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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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DOI:
10.1016/j.schres.2015.05.014

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Document Version
Peer reviewed version

Citation for published version (Harvard):
Cropley, VL, Lin, A, Reniers, RLEP, Wood, SJ, Nelson, B, Yung, AR, Bartholomeusz, CF, Klauser, P, Velakoulis, D, McGorry, P & Pantelis, C 2016, 'Baseline grey matter volume of non-transitioned "ultra high risk" for psychosis individuals with and without attenuated psychotic symptoms at long-term follow-up', *Schizophrenia Research*, vol. 173, no. 3, pp. 152-158. https://doi.org/10.1016/j.schres.2015.05.014

Link to publication on Research at Birmingham portal

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Checked October 2015

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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.

Keywords: ultra-high risk, psychosis, attenuated psychotic symptoms, non-transition, imaging, grey matter volume

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 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 (Garner et al., 2005; Phillips et al., 2002) and no change (McIntosh et al., 2011; Takahashi et al., 2009; 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) (Addington et al., 2011; Haroun et al., 2006; Lemos-Giraldez et al., 2009; Simon and Umbricht, 2010; 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 (Lin et al., 2015; Nelson et al., 2013). 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.

2.3 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 disorganisation. 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.

2.4 MRI acquisition

50.5% of the T1-weighted MRI scans were acquired on a 1.5T GE Signa MR scanner with the following parameters: 124 slices of 1.5mm thickness, TR=1.43s, TE=3.3ms, flip angle 30º, matrix 256x256, FOV 24cm. The remaining 49.5% of MRI scans were acquired on a 3T GE LX Horizon

Scanner: 124 slices of 2mm thickness, TR=3.6s, TE=9ms, flip angle 30º, matrix 410x410, FOV 20cm. The APS and No-APS groups were matched on the proportion undergoing 1.5T versus 3T.

2.5 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, white matter and cerebrospinal fluid. Native-space grey matter segments were then spatially aligned to a high-dimensional Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) template and normalized to MNI space. Grey matter voxels were multiplied by the non-linear components only (modulated normalized – non-linear only) to provide a measure of the absolute amount of tissue corrected for individual brain sizes. Data quality and homogeneity of the images were checked. Images of four participants were excluded from the original dataset due to the covariance being more than two standard deviations removed from the mean. Prior to statistical analysis, images were smoothed with an 8mm full-width-half-maximum Gaussian kernel.

2.6 Statistical analysis

The General Linear Model (GLM) was performed to test for group differences in baseline GMV at each voxel. An independent t-test with age at baseline, sex and field strength of the scanner as nuisance factors was defined to test for volumetric differences between the APS and No-APS groups. Group differences were corrected for statistical type I error with a cluster-based procedure (Friston et al., 1994) using the 3dClustSim tool implemented in AFNI (http://afni.nimh.nih.gov/pub/dist/doc/program_help/3dClustSim.html). A voxel-wise threshold was set to 0.01 to compromise between sensitivity to spatially extended versus focal and intense

differences. Cluster size threshold (i.e. *k* values) was corrected for non-stationarity (Hayasaka et al., 2004) with the VBM8 toolbox (http://dbm.neuro.uni-jena.de/467/).

Statistical analyses of demographic and clinical variables were performed using the Statistical Package for Social Sciences (SPSS, v21.0). Differences in these variables between groups were analysed with independent t-tests or Pearson's χ^2 statistics for continuous and categorical variables, respectively. The Mann-Whitney U Test was performed for non-parametric variables. Correlations were analysed between the mean GMV extracted from the significant cluster detected in the group comparison and clinical variables at follow-up (BPRS, SANS, GAF, HAM-A, HAM-D) using Pearson's correlation coefficient with bootstrapping (5000 samples) or Spearman's correlation coefficient for non-parametric variables. Correlations were performed in the whole (combined) sample and in each group (APS and No-APS) separately. Correlations between mean GMV and clinical variables at baseline, and with change scores (follow-up minus baseline score), were explored. P-values <0.05 was considered statistically significant.

3. Results

3.1 Demographics and clinical characteristics of study sample

Demographic and clinical characteristics of the APS and No-APS groups are presented in Table 1. In this sample, follow-up was conducted between 2 and 12 years after baseline (*M*=7.5; *SD*=3.0; median=6.9). The APS and No-APS groups were well matched in age at baseline, sex, field strength of scanner, time to follow-up and in the UHR membership criteria at intake. At baseline, the APS and No-APS groups showed no differences in positive and negative symptoms and functioning. However the APS group had a significantly lower IQ than the No-APS group. At follow-up, the APS group had significantly higher symptoms (positive, negative, anxiety and depression) and lower functioning. Antipsychotic and antidepressant use at baseline (i.e. at time of scanning) was documented for 70% of the sample. Of these participants, none reported taking

antipsychotics and 10 (13.2%) reported using antidepressants. Antipsychotic and psychiatric medication use for the entire follow-up period (i.e. after baseline) was documented for 90% of the sample. Of these participants, 5 (5.1%) reported using antipsychotic medication and 46 (47%) reported using any psychiatric medication "some or all of the time" in the follow-up period. There was no difference between APS and No-APS individuals in the frequency of reported antipsychotic use. However, those with APS reported using psychiatric medication significantly more than those without APS (68% vs. 39% respectively). 21 (19.3%) of the participants received low-dose antipsychotics and 10 (9.2%) received low-dose lithium as trial treatment at PACE (after study entry). The proportion of individuals receiving trial treatment did not differ between the APS and No-APS groups.

3.2 Voxel-based morphometry

Individuals with APS at follow-up had significantly reduced GMV at baseline compared to those without APS at follow-up (Figure 1 and Table 2). Reduced GMV was found in clusters encompassing the right middle frontal gyrus, right precuneus/posterior cingulate cortex, and left inferior temporal gyrus, inferior orbitofrontal gyrus extending to the temporal pole and parahippocampal gyrus, inferior and superior occipital cortex and pre- and postcentral gyrus. A secondary analysis covarying for baseline IQ did not appreciably change the results. For the other contrast (APS>No-APS), no significant differences were detected.

3.3 Correlations with clinical measures

Mean GMV was negatively correlated with BPRS positive (*rho*=-.27, *p*=.006), SANS (*rho*=-.31, *p*=.001) and HAM-D (*rho*=-.28, *p*=.003) scores, and positively correlated with GAF scores (*r*=.31, *p*=.001) at follow-up in the combined UHR-NT sample (Figure 2). These correlations were not significant when performed in the APS and No-APS groups separately. No relationships were detected between mean GMV and HAM-A scores at follow-up. No significant correlations were

detected between mean GMV and clinical scores or IQ at baseline. Mean GMV was significantly associated with change in GAF score (r=.255, p=.007; follow-up minus baseline).

4. Discussion

This study examined a group of individuals defined as UHR for psychosis at baseline who did not transition to psychosis over a medium to long-term follow-up period (mean of 7 years). We evaluated baseline MRI scans (i.e. at initial identification as UHR) in this cohort by comparing those with APS at the follow-up assessment in comparison to those without such symptoms at follow-up. At baseline, both groups were similar in their clinical and demographic characteristics, including no differences in APS. At follow-up, the two groups differed significantly on measures of positive and negative symptoms, as well as in functioning. Thus, those with attenuated symptoms at follow-up had ongoing symptoms and functional disability, despite not meeting criteria for full-threshold psychosis.

We found that individuals with APS at follow-up had significantly reduced baseline GMV compared to those without APS at follow-up. Regions with reduced GMV included the right middle frontal (dorsolateral prefrontal cortex) and precuneus/posterior cingulate regions, and left temporal, orbital and pre- and postcentral gyri. Reduced volume was also associated with more severe positive, negative and depressive symptoms and lower functioning at follow-up. These associations were not found in the APS and No-APS groups separately, neither at baseline, suggesting that the associations between GMV and later outcome were driven by group membership. Thus, while the UHR-NT subgroups did not differ in their clinical characteristics at baseline, differences in GMV were discernible at this early stage and these differences were associated with APS and measures of psychopathology at follow-up.

The regions showing reduced GMV in the APS group are similar to those reported as reduced in UHR-T. Reduced volumes or thickness have been demonstrated in UHR-T most consistently across temporo-parietal, prefrontal and limbic regions, but also the cerebellum, in cross-sectional (Borgwardt et al., 2007; Koutsouleris et al., 2009; Mechelli et al., 2011; Pantelis et al., 2003) and longitudinal (Borgwardt et al., 2008; Cannon et al., 2015; Dazzan et al., 2012; Job et al., 2005; McIntosh et al., 2011; Pantelis et al., 2003; Ziermans et al., 2012) studies. Our findings in APS are largely consistent with the above findings in UHR-T samples. What is novel with the current study however is that we have focused on a different aspect of long-term outcome, rather than transition as the primary outcome of interest. Thus, our findings suggest that reduced GMV in select frontal, temporal and posterior regions at baseline are associated with not only later transition to psychosis but to the presence of attenuated psychotic symptoms in a population of UHR individuals who did not transition to psychosis after 2-12 years.

At the time of scanning the APS and No-APS groups were clinically indistinguishable. There are several interpretations for the volumetric differences detected between them and the associations with clinical measures of psychopathology. First, the volumetric reductions may be neurobiological markers of an increased risk to psychosis. Thus, an APS outcome in non-transitioned individuals might reflect a continuing risk for transition to psychosis, with reduced GMV at baseline representing a potential marker for the eventual development of a psychotic disorder. Nevertheless, this is unlikely given that the highest risk for transition was found to be within the first 2 years after identification as UHR in this sample (Nelson et al., 2013) and the mean follow-up period of the APS group in our study was 7.4 years. Second, the volumetric reductions might indeed confer increased risk for psychotic disorders, but conventional means for defining psychosis onset are ineffective at detecting this risk. Since the threshold for transition from attenuated to frank psychotic disorder is arbitrary (Lin et al., 2012; Yung et al., 2010), this currently accepted threshold may not be optimal for identifying neurobiological changes associated with psychosis or the

schizophrenia spectrum. In the current and wider sample of this cohort (Lin et al., 2015; Lin et al., 2011), many people who never transition continue to experience functional impairment, negative, depressive and attenuated psychotic symptoms years after identification as UHR. It is therefore conceivable that this clinical presentation represents 'soft' or 'simple' schizophrenia within the schizophrenia spectrum, despite the absence of development of full-threshold psychosis. Our findings showing reduced GMV at baseline in APS and associations with measures of poor outcome supports this view and raises the possibility that brain morphological alterations may occur at lower intensity/frequency of positive symptoms. Finally, the baseline volumetric differences may represent a neurobiological risk marker for later psychopathology/poor prognosis, rather than later presence of psychotic symptoms (threshold or subthreshold) per se. In this context, presence of APS at follow-up may reflect "clinical noise" associated with poor prognosis or non-psychotic clinical conditions. As above, the associations found between baseline GMV and psychopathology supports this view. Although these associations were confounded by group status, it is conceivable that individuals grouped on the basis of psychopathology such as negative and depressive symptoms would show similar volumetric differences. Despite the GMV differences between APS and No-APS remaining unclear, these findings have implications for the identification of vulnerability markers of psychosis and other outcomes and emphasise the need for future studies to include endpoints other than the traditional approach to defining psychosis onset (Lin et al., 2012).

When viewed from the perspective of the No-APS group, our findings suggest that greater GMV at baseline is predictive of better outcome and that regional volume confers neurobiological resilience in the long-term (for discussion see Pantelis and Bartholomeusz, 2014). Importantly, the group with APS at follow-up had also not made the transition to psychosis. Thus, while they may remain chronically at high-risk, this lack of transition suggests that other protective factors may be at play.

An important question our data raises is whether changes in GMV are associated with changes in symptoms and function over time. As described above, longitudinal imaging studies have identified brain changes in UHR-T (for review see Bois et al., 2015), but not in UHR-NT (Borgwardt et al., 2008; McIntosh et al., 2011) individuals. The volumetric differences at baseline may also represent a neurobiological process in those with ongoing psychotic features (threshold or subthreshold), while the opposite may occur in those without ongoing symptoms. This assertion is supported by a recent longitudinal imaging study in UHR-NT individuals (Katagiri et al., 2015), where a relative 'normalization' of white matter integrity correlated with improved clinical outcome. Although we found a significant correlation between baseline GMV and *change* in functioning, it is not known whether there were corresponding changes in GMV. Longitudinal studies examining differences in trajectories between the APS and No-APS groups would help elucidate whether there is on-going neuroprogression or normalization with time associated with different clinical outcomes.

The main strengths of this study are the novel outcome measure (with/without APS) in those who did not transition to psychosis and the long follow-up period. The greatest limitation is the variable length of the follow-up period and the different field strength of the scanners (1.5 and 3T), although these variables were near identical between the APS and No-APS groups and field strength was additionally used as a covariate in the between-group analysis.

This study found that differences in regional GMV were discernible at an early stage of UHR and may be specific to individuals who continue to have attenuated psychotic symptoms 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. Comparison of GMV in the non-transition APS and No-APS groups with a healthy control and transitioned (UHR-T) group, along with longitudinal assessment, will help elucidate the significance of these findings.

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Figure Legends

Figure 1. Voxel-based morphometric differences of grey matter volume between APS and No-APS UHR-NT groups

A). Areas showing reduced grey matter volume at baseline in non-transitioned UHR individuals with APS at follow-up compared to individuals without APS at follow-up (contrast No-APS>APS). Clusters resided in the frontal, temporal and posterior regions. T-values at each voxel are provided by the scale bar. MNI coordinates are shown on the top of each slice for the y-axis, x-axis and z-axis, respectively. B). Plot of the mean grey matter volume in the significant clusters in the APS and No-APS groups. **** p<.0001.

Figure 2. Relationships between grey matter volume and clinical variables at follow-up in UHR-NT

Scatterplots illustrating the significant correlations between mean grey matter volume in the significant cluster in the group comparison with clinical score at follow-up. Reduced grey matter volume was associated with increased positive, negative and depressive symptoms and decreased functioning at follow-up. Blue squares represent APS individuals and red circles represent No-APS individuals. *p<.05, **p<.01.

Table and Figures

Table 1

Demographic and clinical characteristics of study participants

	No-APS (79)	APS (30)	t/χ^2	*p*-value
Age at baseline (years)	19.80 ± 3.47	19.93 ± 3.44	0.18	.855
Sex (M/F)	40/39	15/15	.003	.953
% Scanner Field Strength (1.5T/3T)	51.9/48.1	46.7/53.3	.238	.626
Time to follow-up (years)	7.61 ± 2.89	7.35 ± 3.16	-0.63[a]	.528
% Handedness (R/L)	86.5/13.5	82.1/17.9	0.31	.755
IQ at baseline	103.3 ± 12.1	93.5 ± 15.7	3.39	.001
Intracranial volume	1411 ± 154	1381 ± 148	.923	.358
Use of antidepressants at baseline	16.1%	5.0%	1.58	.209
Use of antipsychotics during follow-up period	2.9%	10.3%	2.40	.148
Use of any psychiatric medication during follow-up period	38.6%	67.9%	6.89	.013
Trial treatment with antipsychotics	19%	20%	0.014	.905
Trial treatment with lithium	8.9%	10%	0.34	.854
BPRS psychotic subscale at baseline	8.77 ± 2.67	9.59 ± 2.81	1.39	.168
SANS total at baseline	17.67 ± 11.48	18.55 ± 11.66	0.617[a]	.537
GAF score at baseline	61.25 ± 11.65	60.33 ± 9.90	0.38	.703
Intake criteria – APS	58.2%	46.7%	1.17	.291
Intake criteria – BLIPS	3.8%	13.3%	3.29	.089
Intake criteria – vulnerability	20.3%	20.0%	.001	.977
Intake criteria – APS and vulnerability	11.4%	13.3%	.078	.780
Intake criteria – APS and BLIPS	3.8%	3.3%	.013	.908
Intake criteria – BLIPS and vulnerability	1.3%	0%	.383	.536
Intake criteria – all three	1.3%	3.3%	.516	.473
BPRS psychotic subscale at follow-up	5.18 ± 1.88	7.20 ± 2.87	3.68[a]	<.001
SANS total at follow-up	5.60 ± 8.26	15.13 ± 15.24	4.157[a]	<.001
Hamilton Anxiety Total at follow-up	5.77 ± 5.45	10.90 ± 8.97	3.032[a]	.002
Hamilton Depression Total	4.97 ± 5.12	12.10 ± 10.03	4.072[a]	<.0001
GAF score at follow-up	72.67 ± 12.13	59.77 ± 10.16	5.176	<.0001

Data are expressed as Mean ± SD

[a]Mann-Whitney U standardized test statistic

BPRS; Brief Psychiatric Rating Scale, SANS; Scale for the Assessment of Negative Symptoms, GAF; Global Assessment of Functioning, APS; Attenuated Psychotic Symptoms, BLIPS; Brief Limited Intermittent Psychotic Symptoms

Table 2

Brain regions demonstrating reduced grey matter volume in APS when compared to No-APS (No-APS>APS), cluster-corrected p-value ($p < 0.05$)

Anatomical location of peak *t*-value	Hemisphere	Cluster extensions	Max *t* value	MNI coordinates of peak *t*-value	Cluster size
Precuneus cortex	Right	Posterior cingulate gyrus	*t*=3.65	x=15, y=-45, z=42	1624
Amygdala	Left	Temporal pole, frontal orbital cortex, parahippocampal gyrus	*t*=3.51	x=-24, y=2, z=-21	949
Middle frontal gyrus	Right		*t*=4.13	x=40, y=21, z=46	927
Inferior temporal gyrus	Left	Temporal fusiform cortex, posterior and anterior division	*t*=4.44	x=-46, y=-15, z=-41	761
Precentral gyrus	Left	Middle frontal gyrus	*t*=3.46	x=-36, y=2, z=54	751

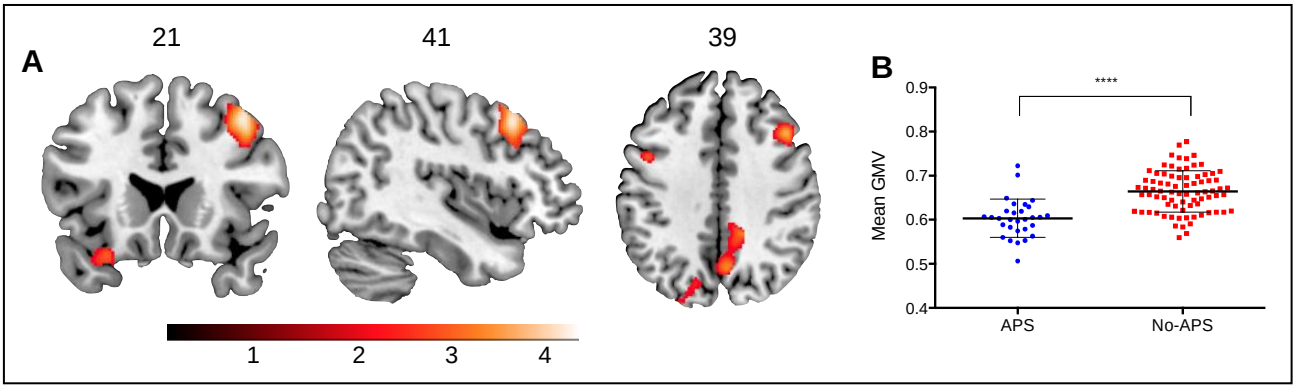

Figure 1. Voxel-based morphometric differences of grey matter volume between APS and No-APS UHR-NT groups

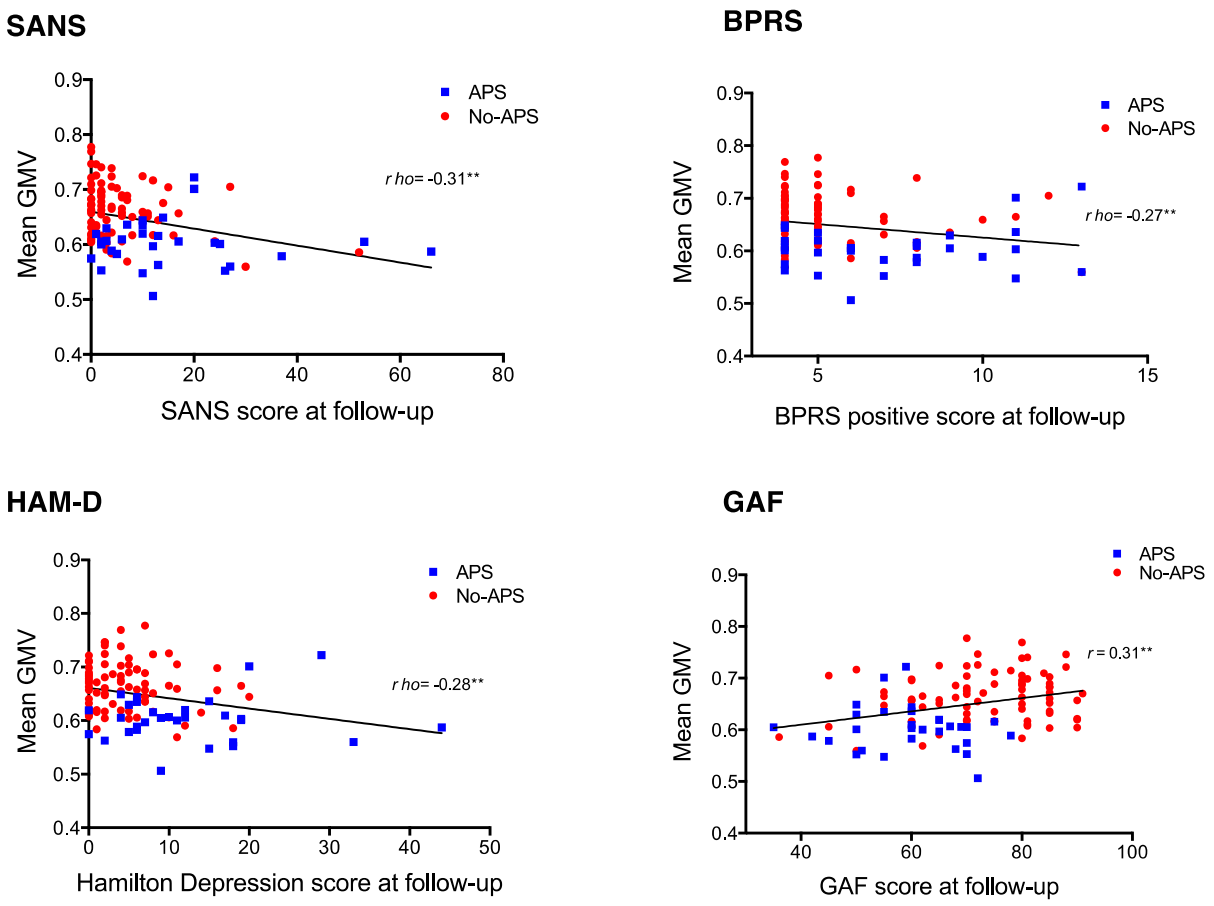

Figure 2. Relationships between grey matter volume and clinical variables at follow-up in UHR-NT

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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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Running Title: Structural imaging in UHR-NP with and without APS

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, but can have persistent attenuated psychotic symptoms (APS). The current study examined whether there were differences in Few studies have examined the biological correlates of persistent APS in such individuals. We evaluated baseline grey matter volume (i.e. at initial identification as UHR) in a UHR-NT cohort individuals whom had by comparing those with APS compared to those without to those without such APSsymptoms (No-APS) assessed 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 aed psychotic disorder oversis the at 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 GMVvolumes wasere associated with more severe positive, negative and depressive symptoms and lower global functioning in the combined UHR-NT cohort across the entire cohort. These associations were independent of later APS outcome.

Discussion: This study found that dDifferences 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.

Keywords: ultra-high risk, psychosis, attenuated psychotic symptoms, non-transition, imaging, grey matter volume

1. Introduction

~~Previous~~ A large body of research has~~has~~ ~~evaluated~~ examined the ~~clinical and biological~~neuroanatomical characteristics of clinical help-seeking samples identified as being at ultra high-risk (UHR) for psychosis. Both ~~C~~rcross-sectional and longitudinal studies have ~~primarily~~ 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~~, as well as in comparison to healthy controls~~ in order to identify vulnerability predictors for transition to psychotic illness. R~~Such r~~esearch employing structural magnetic resonance imaging (MRI) has reported subtle but widespread neuroanatomical ~~structural brain~~ abnormalities in temporo-parietal, prefrontal and limbic regions in UHR, with evidence for more pronounced abnormalities in UHR-T ~~in select frontal, temporal and limbic structures~~ (for reviews see Bois et al., 2015; Fusar-Poli et al., 2011; Smieskova et al., 2010). ~~, suggesting that these regions may be associated with progression to a psychotic illness.~~ 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 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. ~~and recent UHR cohorts have shown decreasing transition rates (Nelson et al., 2013; Yung et al., 2007), suggesting that the proportion of non-transitioned individuals may be even higher.~~ 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 (Garner et al., 2005; Phillips et al., 2002) and no change (McIntosh et al., 2011; Takahashi et al., 2009; 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).

~~In UHR samples, which consist of individuals who will and will not transition to psychosis, brain volume reductions have been identified in a diffuse network including temporo-parietal, bilateral prefrontal and limbic cortex (Fusar-Poli et al., 2011). These findings are typically viewed from the prism of psychosis, with reductions representing widespread neuroanatomical correlates of an increased vulnerability to psychosis. However, given that~~Recent studies have demonstrated that UHR-NT individuals ~~represent a heterogeneous group~~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~~, neuroanatomical alterations in UHR may also represent markers of resilience or outcomes related to non-transition or other disorders, rather than vulnerability to psychosis by itself. Nearly half of UHR studies have not provided characteristics of participants who did not develop psychosis (Simon et al., 2011), demonstrating that there is little understanding of the profile of these individuals. As such, it has been recommended that research studies expand~~

~~the range of outcomes to be assessed. These include the persistence or remission of attenuated symptoms, functional disability, negative symptoms, non-psychotic disorders as well as psychosis (Lin et al., 2012; Lin et al., 2013; Yung et al., 2012).~~

~~Studies have recently begun to examine the outcomes for individuals who have not developed a psychotic disorder at follow-up (i.e. UHR-NT). In addition to presenting 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~~, a~~ proportion (23-50%) of UHR-NT individuals~~–~~ also experience attenuated psychotic symptoms (APS) ~~at follow-up~~ (Addington et al., 2011; Haroun et al., 2006; Lemos-Giraldez et al., 2009; Simon and Umbricht, 2010; 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 ~~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. ~~Examination of brain structural indices associated with different outcomes of APS in those who do not transition is important for refining our understanding of the biological correlates of the at-risk mental state.~~

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~~non-transitioned UHR~~

cohort ~~(UHR-NT)~~. 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 ~~out APS at follow-up (~~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 (Lin et al., 2015; Nelson et al., 2013). 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.

2.3 Clinical measures

At ~~B~~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 disorganisation. 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~~.~~ f~~F~~unctioning ~~was assessed~~ with the GAF.

2.4 MRI acquisition

50.5%~~52%~~ of the T1-weighted MRI scans were acquired on a 1.5T GE Signa MR scanner with the following parameters: 124 slices of 1.5mm thickness, TR=1.43s, TE=3.3ms, flip angle 30º, matrix 256x256, FOV 24cm. The remaining 49.5~~47~~% of MRI scans were acquired on a 3T GE LX Horizon Scanner: 124 slices of 2mm thickness, TR=3.6s, TE=9ms, flip angle 30º, matrix 410x410,

FOV 20cm. The APS and No-APS groups were matched on the proportion undergoing 1.5T versus 3T.

2.5 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, white matter and cerebrospinal fluid. Native-space grey matter segments were then spatially aligned to a high-dimensional Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) template and normalized to MNI space. Grey matter voxels were multiplied by the non-linear components only (modulated normalized – non-linear only) to provide a measure of the absolute amount of tissue corrected for individual brain sizes. Data quality and homogeneity of the images were checked. Images of four participants were excluded from the original dataset due to the covariance being more than two standard deviations removed from the mean. Prior to statistical analysis, images were smoothed with an 8mm full-width-half-maximum Gaussian kernel.

2.6 Statistical analysis

The General Linear Model (GLM) was performed to test for group differences in baseline GMV at each voxel. An independent t-test with age at baseline, sex and field strength of the scanner as nuisance factors was defined to test for volumetric differences between the APS and No-APS groups. Group differences were corrected for statistical type I error with a cluster-based procedure (Friston et al., 1994) using the 3dClustSim tool implemented in AFNI (http://afni.nimh.nih.gov/pub/dist/doc/program_help/3dClustSim.html). A voxel-wise threshold was set to 0.01 to compromise between sensitivity to spatially extended versus focal and intense

differences. Cluster size threshold (i.e. *k* values) was corrected for non-stationarity (Hayasaka et al., 2004) with the VBM8 toolbox (http://dbm.neuro.uni-jena.de/467/).

Statistical analyses of demographic and clinical variables were performed using the Statistical Package for Social Sciences (SPSS, v21.0). Differences in these variables between groups were analysed with independent t-tests or Pearson's χ^2 statistics for continuous and categorical variables, respectively. The Mann-Whitney U Test was performed for non-parametric variables. Correlations were analysed between the mean GMV extracted from the significant cluster detected in the group comparison and clinical variables at follow-up (BPRS, SANS, GAF, HAM-A, HAM-D) using Pearson's correlation coefficient with bootstrapping (5000 samples) or ~~to control for skewed distributions.~~Spearman's correlation coefficient for non-parametric variables. Correlations were performed in the whole (combined) sample and in each group (APS and No-APS) separately. Correlations between mean GMV and clinical variables at baseline, and with change scores (follow-up minus baseline score), were explored. P-values <0.05 was considered statistically significant.

3. Results

3.1 Demographics and clinical characteristics of study sample

Demographic and clinical characteristics of the APS and No-APS groups are presented in Table 1. In this sample, follow-up was conducted between 2 and 12 years after baseline (*M*=7.5; *SD*=3.0; median=6.9). The APS and No-APS groups were well matched in age at baseline, sex, field strength of scanner, time to follow-up and in the UHR membership criteria at intake. At baseline, the APS and No-APS groups showed no differences in positive and negative symptoms and functioning. However the APS group had a significantly lower IQ than the No-APS group. At follow-up, the APS group had significantly higher symptoms (positive, negative, anxiety and depression) and lower functioning. Antipsychotic and antidepressant use at baseline (i.e. at time of scanning) was documented for 70% of the sample. Of these participants, none reported taking

antipsychotics and 10 (13.2%) reported using antidepressants. Antipsychotic and psychiatric medication use for the entire follow-up period (i.e. after baseline) was documented for 90% of the sample. Of these participants, 5 (5.1%) reported using antipsychotic medication and 46 (47%) reported using any psychiatric medication "some or all of the time" in the follow-up period. There was no difference between APS and No-APS individuals in the frequency of reported antipsychotic use. However, those with APS reported using psychiatric medication significantly more than those without APS (68% vs. 39% respectively). 21 (19.3%) of the participants received low-dose antipsychotics and 10 (9.2%) received low-dose lithium as trial treatment at PACE (after study entry). The proportion of individuals receiving trial treatment did not differ between the APS and No-APS groups.

3.2 Voxel-based morphometry

Individuals with APS at follow-up had significantly reduced GMV at baseline compared to those without APS at follow-up (Figure 1 and Table 2). Reduced GMV was found in clusters encompassing the right middle frontal gyrus, right precuneus/posterior cingulate cortex, and left inferior temporal gyrus, inferior orbitofrontal gyrus extending to the temporal pole and parahippocampal gyrus, inferior and superior occipital cortex and pre- and postcentral gyrus. A secondary analysis covarying for baseline IQ did not appreciably change the results. For the other contrast (APS>No-APS), no significant differences were detected.

3.3 Correlations with clinical measures

Mean GMV was negatively correlated with BPRS positive (*rho*=-.273, *p*=.00618), SANS (*rho*=-.313, *p*=.001) and HAM-D (*rho*=-.287, *p*=.0034) scores, and positively correlated with GAF scores (*r*=.31, *p*=.001) at follow-up in the combined UHR-NT sample (Figure 2). These correlations were not significant when performed in the APS and No-APS groups separately.~~When performed separately, only SANS showed a significant correlation with GMV in the No-APS group, whilst no~~

~~variables were significantly associated with GMV in APS.~~ No relationships were detected between mean GMV and HAM-A scores at follow-up. No significant correlations were detected between mean GMV and clinical scores or IQ at baseline. Mean GMV was significantly associated with change in ~~SANS (*r*=-.19, *p*=.048) and~~ GAF score (*r*=.255, *p*=.007~~;) scores~~ ~~(~~follow-up minus baseline).

4. Discussion

This study examined a group of individuals defined as UHR for psychosis at baseline who did not transition to psychosis over a medium to long-term follow-up period (mean of 7 years). We evaluated baseline MRI scans (i.e. at initial identification as UHR) in this cohort by comparing those with APS at the follow-up assessment in comparison to those without such symptoms at follow-up. At baseline, both groups were similar in their clinical and demographic characteristics, including no differences in APS. At follow-up, the two groups differed significantly on measures of ~~BPRS~~ positive and ~~SANS~~ negative symptoms, as well as in functioning ~~(GAF)~~. Thus, those with attenuated symptoms at follow-up had ongoing symptoms and functional disability, despite not meeting criteria for full-threshold psychosis.

We found that individuals with APS at follow-up had significantly reduced baseline GMV compared to those without APS at follow-up. Regions with reduced GMV included the right middle frontal (dorsolateral prefrontal cortex) and precuneus/posterior cingulate regions, and left temporal, orbital and pre- and postcentral gyri. Reduced volume was also associated with more severe positive, negative and depressive symptoms and lower functioning at follow-up. These associations were not found in the APS and No-APS groups separately, neither at baseline, suggesting that the associations between GMV and later outcome were driven by group membership. ~~Interestingly, these correlations were not present at baseline.~~ Thus, while the UHR-NT subgroups did not differ in

their clinical characteristics at baseline, differences in GMV were discernible at this early stage and these differences were associated with APS and measures of psychopathology at follow-up.

The regions showing reduced GMV in the APS group are similar to those reported as reduced in ~~UHR individuals who later develop psychosis (~~UHR-T~~)~~. Reduced volumes or thickness have been demonstrated in UHR-T most consistently across temporo-parietal, prefrontal and limbic regions, but also the cerebellum, in cross-sectional ~~We were the first to report volumetric reductions, namely in the right hippocampal, parahippocampal and cingulate cortex, lateral temporal and inferior frontal cortex, in individuals who transitioned to psychosis (UHR-T) compared to those that didn't~~ (Borgwardt et al., 2007; Koutsouleris et al., 2009; Mechelli et al., 2011; Pantelis et al., 2003)~~.Other regions reported as reduced in UHR-T individuals include the superior temporal gyrus and insula prefrontal and orbitofrontal cortex~~ ~~and left parahippocampus~~ and longitudinal~~.~~ ~~Longitudinal studies have reported progressive reductions in UHR-T compared to UHR-NT individuals in regions including the medial and inferior temporal cortex, orbitofrontal, superior frontal, medial and superior parietal cortex, cingulate cortex and cerebellum~~ (Borgwardt et al., 2008; Cannon et al., 2015; Dazzan et al., 2012; Job et al., 2005; McIntosh et al., 2011; Pantelis et al., 2003; Ziermans et al., 2012) studies. ~~With the exception of the cerebellum and insula,~~ O~~o~~ur findings in ~~the~~ APS ~~group~~ are largely consistent with the above findings in UHR-T samples. What is novel with the current study however is that we have focused on a different aspect of long-term outcome, rather than transition as the primary outcome of interest. Thus, our findings suggest that reduced GMV in select frontal, temporal and posterior regions at baseline are associated with not only later transition to psychosis but to the presence of attenuated psychotic symptoms in a population of UHR individuals who did not transition to psychosis after 2-12 years.

At the time of scanning the APS and No-APS groups were clinically indistinguishable. There are several interpretations for the volumetric differences detected between them and the associations

with clinical measures of psychopathology. First, the volumetric reductions may be neurobiological markers of an increased risk to psychosis. Thus, an APS outcome in non-transitioned individuals might reflect a continuing risk for transition to psychosis, with reduced GMV at baseline representing a potential marker for the eventual development of a psychotic disorder. Nevertheless, this is unlikely given that the highest risk for transition was found to be within the first 2 years after identification as UHR in this sample (Nelson et al., 2013) and the mean follow-up period of the APS group in our study was 7.4 years. Second, the volumetric reductions might indeed confer increased risk for psychotic disorders, but conventional means for defining psychosis onset are ineffective at detecting this risk. Since the threshold for transition from attenuated to frank psychotic disorder is arbitrary (Lin et al., 2012; Yung et al., 2010), this currently accepted threshold may not be optimal for identifying neurobiological changes associated with psychosis or the schizophrenia spectrum. In the current and wider sample of this cohort (Lin et al., 2015; Lin et al., 2011), many people who never transition continue to experience functional impairment, negative, depressive and attenuated psychotic symptoms years after identification as UHR. It is therefore conceivable that this clinical presentation represents 'soft' or 'simple' schizophrenia within the schizophrenia spectrum, despite the absence of development of full-threshold psychosis. Our findings showing reduced GMV at baseline in APS and associations with measures of poor outcome supports this view and raises the possibility that brain morphological alterations may occur at lower intensity/frequency of positive symptoms. Finally, the baseline volumetric differences may represent a neurobiological risk marker for later psychopathology/poor prognosis, rather than later presence of psychotic symptoms (threshold or subthreshold) per se. In this context, presence of APS at follow-up may reflect "clinical noise" associated with poor prognosis or non-psychotic clinical conditions. As above, the associations found between baseline GMV and psychopathology supports this view. Although these associations were confounded by group status, it is conceivable that individuals grouped on the basis of psychopathology such as negative and depressive symptoms would show similar volumetric differences. ~~Although our understanding of~~Despite the GMV

differences between ~~the~~ APS and No-APS ~~groups~~ remain~~ing~~ unclear, these~~our~~ findings have implications for the identification of vulnerability markers of psychosis and other outcomes and emphasise the need for future studies to include endpoints other than the traditional approach to defining psychosis onset (Lin et al., 2012).

When viewed from the perspective of the No-APS group, our findings suggest that greater GMV at baseline is predictive of better outcome and that regional volume confers neurobiological resilience in the long-term (for discussion see Pantelis and Bartholomeusz, 2014). Importantly, the group with APS at follow-up had also not made the transition to psychosis. Thus, while they may remain chronically at high-risk, this lack of transition suggests that other protective factors may be at play.

An important question our data raises is whether changes in GMV are associated with changes in symptoms and function over time. As described above, longitudinal imaging studies ~~in UHR~~ have identified brain changes in ~~individuals that transition to psychosis~~UHR-T (for review see Bois et al., 2015), but not in ~~those who do not transition~~UHR-NT (Borgwardt et al., 2008; McIntosh et al., 2011) individuals. The volumetric differences at baseline may also represent a neurobiological process in those with ongoing psychotic features (threshold or subthreshold), while the opposite may occur in those without ongoing symptoms. This assertion is supported by a recent longitudinal imaging study in UHR-NT individuals (Katagiri et al., 2015)~~who did not transition to psychosis~~, where a relative 'normalization' of white matter integrity correlated with improved clinical outcome. Although we found a significant correlation between baseline GMV and *change* in ~~negative symptoms and~~ function~~ing~~, it is not known whether there were corresponding changes in GMV. Longitudinal studies examining differences in trajectories between the APS and No-APS groups would help elucidate whether there is on-going neuroprogression or normalization with time associated with different clinical outcomes.

The main strengths of this study are the novel outcome measure (with/without APS) in those who did not transition to psychosis and the long follow-up period. The greatest limitation is the variable length of the follow-up period and the different field strength of the scanners (1.5 and 3T), although these variables were near identical between the APS and No-APS groups and field strength was additionally used as a covariate in the between-group analysis.

This study found that differences in regional GMV were discernible at an early stage of UHR and may be specific to individuals who continue to have attenuated psychotic symptoms 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. Comparison of GMV in the non-transition APS and No-APS groups with a healthy control and transitioned (UHR-T) group, along with longitudinal assessment, will help elucidate the significance of these findings.

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Figure Legends

Figure 1. Voxel-based morphometric differences of grey matter volume between APS and No-APS UHR-NT groups

A). Areas showing reduced grey matter volume at baseline in non-transitioned UHR individuals with APS at follow-up compared to individuals without APS at follow-up (contrast No-APS>APS). Clusters resided in the frontal, temporal and posterior regions. T-values at each voxel are provided by the scale bar. MNI coordinates are shown on the top of each slice for the y-axis, x-axis and z-axis, respectively. B). Plot of the mean grey matter volume in the significant clusters in the APS and No-APS groups. **** p<.0001.

Figure 2. Relationships between grey matter volume and clinical variables at follow-up in UHR-NT

Scatterplots illustrating the significant correlations between mean grey matter volume in the significant cluster in the group comparison with clinical score at follow-up. Reduced grey matter volume was associated with increased positive, negative and depressive symptoms and decreased functioning at follow-up. Blue squares represent APS individuals and red circles represent No-APS individuals. *p<.05, **p<.01.

Table and Figures

Table 1

Demographic and clinical characteristics of study participants

	No-APS (79)	APS (30)	t/χ^2	*p*-value
Age at baseline (years)	19.80 ± 3.47	19.93 ± 3.44	0.18	.855
Sex (M/F)	40/39	15/15	.003	.953
% Scanner Field Strength (1.5T/3T)	51.9/48.1	46.7/53.3	.238	.626
Time to follow-up (years)	7.61 ± 2.89	7.35 ± 3.16	-0.63[a]	.528
% Handedness (R/L)	86.5/13.5	82.1/17.9	0.31	.755
IQ at baseline	103.3 ± 12.1	93.5 ± 15.7	3.39	.001
Intracranial volume	1411 ± 154	1381 ± 148	.923	.358
Use of antidepressants at baseline	16.1%	5.0%	1.58	.209
Use of antipsychotics during follow-up period	2.9%	10.3%	2.40	.148
Use of any psychiatric medication during follow-up period	38.6%	67.9%	6.89	.013
Trial treatment with antipsychotics	19%	20%	0.014	.905
Trial treatment with lithium	8.9%	10%	0.34	.854
BPRS psychotic subscale at baseline	8.77 ± 2.67	9.59 ± 2.81	1.39	.168
SANS total at baseline	17.67 ± 11.48	18.55 ± 11.66	0.617[a]	.537
GAF score at baseline	61.25 ± 11.65	60.33 ± 9.90	0.38	.703
Intake criteria – APS	58.2%	46.7%	1.17	.291
Intake criteria – BLIPS	3.8%	13.3%	3.29	.089
Intake criteria – vulnerability	20.3%	20.0%	.001	.977
Intake criteria – APS and vulnerability	11.4%	13.3%	.078	.780
Intake criteria – APS and BLIPS	3.8%	3.3%	.013	.908
Intake criteria – BLIPS and vulnerability	1.3%	0%	.383	.536
Intake criteria – all three	1.3%	3.3%	.516	.473
BPRS psychotic subscale at follow-up	5.18 ± 1.88	7.20 ± 2.87	3.68[a]	<.001
SANS total at follow-up	5.60 ± 8.26	15.13 ± 15.24	4.157[a]	<.001
Hamilton Anxiety Total at follow-up	5.77 ± 5.45	10.90 ± 8.97	3.032[a]	.002
Hamilton Depression Total	4.97 ± 5.12	12.10 ± 10.03	4.072[a]	<.0001
GAF score at follow-up	72.67 ± 12.13	59.77 ± 10.16	5.176	<.0001

Data are expressed as Mean ± SD

[a]Mann-Whitney U standardized test statistic

BPRS; Brief Psychiatric Rating Scale, SANS; Scale for the Assessment of Negative Symptoms, GAF; Global Assessment of Functioning, APS; Attenuated Psychotic Symptoms, BLIPS; Brief Limited Intermittent Psychotic Symptoms

Table 2

Brain regions demonstrating reduced grey matter volume in APS when compared to No-APS (No-APS>APS), cluster-corrected p-value ($p < 0.05$)

Anatomical location of peak *t*-value	Hemisphere	Cluster extensions	Max *t* value	MNI coordinates of peak *t*-value	Cluster size
Precuneus cortex	Right	Posterior cingulate gyrus	*t*=3.65	x=15, y=-45, z=42	1624
Amygdala	Left	Temporal pole, frontal orbital cortex, parahippocampal gyrus	*t*=3.51	x=-24, y=2, z=-21	949
Middle frontal gyrus	Right		*t*=4.13	x=40, y=21, z=46	927
Inferior temporal gyrus	Left	Temporal fusiform cortex, posterior and anterior division	*t*=4.44	x=-46, y=-15, z=-41	761
Precentral gyrus	Left	Middle frontal gyrus	*t*=3.46	x=-36, y=2, z=54	751

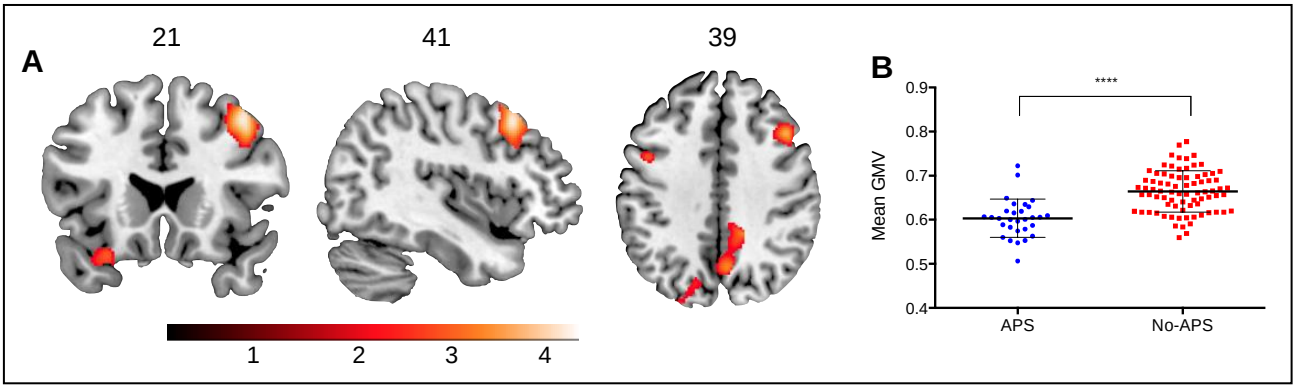

Figure 1. Voxel-based morphometric differences of grey matter volume between APS and No-APS UHR-NT groups

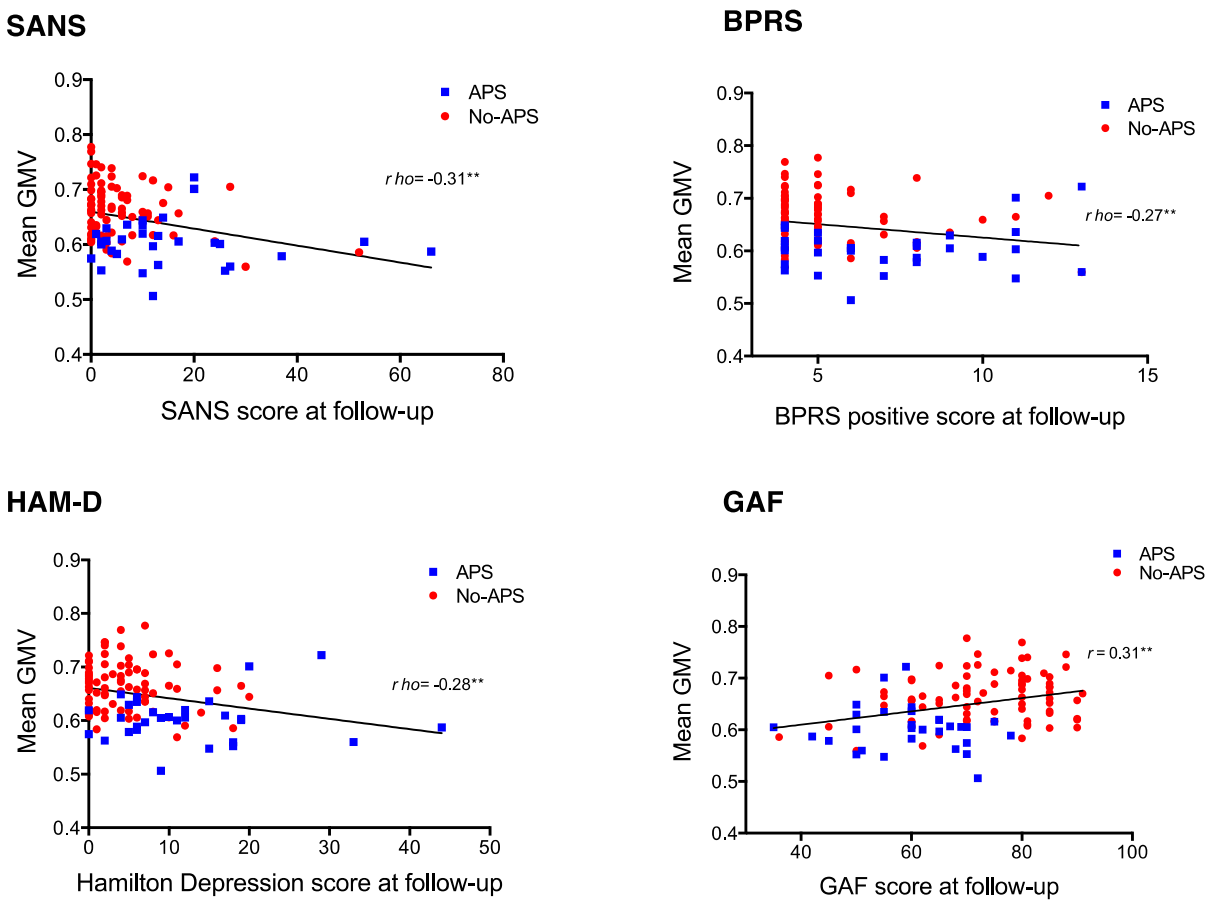

Figure 2. Relationships between grey matter volume and clinical variables at follow-up in UHR-NT

Acknowledgements

Neuroimaging analysis was facilitated by the Neuropsychiatry Imaging Laboratory managed by Ms Bridget Soulsby at the Melbourne Neuropsychiatry Centre and supported by Neurosciences Victoria.

Conflict of Interest Statement

The authors have declared that there are no conflicts of interest in relation to the subject of this study.

Contributions

Authors VC, CP, SW, AL, AY, PM, BN designed the study. Authors VC, RR and PK performed the voxel-based morphometry analysis. Authors VC, CP, SW, RR, PK carried out the statistical analyses. Authors AY, PM, BN, AL, SW, CB, DV, CP provided insight into the clinical and cohort data. Author VC wrote the first draft of the manuscript. All authors contributed to and have approved the manuscript.

Role of the Funding Source

This study was supported by National Health and Medical Research Council of Australia (NHMRC) Project (209062) and Program Grants (350241, 566529), and by the Colonial Foundation. Vanessa Cropley and Ashleigh Lin were each supported by NHMRC Early Career Fellowships (VC: 628880; AL: 1072593). Stephen Wood was supported by a NHMRC Clinical Career Developmental Award (359223) and a NARSAD Young Investigator Award. Alison Yung was supported by a NHMRC Senior Research Fellowship (566593). Paul Klauser was supported by the Swiss National Science Foundation and the Swiss Society for Medicine and Biology Scholarships (148384). Cali Bartholomeusz was supported by a University of Melbourne Department of Psychiatry John and Betty Lynch Fellowship. Barnaby Nelson was supported by an NHMRC Career Development Fellowship (1027532). Renate Reniers was supported by an MRC Research Grant (MR/K013599/1). Patrick McGorry and Christos Pantelis were each supported by NHMRC Senior Principal Research Fellowships (PM:1060996; CP:628386) and NARSAD Distinguished Investigator Awards.