**Accelerated cortical thinning and volume reduction over time in young people at high genetic risk for bipolar disorder**

***Supplementary Material***

**SUPPLEMENTARY METHODS**

**Participants**

Control (CON) participants were defined as those who did not have a first-degree relative with either BD I or II, recurrent major depressive disorder (MDD), schizoaffective disorder, recurrent substance abuse or any past psychiatric hospitalisation. Additionally, they did not have a second-degree relative with a history of psychosis or who had been hospitalised for a mood disorder. High-risk (HR) and CON participants with a lifetime or current presence of psychiatric symptoms (apart from the occurrence of BD) were not excluded from the study. This ecological approach has been used by similar studies of individuals at high genetic risk for BD to recruit both CON and HR cohorts (Nurnberger et al., 2011).

Recruited participants are involved in an ongoing longitudinal study with annual follow-up evaluations. HR participants were recruited from families who had either previously participated in a bipolar disorder (BD) pedigree molecular genetics study, from a specialised BD research clinic, or were otherwise recruited from clinicians, mental health consumer organisations and other forms of publicity. CON participants were recruited via print and electronic media as well as noticeboards in universities and local communities.

As significant differences in brain structures between Asian and Caucasian populations have been demonstrated, Asian subjects were excluded to reduce heterogeneity (Tang et al., 2010; Vadakkumpadan, Tong, & Sun, 2006).

**Total MRI scans and exclusions**

A total of 290 participants completed a baseline scan and 217 participants completed a follow-up scan approximately 2 years later. Eighty-one subjects who were excluded (32 CON and 49 HR) had a usable baseline scan but did not complete a follow-up scan. Eight subjects (3 CON and 5 HR) were excluded because they did not complete a baseline scan but only a scan at follow-up. Of the 209 subjects with scans at both time-points (92 CON and 117 HR), 25 subjects (5 CON and 20 HR) were removed due to excessive head movement, poor image quality, or errors on scans (e.g. unresolved medial surface problems on imaging, errors at the pial boundary greater than 100 contiguous voxels that could not be resolved manually) at one or both time-points. A further 37 subjects (30 CON and 7 HR) were excluded due to non-Caucasian ethnicity, and one CON could not be processed as both scans were corrupted. Thus, the remaining subjects with usable baseline and follow-up scans (56 CON and 90 HR) formed the current sample. There were no significant differences between groups for age at baseline, sex and years between scans in the final sample, and all participants had an IQ above 83.

**MRI Acquisition**

For each subject, a T1-weighted image was acquired using a 3T Philips Achieva scanner (Royal Philips Electronics, Amsterdam, The Netherlands) located at Neuroscience Research Australia in Sydney. One-hundred-and-eighty sagittal T1-weighted three-dimensional turbo field-echo images were obtained (TR/TE – 5.5/2.5ms, flip angle – 8°, field of view – 256 x 256 x 180mm3, voxel size – 1 x 1 x 1mm, scan time – 371s), preceded by a one-minute standard scout image for head positioning and resolution of sensitivity variations.

**MRI Image Processing**

Raw MRI images were manually reviewed for motion, contrast and orientation and was assigned a rating from 1 to 4 (1=None, 2=Mild, 3=Moderate, 4=Unusable). All scans with a rating of 4 were excluded. All scans with ratings of 2 and 3 were assessed for the impact of the artefact on the generated pial and WM surfaces. Scans where an artefact impacted the surface generation were also removed. Automated cortical reconstruction and segmentation was completed using the longitudinal image processing stream included in FreeSurfer version 5.3.0. Specifically, each image was initially processed using the standard cross-sectional image processing stream, involving Talairach registration, intensity normalisation, skull-stripping, surface tessellation, cortical parcellation, subcortical segmentation, and topology correction (Dale, Fischl, & Sereno, 1999; Desikan et al., 2006; Fischl, Liu, & Dale, 2001; Fischl et al., 2002). On the basis of all reconstructed images that were available for a given subject, an unbiased within-subject template image was created using robust, inverse consistent registration (Reuter, Rosas, & Fischl, 2010). This template was then used as a reference in the final processing step of the longitudinal stream, whereby skull stripping, Talairach transformation, atlas registration, production of spherical surface maps, and cortical parcellation were completed for each cross-sectional image using common information from the template image for that subject.

At each step of the longitudinal processing stream, reconstructed cortical surfaces and automated segmentation were manually reviewed and edited using established procedures within the FreeSurfer software package (Reuter, 2015). This was undertaken by three research team members who were blinded to participant group and had previously edited a sample set of twenty cross-sectional images to establish inter-rater reliability. Manual editing was performed in instances where four or more erroneous voxels were observed across two contiguous slices. Five HR images were excluded due to errors at the pial boundary greater than 100 contiguous voxels which could not be resolved through manual editing. For all images that survived this quality control procedure, subject level values were extracted based on the Desikan-Killiany atlas (Desikan et al., 2006). For each participant, per hemisphere, per time-point, we extracted cortical GM volume, cortical WM volume, surface area and thickness for 17 frontotemporal regions of interest (ROIs) (Supplementary Table 1 and Supplementary Figure 1). We also extracted GM volumes bilaterally for an additional 11 subcortical ROIs.

**Auxiliary Analyses**

Subsequent exploratory tests were performed for ROIs that showed a main effect of group or a group by time interaction after correction for multiple comparisons (models that included age and sex as covariates for thickness and models that included age, sex and ICV as covariates for volume). Two sets of linear-mixed effects models were run to determine whether medication influenced the results. The first set used these base models with the addition of a binary predictor for current use of antidepressants (n=15) comprising 11 subjects at baseline (2 CON, 9 HR) and 7 subjects (1 CON, 6 HR) remaining on antidepressant at follow-up, with an additional 4 subjects (1 CON, 3 HR) on antidepressants who were not on medication at baseline. The second set also used the base models with the addition of a binary predictor for current use of any psychotropic medication (n=16). This comprised of 11 subjects at baseline (2 CON, 9 HR) and 9 subjects (1 CON, 8 HR) remaining on psychotropic medication at follow-up, with an additional 5 subjects (1 CON, 4 HR) using psychotropic medications at follow-up only. Correction for multiple testing of main effects (group, time, and group by time interaction) was carried out using FDR correction, where 39 comparisons were ranked separately for GM volume, 30 for GM volume with ICV as a covariate, and 24 for thickness. Similar to the models examining medication effects, the base models were also re-run with the addition of a binary predictor for current mood episode (n=11) to examine possible confounding effects. This comprised of 3 subjects at baseline scan (2 CON, 1 HR) with an additional 8 subjects (2 CON, 6 HR) experiencing a current episode at time of follow-up scan. No subject experiencing a mood episode at baseline was also experiencing an episode at follow-up. Lastly, additional models, similar to the models examining medication effects were run to examine possible confounding effects of IQ; years of education at baseline; lifetime alcohol use or dependence (at baseline and follow-up); proband (offspring vs parent); and body mass index (BMI) at baseline.

Associations between ROI structures and current mood state were explored by including current mood state measures as a predictor in the above base models. The Children's Depression Inventory (Kovacs M, 1992) was administered to participants aged 12-21 years, and both the Montgomery–Åsberg Depression Rating Scale (Montgomery & Åsberg, 1979) and Young Mania Rating Scale (Young, Biggs, Ziegler, & Meyer, 1978) were administered to those aged 22–30 years. As mood state was assessed using separate scales for younger (12-21-year-olds) and older (22-30-year-olds) groups, separate models were run for each age group (all other analyses were run with the total sample). Effects of mood state underwent FDR correction separately in each age group (31 comparisons per age group).

To investigate if our main effects of group or group by time interactions that survived FDR correction for multiple comparisons were influenced by DSM-IV diagnoses in our HR group we performed various exploratory sub-group analyses. Firstly, we sub-divided our HR group and created new variables according to the following criteria: i) new onset of any mood episode (major depressive or manic/hypomanic episode) from baseline to follow-up (n=9); and ii) new onset of any DSM-IV diagnosis from baseline to follow-up (n=11). Two sets of linear-mixed effects models were run to accommodate these three HR sub-group definitions. Each set of sub-group analyses was run by replacing the binary group variable (total CON, total HR) in the base models with one of the sub-group variables mentioned above (CON, HR without new mood episode or any new DSM diagnosis, HR with new mood episode or any new DSM diagnosis). As these analyses were exploratory, main effects did not undergo FDR correction. For group by time interactions, nine simple effects tests (three between-group differences at each time-point, and one time difference within each study group) were run, and for group effects three between-group comparisons were performed with Bonferroni-adjusted significance levels (*p*<0.05/9 for interactions and *p*<0.05/3 for group effects).

**SUPPLEMENTARY RESULTS**

**Participant diagnostic details**

Of the nine subjects (5 CON, 4 HR) who experienced their first major depressive episode (MDE) since baseline, two HR and two CON subjects experienced multiple MDEs. None of the participants had an elevated mood episode at baseline. After baseline, five HR subjects experienced a first manic (two subjects) or hypomanic (three subjects) episode. Four of these five participants had already experienced an MDE at baseline, and the remaining subject did not experience an MDE at baseline or follow-up and only experienced one manic episode. Four participants receiving a first mood episode diagnosis also received a further new diagnosis: one an anxiety diagnosis, one a substance use diagnosis, one a behavioural diagnosis, and one both substance use and a pathological gambling diagnosis. Among the six participants with a behavioural disorder at baseline, one had attention-deficit/hyperactivity disorder, four oppositional defiant disorder and one conduct disorder. The mean age of onset of any anxiety disorder in our sample was 10.4±7.7 years in the CON group, and 11.9±6 years in the HR group.

**ICV, Total Thickness and Total Surface Area**

At both baseline and follow up, ICV, Total Thickness, and Total Surface Area did not differ between the groups (p>0.05 uncorrected).

**Time effects**

After correcting for multiple comparisons, both groups showed reductions in GM volume, thickness and surface area over time, and larger WM volume in numerous brain regions (see Supplementary Table 4).

**Participant medications**

This comprised of 11 subjects at baseline (2 CON, 9 HR) who were all taking antidepressants, 9 subjects (1 CON, 8 HR) remaining on psychotropic medication at follow-up; 5 of these 9 were still taking antidepressants alone, 1 was still taking an antidepressant and added dexamphetamine, 1 was still taking an antidepressant and was also using flixotide and ventolin for asthma, 1 switched from an antidepressant to a mood stabiliser, and the final subject switched from an antidepressant to an antipsychotic and a benzodiazepine. Additionally, 5 subjects (1 CON, 4 HR) were using psychotropic medications at follow-up only; 2 of these 5 were only taking antidepressants, 1 was taking an antidepressant and an antipsychotic, another was taking an antidepressant and a mood stabiliser, while the final subject was taking Valium only.

**BMI results**

When BMI was included as a predictor 4 group by time effects of volume survived prior to but not after controlling for multiple tests (left pars orbitalis p=0.02 uncorrected (with ICV as covariate); right caudal anterior cingulate cortex p=0.02 uncorrected (with ICV as covariate); right pars triangularis p=0.03 uncorrected (with ICV as covariate); right superior frontal gyrus p=0.03 uncorrected (without ICV as covariate)) and one effect of thickness was not significant (the right pars triangularis p=0.058 uncorrected).

**Sub-group results**

Our exploratory sub-group results are presented in Supplementary Table S8 (table of main effects of group and group by time interactions). Exploratory sub-group graphs of group by time interaction effects are presented in Supplementary Figures 2-3 (graphs showing simple effects tests on the group by time interaction when HR group is sub-divided into with versus without new onset of a mood episode or new onset of any DSM IV diagnosis) Exploratory sub-group graphs of group effects (pooled across the two time-points) are presented in Supplementary Figure 4 (graphs showing simple effects tests on group effects when HR group is sub-divided into with versus without new onset of a mood episode or new onset of any DSM IV diagnosis).

All thickness and volume ROIs revealed significant reductions over time in HR subjects without new onset of a mood episode, or new onset of any DSM-IV diagnosis between baseline and follow-up. In HR subjects with new onset of a mood episode, or any DSM-IV diagnosis only a proportion of ROIs revealed significant thickness (3/7 ROIs in HR with new onset of a mood episode and 3/7 ROIs in HR with new onset of any DSM-IV diagnosis) and volume (6/8 ROIs in HR with new onset of a mood episode and 4/8 ROIs in HR with new onset of any DSM-IV diagnosis) reductions over time. For the remaining HR effects over time that were not significant, effect sizes showed that changes over time were about the same in HR subjects with versus without new onset of a mood episode, or any DSM-IV diagnosis (i.e., for 4 thickness ROIs effect sizes were similar for HR subjects with versus without new onset of a mood episode; for 4 thickness ROIs effect sizes were similar for HR subjects with versus without new onset of any DSM-IV diagnosis; for 2 volume ROIs effect sizes were similar for HR subjects with versus without new onset of a mood episode; for 4 volume ROIs effect sizes were similar for HR subjects with versus without new onset of any DSM-IV diagnosis (Supplementary Table S9). Therefore, it is likely that small sample sizes in HR subjects with new onset of a mood episode(n=9) or any DSM-IV diagnosis (n=11) limited our ability to detect effects over time.

**SUPPLEMENTARY TABLES**

**Supplementary Table 1. Cortical and Subcortical Regions of Interest.**

|  |  |
| --- | --- |
| **Cortical Gray Matter/ Subcortical White Matter** | **Subcortical Gray Matter** |
| ***Frontal Lobe*** | Lateral ventricle |
| Caudal anterior cingulate cortex | Inferior lateral ventricle |
| Caudal middle frontal gyrus | Cerebellum cortex |
| Lateral orbitofrontal cortex | Cerebellum white matter |
| Medial orbitofrontal cortex | Thalamus |
| Frontal pole | Caudate |
| Pars opercularis | Putamen |
| Pars orbitalis | Pallidum |
| Pars triangularis | Hippocampus |
| Rostral anterior cingulate cortex | Amygdala |
| Rostral middle frontal gyrus | Accumbens area |
| Superior frontal gyrus |  |
| ***Temporal Lobe*** |  |
| Entorhinal cortex |  |
| Parahippocampal gyrus |  |
| Superior temporal gyrus |  |
| Temporal pole |  |
| Transverse temporal gyrus |  |
| ***Insula*** |  |
| Insula |  |

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| **Supplementary Table S2.** **Baseline: Mean Region of Interest Values per Group.** | | | | | | | | | |
|  | **Surface Area (cm2)** | | | **Thickness (mm)** | | **Gray Matter Volume (cm3)** | | **White Matter Volume (cm3)** | |
|  | *Control* | *At-Risk* | *Control* | | *At-Risk* | *Control* | *At-Risk* | *Control* | *At-Risk* |
|  | *Mean (SD)* | *Mean (SD)* | *Mean (SD)* | | *Mean (SD)* | *Mean (SD)* | *Mean (SD)* | *Mean (SD)* | *Mean (SD)* |
| **Frontal Lobe** |  |  |  | |  |  |  |  |  |
| Caudate anterior cingulate cortex | 7.56  (1.56) | 7.78  (1.29) | 2.92  (0.22) | | 2.83  (0.18) | 2.35  (0.51) | 2.50  (0.49) | 3.07  (0.52) | 3.11  (0.44) |
| Caudal middle frontal gyrus | 23.40  (3.56) | 23.51  (3.55) | 2.75  (0.12) | | 2.79  (0.14) | 7.22  (1.21) | 7.39  (1.33) | 6.38  (0.99) | 6.34  (0.93) |
| Lateral orbitofrontal cortex | 27.65  (3.21) | 27.89  (3.17) | 2.95  (0.13) | | 3.00  (0.14) | 8.75  (1.06) | 9.10  (1.22) | 6.77  (0.89) | 6.80  (0.91) |
| Medial orbitofrontal cortex | 18.70  (2.40) | 19.10  (2.47) | 2.75  (0.14) | | 2.78  (0.16) | 5.83  (0.76) | 6.11  (0.91) | 3.45  (0.59) | 3.48  (0.62) |
| Frontal pole | 2.54  (0.42) | 2.57  (0.38) | 3.15  (0.22) | | 3.21  (0.26) | 1.12  (0.20) | 1.17  (0.20) | 0.27  (0.06) | 0.26  (0.06) |
| Pars opercularis | 15.96  (2.34) | 15.99  (2.35) | 2.87  (0.13) | | 2.88  (0.15) | 5.15  (0.76) | 5.24  (0.91) | 3.56  (0.67) | 3.51  (0.68) |
| Pars orbitalis | 7.32  (0.84) | 7.42  (0.91) | 3.09  (0.18) | | 3.10  (0.20) | 2.85  (0.32) | 2.96  (0.41) | 1.05  (0.19) | 1.03  (0.16) |
| Pars triangularis | 14.44  (2.44) | 14.51  (2.16) | 2.76  (0.15) | | 2.80  (0.15) | 4.58  (0.84) | 4.70  (0.81) | 3.14  (0.56) | 3.14  (0.55) |
| Rostral anterior cingulate cortex | 7.84  (1.39) | 8.00  (1.47) | 3.14  (0.13) | | 3.18  (0.18) | 2.76  (0.49) | 2.88  (0.55) | 2.37  (0.35) | 2.38  (0.35) |
| Rostral middle frontal gyrus | 60.87  (7.51) | 61.75  (7.85) | 2.63  (0.14) | | 2.68  (0.15) | 18.67  (2.61) | 19.48  (3.02) | 12.88  (1.83) | 12.86  (2.09) |
| Superior frontal gyrus | 73.85  (8.86) | 75.00  (8.90) | 3.01  (0.13) | | 3.05  (0.17) | 25.44  (3.11) | 26.40  (3.74) | 18.12  (2.78) | 18.17  (2.77) |
| **Temporal Lobe** |  |  |  | |  |  |  |  |  |
| Entorhinal cortex | 3.71  (0.74) | 3.70  (0.68) | 3.77  (0.22) | | 3.76  (0.23) | 1.89  (0.35) | 1.87  (0.34) | 0.74  (0.19) | 0.73  (0.16) |
| Parahippocampal gyrus | 7.07  (0.94) | 7.24  (1.04) | 3.05  (0.21) | | 3.06  (0.24) | 2.51  (0.31) | 2.57  (0.37) | 1.64  (0.29) | 1.65  (0.29) |
| Superior temporal gyrus | 37.72  (3.92) | 37.76  (4.37) | 3.08  (0.13) | | 3.11  (0.17) | 13.33  (1.59) | 13.59  (1.95) | 7.05  (1.04) | 6.98  (1.12) |
| Temporal pole | 4.51  (0.49) | 4.57  (0.57) | 4.07  (0.21) | | 4.09  (0.21) | 2.63  (0.28) | 2.73  (0.29) | 0.64  (0.11) | 0.64  (0.11) |
| Transverse temporal pole | 3.98  (0.53) | 3.97  (0.68) | 2.66  (0.18) | | 2.71  (0.20) | 1.20  (0.18) | 1.21  (0.22) | 0.67  (0.10) | 0.66  (0.11) |
| **Insula** |  |  |  | |  |  |  |  |  |
| Insula | 22.68  (0.93) | 22.80  (2.86) | 3.24  (0.13) | | 3.27  (0.13) | 7.29  (0.99) | 7.47  (0.99) | 8.95  (1.17) | 8.95  (1.09) |
| **Subcortical** |  |  |  | |  |  |  |  |  |
| Lateral ventricle | N/A | N/A | N/A | | N/A | 6.00  (3.31) | 6.26  (3.57) | N/A | N/A |
| Inferior lateral ventricle | N/A | N/A | N/A | | N/A | 0.20  (0.10) | 0.19  (0.12) | N/A | N/A |
| Cerebellum cortex | N/A | N/A | N/A | | N/A | 58.97  (6.99) | 60.84  (7.26) | N/A | N/A |
| Cerebellum white matter | N/A | N/A | N/A | | N/A | 16.90  (2.50) | 16.99  (1.97) | N/A | N/A |
| Thalamus | N/A | N/A | N/A | | N/A | 8.23  (0.87) | 8.27  (0.86) | N/A | N/A |
| Caudate | N/A | N/A | N/A | | N/A | 4.01  (0.53) | 4.02  (0.53) | N/A | N/A |
| Putamen | N/A | N/A | N/A | | N/A | 5.99  (0.67) | 6.06  (0.77) | N/A | N/A |
| Pallidum | N/A | N/A | N/A | | N/A | 1.50  (0.21) | 1.51  (0.21) | N/A | N/A |
| Hippocampus | N/A | N/A | N/A | | N/A | 5.60  (0.44) | 4.58  (0.44) | N/A | N/A |
| Amygdala | N/A | N/A | N/A | | N/A | 1.79  (0.19) | 1.81  (0.21) | N/A | N/A |
| Accumbens area | N/A | N/A | N/A | | N/A | 0.64  (0.08) | 0.69  (0.10) | N/A | N/A |

Abbreviations: CON, Controls; HR, High Risk; N/A, not applicable

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| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Supplementary Table S3.** **Follow-Up: Mean Region of Interest Values per Group.** | | | | | | | | |
|  | **Surface Area (cm2)** | | **Thickness (mm)** | | **Gray Matter Volume (cm3)** | | **White Matter Volume (cm3)** | |
|  | *Control* | *At-Risk* | *Control* | *At-Risk* | *Control* | *At-Risk* | *Control* | *At-Risk* |
|  | *Mean (SD)* | *Mean (SD)* | *Mean (SD)* | *Mean (SD)* | *Mean (SD)* | *Mean (SD)* | *Mean (SD)* | *Mean (SD)* |
| **Frontal Lobe** |  |  |  |  |  |  |  |  |
| Caudate anterior cingulate cortex | 7.57  (1.63) | 7.72  (1.30) | 2.78  (0.20) | 2.87  (0.21) | 2.31  (0.52) | 2.44  (0.48) | 3.10  (0.52) | 3.12  (0.44 |
| Caudal middle frontal gyrus | 23.15  (3.51) | 23.23  (3.52) | 2.73  (0.13 | 2.74  (0.14) | 7.08  (1.17) | 7.17  (1.29) | 6.39  (0.99) | 6.36  (0.94) |
| Lateral orbitofrontal cortex | 27.53  (3.17) | 27.80  (3.33) | 2.94  (0.13) | 2.96  (0.13) | 8.66  (0.98) | 8.93  (1.20) | 6.81  (0.90) | 6.83  (0.94) |
| Medial orbitofrontal cortex | 18.62  (2.60) | 19.14  (2.52) | 2.73  (0.14) | 2.74  (0.15) | 5.74  (0.75) | 6.01  (0.89) | 3.46  (0.64) | 3.50  (0.62) |
| Frontal pole | 2.54  (0.43) | 2.55  (0.38) | 3.13  (0.21) | 3.16  (0.25) | 1.10  (0.20) | 1.13  (0.21) | 0.27  (0.07) | 0.26  (0.06) |
| Pars opercularis | 15.87  (2,32) | 15.87  (2.35) | 2.84  (0.12) | 2.83  (0.14) | 5.07  (0.72) | 5.10  (0.88) | 3.58  (0.66) | 3.53  (0.67) |
| Pars orbitalis | 7.30  (0.83) | 7.33  (0.91) | 3.07  (0.17) | 3.06  (0.19) | 2.81  (0.31) | 2.88  (0.40) | 1.05  (0.19) | 1.03  (0.17) |
| Pars triangularis | 14.33  (2.38) | 14.35  (2.16) | 2.73  (0.14) | 2.75  (0.14) | 4.50  (0.80) | 4.56  (0.77) | 3.15  (0.57) | 3.14  (0.57) |
| Rostral anterior cingulate cortex | 7.83  (1.40) | 7.96  (1.46) | 3.13  (0.12) | 3.15  (0.17) | 2.73  (0.50) | 2.84  (0.54) | 2.38  (0.35) | 2.40  (0.35) |
| Rostral middle frontal gyrus | 60.51  (7.44) | 61.13  (7.71) | 2.61  (0.12) | 2.63  (0.15) | 18.34  (2.49) | 18.86  (2.91) | 12.94  (1.86) | 12.88  (2.12) |
| Superior frontal gyrus | 73.25  (8.80) | 74.42  (9.10) | 2.98  (0.14) | 2.99  (0.16) | 24.99  (2.95) | 25.69  (3.70) | 18.13  (2.80) | 18.21  (2.84) |
| **Temporal Lobe** |  |  |  |  |  |  |  |  |
| Entorhinal cortex | 3.68  (0.70) | 3.67  (0.66) | 3.77  (0.19) | 3.78  (0.21) | 1.89  (0.32) | 1.87  (0.34) | 0.73  (0.19) | 0.73  (0.16) |
| Parahippocampal gyrus | 7.03  (0.93) | 7.18  (1.05) | 3.01  (0.21) | 3.02  (0.23) | 2.46  (0.31) | 2.51  (0.36) | 1.64  (0.29) | 1.66  (0.29) |
| Superior temporal gyrus | 37.55  (3.88) | 37.50  (4.39) | 3.05  (0.13) | 3.06  (0.15) | 13.11  (1.49) | 13.26  (1.89) | 7.08  (1.04) | 7.04  (1.14) |
| Temporal pole | 4.49  (0.49) | 4.55  (0.59) | 4.07  (0.22) | 4.08  (0.21) | 2.62  (0.28) | 2.70  (0.30) | 0.64  (0.11) | 0.64  (0.11) |
| Transverse temporal pole | 3.94  (0.51) | 3.91  (0.68) | 2.63  (0.18) | 2.67  (0.17) | 1.17  (0.17) | 1.18  (0.20) | 0.66  (0.10) | 0.66  (0.12) |
| **Insula** |  |  |  |  |  |  |  |  |
| Insula | 22.58  (2.84) | 22.70  (2.84) | 3.21  (0.13) | 3.23  (0.13) | 7.18  (0.94) | 7.35  (0.98) | 8.95  (1.16) | 8.95  (1.10) |
| **Subcortical** |  |  |  |  |  |  |  |  |
| Lateral ventricle | N/A | N/A | N/A | N/A | 6.31  (3.63) | 6.62  (3.76) | N/A | N/A |
| Inferior lateral ventricle | N/A | N/A | N/A | N/A | 0.20  (0.10) | 0.20  (0.10) | N/A | N/A |
| Cerebellum cortex | N/A | N/A | N/A | N/A | 57.95  (6.80) | 60.13  (7.24) | N/A | N/A |
| Cerebellum white matter | N/A | N/A | N/A | N/A | 16.78  (2.41) | 16.95  (1.94) | N/A | N/A |
| Thalamus | N/A | N/A | N/A | N/A | 8.17  (0.84) | 8.21  (0.86) | N/A | N/A |
| Caudate | N/A | N/A | N/A | N/A | 3.99  (0.53) | 3.98  (0.53) | N/A | N/A |
| Putamen | N/A | N/A | N/A | N/A | 5.95  (0.66) | 5.99  (0.76) | N/A | N/A |
| Pallidum | N/A | N/A | N/A | N/A | 1.50  (0.21) | 1.52  (0.22) | N/A | N/A |
| Hippocampus | N/A | N/A | N/A | N/A | 4.57  (0.46) | 4.57  (0.46) | N/A | N/A |
| Amygdala | N/A | N/A | N/A | N/A | 1.79  (0.19) | 1.80  (0.21) | N/A | N/A |
| Accumbens area | N/A | N/A | N/A | N/A | 0.64  (0.08) | 0.68  (0.10) | N/A | N/A |

Abbreviations: CON, Controls; HR, High Risk; N/A, not applicable

**Supplementary Table 4.** **Time Effects for all Regions of Interest***.*

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Baseline (B)** | | **Follow Up**  **(FW)** | | **FW vs. B controlling for Age and Sex** | | | | **FW vs. B controlling for Age, Sex and ICV/TSAb** | | | | | |
|  | | | |  | | | | | |
|  | *Mean (SD)* | *Mean (SD)* | | *p* | | *FDR q* | | *Direction* | | *p* | | *FDR q* | | *Direction* |
| **Surface Area** **(cm2)** |  |  | |  | |  | |  | |  | |  | |  |
| *Frontal lobe* |  |  | |  | |  | |  | |  | |  | |  |
| RH caudal anterior cingulate cortex | 8.24 (1.65) | 8.21 (1.63) | | 2.5x10-2 | | 1.0x10-2 | | B>FW | | 2.5x10-2 | | 1.0x10-2 | | B>FW |
| LH caudal middle frontal gyrus | 24.24 (4.05) | 23.95 (4.01) | | 5.7x10-18 | | 1.5x10-3 a | | B>FW | | 5.7x10-18 | | 1.0x10-3 a | | B>FW |
| RH caudal middle frontal gyrus | 22.70 (3.75) | 22.46 (3.73) | | 2.9x10-13 | | 2.0x10-3 a | | B>FW | | 2.9x10-13 | | 1.5x10-3 a | | B>FW |
| LH lateral orbitofrontal cortex | 27.69 (3.23) | 27.51 (3.22) | | 6.5x10-5 | | 7.4x10-3 a | | B>FW | | 6.5x10-5 | | 6.9x10-3 a | | B>FW |
| LH frontal pole | 2.15 (0.41) | 2.11 (0.42) | | 3.7x10-3 | | 9.8x10-3 a | | B>FW | | 3.7x10-3 | | 9.8x10-3 a | | B>FW |
| LH pars opercularis | 17.40 (2.81) | 17.27 (2.77) | | 2.0x10-9 | | 3.9x10-3 a | | B>FW | | 2.0x10-9 | | 3.4x10-3 a | | B>FW |
| RH pars opercularis | 14.55 (2.41) | 14.47 (2.43) | | 1.3x10-6 | | 5.9x10-3 a | | B>FW | | 1.3x10-6 | | 5.4x10-3 a | | B>FW |
| LH pars orbitalis | 6.58 (0.81) | 6.51 (6.51) | | 1.6x10-4 | | 8.3x10-3 a | | B>FW | | 1.6x10-4 | | 8.3x10-3 a | | B>FW |
| RH pars orbitalis | 8.19 (1.16) | 8.12 (1.15) | | 1.4x10-3 | | 8.8x10-3 a | | B>FW | | 1.4x10-3 | | 8.8x10-3 a | | B>FW |
| LH pars triangularis | 13.39 (2.23) | 13.27 (2.21) | | 7.7x10-9 | | 4.4x10-3 a | | B>FW | | 7.7x10-9 | | 3.9x10-3 a | | B>FW |
| RH pars triangularis | 15.57 (2.78) | 15.42 (2.75) | | 3.8x10-8 | | 5.4x10-3 a | | B>FW | | 3.8x10-8 | | 4.9x10-3 a | | B>FW |
| LH rostral middle frontal gyrus | 60.22 (8.05) | 59.66 (7.97) | | 3.3x10-8 | | 4.9x10-3 a | | B>FW | | 3.3x10-8 | | 4.4x10-3 a | | B>FW |
| RH rostral middle frontal gyrus | 62.60 (8.09) | 62.13 (7.92) | | 3.5x10-6 | | 6.4x10-3 a | | B>FW | | 3.5x10-6 | | 5.9x10-3 a | | B>FW |
| LH superior frontal gyrus | 75.79 (9.14) | 75.21 (9.21) | | 4.0x10-12 | | 2.9x10-3 a | | B>FW | | 4.0x10-12 | | 2.5x10-3 a | | B>FW |
| RH superior frontal gyrus | 73.33 (9.18) | 72.73 (9.28) | | 5.3x10-16 | | 5.0x10-3 a | | B>FW | | 5.3x10-16 | | 1.0x10-3 a | | B>FW |
| *Temporal lobe* |  |  | |  | |  | |  | |  | |  | |  |
| LH parahippocampal gyrus | 7.30 (1.06) | 7.26 (1.05) | | 2.2x10-3 | | 9.3x10-3 a | | B>FW | | 2.2x10-3 | | 9.3x10-3 a | | B>FW |
| RH parahippocampal gyrus | 7.04 (1.09) | 6.99 (1.10) | | 4.4x10-6 | | 6.4x10-3 a | | B>FW | | 4.4x10-6 | | 6.4x10-3 a | | B>FW |
| LH superior temporal gyrus | 38.66 (4.72) | 38.43 (4.73) | | 4.8x10-13 | | 2.0x10-3 a | | B>FW | | 4.8x10-13 | | 2.0x10-3 a | | B>FW |
| RH superior temporal gyrus | 36.81 (4.06) | 36.60 (4.06) | | 1.3x10-11 | | 2.9x10-3 a | | B>FW | | 1.3x10-11 | | 2.9x10-3 a | | B>FW |
| LH transverse temporal gyrus | 4.56 (0.78) | 4.51 (0.76) | | 1.3x10-4 | | 7.8x10-3 a | | B>FW | | 1.3x10-4 | | 7.8x10-3 a | | B>FW |
| RH transverse temporal gyrus | 3.39 (0.61) | 3.34 (0.60) | | 9.7x10-5 | | 7.4x10-3 a | | B>FW | | 9.6x10-5 | | 7.4x10-3 a | | B>FW |
|  |  |  | |  | |  | |  | |  | |  | |  |
| *Insula* |  |  | |  | |  | |  | |  | |  | |  |
| LH insula | 22.77 (2.96) | 22.62 (2.95) | | 2.8x10-2 | | 1.1x10-2 | | B>FW | | 2.8x10-2 | | 1.1x10-2 | | B>FW |
| **Gray Matter Volume** (**cm3)** |  |  | |  | |  | |  | |  | |  | |  |
| *Frontal lobe* |  |  | |  | |  | |  | |  | |  | |  |
| LH caudal anterior cingulate cortex | 2.26 (0.63) | 2.21 (0.62) | | 2.1x10-14 | | 6.4x10-3 a | | B>FW | | 3.5x10-16 | | 3.9x10-3 a | | B>FW |
| RH caudal anterior cingulate cortex | 2.62 (0.59) | 2.58 (0.59) | | 9.9x10-17 | | 3.9x10-3 a | | B>FW | | 4.3x10-14 | | 5.9x10-3 a | | B>FW |
| LH caudal middle frontal gyrus | 7.50 (1.41) | 7.31 (1.37) | | 5.3x10-14 | | 7.4x10-3 a | | B>FW | | 4.3x10-14 | | 6.4x10-3 a | | B>FW |
| RH caudal middle frontal gyrus | 7.15 (1.37) | 6.96 (1.34) | | 4.4x10-14 | | 6.9x10-3 a | | B>FW | | 5.2x10-14 | | 7.4x10-3 a | | B>FW |
| LH lateral orbitofrontal cortex | 9.04 (1.16) | 8.87 (1.10) | | 1.2x10-13 | | 8.3x10-3 a | | B>FW | | 2.2x10-13 | | 8.3x10-3 a | | B>FW |
| RH lateral orbitofrontal cortex | 8.89 (1.24) | 8.78 (1.20) | | 4.1x10-3 | | 1.5x10-2 a | | B>FW | | 2.1x10-5 | | 1.4x10-2 a | | B>FW |
| LH medial orbitofrontal cortex | 5.90 (0.94) | 5.78 (0.92) | | 5.6x10-6 | | 1.3x10-2 a | | B>FW | | 3.9x10-6 | | 1.3x10-2 a | | B>FW |
| RH medial orbitofrontal cortex | 6.10 (0.90) | 6.04 (0.89) | | 4.1x10-3 | | 1.6x10-2 a | | B>FW | | 2.3x10-3 | | 1.5x10-2 a | | B>FW |
| LH frontal pole | 0.97 (0.21) | 0.94 (0.21) | | 5.4x10-14 | | 7.8x10-3 a | | B>FW | | 4.9x10-14 | | 6.9x10-3 a | | B>FW |
| RH frontal pole | 1.33 (0.26) | 1.29 (0.26) | | 2.2x10-7 | | 1.3x10-2 a | | B>FW | | 1.3x10-7 | | 1.3x10-2 a | | B>FW |
| LH pars opercularis | 5.70 (1.03) | 5.56 (0.99) | | 5.6x10-19 | | 1.0x10-3 a | | B>FW | | 1.5x10-18 | | 1.0x10-3 a | | B>FW |
| RH pars opercularis | 4.71 (0.84) | 4.61 (0.81) | | 4.3x10-16 | | 4.9x10-3 a | | B>FW | | 8.3x10-16 | | 4.4x10-3 a | | B>FW |
| LH pars orbitalis | 2.63 (0.35) | 2.56 (0.34) | | 1.1x10-12 | | 9.3x10-3 a | | B>FW | | 1.0x10-12 | | 8.8x10-3 a | | B>FW |
| RH pars orbitalis | 3.21 (0.50) | 3.14 (0.49) | | 5.7x10-17 | | 2.5x10-3 a | | B>FW | | 1.3x10-11 | | 9.3x10-3 a | | B>FW |
| LH pars triangularis | 4.26 (0.81) | 4.14 (0.77) | | 5.7x10-17 | | 2.9x10-3 a | | B>FW | | 8.3x10-17 | | 2.9x10-3 a | | B>FW |
| RH pars triangularis | 5.04 (0.98) | 4.92 (0.93) | | 2.5x10-13 | | 8.8x10-3 a | | B>FW | | 1.7x10-13 | | 7.8x10-3 a | | B>FW |
| LH rostral anterior cingulate cortex | 3.25 (0.66) | 3.20 (0.65) | | 6.7x10-10 | | 1.1x10-2 a | | B>FW | | 2.2x10-9 | | 1.2x10-2 a | | B>FW |
| RH rostral anterior cingulate cortex | 2.43 (0.53) | 2.40 (0.52) | | 2.0x10-4 | | 1.4x10-2 a | | B>FW | | 1.4x10-4 | | 1.5x10-2 a | | B>FW |
| LH rostral middle frontal gyrus | 18.70 (2.88) | 18.15 (2.77) | | 6.2x10-15 | | 5.4x10-3 a | | B>FW | | 3.6x10-15 | | 4.9x10-3 a | | B>FW |
| LH superior frontal gyrus | 26.47 (3.57) | 25.79 (3.45) | | 2.5x10-21 | | 4.9x10-4 a | | B>FW | | 5.7x10-21 | | 4.9x10-4 a | | B>FW |
| RH superior frontal gyrus | 25.59 (3.67) | 25.05 (3.61) | | 1.2x10-14 | | 5.9x10-3 a | | B>FW | | 1.6x10-14 | | 5.4x10-3 a | | B>FW |
| *Temporal lobe* |  |  | |  | |  | |  | |  | |  | |  |
| LH parahippocampal gyrus | 2.64 (0.39) | 2.59 (0.38) | | 3.5x10-16 | | 4.4x10-3 a | | B>FW | | 2.2x10-16 | | 3.4x10-3 a | | B>FW |
| RH parahippocampal gyrus | 2.45 (0.37) | 2.40 (0.37) | | 5.7x10-17 | | 3.4x10-3 a | | B>FW | | 6.4x10-17 | | 2.5x10-3 a | | B>FW |
| LH superior temporal gyrus | 13.68 (1.91) | 13.40 (1.86) | | 2.6x10-18 | | 1.5x10-3 a | | B>FW | | 1.1x10-17 | | 2.0x10-3 a | | B>FW |
| RH superior temporal gyrus | 13.30 (1.85) | 13.01 (1.76) | | 3.4x10-18 | | 2.0x10-3 a | | B>FW | | 7.1x10-18 | | 1.5x10-3 a | | B>FW |
| LH temporal pole | 2.83 (0.37) | 2.80 (0.37) | | 9.3x10-5 | | 1.4x10-2 a | | B>FW | | 7.7x10-5 | | 1.4x10-2 a | | B>FW |
| LH transverse temporal gyrus | 1.36 (0.24) | 1.33 (0.23) | | 9.4x10-10 | | 1.2x10-2 a | | B>FW | | 7.4x10-10 | | 1.1x10-2 a | | B>FW |
| RH transverse temporal gyrus | 1.05 (0.20) | 1.02 (0.20) | | 4.1x10-11 | | 1.1x10-2 a | | B>FW | | 5.9x10-11 | | 1.1x10-2 a | | B>FW |
| *Insula* |  |  | |  | |  | |  | |  | |  | |  |
| LH insula | 7.44 (1.00) | 7.32 (0.99) | | 2.2x10-11 | | 9.8x10-3 a | | B>FW | | 5.1x10-11 | | 1.0x10-2 a | | B>FW |
| RH insula | 7.36 (1.03) | 7.25 (1.00) | | 1.0x10-7 | | 1.2x10-2 a | | B>FW | | 7.5x10-8 | | 1.2x10-2 a | | B>FW |
| *Subcortical* |  |  | |  | |  | |  | |  | |  | |  |
| LH lateral ventricle | 6.14 (3.63) | 6.42 (3.74) | | 1.0x10-5 | | 3.0x10-3 a | | B<FW | | 3.5x10-8 | | 3.0x10-3 a | | B<FW |
| RH lateral ventricle | 6.18 (3.61) | 6.57 (3.98) | | 4.1x10-3 | | 6.8x10-3 a | | B<FW | | 1.8x10-3 | | 8.3x10-3 a | | B<FW |
| LH cerebellum cortex | 59.72 (7.18) | 58.91 (7.15) | | 5.8x10-11 | | 8.0x10-4 a | | B>FW | | 1.5x10-9 | | 8.0x10-4 a | | B>FW |
| RH cerebellum cortex | 60.53 (7.34) | 59.69 (7.28) | | 3.6x10-10 | | 2.3x10-3 a | | B>FW | | 4.9x10-9 | | 2.3x10-3 a | | B>FW |
| LH thalamus | 8.92 (0.99) | 8.85 (0.98) | | 4.1x10-5 | | 4.5x10-3 a | | B>FW | | 1.9x10-4 | | 5.3x10-3 a | | B>FW |
| RH thalamus | 7.59 (0.78) | 7.53 (0.76) | | 1.1x10-5 | | 3.8x10-3 a | | B>FW | | 2.7x10-5 | | 4.5x10-3 a | | B>FW |
| LH caudate | 4.06 (0.52) | 4.03 (0.52) | | 1.5x10-2 | | 9.1x10-3 | | B>FW | | 4.9x10-4 | | 6.1x10-3 a | | B>FW |
| RH caudate | 3.97 (0.56) | 3.94 (0.57) | | 3.7x10-2 | | 1.1x10-2 | | B>FW | | 1.6x10-3 | | 7.6x10-3 a | | B>FW |
| LH putamen | 6.27 (0.79) | 6.21 (0.78) | | 2.7x10-10 | | 1.5x10-3 a | | B>FW | | 2.3x10-9 | | 1.5x10-3 a | | B>FW |
| RH putamen | 5.79 (0.70) | 5.75 (0.70) | | 1.3x10-4 | | 5.3x10-3 a | | B>FW | | 6.8x10-6 | | 3.8x10-3 a | | B>FW |
| LH hippocampus | 4.57 (0.46) | 4.55 (0.47) | | 6.1x10-3 | | 7.6x10-3 a | | B>FW | | 7.2x10-3 | | 9.1x10-3 a | | B>FW |
| RH hippocampus | 4.60 (0.45) | 4.58 (0.47) | | 1.9x10-2 | | 1.0x10-2 | | B>FW | | 2.1x10-2 | | 1.0x10-2 | | B>FW |
| LH amygdala | 1.70 (0.20) | 1.68 (0.21) | | 1.7x10-2 | | 9.8x10-3 | | B>FW | | 1.1x10-2 | | 9.8x10-3 | | B>FW |
| **White Matter Volume** **(cm3)** |  |  | |  | |  | |  | |  | |  | |  |
| *Frontal lobe* |  |  | |  | |  | |  | |  | |  | |  |
| RH caudal anterior cingulate cortex | 3.13 (0.50) | 3.16 (0.49) | | 6.1x10-3 | | 2.5x10-3 | | B<FW | | 3.9x10-2 | | 3.4x10-3 | | B<FW |
| RH caudal middle frontal gyrus | 5.96 (1.00) | 5.98 (1.01) | | 3.3x10-2 | | 4.9x10-3 | | B<FW | | ns | | ns | | ns |
| RH lateral orbitofrontal cortex | 6.90 (0.98) | 6.96 (1.02) | | 1.6x10-6 | | 1.0x10-3 a | | B<FW | | 1.3x10-5 | | 4.9x10--4 a | | B<FW |
| LH pars opercularis | 3.70 (0.75) | 3.72 (0.76) | | 1.3x10-6 | | 4.9x10-4 a | | B<FW | | 2.0x10-5 | | 1.0x10-3 a | | B<FW |
| RH rostral anterior cingulate cortex | 2.05 (0.34) | 2.06 (0.34) | | 2.3x10-2 | | 3.9x10-3 | | B<FW | | 3.9x10-2 | | 3.4x10-3 | | B<FW |
| RH rostral middle frontal gyrus | 13.13 (2.07) | 13.18 (2.10) | | 1.0x10-2 | | 2.9x10-3 | | B<FW | | ns | | ns | | ns |
| *Temporal lobe* |  |  | |  | |  | |  | |  | |  | |  |
| RH parahippocampal gyrus | 1.64 (0.34) | 1.65 (0.33) | | 3.5x10-2 | | 5.4x10-3 | | B<FW | | ns | | ns | | ns |
| LH superior temporal gyrus | 7.48 (1.28) | 7.54 (1.28) | | 1.5x10-3 | | 1.5x10-3 | | B<FW | | 2.7x10-2 | | 2.5x10-3 | | B<FW |
| RH superior temporal gyrus | 6.53 (1.01) | 6.57 (1.03) | | 1.5x10-2 | | 3.4x10-3 | | B<FW | | ns | | ns | | ns |
| RH transverse temporal gyrus | 0.56 (0.11) | 0.55 (0.11) | | 4.5x10-3 | | 2.0x10-3 | | B>FW | | 2.8x10-3 | | 1.5x10-3 | | B>FW |
| **Thickness (mm)** |  |  | |  | |  | |  | |  | |  | |  |
| *Frontal lobe* |  |  | |  | |  | |  | |  | |  | |  |
| LH caudal anterior cingulate cortex | 2.91 (0.24) | 2.86 (0.25) | | 9.5x10-5 | | 1.1x10-2 a | | B>FW | | N/A | | N/A | | N/A |
| RH caudal anterior cingulate cortex | 2.86 (0.26) | 2.82 (0.26) | | 6.2x10-8 | | 6.4x10-3 a | | B>FW | | N/A | | N/A | | N/A |
| LH caudal middle frontal gyrus | 2.76 (0.14) | 2.72 (0.14) | | 2.3x10-6 | | 8.3x10-3 a | | B>FW | | N/A | | N/A | | N/A |
| RH caudal middle frontal gyrus | 2.79 (0.15) | 2.75 (0.15) | | 1.1x10-7 | | 6.9x10-3 a | | B>FW | | N/A | | N/A | | N/A |
| LH lateral orbitofrontal cortex | 3.00 (0.14) | 2.96 (0.14) | | 6.2x10-8 | | 6.4x10-3 a | | B>FW | | N/A | | N/A | | N/A |
| RH lateral orbitofrontal cortex | 2.97 (0.16) | 2.94 (0.14) | | 1.4x10-3 | | 1.4x10-2 a | | B>FW | | N/A | | N/A | | N/A |
| LH medial orbitofrontal cortex | 2.74 (0.17) | 2.69 (0.16) | | 3.9x10-5 | | 9.8x10-3 a | | B>FW | | N/A | | N/A | | N/A |
| RH medial orbitofrontal cortex | 2.81 (0.18) | 2.78 (0.16) | | 3.5x10-3 | | 1.5x10-2 a | | B>FW | | N/A | | N/A | | N/A |
| LH frontal pole | 3.18 (0.31) | 3.14 (0.31) | | 1.4x10-5 | | 9.3x10-3 a | | B>FW | | N/A | | N/A | | N/A |
| RH frontal pole | 3.18 (0.28) | 3.15 (0.27) | | 5.5x10-3 | | 1.6x10-2 a | | B>FW | | N/A | | N/A | | N/A |
| LH pars opercularis | 2.87 (0.15) | 2.81 (0.14) | | 4.9x10-15 | | 4.9x10-4 a | | B>FW | | N/A | | N/A | | N/A |
| RH pars opercularis | 2.88 (0.16) | 2.85 (0.15) | | 1.7x10-8 | | 5.4x10-3 a | | B>FW | | N/A | | N/A | | N/A |
| LH pars orbitalis | 3.10 (0.21) | 3.06 (0.20) | | 1.6x10-6 | | 7.4x10-3 a | | B>FW | | N/A | | N/A | | N/A |
| RH pars orbitalis | 3.10 (0.22) | 3.07 (0.22) | | 1.6x10-4 | | 1.1x10-2 a | | B>FW | | N/A | | N/A | | N/A |
| LH pars triangularis | 2.77 (0.17) | 2.71 (0.15) | | 4.5x10-12 | | 2.5x10-3 a | | B>FW | | N/A | | N/A | | N/A |
| RH pars triangularis | 2.80 (0.16) | 2.77 (0.16) | | 1.8x10-6 | | 7.8x10-3 a | | B>FW | | N/A | | N/A | | N/A |
| LH rostral anterior cingulate cortex | 3.13 (0.21) | 3.10 (0.20) | | 1.2x10-2 | | 1.8x10-2 a | | B>FW | | N/A | | N/A | | N/A |
| RH rostral anterior cingulate cortex | 3.20 (0.20) | 3.18 (0.20) | | 3.7x10-3 | | 1.5x10-2 a | | B>FW | | N/A | | N/A | | N/A |
| LH rostral middle frontal gyrus | 2.64 (0.15) | 2.59 (0.14) | | 5.2x10-9 | | 4.9x10-3 a | | B>FW | | N/A | | N/A | | N/A |
| RH rostral middle frontal gyrus | 2.68 (0.16) | 2.65 (0.15) | | 4.7x10-4 | | 1.2x10-2 a | | B>FW | | N/A | | N/A | | N/A |
| LH superior frontal gyrus | 3.03 (0.16) | 2.97 (0.16) | | 3.9x10-14 | | 1.5x10-3 a | | B>FW | | N/A | | N/A | | N/A |
| RH superior frontal gyrus | 3.04 (0.16) | 3.00 (0.15) | | 3.6x10-8 | | 5.9x10-3 a | | B>FW | | N/A | | N/A | | N/A |
| *Temporal Lobe* |  |  | |  | |  | |  | |  | |  | |  |
| LH parahippocampal gyrus | 3.08 (0.27) | 3.04 (0.27) | | 7.8x10-11 | | 4.4x10-3 a | | B>FW | | N/A | | N/A | | N/A |
| RH parahippocampal gyrus | 3.03 (0.24) | 2.99 (0.23) | | 2.0x10-11 | | 3.4x10-3 a | | B>FW | | N/A | | N/A | | N/A |
| LH superior temporal gyrus | 3.08 (0.16) | 3.04 (0.14) | | 3.6x10-14 | | 1.0x10-3 a | | B>FW | | N/A | | N/A | | N/A |
| RH superior temporal gyrus | 3.12 (0.17) | 3.08 (0.16) | | 1.4x10-13 | | 2.0x10-3 a | | B>FW | | N/A | | N/A | | N/A |
| LH transverse temporal gyrus | 2.67 (0.23) | 2.63 (0.21) | | 9.0x10-5 | | 1.0x10-2 a | | B>FW | | N/A | | N/A | | N/A |
| RH transverse temporal gyrus | 2.71 (0.20) | 2.68 (0.19) | | 4.7x10-4 | | 1.2x10-2 a | | B>FW | | N/A | | N/A | | N/A |
| *Insula* |  |  | |  | |  | |  | |  | |  | |  |
| LH insula | 3.27 (0.14) | 3.23 (0.13) | | 1.7x10-11 | | 2.9x10-3 a | | B>FW | | N/A | | N/A | | N/A |
| RH insula | 3.25 (0.15) | 3.21 (0.15) | | 4.1x10-6 | | 8.8x10-3 a | | B>FW | | N/A | | N/A | | N/A |
|  |  | |  | |  |  |  | |  | |  | |  | |

a Effects that survive FDR correction at a threshold of *p*<0.05. All other regions reported in the table are significant (*p*<.05). b TSA only applicable to surface area regions whereas ICV applicable to all other regions except thickness. Abbreviations: CON, Controls; HR, High Risk; BD, ICV, intracranial volume; TSA, total surface area; LH, left hemisphere; RH, right hemisphere; ns, not significant.

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Supplementary Table 5. Group Effects that Survived Correction for Multiple Comparisons.** | | | | | | | | | | | | |
|  | **CON** | **HR** |  |  | |  |  | |  | |  | |
| **HR vs. CON controlling for Age and Sex** | | | | **HR vs. CON controlling for Age, Sex and ICV** | | | | | |
|  | | | |  | | | | | |
|  | *Mean (SD)* | *Mean (SD)* | *p* | *FDR q* | | *Direction* | *p* | *FDR q* | | *Direction* | | |
| **Gray Matter Volume (cm3)** |  |  |  |  | |  |  |  | |  | | |
| *Frontal lobe* |  |  |  |  | |  |  |  | |  | | |
| LH lateral orbitofrontal cortex | 8.78 (1.00) | 9.06 (1.20) | 2.0x10-2 | 2.2x10-2 a | | HR>CON | 3.4x10-2 | 2.3x10-2 b | | HR>CON | | |
| RH lateral orbitofrontal cortex | 8.63 (1.09) | 8.97 (1.28) | 9.1x10-3 | 1.8x10-2 a | | HR>CON | 1.6x10-2 | 1.91x10-2 a | | HR>CON | | |
| LH medial orbitofrontal cortex | 5.67 (0.81) | 5.94 (0.98) | 1.8x10-2 | 2.0x10-2 a | | HR>CON | 2.4x10-2 | 2.16x10-2 b | | HR>CON | | |
| RH medial orbitofrontal cortex | 5.9 (0.84) | 6.18 (0.91) | 9.1x10-3 | 1.9x10-2 a | | HR>CON | 1.2x10-2 | 1.9x10-2 a | | HR>CON | | |
| RH rostral middle frontal gyrus | 18.92 (2.63) | 19.72 (3.22) | 1.8x10-2 | 2.1x10-2 a | | HR>CON | 2.3x10-2 | 2.1x10-2 b | | HR>CON | | |
| *Subcortical* |  |  |  |  | |  |  |  | |  | | |
| RH accumbens area | 0.61 (0.09) | 0.66 (0.10) | 3.7x10-4 | 8.0x10-4 a | | HR>CON | 1.0x10-3 | 6.8x10-3 a | | HR>CON | | |
| **Thickness (mm)** |  |  |  | |  |  |  |  | |  | |
| *Frontal lobe* |  |  |  | |  |  |  |  | |  | |
| LH caudal anterior cingulate cortex | 2.81 (0.24) | 2.93 (0.24) | 6.0x10-3 | | 1.6 x10-2 a | HR>CON | N/A | N/A | | N/A | |
| RH lateral orbitofrontal cortex | 2.91 (0.13) | 2.97 (0.16) | 2.5x10-3 | | 1.4 x10-2 a | HR>CON | N/A | N/A | | N/A | |

a Effects that survive FDR correction at a threshold of *p*<.05. b Significant effects (*p*<.05) prior to controlling for multiple tests. Abbreviations: CON, controls; HR, high-risk; ICV, intracranial volume; LH, left hemisphere; RH, right hemisphere; N/A, not applicable.

**Supplementary Table 6.** **Group Effectsthat were Significant Prior to Correcting for Multiple Tests.**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | | | **CON** | | **HR** | | |  | |  | | |  |  | | | |  | | |  | |
| **HR vs. CON controlling for** | | | | | | **HR vs. CON controlling for** | | | | | | | | |
| **Age and Sex** | | | | | | **Age, Sex and ICV/TSA**b | | | | | | | | |
|  | | | *Mean (SD)* | | *Mean (SD)* | | | *p* | | *FDR q* | | | *Direction* | *p* | *FDR q* | | | | | *Direction* | | |
| **Surface area (cm2)** | |  |  | |  | |  |  | |  | | |  | | | |  |  | |  | | | | |
| *Frontal lobe* | |  |  | |  | |  |  | |  | | |  | | | |  |  | |  | | | | |
| LH superior temporal gyrus | | | 3.88 (0.45) | | 3.84 (0.49) | | | ns | | ns | | | ns | 4.4x10-2 | 1.2x10-2 | | | | | CON>HR | | |
| **Gray Matter Volume** (**cm3)** | | |  | |  | | |  | |  | | |  |  |  | | | | |  | | |
| *Frontal lobe* | | |  | |  | | |  | |  | | |  |  |  | | | | |  | | |
| LH rostral anterior cingulate cortex | | | 3.1 (0.66) | | 3.30 (0.64) | | | 4.0x10-2 | | 2.3x10-2 | | | HR>CON | 3.4x10-2 | 2.3x10-2 | | | | | HR>CON | | |
| *Subcortical* | | |  | |  | | |  | |  | | |  |  |  | | | | |  | | |
| LH accumbens area | | | 0.67 (0.10) | | 0.71 (0.12) | | | 1.2x10-2 | | 8.3x10-3 | | | HR>CON | 2.3x10-2 | 1.1x10-2 | | | | | HR>CON | | |
| **Thickness (mm)** | | |  | |  | | |  | | |  | |  |  |  | | | | |  | |
| *Frontal lobe* | | |  | |  | | |  | | |  | |  |  |  | | | | |  | |
| LH rostral middle frontal gyrus | | | 2.59 (0.12) | | 2.63 (0.16) | | | 3.9x10-2 | | | 2.0x10-2 | | HR>CON | N/A | N/A | | | | | N/A | |

Effects that are significant (*p*<0.05) prior to controlling for multiple tests. b TSA only applicable to surface area regions whereas ICV applicable to all other regions except thickness. Abbreviations: CON, controls; HR, high-risk; ICV, intracranial volume; TSA, total surface area; LH, left hemisphere; RH, right hemisphere; ns, not significant; N/A, not applicable.

**Supplementary Table 7.** **Group by Time Effects that were Significant Prior to Correcting for Multiple Tests.**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Baseline (B)** | | **Follow Up (FW)** | | **Interaction effects controlling for Age, Sex** | | | **Interaction effects controlling for Age, Sex, ICV/TSAb** | | |
|  | **CON**  *Mean (SD)* | **HR**  *Mean (SD)* | **CON**  *Mean (SD)* | **HR**  *Mean (SD)* | *p* | *FDR q* | *Simple effects* | *p* | *FDR q* | *Simple effects* |
| **Surface area (cm2)** |  |  |  |  |  |  |  |  |  |  |
| *Frontal lobe* |  |  |  |  |  |  |  |  |  |  |
| RH frontal pole | 2.95 (0.56) | 2.99 (0.49) | 2.95 (0.58) | 2.94 (0.49) | 4.1x10-2 | 1.2x10-2 | HR B > HR FW *p*= 2.5x10-3 \*\* | 4.1x10-2 | 1.2x10-2 | HR B > HR FW *p*= 2.5x10-3 \*\* |
| RH pars orbitalis | 8.10 (1.04) | 8.24 (1.24) | 8.08 (1.04) | 8.15 (1.22) | 2.6x10-2 | 1.0x10-2 | HR B > HR FW *p*=1.7x10-5 \*\*\* | 2.6x10-2 | 1.0x10-2 | HR B > HR FW *p*= 1.7x10-5 \*\*\* |
| **Gray matter volume (cm3)** |  |  |  |  |  |  |  |  |  |  |
| *Frontal lobe* |  |  |  |  |  |  |  |  |  |  |
| LH pars opercularis | 5.62 (0.86) | 5.76 (1.12) | 5.50 (0.83) | 5.59 (1.08) | 4.4x10-2 | 2.4x10-2 | CON B > CON FW *p*= 5.0x10-7 \*\*\*  HR B > HR FW *p*= 4.4x10-18 \*\*\* | ns | ns | ns |
| LH pars triangularis | 4.20 (0.75) | 4.29 (0.85) | 4.12 (0.72) | 4.15 (0.80) | 3.3x10-2 | 2.2x10-2 | CON B > CON FW *p*= 6.0x10-6 \*\*\*  HR B > HR FW *p*=1.0x10-16 \*\*\* | 4.2x10-2 | 2.3x10-2 | CON B > CON FW *p*= 5.0x10-6 \*\*\*  HR B > HR FW *p*= 2.2x10-16 \*\*\* |
| LH rostral middle frontal gyrus | 18.30 (2.75) | 18.954 (2.95) | 17.89 (2.55) | 18.31 (2.89) | 4.9x10-2 | 2.5x10-2 | CON B > CON FW *p*=3.2x10-5 \*\*\*  HR B > HR FW *p*= 1.0x10-14 \*\*\* | ns | ns | ns |
| LH superior frontal gyrus | 25.95 (3.15) | 26.80 (3.80) | 25.42 (2.91) | 26.02 (3.75) | 4.3x10-2 | 2.3x10-2 | CON B > CON FW *p*= 1.0x10-4 \*\*\*  HR B > HR FW *p*= 5.6x10-20 \*\*\* | ns | ns | ns |
| *Temporal lobe* |  |  |  |  |  |  |  |  |  |  |
| RH superior temporal gyrus | 13.09 (1.64) | 13.43 (1.96) | 12.87 (1.54) | 13.10 (1.89) | 4.3x10-2 | 2.4x10-2 | CON B > CON FW *p*= 1.0x10-6 \*\*\*  HR B > HR FW *p*= 5.2x10-15 \*\*\* | ns | ns | ns |
| **White Matter Volume (cm3)** |  |  |  |  |  |  |  |  |  |  |
| *Frontal lobe* |  |  |  |  |  |  |  |  |  |  |
| RH frontal pole | 0.32 (0.09) | 0.32 (0.08) | 0.33 (0.10) | 0.31 (0.08) | 2.6x10-2 | 4.4x10-3 | ns | 3.1x10-2 | 2.9x10-3 | ns |
| **Thickness (mm)** |  |  |  |  |  |  |  |  |  |  |
| *Frontal lobe* |  |  |  |  |  |  |  |  |  |  |
| RH caudal middle frontal gyrus | 2.76 (0.14) | 2.80 (0.16) | 2.74 (0.15) | 2.75 (0.15) | 3.8x10-2 | 1.9x10-2 | HR B > HR FW *p*= 6.0x10-9 \*\*\* | N/A | N/A | N/A |
| RH rostral anterior cingulate cortex | 3.19 (0.17) | 3.21 (0.22) | 3.18 (0.17) | 3.18 (0.22) | 4.1x10-2 | 2.0x10-2 | HR B > HR FW *p*=8.8x10-5 \*\*\* | N/A | N/A | N/A |
| *Temporal lobe* |  |  |  |  |  |  |  |  |  |  |
| LH superior temporal gyrus | 3.05 (0.13) | 3.09 (0.17) | 3.03 (0.13) | 3.04 (0.15) | 4.8x10-2 | 2.1x10-2 | CON B > CON FW *p*=7.1x10-5 \*\*\*  HR B > HR FW *p*=4.1x10-14 \*\*\* | N/A | N/A | N/A |
|  |  |  |  |  |  |  |  |  |  |  |

Effects that are significant (*p*<0.05) prior to controlling for multiple tests. b TSA only applicable to surface area regions whereas ICV applicable to all other regions except thickness. Abbreviations: CON, controls; HR, high-risk; ICV, intracranial volume; TSA, total surface area; ns, not significant; N/A, not applicable. Simple effects tests were tested against Bonferroni-adjusted significance levels (p < α/4). Abbreviations: ICV, intracranial volume; TSA, total surface area; CON, controls; HR, high-risk; LH, left hemisphere; RH, right hemisphere; ns, not significant; N/A, not applicable. \*\**p*<0.01/4, \*\*\**p*<0.001/4.

**Supplementary Table S8. Exploratory Subgroup Analyses: HR with New Onset of Mood episode/diagnosis from Baseline to Follow-up, HR Without New Onset of Mood episode/diagnosis from Baseline to Follow-up and Total CON.**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Group Effects** | |  |  | |  | |  |
|  | |  | **New Mood Episode (*p*)** | | **New DSM-IV**  **Diagnosis (*p*)** | |  |
| **Gray Matter Volume (cm3)** | |  |  | |  | |  |
| *Frontal lobe* | |  |  | |  | |  |
| RH medial orbitofrontal cortex | |  | 3.6x10-2 \* | | 2.4x10-2\* | |  |
| RH accumbens area | |  | 3.6x10-3 \*\* | | 3.0x10-3\*\* | |  |
| **Thickness (mm)** | |  |  | |  | |  |
| *Frontal lobe* | |  |  | |  | |  |
| LH caudal anterior cingulate cortex | |  | 1.8x10-2 \*  2.2x10-2\* | | 2.3x10-2\* | |  |
| **Group by Time Effects** | | | |  | |  |  | |
| **Gray Matter Volume (cm3)** |  | | |  | |  |  | |
| *Frontal lobe* |  | | |  | |  |  | |
| RH caudal anterior cingulate cortex |  | | | 5.6x10-2 | | 1.9x10-2\* |  | |
| RH lateral orbitofrontal cortex |  | | | 3.9x10-2 \* | | 6.2x10-2 |  | |
| RH frontal pole |  | | | 3.2x10-2 \* | | 3.3x10-2\* |  | |
| RH pars opercularis |  | | | 3.3x10-3 \*\* | | 5.2x10-3\*\* |  | |
| LH pars orbitalis |  | | | 1.4x10-2 \* | | 2.4x10-2\* |  | |
| RH pars orbitalis |  | | | 8.4x10-3 \*\* | | 7.9x10-3\*\* |  | |
| RH pars triangularis |  | | | 2.4x10-2 \* | | 2.8x10-2\* |  | |
| RH rostral middle frontal gyrus |  | | | 2.4x10-2 \* | | 2.8x10-2\* |  | |
| **Thickness (mm)** |  | | |  | |  |  | |
| *Frontal lobe* |  | | |  | |  |  | |
| RH lateral orbitofrontal cortex |  | | | 3.0x10-3 \*\* | | 2.0x10-3\*\* |  | |
| RH frontal pole |  | | | 4.4x10-2 \* | | 3.0x10-2\* |  | |
| RH pars opercularis |  | | | 3.0x10-3 \*\* | | 1.9x10-3\*\* |  | |
| RH pars triangularis |  | | | 5.5x10-2  2.4x10-2\* | | 2.8x10-2\* |  | |
| RH rostral middle frontal gyrus |  | | | 2.8x10-2 \* | | 2.4x10-2\* |  | |
| LH superior frontal gyrus |  | | | 1.4x10-2 \* | | 2.4x10-2\* |  | |
| RH superior frontal gyrus |  | | | 2.2x10-2 \* | | 2.6x10-2\* |  | |

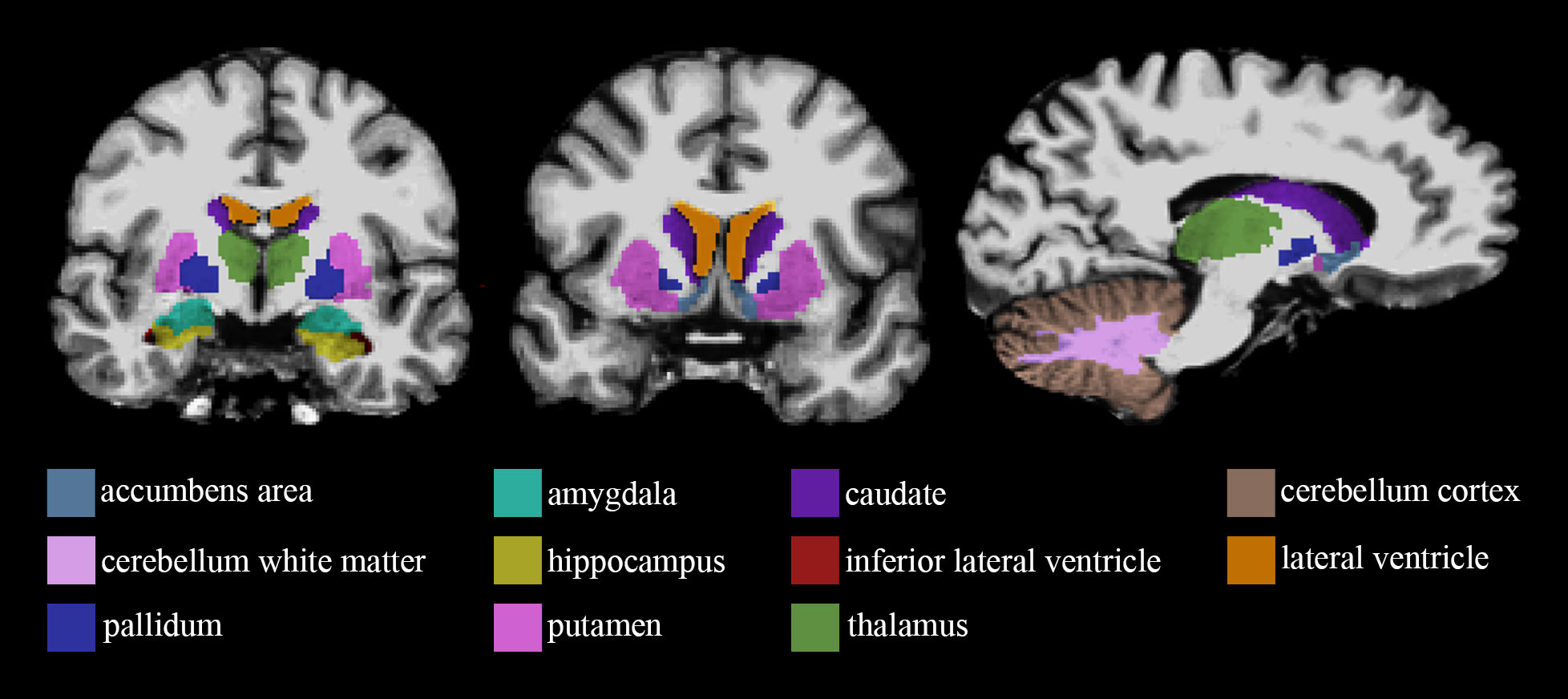
For regions that showed a main effect of group or a group by time interaction;(for thickness ROI’s we covaried for age and sex and for volume variables we covaried for age, sex and ICV), additional sub-group analyses were run. The main effect of group and interaction effect of group by time from our sub-group analyses are described in this table. The sub-group variables were created by sub-dividing our HR group according to the following criteria: i) new onset of any mood episode (major depressive or manic/hypomanic episode) from baseline to follow-up ; ii) new onset of any DSM IV diagnosis from baseline to follow-up. \* *p*<.05, \*\* *p*<.01. As these analyses were exploratory, *p* values did not undergo FDR correction.

**SUPPLEMENTARY FIGURES**

**Supplementary Figure 1. Cortical (A) and Subcortical (B) Regions of Interest.**

**A screenshot of a cell phone

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**B**

**Supplementary Figure 2. Subgroup Analyses for Group by Time Interaction (Volume with ICV) for ROIs Surviving FDR Correction**

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Simple effects tests were tested against Bonferroni-adjusted significance levels (p < α/9). CON: Control; HR ̂: HR minus HR with new onset of mood episode; N\_mood: HR with new onset of a mood episode; HR x: HR minus HR with new onset of any DSM-IV diagnosis; N\_anyDSM: HR with new onset of any DSM-IV diagnosis. \**p*<.05/9, \*\**p*<.01/9 and \*\*\**p*<.001/9.

**Figure S3. Subgroup Analyses for Group by Time Interaction (Thickness) for ROIs Surviving FDR Correction**

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**A close up of a logo

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Simple effects tests were tested against Bonferroni-adjusted significance levels (p < α/9). CON: Control; HR ̂: HR minus HR with new onset of mood episode; N\_mood: HR with new onset of a mood episode; HR x: HR minus HR with new onset of any DSM-IV diagnosis; N\_anyDSM: HR with new onset of any DSM-IV diagnosis. \**p*<.05/9, \*\**p*<.01/9 and \*\*\**p*<.001/9.

**Figure S4. Subgroup Analyses for Group Effect (Volume and Thickness) for ROIs Surviving FDR Correction.**

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Simple effects tests were tested against Bonferroni-adjusted significance levels (p < α/3). CON: Control; HR ̂: HR minus HR with new onset of mood episode; N\_mood: HR with new onset of a mood episode; HR x: HR minus HR with new onset of any DSM-IV diagnosis; N\_anyDSM: HR with new onset of any DSM-IV diagnosis. \**p*<.05/3, \*\**p*<.01/3 and \*\*\**p*<.001/3.

**Supplementary Table S9. Effect Sizes for Longitudinal Subgroup Analyses: Effects Over Time in HR Subgroups**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  |  |  |  |
|  | **New mood episode** | | **New onset any DSM-IV** | |
|  | HR with new mood episode, (*d*) | HR minus HR with new mood episode, (*d*) | HR with new onset of any DSM-IV diagnosis,  (*d*) | HR minus HR with new onset of any DSM-IV diagnosis,  (*d*) |
| **Gray Matter Volume (cm3)** |  |  |  |  |
| *Frontal lobe* |  |  |  |  |
| RH caudal anterior cingulate cortex | 0.06 | 0.10 | 0.04# | 0.11 |
| RH lateral orbitofrontal cortex | 0.13^ | 0.12 | 0.10# | 0.12 |
| RH frontal pole | 0.18^ | 0.17 | 0.19# | 0.17 |
| RH pars opercularis | 0.17 | 0.14 | 0.17 | 0.14 |
| LH pars orbitalis | 0.23 | 0.22 | 0.17 | 0.23 |
| RH pars orbitalis | 0.21 | 0.15 | 0.19 | 0.15 |
| RH pars triangularis | 0.21 | 0.16 | 0.19 | 0.16 |
| RH rostral middle frontal gyrus | 0.16 | 0.19 | 0.14# | 0.19 |
|  |  |  |  |  |
| **Thickness (mm)** |  |  |  |  |
| *Frontal lobe* |  |  |  |  |
| RH lateral orbitofrontal cortex | 0.19^ | 0.30 | 0.12# | 0.31 |
| RH frontal pole | 0.19^ | 0.17 | 0.30# | 0.16 |
| RH pars opercularis | 0.35 | 0.29 | 0.37 | 0.28 |
| RH pars triangularis | 0.21^ | 0.29 | 0.45 | 0.26 |
| RH rostral middle frontal gyrus | 0.20^ | 0.27 | 0.26# | 0.26 |
| LH superior frontal gyrus | 0.43 | 0.39 | 0.42 | 0.39 |
| RH superior frontal gyrus | 0.28 | 0.31 | 0.25# | 0.31 |

Effects sizes are shown for differences over time in HR subgroups. ^; Simple effect test (shown in Supplementary Figures 2 and 3) did not reveal a significant difference over time in HR subjects with new onset of a mood episode. #; Simple effect test (shown in Supplementary Figures 2 and 3) did not reveal a significant difference over time in HR subjects with a DSM IV diagnosis.

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