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Progression of neuroanatomical abnormalities after first-episode of psychosis: A 3-year longitudinal sMRI study

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1 Introduction

Structural magnetic resonance imaging (sMRI) studies have frequently demonstrated that neuroanatomical abnormalities are already present at the point that first-episode of psychosis (FEP) is identified (Dazzan *et al.* 2012; Olabi *et al.* 2011). The initial phase of psychotic illness may represent a particularly vulnerable time for progression of neuroanatomical abnormalities (Cahn *et al.* 2002; Andreasen *et al.* 2011) with suggestions of a potential plateau effect on progression of grey matter (GM) deficits across the brain in longitudinal studies of more established schizophrenia (Hulshoff Pol and Kahn, 2008; van Haren *et al.* 2012). The most consistent neuroanatomical changes seen in longitudinal studies of FEP relate to progressive lateral ventricular (LV) enlargement (Kempton *et al.* 2010; Olabi *et al.* 2011), and reduction in total GM volume (Olabi *et al.* 2011; Gutierrez-Galve *et al.* 2014).

Progressive morphometric abnormalities such as reduction in deep GM volume and cortical thinning in the initial years after the onset of psychotic illness may be inherent to the pathogenesis of psychosis and/or related to other factors including cumulative antipsychotic medication usage (Ho *et al.* 2011; Vita *et al.* 2012), genetic susceptibility (Andreassen *et al.* 2013; Vazquez-Bourgon *et al.* 2016) and cannabis use (Rais *et al.* 2008). In contrast to the ventricular and whole-brain cortical GM findings, reports of progressive change in subcortical volumes and regional cortical thickness have been inconsistent (see Table 1 for a summary of longitudinal studies to-date). A meta-analysis of longitudinal MRI studies of first episode schizophrenia patients showed a significant pattern of progressive GM tissue loss in the frontal, temporal, parietal lobes and in the Heschl's gyrus relative to healthy controls (HCs) (Vita *et al.* 2012). Additionally, several other studies have demonstrated increased global cortical thinning, particularly pronounced in the frontal cortex (Roiz-Santianez *et al.* 2014; Guo *et al.* 2015) with significant tissue loss in the frontal, temporal and parietal cortices of FEP patients compared to HCs over time (de Castro-Manglano *et al.* 2011). However, this remains an inconsistent finding with other studies demonstrating no such changes (Dickey *et al.* 2004; Haukvik *et al.* 2016).

These inconsistencies regarding neuroanatomical progression after FEP may be due to embedded study heterogeneities of a clinical (including variable clinical severity, antipsychotic medication use and follow-up periods) and methodological (including different image acquisition and analysis techniques) nature.

The current, naturalistic, longitudinal study aims to overcome these issues in order to determine whether there were progressive volumetric changes in the cortico-subcortical regions and ventricles

over a 3-year follow-up period in FEP patients who underwent MRI scanning very shortly after presentation to mental health services. It also aims to ascertain whether any neuroanatomical changes were related to particular clinical variables including symptom severity, cumulative dose of antipsychotic medications and level of functioning. We hypothesised that, compared with HCs, individuals with FEP would demonstrate greater ventricular enlargement, increased cortical thinning and reduction in the volume of subcortical GM structures over time. We also hypothesised that progressive changes would be associated with measures of poorer outcome including decreased functioning, more negative symptoms and greater use of antipsychotic medication in patients.

2 Methods

2.1 Study design and setting

Participants were included if they had previously participated in the initial phase of this study (Scanlon *et al.* 2014) and had no contraindications to MRI procedures. Exclusion criteria for all participants included a history of neurological disorders, intellectual disability, life-time substance dependency (as defined by DSM-IV-TR), a history of head injury resulting in loss of consciousness for over 5 minutes and oral steroid use in the past 3 months. HCs were excluded if they had a personal or family history of any psychotic illness. Written informed consent was provided by all participants at both time-points and ethical approval was obtained from the National University of Ireland Galway and Galway University Hospitals Research Ethics Committees.

2.2 Participants

Participants were recruited from the Galway University Hospital and the Mental Health Services within the West of Ireland. The original baseline sample comprised 46 patients presenting with FEP (defined as having at least one psychotic symptom) and 46 controls (Scanlon et al. 2014). Patients underwent MRI scanning as soon as feasible after presentation and within 8 weeks of commencing antipsychotic medication (the median duration of treatment was 14 days). Re-recruitment of all original participants was attempted. Five patients from the original patient cohort were un-contactable and 13 refused to participate. Two healthy volunteers were later excluded as imaging data was acquired on a different MRI scanner, while others within this cohort were un-contactable (n=4) or declined our invitation to participate (n=12). Thus, at follow-up the final successful re-recruitment rate was 61%, with 28 FEP individuals and 28 HCs re-recruited to the current longitudinal study. There was no significant difference in age, gender, age of illness onset and daily medication

dose prescribed at baseline in patients from the original cohort who were successfully re-recruited at follow-up (n=28) compared to those not re-recruited (n=18).

2.3 Clinical assessment

The baseline clinical assessments were described previously in detail (Scanlon *et al.* 2014) and were repeated at follow-up. Briefly, the Structured Clinical Interview (SCID) for DSM-IV Research Version (First *et al.* 2002) was repeated to establish updated diagnostic status given its potential variation (Fusar-Poli *et al.* 2016). As previously (Kenney *et al.* 2015), schizophrenia, schizoaffective disorder, psychotic disorder not otherwise specified (NOS), substance induced psychosis and delusional disorder were defined as non-affective types of psychoses (n=16) whereas bipolar I disorder and major depressive disorder were defined as affective types of psychoses (n=12) for further subcategory analyses in patients. Ratings of symptomatology and functioning were carried out using the Positive and Negative Syndrome Scale (PANSS: 0–6 scale) (Kay *et al.* 1987) and the Global Assessment of Functioning score (GAF) (Hall, 1995) respectively. HCs were also re-screened for the presence of psychotic illness using the SCID-NP (non-patient) edition (First *et al.* 2002). Total antipsychotic medication administered during the follow-up period was converted to chlorpromazine (CPZ) equivalents (Taylor *et al.* 2007; Woods, 2003) from detailed clinical interviews and review of clinical notes. Similarly, information on cannabis use was collected from clinical interviews and supplemented by a review of clinical notes and categorised via binary coding based on the adapted criteria of the Centre for Addiction and Mental Health (Boak *et al.* 2017) for either heavy use (≥ 12 times on a lifetime basis and at least once during the past year) or none/minimal use (0-11 times on a lifetime basis and none during the past year).

2.4 MRI data acquisition and processing

Identical MRI data acquisition protocols, on the same 1.5 Tesla Siemens Magnetom Symphony scanner (Erlangen, Germany), and identical image pre-processing approaches with non-parametric non-uniform intensity normalisation (N3) (Scanlon *et al.* 2015) were implemented at follow-up as at baseline. The longitudinal FreeSurfer processing pipeline (v.5.3.0, Reuter *et al.* 2012) was employed for segmentation of subcortical structures, ventricles and to examine the progression of cortical thickness changes over time. Detailed descriptions of the MRI image acquisition and processing protocols are provided in the supplementary material.

2.5 Statistical analyses

Statistical analyses were performed with the Statistical Package for Social Sciences (SPSS, v.24.0) and the FreeSurfer statistical tools (QDEC®).

The Kolmogorov-Smirnov test was used to examine the distribution of data for normality. Clinical and demographic differences between groups over time were assessed using chi-square or independent t-test. Paired t-tests were used to assess longitudinal changes in clinical symptom and functionality scores within FEP individuals. The bilateral FreeSurfer segmented brain volumes of deep grey matter structures (i.e., caudate, putamen, globus pallidus, nucleus accumbens, thalamus, hippocampus, amygdala) and lateral ventricles were summed. Furthermore, changes in the third ventricle, total grey and white matter were investigated. In total, 11 regional volumes were examined, together with the manually segmented hippocampal volumes and are referred to as the region-of-interest (ROI).

FreeSurfer automatically segments the brain based on a subject-independent probabilistic atlas to provide subject-specific measured values of both cortical and subcortical structures. However, this probabilistic atlas was created from a manually labelled training set which was mapped into Talairach space in which all the subjects' images are registered to during the process of segmentation (Fischl et al. 2004). In an explorative cortical analysis where findings may span over portions of several atlas-defined regions, this approach becomes less reliable at localising changes within specific lobular subregions (DeLisi, 2008). Thus, an analyses approach that examines thickness change at each vertex of the cortical surface is considered more appropriate for our explorative cortical analyses.

The QDEC (Query, Design, Estimate, Contrast) is a single-binary application included in the FreeSurfer distribution which uses a vertex-wise approach to perform group averaging and inference on cortical morphometric data. Following the FreeSurfer recommendations (http://surfer.nmr.mgh.harvard.edu/) for a robust measure of cortical thickness change with increased statistical power, we used the vertex-wise linear regressions in the QDEC interface [longitudinal two-stage model (Reuter et al. 2012;https://surfer.nmr.mgh.harvard.edu/fswiki/LongitudinalTwoStageModel)] for our hypothesis-free investigation of the entire cortical mantle. However, we did not apply the vertex-wise approach for the investigations in relation to the subcortical and ventricular volumes because volumetric segmentation of this structures are not prone to the limitation described above, hence, a repeated-measures ANCOVA was employed in our analyses relating to the a priori hypotheses.

2.6 Subcortical and ventricular volume analyses

Repeated-measures analysis of co-variance (ANCOVA) with Greenhouse-Geisser corrections was used to investigate differences in the progression of regional morphometric abnormalities over the 3-year follow-up period. In each general linear model, the dependent measures were MRI volumes and the independent measure was group (FEP vs. HC) or (affective vs non-affective) in a patient subgroup comparison. The within-subject factor was time (baseline vs. follow-up) with hemisphere (left vs. right) added for bilateral structures. Given the potential of age, gender and intracranial volume (ICV) to confound results in brain morphometric investigations (Barnes *et al.* 2010), all analyses included these covariates. Where there were significant findings, further post-hoc within-group analyses of variances were conducted to identify the direction of lateralised effects. To better quantify the significant findings, effect sizes were calculated from the adjusted percent volume differences at baseline and follow-up for each region of interest (ROI). Given the relatively small sample size, Hedges' g was adopted (Hedges and Olkin, 1985) for unbiased effect sizes (Calin-Jageman, 2018) (See Table 2 Legend). The adjusted (for age, gender and ICV) percent volume difference (pvd) of each ROI was computed as:

pvd = 100 x [(adjusted vol. at follow-up – adjusted vol. at baseline)/adjusted vol. at baseline] eqn (1)

2.7 Cortical thickness analyses

In QDEC®, global longitudinal vertex-wise linear regressions were conducted to determine the effect of diagnosis on the dependent variable of symmetrised percent thickness change (spc) (% per year) across the cortical mantle while controlling for age at baseline. Scan interval was not included in the rate of change model as it was already accounted for in the calculation of the dependent variable. Furthermore, spc does not depend on intracranial volume, and is less dependent on baseline values than measures such as percent change (Berry and Ayers, 2001). For the group effect of diagnosis on progressive cortical thickness change, participants were contrasted as FEP patients and HCs. The Monte Carlo null-z strategy which employs 10000 vertex-wise iterations was implemented (Hagler *et al.* 2006), with an initial cluster-forming threshold of $p<0.05$ for multiple comparisons to reduce the probability of type I errors. The identified clusters were extracted and averaged for further analyses. We conducted independent ANCOVAs to compute group (FEP vs HCs) and subgroup (affective vs non-affective vs HCs) comparisons over the extracted ROI cortical thickness of change measure (spc).

2.8 Correlation analyses

For brain regions demonstrating significant progressive volume and rates of cortical thickness change over time, partial correlations controlling for age, gender and ICV (only in the case of volume) were

used to determine the strength of potential associations between percent volume/rate of thickness change in ROI and change ($Time_2$ - $Time_1$) in clinical or functional variables. A two-tailed α level of 0.05 was used for statistical testing. Given that brain structures are not independent (Haukvik *et al.* 2016) and our study was being driven by *a priori* hypotheses of progressive brain change, we did not apply a Bonferroni correction for these group analyses, as per similar previous studies (Ayesa-Arriola *et al.* 2013; Roiz-Santiánez *et al.* 2014).

3 Results

3.1 Clinico-demographic characteristics

Demographic and clinical data are presented in Table 3. It proved more challenging to re-recruit younger controls from the original sample, and individuals with FEP were significantly younger than HCs in this longitudinal phase of the study ($t_{(54)} = -2.07$, $p = 0.04$). They had also engaged in less years of education ($t_{(54)} = -2.37$, $p = 0.02$). There were no differences between the groups in gender distribution or time between scans. Formal SCID diagnoses of the patients at follow up were: schizophrenia (n=8), bipolar I disorder (n=9), major depressive disorder (n=3), schizoaffective disorder (n=3), psychotic disorder not otherwise specified (NOS) (n=3), delusional disorder (n=1) and substance induced psychotic disorder (n=1). At baseline, 24 patients were taking second-generation antipsychotic (SGA) medication, 1 was taking a first-generation antipsychotic (FGA) medication and 3 participants were not taking antipsychotic medication. At follow-up, 16 individuals were treated with SGAs comprising olanzapine (n=6), aripiprazole (n=5), risperidone (n=3), clozapine (n=2), quetiapine (n=2), amisulpride (n=1) and no patients were treated with a FGA medication. Three individuals were treated with more than one SGA. In addition to a SGA, 7 patients were prescribed antidepressants and 4 patients were prescribed mood stabilisers. Nine patients were on no psychotropic medications at follow-up. Within the patient group, there were significant reductions in positive ($t_{(27)} = 5.41$, $p<0.001$) and general psychopathology ($t_{(27)} = 3.89$, $p<0.001$) subscale symptoms of the PANSS between baseline and follow-up, with a reduction in negative symptoms also demonstrated, that did not reach statistical significance ($t_{(27)} = 1.92$, $p=0.07$). GAF scores increased significantly ($t_{(27)} = -7.87$, $p<0.001$) between baseline and follow-up assessments (Table 3).

3.2 Group comparison of progressive subcortical and ventricular changes over time

As demonstrated in Table 2 and Figure 1, significant group x time interactions were found, indicating progressively greater volume reduction of the caudate [$F(1,51)=5.86$, $p=0.02$, Hedges' $g=0.66$], putamen [$F(1,51)=6.06$, $p=0.02$, $g=0.67$] and thalamus [$F(1,51)=6.99$, $p=0.01$, $g=0.72$] in FEP patients compared with HCs. There was also a trend towards significance for increased LV volume over time in

patients [F(1,51)=3.37, p=0.07, g=0.50]. A significant effect of group x time x laterality [F(1,51)=4.38, p=0.04, g=0.57] was demonstrated for LV enlargement in patients compared to controls. Post-hoc analysis demonstrated significant right LV enlargement over time in patients compared to controls [F(1,51)=4.03, p=0.05)] which was not significant for left LV enlargement [F(1,51)=2.66, p=0.11)]. Further patient subgroup comparisons (affective versus non-affective) for longitudinal changes showed no significant volume differences (see Table S4) in subcortical and ventricular findings, however, we remain potentially underpowered to detect such a difference.

Given the potential effects of covariates which differ between groups (Miller and Chapman, 2001), we also ran a number of confirmatory analyses, showing that these findings were essentially unaltered when age was removed as a covariate and when scan interval time was added as a covariate in all analyses, indicating that our results are unlikely to be driven by these factors. There were no progressive volume deficits identified in medial temporal lobe structures, including the hippocampus which was manually segmented as previously (Akudjedu *et al.* 2018).

3.3 Group comparison of rates of progressive cortical brain change overtime

Increased rates of progressive cortical thinning were observed in FEP patients relative to HCs, mostly in the left frontal and temporal regions. Specifically, significant clusters were observed in the regions of the left lateral orbitofrontal cortex, superiorparietal, lingual, and superiortemporal gyrus, the banks of the superior temporal sulcus, fusiform gyrus and the bilateral superiorfrontal gyrus (Fig. S1 and Table S2, all uncorrected, $p<0.05$). There were no regions of cortical thickening over time in patients compared with controls. After correction for multiple comparisons, a cluster of progressive cortical thinning was observed [Fig. 2, all corrected $p<0.05$] in FEP patients at the left lateral orbitofrontal cortex extending into aspects of the left pars orbitalis, pars triangularis, rostral middle frontal gyrus and frontal pole. A significantly reduced spc [F(1,52)=5.11, p=0.03)] in individuals with FEP relative to HCs, with a mean difference of 0.84% [95% CI (0.10, 1.59)] (Fig. S2A) over the 3-year period was demonstrated for this left lateral orbitofrontal region (LLOFR). On patient subgroup analysis, there was a trend towards significance for progressive thinning [F(2,51)=2.87, p=0.07)] in the LLOFR. Compared to controls, there was a significant mean regional thinning difference of 1.01% [95% CI (0.15, 1.86), p=0.02] in the non-affective subgroup and a non-significant thinning of 0.58%/year [95% CI (-0.42, 1.58), p=0.25] in the affective subgroup (Fig. S2B). Further pairwise comparisons showed no significant mean difference [0.43%, 95 CI (-0.63, 1.48), p=0.42] in cortical thickness of this ROI between the affective and non-affective subgroups (Fig. S2B). The main group differences remained significant (Fig. S3) when these analyses were repeated using a cluster-forming threshold of <0.01.

3.4 Association of progressive neuroanatomical changes with change in clinical and functional variables

Table S3 displays the partial correlation coefficients of clinical and functional measures assessed with and change in volume of the regions-of-interest and spc of the LLOFR in FEP patients. A greater reduction of putamen (r=0.49, p=0.01; Fig. S4A) and globus pallidum volume (r=0.44, p=0.03) was associated with lower cumulative antipsychotic medication over the 3-year follow-up period. Increased right LV (r=0.43, p=0.03), total LV (r=0.41, p=0.04; Fig. S4B) and 3rd ventricular (r=0.55, p=0.004) volume over time was associated with worsening negative symptoms on the PANSS. Additionally, increased right LV (r=-0.43, p=0.03), total LV (r=0.41, p=0.04; Fig. S4C) and 3rd ventricular (r=-0.49, p=0.01) volume over time was associated with reduced GAF scores. A moderate correlation between antipsychotic medication use and total GM loss over time was also found (r=-0.45, p=0.02). Furthermore, the ventricular enlargement over time was associated with thalamic and striatal reduction but not with cortical thinning (Table S3 and Fig.S5). Cortical thinning in the LLOFR was not associated with changes in clinical or functional measures over time.

4 Discussion

Our results indicate that there is regionally specific progression of neuroanatomical deficits amongst patients in the years after their first-episode of psychosis. These deficits are characterised by a relatively greater volume reduction in the dorsal striatal and thalamic regions, by right lateral ventricular enlargement and by a greater progressive rate for cortical thinning of the LLOFR in FEP patients relative to HCs. In contrast, there was relative preservation of other regions, and in particular of the medial temporal lobe structures. Additionally, the progressive changes in LV volume were associated with indices of poorer outcome amongst patients, as evidenced by worsening negative symptoms and functioning scores over 3-years.

4.1 Progressive subcortical and ventricular changes

Striatal volume reductions over time have been reported in some previous studies of FEP patients (Theberge *et al.* 2007; Boonstra *et al.* 2011) and at-risk-mental state (ARMS) patients who were treatment naive (Smieskova *at al.* 2013). However, other studies have reported increased putaminal and caudate volume (Massana *et al.* 2005; Glenthoj *et al.* 2007; Roiz-Santiánez *et al.* 2014) or no significant volumetric differences between FEP patients and HCs (Lang *et al.* 2001; Haukvik *et al.* 2016) (see Table 1). Long exposure to antipsychotic medications has also been linked to increased striatal volume (Okugawa *et al.* 2007; van Haren *et al.* 2007). Other longitudinal studies examining treatment naïve ARMS patients have reported reduced striatal volumes compared to those treated

with antipsychotic medication (Smieskova *at al.* 2013; Katagiri *et al.* 2019). Thus, the use of antipsychotic medication in some cohorts may be obscuring basal ganglia reduction which is more readily detected in medication naïve sample or in those with minimal medication exposure, as in this study. Here, patients were minimally medicated (<3 weeks) prior to their baseline scan, and only 57% were treated with SGAs at the time of follow-up MRI scan (none with FGAs). In further support of this interpretation, high cumulative antipsychotic medication during the interscan period was correlated with increased putaminal and pallidal volumes over time.

The progressive thalamic volume reduction observed in this study is consistent with some longitudinal studies of FEP (Theberge *et al.* 2007; Andreasen *et al.* 2011) and established psychosis (van Haren *et al.* 2007; Cobia *et al.* 2017). Moreover, reduced thalamic volume has also been observed over time in ARMS patients (Harrisberger *et al.* 2016) and in those at high genetic liability for schizophrenia (Lawrie *et al.* 2001; McDonald *et al.* 2004). Others have reported increased thalamic volume after a short period of antipsychotic treatment (Deng *et al.* 2009; Dazzan *et al.* 2005) and no significant thalamic changes were observed in an adolescent cohort after a 3-year follow-up (de Castro-Manglano *et al.* 2011). In the current study, progressive thalamic volume reductions were not associated with any measurements of clinical outcome; however, other measurements of functional and cognitive performance were not assessed.

While total LV change is not statistically significant in this study, a pattern of progressive increase of right LV volume over time with medium effect size in FEP patients compared to controls is consistent with a number of previous longitudinal studies (Cahn *et al.* 2002; Andreasen *et al.* 2011; Suárez-Pinilla *et al.* 2015). However, other studies failed to demonstrate significant LV enlargement over time (Puri *et al.* 2001; Nakamura *et al.* 2007; Boonstra *et al.* 2011) potentially due to its highly variable structure. Our findings further indicate that the neuroprogressive process of LVs in poor clinical outcome patients, possibly relates to the observed regionally specific shrinkage of adjacent (thalamus and caudate) and remote (putamen) subcortical GM structures over time, considering the significant association between LVs and these subcortical structures. These findings are consistent with Gaser and colleagues (2004) who reported similar associations between ventricular enlargement and volume reductions of the thalamus, striatum and the superior temporal cortex in a schizophrenia cohort. Thus, these associations suggest that such volumetric progression could potentially be viewed as a biomarker of poor outcome in the illness. Additionally, LV enlargement over time has previously been associated with poorer clinical outcomes in a number of previous studies (Lieberman *et al.* 2001; Saijo *et al.* 2008) however, this is not a consistent finding (Cahn *et al.* 2002; Andreasen *et al.* 2011).

4.2 Progressive cortical changes

Cortical thinning was identified most prominently in the left prefrontal region of the brain after the first 3-years of FEP. With this finding consistent with other studies in FEP patients (Andreasen *et al.* 2011; Buchy *et al.* 2017), ARMS patients (Cannon *et al.* 2015) and in individuals with established schizophrenia (van Haren *et al.* 2011; Cobia *et al.* 2012). Of note, cortical thinning was present in this broad and typical sample of patients after their FEP covering a range of psychotic diagnoses and with variable clinical outcomes with a substantial proportion of the cohort not taking antipsychotic medication at follow-up. Indeed, we found similar rates of cortical thinning in affective and non-affective psychosis. In contrast, no significant cortical thinning in some other heterogenous FEP samples were detected (Haukvik *et al.* 2016; Palaniyappan *et al.* 2019), however this inconsistency may be related to a relatively short follow-up period (1 year, Haukvik *et al.* 2016) or small sample size (n=18, Palaniyappan *et al.* 2019) in these studies.

Progression of cortical deficits in the years after FEP is considered a major neurobiological trait of psychotic illness (Cobia *et al.* 2012); however, the specific mechanisms underlying progressive loss of frontal lobe thickness still remain unclear. Some evidence suggests neuropil pruning as a potential cause of progressive reduction of grey matter in schizophrenia (Selemon and Goldman-Rakic, 1999) resulting in a distributed cortical reorganisation mostly leading to synaptic dysfunction in response to psychosis (Palaniyappan *et al.* 2018). Thus, our reported pattern of progressive change may suggest an active but inefficient cortical reorganisation which is likely initiated from the left prefrontal cortex in the early years after FEP with further progression to other cortices across the entire course of illness (van Haren *et al.* 2011).

4.3 Associations of progressive neuroanatomical change

Although the identified volume reduction of subcortical structures were not significantly associated with cortical deficits and LV enlargement in the same FEP patients, the observed changes in these structures potentially indicate an early emergence of an aberrant functional coupling in neuroanatomy after FEP (Steullet, 2019), with a diffusion imaging study observing microstructural alterations in the mediodorsal and pulvinar regions of the thalamus, that directly connected to the orbitofrontal, latero-temporal cortices and basal ganglia (Cho *et al.* 2019). Furthermore, the observed poor association of cortical deficits with volume reduction in the dorsal striatum may be related to a subregional striatal response to antipsychotic medication (Massana *et al.* 2005; Roiz-Santiánez *et al.* 2014). Additionally, no association was noted between cumulative antipsychotic medication and

cortical thinning of the LLOFR, which is consistent with studies in both FEP (Gutiérrez-Galve *et al.* 2015) and in established schizophrenia (Cobia *et al.* 2012), suggesting that regional cortical thinning is an inherent feature of progressive psychotic illness (Nesvag *et al.* 2008) and may reflect an underlying neuropathophysiological process associated with psychosis onset.

4.4 Anatomically preserved regions

There was relative anatomical preservation of medial temporal lobe volume and global brain tissues observed in this study, a finding concordant with some other studies (Schaufelberger *et al.* 2011; Wood *et al.* 2001; Asami *et al.* 2012). These may be a potential characteristic feature of the initial stages of psychosis (Zipursky *et al.* 2004). While the FreeSurfer-derived hippocampal volumes were larger than manually-segmented volumes, comparable case-control differences were found with both approaches, indicating that this finding does not relate to methodological bias. Interestingly, there was a moderate correlation at a statistical trend level between progressive volumetric deficit of manually segmented hippocampal volume and poorer clinical outcome, which was not evident in the larger FreeSurfer segmented structure. This may be because the manually segmented hippocampus focusses upon the functionally specific hippocampus proper and dentate; whereas FreeSurfer segmented hippocampus includes more functionally diverse structures, including variable amounts of subiculum and tail (Akudjedu *et al.* 2018). If confirmed in a larger sample, this would be consistent with the study of Lappin and colleagues (2014) that hippocampal volume enlargement after FEP is a marker of good clinical outcome. Similarly, total GM volume changes were associated with cumulative antipsychotic medication use, consistent with meta-analytical findings (Vita *et al.* 2015) of a significant association between progressive loss of cortical GM volume and cumulative antipsychotic intake.

4.5 Strengths and limitations

The main strength of the study is its application of a longitudinal design to a cohort of psychotic patients who were originally assessed shortly after presentation to the services and with minimal antipsychotic exposure. We were also able to employ the same scanner and acquisition sequences, without any major soft/hardware upgrades during the study period, and the participants were scanned in a random order at each time-point, thus minimising any acquisition bias due to changes in scanner characteristics over time, which is known to potentially confound group diagnostic differences. We used the longitudinal FreeSurfer pipeline, which has the advantage, compared to other analysis approaches, of accounting for inter-subject variability by creating an unbiased subject-specific anatomical template (Reuter *et al.* 2010) from the images at both time-points, resulting in higher anatomical accuracy in identifying subtle changes over time. Furthermore, the application of a

global longitudinal vertex-wise analyses approach, unlike the surface-based approaches which are less reliable at localising changes within specific lobular subregions (DeLisi, 2008; Cercignani *et al.* 2018), has enabled a hypothesis-free investigation over the entire cortical mantle. We recruited a broad psychosis phenotype for our study, rather than focus on non-affective disorders alone, which is more generally representative of FEP patients presenting to the services. Despite the potential increase in clinical heterogeneity associated with this approach, we were able to detect regions of sub/cortical progression and link these with measures of clinical outcome that were not confined to a non-affective psychosis category.

The main limitation of the study was the relatively small sample size and consequent risk of type II error and lack of generalisability of the results. We did not employ a stringent statistical approach to control for multiple comparisons as we sought a balance between type 1 and type 2 errors; none of the subcortical findings would survive stringent multiple testing correction, however our major findings were hypothesised in the direction found *a priori* based on current literature. Thus, these findings would benefit from replication in a larger sample. Furthermore, after repeating the cortical analyses using a cluster-forming threshold of $p<0.01$, the main group difference remained significant (Fig. S3). Due to the limited data availability (functional measures but no childhood measures, cognition or physiological metrics), we were not able to assess in detail the contribution of other medications (e.g. mood stabilisers) and environmental exposures (e.g. childhood trauma, cannabis use) on the neuroanatomical measures acquired.

4.6 Conclusion

In conclusion, this study demonstrated the existence of localised progressive prefrontal cortical thinning, volume deficits in the dorsal striatum and thalamus, and right lateral ventricular enlargement over a 3-year period after patients first presented with psychotic illness. Taken together, these may be indicative of a progressive disturbance in the structural integrity of a subnetwork of the associative/cognitive component of the cortico-striato-thalamo-cortical circuitry involving the lateral orbitofrontal regions of the prefrontal cortex. This finding lends weight to the evidence that there is early regional neuroanatomical progression after FEP and thus such knowledge could potentially contribute to the identification of imaging biomarkers for psychosis which would be particularly beneficial in the critical early stages of the disorder. Future studies should also focus on comprehensively elucidating the functional consequences of anatomical progression by incorporating multimodal imaging and cognitive/functional measures in large longitudinal studies with multiple assessment points.

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