of 416 UHR individuals, described previously (Nelson et al., 2013; Lin et al., 2015). The current study involves only the UHR-NT individuals whom had undergone a structural MRI scan at baseline (N = 114). Of these participants, 34 presented with current APS at follow-up that were at/above the threshold for UHR (but below the threshold for transition) and 80 reported no APS (below UHR threshold; No-APS) at follow-up (see Lin et al., 2015 for full description of APS in the wider PACE sample). The presence of APS was not measured in the interim of the baseline and follow-up assessment. Of this dataset, 5 scans were excluded; one for having a different voxel size to the rest of the scans and 4 for having poor covariance after preprocessing, leaving a total sample of 109 individuals (30 APS, 79 No-APS at follow-up) in the current study.

At baseline, participants were aged 15 to 30 years and met UHR criteria, defined by presenting with at least one of: 1) attenuated psychotic symptoms, 2) brief limited intermittent psychotic symptoms, and/or 3) trait vulnerability for psychotic illness (schizotypal personality disorder or history of psychosis in a first-degree relative) and deterioration in functioning or chronic low functioning (see Nelson et al., 2013 for full description of UHR criteria of this cohort). Exclusion criteria for entry to PACE are a previous psychotic episode, organic cause for presentation or past anti-psychotic exposure equivalent to a haloperidol dose of >15 mg. Participants with and without APS were matched for age and gender. The local Research and Ethics Committee approved the study. All participants provided written informed consent.

2.2. Clinical measures

At baseline, psychopathology was measured using the psychotic subscale of the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962), Scale of Assessment for Negative Symptoms (SANS) (Andreasen, 1981) and The Comprehensive Assessment of At-Risk Mental States (CAARMS) (Yung et al., 2005). CAARMS positive subscales were disorders of thought content, perceptual abnormalities and conceptual disorganization. Functioning was assessed with the Global Assessment of Functioning (GAF) (Endicott et al., 1976) and current IQ with the Wechsler Adult Intelligence Scale-Revised (WAIS-R; Wechsler, 1981) or the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) following the procedure outlined in Lin et al. (2011). Younger participants were assessed using the Wechsler Intelligence Scale for Children (WISC-III; Wechsler, 1991) as an alternative to the WAIS-R. At follow-up the CAARMS was used to assess the presence of APS. Psychopathology was measured using the BPRS, SANS, Hamilton Anxiety Rating Scale (HAM-A) (Hamilton, 1959) and Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960) and functioning with the GAF.

2.3. MRI acquisition

50.5% of the T1-weighted MRI scans were acquired on a 1.5 T GE Signa MR scanner with the following parameters: 124 slices of 1.5 mm thickness, TR = 1.43 s, TE = 3.3 ms, flip angle 30°, matrix 256 × 256, and FOV 24 cm. The remaining 49.5% of MRI scans were acquired on a 3 T GE LX Horizon Scanner: 124 slices of 2 mm thickness, TR = 3.6 s, TE = 9 ms, flip angle 30°, matrix 410 × 410, and FOV 20 cm. The APS and No-APS groups were matched on the proportion undergoing 1.5 T versus 3 T.

2.4. Voxel-based morphometry

Whole-brain voxelwise analysis of baseline GMV was conducted using optimized voxel-based morphometry (VBM8), as implemented in statistical parametric mapping (SPM8) software (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/) running in Matlab R2014b http://www.mathworks.com.au/products/matlab/). Briefly, T1 images were normalized to a template space and segmented into grey matter,