Title: Effects of environmental risks and polygenic loading for schizophrenia on cortical thickness

Emma Neilson [1a*], Catherine Bois [1b], Jude Gibson [1c], Barbara Duff [1d], Andrew Watson [1,2e], Neil Roberts [3f], Nicholas J. Brandon [4g], John Dunlop [4h], Jeremy Hall [5i], Andrew M. McIntosh [1,2j], Heather C. Whalley [1k] and Stephen M. Lawrie [1,2l]

[1] *Division of Psychiatry, Centre for Brain Sciences, School of Clinical Sciences, University of Edinburgh, Royal Edinburgh Hospital, Morningside Park, Edinburgh, UK*
[2]*Royal Edinburgh Hospital, Morningside Park, Edinburgh, UK*
[3]*MRC Centre for Inflammation Research Centre for Brain Sciences, University of Edinburgh, The Queen's Medical Research Institute, 47 Little France Crescent, Edinburgh, UK*
[4]*AstraZeneca, IMED Neuroscience Unit, Waltham, MA, USA*
[5]*Neuroscience and Mental Health Research Institute, Cardiff University School of Medicine, Cardiff, UK*

a: Emma Neilson, Address: Division of Psychiatry, 7th Floor Kennedy Tower, University of Edinburgh, Royal Edinburgh Hospital, Morningside Park, Edinburgh, EH10 5HF. Email: s0830415@sms.ed.ac.uk
Mobile: 0131 537 6687

b: C.bois@sms.ed.ac.uk
c: jude.gibson@ed.ac.uk
d: barbara.duff@ed.ac.uk
e: awatson3@nhs.net
f: neil.roberts@ed.ac.uk
g: nick.brandon@azneuro.com
h: john.dunlop@azneuro.com
i: hallj10@cardiff.ac.uk
j: andrew.mcintosh@ed.ac.uk
k: heather.whalley@ed.ac.uk
l: s.lawrie@ed.ac.uk

Abstract	248
Article Body	4,234
Figures	3
Tables	3
Supplementary Material (Tables and Figures)	24

Abstract

There are established differences in cortical thickness (CT) in schizophrenia (SCZ) and bipolar (BD) patients when compared to healthy controls (HC). However, it is unknown to what extent environmental or genetic risk factors impact on CT in these populations. We have investigated the effect of Environmental Risk Scores (ERS) and Polygenic Risk Scores for SCZ (PGRS-SCZ) on CT.

Structural MRI scans were acquired at 3T for patients with SCZ or BD (*n*=57) and controls (*n*=41). Cortical reconstructions were generated in FreeSurfer (v5.3). The ERS was created by determining exposure to cannabis use, childhood adverse events, migration, urbanicity and obstetric complications. The PGRS-SCZ were generated, for a subset of the sample (Patients=43, HC=32), based on the latest PGC GWAS findings. ANCOVAs were used to test the hypotheses that ERS and PGRS-SCZ relate to CT globally, and in frontal and temporal lobes.

An increase in ERS was negatively associated with CT within temporal lobe for patients. A higher PGRS-SCZ was also related to global cortical thinning for patients. ERS effects remained significant when including PGRS-SCZ as a fixed effect. No relationship which survived FDR correction was found for ERS and PGRS-SCZ in controls.

Environmental risk for SCZ was related to localised cortical thinning in patients with SCZ and BD, while increased PGRS-SCZ was associated with global cortical thinning. Genetic and environmental risk factors for SCZ appear therefore to have differential effects. This provides a mechanistic means by which different risk factors may contribute to the development of SCZ and BD.

Keywords: *Environmental risk, Polygenic risk, Schizophrenia, Bipolar Disorder, Structural MRI*

1. Introduction

Schizophrenia (SCZ) and bipolar disorder (BD) are psychiatric disorders characterised by overlapping symptomatology (Hilty et al., 2006; Bois et al., 2015) and multifactorial aetiologies (Hilty et al., 2006; Jablensky, 1997). Both are highly heritable (around 80%) due to a large number of relatively common genes of small effect (McGuffin et al., 2003; Matheson et al., 2011). Both have been proposed to be consistent with a neurodevelopmental model (Weinberger, 1987; Rapoport et al., 2012) which posits that SCZ and related disorders are influenced by both genetic and environmental factors impacting on the brain, at different developmental stages (Rapoport et al., 2012). Significant widespread cortical thinning is consistently found when comparing SCZ and BD patients to healthy controls (HC) (Kuperberg et al., 2003; Goldman et al., 2009; Rimol et al., 2010; Nesvåg et al., 2012; Knöchel et al., 2016). It is unclear however whether these differences are related to genetic and/or environmental risk factors previously associated with SCZ. Elucidating these components would help to further understand the underlying aetiologies of these disorders.

Decreases in grey matter volumes have been found before disease onset (McIntosh et al., 2011) and thinner cortices have been noted in SCZ patients when compared to HC in all lobes (Kuperberg et al., 2003; Goldman et al., 2009; Rimol et al., 2010). However, the most consistent findings have suggested that cortical thinning is most prominent in frontal and temporal regions (Kuperberg et al., 2003; Goldman et al., 2009; Rimol et al., 2010; van Haren et al., 2011; Sprooten et al., 2013), where it continues to decline after disease onset (Cobia et al., 2012). Despite reports of disease specific cortical thinning associated with BD, e.g. in orbitofrontal regions (Knöchel et al., 2016), many studies have also highlighted cortical thinning findings which overlap with the aforementioned SCZ deficits (Rimol

et al., 2010; Hanford et al., 2016; Knöchel et al., 2016). Hence, frontal and temporal lobes are regions of interest for investigation of factors that could impact cortical deficits within SCZ and BD.

Both SCZ and BD have been associated with several environmental risk factors (van Os et al., 2010; Lawrie et al., 2011; Marangoni et al., 2016). Cannabis use, childhood adversity and obstetric complications (OC) have the strongest epidemiological evidence for an association with an increased risk of SCZ and BD, (Krabbendam & van Os, 2005; van Os et al., 2010; Rapoport et al., 2012; Matheson et al., 2013; Radhakrishnan et al., 2014; Stepniak et al., 2014; Marangoni et al., 2016). Urbanicity and migration are also strongly linked to SCZ (Krabbendam & van Os, 2005; van Os et al., 2010; Rapoport et al., 2012; Stepniak et al., 2014); however, as environmental risk factors for BD the evidence is less conclusive. Nevertheless, both migration and urbanicity have been linked to an increased incidence of BD (Pedersen & Mortensen, 2006; Cantor-Graae & Pedersen, 2013).

Although the evidence is limited, some of these factors have also been linked to deficits in cortical volume and thickness. Cannabis use has been associated with reduced global and frontal lobe volumes (Welch et al., 2011), cortical thinning in general (Habets et al., 2011), and, more specifically, in dorso-lateral prefrontal cortex (DLPFC) and anterior cingulate cortex (Rais et al., 2010). Childhood adversity/trauma has been associated with global cortical thinning globally (Habets et al., 2011) and in the limbic system (Souza-Queiroz et al., 2016), as well as decreased subcortical structure volumes (Hoy et al., 2012; Barker et al., 2016a). So far, OC have not been significantly related to cortical thinning (Haukvik et al., 2009; Smith et

al., 2015) but birth complications have been previously linked to reduced hippocampal and cortical volume (Cannon et al., 2002; van Erp et al., 2002) and may, alone or in accumulation with other risk factors, be linked to deficits in cortical thickness (CT). Migration and urbanicity are yet to be investigated in relation to CT but urbanicity has been linked with decreased grey matter volume in DLPFC within a healthy sample (Haddad et al., 2015).

Our knowledge of how these environmental risk factors impact upon CT in SCZ and BD is therefore inconclusive. Given a lack of knowledge about how these factors confer risk, it is desirable to determine if an accumulation of these risk factors has additional effects; some are likely to occur and impact development at different stages of life (Dean & Murray, 2005; Stepniak et al., 2014) and several of these factors can be experienced by any individual. Prima facie, it seems likely that a higher number of insults may result in greater biological effects. One aim of the current study is therefore to determine the impact of environmental risk factors, in accumulation, on CT.

Genome Wide Association Studies (GWAS) have advanced our understanding of the genetic underpinnings of SCZ and BD. Recently, the Schizophrenia Working Group of the Psychiatric Genomics Consortium (SWG-PGC) GWAS (2014) identified 108 genetic loci associated with SCZ, as well as several other markers that failed to reach genome-wide significance, suggesting a polygenic foundation to SCZ, with many genetic variants of individually small effect contributing to the overall phenotypic variation (International Schizophrenia Consortium., 2009). Strong evidence also exists for a polygenic basis for BD, with a strong overlap in the genetic variants associated with SCZ and BD (International Schizophrenia Consortium, 2009; Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013; Ripke et al., 2013). Using the summary data from the SWG-PGC GWAS (including alleles associated with the risk

of SCZ as well as their effect sizes) as the training dataset, PGRS-SCZ can be created in an independent sample. Risk variants in the independent sample which are common to the training dataset are identified, these are then weighted by the effect sizes reported in the SWG-PGC GWAS and summed across individual genotypes in the independent sample (International Schizophrenia Consortium., 2009; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014; Euesden et al., 2015). Higher positive scores indicate a greater polygenic risk for SCZ disorder.

Several studies have investigated the effect of these PGRS for SCZ (PGRS-SCZ) on clinical and cognitive phenotypes (McIntosh et al., 2013; Stepniak et al., 2014; Whalley et al., 2016). Thus far, structural neuroimaging phenotypes have been assessed with regard to the first SWG-PGC GWAS data, which identified 7 associated loci (Schizophrenia Psychiatric Genome-Wide Association Study Consortium, 2011), with inconsistent results (Terwisscha van Scheltinga et al., 2013; Papiol et al., 2014), making further investigation warranted.

Despite the fact that risk variants have been identified for BD separately (Psychiatric GWAS Consortium Bipolar Disorder Working Group, 2011), there is still a substantial amount of shared variation between these psychiatric disorders (Cross-Disorder Group of the Psychiatric Genomics Conosrtium, 2013; Ripke et al., 2013). Furthermore, PGRS-SCZ have been previously used for analysis within a combined BD and SCZ patient group (Ruderfer et al., 2014). Therefore, as the intention of the current study is to determine whether risks common to the development of both BD and SCZ are linked to CT, and the SCZ GWAS is more highly powered than the BD GWAS (Psychiatric GWAS Consortium Bipolar Disorder Working Group, 2011; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014),

we have used the PGRS-SCZ. A second aim of the current study is to determine if a relationship exists between PGRS-SCZ, created using the most recent PGC SCZ data, and CT.

Within the current study, global, frontal and temporal regions of CT were analysed to determine their relationship with PGRS-SCZ and environmental risk associated with SCZ. We hypothesised that both PGRS-SCZ and an accumulation of environmental risk factors would be inversely associated with cortical thinning in these regions, for both the patients and controls separately and when assessing differences between patients and controls. Due to the aforementioned overlap between structural findings, environmental, and genetic risk factors, and in order to increase power within the sample, SCZ and BD patient data were combined into one patient groups for analyses.

2. Methods

2.1 Participants

Detailed participant information has been reported previously (Whalley et al., 2015). Briefly, participants were recruited as part of the Scottish Family Mental Health Study, approved by the Multicentre Research Ethics Committee for Scotland (09/MRE00/81). Detailed clinical and MRI data were obtained for HC (n=41) and patients with a DSM-IV diagnosis of SCZ (n=38) or BD (n=20) aged between 18 and 67 years. Clinical diagnoses were established using the structural interview for the DSM-IV (SCID; (First et al., 2002) conducted by one of two trained psychiatrists. For analyses purposes, SCZ and BD participants were combined into one patient group. Table 1 shows demographic information for both groups.

Insert Table 1 Here

2.2 Imaging Procedures

MR imaging was performed at Edinburgh's Clinical Research Imaging Centre (CRIC) (http://www.cric.ed.ac.uk/) on a Siemens Verio 3T MRI system (Siemens Medical Systems, Erlangen). Structural brain images were acquired using a T1-weighted magnetization prepared rapid acquisition gradient sequence parallel to the AC-PC line (repetition time 2300ms, echo time 2.98ms, inversion time 900ms, flip angle 9°) resulting in 160 contiguous 1mm slices of 256x256 voxels.

Brain scans were anonymised at the time of acquisition and a set protocol was adhered to for pre-processing of scans, regardless of clinical status. Structural images were processed using FreeSurfer (v5.3) (http://surfer.nmr.mgh.harvard.edu/fswiki/) to quantify thickness of cortical anatomical regions, volumetric segmentation, cortical surface reconstructions and cortical parcellation. See Supplement 1 for full procedure. The Desikan-Killiany atlas was used to define cortical anatomical regions (Desikan et al., 2006). A list of the regions of interest included in frontal and temporal lobes, using this atlas, can be found in Supplement 1.

A trained rater (E.N.) checked all scans for inaccuracies, blinded to group status. All scans were edited adhering to FreeSurfer procedures (http://freesurfer.net/fswiki/Edits) in order to increase the accuracy of the pial surface. Following this procedure, one scan was removed due to defective surface generation that could not be corrected by manual editing (HC=41, Patient=57). Average global and lobar CT values were extracted from each scan for analysis.

2.3 Environmental Measures

Environmental risk information was collected for all 98 participants. The risk factor measures and subsequent calculation of an Environmental Risk Score (ERS) were based upon methods developed by Stepniak et al. (2014) and included three factors for controls; Childhood Adverse Events (CAE), Migration, and Cannabis Use, with a further two for the patient group; OC and Urbanicity. Environmental measures were defined as follows: *CAE* – measured using the Childhood Life Events Questionnaire (CLEQ, www.bdrn.org) which determined if participants had experienced one or more event out of a possible list of 13 adverse childhood events including death of a parent/friend, parental divorce and personal/parental hospitalisation. Abuse and bullying are not specifically enquired about, however a final question allows participants to disclose any other CAE not previously specified. Risk was recorded if the participant experienced one or more of the possible events as opposed to none; *Migration* – whether the participant migrated to the United Kingdom from another country; *Cannabis Use* – any recorded cannabis use before the time of scan; *OCs* – any deviation from normal pregnancy or delivery (e.g. premature birth, jaundice); *Urbanicity* – calculated using the measure from Stepniak et al. (2014), to determine the cities that patients lived in from birth to 18 years old. Each city was placed into a category depending on its population (1: </= 10,000, 2: 10,001-50,000, 3: 50,001-100,000, 4: > 100,000) and was multiplied depending on the number of years spent living in that place. This was repeated for each city if the participant relocated and all scores were summed. The total score was then split into one of 2 groups - rural (score 18-45) and urban (score 46-72) upbringing, with placement in the urban group conferring risk. Environmental measures were scored as 1 or 0; with 1 representing that the risk was present for each participant. Frequencies of the individual factors for the combined patient groups and controls are displayed in Supplement 2, Tables S1-2. Participants with unavailable information (NA) on factors were rated, conservatively, as 0, however, analyses

with NA removed were also conducted with results reported in Supplement 2. The continuous ERS was determined by totalling the number of environmental measures experienced by each participant.

2.4 Genotyping and derivation of PGRS

Information on the genotyping process are presented in Supplement 1.

Polygenic profile scores were generated using imputed genotype data. Imputation was performed in accordance with the ENIGMA 1000 genomes protocol (ENIGMA2 Genetics Support Team, 2013) Single nucleotide polymorphisms (SNPs) with an imputation R-squared quality score of >0.3 were retained for further analysis resulting in 6,145,246 SNPs. All subsequent analyses were performed in PLINK (Purcell et al., 2007). Further QC criteria were applied to imputed data. Individuals with missingness >2% were excluded, as were SNPs with a genotype call rate of <98%, Hardy-Weinberg equilibrium p-value $<1 \times 10^{-6}$, a minor allele frequency of <5%, or those that were strand ambiguous. Clump-based linkage disequilibrium pruning (r^2 0.2, 300kb window) was performed to create a SNP-set in approximate linkage equilibrium. Marker weights (logarithm of the Odds Ratio) and p-value association statistics for SNPs were derived from the most recent PGC GWAS of schizophrenia (9.8 million autosomal SNPs) (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Five scores were generated for each individual, using SNPs selected according to the significance of their association with the phenotype in the discovery GWAS at nominal P-value thresholds of 0.01, 0.05, 0.1, 05, 1, as previously described (International Schizophrenia Consortium, 2009). These data were not available for 11 of the patients and 8 of the controls and they were therefore excluded (Patients=46, HC=33).

Multi-dimensional scaling (MDS) was conducted to identify outliers within the population stratification using previously described protocols (ENIGMA2 Genetics Support Team, 2013). In plotting the MDS components, three outliers were identified and removed (Supplement 1, Figure S1). Four MDS components were included in subsequent PGRS-SCZ analysis models within this study, consistent with previous publications (McIntosh et al., 2013; Whalley et al., 2015). Where sibling pairs were present in the sample, one half was removed to avoid relatedness issues, making the final sample with genotyped information HC=32, Patients=43.

2.5 Statistical analysis

Statistical analyses were conducted in R (v3.2.2). The effects of left and right global, frontal and temporal CT were investigated in line with our hypotheses. SCZ and BD patient data were combined into one patient group due to overlap between genetic risk, environmental risk and structural MRI findings. However, a secondary analysis examining the patients separately was performed and reported in Supplement 3.

Firstly, we assessed whether an accumulative ERS and, post-hoc, individual environmental risks were related to CT. Secondly, we tested for associations between CT and PGRS-SCZ and finally, we calculated whether any environmental effects remained after controlling for potential genetic effects. As the aim of the study was to determine whether there was an effect of environmental and polygenic risk on CT, and more environmental information was available for patients than controls, analyses were conducted separately for each of these groups. However, we also tested for potential differential effects when comparing patients and controls using the three environmental factors common to both groups, as well as the PGRS-SCZ. ANCOVAs were run for each anatomical structure with the structure of interest entered as the outcome variable and ERS/PGRS-SCZ as the predictor variable. Results for all lobar structure

analyses for ERS and PGRS analyses were corrected for multiple comparisons using a False Discovery Rate (FDR) correction, with a rate of p=0.05 (Genovese et al., 2002). Post-hoc analyses were run to test for the effects of individual environmental risk factors on CT. Due to these factors all being correlated with the ERS (Supplement 1, Table S1-2), post-hoc analyses were FDR corrected across lobes and all individual environmental risk factors.

For the ERS analyses, using the combined patient group and controls separately, covariates included age (mean centred) and gender, with group (SCZ/BD) added as a fixed effect within patient models to control for potential group differences. ERS was the predictor of interest within the main environmental analysis. For additional post-hoc analyses the individual risk factor was the predictor variable. Age (mean centred), gender, and group for the patient analyses, were also included as fixed effects in the PGRS analyses as well as four MDS components and the standardised PGRS at threshold $p \leq 0.1$. This threshold was utilised as it was shown to explain the most phenotypic variance in the discovery cohort (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Results at the 4 other thresholds ($p \leq 0.01$, 0.05, 0.5 and 1) are presented in Supplement 2. Total average thickness was added as a covariate for all frontal and temporal lobar analyses. The same models with the inclusion of an ERS or individual environmental risk factor/PGRS-SCZ by group interaction factor was also run to investigate potential group differences between the combined patient group and controls.

A further analysis model, including the above ERS covariates, the PGRS-SCZ variables included as fixed effects and ERS as the predictor variable, was tested to determine the effect of ERS whilst controlling for PGRS-SCZ.

Power was also calculated for the environmental risk analyses. As there is no previous effect size in the literature that links an accumulative ERS to CT, we estimated this based on a review by Lawrie et al. (2011), which includes the OR of many of the risk factors within the current study. Based on this review, we took an overall summary OR of 2 which is conservative as the OR for immigration for example is 5 (Lawrie et al., 2011). We converted this OR to an effect size using methods described in Chinn et al. (2000). Using this effect size in conjunction with sample size information for the current sample, we calculated power for the current study using the 'pwr' package in R. The results suggest that we have 88-96% power to detect relationships at p=0.05 within the current sample.

Chlorpromazine equivalents (CPZE) of patient's antipsychotic use were calculated using previous methods (Woods, 2003). Spearman's rank correlations revealed no significant relationship between CPZE and the current brain parameters.

3. Results

3.1 Group Differences

No significant differences were found for age, gender or premorbid IQ between the combined patient group and controls, but significant differences were found for SES, YMRS, HDRS and symptom severity (Table 1).

There was a significant difference in CT between patients and controls in global left and right, and right temporal lobes (Table 2), due to patients having significantly thinner cortices in these regions compared to controls.

Insert Table 2 Here

A significant difference in PGRS-SCZ was also evident between groups (Table 1); patients had a higher mean score than controls at the p≤0.1 threshold ($t_{69.17}$=-2.62, p=0.01). Supplement 2, Table S3 presents differences at other thresholds.

There was also a significant group difference in ERS (Table 1); patients experienced a higher mean number of environmental risks compared to controls ($t_{78.75}$= -2.3, p=0.02).

Analyses were also conducted to determine potential group differences between SCZ and BD patients and are reported in Supplement 3, Table S1-2. No significant differences were found between these groups, with the exception of PANSS Positive Symptoms.

3.2 Patient Analyses

3.2.1 ERS Analyses

A significant main effect was found for ERS ($F_{1,51}$=7.23, p=0.01) which survived FDR correction ($p_{corrected}$=0.04); an increase in ERS was associated with a thinner right temporal cortex (Table 3).

Insert Table 3 Here

3.2.1.1 Post-hoc Analyses of Individual Environmental Risk Factors

Post-hoc analyses of individual environmental risk factors revealed no significant main effects which survived FDR correction (Supplement 2, Table S4).

No effects of group were found for the ERS or individual environmental risk analyses.

3.2.2 PGRS-SCZ Analyses

A significant main effect of PGRS-SCZ on Global CT was found in left ($F_{1,33}$=4.33, p=0.05) and right ($F_{1,33}$=4.54, p=0.04) hemispheres, due to a negative relationship between PGRS-SCZ and CT (Figures 1a and b). No main effect of group was found in these regions. No significant effects were found for any other structures (Supplement 2, Table S12).

Insert Figures 1a and b Here

3.2.3 ERS controlling for PGRS-SCZ Analyses

When adjusting for possible effects of PGRS-SCZ, the main effects of ERS on CT in right temporal lobe remained significant ($F_{1,31}$=5.74, p=0.02).

3.3 HC Analyses

3.3.1 ERS Analyses

A main effect of ERS was apparent in controls within left and right temporal lobes but did not survive FDR correction. The pattern of this effect suggested that a higher ERS was associated with thicker temporal cortices.

3.3.1.1 Post-hoc Analyses of Individual Environmental Risk Factors

Post-hoc analyses of individual factors suggested a main effect of CAE on left and right temporal lobes which did not survive FDR correction but displayed the pattern that those who had experienced CAE had greater CT within these regions, compared to those who had not. No other factor had a significant effect (Supplement 2, Table S6).

3.3.2 PGRS Analyses

PGRS-SCZ did not have an effect on any of the structural parameters in controls. (Supplement 2, S13)

3.4 Interaction Analyses

*3.4.1 Group*Environmental Risk Analyses*

There was a significant ERS by group interaction in right temporal lobes ($F_{1,91}$=6.23, p=0.01); a higher risk score was associated with a thicker right temporal cortex within controls, but a thinner cortex within patients. However, after FDR correction, this result only revealed a trend towards significance ($p_{corrected}$=0.06). There were no other associations for any other structures and there were no significant main effects for ERS (Supplement 2, Table S8 and S10).

3.4.1.1 Post-hoc Analyses of Individual Environmental Risk Factors

Post-hoc analyses revealed significant CAE by group interactions in right temporal lobe, surviving FDR correction ($F_{1,91}$=6.27, p=0.01, $p_{corrected}$=0.04). This was due to thicker cortices

for those controls who had experienced CAE compared to those who had not; whereas, in the patient group, the opposite pattern was apparent. No other individual risk factors were significant (Supplement 2, Table S8 and S10).

*3.4.2 Group*PGRS-SCZ Analyses*

There was a significant main effect of PGRS-SCZ in left ($F_{1,64}$=8.41, p=0.01) and right ($F_{1,64}$=10.22, p<0.01) hemispheres; an increase in PGRS-SCZ was associated with a thinner cortex within these regions, regardless of group (Figures 2a and b). There were no other significant main effects (Supplement 2, Table S14).

Insert Figures 2a and b Here

There was also a significant group by PGRS-SCZ interaction in left temporal lobe which withstood FDR correction ($F_{1,63}$=6.88, p=0.01, $p_{corrected}$=0.04). This was due to an increase in PGRS-SCZ being associated with a thinner cortex within patients (Figure 3a) but having no relationship in controls (Figure 3b). No other interactions reached significance (Supplement 2, Table S15).

Insert Figures 3a and b Here

---

*3.4.3 Group*ERS controlling for PGRS Analyses*

When controlling for potential effects of PGRS on ERS, the significant ERS by group interaction remained for right temporal lobe ($F_{1,62}$=4.51, p=0.04). The CAE group interaction, also remained significant ($F_{1,62}$=7.22, p=0.01).

4. Discussion

We examined whether an ERS, as well as PGRS-SCZ were associated with CT within a patient group (SCZ/BD) and HC. We report that an ERS for SCZ negatively affected right temporal CT within patients. Importantly, these effects were robust to controlling for PGRS-SCZ, and to FDR correction. Environmental risk factors were associated with a thicker cortex within controls, but did not survive FDR correction. Interaction analyses revealed a significant group by ERS interaction in right temporal lobe, in that, a thinner cortex was associated with increased ERS within patients whereas the opposite pattern was apparent within controls; albeit this interaction was a trend after FDR correction. There was also a significant group by PGRS-SCZ interaction in left temporal lobe, with higher PGRS-SCZ being related to a thinner cortex within patients whereas no relationship was apparent for controls.

Cortical thinning in temporal lobe is commonly found in patients with SCZ and BD (Kuperberg et al., 2003; Goldman et al., 2009; Rimol et al., 2010; van Haren et al., 2011; Hanford et al., 2016). As far as we are aware, our results provide the first evidence that an accumulation of environmental risk factors contribute to cortical thinning within this area. The opposite effect was seen in the separate analyses of control individuals, and in the interaction between the two groups, but these results did not survive FDR correction, possibly due to comparatively low power for these analyses.

We also found an interaction within right temporal lobe due to a thicker cortex in HC in association with experiencing CAE, whereas patients who experienced the same insult had thinner temporal cortices. Although CAE have been formerly linked to thinner cortices in patients (Habets et al., 2011), they have not been previously associated with a thicker cortex in controls. Habets et al. (2011) found a thicker cortex to be associated with increased levels of developmental trauma in siblings of SCZ patients, but not in controls. We, however, did not previously find this effect in those at familial high-risk (Barker et al., 2016b). Our current replication of Habets et al. (2011) does support the possibility that experiencing CAE could thicken the cortex and may be related to resilience to developing a psychotic disorder. Within healthy populations, studies have shown that increased participation in practices which may promote mental wellbeing, such as meditation (Lazar et al., 2005; Kang et al., 2013) and physical exercise (Reiter et al., 2015), is associated with having a thicker temporal cortex, amongst other areas.

An important point to acknowledge is that we received less full histories for ERS derivation in controls than patients; however, the present study has also directly compared the environmental risk factors common to both patients and controls. We report a group by ERS interaction in right temporal CT, whereby higher ERS was associated with a thinner cortex within patients but a thicker cortex in controls. We also report a group by CAE interaction in right temporal lobe. These results suggest a differential effect of environmental risk in patients and controls but must be interpreted with caution and require replication in much larger cohorts.

We also report significant negative relationships between PGRS-SCZ and global CT within both the patient only analysis, and the full sample, irrespective of group. To our knowledge, this has not been previously reported – although we and others have reported thinner cortices

in those at familial high-risk of SCZ (Goghari et al., 2007; Byun et al., 2012; Sprooten et al., 2013). Previously, increased PGRS-SCZ have been linked to a reduction in white matter volume (Terwisscha van Scheltinga et al., 2013) and decreased gyrification in general populations (Liu et al., 2016) however this is the first evidence linking genetic loading for SCZ to CT. Based on our findings we hypothesise that genetic risk for SCZ could disrupt global CT during development and thereby increase the risk of developing SCZ.

A significant group by PGRS-SCZ interaction was reported; a thinner cortex in left temporal lobe was associated with higher PGRS-SCZ in the patient group, but had no association with PGRS-SCZ in controls. This suggests potential localised differential effects between patients and controls.

In the current study, we used PGRS for SCZ rather than BD for several reasons. Firstly, we were interested in determining the commonalities between these disorders and how they may impact upon CT. Secondly, PGRS-SCZ have been used previously within BD populations (Ruderfer et al., 2014). Thirdly, the original GWAS for SCZ was better powered that that for BD (Psychiatric GWAS Consortium Bipolar Disorder Working Group, 2011; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). However, it would be of interest for future studies to determine the effects of the PGRS-BD in a larger sample.

Given the potential interactive effects of genetic and environmental risk factors for SCZ on neuroanatomy, we conducted further analyses to determine whether the effects of environmental factors persisted after controlling for PGRS-SCZ. We report that all environmental effects remained significant after so doing. We cannot rule out a gene-

environment interaction of PGRS-SCZ and ERS on CT, but our results do suggest that the effects of genetic and environmental risks for SCZ are not the same.

A further limitation within this study is that we were not able to conduct corroborative interviews with e.g. parents therefore, it is likely that there is some missing information for individual environmental risk factors. We therefore decided that missing information (NAs) should be recorded as a 0 when calculating the ERS. This was considered the best approach, in order to include as much information as possible without potentially overstating the effect of environmental factors on brain structure. Additional analyses were also conducted with all NAs removed and are reported in Supplement 2. The results of these analyses showed a similar pattern to those reported here but did not survive FDR correction. However, by removing the NAs a substantial amount of data was lost suggesting that the lack of significance may reflect low power rather than the lack of an effect. This outcome provides further support for the current approach, but analyses within a larger cohort is necessary to determine if the effects can be replicated.

Together, our results suggest that experiencing environmental risks for SCZ contributes to localised cortical thinning in patients with SCZ and BD. Higher genetic loading is associated with global cortical thinning but does not account for the effects of environmental risk. We thus provide further evidence for a neurodevelopmental model for SCZ which posits that both environmental and genetic factors contribute to the development of the disorders. Further, our results suggest that it might be possible to develop intervention strategies to address environmental risks for SCZ and measure their effect on CT.

Contributors

Conceived and designed the experiments: N.B., J.D., J.H., A.M.M., and S.M.L. Performed the experiments: H.C.W., B.D., J.H., A.W., N.J.B., J.D., A.M.M. and S.M.L. Analysed the data: E.N. and J.G. Contributed reagents/materials/analysis tools: J.G. and N.R. Manuscript preparation: E.N.; additional editing: S.M.L. All authors commented on drafts of the paper.

Conflicts of Interest

The author SML has received financial support for research, in the past 3 years, from Roche Abbvie, Sunovion and Janssen, in relation to therapeutic studies of people with schizophrenia. He has also received personal payments for advisory panels and/or educational meetings from Janssen Forum and Otsuka. AMM has previously received financial support from Janssen and Lilly. HCW is supported by a JMAS SIM Fellowship from the Royal College of Physicians of Edinburgh and by an ESAT College Fellowship from the University of Edinburgh. AMM, SML and HCW have also previously received support from Pfizer (formerly Wyeth). These received funds do not present a conflict of interest with the present study. JD and NB were full time employees and shareholders of Pfizer at the time of these studies. None of the other authors has any biomedical financial interests or potential conflicts of interest to disclose.

Acknowledgments

We acknowledge Douglas Blackwood (University of Edinburgh) for his assistance with study design and data collection. The investigators also acknowledge the Scottish Mental Health Research Network (http://www.smhrn.org.uk) for providing further assistance with participant recruitment and cognitive assessments. We would like to thank both, the participants who took part in the study and the radiographers who acquired the MRI scans. Scans were collected at the Clinical Research Imaging Centre (http://cric.ed.ac.uk). This work was funded by an award from the Translational Medicine Research Collaboration (NS_EU_166) – a consortium

consisting of the Universities of Edinburgh, Aberdeen, Dundee and Glasgow, the four associated NHS Health Boards (Grampian, Tayside, Lothian and Greater Glasgow and Clyde), Scottish Enterprise and Pfizer. The Dr Mortimer and Theresa Sackler Foundation also offered financial support for imaging aspects of this study.

References

Barker, V., Bois, C., Johnstone, E. C., Owens, D. G., Whalley, H. C., McIntosh, A. M., & Lawrie, S. M., 2016a. Childhood adversity and cortical thickness and surface area in a population at familial high risk of schizophrenia. Psychol. Med. 46 (4), 891-896.

Barker, V., Bois, C., Neilson, E., Johnstone, E. C., Owens, D. G., Whalley, H. C., McIntosh, A. M., Lawrie, S. M., 2016b. Childhood adversity and hippocampal and amygdala volumes in a population at familial high risk of schizophrenia. Schizophr. Res. 175 (1-3), 42-47

Bois, C., Whalley, H. C., McIntosh, A. M., & Lawrie, S. M., 2015. Structural magnetic resonance imaging markers of susceptibility and transition to schizophrenia: a review of familial and clinical high risk population studies. J. Psychopharmacol. 29 (2), 144-154.

Byun, M. S., Kim, J. S., Jung, W. H., Jang, J. H., Choi, J. S., Kim, S. N., Choi, C. H., Chung, C. K., An, S. K., Kwon, J. S., 2012. Regional cortical thinning in subjects with high genetic loading for schizophrenia. Schizophr. Res. 141 (2-3), 197-203.

Cannon, T. D., van Erp, T. G., Rosso, I. M., Huttunen, M., Lönnqvist, J., Pirkola, T., Salonen, O., Valanne, L., Poutamen, V. P., Standertskjöld-Nordenstam, C. G., 2002. Fetal hypoxia and structural brain abnormalities in schizophrenic patients, their siblings, and controls. Arch. Gen. Psychiatry. 59 (1), 35-41.

Cantor-Graae, E. Pedersen, C. B., 2013. Full spectrum of psychiatric disorders related to foreign migration: a Danish population-based cohort study. JAMA Psychiatry. 70 (4), 427-435.

Chinn, S., 2000. A simple method for converting an odds ratio to effect size for use in meta-analysis. Statist. Med. 19, 3127-3131.

Cobia, D. J., Smith, M. J., Wang, L., & Csernansky, J. G., 2012. Longitudinal progression of frontal and temporal lobe changes in schizophrenia. Schizophr. Res. 139 (1-3), 1-6.

Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013. Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. Lancet. 381 (9875), 1371-1379.

Dean, K., & Murray, R. M., 2005. Environmental risk factors for psychosis. Dialogues. Clin. Neurosci. 7 (1), 69-80.

Desikan, R. S., Ségonne, F., Fischl, B., Quinn, B. T., Dickerson, B. C., Blacker, D., Buckner, L., Dale, A.M., Maguire, P., Hyman, B.T., Albert, M.S., Killiany, R. J., 2006. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage. 31 (3), 968-980.

ENIGMA2 Genetics Support Team, 2013. ENIGMA2 1KGP Cookbook (v3) [Online]. The Enhancing Neuroimaging Genetics through MetaAnalysis (ENIGMA) Consortium. http://enigma.ini.usc.edu/wpcontent/uploads/2012/07/ENIGMA2_1KGP_cookbook_v3.pdf [19 July 2016]

Euesden, J., Lewis, C. M., O'Reilly, P. F., 2015. PRSice: Polygenic Risk Score software. Bioinformatics. 31 (9), 1466-1468.

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. W., 2002. Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition with Psychotic Screen. New York State Psychiatric Institute, New York.

Genovese, C.R., Lazar, N.A., Nichols, T., 2002. Thresholding of Statistical Maps in Functional Neuroimaging Using the False Discovery Rate. NeuroImage. 15 (4), 870-878.

Goghari, V. M., Rehm, K., Carter, C. S., & MacDonald, A. W., 2007. Regionally specific cortical thinning and gray matter abnormalities in the healthy relatives of schizophrenia patients. Cereb. Cortex. 17 (2), 415-424.

Goldman, A. L., Pezawas, L., Mattay, V. S., Fischl, B., Verchinski, B. A., Chen, Q., Weinberger, D. R., Meyer-Lindenberg, A., 2009. Widespread reductions of cortical thickness in schizophrenia and spectrum disorders and evidence of heritability. Arch. Gen. Psychiatry. 66 (5), 467-477.

Habets, P., Marcelis, M., Gronenschild, E., Drukker, M., van Os, J., & Genetic Risk and Outcome of Psychosis (G.R.O.U.P), 2011. Reduced cortical thickness as an outcome of differential sensitivity to environmental risks in schizophrenia. Biol. Psychiatry. 69 (5), 487-494.

Haddad, L., Schäfer, A., Streit, F., Lederbogen, F., Grimm, O., Wüst, S., Deuschle, M., Kirsch, P., Tost, H., Meyer-Lindenberg, A., 2015. Brain structure correlates of urban upbringing, an environmental risk factor for schizophrenia. Schizophr. Bull. 41 (1), 115-122.

Hanford, L. C., Nazarov, A., Hall, G. B., & Sassi, R. B., 2016. Cortical thickness in bipolar disorder: a systematic review. Bipolar Disord. 18 (1), 4-18.

Haukvik, U. K., Lawyer, G., Bjerkan, P. S., Hartberg, C. B., Jönsson, E. G., McNeil, T., & Agartz, I., 2009. Cerebral cortical thickness and a history of obstetric complications in schizophrenia. J Psychiatr. Res. 43 (16), 1287-1293.

Hilty, D. M., Leamon, M. H., Lim, R. F., Kelly, R. H., & Hales, R. E., 2006. A review of bipolar disorder in adults. Psychiatry. 3 (9), 43-55.

Hoy, K., Barrett, S., Shannon, C., Campbell, C., Watson, D., Rushe, T., Shevlin, M., Bai, F., Cooper, S., Mulholland, C., 2012. Childhood trauma and hippocampal and amygdalar volumes in first-episode psychosis. Schizophr. Bull. 38 (6), 1162-1169.

International Schizophrenia Consortium, 2009. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. Nature. 460 (7256), 748-752.

Jablensky, A., 1997. The 100-year epidemiology of schizophrenia. Schizophr. Res. 28 (2-3), 111-125.

Kang, D. H., Jo, H. J., Jung, W. H., Kim, S. H., Jung, Y. H., Choi, C. H., Lee, U. S., An, S. C., Jang, J. H., Kwon, J. S., 2013. The effect of meditation on brain structure: cortical thickness mapping and diffusion tensor imaging. Soc. Cogn. Affect. Neurosci. 8 (1), 27-33.

Knöchel, C., Reuter, J., Reinke, B., Stäblein, M., Marbach, K., Feddern, R., Kuhlmann, K., Alves, G., Prvulovic, D., Wenzler, S., Linden, D. E. J., Oertel-Knöchel, V., 2016. Cortical thinning in bipolar disorder and schizophrenia. Schizophr. Res. 172 (1-3), 78-85.

Krabbendam, L., & van Os, J., 2005. Schizophrenia and urbanicity: a major environmental influence--conditional on genetic risk. Schizophr. Bull. 31 (4), 795-799.

Kuperberg, G. R., Broome, M. R., McGuire, P. K., David, A. S., Eddy, M., Ozawa, F., Goff, D., West, C., Williams, S. C. R., van der Kouwe, A. J. W., Salat, D. H., Dale, A. M., Fischl, B., 2003. Regionally localized thinning of the cerebral cortex in schizophrenia. Arch. Gen. Psychiatry. 60 (9), 878-888.

Lawrie, S. M., Olabi, B., Hall, J., & McIntosh, A. M., 2011. Do we have any solid evidence of clinical utility about the pathophysiology of schizophrenia? World Psychiatry, 10 (1), 19-31.

Lazar, S. W., Kerr, C. E., Wasserman, R. H., Gray, J. R., Greve, D. N., Treadway, M. T., McGarvey, M., Quinn, B. T., Dusek, J. A., Herbert, B., Rauch, S. L., Moore, C. I., Fischl, B., 2005. Meditation experience is associated with increased cortical thickness. Neuroreport. 16 (17), 1893-1897.

Liu, B., Zhang, X., Cui, Y, Qin, W, Tao, Y., Li, J., Yu, C., Jiang, T., 2016. Polygenic risk for schizophrenia influences cortical gyrification in 2 independent general populations. Schizophr. Bull. In Press.

Matheson, S. L., Shepherd, A. M., Laurens, K. R., & Carr, V. J., 2011. A systematic meta-review grading the evidence for non-genetic risk factors and putative antecedents of schizophrenia. Schizophr. Res. 133 (1-3), 133-142.

Matheson, S. L., Shepherd, A. M., Pinchbeck, R. M., Laurens, K. R., & Carr, V. J., 2013. Childhood adversity in schizophrenia: a systematic meta-analysis. Psychol. Med. 43 (2), 225-238.

Marangoni, C., Hernandez, M., Faedda, G. L., 2016. The role of environmental exposures as risk factors for bipolar disorder: A systematic review of longitudinal studies. J. Affect. Disord. 193, 165-174.

McGuffin, P., Rijsdijk, F., Andrew, M., Sham, P., Katz, R., & Cardno, A., 2003. The heritability of bipolar affective disorder and the genetic relationship to unipolar depression. Arch. Gen. Psychiatry, 60 (5), 497-502.

McIntosh, A. M., Owens, D. C., Moorhead, W. J., Whalley, H. C., Stanfield, A. C., Hall, J., Johnstone, E. C., Lawrie, S. M., 2011. Longitudinal volume reductions in people at high genetic risk of schizophrenia as they develop psychosis. Biol. Psychiatry. 69 (10), 953-958.

McIntosh, A. M., Gow, A., Luciano, M., Davies, G., Liewald, D. C., Harris, S. E., Corley, J., Hall, J., Starr, J. M., Porteous, D. J., Tenesa, A., Visscer, P. M., Deary, I. J., 2013. Polygenic risk for schizophrenia is associated with cognitive change between childhood and old age. Biol. Psychiatry. 73 (10), 938-943.

Nesvåg, R., Bergmann, Ø., Rimol, L. M., Lange, E. H., Haukvik, U. K., Hartberg, C. B., Fagerberg, T., Söderman, E., Jönsson, E. G., Agartz, I., 2012. A 5-year follow-up study of brain cortical and subcortical abnormalities in a schizophrenia cohort. Schizophr. Res. 142 (1-3), 209-216.

Papiol, S., Mitjans, M., Assogna, F., Piras, F., Hammer, C., Caltagirone, C., Arias, B., Ehrenreich, H., Spalletta, G., 2014. Polygenic determinants of white matter volume derived from GWAS lack reproducibility in a replicate sample. Transl. Psychiatry. 4 (2), e362.

Pedersen, C. B., Mortensen, P. B., 2006. Urbanicity during upbringing and bipolar affective disorder in Denmark. Bipolar. Disord. 8 (3), 242-247.

Psychiatric GWAS Consortium Bipolar Disorder Working Group, 2011. Large-scale genome-wide association analysis of bipolar disorder identifies a new susceptibility locus near ODZ4. Nat Genet, 43 (10), 977-983.

Purcell, S. M., Neale, B., Todd-Brown, K., Thomas, L., Ferreira, M. A., Bender, D., Maller, J., Sklar, P., de Bakker, P. I. W., Daly, M. J., Sham, P. C., 2007. PLINK: a tool set for whole-genome association and population-based linkage analyses. Am. J. Hum. Genet. 81 (3), 559-575.

Radhakrishnan, R., Wilkinson, S. T., & D'Souza, D. C., 2014. Gone to Pot - A Review of the Association between Cannabis and Psychosis. Front. Psychiatry. 5 (54), 1-24.

Rais, M., van Haren, N. E., Cahn, W., Schnack, H. G., Lepage, C., Collins, L., Evans, A. C., Hulshoff Pol, H. E., Kahn, R. S., 2010. Cannabis use and progressive cortical thickness loss in areas

rich in CB1 receptors during the first five years of schizophrenia. Eur. Neuropsychopharmacol. 20 (12), 855-865.

Rapoport, J. L., Giedd, J. N., & Gogtay, N., 2012. Neurodevelopmental model of schizophrenia: update 2012. Mol. Psychiatry. 17 (12), 1228-1238.

Reiter, K., Nielson, K. A., Smith, T. J., Weiss, L. R., Alfini, A. J., & Smith, J. C., 2015. Improved Cardiorespiratory Fitness Is Associated with Increased Cortical Thickness in Mild Cognitive Impairment. J. Int. Neuropsychol. Soc. 21 (10), 757-767.

Rimol, L. M., Hartberg, C. B., Nesvåg, R., Fennema-Notestine, C., Hagler, D. J., Pung, C. J., Jennings, R. G., Haukvik, U. K. Lange, E., Nakstad, P. H., Melle, I., Andreassen, O. A., Dale, A. M., Agartz, I., 2010. Cortical thickness and subcortical volumes in schizophrenia and bipolar disorder. Biol. Psychiatry. 68 (1), 41-50.

Ripke, S., O'Dushlaine, C., Chambert, K., Moran, J.L., Kähler, A.K., Akterin, S., Bergen, S.E., Collins, A.L., Crowley, J.J., Fromer, M., Kim, Y., Lee, S.H., Magnusson, P.K., Sanchez, N., Stahl, E.A., Williams, S., Wray, N.R., Xia, K., Bettella, F., Borglum, A.D., Bulik-Sullivan, B.K., Cormican, P., Craddock, N., de Leeuw, C., Durmishi, N., Gill, M., Golimbet, V., Hamshere, M.L., Holmans, P., Hougaard, D.M., Kendler, K.S., Lin, K., Morris, D.W., Mors, O., Mortensen, P.B., Neale, B.M., O'Neill, F.A., Owen, M.J., Milovancevic, M.P., Posthuma, D., Powell, J., Richards, A.L., Riley, B.P., Ruderfer, D., Rujescu, D., Sigurdsson, E., Silagadze, T., Smit, A.B., Stefansson, H., Steinberg, S., Suvisaari, J., Tosato, S., Verhage, M., Walters, J.T., Multicenter Genetic Studies of Schizophrenia Consortium, Psychosis Endophenotypes International Consortium, Wellcome Trust Case Control Consortium 2, Bramon, E., Corvin, A.P., O'Donovan, M.C., Sklar, P., Hultman, C. M., Sullivan, P. F., 2013. Genome-wide association analysis identifies 13 new risk loci for schizophrenia. Nat. Genet. 45 (10), 1150–1159.

Ruderfer, D.M., Fanous, A. H., Ripke, S., McQuillin, A., Amdur, R. L., Schizophrenia Workign Group of Psychiatric Genomics Consortium, Bipolar Disorder Working Group of the Psychiatric Genomics Consortium, Gejman, P. V., O'Donovan, M. C., Andreassen, O. A., Djurovic, S., Hultman, C. M., Kelsoe, J.R., Jamain, S., Landén, M., Leboyer, M.,

Nimgaonkar, V., Nurnberger, J., Smoller, J. W., Craddock, N., Corvin, A., Sullivan, P. F., Holmans, P., Sklar, P., Kendler, K. S., 2014. Polygenic dissection of diagnosis and clinical dimensions of bipolar disorder and schizophrenia. Mol. Psychiatry. 19 (9), 1017-1024.

Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium, 2011. Genome-wide association study identifies five new schizophrenia loci. Nat. Genet. 43 (10), 969-976.

Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014. Biological insights from 108 schizophrenia-associated genetic loci. Nature. 511 (7510), 421-427.

Smith, G. N., Thornton, A. E., Lang, D. J., MacEwan, G. W., Kopala, L. C., Su, W., & Honer, W. G., 2015. Cortical morphology and early adverse birth events in men with first-episode psychosis. Psychol. Med. 45 (9), 1825-1837.

Souza-Queiroz, J., Boisgontier, J., Etian, B., Duclap, D., d'Albis, M. A., Daban, C., Hamdani, N., Le Corvoisier, P., Delavest, M., Bellivier, F., Guevara, P., Leboyer, M., Henry, C., Houenou, J., 2016. Childhood trauma and the limbic network: a multimodal MRI study in patients with bipolar disorder and controls. J. Affect. Disord. 200, 159-164.

Sprooten, E., Papmeyer, M., Smyth, A. M., Vincenz, D., Honold, S., Conlon, G. A., Moorehead, W. J., Job, D., Whalley, H. C., Hall, J., McIntosh, A. M., Owens, D. C. G., Johnstone, E. C., Lawrie, S. M., 2013. Cortical thickness in first-episode schizophrenia patients and individuals at high familial risk: a cross-sectional comparison. Schizophr. Res. 151 (1-3), 259-264.

Stepniak, B., Papiol, S., Hammer, C., Ramin, A., Everts, S., Hennig, L., Begemann, M., Ehrenreich, H., 2014. Accumulated environmental risk determining age at schizophrenia onset: a deep phenotyping-based study. Lancet Psychiatry. 1 (6), 444-453.

Terwisscha van Scheltinga, A. F., Bakker, S. C., van Haren, N. E., Derks, E. M., Buizer-Voskamp, J. E., Boos, H. B. M., Cahn, W., Hulshoff Pol, H. E., Ripke, S., Psychiatric Genome-Wide Associaiton Study (GWAS) Consortium, Ophoff, R. A., Kahn, R. S., 2013. Genetic schizophrenia risk variants jointly modulate total brain and white matter volume. Biol. Psychiatry. 73 (6), 525-531.

van Erp, T. G., Saleh, P. A., Rosso, I. M., Huttunen, M., Lönnqvist, J., Pirkola, T., Salonen, O., Valanne, L., Poutanen, V. P., Standertskjöld-Nordenstam, C. G., Cannon, T. D., 2002. Contributions of genetic risk and fetal hypoxia to hippocampal volume in patients with schizophrenia or schizoaffective disorder, their unaffected siblings, and healthy unrelated volunteers. Am. J. Psychiatry. 159 (9), 1514-1520.

van Haren, N. E., Schnack, H. G., Cahn, W., van den Heuvel, M. P., Lepage, C., Collins, L., Evans, A. C., Hulshoff Pol, H. E., Kahn, R. S., 2011. Changes in cortical thickness during the course of illness in schizophrenia. Arch. Gen. Psychiatry. 68 (9), 871-880.

van Os, J., Kenis, G., & Rutten, B. P., 2010. The environment and schizophrenia. Nature. 468 (7321), 203-212.

Weinberger, D. R., 1987. Implications of normal brain development for the pathogenesis of schizophrenia. Arch. Gen. Psychiatry. 44 (7), 660-669.

Welch, K. A., McIntosh, A. M., Job, D. E., Whalley, H. C., Moorhead, T. W., Hall, J., Owens, D. G. C. Lawrie, S. M., Johnstone, E. C., 2011. The impact of substance use on brain structure in people at high risk of developing schizophrenia. Schizophr. Bull. 37 (5), 1066-1076.

Whalley, H. C., Hall, L., Romaniuk, L., Macdonald, A., Lawrie, S. M., Sussmann, J. E., & McIntosh, A. M., 2015. Impact of cross-disorder polygenic risk on frontal brain activation with specific effect of schizophrenia risk. Schizophr. Res. 161 (2-3), 484-489.

Whalley, H.C., Adams, M.J., Hall, L.S., Clarke, T-K., Fernandez-Pujals, A.M., Gibson, J., Wigmore, E., Hafferty, J., Hagenaars, S.P., Davies, G., Campbell, A., Hayward, C., Lawrie, S.M., Porteous, D.J., Deary, I.J., McIntosh, A.M., 2016. Dissection of major depressive disorder using polygenic risk scores for schizophrenia in two independent cohorts. Transl. Psychiatry. 6, e938.

Woods, S. W., 2003. Chlorpromazine equivalent doses for the newer atypical antipsychotics. J. Clin. Psychiatry. 64 (6), 663-667.

Figure Legends

Figure 1. Global a) left and b) right cortical thickness, in mm^2, and polygenic risk scores for schizophrenia in the combined patient group (SZ=37, BD=20).

Figure 2. Graphs showing that global a) left and b) right cortical thickness, in mm^2, is negatively associated with increased polygenic risk scores for schizophrenia, regardless of group (HC=32, Patient=43).

Figure 3. Graphs showing left temporal lobe cortical thickness, is a) negatively associated with polygenic risk scores in the combined patient group (n=43) and b) has no relationship with polygenic risk scores for schizophrenia in the HC group (n=32).

Tables

Table 1. Demographic information in healthy controls and combined patient group

	HC	**Patient** M(SD)	**t/X2**	**p**
N	41	57		
Age	38.22	39.21	0.47	0.64
Gender (Male/Female)	23/18	37/20	0.45	0.50
Illness Duration	-	17.95 (11.81) Range: 0-45	-	-
Age of Onset	-	21.96 (9.17) Range: 7-53	-	-
CPZ equivalent (ENIGMA)	-	252.55	-	-
PANSS Total	31.54	54.38	-9.02	**6.136e-13**
PANNS Positive	7.17	12.45	-7.44	**5.572e-10**
PANSS Negative	7.29	13.38	-6.40	**2.48e-08**
PANSS General	17.07	28.55	-8.59	**8.217e-13**
SES			29.71	**1.683e-05**
Unemployed/Retired	1/5	26/8		
Manual/non-manual	8/28	7/15		
Young Mania Rating Scale	0.14	2.75	-4.96	**6.385e-06**
Hamilton Depression Rating Scale	0.87	9.98	-7.50	**1.434e-10**
Paternal Age	-	31.05 (6.68)	-	-
NART IQ	111.2	110.5	0.44	0.66
PGRS	-0.33	0.25	-2.62	**0.01**
ERS	1.292	1.684	-2.311	**0.02**

Table 2. Mean group differences in cortical thickness with standard deviations and p values

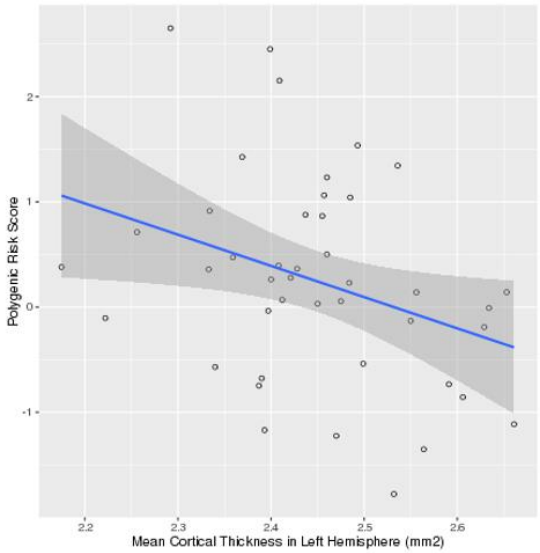
	Controls (n=41)	Patients (n=57)		
	Mean (SD)	**Mean (SD)**	**F**	**P**
Left	2.52 (0.10)	2.44 (0.11)	11.63	**0.001**
Right	2.51 (0.09)	2.43 (0.10)	14.78	**0.0002**
Frontal Left	2.56 (0.11)	2.49 (0.13)	0.83	0.36
Frontal Right	2.49 (0.11)	2.44 (0.13)	3.64	0.06
Temporal Left	2.86 (0.12)	2.74 (0.17)	1.61	0.21
Temporal Right	2.91 (0.12)	2.77 (0.15)	5.60	**0.02**

Table 3. Adjusted Mean Thickness, along with standard errors (SE), in Right Temporal Lobe dependent on the number of environmental risk factors experienced by the patients (*n*=57)

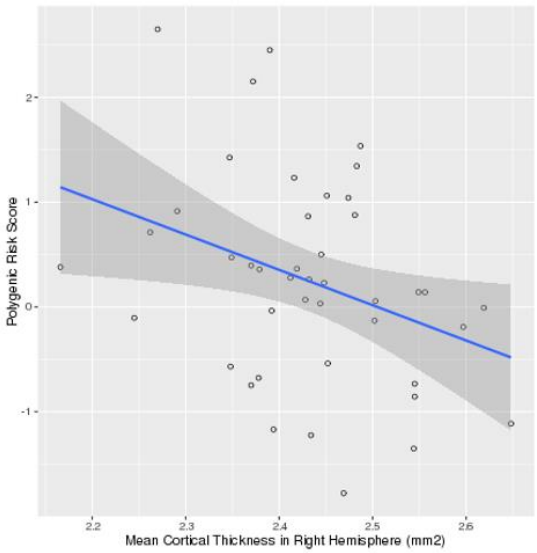
	0 Risks	**1 Risk**	**2 Risks**	**3 Risks**	**4 Risks**	**5 Risks**
Adjusted Mean Thickness (mm^2)	2.85	2.82	2.79	2.76	2.73	2.70
SE	0.03	0.02	0.01	0.01	0.02	0.03

Figures

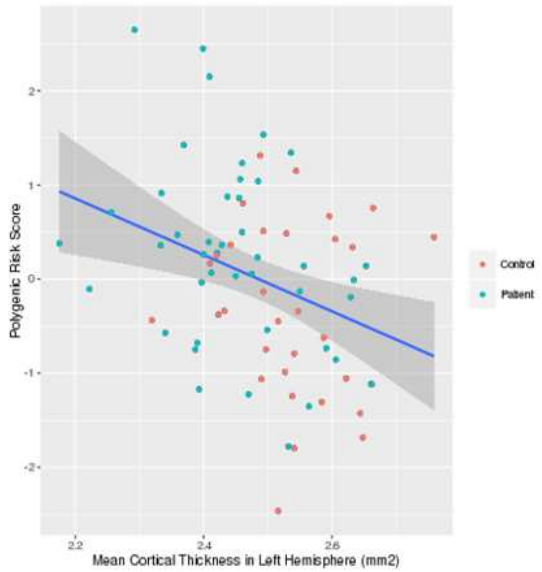
1a)



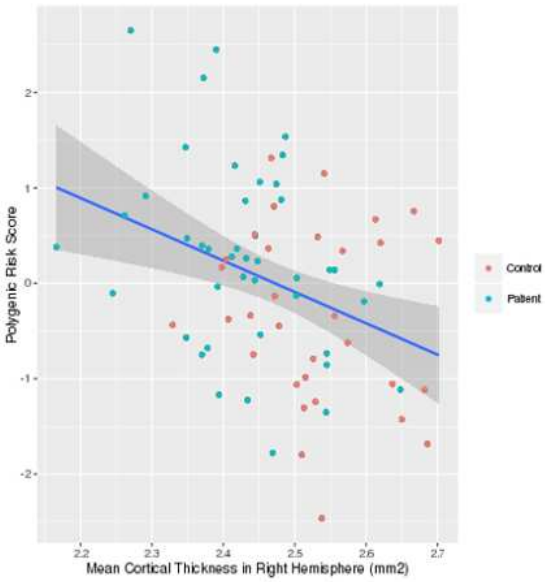
1b)



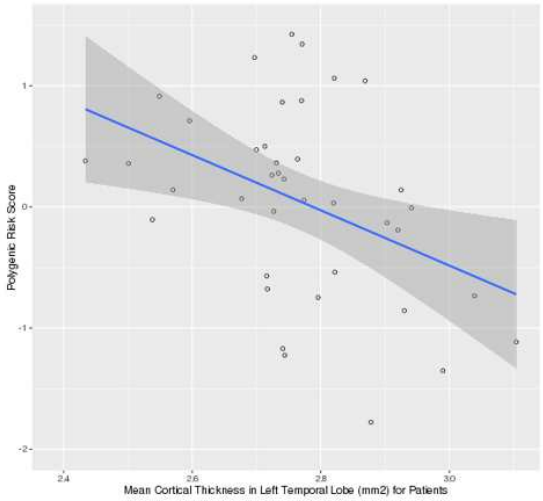
2a)



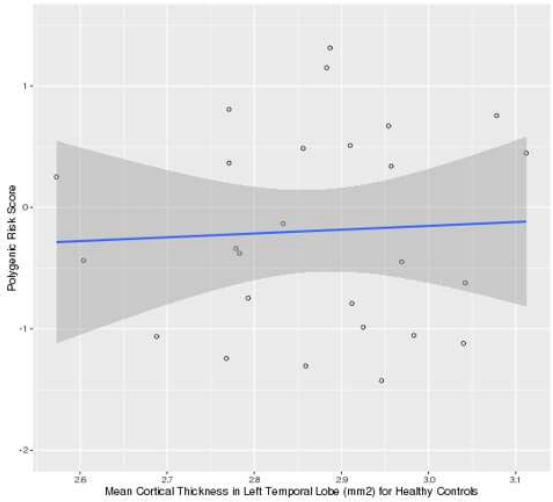
2b)



3a)


Polygenic Risk Score
1
0
-1
-2
2.4
2.6
2.8
3.0
Mean Cortical Thickness in Left Temporal Lobe (mm2) for Patients

3b)


Polygenic Risk Score
1
0
-1
-2
2.6
2.7
2.8
2.9
3.0
3.1
Mean Cortical Thickness in Left Temporal Lobe (mm2) for Healthy Controls