

Original Research

# Aberrant callosal morphology in ex-smokers

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## Abstract

**Background:** Cigarette smoking is associated with widespread structural alterations in both brain hemispheres as well as of the corpus callosum (i.e., the brain's main interhemispheric white matter pathway). While similar hemispheric alterations have also been reported in ex-smokers, no study has yet examined the corpus callosum in ex-smokers. **Methods:** We compared callosal morphology in a sample of 107 ex-smokers (57 males/50 females) and 193 non-smokers (73 males/120 females), aged between 42 and 97 years. More specifically, we measured the total callosal area as well as seven callosal subregions using the Witelson parcellation scheme. **Results:** At uncorrected levels, we detected significantly smaller callosal areas in ex-smokers than in non-smokers within the posterior midbody, genu, and isthmus (albeit the latter only on a trend level). When applying corrections for multiple comparisons, only the effect within the posterior midbody remained significant. **Conclusions:** Our findings suggest a weaker interhemispheric connectivity in ex-smokers compared to non-smokers, specifically between frontal and temporal areas.

**Keywords:** brain; corpus callosum; ex-smokers; posterior midbody; smoking; structural MRI; white matter

## 1. Introduction

Despite global reductions in smoking prevalence, tobacco usage remains a significant public health issue [1,2]. Smoking is known to cause degradation across multiple body systems [3], including the nervous system [4,5], presumably due to the toxic effects of nicotine and other chemicals found in commercial tobacco [5]. Various cross-sectional studies have demonstrated less gray matter [6–10] and altered white matter [10–12] in smokers compared to non-smokers, along with predominantly negative correlations between brain tissue measures and cumulative smoking load [6,8,9], but also see [7,9,13] reporting positive links. Surprisingly, the smoking-related literature pertaining to the brain's largest white matter fiber tract—the corpus callosum—is rather sparse, albeit a few studies exist [14–16]. More specifically, Choi *et al.* [14] reported a smaller total callosal volume in smokers than non-smokers as well as negative correlations between total callosal volume and cumulative smoking load. Durazzo *et al.* [15] observed a greater age-related callosal volume loss in smokers than non-smokers. Finally, Bjornholm *et al.* [16] detected smaller callosal volumes in male adolescents exposed to prenatal cigarette smoke compared to unexposed adolescents, but failed to replicate this effect in independent cohorts in the same study.

While there is some evidence for brain alterations in smokers/individuals exposed to smoking, there is hardly any research in ex-smokers (i.e., people who have quit

smoking). To our knowledge, only two imaging studies have analyzed links between brain anatomy and smoking cessation: Karama *et al.* [17] reported a negative correlation between cortical thickness and cumulative smoking load in ex-smokers; they also noted a positive correlation between cortical thickness and years of abstinence. Gons *et al.* [12] observed a normalization of white matter fiber integrity in ex-smokers as the years of abstinence increased; ex-smokers who had been abstinent for more than 20 years displayed mean diffusivity (MD) and fractional anisotropy (FA) values comparable to those observed in non-smokers. So, the few existing studies point to brain alterations in ex-smokers, where tissue attributes may indeed normalize over time. Nevertheless, it remains entirely unclear if such dose-dependent effects (e.g., significant correlations between smoking load/years of abstinence and brain measures in ex-smokers) and group differences (e.g., significantly altered brain measures in ex-smokers) also exist for the corpus callosum.

Thus, in order to expand an understudied but relevant field of research, we conducted the current study analyzing callosal anatomy in a relatively large sample ( $N = 300$ ) of ex-smokers and non-smokers. Group comparisons between ex-smokers and non-smokers were enhanced by correlational analyses within ex-smokers, linking callosal measures with relevant smoking parameters.



**Table 1. Study sample.**

	Ex-smokers	Non-smokers	<i>p</i>
Age (mean age $\pm$ SD (age range))	70.77 $\pm$ 8.11 (46–95)	67.5 $\pm$ 9.38 (42–97)	0.002 <sup>b</sup>
Sex (female/male)	50/57	120/73	0.010 <sup>c</sup>
Handedness (right-handed/non right-handed)	96/11	175/18	0.789 <sup>c</sup>
TIV (mean mL $\pm$ SD (mL range))	1398 $\pm$ 142 (1084–1754)	1370 $\pm$ 159 (958–1776)	0.414 <sup>b</sup>
Scanner (Biograph/Sonata/Trio/Vision)	8/3/89/7	12/10/159/12	0.782 <sup>c</sup>
Years abstained from smoking (mean $\pm$ SD (range))	31.00 $\pm$ 14.24 (1–65)	-	-
Years of smoking (mean $\pm$ SD (range))	19.18 $\pm$ 12.86 (1–52)	-	-
Cigarette packs per day (mean $\pm$ SD (range))	1.75 $\pm$ 0.95 (0.5–4.0)	-	-
Packyears <sup>a</sup> (mean $\pm$ SD (range))	28.00 $\pm$ 33.37 (0.50–156.00)	-	-

SD, standard deviation; TIV, total intracranial volume. <sup>a</sup> calculated as ‘years of smoking’ times ‘cigarette packs per day’. <sup>b</sup> determined using a two-sample *t*-test. <sup>c</sup> determined using a chi-square test.

## 2. Materials and methods

### 2.1 Participants

The final study sample consisted of 107 ex-smokers (age range = 46–95 years; 47% female) and 193 non-smokers (age range 42–97 years; 62% female), and was obtained through the Open Access Series of Imaging Studies-3 (OASIS-3) database (<http://oasis-brains.org>). To compile the dataset for the current study, first we inspected the participants’ accompanying clinical data excluding those with any documented cognitive impairment or acute disorder. Additional exclusion criteria were any diagnosis or history of neurological disorders, cerebrovascular disorder, psychiatric disorder, or head trauma (except for minor head trauma if it was neither acute nor recent). In order to avoid possible artefacts of temporary hypoperfusion and concurrent structural brain alterations, we also excluded participants with a history of cardiac arrest, congestive heart failure or cardiac bypass procedures. For the remaining 508 participants, we inspected the brain images and excluded those corrupted by artefacts or noise. The resulting sample of 485 healthy participants included 371 participants for whom smoking status had been established within one year before or after the brain scan. Of those, 14 active smokers were excluded (as the current study focused on ex-smokers and non-smokers). Of the remaining 357 participants, 300 participants (107 ex-smokers and 193 non-smokers) had complete and consistent accompanying information with respect to smoking/non-smoking. Sample characteristics are given in Table 1. All subjects gave written informed consent to participate and to publicly share their anonymized data [18,19].

### 2.2 Image acquisition and pre-processing

High resolution T1-weighted brain images were obtained on a 1.5T Siemens Vision scanner, a 1.5T Siemens Sonata scanner, a 3T Siemens Biograph scanner or a 3T Siemens Trio scanner. The acquisition parameters for each scanner are detailed elsewhere (<http://oasis-brains.org>). The voxel sizes differed slightly across the three scanners, measuring  $1 \times 1 \times 1.25 \text{ mm}^3$  (Vision),  $1 \times 1 \times 1 \text{ mm}^3$  (Sonata),  $1.2 \times 1.05 \times 1.05 \text{ mm}^3$  (Biograph) and  $1 \times 1 \times$

$1 \text{ mm}^3$  (Trio), which was accounted for by adding scanner as a nuisance variable to the statistical model (see Section 2.4). All brain images were processed using CAT12 (<http://www.neuro.uni-jena.de/cat/>), SPM12 (<https://www.fil.ion.ucl.ac.uk/spm/software/spm12/>) and MATLAB (<https://au.mathworks.com/products/matlab.html>) applying bias field corrections as well as rigid-body spatial normalizations to MNI space. In addition, images were tissue-classified into gray matter, white matter and cerebrospinal fluid to calculate the total intracranial volume (TIV) to be added as a nuisance variable to the statistical model (see Section 2.4).

### 2.3 Callosal tracing and area measures

Each corpus callosum was traced manually at the mid-sagittal brain section by a single rater (CD) blind to the participant’s smoking status. Before tracing this particular dataset, intra- and inter-rater reliability were established by tracing an independent set of twenty scans twice and comparing these traces to those of an experienced rater (FK). Both intra- and inter-rater reliability were high, with dice indices of 0.97 and 0.94 respectively. Seven callosal subareas were defined according to the Witelson parcellation scheme (see Fig. 1), followed by calculating the areas of the (a) rostrum, (b) genu, (c) rostral body, (d) anterior midbody, (e) posterior midbody, (f) isthmus and (g) splenium [20].

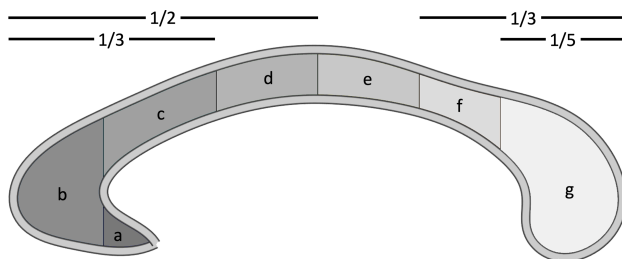
### 2.4 Statistical analysis

These seven subareas were compared between ex-smokers and non-smokers using a one-way multivariate analysis of covariance (MANCOVA), with age, sex, TIV, and scanner treated as nuisance variables. A significant omnibus test was followed up by seven area-specific post hoc analyses using the same nuisance variables. To assess potential sex differences in the effects of smoking, a group-by-sex interaction was calculated, which failed to reach significance ( $p = 0.909$ ), indicating that the effects of smoking were similar in males and females. The interaction term was therefore omitted in the main statistical model. In addition to these group comparisons (ex-smokers vs. non-smokers),

**Table 2. Findings.**

Callosal subarea	Group	Mean (mm <sup>2</sup> )	Standard deviation (mm <sup>2</sup> )	Significance ( <i>p</i> )
Rostrum	Ex-smokers	25.97	9.67	0.332
	Non-smokers	24.83	10.31	
Genu	Ex-smokers	122.95	27.27	0.015*
	Non-smokers	130.49	31.03	
Rostral body	Ex-smokers	93.57	14.61	0.594
	Non-smokers	92.61	16.37	
Anterior midbody	Ex-smokers	76.90	11.08	0.201
	Non-smokers	78.51	13.14	
Posterior midbody	Ex-smokers	71.51	10.20	0.002**
	Non-smokers	75.11	11.80	
Isthmus	Ex-smokers	58.00	12.89	0.059 <sup>T</sup>
	Non-smokers	60.63	12.95	
Splenium	Ex-smokers	199.80	29.20	0.175
	Non-smokers	204.70	32.17	

<sup>T</sup> significant, uncorrected on a trend level. \* significant, uncorrected. \*\* significant, corrected.



**Fig. 1. The Witelson parcellation scheme.** Shown are callosal subareas/proportions (from anterior to posterior): The rostrum (a), genu (b), and rostral body (c) comprise the anterior third of the corpus callosum. The anterior midbody (d) and the posterior midbody (e) comprise the middle third of the corpus callosum. The splenium (g) constitutes the callosal posterior fifth and, together with the isthmus (f), makes up the posterior third of the corpus callosum.

correlation analyses were performed within the ex-smoking group, specifically relating the seven callosal area measures to (1) the years of abstinence; (2) the years of smoking; (3) the cigarette packs per day; and (4) the pack years (i.e., the cumulative smoking load, calculated as ‘years of smoking’ times ‘cigarette packs per day’). Again, age, sex, TIV, and scanner were treated as nuisance variables. Bonferroni corrections were applied to account for multiple comparisons, yielding an adjusted significance threshold of  $p \leq 0.007$  (0.05/7).

### 3. Results

#### 3.1 Group comparisons

The MANCOVA indicated a significant main effect of group ( $p = 0.032$ ). The subsequent post hoc tests revealed that ex-smokers had a significantly smaller genu ( $p = 0.015$ )

and posterior midbody ( $p = 0.002$ ) than non-smokers, and also showed a trend for a significantly smaller isthmus ( $p = 0.059$ ). However, only the effect within the posterior midbody survived statistical corrections for multiple comparisons (see Table 2).

#### 3.2 Correlation analyses

No significant associations, not even at uncorrected significance levels, emerged between any of the callosal area measures and (1) years of abstinence; (2) years of smoking; (3) cigarette packs per day; and (4) pack years.

### 4. Discussion

The present study investigated differences in mid-sagittal callosal area between ex-smokers and non-smokers, detecting smaller corpora callosa in ex-smokers within the genu, posterior midbody, and isthmus. Of these areas, only the effects in the posterior midbody survived statistical corrections for multiple comparisons. Correlational analyses within ex-smokers group yielded no significant associations.

#### 4.1 Correspondence with previous findings

The smoking-related literature on the corpus callosum is sparse. Nevertheless, the nature of our findings seems to agree with previous studies reporting smaller callosal volumes [14], greater age-related callosal volume loss [15], as well as an altered callosal fiber integrity [13,21,22] in smokers. Another study outside the framework of smoking, points to negative links between callosal fiber integrity and positive drug tests (cocaine) over a period of eight weeks [23]. There is a lack of research on the corpus callosum within ex-smokers (rather than active smokers), but some structural alterations/normalizations have been reported [12,17], as detailed in the introduction. One of those

studies revealed that FA and MD (indicators of white matter fiber integrity) were aberrant in ex-smokers but normalized after 20 years [12] suggesting that negative effects of smoking may reverse eventually. However, this trend might not be true for all brain measures/regions. For example, the current study—where the average smoking cessation time was 31 years—revealed that callosal aberrations persist within the posterior midbody (and perhaps also within the genu and isthmus). In potential support of this assumption, there were no significant correlations between callosal area measures and the number of years abstained from smoking.

#### 4.2 Possible mechanisms

A smaller midsagittal callosal area may reflect a reduction in the number of interhemispheric axons and/or a reduction in the axonal fiber diameter, caused for example by decreasing myelin sheaths. As detailed in the following, smoking may affect the brain's white matter (and as such also the corpus callosum) through different mechanisms, either separately or in conjunction.

Smoking has been shown to lead to progression in white matter hyperintensities proportionate to cumulative smoking load [24]. These smoking-induced hyperintensities are caused by potentially reversible changes in interstitial fluid mobility and water content that become permanent (due to axonal lesions and demyelination) when the smoking continues [25]. Interestingly, smoking has also been shown to affect axonal myelination without directly damaging the axon by reducing the gene transcription factors of myelin-producing oligodendrocytes [26]. After smoking cessation, less than 25% of this demyelination seems to recover [26]. Finally, smoking drives the release of glutamate, which can be neurotoxic in high concentrations [27], with effects contributing to the gray matter loss in smokers in prefrontal, cingulate, temporal, thalamic, cerebellar and supplementary motor regions [6–9,28,29]. These gray matter losses may result in the degeneration of the respective callosal fibers (i.e., those that connect some of the aforementioned areas) as a direct result of neuron loss.

#### 4.3 Regional specificity

The corpus callosum was smaller in ex-smokers within the posterior midbody as well as within the genu and isthmus (albeit the latter two only when using less conservative thresholds). Although the literature is sparse with respect to ex-smokers, these findings are in agreement with studies that observed an altered fiber integrity in the genu, posterior midbody, and isthmus of smokers compared to non-smokers [21,22] as well as a negative association between fiber integrity and cumulative smoking load within the genu [13].

Fibers travelling through the posterior midbody connect the supplementary motor area (SMA) [30], a region associated with gray matter loss in smokers [28]. The SMA comprises part of the neural pathway governing response

inhibition, with lower gray matter volumes linked to greater impulsivity [31]. Impulsivity is regarded as a manifestation of inhibitory control dysfunction underlying lapses into addictive behavior [32], such as smoking. Fibers travelling through the callosal genu connect the prefrontal cortex [30,33], another region associated with gray matter loss in smokers [6,8–10], potentially due to neurotoxic glutamate exposure [27] and associated with impaired self-control, executive function and emotion regulation [34]. Fibers travelling through the callosal *isthmus* connect the inferior temporal cortex, yet another region associated with gray matter loss in smokers [6,28,35]. The inferior temporal cortex has been linked to emotional regulation and semantic cognition [35] and any dysfunction may bias the emotional response to smoking-related cues in the environment, leading to the maintenance of addiction [35]. The interplay between these factors is likely complex: A loss of neurons in the aforementioned cortical regions might cause (or be caused by) a loss of their respective transcallosal axons in the corpus callosum, which in turn may further enhance specific (smoking-related) impulses and habits.

## 5. Conclusions

The current study provides evidence that smoking results in sustained callosal changes, with ex-smokers presenting with smaller midsagittal callosal areas that showed no systematic associations with the length of time a person has been an ex-smoker. Future studies, optimally based on longitudinal designs and controlling for alcohol consumption and other lifestyle factors, are certainly indicated to replicate and further investigate the present results. Such future studies may also benefit from applying multimodal strategies by additionally investigating white matter integrity, local gray matter volumes, and/or the effect of smoking on nicotinic acetylcholine receptors, e.g., using positron emission tomography [36].

## Abbreviations

FA, Fractional Anisotropy; MD, Mean Diffusivity; OASIS-3, Open Access Series of Imaging Studies-3; SMA, supplementary motor area; TIV, total intracranial volume; UoA, University of Auckland.

## Author contributions

EL and FK conceived and designed the experiments; CD and DK performed the experiments; CD and FK analyzed the data; CD, EL and FK wrote the paper; CD, DK, EL and FK revised and approved the final manuscript.

## Ethics approval and consent to participate

All OASIS-3 participants gave written informed consent to participate and to publicly share their anonymized data (Marcus *et al.*, 2010; Marcus *et al.*, 2007). Additional local ethics approval for the data analysis was granted by



the University of Auckland (UoA) ethics committee (Protocol No. 022375).

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## Conflict of interest

The authors declare no conflict of interest.

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