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

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Original Article

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Abstract

Background. Cigarette smoking is associated with worse cognition and decreased cortical volume and thickness in healthy cohorts. Chronic cigarette smoking is prevalent in schizophrenia spectrum disorders (SSD), but the effects of smoking status on the brain and cognition in SSD are not clear. This study aimed to understand whether cognitive performance and brain morphology differed between smoking and non-smoking individuals with SSD compared to healthy controls.

Methods. Data were obtained from the Australian Schizophrenia Research Bank. Cognitive functioning was measured in 299 controls and 455 SSD patients. Cortical volume, thickness and surface area data were analysed from T1-weighted structural scans obtained in a subset of the sample ($n = 82$ controls, $n = 201$ SSD). Associations between smoking status (cigarette smoker/non-smoker), cognition and brain morphology were tested using analyses of covariance, including diagnosis as a moderator.

Results. No smoking by diagnosis interactions were evident, and no significant differences were revealed between smokers and non-smokers across any of the variables measured, with the exception of a significantly thinner left posterior cingulate in smokers compared to non-smokers. Several main effects of smoking in the cognitive, volume and thickness analyses were initially significant but did not survive false discovery rate (FDR) correction.

Conclusions. Despite the general absence of significant FDR-corrected findings, trend-level effects suggest the possibility that subtle smoking-related effects exist but were not uncovered due to low statistical power. An investigation of this topic is encouraged to confirm and expand on our findings.

Introduction

Cognitive dysfunction is a common feature of schizophrenia spectrum disorders (SSD) (Carruthers, Van Rheenen, Gurvich, Sumner, & Rossell, 2019; Van Rheenen et al., 2017) and a key predictor of functional outcomes (Bowie, Reichenberg, Patterson, Heaton, & Harvey, 2006). Additionally, widespread brain morphological changes are being increasingly documented in SSD patients (Van Rheenen et al., 2018), and these may partially underpin the cognitive dysfunction seen in the disorder (Antonova et al., 2005; Karantonis et al., n.d.). Cigarette smoking has been consistently associated with these factors in the general population (Durazzo, Meyerhoff, & Nixon, 2010; Elbejjani et al., 2019; Karama et al., 2015), and is highly prevalent in SSD. Indeed, compared to the general population, smoking rates are estimated at around 62% *v.* 25%, respectively (De Leon & Diaz, 2005; Reitsma et al., 2017). Smokers with SSD are also reported to have higher levels of cigarette craving (Lo et al., 2011), reduced rates of cessation (D'Souza & Markou, 2012) and take in more nicotine with each puff (Williams et al., 2010) compared to smokers without SSD.

It is relatively well accepted that *acute* nicotine administration can result in an increase in performance in different areas of cognitive functioning within chronic smokers (Azizian, Monterosso, O'Neill, & London, 2009; Sharma & Brody, 2009). This is believed to be related, in part, to a nicotine-induced increase in activity in several brain regions, such as the

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dorsolateral prefrontal cortex (DLPFC) and thalamus (Azizian et al., 2009; Sharma & Brody, 2009). However, there also appears to be a simultaneous effect of long-term cigarette smoking, which acts through different mechanisms in the same population and results in decreased cognitive performance (Campos, Serebrisky, & Castaldelli-Maia, 2016). Relevantly, cigarette smoking has been shown to impact neurotransmission systems and vascular endothelium, both of which have been implicated in cognitive impairment (Mackowick et al., 2014). Further, research has suggested that the cerebral arteries may be particularly susceptible to atherosclerosis as a result of smoking (Liu et al., 2014), which is argued to contribute to cognitive deficits (Dearborn et al., 2017; Fareed et al., 2018). Indeed, evidence from healthy cohorts suggests that smoking has a significant negative impact on cognition (Durazzo et al., 2010), grey matter volume (Brody et al., 2004; Elbejjani et al., 2019; Gallinat et al., 2006; Liao, Tang, Liu, Chen, & Hao, 2012) and cortical thickness (Karama et al., 2015; Kühn, Schubert, & Gallinat, 2010; Li et al., 2015). Moreover, cigarette smoking has been associated with brain morphology in several clinical samples (Durazzo, Mon, Gazdzinski, & Meyerhoff, 2013; Morales, Hellemann, Lee, London, & O'Neill, 2012; Zorlu et al., 2017). Given the increased prevalence of smoking in SSD, it is thus plausible that cognitive and brain morphological abnormalities could be amplified in smokers with these disorders. Currently however, the effects of smoking on these factors in SSD remain unclear.

That is, while some SSD studies have demonstrated that smokers *outperform* non-smokers across a number of cognitive domains (Ahlers et al., 2014; Hahn et al., 2012; Morisano, Wing, Sacco, Arenovich, & George, 2013; Wing, Sacco, & George, 2011b), others have reported *worse* cognition in SSD smokers (Depp et al., 2015; Iasevoli, Balletta, Gilardi, Giordano, & de Bartolomeis, 2013; Reed, Harris, & Olincy, 2016; Roth, Hong, McMahon, & Fuller, 2013; Stramecki et al., 2018; Zhang et al., 2012). There are also reports of an absence of associations between cognition and smoking status altogether (Ekinci & Ekinci, 2012; Sánchez-Gutiérrez et al., 2018; Zhang et al., 2013). The only two meta-analyses on this topic in SSD showed that smoking *v.* non-smoking patients had worse cognitive performance in some domains but not others (Coustals et al., 2020; Wang et al., 2019). However, in one of these meta-analyses, data from just seven of 11 relevant studies were meta-analysable, and in both, sample sizes across the individual studies were relatively small. Given the inconsistent effects across the individual studies on this topic, further research is warranted.

With respect to the widespread brain changes documented in SSD patients (Van Erp et al., 2016, 2018), only four SSD studies have explored associations between smoking status and brain morphology. The first study showed *increased* grey matter volume in the superior temporal gyri and lateral prefrontal cortex in 14 SSD smokers compared to 18 SSD non-smokers (Tregellas et al., 2007). In contrast, Schneider et al. (2014) found *reduced* right hippocampus, right amygdala and left DLPFC volumes, as well as *reduced* right primary visual cortex thickness in 53 SSD smokers compared to 59 SSD non-smokers. Jørgensen et al. (2015) also found thickness *reductions* in their transdiagnostic sample of SSD, bipolar disorder or other psychotic disorders when comparing 250 smokers to 256 non-smokers, however only in the left insula and left anterior cingulate. The single *longitudinal* study in SSD showed an absence of volume differences between 54 smokers and 42 non-smokers cross-sectionally, although grey matter volume reductions were evident in heavy smokers (>25 cigarettes per day) with SSD over 5 years (Van Haren et al., 2010).

The results of the cognition and brain morphology studies reviewed above show inconsistencies both amongst themselves and in reference to findings in healthy cohorts. They have also been limited by the use of small samples (Morisano et al., 2013; Reed et al., 2016; Tregellas et al., 2007) and/or lack of appropriate control comparators (Depp et al., 2015; Ekinci & Ekinci, 2012; Reed et al., 2016; Roth et al., 2013; Schneider et al., 2014). It is also notable that neither of the two studies that examined cortical thickness examined surface area – the other component measure that contributes to brain volume. Cortical surface area is proposed to have more of an early neurodevelopmental origin (Budday, Steinmann, & Kuhl, 2015; Habets, Marcelis, Gronenschild, Drukker, & Van Os, 2011), while cortical thickness has been found to be particularly influenced by changeable environmental factors (Gold et al., 2016; Jha et al., 2019). Thus, cortical thickness may be potentially more sensitive to the subtle effects of smoking compared to surface area, but no studies have explicitly compared the influence of smoking status on these two measures of brain morphology to date.

In the current study, we aimed to overcome these limitations, by investigating differences between smoking and non-smoking SSD patients compared to smoking and non-smoking controls in the context of a range of cognition and brain morphology measures. We focused our analyses of the latter on global volume, thickness and surface area measures, as well as specific regions of interest (ROIs) including the cingulate cortex, ventrolateral prefrontal cortex (vlPFC), orbitofrontal cortex (OFC), DLPFC, superior temporal gyrus and insula (refer to Fig. 1 for visual depiction). We also examined subcortical thalamic, hippocampal and amygdala volume. These ROIs were selected given; (i) the only studies to have explored the effects of smoking on volume in SSD reported volume differences in the DLPFC, vlPFC, hippocampus, amygdala and superior temporal gyrus (Schneider et al., 2014; Tregellas et al., 2007; Van Haren et al., 2010); (ii) thickness differences between SSD smoking and non-smoking groups have been reported in the cingulate cortex and the insula (Jørgensen et al., 2015); and (iii) the cingulate cortex, OFC and thalamus are regions of reported volume and thickness reduction in healthy smokers that share some overlap with regions of reported volume and thickness reduction in SSD (Brody et al., 2004; Gallinat et al., 2006; Glahn et al., 2008; Rimol et al., 2010; van der Kouwe et al., 2003). As previous studies have shown laterality effects, the ROIs for each hemisphere were analysed separately.

We predicted that smokers would have reduced volume and thinner cortices in these regions in both the control and SSD groups. Further, we hypothesised that no surface area differences would be present when comparing smoking and non-smoking participants, irrespective of diagnosis. We also expected cognitive performance to differ between smoking and non-smoking participants, although the direction of effects remained an open question.

Methods

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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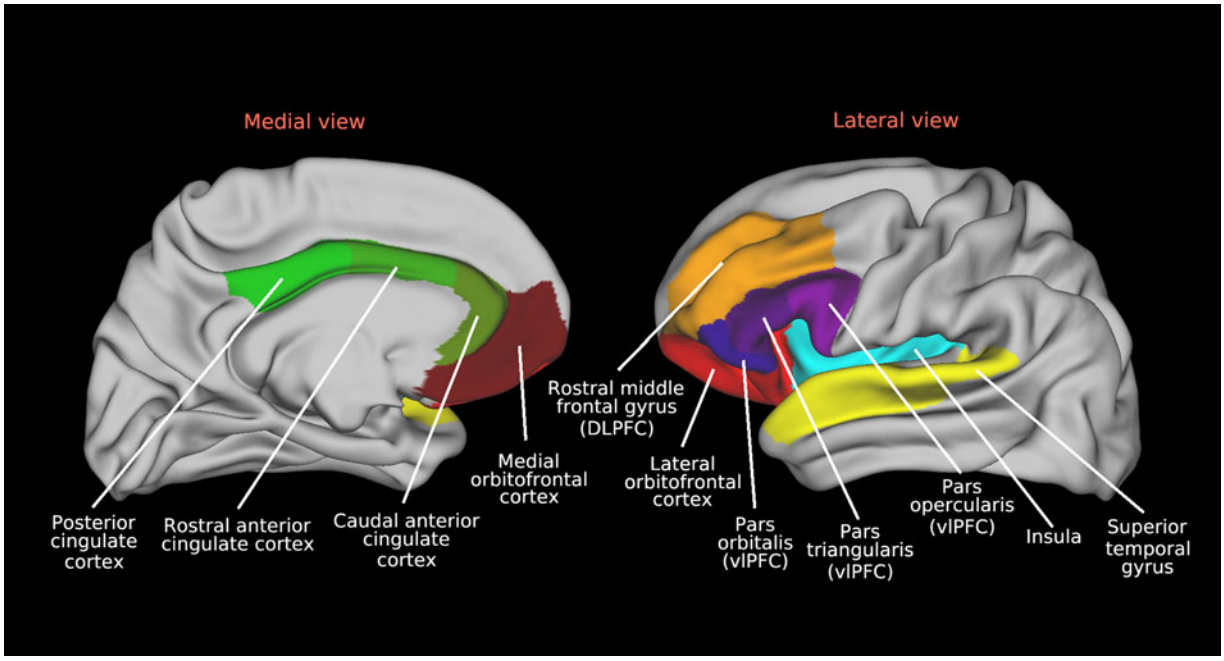

Fig. 1. Selected regions of interest (ROIs). Cortical map depicting the parcellated regions that were selected for the current study based on the Desikan–Killiany atlas. Subcortical regions of interest for the grey matter volume analysis (hippocampus, thalamus and amygdala) are not depicted here.

Participants

Data for the current paper were accessed through the Australian Schizophrenia Research Bank (ASRB) (Loughland et al., 2010), representing data collected across four Australian states (New South Wales, Victoria, Queensland and Western Australia). Smoking and cognitive data were available for 754 individuals included in the study. Of this, $n = 455$ individuals met DSM-IV criteria for schizophrenia ($n = 388$) or schizoaffective disorder ($n = 67$) as part of the SSD group ($n = 321$ smokers, $n = 134$ non-smokers) and $n = 299$ individuals were healthy comparison subjects ($n = 128$ smokers, $n = 171$ non-smokers). Imaging data were also available for a subset of $n = 283$ participants, $n = 201$ of whom had an SSD ($n = 132$ smokers, $n = 69$ non-smokers) and $n = 82$ healthy controls ($n = 26$ smokers, $n = 56$ non-smokers).

All participants provided written informed consent for the future analysis of their stored data in accordance with the Human Research Ethics Committee of participating hospitals/institutions. Details of participant characterisation for this sample are given in the online Supplementary material.

Measures

Smoking status

Information was collected for all participants regarding smoking status through structured interviews as part of the ASRB protocol. Participants were considered non-smokers if they responded 'no' to the question 'have you ever smoked cigarettes, tobacco, cigars, pipe regularly?' and current smokers if they responded 'yes' to the question 'do you currently smoke cigarettes daily?' Participants that answered yes to the first question, but no to the second were excluded from the study, due to the limited number of participants that fell into this category both in the full sample ($n = 47$ SSD, $n = 29$ HC) and imaging subset ($n = 7$ SSD, $n = 6$ HC). Participants were also asked how many cigarettes they smoked per day and placed into one of four groups (10 cigarettes or less per day, 11–20 cigarettes per day, 21–30 cigarettes per day, 31 or more cigarettes per day). As per the methodology of Jørgensen et al. (2015), participants were coded for the current study as either 'low' (1–10 cigarettes per day), 'moderate' (11–20 cigarettes per day) or 'high' (>21 cigarettes per day) frequency smokers.

Cognitive assessment

The Wechsler's Test of Adult Reading (WTAR) was administered as a measure of estimated premorbid IQ. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) was administered to measure cognitive functioning. Five age-adjusted domain scores (immediate memory, language, visuospatial/constructional, delayed memory and attention) and a total scaled score were calculated. Details are provided elsewhere (Loughland et al., 2010).

Neuroimaging

Structural MRI was used to attain whole-brain T1-weighted images from a subset of the participants using Siemens Avanto 1.5-Tesla (Siemens, Erlangen, Germany) MRI scanners located in Melbourne, Sydney, Brisbane, Perth and Newcastle. Information regarding participant distribution for the scanning sites is provided in online Supplementary Table S1[†1]. An optimised magnetisation-prepared rapid acquisition gradient echo (MP-RAGE) sequence with the following parameters was used: 176 sagittal slices of 1 mm thickness without gap; field of view

[†]The notes appear after the main text.

[1]Given the unequal distribution of participants across scanning sites [e.g. there were no healthy controls from one site (Perth) and only non-smoking health controls from another (Newcastle)], additional analyses were conducted to ensure site did not affect the findings, restricted to the three sites where data were available across all groups (Melbourne, Sydney, Brisbane). The results remained largely unchanged and thus site was not considered a concern.

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= 250 × 250 mm^2; repetition time/echo time = 1980/4.3 ms; data matrix size = 256 × 256; voxel dimensions = 0.98 × 0.98 × 1.0 mm^3. The same acquisition sequence was used across all ASRB sites. An individual travelled to all five sites and was scanned at each site to quantify gross inter-site differences. A Siemens MRI phantom was also scanned at each site to enable inter-site calibration.

Both cortical reconstruction and volumetric segmentation of images were completed using the FreeSurfer image analysis suite (version 5.1.0; Martinos Centre for Biomedical Imaging, Harvard-MIT, Boston, MA, USA; http://surfer.nmr.mgh.harvard.edu/). Image processing comprised an automated volume-based and surface-based stream. The former was used to extract volume estimates for select cortical and subcortical regions using an automatic labelling system. The surface-based stream extracted cortical thickness and surface area measurements by reconstructing a three-dimensional cortical surface model. Details of the pre-processing procedure are provided in the online Supplementary material.

Data analysis

All analyses were completed using the Statistical Package for the Social Sciences (SPSS) version 25 (IBM). Details of preliminary analyses and statistical assumption checks are given in the online Supplementary material. Differences in clinical and demographic data between smokers and non-smokers in both diagnostic groups were assessed using χ^2 tests for categorical variables and parametric tests (Student's *t* test or one-way ANOVA) for quantitative variables. Cognitive performance was analysed in a series of ANCOVAs, where the five RBANS domain scores and the total score were specified as dependent variables, and smoking status, diagnostic group and their interaction as the independent variables of interest[2]. Age, sex and recruitment/scanning site were selected as covariates *a priori*. The total and mean regional volume, thickness and surface area estimates obtained in the imaging subset of the sample were imported into SPSS after extraction from FreeSurfer. Mean global (total grey matter volume, total mean thickness and total mean surface area) and regional volume, thickness, and surface area estimates for each participant were imported into SPSS after extraction from FreeSurfer. The global scores and selected ROIs were then analysed in a series of ANCOVAs. The analyses included the independent and covariate variables specified above, alongside either (i) global volume, thickness and surface area; or the ROIs of (ii) left and right cortical and subcortical volume; (iii) left and right cortical thickness; or (iv) left and right cortical surface area as dependent variables[3]. For the global estimates, and volume and surface area ROI analyses, intracranial volume (ICV) was added as a covariate[4].

A false discovery rate (FDR) of $p < 0.05$ was applied to all results to account for multiple comparisons using the Benjamini–Hochberg method (Benjamini & Hochberg, 1995). Details concerning the methodology of the corrections are supplied in the online Supplementary material.

Results

Descriptive statistics

Demographic and clinical characteristics of the full sample and of the imaging subset are presented in Tables 1 and 2, respectively. In the full sample, SSD smokers were significantly younger than control smokers. There were also a significantly higher number of males in the SSD group compared to controls, regardless of smoking status. Further, a significant difference in the distribution of smoking frequency between smokers with and without an SSD diagnosis was evident, with significantly more high-frequency and significantly fewer low-frequency smokers in the SSD subgroups, but an equivalent number of moderate-frequency smokers in both groups.

There were no significant differences in current negative symptoms, current positive symptoms, duration of illness or age of illness onset in SSD patients who were and were not smokers. However, smokers in the SSD group had significantly lower estimated premorbid IQ scores in comparison to the other three groups, and non-smokers in the SSD group had significantly lower estimated premorbid IQ scores in comparison to the control non-smoking group[5]. In the imaging subset, group comparisons on demographic and clinical variables did not differ from that reported above, except that age did not differ significantly between the groups. ICV was also significantly higher in smokers from the SSD group than control non-smokers.

Primary analyses

As the main effects of diagnosis have been reported for all variables of interest in the ASRB data previously, the statistical values for these effects in all current analyses are reported in the online Supplementary material for brevity. Note that several main effects of smoking status were initially significant but did not survive FDR correction. Below we report on the FDR-corrected results, but details of the uncorrected results (with accompanying effect size calculations) can be found in the tables.

Cognition

Smoking group comparisons and interaction effects are reported in Table 3. There were no significant main effects of smoking or smoking status × diagnostic group interactions. However, a main effect of diagnostic group was apparent, with decreased performance in immediate memory, visuospatial/constructional, language, attention, delayed memory and total scale score, evident in SSD patients compared to controls.

Brain morphology

Group comparisons and statistical values for all brain morphology ROI measures are reported in Table 4.

[2]Given known effects of anticholinergic drugs on cognition, the analyses of cognitive functioning were re-run, excluding participants taking these drugs. This had no effect, and the findings are not presented for brevity.

[3]Given previous research has suggested that smoking contributes to age-accelerated cortical thinning, all morphology analyses were re-run looking at smoking status × age and smoking status × age × diagnosis interactions. Results were not significant and thus are not presented for brevity.

[4]In order to examine the influence of high *v.* low smoking frequency behaviour, analyses were re-run comparing low- and high-frequency smokers only. All other factors in both models remained the same. No significant effects of any kind were found for the brain morphology analyses. Similarly, there were no significant smoking frequency × diagnostic group interaction effects for the cognition analysis, although worse attention was evident in high- compared to low-frequency smokers irrespective of diagnostic group ($p < 0.05$ corrected). Group comparisons and statistical values for this analysis are reported in the online Supplementary material.

[5]Given estimated premorbid IQ differences between groups, all analyses were re-run including estimated premorbid IQ as a covariate. This had no effect, and the findings are not presented for brevity.

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Table 1. Demographics characteristics of the full cohort

Characteristic[a]	Schizophrenia smoker ($n = 321$)	Schizophrenia non-smoker ($n = 134$)	Healthy control smoker ($n = 128$)	Healthy control non-smoker ($n = 171$)	Comparison	Post hoc comparisons*
Sex (m/f)	223/98	71/63	56/72	71100	$\chi^2 = 46.4$, $p < 0.001$*	–
Age (years)	38.7 ± 10.4	40.1 ± 10.4	42.9 ± 13.7	40.1 ± 13.6	(Welch's) $F = 3.3$, p = 0.025*	SSD S < HC S
Smoking frequency (low/moderate/high)	119/84/118	–	70/33/24	–	$\chi^2 = 16.2$, $p < 0.001$*	–
Premorbid IQ	95.4 ± 15.8	101.5 ± 13.6	103.6 ± 10.6	106.3 ± 11.4	(Welch's) $F = 9.2$, $p < 0.001$*	SSD S < SSD NS, HC S and HC NS
Current negative symptoms (SANS)	28.4 ± 18.2	29.6 ± 18.7	–	–	$t = -0.6$, $p = 0.547$	–
Current positive symptoms (DIP)	2.3 ± 2.7	2.1 ± 2.9	–	–	$t = 0.7$, $p = 0.491$	–
Duration of illness (years)	16.0 ± 9.9	15.8 ± 9.7	–	–	$t = 0.2$, $p = 0.850$	–
Age of illness onset (years)	22.9 ± 5.9	24.3 ± 7.7	–	–	(Welch's) $t = -1.9$, $p = 0.054$	–
Current antipsychotic use (using/not using)	275/46 (85.7%)	119/15 (88.8%)	–	–	$\chi^2 = 0.8$, $p = 0.371$	–
Typical	39/282 (12.1%)	16/118 (11.9%)	–	–	$\chi^2 = 0.004$, $p = 0.950$	–
Atypical	254/67 (79.1%)	111/23 (82.8%)	–	–	$\chi^2 = 0.8$, $p = 0.371$	–
Current antidepressant use	95/226 (29.6%)	41/93 (30.6%)	–	–	$\chi^2 = 0.05$, $p = 0.831$	–
Current mood stabiliser/anticonvulsant use	44/277 (13.7%)	25/109 (18.7%)	–	–	$\chi^2 = 1.8$, $p = 0.180$	–
Current anticholinergic use	12/309 (3.7%)	5/129 (3.7%)	–	–	$\chi^2 < 0.001$, $p = 0.997$	–
Current anxiolytic/sedative use	40/281 (12.5%)	12/122 (8.6%)	–	–	$\chi^2 = 1.2$, $p = 0.284$	–
Current clozapine use	67/254 (20.9%)	22/112 (16.4%)	–	–	$\chi^2 = 1.2$, $p = 0.275$	–
Current lithium use	15/306 (4.7%)	8/126 (6.0%)	–	–	$\chi^2 = 0.3$, $p = 0.565$	–
No medication	33/288 (10.3%)	15/119 (11.2%)	–	–	$\chi^2 = 0.08$, $p = 0.772$	–

SANS, the Scale for the Assessment of Negative Symptoms; DIP, the Diagnostic Interview for Psychoses.
Data are expressed as mean ± s.d.
[a]Data missing for negative symptoms ($n = 12$), positive symptoms ($n = 42$).
– Data not applicable.
*Significant at $p < 0.05$.

Table 2. Demographic characteristics of the subset with imaging data

Characteristic[a]	Schizophrenia smoker ($n = 132$)	Schizophrenia non-smoker ($n = 69$)	Healthy control smoker ($n = 26$)	Healthy control non-smoker ($n = 56$)	Comparison	Post hoc comparisons*
Sex (m/f)	100/32	41/28	19/7	22/34	$\chi^2 = 24.1$, $p < 0.001$*	–
Age (years)	37.2 ± 10.0	38.1 ± 9.4	40.9 ± 12.8	37.2 ± 14.7	(Welch's) $F = 0.7$, p = 0.35	–
ICV	1633188.2 ± 142909.8	1595568.6 ± 147195.7	1657513.5 ± 166120.3	1569208.2 ± 149901.7	$F = 3.6$, $p = 0.014$*	HC NS < SSD S
Smoking frequency (low/moderate/high)	52/41/39	–	18/5/3	–	$\chi^2 = 8.1$, $p = 0.018$*	–
Premorbid IQ	98.9 ± 13.7	103.1 ± 12.0	107.2 ± 9.5	108.5 ± 12.3	$F = 8.9$, $p < 0.001$*	SSD S < SSD NS, HC S and HC NS
Current negative symptoms (SANS)	24.3 ± 16.7	26.2 ± 17.8	–	–	$t = -0.8$, $p = 0.449$	–
Current positive symptoms (DIP)	1.9 ± 2.5	1.6 ± 2.7	–	–	$t = 0.9$, $p = 0.375$	–
Duration of illness (years)	14.5 ± 9.5	13.7 ± 8.8	–	–	$t = 0.6$, $p = 0.566$	–
Age of illness onset (years)	22.7 ± 5.4	24.4 ± 7.2	–	–	(Welch's) $t = -1.7$, $p = 0.089$	–
Current antipsychotic use (using/not using)	111/21 (84.1%)	62/7 (89.9%)	–	–	$\chi^2 = 1.3$, $p = 0.262$	–
Typical	11/121 (8.3%)	6/63 (8.7%)	–	–	$\chi^2 = 0.008$, $p = 0.930$	–
Atypical	106/26 (80.3%)	61/8 (88.4%)	–	–	$\chi^2 = 2.1$, $p = 0.146$	–
Current antidepressant use	44/88 (33.3%)	23/46 (33.3%)	–	–	$\chi^2 < 0.001$, $p = 1.00$	–
Current mood stabiliser/anticonvulsant use	17/115 (12.9%)	12/57 (17.4%)	–	–	$\chi^2 = 0.7$, $p = 0.387$	–
Current anxiolytic/sedative use	16/116 (12.1%)	8/61 (11.6%)	–	–	$\chi^2 = 0.01$, $p = 0.913$	–
Current clozapine use	21/112 (15.9%)	11/57 (15.9%)	–	–	$\chi^2 = 0.2$, $p = 0.680$	–
Current lithium use	5/127 (3.8%)	4/65 (5.7%)	–	–	(Fisher's) $\chi^2 = 0.4$, $p = 0.497$	–
No medication	16/116 (12.1%)	7/62 (10.1%)	–	–	$\chi^2 = 0.2$, $p = 0.68$	–

ICV, intracranial volume; SANS, the Scale for the Assessment of Negative Symptoms; DIP, the Diagnostic Interview for Psychoses.
Data are expressed as mean ± S.D.
[a]Data missing for negative symptoms ($n = 10$), positive symptoms ($n = 12$).
– Data not applicable.
*Significant at $p < 0.05$.

Table 3. Group comparisons of cognitive domains

Domain	Comparisons[a]	Group	M[b]	S.D.	Post-hoc[c]	*d*[d]
Main effect of smoking						
Immediate memory	**$F_{(1,744)} = 4.21$, $p = 0.041$**	S	88.88	18.71	–	0.15
		NS	91.59	17.13		
Visuospatial/constructional	**$F_{(1,744)} = 3.91$, $p = 0.048$**	S	89.73	17.03	–	0.15
		NS	92.11	15.60		
Language	$F_{(1,744)} = 0.27$, $p = 0.603$	S	99.94	12.55	–	0.04
		NS	100.40	11.49		
Attention	$F_{(1,744)} = 0.34$, $p = 0.559$	S	92.51	17.88	–	0.04
		NS	93.25	16.36		
Delayed memory	$F_{(1,744)} = 3.64$, $p = 0.057$	S	89.43	15.78	–	0.14
		NS	91.57	14.45		
Total score	**$F_{(1,744)} = 4.21$, $p = 0.040$**	S	89.67	14.47	–	0.15
		NS	91.77	13.24		
Smoking × diagnosis interaction effect						
Immediate memory	$F_{(1,744)} = 0.002$, $p = 0.967$	SSD S	79.40	17.21	–	N/A
		SSD NS	82.17	16.70		
		HC S	98.36	17.09		
		HC NS	101.02	17.06		
Visuospatial/constructional	$F_{(1,744)} = 0.04$, $p = 0.851$	SSD S	85.04	15.66	–	N/A
Visuospatial cont.		SSD NS	87.65	15.47		
		HC S	94.42	15.55		
		HC NS	96.58	15.53		
Language	$F_{(1,744)} = 0.73$, $p = 0.394$	SSD S	93.79	11.54	–	N/A
		SSD NS	95.004	11.40		
		HC S	106.09	11.46		
		HC NS	105.80	11.44		
Attention	$F_{(1,744)} = 1.71$, $p = 0.192$	SSD S	81.89	16.44	–	N/A
		SSD NS	84.28	16.42		
		HC S	103.13	16.33		
		HC NS	102.22	16.30		
Delayed memory	$F_{(1,744)} = 0.10$, $p = 0.752$	SSD S	82.53	14.51	–	N/A
		SSD NS	85.02	14.34		
		HC S	96.34	14.41		
		HC NS	98.12	14.39		
Total score	$F_{(1,744)} = 0.41$, $p = 0.523$	SSD S	79.97	13.30	–	N/A
		SSD NS	82.73	13.14		
		HC S	99.36	13.22		
		HC NS	100.81	13.19		

SSD, schizophrenia spectrum disorder; HC, healthy controls; S, smoker; NS, non-smoker.
Given the focus of this study, main effects of diagnostic group are reported in the online Supplementary material for brevity.
[a]Unadjusted for multiple comparisons.
[b]All values are adjusted for age, gender and site.
[c]If post-hoc relationship is not reported, finding was not significant prior or after FDR correction. SSD < HC implies significant reductions relative to HC.
[d]*d* = Cohen's *d* effect sizes.
*Significant at $p < 0.05$ after Benjamini–Hochberg FDR correction for multiple comparisons.
Bold values = significant before Benjamini–Hochberg FDR.

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Table 4. Group comparisons of volume, cortical thickness and surface area regions of interest

Regions	Comparisons[a]	Group	LH M[b]	LH s.d.	LH Post-hoc[c]	LH d[d]	RH M[b]	RH s.d.	RH Post-hoc[c]	RH d[d]
***Volume* (*ml*)** – *main effect of smoking*										
Subcortical regions										
Thalamus	LH: $F_{(1,271)} = 1.07$, $p = 0.301$	S	7799.87	818.09	–	−0.12	7934.91	802.88	–	−0.14
	RH: $F_{(1,271)} = 1.42$, $p = 0.235$	NS	7709.43	615.77			7832.82	604.32		
Hippocampus	LH: $F_{(1,271)} = 0.05$, $p = 0.820$	S	4214.95	481.75	–	−0.03	4315.86	499.45	–	0.06
	RH: $F_{(1,271)} = 0.22$, $p = 0.640$	NS	4203.24	362.61			4340.85	374.93		
Amygdala	LH: $F_{(1,271)} = 0.27$, $p = 0.606$	S	1568.25	208.95	–	0.06	1611.21	221.01	–	0.10
	RH: $F_{(1,271)} = 0.64$, $p = 0.423$	NS	1579.76	157.28			1630.14	166.35		
Cortical regions										
Caudal anterior cingulate	LH: $F_{(1,271)} = 3.59$, $p = 0.059$	S	1919.18	639.47	–	0.23	2381.52	731.00	–	−0.02
	RH: $F_{(1,271)} = 2.56$, $p = 0.111$	NS	2048.52	481.33			2256.64	550.22		
Rostral anterior cingulate	LH: $F_{(1,271)} = 0.90$, $p = 0.344$	S	2910.71	635.35	–	0.11	2361.71	562.40	–	0.00
	RH: $F_{(1,2731)} = 0.0002$, $p = 0.990$	NS	2975.05	478.22			2362.49	423.31		
Posterior cingulate	LH: $F_{(1,271)} = 0.002$, $p = 0.960$	S	3378.97	652.42	–	0.01	3367.64	616.63	–	0.11
	RH: $F_{(1,271)} = 0.81$, $p = 0.370$	NS	3382.44	491.07			3426.81	464.14		
Pars opercularis	LH: $F_{(1,271)} = 2.31$, $p = 0.130$	S	5070.07	1099.08	–	0.18	4201.35	876.80	–	0.18
	RH: $F_{(1,271)} = 2.12$, $p = 0.147$	NS	5248.34	827.27			4337.49	659.96		
Pars orbitalis	LH: $F_{(1,271)} = 0.24$, $p = 0.626$	S	2314.27	374.25	–	0.06	2794.24	514.84	–	0.26
	RH: $F_{(1,271)} = 4.72$, $p = 0.031$	NS	2333.76	281.70			2913.62	387.51		
Pars triangularis	LH: $F_{(1,271)} = 1.23$, $p = 0.269$	S	3739.71	769.32	–	0.13	4507.39	966.18	–	0.11
	RH: $F_{(1,271)} = 0.79$, $p = 0.375$	NS	3830.71	579.06			4598.95	727.24		
Rostral middle frontal	LH: $F_{(1,271)} = 1.62$, $p = 0.204$	S	16814.93	2069.20	–	0.15	17619.94	2283.98	–	0.01
	RH: $F_{(1,271)} = 0.013$, $p = 0.910$	NS	17096.03	1557.47			17647.55	1719.13		
Lateral orbitofrontal	LH: $F_{(1,271)} = 0.002$, $p = 0.967$	S	8122.38	877.15	–	−0.01	8001.23	921.29	–	0.07
	RH: $F_{(1,271)} = 0.36$, $p = 0.548$	NS	8118.46	660.22			8060.38	693.45		
Medial orbitofrontal	LH: $F_{(1,271)} = 1.26$, $p = 0.263$	S	5713.68	812.27	–	0.14	5481.71	671.35	–	0.28
	RH: $F_{(1,271)} = 5.49$, $p = 0.020$	NS	5810.88	611.39			5649.56	505.32		
Superior temporal	**LH: $F_{(1,271)} = 5.96$, $p = 0.015$**	S	12483.07	1539.07	–	0.29	12072.93	1493.99	–	0.27
	RH: $F_{(1,271)} = 5.20$, $p = 0.023$	NS	12884.42	1158.45			12436.42	1124.52		
Insula	LH: $F_{(1,271)} = 0.29$, $p = 0.594$	S	7438.71	820.15	–	0.06	7703.02	987.26	–	0.01
	RH: $F_{(1,271)} = 0.008$, $p = 0.927$	NS	7485.44	617.32			7712.72	961.15		

Volume (ml) *– smoking × diagnosis interaction effect*										
Subcortical regions										
Thalamus	LH: $F_{(1,271)} = 1.13$, $p = 0.289$	SSD S	7709.18	604.85	–	N/A	7879.59	593.60	–	N/A
	RH: $F_{(1,271)} = 1.06$, $p = 0.305$	SSD NS	7708.38	606.54			7862.67	595.26		
		HC S	7890.56	602.39			7990.24	591.19		
		HC NS	7710.48	616.17			7802.97	604.72		
Hippocampus	LH: $F_{(1,271)} = 0.19$, $p = 0.667$	SSD S	4135.28	365.18	–	N/A	4252.06	369.27	–	N/A
	RH: $F_{(1,271)} = 0.33$, $p = 0.567$	SSD NS	4144.98	357.17			4306.63	370.30		
		HC S	4294.61	354.73			4379.67	367.76		
		HC NS	4261.50	362.85			4375.07	376.18		
Amygdala	LH: $F_{(1,271)} = 1.07$, $p = 0.302$	SSD S	1542.71	154.49	–	N/A	1597.24	163.40	–	N/A
	RH: $F_{(1,271)} = 0.08$, $p = 0.775$	SSD NS	1576.50	154.92			1622.69	163.86		
		HC S	1593.79	153.86			1625.18	162.73		
		HC NS	1583.02	157.38			1637.58	166.46		
Cortical regions										
Caudal anterior cingulate	LH: $F_{(1,271)} = 0.06$, $p = 0.803$	SSD D	1907.38	472.79	–	N/A	2279.83	540.46	–	N/A
	RH: $F_{(1,271)} = 0.39$, $p = 0.533$	SSD NS	2020.26	474.11			2202.002	541.96		
		HC S	1930.97	470.86			2483.21	538.36		
		HC NS	2076.78	481.64			2311.28	550.57		
Rostral anterior cingulate	LH: $F_{(1,271)} = 0.52$, $p = 0.473$	SSD S	2884.07	469.74	–		2364.99	415.80	–	N/A
	RH: $F_{(1,2731)} = 0.001$, $p = 0.905$	SSD NS	2901.31	471.05		N/A	2372.69	416.96		
		HC S	2937.35	467.83			2358.42	414.11		
		HC NS	3048.78	491.39			2352.29	423.59		
Posterior cingulate	LH: $F_{(1,271)} = 0.08$, $p = 0.778$	SSD S	3381.90	482.36	–	N/A	3376.55	455.90	–	N/A
	RH: $F_{(1,271)} = 0.15$, $p = 0.695$	SSD NS	3404.39	483.71			3410.76	457.17		
		HC S	3376.04	480.40			3358.73	414.11		
		HC NS	3360.49	491.39			3442.85	423.59		
Pars opercularis	LH: $F_{(1,271)} = 0.84$, $p = 0.360$	SSD S	5079.00	812.59	–		4186.84	648.26	–	N/A
	RH: $F_{(1,271)} = 0.25$, $p = 0.615$	SSD NS	5153.18	814.86		N/A	4277.44	650.07		
		HC S	5061.14	809.29			4215.86	645.62		
		HC NS	5343.50	827.81			4397.55	660.39		
Pars orbitalis	LH: $F_{(1,271)} = 1.71$, $p = 0.192$	SSD S	2280.10	276.70	–	N/A	2764.43	380.64	–	N/A
	RH: $F_{(1,271)} = 0.64$, $p = 0.425$	SSD NS	2249.11	277.47			2841.35	381.70		
		HC S	2348.44	275.57			2824.05	379.09		
		HC NS	2418.42	281.88			2985.89	387.77		
Pars triangularis	LH: $F_{(1,271)} = 0.62$, $p = 0.430$	SSD S	3721.43	568.79	–	N/A	4409.47	714.33	–	N/A
	RH: $F_{(1,271)} = 0.13$, $p = 0.716$	SSD NS	3749.73	570.38			4464.72	716.33		

(*Continued*)

Table 4. (*Continued.*)

Regions	Comparisons[a]	Group	LH M[b]	LH S.D.	LH Post-hoc[c]	LH *d*[d]	RH M[b]	RH S.D.	RH Post-hoc[c]	RH *d*[d]
		HC S	3757.98	566.48			4605.32	711.43		
		HC NS	3911.68	579.44			4733.19	727.71		
Rostral middle frontal	LH: $F_{(1,271)} = 1.61$, $p = 0.206$	SSD S	16698.82	1529.85	–	N/A	17312.10	1699.64	–	N/A
	RH: $F_{(1,271)} = 0.31$, $p = 0.580$	SSD NS	16709.13	1534.11			17470.27	1693.35		
		HC S	16931.05	1523.62			17927.78	1681.77		
		HC NS	17482.93	1558.49			17824.82	1720.25		
Lateral orbitofrontal	LH: $F_{(1,271)} = 0.17$, $p = 0.682$	SSD S	8017.38	648.51	–	N/A	7900.91	681.14	–	N/A
	RH: $F_{(1,271)} = 0.001$, $p = 981$	SSD NS	8050.37	650.32			8101.55	678.37		
		HC S	8227.37	645.87			7957.74	683.05		
		HC NS	8186.31	660.65			8163.02	693.90		
Medial orbitofrontal	LH: $F_{(1,271)} < 0.001$, $p = 0.997$	SSD S	5679.76	600.56	–	N/A	5426.51	496.35	–	N/A
	RH: $F_{(1,271)} = 0.002$, $p = 0.963$	SSD NS	5777.31	602.22			5536.91	494.33		
		HC S	5747.61	598.10			5591.17	497.74		
		HC NS	5844.46	611.79			5707.95	505.65		
Superior temporal	LH: $F_{(1,271)} = 0.03$, $p = 0.854$	SSD S	12366.12	1137.90	–	N/A	12008.93	1104.57	–	N/A
	RH: $F_{(1,271)} = 0.08$, $p = 0.780$	SSD NS	12796.80	1141.07			12329.26	1107.65		
		HC S	12600.03	1133.27			12136.93	1100.08		
		HC NS	12972.02	1159.20			12543.57	1125.25		
Insula	LH: $F_{(1,271)} = 0.05$, $p = 0.829$	SSD S	7402.70	606.37	–	N/A	7631.51	729.93	–	N/A
	RH: $F_{(1,271)} = 0.07$, $p = 0.798$	SSD NS	7467.71	608.07			7667.29	731.96		
		HC S	7474.71	603.91			7774.54	726.95		
		HC NS	7503.17	617.73			7758.14	617.73		
Thickness (mm) – main effect of smoking										
Caudal anterior cingulate	LH: $F_{(1,273)} = 0.36$, $p = 0.059$	S	2.65	0.32	–	0.23	2.63	0.30	–	−0.05
	RH: $F_{(1,273)} = 0.13$, $p = 0.718$	NS	2.72	0.24			2.62	0.23		
Rostral anterior cingulate	**LH: $F_{(1,273)} = 4.98$, $p = 0.026$**	S	2.91	0.28	–	0.27	3.00	0.30	–	0.08
	RH: $F_{(1,273)} = 3.02$, $p = 0.22$	NS	2.98	0.21			3.02	0.22		
Posterior cingulate	**LH: $F_{(1,273)} = 9.61$, $p = 0.002$***	S	2.56	0.21	S < NS	0.37	2.52	0.21	–	0.32
	RH: $F_{(1,273)} = 7.01$, $p = 0.009$	NS	2.63	0.16			2.58	0.16		
Superior temporal gyrus	LH: $F_{(1,273)} = 2.80$, $p = 0.095$	S	2.79	0.20	–	0.20	2.83	0.19	–	0.25
	RH: $F_{(1,273)} = 4.23$, $p = 0.041$	NS	2.83	0.15			2.87	0.14		
Rostral middle frontal	LH: $F_{(1,273)} = 2.029$, $p = 0.155$	S	2.51	0.16	–	0.17	2.53	0.17	–	0.12
	RH: $F_{(1,273)} = 1.00$, $p = 0.318$	NS	2.53	0.12			2.55	0.13		
Lateral orbitofrontal	LH: $F_{(1,273)} = 0.01$, $p = 0.922$	S	2.70	0.21	–	−0.01	2.70	0.21	–	0.16

	RH: $F_{(1,273)} = 1.74$, $p = 0.188$	NS	2.70	0.16			2.73	0.16		
Medial orbitofrontal	LH: $F_{(1,273)} = 2.90$, $p = 0.090$	S	2.60	0.22	–	0.21	2.56	0.20	–	0.31
	RH: $F_{(1,273)} = 6.37$, $p = 0.012$	NS	2.64	0.17			2.62	0.16		
Pars orbitalis	LH: $F_{(1,273)} = 1.073$, $p = 0.301$	S	2.79	0.27	–	0.12	2.83	0.27	–	0.14
	RH: $F_{(1,273)} = 1.20$, $p = 0.275$	NS	2.82	0.21			2.86	0.21		
Pars opercularis	**LH: $F_{(1,273)} = 7.53$, $p = 0.006$**	S	2.60	0.19	–	0.33	2.64	0.20	–	0.12
	RH: $F_{(1,273)} = 1.08$, $p = 0.299$	NS	2.66	0.15			2.66	0.15		
Pars triangularis	LH: $F_{(1,273)} = 0.005$, $p = 0.942$	S	2.56	0.21	–	0.01	2.58	0.20	–	0.14
	RH: $F_{(1273)} = 1.34$, $p = 0.248$	NS	2.56	0.16			2.61	0.15		
Insula	LH: $F_{(1,273)} = 0.34$, $p = 0.528$	S	3.08	0.21	–	0.08	3.02	0.24	–	0.21
	RH: $F_{(1,273)} = 3.07$, $p = 0.081$	NS	3.09	0.17			3.07	0.18		
Thickness (mm) – smoking × diagnosis interaction effect										
Caudal anterior cingulate	LH: $F_{(1,273)} = 0.32$, $p = 0.572$	SSD S	2.64	0.24	–	N/A	2.59	0.22	–	N/A
	RH: $F_{(1,273)} = 0.09$, $p = 0.766$	SSD NS	2.72	0.24			2.59	0.22	–	
		HC S	2.67	0.23			2.68	0.22	–	
		HC NS	2.71	0.24			2.67	0.23	–	
Rostral anterior cingulate	LH: $F_{(1,273)} = 0.02$, $p = 0.883$	SSD S	2.89	0.21	–	N/A	2.98	0.22	–	N/A
	RH: $F_{(1,273)} = 0.004$, $p = 0.953$	SSD NS	2.95	0.21			3.00	0.22	–	
		HC S	2.94	0.21			3.02	0.22	–	
		HC NS	3.01	0.21			3.03	0.22	–	
Posterior cingulate	LH: $F_{(1,273)} = 0.10$, $p = 0.754$	SSD S	2.56	0.15	–	N/A	2.53	0.16	–	N/A
	RH: $F_{(1,273)} = 1.98$, $p = 0.161$	SSD NS	2.63	0.16			2.56	0.16		
		HC S	2.57	0.15			2.50	0.16		
		HC NS	2.64	0.16			2.59	0.16		
Superior temporal gyrus	LH: $F_{(1,273)} = 0.005$, $p = 0.941$	SSD S	2.76	0.15	–	N/A	2.80	0.14	–	N/A
	RH: $F_{(1,273)} = 0.006$, $p = 0.939$	SSD NS	2.80	0.15			2.83	0.14		
		HC S	2.82	0.15			2.86	0.14		
		HC NS	2.86	0.15			2.91	0.14		
Rostral middle frontal	LH: $F_{(1,273)} = 0.07$, $p = 0.793$	SSD S	2.49	0.12	–	N/A	2.50	0.12	–	N/A
	RH: $F_{(1,273)} = 0.14$, $p = 0.707$	SSD NS	2.52	0.12			2.53	0.12		
		HC S	2.53	0.12			2.55	0.12		
		HC NS	2.55	0.12			2.57	0.13		
Lateral orbitofrontal	LH: $F_{(1,273)} = 0.11$, $p = 0.735$	SSD S	2.65	0.16	–	N/A	2.66	0.16	–	N/A
	RH: $F_{(1,273)} = 0.28$, $p = 0.597$	SSD NS	2.65	0.16			2.67	0.16		
		HC S	2.76	0.15			2.74	0.15		
		HC NS	2.75	0.16			2.67	0.16		
Medial orbitofrontal	LH: $F_{(1,273)} = 0.54$, $p = 0.462$	SSD S	2.57	0.17	–	N/A	2.52	0.16	–	N/A

(*Continued*)

Table 4. (*Continued.*)

Regions	Comparisons[a]	Group	LH M[b]	LH S.D.	LH Post-hoc[c]	LH *d*[d]	RH M[b]	RH S.D.	RH Post-hoc[c]	RH *d*[d]
	RH: $F_{(1,273)} = 0.12$, $p = 0.726$	SSD NS	2.59	0.17			2.58	0.16		
		HC S	2.63	0.16			2.60	0.15		
		HC NS	2.69	0.17			2.65	0.16		
Pars orbitalis	LH: $F_{(1,273)} = 3.88$, $p = 0.05$	SSD S	2.76	0.20	–	N/A	2.80	0.20	–	N/A
	RH: $F_{(1,273)} = 0.02$, $p = 0.876$	SSD NS	2.74	0.20			2.83	0.20		
		HC S	2.82	0.20			2.87	0.20		
		HC NS	2.90	0.21			2.89	0.20		
Pars opercularis	LH: $F_{(1,273)} = 0.33$, $p = 0.565$	SSD S	2.59	0.14	–	N/A	2.60	0.15	–	N/A
	RH: $F_{(1,273)} = 0.13$, $p = 0.719$	SSD NS	2.63	0.14			2.63	0.15		
		HC S	2.62	0.14			2.68	0.15		
		HC NS	2.68	0.15			2.70	0.15		
Pars triangularis	LH: $F_{(1,273)} = 3.30$, $p = 0.072$	SSD S	2.52	0.16	–	N/A	2.55	0.15	–	N/A
	RH: $F_{(1,273)} = 0.03$, $p = 0.854$	SSD NS	2.57	0.16			2.58	0.15		
		HC S	2.63	0.16			2.61	0.15		
		HC NS	2.59	0.16			2.63	0.15		
Insula	LH: $F_{(1,273)} = 0.26$, $p = 0.608$	SSD S	3.04	0.16	–	N/A	3.01	0.17	–	N/A
	RH: $F_{(1,273)} = 0.99$, $p = 0.320$	SSD NS	3.05	0.16			3.03	0.17		
		HC S	3.11	0.16			3.04	0.17		
		HC NS	3.14	0.16			3.10	0.18		
Surface area (cm^3) – main effect of smoking										
Caudal anterior cingulate	LH: $F_{(1,273)} = 1.07$, $p = 0.302$	S	671.73	176.03	–	0.12	818.94	206.87	–	−0.23
	RH: $F_{(1,273)} = 3.73$, $p = 0.055$	NS	691.15	132.50			776.32	155.71		
Rostral anterior cingulate	LH: $F_{(1,273)} = 0.005$, $p = 0.946$	S	875.95	180.04	–	0.01	710.64	160.50	–	−0.06
	RH: $F_{(1,273)} = 0.26$, $p = 0.610$	NS	877.24	135.52			701.88	120.96		
Posterior cingulate	LH: $F_{(1,273)} = 0.60$, $p = 0.440$	S	1202.30	207.68	–	−0.09	1217.95	207.93	–	0.00
	RH: $F_{(1,273)} < 0.001$, $p = 0.983$	NS	1185.16	156.32			1218.42	156.50		
Superior temporal gyrus	LH: $F_{(1,273)} = 1.55$, $p = 0.214$	S	3903.36	383.32	–	0.15	3720.73	399.29	–	0.06
	RH: $F_{(1,273)} = 0.27$, $p = 0.604$	NS	3954.37	288.52			3742.84	300.54		
Rostral middle frontal	LH: $F_{(1,273)} = 0.25$, $p = 0.618$	S	5921.79	712.34	–	0.06	6133.84	696.99	–	−0.03
	RH: $F_{(1,273)} = 0.047$, $p = 0.828$	NS	5959.73	536.17			6117.68	524.62		
Lateral orbitofrontal	LH: $F_{(1,273)} = 0.04$, $p = 0.839$	S	2758.64	284.60	–	0.02	2730.97	314.78	–	−0.01
	RH: $F_{(1,273)} = 0.004$, $p = 0.948$	NS	2764.81	214.22			2728.78	236.93		
Medial orbitofrontal	LH: $F_{(1,273)} = 0.15$, $p = 0.697$	S	1945.48	284.06	–	0.05	1889.62	207.43	–	0.07
	RH: $F_{(1,273)} = 0.30$, $p = 0.585$	NS	1957.32	213.81			1901.72	156.13		

Pars orbitalis	LH: $F_{(1,273)} = 0.12$, $p = 0.730$	S	662.43	88.30	–	−0.04	800.46	120.31	–	0.19
	RH: $F_{(1,273)} = 2.43$, $p = 0.121$	NS	659.17	66.46			820.46	90.56		
Pars opercularis	LH: $F_{(1,273)} = 0.09$, $p = 0.768$	S	1731.22	343.26	–	0.04	1428.25	298.11	–	0.14
	RH: $F_{(1,273)} = 1.43$, $p = 0.234$	NS	1742.02	258.37			1466.24	224.39		
Pars triangularis	LH: $F_{(1,273)} = 0.45$, $p = 0.505$	S	1303.09	237.70	–	0.08	1539.87	312.96	–	0.03
	RH: $F_{(1,273)} = 0.07$, $p = 0.797$	NS	1320.01	178.91			1548.56	235.56		
Insula	LH: $F_{(1,273)} = 0.05$, $p = 0.821$	S	2369.31	249.31	–	−0.03	2465.54	316.55	–	−0.08
	RH: $F_{(1,273)} = 0.44$, $p = 0.508$	NS	2363.29	187.65			2443.18	238.25		
Surface area (cm^3) – smoking × diagnosis interaction effect										
Caudal anterior cingulate	LH: $F_{(1,273)} = 0.10$, $p = 0.748$	SSD S	667.77	130.14	–	N/A	799.30	152.95	–	N/A
	RH: $F_{(1,273)} = 0.55$, $p = 0.461$	SSD NS	681.34	130.51			764.68	153.38	–	
		HC S	675.70	129.62			838.59	152.33	–	
		HC NS	700.97	132.58			787.96	155.81	–	
Rostral anterior cingulate	LH: $F_{(1,273)} = 0.58$, $p = 0.449$	SSD S	877.43	133.11	–	N/A	715.79	118.81	–	N/A
	RH: $F_{(1,273)} = 0.02$, $p = 0.886$	SSD NS	864.64	133.48			709.40	119.14		
		HC S	874.47	132.57			705.50	118.33		
		HC NS	889.85	135.60			694.36	121.04		
Posterior cingulate	LH: $F_{(1,273)} = 0.02$, $p = 0.888$	SSD S	1209.69	153.54	–	N/A	1216.14	153.73	–	N/A
	RH: $F_{(1,273)} = 0.07$, $p = 0.797$	SSD NS	1195.59	153.97			1222.13	154.16		
		HC S	1194.91	152.92			1219.75	153.10		
		HC NS	1174.74	156.42			1214.70	156.61		
Superior temporal gyrus	LH: $F_{(1,273)} = 0.20$, $p = 0.656$	SSD S	3894.34	283.40	–	N/A	3732.83	295.21	–	N/A
	RH: $F_{(1,273)} = 0.001$, $p = 0.970$	SSD NS	3962.99	284.19			3756.48	296.04		
		HC S	3912.38	282.25			3708.63	294.01		
		HC NS	3945.75	288.71			3729.21	300.74		
Rostral middle frontal	LH: $F_{(1,273)} = 1.81$, $p = 0.180$	SSD S	5914.11	526.66	–	N/A	6094.47	515.31	–	N/A
	RH: $F_{(1,273)} = 0.22$, $p = 0.642$	SSD NS	5853.16	528.13			6111.76	516.75		
		HC S	5929.48	524.52			6173.21	513.22		
		HC NS	6066.30	536.52			6123.60	524.96		
Lateral orbitofrontal	LH: $F_{(1,273)} = 0.15$, $p = 0.698$	SSD S	2775.09	210.42	–	N/A	2725.39	232.73	–	N/A
	RH: $F_{(1,273)} = 0.68$, $p = 0.411$	SSD NS	2792.65	211.00			2749.95	233.38		
		HC S	2742.19	209.56			2736.54	231.78		
		HC NS	2736.97	214.35			2707.61	237.08		
Medial orbitofrontal	LH: $F_{(1,273)} = 0.005$, $p = 0.942$	SSD S	1965.86	210.01	–	N/A	1906.32	153.36	–	N/A
	RH: $F_{(1,273)} = 0.21$, $p = 0.645$	SSD NS	1979.84	210.60			1908.55	153.79		
		HC S	1925.11	209.16			1872.91	152.74		
		HC NS	1934.80	213.95			1894.88	156.24		

(*Continued*)

Table 4. (*Continued.*)

Regions	Comparisons[a]	Group	LH M[b]	LH S.D.	LH Post-hoc[c]	LH d[d]	RH M[b]	RH S.D.	RH Post-hoc[c]	RH d[d]
Pars orbitalis	LH: $F_{(1,273)} = 0.01$, $p = 0.909$	SSD S	658.76	65.28	–	N/A	801.54	88.95	–	N/A
	RH: $F_{(1,273)} = 0.02$, $p = 0.876$	SSD NS	656.54	65.01			808.28	89.20		
		HC S	666.11	65.47			799.37	88.59		
		HC NS	661.80	66.51			832.64	90.62		
Pars opercularis	LH: $F_{(1,273)} = 0.25$, $p = 0.617$	SSD S	1736.86	253.79	–	N/A	1449.41	220.41	–	N/A
	RH: $F_{(1,273)} = 0.55$, $p = 0.461$	SSD NS	1729.93	254.50			1464.67	221.02		
		HC S	1725.58	252.76			1407.08	219.51		
		HC NS	1754.11	258.54			1467.81	224.53		
Pars triangularis	LH: $F_{(1,273)} = 2.24$, $p = 0.136$	SSD S	1317.88	175.74	–	N/A	1519.25	231.38	–	N/A
	RH: $F_{(1,273)} = 0.16$, $p = 0.691$	SSD NS	1298.11	176.23			1514.97	232.03		
		HC S	1288.31	175.02			1560.49	230.44		
		HC NS	1341.91	179.03			1581.95	235.71		
Insula	LH: $F_{(1,273)} = 0.31$, $p = 0.578$	SSD S	2384.39	184.32	–	N/A	2468.90	234.03	–	N/A
	RH: $F_{(1,273)} = 0.17$, $p = 0.685$	SSD ND	2392.71	184.84			2459.75	234.69		
		HC S	2354.24	183.57			2462.17	233.08		
		HC NS	2333.87	187.78			2426.50	238.41		

SSD, schizophrenia spectrum disorder; HC, healthy controls; S, smoker; NS, non-smoker; LH, left hemisphere; RH, right hemisphere.
Given the focus of this study, main effects of diagnostic group are reported in the online Supplementary material for brevity.
[a]Unadjusted for multiple comparisons.
[b]All values are adjusted for age, gender, ICV and site.
[c]If post-hoc relationship is not reported, finding was not significant prior or after FDR correction. SSD < HC implies significant reductions relative to HC.
[d]d = Cohen's d effect sizes.
*Significant at $p < 0.05$ after Benjamini–Hochberg correction for multiple comparisons.
Bold values = significant before Benjamini–Hochberg correction.

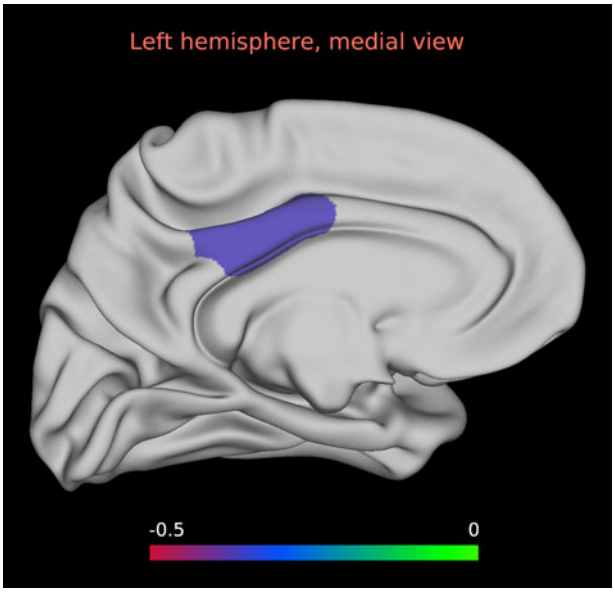

Fig. 2. Main effect of smoking status on left posterior cingulate cortex thickness. Statistical map depicting effect size of thickness reductions in smoking and non-smoking participants in the whole sample for left posterior cingulate cortex thickness. The main effect of left posterior cingulate cortex thickness was the only main effect to survive FDR correction.

Global morphology estimates: A main effect of diagnostic group was evident for global volume and thickness, with both measures showing significant reductions in SSD patients compared to healthy controls. Global surface area was not significantly affected by diagnostic group, nor were there any significant main effects of smoking status, and smoking status × diagnostic group interactions for any of the global measures analysed. Due to the lack of significant findings, the statistical values for these effects are reported in the online Supplementary material for brevity

Cortical and subcortical grey matter volume: There were no significant main effects of diagnosis[6] or smoking status, and no smoking status × diagnostic group interactions for any of the regions analysed.

Cortical thickness: There were no significant smoking status × diagnostic group interactions in any of the regions analysed. A main effect of diagnostic group was evident, with reduced thickness in SSD patients compared to healthy controls in the right caudal ACC and pars opercularis, and the lateral OFC, medial OFC, pars orbitalis, pars triangularis, DLPFC, superior temporal gyrus and insula bilaterally. A significant main effect of smoking status was also observed in the left posterior cingulate cortex (PCC), with reduced thickness in smokers compared to non-smokers (Fig. 2).

Surface area: There were no significant main effects of smoking status or smoking status × diagnostic group interaction effects in any of the regions analysed. There was a main effect of diagnostic group, with reduced regional surface area in SSD patients compared to healthy controls in the right DLPFC, pars orbitalis and pars triangularis. There was a significant increase in surface area in the bilateral lateral OFC in SSD patients compared to controls.

[6]The regional grey matter volume analysis was controlling for an age × diagnosis interaction, which was significant, hence the main effect of diagnosis was not. Refer to 'Preliminary analysis and assumption checking' in online Supplementary material for details.

Discussion

The findings of the current study showed no statistically significant effects of smoking on cognition, grey matter volume, cortical thickness and surface area in both SSD and healthy controls, with the exception of a thinner left PCC in smokers compared to non-smokers, irrespective of diagnostic group. Nonetheless, the effect of smoking on several cognitive and brain morphology measures was in the expected direction and was significant initially but did not survive correction. There was also a significant difference between smokers and non-smokers in premorbid IQ, and a significant difference between light and heavy smokers in the attention domain of cognition. Thus, a *subtle* effect of smoking does appear to be suggested by the data, but the study may not have been powered enough for the effects to reach our stringent statistical thresholds.

The absence of statistically significant smoking effects on the cognitive measures conflicts with some previous studies suggesting either worse (Depp et al., 2015; Iasevoli et al., 2013; Reed et al., 2016; Roth et al., 2013; Stramecki et al., 2018; Zhang et al., 2012) or improved (Ahlers et al., 2014; Hahn et al., 2012; Morisano et al., 2013; Sacco et al., 2005; Wing, Bacher, Sacco, & George, 2011a) cognitive performance in smoking relative to non-smoking SSD patients. However, they are consistent with a number of other studies that have reported no smoking effect in SSD samples (Ekinci & Ekinci, 2012; Iasevoli et al., 2013; Sánchez-Gutiérrez et al., 2018; Zhang et al., 2013).

The absence of cortical surface area differences between smokers and non-smokers in either diagnostic group supported our hypothesis, although the absence of an effect of smoking on all relevant volume and most of the thickness measurements did not. Two factors related to this finding must be noted. First, our hypotheses regarding smoking and brain volume and thickness in SSD were borne from a sparse literature in which extant studies report mixed findings and encompass several limitations. Second, findings were in the expected direction for many measures (0.20–0.40 Cohen's *d* effect size range), with many volume and thickness regions showing reductions that were initially significant but did not survive correction for multiple comparisons.

Notably, smoking in comparison with non-smoking participants had significantly *reduced* thickness in the left PCC, an area previously implicated in smoking-related addiction in healthy cohorts (Jarraya et al., 2010; Mondino et al., 2018). Although the right PCC finding did not survive correction for multiple comparisons, mean thickness within this region *was* reduced in the smoking group (Cohen's $d = 0.32$). These data together raise the possibility of an association between the PCC and smoking behaviour. The cingulate cortices contain high densities of nicotinic acetylcholine receptors (nAChR) (Picard et al., 2013), which are shown to be upregulated in smokers (Govind, Vezina, & Green, 2009) and have thus been related to smoking addiction. Notably, nAChR genes have been recently linked with risk for SSD (Hong et al., 2011). Given the significantly higher number of SSD smokers compared to HC smokers, it is plausible that the significant finding was driven by SSD smokers.

An emerging idea within recent literature is of an overlapping circuitry that may involve both smoking addiction and neurobiological mechanisms associated with SSD (Moran, Sampath, Kochunov, & Hong, 2013; Moran, Sampath, Stein, & Hong,

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2012). Several studies have implicated the PCC as a key node in the default mode network (Buckner, Andrews-Hanna, & Schacter, 2008; Hahn et al., 2007), which has been shown to function abnormally in SSD resting-state functional MRI studies (Brennan, Harris, & Williams, 2013; Karbasforoushan & Woodward, 2013). Moreover, the PCC has an important role in the consolidation of complex memories (Bird, Keidel, Ing, Horner, & Burgess, 2015) and retrieval of episodic memories (Natu et al., 2019), and the disruption of these has been argued to be associated with positive symptoms in psychosis (Sharp, Tomitaka, Bernaudin, & Tomitaka, 2001). Indeed, two drug models of psychosis – ketamine and psilocybin – have shown marked effects on the activity of the PCC (Leech & Sharp, 2014; Newell, Zavitsanou, & Huang, 2005). Given what is known about the PCC and smoking addiction, these findings give credence to the idea of an overlapping circuitry involving both smoking addiction and SSD.

Some limitations of the current data should be considered. First, as our sample was taken from a research bank not explicitly designed to research smoking, the number of high-frequency smokers in the control sample was low (see Table 1). Although our additional analysis showed a general absence of differences between high- and low-frequency smokers in terms of cognition and brain morphology (see online Supplementary material), we cannot discount that this may have influenced the capacity to discern subtle smoking effects. In addition, the *total* number of control smokers in the imaging subset was low, which may have further impacted the results. It is becoming increasingly recognised that much larger sample sizes are needed to reliably identify morphological differences, and hence our sample may have been too small to accurately demonstrate differences between the groups. Further, the prevalence of smoking is significantly higher in SSDs compared to the general population, and thus the nature of smoking behaviour within the sample was not random.

Second, incomprehensive, and incomplete smoking data meant we were unable to explore the effect of several important smoking factors (duration of smoking/age of smoking initiation/smoking dependence) on the relationships analysed. Further, the collection of smoking history data relied on self-report, which may be biased by subjective recall (Gorber, Schofield-Hurwitz, Hardt, Levasseur, & Tremblay, 2009). It is relatively well accepted that acute nicotine administration can improve cognitive functioning (Azizian et al., 2009; Sharma & Brody, 2009), and that chronic smokers experience withdrawal effects, including worsening of cognition (Ashare, Falcone, & Lerman, 2014). Thus, without exact measures of nicotine in the system, we were unable to control for the confounding influence of acute nicotine consumption or withdrawal. There is also a possibility that outcomes associated with chronic cigarette exposure are a result of other toxic compounds inhaled, as opposed to nicotine. As we did not include a direct measure of nicotine, this possibility cannot be excluded. Further, limited medication data also meant we were unable to control for the effects of medication, a relevant consideration given the hypothesised effects of antipsychotics on both cognition and brain morphology (Huhtaniska et al., 2017; Veselinović et al., 2019).

Third, the study was cross-sectional in nature, which precludes inferences concerning the causality of the associations. This design may also not be sensitive enough to capture associations between smoking and key variables of interest. Indeed, Van Haren et al. (2010) found that heavy smoking was related to brain volume loss *over time*, but it did not explain volume abnormalities in their baseline analyses. It is probable that the dynamic trajectory of smoking is more important than a single-time point, and subsequent studies should consider the effects of smoking in SSD longitudinally. Fourth, although the brain morphology ROIs were chosen based on the results of past literature, this method may have excluded some brain regions of relevance to smoking. Moreover, as the ROIs were selected partly based on literature showing changes in healthy smokers, findings may have been limited to regions that show changes in both cohorts, as opposed to SSD alone.

Finally, it must be noted that the patient group had a relatively low symptom load and long duration of illness, limiting generalisability. However, due to the multi-site method, the current dataset does constitute a representative sample of *community-dwelling* SSD patients. Other strengths include the large sample size for the cognitive analysis, and resulting increased statistical power compared to most previous studies on the topic. The study also provided an assessment of smoking status on several key features of SSD using a well-validated cognitive battery and measures of both cortical thickness and surface area in addition to brain volume, where only the latter has been of predominant focus in the sparse literature to date.

In sum, although the current study reported no group differences or interactions with the exception of reduced thickness in the left PCC, several results were in the expected direction and met significance initially but did not survive correction. These trends suggest the possibility of an effect that was not uncovered for the reasons mentioned above. Thus, future research on this topic is encouraged to determine if our findings replicate. Such research would do well to collect detailed smoking histories inclusive of direct nicotinergic assessment and dependency data, using large samples and employing longitudinal study designs.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291720005152

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