**The impact of smoking status on cognition and brain morphology in schizophrenia spectrum disorders.**

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*­***Supplementary Material**

***Participant Characterisation***

Data from 455 patients with schizophrenia or schizoaffective disorder and 299 healthy controls aged 18-65 was accessed through the Australian Schizophrenia Research Bank (ASRB). Data collection was overseen by scientific collaborators from five Australian states and territories (New South Wales, Victoria, Queensland, Australian Capital Territory, and Western Australia). The exclusion criteria for individuals participating in the ASRB included age less than 18 years old, movement disorders, organic brain syndrome, severe brain injury, mental retardation as categorised by an intellectual quotient (IQ) lower than 70, current substance dependence, or electroconvulsive therapy (ECT) in the six months prior to participation. Additional exclusion criteria were in place for healthy controls and included a history of any psychosis or bipolar 1 disorder. Detailed information concerning the consent procedure is provided elsewhere (Loughland et al., 2010). Both the clinical and diagnostic characteristics of participants in the SSD cohort were assessed using the Diagnostic Interview for Psychoses (DIP) (Castle et al., 2006) and the Scale for Assessment of Negative Symptoms (SANS) (Andreasen, 1989). Methodology by Green et al. (Green et al., 2014) was followed in order to evaluate current positive symptoms based on 11 DIP items, regarding experiences of both hallucinations and delusions. The SANS was used in order to calculate a sum score of negative symptoms.

***FreeSurfer processing***

Image processing was completed using the FreeSurfer image analysis suite (version 5.1.0; Martinos Centre for Biomedical Imaging, Harvard-MIT, Boston, MA; <http://surfer.nmr.mgh.harvard.edu/>), which comprised an automated volume-based and surface-based stream. These were used to extract volume estimates for select cortical and subcortical regions using an automatic labelling system. Using a probabilistic atlas and a Bayesian classification rule, a neuroanatomical label is assigned to each voxel or vertex on the cortical surface (Fischl et al., 2002, 2004). Mean volumes from the hippocampus, amygdala, thalamus, superior temporal gyrus, DLPFC, vlPFC, cingulate cortex (rostral ACC, caudal ACC, and posterior cingulate cortex (PCC)), OFC (medial OFC, and lateral OFC), and insula from each hemisphere were selected as regions-of-interest (ROI) (n = 28). The rostral middle frontal gyrus (from the Desikan-Killiany atlas) corresponds most closely with the DLPFC (Kikinis et al., 2010) and hence will be used in the analysis (and herein referred to as the DLPFC). The vlPFC is located on the inferior frontal gyrus, which corresponds to the pars orbitalis, pars triangularis, and pars opercularis in the Desikan-Killiany atlas (Desikan et al., 2006), and so these regions were used in the analysis (and herein referred to collectively as vlPFC, or individually where necessary).

 The surface-based stream was used to reconstruct a 3-dimensional cortical surface model to extract cortical thickness and surface area measurements. The process involves motion correction, correction of non-uniform intensity, Talairach computation, intensity normalisation, removal of any tissue that is not brain, subcortical segmentation, tessellation of the grey/white matter boundary, automated topology correction in order to remove defects, and cortical parcellation (Dale, Fischl, & Sereno, 1999). Information from the MRI volume concerning image intensity and continuity is used, in order to perform segmentation of the grey/white matter boundaries and the pial surface in each hemisphere. Cortical thickness was calculated as the distance at each vertex between the grey-white matter boundary and the grey matter / CSF boundary. Mean regional thickness measurements from the superior temporal gyrus, DLPFC, vlPFC, cingulate cortex (rostral ACC, caudal ACC, and PCC), OFC (medial OFC, and lateral OFC), and insula were selected from both the left and right hemisphere as ROIs (n = 22). Additionally, mean surface area measurements from the same ROIS (n = 22) were also selected.

The Desikan-Killiany atlas included in the Free Surfer package was used to define the regions. Quality control for all images was conducted through visual inspection, prior to the extraction of cortical thickness and surface area. If any segmentation errors were present, images were corrected manually with FreeSurfer’s editing tools according to a standardised protocol.

***Preliminary analysis and assumption checking****.*

Before conducting the primary analyses, several preliminary tests were conducted in order to assess the suitability of the data for use with analysis of covariance (ANCOVA), where age, sex, site and ICV (for volume/surface area analyses) were selected as covariates a-priori. All cognitive domains in the SSD smoker group were not normally distributed. Further, delayed memory and visuospatial/constructional were not normally distributed in the SSD non-smoker, and HC non-smoker groups. Consequently, the assumption of normality of distributions was violated for the cognitive analyses. However, it has been shown that non-normality does not greatly affect type 1 error rate (1,2). Thus, this violation was not considered a concern. The assumption of homogeneity of variance was also violated for the domain of delayed memory in the cognitive analyses. ANCOVA has been said to be robust to violations of homogeneity of variance when sample sizes are of a similar ratio (up to 1:1.5) (3)**,** which they are for both the main effect of diagnosis and main effect of smoking analyses, and thus these were also not considered a concern. The smoking\*dx interaction analysis, however, was not a similar ratio. Therefore, we followed the procedure of Allen and Bennet (2008) (4)and used a stricter alpha level of 0.001 when evaluating the delayed memory results. As these results were not close to being significant, this did not affect the outcome of our results. All other assumptions were met, with the exception of homogeneity of regression slopes. That is, there were diagnosis\*age interactions for regional volume (right pars triangularis F = 1.46, p = 0.002, right pars orbitalis F = 9.59, p = 0.002) and surface area (right pars orbitalis F = 13.89, p < 0.01, right pars triangularis F = 12.82, p < 0.01, right lateral OFC F = 8.04, p = 0.005, right DLPFC F = 7.59, p = 0.006, left lateral OFC F = 6.36, p = 0.012) analyses (but not regional thickness estimates or cognitive tests). Therefore, we included age as a dependent variable in the primary analysis of volume and cortical surface area (see below), with ICV, sex and site specified as covariates. The primary statistical models for cortical thickness and cognitive performance outcomes however, included age as a covariate, alongside sex and site.

***FDR correction***

The corrections were conducted *separately* at the level of main effect of smoking status, main effect of diagnostic group, and smoking status\* diagnostic group interaction effect for each of the following analyses: (1) *cognition,* (2) *global volume, thickness, and surface area,* (3) *cortical and subcortical grey matter volume,* (4) *cortical thickness,* (5) *cortical surface area.* Analysis 3 was conducted on the 14 cortical and subcortical regions of interest, and analyses 4 and 5 were conducted on the 11 cortical regions of interest; the left and right hemispheres were corrected together using an FDR rate of p<.05 (28 comparisons for volume, and 22 comparisons for cortical thickness and surface area).

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **SSD smoker** | **SSD non-smoker** | **HC smoker** | **HC non-smoker** | **Total** |
| Melbourne | 35 | 25 | 8 | 19 | 87 |
| Sydney | 32 | 20 | 7 | 20 | 79 |
| Brisbane | 54 | 13 | 11 | 12 | 90 |
| Perth | 4 | 8 | 0 | 0 | 12 |
| Newcastle | 7 | 3 | 0 | 5 | 15 |

*Supplementary Table 1. Participant distribution across scanning sites.*

*Supplementary Table 2. Main effects of dx on cognition*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Domain**  | **Comparisonsa** | **Group** | **Mb** | **SD** | **Post-Hocc** | **dd** |
| Immediate memory | **F (1,744) = 195.22, p < 0.001\*** | SSD | 80.78 | 18.66 | SSD < HC | 1.05 |
|  |  | HC | 99.69 | 17.41 | --- |  |
| Visuospatial/constructional | **F (1,744) = 55.32, p < 0.001\*** | SSD | 86.34 | 16.98 | SSD < HC | 0.56 |
|  |  | HC | 95.50 | 15.86 | ---- |  |
| Language  | **F (1,744) = 161.99, p < 0.001\*** | SSD | 94.40 | 12.52 | SSD < HC | 0.95 |
|  |  | HC | 105.95 | 11.69 | ---- |  |
| Attention  | **F (1,744) = 229.53, p < 0.001\*** | SSD | 83.09 | 17.83 | SSD < HC | 1.14 |
|  |  | HC | 102.67 | 16.63 | ---- |  |
| Delayed memory  | **F (1,744) = 139.02, p < 0.001\*** | SSD | 83.77 | 15.74 | SSD < HC | 0.88 |
|  |  | HC | 97.23 | 14.70 | ---- |  |
| Total score  | **F (1,744) = 320.79, p < 0.001\*** | SSD | 81.35 | 14.42 | SSD < HC | 1.34 |
|  |  | HC | 100.09 | 13.47 | ---- |  |

*Note:* SSD, schizophrenia spectrum disorder; HC, healthy controls; S, smoker; NS, non-smoker

aUnadjusted for multiple comparisons

bAll values are adjusted for age, gender, and site.

cIf post-hoc relationship is not reported, finding was not significant prior or after FDR correction. SSD < HC implies significant reductions relative to HC.

dd = Cohen’s d effect sizes

\*Significant at p < .05 after Benjamini-Hochberg correction for multiple comparisons

Bold values = significant before Benjamini-Hochberg correction

*Supplementary Table 3. Main effects of diagnosis on global morphology estimates*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Domain**  | **Comparisonsa** | **Group** | **Mb** | **SD** | **Post-Hocc** | **dd** |
| Volume (ml) | **F (1,272) = 7.70, p = 0.006\*** | SSD | 690538.13 | 30635.98 | ---- | 0.37 |
|  |  | HC | 701967.85 | 31354.08 |  |  |
| Cortical Thickness (mm) | **F (1,272) = 11.89, p = 0.001\*** | SSD | 2.60 | 0.10 | ---- | 0.47 |
|  |  | HC | 2.65 | 0.10 |  |  |
|  |  |  |  |  |  |  |
| Surface Area (cm3) | F (1,272) = 0.87, p = 0.352 | SSD | 2516.45 | 105.61 | ---- | 0.12 |
|  |  | HC | 2529.68 | 108.09 |  |  |

*Note:* Given the focus of this study, main effects of diagnostic group are reported in the supplementary material for brevity; SSD = schizophrenia spectrum disorder; HC= healthy controls; S = smoker; NS = non-smoker

aUnadjusted for multiple comparisons

bAll values are adjusted for age, gender, and site.

cIf post-hoc relationship is not reported, finding was not significant prior or after FDR correction. SSD < HC implies significant reductions relative to HC.

dd = Cohen’s d effect sizes.

\*Significant at p < .05 after Benjamini-Hochberg FDR correction for multiple comparisons

Bold values = significant before Benjamini-Hochberg FDR

*Supplementary Table 4. Group comparisons of global volume, global cortical thickness and global cortical surface area*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Domain**  | **Comparisonsa** | **Group** | **Mb** | **SD** | **Post-Hocc** | **dd** |
| *Main effect of smoking.*  |  |  |  |  |  |  |
| Volume (ml) | F (1,272) = 0.86, p = 0.355 | S | 694289.09 | 39646.22 | ---- | 0.11 |
|  |  | NS | 698216.89 | 29988.04 |  |  |
| Cortical Thickness (mm) | **F (1,272) = 4.96, p = 0.027** | S | 2.61 | 0.12 | ---- | 0.26 |
|  |  | NS | 2.64 | 0.09 |  |  |
|  |  |  |  |  |  |  |
| Surface Area (cm3) | F (1,272) = 0.18, p = 0.672 | S | 2526.16 | 136.68 | ---- | -0.05 |
|  |  | NS | 2519.97 | 103.38 |  |  |
| *Smoking\*diagnosis interaction effect.* |  |  |  |  |  |  |
| Volume (ml) | F (1,272) < 0.001, p = 0.994 | SSD S | 688589.63 | 29454.74 | ---- | N/A |
|  |  | SSD NS | 692486.63 | 29547.05 |  |  |
|  |  | HC S | 699988.56 | 29199.39 |  |  |
|  |  | HC NS | 703947.15 | 30008.07 |  |  |
| Cortical Thickness (mm) | F (1,272) = 0.002, p = 0.961 | SSD S | 2.59 | 0.09 | ---- | N/A |
|  |  | SSD NS | 2.62 | 0.09 |  |  |
|  |  | HC S | 2.63 | 0.09 |  |  |
|  |  | HC NS | 2.66 | 0.09 |  |  |
| Surface Area (cm3) | F (1,272) = 0.03, p = 0.864 | SSD S | 2520.75 | 101.54 | ---- | N/A |
|  |  | SSD NS | 2512.14 | 101.86 |  |  |
|  |  | HC S | 2531.56 | 100.66 |  |  |
|  |  | HC NS | 2527.80 | 103.45 |  |  |

*Note:* Given the focus of this study, main effects of diagnostic group are reported in the supplementary material for brevity; SSD = schizophrenia spectrum disorder; HC= healthy controls; S = smoker; NS = non-smoker

aUnadjusted for multiple comparisons

bAll values are adjusted for age, gender, and site.

cIf post-hoc relationship is not reported, finding was not significant prior or after FDR correction. SSD < HC implies significant reductions relative to HC.

dd = Cohen’s d effect sizes.

\*Significant at p < .05 after Benjamini-Hochberg FDR correction for multiple comparisons

Bold values = significant before Benjamini-Hochberg FDR

*Supplementary Table 5. Main effects of diagnosis on cortical volume, cortical thickness and surface area*

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  | **LH** |  |  |  | **RH** |  |  |  |
| **Regions**  | **Comparisonsa** | **Group** | **Mb** | **SD** | **Post-Hocc** | **dd** | **Mb** | **SD** | **Post-Hocc** | **dd** |
| ***Volume (ml)*** |  |  |  |  |  |  |  |  |  |  |
| ***Subcortical Regions*** |  |  |  |  |  |  |  |  |  |  |
| Thalamus | LH: F (1,271) = 0.19, p = 0.660 | SSD | 7708.78 | 628.87 | ---- | 0.14 | 7871.13 | 617.18 | ---- | 0.04 |
|  | RH: F (1,271) = 2.04, p = 0.154 | HC | 7800.52 | 645.09 |  |  | 7896.60 | 633.09 |  |  |
| Hippocampus | LH: F (1,271) = 1.17, p = 0.280 | SSD | 4140.13 | 370.33 | ---- | 0.37 | 4279.35 | 383.93 | ---- | 0.25 |
|  | RH: F (1,271) = 0.61, p = 0.434 | HC | 4278.05 | 379.87 |  |  | 4377.37 | 393.83 |  |  |
| Amygdala  | LH: F (1, 271) = 0.93, p = 0.337 | SSD | 1559.60 | 160.62 | ---- | 0.18 | 1609.97 | 169.89 | ---- | 0.12 |
|  | RH: F (1, 271) = 2.15, p = 0.143 | HC | 1588.40 | 164.76 |  |  | 1631.38 | 174.27 |  |  |
| ***Cortical Regions***  |  |  |  |  |  |  |  |  |  |  |
| Caudal Anterior Cingulate  | LH: F (1, 271) = 1.23, p = 0.268 | SSD | 1963.82 | 491.57 | ---- | 0.08 | 2240.92 | 561.92 | ---- | 0.27 |
|  | RH: F (1, 271) = 1.00, p = 0.318 | HC | 2003.88 | 504.24 |  |  | 2397.25 | 576.41 |  |  |
| Rostral Anterior Cingulate  | LH: F (1, 271) = 0.82, p = 0.366 | SSD | 2892.69 | 488.40 | ---- | 0.20 | 2368.84 | 432.32 | ---- | -0.03 |
|  | RH: F (1, 2731 = 0.05, p = 0.824 | HC | 2993.07 | 500.99 |  |  | 2355.36 | 443.46 |  |  |
| Posterior Cingulate  | LH: F (1, 271) = 0.008, p = 0.929 | SSD | 3393.15 | 501.52 | ---- | -0.05 | 3393.65 | 474.01 | ---- | 0.01 |
|  | RH: F (1, 271) = 0.85, p = 0.357 | HC | 3368.26 | 514.45 |  |  | 3400.79 | 486.46 |  |  |
| Pars Opercularis  | LH: F (1, 271) = 1.89, p = 0.170 | SSD | 5116.09 | 844.87 | ---- | 0.10 | 4232.14 | 674.00 | ---- | 0.11 |
|  | RH: F (1, 271) = 0.73, p = 0.393 | HC | 5202.32 | 866.65 |  |  | 4306.70 | 691.38 |  |  |
| *Supplementary Table 5* Continued. |  |  |  |  |  |  |  |  |  |  |
|  |  |  | **LH** |  |  |  | **RH** |  |  |  |
| **Regions**  | **Comparisonsa** | **Group** | **Mb** | **SD** | **Post-Hocc** | **dd** | **Mb** | **SD** | **Post-Hocc** | **dd** |
| Pars Orbitalis  | LH: F (1, 271) = 4.60, p > 0.999 | SSD | 2264.61 | 287.69 | ---- | 0.41 | 2802.70 | 395.76 | ---- | 0.25 |
|  | **RH: F (1, 271) = 5.07, p = 0.025**  | HC | 2383.43 | 295.11 |  |  | 2904.97 | 405.96 |  |  |
| Pars Triangularis  | LH: F (1, 271) = 0.10, p = 0.747 | SSD | 3735.58 | 591.38 | ---- | 0.17 | 4437.09 | 742.71 | ---- | 0.31 |
|  | **RH: F (1, 271) = 4.88, p = 0.028** | HC | 3834.83 | 606.63 |  |  | 4669.26 | 761.85 |  |  |
| Rostral Middle Frontal  | LH: F (1, 271) = 0.60, p = 0.440  | SSD | 16703.98 | 1590.61 | ---- | 0.31 | 17391.19 | 1755.71 | ---- | 0.27 |
|  | RH: F (1, 271) = 0.57, p = 0.452 | HC | 17206.99 | 1631.61 |  |  | 17876.30 | 1800.96 |  |  |
| Lateral Orbitofrontal  | LH: F (1, 271) = 3.10, p = 0.079 | SSD | 8034.00 | 674.27 | ---- | 0.25 | 7929.32 | 708.20 | ---- | 0.28 |
|  | RH: F (1, 271) = 1.24, p = 0.267 | HC | 8206.84 | 691.65 |  |  | 8132.28 | 726.45 |  |  |
| Medial Orbitofrontal  | LH: F (1, 271) = 1.81, p = 0.180 | SSD | 5728.53 | 624.40 | ---- | 0.11 | 5508.84 | 516.07 | ---- | 0.22 |
|  | RH: F (1, 271) = 0.38, p = 0.538 | HC | 5796.03 | 640.49 |  |  | 5622.43 | 529.37 |  |  |
| Superior Temporal  | LH: F (1, 271) = 0.45, p = 0.504 | SSD | 12581.46 | 1183.09 | ---- | 0.17 | 12169.09 | 1148.44 | ---- | 0.15 |
|  | RH: F (1, 271) = 0.31, p = 0.577 | HC | 12786.03 | 1213.59 |  |  | 12340.25 | 1178.05 |  |  |
| Insula | LH: F (1 ,271) = 2.63, p = 0.106 | SSD | 7435.20 | 630.46 | ---- | 0.08 | 7649.40 | 758.92 | ---- | 0.15 |
|  | RH: F (1, 271) = 0.21, p = 0.650 | HC | 7488.94 | 646.71 |  |  | 7766.34 | 778.47 |  |  |
| ***Cortical thickness (mm)*** |  |  |  |  |  |  |  |  |  |  |
| Caudal Anterior Cingulate  | LH: F (1,273) = 0.09, p = 0.765 | SSD | 2.68 | 0.25 | ---- | 0.04 | 2.59 | 0.23 | SSD < HC | 0.33 |
|  | **RH: F (1,273) = 6.21, p = 0.013\*** | HC | 2.69 | 0.25 |  |  | 2.67 | 0.24 |  |  |
| Rostral Anterior Cingulate | LH: F (1,273) = 3.04, p = 0.082 | SSD | 2.92 | 0.22 | ---- | 0.23 | 2.99 | 0.23 | ---- | 0.15 |
|  | RH: F (1,273) = 1.25, p = 0.265 | HC | 2.97 | 0.23 |  |  | 3.03 | 0.23 |  |  |
| *Supplementary Table 5.* Continued. |  |  |  |  |  |  |  |  |  |  |
|  |  |  | **LH** |  |  |  | **RH** |  |  |  |
| **Regions**  | **Comparisonsa** | **Group** | **Mb** | **SD** | **Post-Hocc** | **dd** | **Mb** | **SD** | **Post-Hocc** | **dd** |
| Posterior Cingulate  | LH: F (1, 273) = 0.29, p = 0.589 | SSD | 2.59 | 0.16 | ---- | 0.07 | 2.55 | 0.16 | ---- | 0.01 |
|  | RH: F (1, 273) = 0.002, p = 0.964 | HC | 2.60 | 0.16 |  |  | 2.55 | 0.17 |  |  |
| Superior Temporal Gyrus | **LH: F (1, 273) = 7.18, p = 0.008\*** | SSD | 2.78 | 0.15 | SSD < HC | 0.36 | 2.82 | 0.14 | SSD < HC | 0.45 |
|  | **RH: F (1, 273) = 11.31, p = 0.001\*** | HC | 2.84 | 0.16 |  |  | 2.88 | 0.15 |  |  |
| Rostral Middle Frontal  | **LH: F (1, 273) = 4.36, p = 0.038\*** | SSD | 2.50 | 0.13 | SSD < HC | 0.28 | 2.51 | 0.13 | SSD < HC | 0.35 |
|  | **RH: F (1, 273) = 7.24, p = 0.008\*** | HC | 2.54 | 0.13 |  |  | 2.56 | 0.13 |  |  |
| Lateral Orbitofrontal | **LH: F (1, 273) = 23.54, p < 0.001\*** | SSD | 2.65 | 0.16 | SSD < HC | 0.64 | 2.67 | 0.16 | SSD < HC | 0.56 |
|  | **RH: F (1, 273) = 18.13, p < 0.001\*** | HC | 2.75 | 0.16 |  |  | 2.76 | 0.17 |  |  |
| Medial Orbitofrontal  | **LH: F (1, 273) = 11.13, p = 0.001\*** | SSD | 2.58 | 0.17 | SSD < HC | 0.44 | 2.55 | 0.16 | SSD < HC | 0.46 |
|  | **RH: F (1, 273) = 12.29, p = 0.001\*** | HC | 2.66 | 0.18 |  |  | 2.62 | 0.17 |  |  |
| Pars Orbitalis  | **LH: F (1, 273) = 14.81, p < 0.001\*** | SSD | 2.75 | 0.21 | SSD < HC | 0.51 | 2.81 | 0.21 | SSD < HC | 0.33 |
|  | **RH: F (1, 273) = 5.97, p = 0.015\*** | HC | 2.86 | 0.22 |  |  | 2.88 | 0.21 |  |  |
| Pars Triangularis | **LH: F (1, 273) = 8.05, p = 0.005\*** | SSD | 2.54 | 0.16 | SSD < HC | 0.38 | 2.57 | 0.15 | SSD < HC | 0.33 |
|  | **RH: F (1, 273) = 6.24, p = 0.013\*** | HC | 2.61 | 0.17 |  |  | 2.62 | 0.16 |  |  |
| Pars Opercularis  | LH: F (1, 273) = 3.72, p = 0.055 | SSD | 2.61 | 0.15 | ---- | 0.25 | 2.62 | 0.16 | SSD < HC | 0.46 |
|  | **RH: F (1, 273) = 11.97, p = 0.001\*** | HC | 2.65 | 0.15 |  |  | 2.69 | 0.16 |  |  |
| Insula  | **LH: F (1,273) = 13.96, p < 0.001\*** | SSD | 3.04 | 0.17 | SSD < HC | 0.49 | 3.02 | 0.18 | SSD < HC | 0.28 |
|  | **RH: F (1,273) = 4.70, p = 0.031\*** | HC | 3.13 | 0.17 |  |  | 3.07 | 0.19 |  |  |
| ***Surface Area (cm3)*** |  |  |  |  |  |  |  |  |  |  |
| Caudal Anterior Cingulate  | LH: F (1,273) = 0.09, p = 0.438 | SSD | 674.55 | 135.31 | ---- | 0.10 | 781.99 | 159.03 | ---- | 0.19 |
| *Supplementary Table 5.* Continued. |  |  |  |  |  |  |  |  |  |  |
|  |  |  | **LH** |  |  |  | **RH** |  |  |  |
| **Regions**  | **Comparisonsa** | **Group** | **Mb** | **SD** | **Post-Hocc** | **dd** | **Mb** | **SD** | **Post-Hocc** | **dd** |
| Caudal Anterior cingulate cont. | RH: F (1,273) = 0.61, p = 0.266 | HC | 688.33 | 138.80 |  |  | 813.28 | 163.12 |  |  |
| Rostral Anterior Cingulate | LH: F (1,273) = 3.09, p = 0.080 | SSD | 871.03 | 128.40 | ---- | 0.08 | 712.60 | 123.53 | ---- | -0.10 |
|  | RH: F (1,273) = 0.004, p = 0.948 | HC | 882.16 | 141.97 |  |  | 699.93 | 126.71 |  |  |
| Posterior Cingulate  | LH: F (1, 273) = 0.44, p = 0.510 | SSD | 1202.64 | 159.64 | ---- | -0.01 | 1219.14 | 159.83 | ---- | 0.01 |
|  | RH: F (1, 273) = 0.23, p = 0.634 | HC | 1184.83 | 163.76 |  |  | 1217.23 | 163.95 |  |  |
| Superior Temporal Gyrus | LH: F (1, 273) = 2.32, p = 0.129 | SSD | 3928.66 | 294.66 | ---- | 0.00 | 3744.65 | 306.94 | ---- | -0.08 |
|   | RH: F (1, 273) = 3.06, p = 0.082 | HC | 3929.07 | 302.25 |  |  | 3718.92 | 314.85 |  |  |
| Rostral Middle Frontal  | LH: F (1, 273) = 2.43, p = 0.120 | SSD | 5883.63 | 547.58 | ---- | -0.21 | 6103.12 | 535.78 | SSD < HC | 0.08 |
|  | **RH: F (1, 273) = 5.54, p = 0.019\*** | HC | 5597.89 | 561.70 |  |  | 6148.40 | 546.59 |  |  |
| Lateral Orbitofrontal | **LH: F (1, 273) = 8.02, p = 0.005\*** | SSD | 2783.87 | 218.77 | SSD > HC | -0.20 | 2737.67 | 241.97 | SSD > HC | -0.06 |
|  | **RH: F (1, 273) = 7.77, p = 0.006\*** | HC | 2739.58 | 224.41 |  |  | 2722.08 | 248.21 |  |  |
| Medial Orbitofrontal  | LH: F (1, 273) = 1.40, p = 0.238 | SSD | 1972.85 | 218.36 | ---- | -0.19 | 1907.44 | 159.46 | ---- | -0.015 |
|  | RH: F (1, 273) = 1.02, p = 0.314 | HC | 1929.96 | 223.99 |  |  | 1883.90 | 163.57 |  |  |
| Pars Orbitalis  | LH: F (1, 273) = 1.30, p = 0.255 | SSD | 657.65 | 67.88 | ---- | 0.09 | 804.91 | 92.48 | SSD < HC | 0.12 |
|  | **RH: F (1, 273) = 10.05, p = 0.002\*** | HC | 663.95 | 69.63 |  |  | 816.003 | 94.87 |  |  |
| Pars Triangularis | LH: F (1, 273) = 0.11, p = 0.740 | SSD | 1308.00 | 182.72 | ---- | 0.04 | 1517.12 | 240.57 | SSD < HC | 0.22 |
|  | **RH: F (1, 273) = 7.73, p = 0.006\*** | HC | 1315.12 | 187.43 |  |  | 1571.22 | 246.77 |  |  |
| Pars Opercularis  | **LH: F (1, 273) = 3.95, p = 0.048** | SSD | 1733.40 | 263.87 | ---- | 0.02 | 1457.04 | 229.16 | ---- | -0.08 |
|  | RH: F (1, 273) = 2.91, p = 0.089 | HC | 1739.85 | 270.67 |  |  | 1437.44 | 235.07 |  |  |
| Insula | LH: F (1, 273) = 1.48, p = 0.224 | SSD | 2388.55 | 191.65 | ---- | -0.23 | 2464.33 | 243.33 | ---- | -0.08 |
| *Supplementary Table 5.* Continued. |  |  |  |  |  |  |  |  |  |  |
|  |  |  | **LH** |  |  |  | **RH** |  |  |  |
| **Regions**  | **Comparisonsa** | **Group** | **Mb** | **SD** | **Post-Hocc** | **dd** | **Mb** | **SD** | **Post-Hocc** | **dd** |
| Insula cont.  | RH: F (1, 273) = 1.14, p = 0.287 | HC | 2344.06 | 196.58 |  |  | 2444.34 | 249.60 |  |  |

*Note:* SSD, schizophrenia spectrum disorder; HC, healthy controls; S, smoker; NS, non-smoker; LH, left hemisphere; RH, right hemisphere.

aUnadjusted for multiple comparisons

bAll values are adjusted for age, gender, ICV, and site.

cIf post-hoc relationship is not reported, finding was not significant prior or after FDR correction. SSD < HC implies significant reductions relative to HC.

dd = Cohen’s d effect sizes

\*Significant at p < .05 after Benjamini-Hochberg correction for multiple comparisons

Bold values = significant before Benjamini-Hochberg correction

*Supplementary Table 6*. *Group Comparisons of Cognitive Domains (Light and heavy smokers only)*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Domain**  | **Comparisonsa** | **Group** | **Mb** | **SD** | **Post-Hocc** | **dd** |
| *Main effect of smoking.*  |  |  |  |  |  |  |
| Immediate memory | F (1, 321) = 1.66, p = 0.199 | LS | 89.79 | 17.39 | ---- | 0.15 |
|  |  | HS | 86.78 | 22.88 |  |  |
| Visuospatial/constructional | F (1, 321) = 1.03, p = 0.311 | LS | 89.96 | 16.40 | ---- | -0.12 |
|  |  | HS | 92.20 | 21.57 |  |  |
|  |  |  |  |  |  |  |
| Language  | F (1, 321) = 0.23, p = 0.629 | LS | 99.80 | 11.96 | ---- | -0.06 |
|  |  | HS | 100.57 | 15.73 |  |  |
| Attention  | **F (1, 321) = 7.46, p = 0.007**\* | LS | 94.71 | 17.73 | HS < LS | 0.31 |
|  |  | HS | 88.2 | 23.32 |  |  |
| Delayed memory  | F (1, 321) = 0.07, p = 0.787 | LS | 89.64 | 14.46 | ---- | -0.03 |
|  |  | HS | 90.16 | 19.02 |  |  |
| Total score  | F (1, 321) = 0.59, p = 0.443 | LS | 90.48 | 13.56 | ---- | 0.09 |
|  |  | HS | 89.08 | 17.83 |  |  |
| *Smoking\*diagnosis interaction effect* |  |  |  |  |  |  |
| Immediate memory | **F (1, 321) = 5.73, p = 0.017** | SSD LS | 78.15 | 16.81 | ---- | N/A |
|  |  | SSD HS | 80.72 | 16.66 |  |  |
|  |  | HC LS | 101.43 | 17.31 |  |  |
|  |  | HC HS | 92.85 | 17.29 |  |  |
| Visuospatial/constructional | F (1, 321) = 0.37, p = 0.545 | SSD LS | 85.60 | 15.85 | ---- | N/A |
|  |  | SSD HS | 86.50 | 15.72 |  |  |
|  |  | HC LS | 94.33 | 16.32 |  |  |
|  |  | HC HS | 97.90 | 16.31 |  |  |
| *Supplementary Table 6.* Continued.  |  |  |  |  |  |  |
| **Domain**  | **Comparisonsa** | **Group** | **Mb** | **SD** | **Post-Hocc** | **dd** |
| Language  | F (1, 321) = 1.12, p = 0.290 | SSD LS | 94.08 | 11.55 | ---- | N/A |
|  |  | SSD HS | 93.16 | 11.46 |  |  |
|  |  | HC LS | 105.52 | 11.90 |  |  |
|  |  | HC HS | 107.99 | 11.88 |  |  |
| Attention  | F (1, 321) = 0.46, p = 0.500 | SSD LS | 84.19 | 17.14 | ---- | N/A |
|  |  | SSD HS | 79.29 | 16.99 |  |  |
|  |  | HC LS | 105.22 | 17.65 |  |  |
|  |  | HC HS | 97.11 | 17.63 |  |  |
|  |  |  |  |  |  |  |
| Delayed memory  | F (1, 321) = 0.003, p = 0.955 | SSD LS | 82.46 | 13.97 | ---- | N/A |
|  |  | SSD HS | 82.87 | 13.85 |  |  |
|  |  | HC LS | 96.82 | 14.39 |  |  |
|  |  | HC HS | 97.45 | 14.37 |  |  |
| Total score  | F (1, 321) = 0.42, p = 0.516 | SSD LS | 80.24 | 13.10 | ---- | N/A |
|  |  | SSD HS | 80.01 | 12.99 |  |  |
|  |  | HC LS | 100.72 | 13.50 |  |  |
|  |  | HC HS | 98.14 | 13.48 |  |  |

*Note:* SSD, schizophrenia spectrum disorder; HC, healthy controls; LS, light-smoker; HS, heavy-smoker

aUnadjusted for multiple comparisons

bAll values are adjusted for age, gender, and site.

cIf post-hoc relationship is not reported, finding was not significant prior or after FDR correction. HS < LS implies significant reductions relative to LS.

dd = Cohen’s d effect sizes

\*Significant at p < .05 after Benjamini-Hochberg correction for multiple comparisons

Bold values = significant before Benjamini-Hochberg correction.

*Supplementary Table 7. Group Comparisons of global Volume, Cortical thickness, and Surface area (Light and Heavy smokers only)*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Domain**  | **Comparisonsa** | **Group** | **Mb** | **SD** | **Post-Hocc** | **dd** |
| *Main effect of smoking.*  |  |  |  |  |  |  |
| Volume (ml) | F (1,101) = 0.090, p = 0.764 | LS | 707518.86 | 36390.85 | ---- | -0.06 |
|  |  | HS | 704183.65 | 64986.93 |  |  |
| Cortical Thickness (mm) | F (1,101) = 0.13, p = 0.911 | LS | 2.61 | 0.10 | ---- | 0.02 |
|  |  | HS | 2.62 | 0.18 |  |  |
|  |  |  |  |  |  |  |
| Surface Area (cm3) | F (1,101) = 0.002, p = 0.964 | LS | 2562.48 | 106.30 | ---- | -0.01 |
|  |  | HS | 2561.05 | 187.05 |  |  |
| *Smoking\*diagnosis interaction effect.* |  |  |  |  |  |  |
| Volume (ml) | F (1,101) = 0.11, p = 0.917 | SSD LS | 701893.12 | 32922.56 | ---- | N/A |
|  |  | SSD HS | 697413.59 | 33142.90 |  |  |
|  |  | HC LS | 713144.58 | 32127.05 |  |  |
|  |  | HC HS | 710953.71 | 33412.85 |  |  |
| Cortical Thickness (mm) | F (1,101) = 0.001, p = 0.975 | SSD LS | 2.58 | 0.09 | ---- | N/A |
|  |  | SSD HS | 2.58 | 0.09 |  |  |
|  |  | HC LS | 2.65 | 0.09 |  |  |
|  |  | HC HS | 2.65 | 0.09 |  |  |
| Surface Area (cm3) | F (1,101) = 0.54, p = 0.466 | SSD LS | 2577.47 | 94.76 | ---- | N/A |
|  |  | SSD HS | 2552.99 | 95.40 |  |  |
|  |  | HC LS | 2547.49 | 92.47 |  |  |
|  |  | HC HS | 2569.10 | 96.17 |  |  |

*Note:* Given the focus of this study, main effects of diagnostic group are reported in the supplementary material for brevity; SSD = schizophrenia spectrum disorder; HC= healthy controls; S = smoker; NS = non-smoker

aUnadjusted for multiple comparisons

bAll values are adjusted for age, gender, and site.

cIf post-hoc relationship is not reported, finding was not significant prior or after FDR correction. SSD < HC implies significant reductions relative to HC.

dd = Cohen’s d effect sizes.

\*Significant at p < .05 after Benjamini-Hochberg FDR correction for multiple comparisons

Bold values = significant before Benjamini-Hochberg FDR

*Supplementary Table 8. Group comparisons of Volume, Cortical Thickness, and Surface Area (Light and heavy smokers only)*

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  | **LH** |  |  |  | **RH** |  |  |  |
| **Regions**  | **Comparisonsa** | **Group** | **Mb** | **SD** | **Post-Hocc** | **dd** | **Mb** | **SD** | **Post-Hocc** | **dd** |
| ***Volume (ml)*** *- Main effect of smoking severity* |  |  |  |  |  |  |  |  |  |  |
| ***Subcortical Regions*** |  |  |  |  |  |  |  |  |  |  |
| Thalamus | LH: F (1,101) = 0.20, p = 0.652 | LS | 7881.85 | 650.04 | ---- | 0.09 | 8056.70 | 687.38 | ---- | 0.00 |
|  | RH: F (1,271) = 0.00, p = 0.984 | HS | 7970.10 | 1143.88 |  |  | 8052.58 | 1209.57 |  |  |
| Hippocampus | LH: F (1,101) = 1.14, p = 0.288 | LS | 4235.96 | 401.49 | ---- | 0.22 | 4342.13 | 415.14 | ---- | 0.14 |
|  | RH: F (1, 101) = 0.43, p = 0.514 | HS | 4364.83 | 706.50 |  |  | 4423.81 | 730.52 |  |  |
| Amygdala  | LH: F (1, 101) = 0.24, p = 0.624 | LS | 1605.24 | 171.43 | ---- | -0.10 | 1653.97 | 182.75 | ---- | -0.07 |
|  | RH: F (1, 101) = 0.11, p = 0.738 | HS | 1579.90 | 301.66 |  |  | 1635.54 | 321.58 |  |  |
| ***Cortical Regions***  |  |  |  |  |  |  |  |  |  |  |
| Caudal Anterior Cingulate  | LH: F (1, 101) = 0.01, p = 0.925 | LS | 1967.19 | 517.22 | ---- | -0.08 | 2389.52 | 567.76 | ---- | -0.14 |
|  | RH: F (1, 101) = 0.44, p = 0.508 | HS | 1905.26 | 910.16 |  |  | 2276.23 | 999.08 |  |  |
| Rostral Anterior Cingulate  | LH: F (1, 101) = 0.37, p = 0.546 | LS | 2967.76 | 560.47 | ---- | -0.13 | 2381.74 | 446.87 | ---- | 0.08 |
|  | RH: F (1, 2731 = 0.15, p = 0.698 | HS | 2865.73 | 986.26 |  |  | 2433.91 | 786.36 |  |  |
| Posterior Cingulate  | LH: F (1, 101) = 1.03, p = 0.314 | LS | 3523.58 | 553.15 | ---- | -0.21 | 3512.83 | 570.32 | ---- | -0.34 |
|  | RH: F (1, 101) = 2.70, p = 0.104 | HS | 3355.46 | 973.37 |  |  | 3231.60 | 1003.58 |  |  |
| Pars Opercularis  | LH: F (1, 101) = 1.10, p = 0.297 | LS | 5248.10 | 989.06 | ---- | -0.22 | 4186.45 | 749.62 | ---- | -0.08 |
|  | RH: F (1, 101) = 0.16, p = 0.694 | HS | 4937.05 | 1740.43 |  |  | 4275.14 | 1319.10 |  |  |
|  |  |  |  |  |  |  |  |  |  |  |
| *Supplementary Table 8.* Cont. |  |  |  |  |  |  |  |  |  |  |
|  |  |  | **LH** |  |  |  | **RH** |  |  |  |
| **Regions**  | **Comparisonsa** | **Group** | **Mb** | **SD** | **Post-Hocc** | **dd** | **Mb** | **SD** | **Post-Hocc** | **dd** |
| Pars Orbitalis  | LH: F (1, 101) = 0.57, p = 0.454 | LS | 2355.96 | 331.79 | ---- | -0.16 | 2845.47 | 452.34 | ---- | 0.03 |
|  | RH: F (1, 101) = 0.023, p = 0.879  | HS | 2281.03 | 583.85 |  |  | 2866.11 | 795.99 |  |  |
| Pars Triangularis  | LH: F (1, 101) = 0.039, p = 0.843 | LS | 3824.33 | 676.64 | ---- | -0.04 | 4637.16 | 770.16 | ---- | 0.00 |
|  | RH: F (1, 101) = 0.00, p = 0.999 | HS | 3784.08 | 1190.69 |  |  | 4636.73 | 1355.24 |  |  |
| Rostral Middle Frontal | LH: F (1, 101) = 0.16, p = 0.69 | LS | 17025.82 | 1952.23 | ---- | 0.08 | 17887.60 | 1937.96 | ---- | 0.10 |
|  | RH: F (1, 101) = 0.24, p = 0.625 | HS | 17257.46 | 3435.33 |  |  | 18173.10 | 3410.21 |  |  |
| Lateral Orbitofrontal | LH: F (1, 101) = 0.009, p = 0.925 | LS | 8229.03 | 716.35 | ---- | 0.02 | 8076.32 | 786.80 | ---- | 0.04 |
|  | RH: F (1, 101) = 0.045, p = 0.833 | HS | 8249.42 | 1260.56 |  |  | 8126.30 | 1384.53 |  |  |
| Medial Orbitofrontal | LH: F (1, 101) = 1.92, p = 0.169 | LS | 5893.13 | 680.47 | ---- | -0.29 | 5592.19 | 594.50 | ---- | -0.14 |
|  | RH: F (1, 101) = 0.47, p = 0.493 | HS | 5610.31 | 1197.41 |  |  | 5469.37 | 1046.13 |  |  |
| Superior Temporal  | LH: F (1, 101) = 0.006, p = 0.93 | LS | 12731.60 | 1429.45 | ---- | -0.02 | 12215.76 | 1311.46 | ---- | 0.14 |
|  | RH: F (1, 101) = 0.42, p = 0.519 | HS | 12698.05 | 2515.38 |  |  | 12470.61 | 2307.76 |  |  |
|  |  |  |  |  |  |  |  |  |  |  |
| Insula | LH: F (1, 101) = 1.97, p = 0.163 | LS | 7453.54 | 691.18 | ---- | 0.29 | 7840.84 | 783.89 | ---- | -0.11 |
|  | RH: F (1, 101) = 0.26, p = 0.609 | HS | 7835.13 | 1216.27 |  |  | 7720.11 | 1379.41 |  |  |
| ***Volume (ml) -*** *Smoking severity\*diagnosis interaction effect* |  |  |  |  |  |  |  |  |  |  |
| ***Subcortical Regions*** |  |  |  |  |  |  |  |  |  |  |
| Thalamus | LH: F (1, 101) = 2.61, p = 0.109 | SSD LS | 7671.46 | 579.49 | ---- | N/A | 7873.92 | 612.77 | ---- | N/A |
| *Supplementary Table 8.* Cont.  |  |  |  |  |  |  |  |  |  |  |
|  |  |  | **LH** |  |  |  | **RH** |  |  |  |
| **Regions**  | **Comparisonsa** | **Group** | **Mb** | **SD** | **Post-Hocc** | **dd** | **Mb** | **SD** | **Post-Hocc** | **dd** |
| Thalamus cont. | RH: F (1, 101) = 3.21, p = 0.076 | SSD HS | 8070.95 | 583.37 |  |  | 8234.96 | 616.87 |  |  |
|  |  | HC LS | 8092.23 | 565.49 |  |  | 8239.46 | 597.97 |  |  |
|  |  | HC HS | 7869.24 | 588.12 |  |  | 7870.20 | 621.90 |  |  |
| Hippocampus | LH: F (1, 101) = 0.74, p = 0.392 | SSD LS | 4159.97 | 357.92 | ---- | N/A | 4270.85 | 370.09 | ---- | N/A |
|  | RH: F (1, 101) = 0.52, p = 0.472 | SSD HS | 4186.54 | 360.31 |  |  | 4263.80 | 372.56 |  |  |
|  |  | HC LS | 4311.95 | 349.27 |  |  | 4413.42 | 361.14 |  |  |
|  |  | HC HS | 4543.12 | 363.25 |  |  | 4583.82 | 375.60 |  |  |
| Amygdala  | LH: F (1, 101) = 0.031, p = 0.861 | SSD LS | 1572.53 | 152.82 | ---- | N/A | 1644.15 | 162.91 | ---- | N/A |
|  | RH: F (1, 101) = 0.12, p = 0.734 | SSD HS | 1538.27 | 153.85 |  |  | 1607.27 | 164.00 |  |  |
|  |  | HC LS | 1637.95 | 149.13 |  |  | 1663.78 | 150.98 |  |  |
|  |  | HC HS | 1621.54 | 155.10 |  |  | 1663.81 | 165.34 |  |  |
| ***Cortical Regions***  |  |  |  |  |  |  |  |  |  |  |
| Caudal Anterior Cingulate  | LH: F (1, 101) = 0.13, p = 0.723 | SSD LS | 2042.59 | 461.09 | ---- | N/A | 2289.26 | 506.14 | ---- | N/A |
|  | RH: F (1, 101) = 1.002, p = 0.319 | SSD HS | 1926.21 | 464.17 |  |  | 2344.39 | 509.53 |  |  |
|  |  | HC LS | 1891.79 | 449.95 |  |  | 2489.78 | 493.91 |  |  |
|  |  | HC HS | 1884.31 | 467.95 |  |  | 2208.08 | 513.68 |  |  |
| Rostral Anterior Cingulate  | LH: F (1, 101) = 0.06, p = 0.798 | SSD LS | 2981.16 | 499.64 | ---- | N/A | 2364.06 | 398.37 | ---- | N/A |
|  | RH: F (1, 101) = 0.34, p = 0.559 | SSD HS | 2921.80 | 502.99 |  |  | 2493.94 | 401.04 |  |  |
|  |  | HC LS | 2954.36 | 487.57 |  |  | 2399.43 | 388.75 |  |  |
|  |  | HC HS | 2809.66 | 507.08 |  |  | 2773.87 | 404.31 |  |  |
| Posterior Cingulate  | LH: F (1, 101) = 0.11, p = 0.741 | SSD LS | 3548.97 | 493.11 | ---- | N/A | 3505.62 | 508.42 | ---- | N/A |
|  | RH: F (1, 101) = 1.24, p = 0.269 | SSD HS | 3435.15 | 496.41 |  |  | 3412.24 | 511.82 |  |  |
|  |  | HC LS | 3498.19 | 481.19 |  |  | 3520.04 | 496.13 |  |  |
|  |  | HC HS | 3275.76 | 506.45 |  |  | 3050.95 | 515.99 |  |  |
| *Supplementary Table 8.* Cont.  |  |  |  |  |  |  |  |  |  |  |
|  |  |  | **LH** |  |  |  | **RH** |  |  |  |
| **Regions**  | **Comparisonsa** | **Group** | **Mb** | **SD** | **Post-Hocc** | **dd** | **Mb** | **SD** | **Post-Hocc** | **dd** |
|  |  |  |  |  |  |  |  |  |  |  |
| Pars Opercularis  | LH: F (1, 101) = 0.10, p = 0.756 | SSD LS | 5287.79 | 881.71 | ---- | N/A | 4134.41 | 668.26 | ---- | N/A |
|  | RH: F (1, 101) = 0.41, p = 0.526 | SSD HS | 5067.90 | 887.61 |  |  | 4364.53 | 672.73 |  |  |
|  |  | HC LS | 5208.41 | 860.40 |  |  | 4238.48 | 652.11 |  |  |
|  |  | HC HS | 4806.21 | 894.84 |  |  | 4185.75 | 678.21 |  |  |
| Pars Orbitalis  | LH: F (1, 101) = 0.49, p = 0.487 | SSD LS | 2301.63 | 295.78 | ---- | N/A | 2839.18 | 403.25 | ---- | N/A |
|  | RH: F (1, 101) = 0.56, p = 0.457 | SSD HS | 2295.25 | 297.76 |  |  | 2759.65 | 405.95 |  |  |
|  |  | HC LS | 2410.28 | 288.63 |  |  | 2851.76 | 393.51 |  |  |
|  |  | HC HS | 2266.81 | 300.18 |  |  | 2972.57 | 409.25 |  |  |
| Pars Triangularis  | LH: F (1, 101) < 0.001, p = 0.997 | SSD LS | 3821.64 | 603.21 | ---- | N/A | 4560.80 | 686.57 | ---- | N/A |
|  | RH: F (1, 101) = 0.89, p = 0.347 | SSD HS | 3782.20 | 607.24 |  |  | 4344.85 | 691.16 |  |  |
|   |  | HC LS | 3827.02 | 588.63 |  |  | 4713.51 | 669.98 |  |  |
|  |  | HC HS | 3785.87 | 612.19 |  |  | 4928.61 | 696.79 |  |  |
| Rostral Middle Frontal  | LH: F (1, 101) = 0.04, p = 0.841 | SSD LS | 16989.36 | 1740.35 | ---- | N/A | 17747.94 | 1727.62 | ---- | N/A |
|  | RH: F (1, 101) = 0.75, p = 0.389 | SSD HS | 17104.71 | 1752.00 |  |  | 17537.06 | 1739.18 |  |  |
|  |  | HC LS | 17062.28 | 1698.30 |  |  | 18027.25 | 1685.88 |  |  |
|  |  | HC HS | 17410.22 | 1766.27 |  |  | 18809.14 | 1753.35 |  |  |
| Lateral Orbitofrontal | LH: F (1, 101) = 0.06, p = 0.815 | SSD LS | 8107.26 | 638.60 | ---- | N/A | 7926.83 | 701.41 | ---- | N/A |
|  | RH: F (1, 101) < 0.001, p = 991 | SSD HS | 8077.77 | 642.88 |  |  | 7979.37 | 706.10 |  |  |
|  |  | HC LS | 8350.81 | 623.17 |  |  | 8225.81 | 684.46 |  |  |
|  |  | HC HS | 8421.06 | 648.11 |  |  | 8273.23 | 711.85 |  |  |
| Medial Orbitofrontal  | LH: F (1, 101) = 2.62, p = 0.108 | SSD LS | 5806.57 | 606.61 | ---- | N/A | 5507.85 | 529.97 | ---- | N/A |
|  | RH: F (1, 101) = 0.62, p = 0.963 | SSD HS | 5850.39 | 610.67 |  |  | 5523.56 | 533.52 |  |  |
|  |  | HC LS | 5979.69 | 591.95 |  |  | 5676.54 | 517.17 |  |  |
|  |  | HC HS | 5370.24 | 615.65 |  |  | 5415.17 | 537.86 |  |  |
|  |  |  |  |  |  |  |  |  |  |  |
| *Supplementary Table 8.* Cont.  |  |  |  |  |  |  |  |  |  |  |
|  |  |  | **LH** |  |  |  | **RH** |  |  |  |
| **Regions**  | **Comparisonsa** | **Group** | **Mb** | **SD** | **Post-Hocc** | **dd** | **Mb** | **SD** | **Post-Hocc** | **dd** |
| Superior Temporal  | LH: F (1, 101) = 0.06, p = 0.811 | SSD LS | 12574.79 | 1274.30 | ---- | N/A | 12172.58 | 1169.12 | ---- | N/A |
|  | RH: F (1, 101) = 0.47, p = 0.496 | SSD HS | 12439.68 | 1282.83 |  |  | 12161.79 | 1176.94 |  |  |
|  |  | HC LS | 12888.41 | 1243.51 |  |  | 12258.93 | 1140.87 |  |  |
|  |  | HC HS | 12956.43 | 1293.28 |  |  | 12779.43 | 1186.53 |  |  |
| Insula | LH: F (1, 101) = 0.67, p = 0.415 | SSD LS | 7481.47 | 616.17 | ---- | N/A | 7709.38 | 698.81 | ---- | N/A |
|  | RH: F (1, 101) = 1.22, p = 0.271 | SSD HS | 7605.35 | 620.29 |  |  | 7845.62 | 703.49 |  |  |
|  |  | HC LS | 7605.62 | 601.28 |  |  | 7972.29 | 681.93 |  |  |
|  |  | HC HS | 8064.90 | 625.34 |  |  | 7594.60 | 709.22 |  |  |
| ***Thickness (mm) -*** *Main effect of smoking severity* |  |  |  |  |  |  |  |  |  |  |
| Caudal Anterior Cingulate  | LH: F (1, 102) = 0.37, p = 0.547 | LS | 2.67 | 0.27 | ---- | -0.13 | 2.62 | 0.25 | ---- | -0.11 |
|  | RH: F (1, 102) = 0.27, p = 0.608 | HS | 2.62 | 0.47 |  |  | 2.66 | 0.45 |  |  |
| Rostral Anterior Cingulate | LH: F (1, 102) = 0.13, p = 0.718 | LS | 2.94 | 0.24 | ---- | -0.07 | 3.01 | 0.24 | ---- | -0.04 |
|  | RH: F (1, 102) = 0.03, p = 0.856 | HS | 2.91 | 0.43 |  |  | 2.99 | 0.43 |  |  |
| Posterior Cingulate  | LH: F (1, 102) = 3.37, p = 0.069 | LS | 2.59 | 0.18 | ---- | -0.39 | 2.52 | 0.19 | ---- | 0.06 |
|  | RH: F (1, 102) = 0.08, p = 0.781 | HS | 2.50 | 0.31 |  |  | 2.54 | 0.33 |  |  |
| Superior Temporal Gyrus  | LH: F (1, 102) = 0.37 p = 0.543 | LS | 2.80 | 0.18 | ---- | -0.13 | 2.83 | 0.15 | ---- | -0.08 |
|  | RH: F (1, 102) = 0.15, p = 0.704 | HS | 2.77 | 0.32 |  |  | 2.82 | 0.27 |  |  |
| Rostral Middle Frontal  | LH: F (1, 102) = 0.003, p = 0.959 | LS | 2.50 | 0.14 | ---- | -0.01 | 2.52 | 0.14 | ---- | 0.10 |
| *Supplementary Table 8.* Cont.  |  |  |  |  |  |  |  |  |  |  |
|  |  |  | **LH** |  |  |  | **RH** |  |  |  |
| **Regions**  | **Comparisonsa** | **Group** | **Mb** | **SD** | **Post-Hocc** | **dd** | **Mb** | **SD** | **Post-Hocc** | **dd** |
| Rostral Middle Frontal cont. | RH: F (1, 102) = 0.21, p = 0.647 | HS | 2.50 | 0.24 |  |  | 2.54 | 0.24 |  |  |
| Lateral Orbitofrontal | LH: F (1, 102) = 1.96, p = 0.164 | LS | 2.72 | 0.18 | ---- | -0.29 | 2.70 | 0.17 | ---- | -0.15 |
|  | RH: F (1, 102) = 0.52, p = 0.471 | HS | 2.64 | 0.32 |  |  | 2.67 | 0.30 |  |  |
| Medial Orbitofrontal  | LH: F (1, 102) = 1.92, p = 0.164 | LS | 2.62 | 0.18 | ---- | -0.29 | 2.56 | 0.17 | ---- | -0.03 |
|  | RH: F (1, 102) = 0.03, p = 0.873 | HS | 2.54 | 0.32 |  |  | 2.55 | 0.31 |  |  |
| Pars Orbitalis  | LH: F (1, 102) = 0.06, p = 0.801 | LS | 2.77 | 0.23 | ---- | 0.05 | 2.84 | 0.22 | ---- | -0.26 |
|  | RH: F (1, 102) = 1.47, p = 0.228 | HS | 2.79 | 0.41 |  |  | 2.76 | 0.39 |  |  |
| Pars Opercularis  | LH: F (1, 102) = 0.11, p = 0.740 | LS | 2.61 | 0.16 | ---- | -0.07 | 2.64 | 0.17 | ---- | -0.15 |
|  | RH: F (1, 102) = 0.50, p = 0.481 | HS | 2.60 | 0.28 |  |  | 2.60 | 0.29 |  |  |
| Pars Triangularis  | LH: F (1, 102) = 0.18, p = 0.675 | LS | 2.56 | 0.17 | ---- | 0.09 | 2.58 | 0.16 | ---- | 0.12 |
|  | RH: F (1, 102) = 0.31, p = 0.581 | HS | 2.58 | 0.30 |  |  | 2.60 | 0.29 |  |  |
| Insula | LH: F (1, 102) = 0.04, p = 0.843 | LS | 3.08 | 0.19 | ---- | -0.04 | 3.02 | 0.20 | ---- | 0.21 |
|  | RH: F (1, 102) = 0.95, p = 0.333 | HS | 3.07 | 0.34 |  |  | 3.08 | 0.35 |  |  |
| ***Thickness (mm) -*** *Smoking severity\*diagnosis interaction effect.*  |  |  |  |  |  |  |  |  |  |  |
| Caudal Anterior Cingulate  | LH: F (1, 102) = 0.24, p = 0.622 | SSD LS | 2.68 | 6.24 | ---- | N/A | 2.57 | 0.23 | ---- | N/A |
|  | RH: F (1, 102) = 0.40, p = 0.528 | SSD HS | 2.59 | 0.24 |  |  | 2.56 | 0.23 |  |  |
|  |  | HC LS | 2.66 | 0.23 |  |  | 2.68 | 0.22 |  |  |
| *Supplementary Table 8.* Cont.  |  |  |  |  |  |  |  |  |  |  |
|  |  |  | **LH** |  |  |  | **RH** |  |  |  |
| **Regions**  | **Comparisonsa** | **Group** | **Mb** | **SD** | **Post-Hocc** | **dd** | **Mb** | **SD** | **Post-Hocc** | **dd** |
| Caudal ACC cont.  |  | HC HS | 2.65 | 0.24 |  |  | 2.76 | 0.23 |  |  |
| Rostral Anterior Cingulate | LH: F (1, 102) = 0.68, p = 0.413 | SSD LS | 2.93 | 0.22 | ---- | N/A | 2.98 | 0.22 | ---- | N/A |
|  | RH: F (1, 102) = 0.04, p = 0.846 | SSD HS | 2.85 | 0.22 |  |  | 2.95 | 0.22 |  |  |
|  |  | HC LS | 2.94 | 0.21 |  |  | 3.03 | 0.21 |  |  |
|  |  | HC HS | 2.98 | 0.22 |  |  | 3.03 | 0.22 |  |  |
| Posterior Cingulate  | LH: F (1, 102) = 2.33, p = 0.130 | SSD LS | 2.56 | 0.16 | ---- | N/A | 2.52 | 0.17 | ---- | N/A |
|  | RH: F (1, 102) = 0.001, p = 0.897 | SSD HS | 2.54 | 0.16 |  |  | 2.54 | 0.17 |  |  |
|  |  | HC LS | 2.63 | 0.15 |  |  | 2.52 | 0.16 |  |  |
|  |  | HC HS | 2.45 | 0.16 |  |  | 2.54 | 0.17 |  |  |
| Superior Temporal Gyrus | LH: F (1, 102) = 0.08, p = 0.775 | SSD LS | 2.75 | 0.16 | ---- | N/A | 2.77 | 0.14 | ---- | N/A |
|  | RH: F (1, 102) = 1.64, p = 0.203 | SSD HS | 2.73 | 0.16 |  |  | 2.80 | 0.14 |  |  |
|  |  | HC LS | 2.85 | 0.16 |  |  | 2.90 | 0.13 |  |  |
|  |  | HC HS | 2.80 | 0.16 |  |  | 2.83 | 0.14 |  |  |
| Rostral Middle Frontal  | LH: F (1, 102) = 1.29, p = 0.259 | SSD LS | 2.46 | 0.12 | ---- | N/A | 2.48 | 0.12 | ---- | N/A |
|  | RH: F (1, 102) = 0.24, p = 0.628 | SSD HS | 2.51 | 0.12 |  |  | 2.52 | 0.12 |  |  |
|  |  | HC LS | 2.54 | 0.12 |  |  | 2.57 | 0.12 |  |  |
|  |  | HC HS | 2.50 | 0.12 |  |  | 2.57 | 0.12 |  |  |
| Lateral Orbitofrontal | LH: F (1, 102) = 0.11, p = 0.735 | SSD LS | 2.64 | 0.16 | ---- | N/A | 2.64 | 0.15 | ---- | N/A |
|  | RH: F (1, 102) = 1.60, p = 0.209 | SSD HS | 2.63 | 0.16 |  |  | 2.63 | 0.15 |  |  |
|  |  | HC LS | 2.79 | 0.16 |  |  | 2.77 | 0.15 |  |  |
|  |  | HC HS | 2.65 | 0.16 |  |  | 2.70 | 0.15 |  |  |
| Medial Orbitofrontal  | LH: F (1, 102) = 1.10, p = 0.296 | SSD LS | 2.58 | 0.16 | ---- | N/A | 2.47 | 0.15 | ---- | N/A |
|  | RH: F (1, 102) = 1.55, p = 0.216 | SSD HS | 2.56 | 0.16 |  |  | 2.54 | 0.16 |  |  |
|  |  | HC LS | 2.66 | 0.16 |  |  | 2.64 | 0.15 |  |  |
|  |  | HC HS | 2.53 | 0.17 |  |  | 2.57 | 0.16 |  |  |
|  |  |  |  |  |  |  |  |  |  |  |
| *Supplementary Table 8.* Cont.  |  |  |  |  |  |  |  |  |  |  |
|  |  |  | **LH** |  |  |  | **RH** |  |  |  |
| **Regions**  | **Comparisonsa** | **Group** | **Mb** | **SD** | **Post-Hocc** | **dd** | **Mb** | **SD** | **Post-Hocc** | **dd** |
| Pars Orbitalis  | LH: F (1, 102) = 0.23, p = 0.636 | SSD LS | 2.72 | 0.21 | ---- | N/A | 2.80 | 0.20 | ---- | N/A |
|  | RH: F (1, 102) = 1.08, p = 0.897 | SSD HS | 2.77 | 0.21 |  |  | 2.78 | 0.20 |  |  |
|   |  | HC LS | 2.82 | 0.20 |  |  | 2.89 | 0.19 |  |  |
|  |  | HC HS | 2.80 | 0.21 |  |  | 2.75 | 0.20 |  |  |
| Pars Opercularis | LH: F (1, 102) = 0.71, p = 0.400 | SSD LS | 2.57 | 0.14 | ---- | N/A | 2.58 | 0.15 | ---- | N/A |
|  | RH: F (1, 102) = 2.13, p = 0.148 | SSD HS | 2.59 | 0.15 |  |  | 2.62 | 0.15 |  |  |
|  |  | HC LS | 2.64 | 0.14 |  |  | 2.70 | 0.15 |  |  |
|  |  | HC HS | 2.59 | 0.15 |  |  | 2.59 | 0.15 |  |  |
| Pars Triangularis  | LH: F (1,273) = 0.09, p = 0.768 | SSD LS | 2.50 | 0.15 | ---- | N/A | 2.53 | 0.15 | ---- | N/A |
|  | RH: F (1,273) = 0.02, p = 0.897 | SSD HS | 2.53 | 0.15 |  |  | 2.56 | 0.15 |  |  |
|  |  | HC LS | 2.63 | 0.15 |  |  | 2.62 | 0.14 |  |  |
|  |  | HC HS | 2.64 | 0.16 |  |  | 2.65 | 0.15 |  |  |
| Insula  | LH: F (1, 102) = 0.10, p = 0.750 | SSD LS | 3.03 | 0.17 | ---- | N/A | 2.99 | 0.18 | ---- | N/A |
|  | RH: F (1, 102) = 0.63, p = 0.429 | SSD HS | 3.04 | 0.17 |  |  | 3.00 | 0.18 |  |  |
|  |  | HC LS | 3.14 | 0.17 |  |  | 3.05 | 0.17 |  |  |
|  |  | HC HS | 3.11 | 0.17 |  |  | 3.16 | 0.18 |  |  |
|  |  |  |  |  |  |  |  |  |  |  |
| ***Surface Area (cm3) -*** *Main effect of smoking severity.* |  |  |  |  |  |  |  |  |  |  |
| Caudal Anterior Cingulate  | LH: F (1, 102) = 0.78, p = 0.381 | LS | 692.82 | 166.83 | ---- | -0.18 | 822.25 | 170.41 | ---- | 0.18 |
|  | RH: F (1, 102) = 0.74, p = 0.390 | HS | 648.84 | 292.59 |  |  | 778..25 | 298.87 |  |  |
| Rostral Anterior Cingulate | LH: F (1, 102) = 0.24, p = 0.628 | LS | 886.10 | 181.41 | ---- | -0.10 | 714.39 | 142.30 | ---- | -0.03 |
| *Supplementary Table 8.* Cont.  |  |  |  |  |  |  |  |  |  |  |
|  |  |  | **LH** |  |  |  | **RH** |  |  |  |
| **Regions**  | **Comparisonsa** | **Group** | **Mb** | **SD** | **Post-Hocc** | **dd** | **Mb** | **SD** | **Post-Hocc** | **dd** |
| Rostral ACC cont.  | RH: F (1, 102) = 0.02, p = 0.892 | HS | 859.71 | 318.16 |  |  | 708.29 | 261.85 |  |  |
| Posterior Cingulate  | LH: F (1, 102) = 0.84, p = 0.361 | LS | 1243.00 | 196.18 | ---- | -0.19 | 1266.37 | 214.31 | ---- | -0.44 |
|  | **RH: F (1, 102) = 4.41, p = 0.03** | HS | 1189.13 | 344.08 |  |  | 1131.60 | 375.88 |  |  |
| Superior Temporal Gyrus  | LH: F (1, 102) = 0.08, p = 0.773 | LS | 3972.69 | 434.52 | ---- | -0.06 | 3773.19 | 407.33 | ---- | 0.01 |
|  | RH: F (1, 102) = 0.003, p = 0.955 | HS | 3935.13 | 762.09 |  |  | 3780.04 | 714.40 |  |  |
| Rostral Middle Frontal  | LH: F (1, 102) = 0.03, p = 0.869 | LS | 6008.82 | 824.02 | ---- | -0.03 | 6256.98 | 767.46 | ---- | -0.10 |
|  | RH: F (1, 102) = 0.22, p = 0.637 | HS | 5968.09 | 1445.22 |  |  | 6148.14 | 1346.02 |  |  |
| Lateral Orbitofrontal | LH: F (1, 102) = 0.35, p = 0.555 | LS | 2784.14 | 286.95 | ---- | 0.12 | 2751.87 | 304.39 | ---- | 0.04 |
|  | RH: F (1, 102) = 0.03, p = 0.865 | HS | 2834.99 | 503.26 |  |  | 2767.39 | 533.86 |  |  |
| Medial Orbitofrontal  | LH: F (1, 102) = 1.18, p = 0.279 | LS | 1998.05 | 267.24 | ---- | -0.23 | 1928.91 | 233.33 | ---- | -0.22 |
|  | RH: F (1, 102) = 1.10, p = 0.297 | HS | 1910.97 | 468.71 |  |  | 1855.65 | 409.22 |  |  |
| Pars Orbitalis  | LH: F (1, 102) = 1.23, p = 0.270 | LS | 675.34 | 78.91 | ---- | -0.23 | 811.60 | 125.14 | ---- | 0.08 |
|  | RH: F (1, 102) = 0.13, p = 0.717 | HS | 649.12 | 138.39 |  |  | 825.23 | 219.47 |  |  |
| Pars Opercularis  | LH: F (1, 102) = 1.87, p = 0.174 | LS | 1792.05 | 324.04 | ---- | -0.29 | 1429.94 | 273.36 | ---- | 0.05 |
|  | RH: F (1, 102) = 0.05, p = 0.821 | HS | 1659.28 | 568.33 |  |  | 1448.46 | 479.44 |  |  |
| Pars Triangularis  | LH: F (1, 102) = 0.39, p = 0.537 | LS | 1338.50 | 230.15 | ---- | -0.13 | 1585.03 | 272.75 | ---- | -0.09 |
|  | RH: F (1, 102) = 0.18, p = 0.671 | HS | 1295.77 | 403.64 |  |  | 1550.23 | 478.37 |  |  |
| Insula  | LH: F (1, 102) = 0.02, p = 0.881 | LS | 2404.79 | 270.80 | ---- | 0.03 | 2510.64 | 332.22 | ---- | -0.24 |
|  | RH: F (1, 102) = 1.35, p = 0.247 | HS | 2417.01 | 474.94 |  |  | 2394.91 | 582.67 |  |  |
|  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |
| *Supplementary Table 8.* Cont.  |  |  |  |  |  |  |  |  |  |  |
|  |  |  | **LH** |  |  |  | **RH** |  |  |  |
| **Regions**  | **Comparisonsa** | **Group** | **Mb** | **SD** | **Post-Hocc** | **dd** | **Mb** | **SD** | **Post-Hocc** | **dd** |
| ***Surface Area -*** *Smoking severity\*diagnosis interaction effect.* |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |
| Caudal Anterior Cingulate  | LH: F (1, 102) = 0.30, p = 0.584 | SSD LS | 707.40 | 148.27 | ---- | N/A | 803.78 | 151.45 | ---- | N/A |
|  | RH: F (1, 102) = 2.72, p = 0.103 | SSD HS | 690.24 | 149.19 |  |  | 842.03 | 152.39 |  |  |
|  |  | HC LS | 678.25 | 144.92 |  |  | 840.73 | 148.03 |  |  |
|  |  | HC HS | 607.44 | 150.06 |  |  | 714.48 | 153.28 |  |  |
| Rostral Anterior Cingulate | LH: F (1, 102) = 0.58, p = 0.449 | SSD LS | 881.71 | 161.23 | ---- | N/A | 713.71 | 132.70 | ---- | N/A |
|  | RH: F (1, 102) = 1.62, p = 0.206 | SSD HS | 916.83 | 162.23 |  |  | 763.22 | 133.52 |  |  |
|  |  | HC LS | 890.50 | 157.59 |  |  | 715.07 | 129.69 |  |  |
|  |  | HC HS | 802.59 | 163.17 |  |  | 653.35 | 134.29 |  |  |
| Posterior Cingulate  | LH: F (1, 102) = 0.43, p = 0.513 | SSD LS | 1260.70 | 174.37 | ---- | N/A | 1260.63 | 190.48 | ---- | N/A |
|  | RH: F (1, 102) = 2.71, p = 0.103 | SSD HS | 1244.59 | 175.44 |  |  | 1229.30 | 191.66 |  |  |
|  |  | HC LS | 1225.30 | 170.42 |  |  | 1272.10 | 186.17 |  |  |
|  |  | HC HS | 1133.67 | 176.46 |  |  | 1033.90 | 192.77 |  |  |
| Superior Temporal Gyrus | LH: F (1, 102) = 0.42, p = 0.520 | SSD LS | 3952.32 | 386.20 | ---- | N/A | 3818.59 | 362.03 | ---- | N/A |
|  | RH: F (1, 102) = 0.02, p = 0.887 | SSD HS | 3996.85 | 388.59 |  |  | 3803.41 | 364.28 |  |  |
|  |  | HC LS | 3993.06 | 377.46 |  |  | 3732.78 | 353.84 |  |  |
|  |  | HC HS | 3873.42 | 390.85 |  |  | 3756.68 | 366.39 |  |  |
| Rostral Middle Frontal  | LH: F (1, 102) = 0.26, p = 0.612 | SSD LS | 6007.61 | 732.29 | ---- | N/A | 6244.78 | 682.12 | ---- | N/A |
|  | RH: F (1, 102) = 0.16, p = 0.688 | SSD HS | 6089.78 | 736.92 |  |  | 6226.40 | 686.34 |  |  |
|  |  | HC LS | 6010.03 | 715.81 |  |  | 6269.17 | 666.68 |  |  |
|  |  | HC HS | 5846.40 | 741.19 |  |  | 6069.89 | 690.32 |  |  |
| Lateral Orbitofrontal | LH: F (1, 102) = 0.002, p = 0.962 | SSD LS | 2791.82 | 255.04 | ---- | N/A | 2734.68 | 270.54 | ---- | N/A |
| *Supplementary Table 8.* Cont.  |  |  |  |  |  |  |  |  |  |  |
|  |  |  | **LH** |  |  |  | **RH** |  |  |  |
| **Regions**  | **Comparisonsa** | **Group** | **Mb** | **SD** | **Post-Hocc** | **dd** | **Mb** | **SD** | **Post-Hocc** | **dd** |
| Lateral OFC cont.  | RH: F (1, 102) = 0.50, p = 0.483 | SSD HS | 2846.68 | 256.61 |  |  | 2812.99 | 272.21 |  |  |
|  |  | HC LS | 2776.46 | 249.27 |  |  | 2769.05 | 264.42 |  |  |
|  |  | HC HS | 2823.31 | 258.10 |  |  | 2721.80 | 273.79 |  |  |
| Medial Orbitofrontal  | LH: F (1, 102) = 3.81, p = 0.054 | SSD LS | 1991.19 | 237.52 | ---- | N/A | 1937.51 | 207.38 | ---- | N/A |
|  | RH: F (1, 102) = 1.41, p = 0.483 | SSD HS | 2056.83 | 239.00 |  |  | 1945.33 | 208.66 |  |  |
|  |  | HC LS | 2004.90 | 232.15 |  |  | 1920.32 | 202.69 |  |  |
|  |  | HC HS | 1765.10 | 240.38 |  |  | 1765.96 | 209.87 |  |  |
| Pars Orbitalis  | LH: F (1, 102) = 1.82, p = 0.181 | SSD LS | 664.74 | 70.13 | ---- | N/A | 819.08 | 111.22 | ---- | N/A |
|  | RH: F (1, 102) = 0.19, p = 0.662 | SSD HS | 669.69 | 70.56 |  |  | 816.62 | 111.91 |  |  |
|  |  | HC LS | 685.93 | 68.54 |  |  | 804.11 | 108.70 |  |  |
|  |  | HC HS | 628.92 | 70.97 |  |  | 833.84 | 112.56 |  |  |
| Pars Opercularis | LH: F (1, 102) = 0.55, p = 0.459 | SSD LS | 1811.48 | 288.01 | ---- | N/A | 1442.10 | 242.96 | ---- | N/A |
|  | RH: F (1, 102) = 0.48, p = 0.488 | SSD HS | 1749.23 | 289.79 |  |  | 1516.34 | 244.47 |  |  |
|  |  | HC LS | 1772.61 | 281.49 |  |  | 1417.77 | 237.47 |  |  |
|  |  | HC HS | 1569.33 | 291.47 |  |  | 1380.58 | 245.89 |  |  |
| Pars Triangularis  | LH: F (1,273) = 0.27, p = 0.608 | SSD LS | 1358.77 | 204.55 | ---- | N/A | 1573.10 | 242.42 | ---- | N/A |
|  | RH: F (1,273) = 0.07, p = 0.795 | SSD HS | 1350.76 | 205.82 |  |  | 1517.50 | 243.92 |  |  |
|  |  | HC LS | 1318.23 | 199.92 |  |  | 1596.95 | 236.94 |  |  |
|  |  | HC HS | 1240.78 | 207.01 |  |  | 1582.95 | 245.34 |  |  |
| Insula | LH: F (1, 102) = 0.45, p = 0.520 | SSD LS | 2404.98 | 240.68 | ---- | N/A | 2485.62 | 295.28 | ---- | N/A |
|  | RH: F (1, 102) = 4.41, p = 0.038 | SSD ND | 2470.09 | 242.17 |  |  | 2574.40 | 297.11 |  |  |
|  |  | HC LS | 2404.61 | 235.24 |  |  | 2535.66 | 288.60 |  |  |
|  |  | HC HS | 2363.92 | 243.58 |  |  | 2215.43 | 298.83 |  |  |

*Note:* SSD, schizophrenia spectrum disorder; HC, healthy controls; LS, light-smoker; HS, heavy-smoker; LH, left hemisphere; RH, right hemisphere.

aUnadjusted for multiple comparisons

bAll values are adjusted for age, gender, ICV, and site.

cIf post-hoc relationship is not reported, finding was not significant prior or after FDR correction. SSD < HC implies significant reductions relative to HC.

dd = Cohen’s d effect sizes

\*Significant at p < .05 after Benjamini-Hochberg correction for multiple comparisons

Bold values = significant before Benjamini-Hochberg correction.

**References**

Allen, P., & Bennet, K. (2007). *SPSS for the health and behavioural sciences*. Cengage Learning Australia.

Andreasen, N. C. (1989). Scale for the Assessment of Negative Symptoms (SANS). *British Journal of Psychiatry*.

Castle, D., Jablensky, A., Vaughan, C. J., Morgan, V. A., Waterreus, A., Valuri, G., … Farmer, A. (2006). The diagnostic interview for psychoses (DIP): development, reliability and applications. *Cambridge Univerity Press*, *36*(1), 69–80. https://doi.org/https://doi.org/10.1017/S0033291705005969

Dale, A. M., Fischl, B., & Sereno, M. I. (1999). Cortical surface-based analysis. *NeuroImage*, *9*, 179–194. https://doi.org/10.1006/nimg.1998.0396

Desikan, R. S., Ségonne, F., Fischl, B., Quinn, B. T., Dickerson, B. C., Blacker, D., … 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. https://doi.org/10.1016/j.neuroimage.2006.01.021

Fischl, B., Salat, D. H., Busa, E., Albert, M., Dieterich, M., Haselgrove, C., … Dale, A. M. (2002). Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron*, *33*(3), 341–355.

Fischl, B., Van Der Kouwe, A., Destrieux, C., Halgren, E., Ségonne, F., Salat, D. H., … Dale, A. M. (2004). Automatically parcellating the human cerebral cortex. *Cerebral Cortex*, *14*(1), 11–22. https://doi.org/10.1093/cercor/bhg087

Glass P. D.; Sanders, J. R., G. V. . P. (1972). Consequences of failure to meet assumptions underlying the fixed effects analyses of variance and covariance. *Review of Educational Research*.

Green, M. J., Chia, T. Y., Cairns, M. J., Wu, J., Tooney, P. A., Scott, R. J., & Carr, V. J. (2014). Catechol-O-methyltransferase (COMT) genotype moderates the effects of childhood trauma on cognition and symptoms in schizophrenia. *Journal of Psychiatric Research*, *49*, 43–50. https://doi.org/10.1016/j.jpsychires.2013.10.018

Kikinis, Z., Fallon, J. H., Niznikiewicz, M., Nestor, P., Davidson, C., Bobrow, L., … Shenton, M. E. (2010). Gray matter volume reduction in rostral middle frontal gyrus in patients with chronic schizophrenia. *Schizophrenia Research*, *123*, 153–159. https://doi.org/10.1016/j.schres.2010.07.027

Loughland, C., Draganic, D., McCabe, K., Richards, J., Nasir, A., Allen, J., … Carr, V. J. (2010). Australian Schizophrenia Research Bank: A database of comprehensive clinical, endophenotypic and genetic data for aetiological studies of schizophrenia. *Australian and New Zealand Journal of Psychiatry*, *44*(11), 1029–1035.

Mardia, K. V. (1971). The effect of nonnormality on some multivariate tests and robustness to nonnormality in the linear model. *Biometrika*. https://doi.org/10.1093/biomet/58.1.105

Tabachnick, B. ., & Fidell, L. . (2014). *Using multivariate statistics* (6th ed.). Harlow, England.: Pearson.