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RESEARCH REPORT

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Altered morphological traits along central olfactory centres in congenitally blind subjects

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Abstract

It is well documented that early sensory loss typically alters brain morphology in the areas associated with the lost sense. However, much less is known about the impact of early sensory loss on the remainder of the sensory regions. Therefore, we investigated whether congenitally blind (CB) individuals show brain alterations in the olfactory system by comparing cortical morphology and olfactory bulb (OB) volume between 16 congenitally blind individuals and 16 sighted matched controls. Our results showed that not only CB blind individuals exhibited smaller OB but also alterations of cortical density in some higher olfactory processing centres, but unchanged cortical thickness. Our current findings suggest that a lifelong absence of visual input leads to morphological alterations in olfactory processing areas.

KEYWORDS
congenital blindness, magnetic resonance imaging (MRI), neuroplasticity, olfactory bulb, olfactory perception, olfactory system

1 | INTRODUCTION

Although olfaction and vision operate via anatomically distinct brain pathways, they both essentially serve the same function of object identification (Gottfried, 2010). The relation between both systems appears to be strong and bidirectional; each system can significantly influence the behavioural outcome of the other. It is well

Abbreviations: ACC, anterior cingulate cortex; AFC, alternative forced-choice; CB, congenitally blind; CSF, cerebrospinal fluid; GM, grey matter; MRI, magnetic resonance imaging; OB, olfactory bulb; OFC, orbitofrontal cortex; PC, piriform cortex; PEA, phenyl ethyl alcohol; ROI, region of interest; TDI, sum of threshold, discrimination and identification scores; TIV, total intracranial volume; VBM, voxel-based morphometry; WM, white matter.

known that visual stimuli can facilitate odour detection (Gottfried & Dolan, 2003) and identification (Demattè et al., 2009), but olfaction can also influence visual perception. For example, odours can influence eye movements (Seigneuric et al., 2010; Seo et al., 2010) and visual perception in binocular rivalry (Zhou et al., 2010). In addition, animal studies provide useful anatomical avenues by which these olfactory–visual associations may occur in the human brain. More specifically, primates, rodents and other species show that many olfactory-related regions, such as the primary olfactory cortex, receive convergent projections from the olfactory bulbs (OB) and retina (Cooper et al., 1994; Mick et al., 1993). The orbitofrontal cortex (OFC) also receives afferent inputs from both primary olfactory cortex and high-order visual areas and contains populations of bimodal neurons that are responsive to olfactory and visual stimulations (Öngür & Price, 2000; Rolls & Baylis, 1994). Taken together, these studies suggest an innate functional relationship between visual and olfactory systems among animals that may be present as well in humans.

Does the absence of visual experience prevent blind individuals from developing normal olfactory abilities? Independently to vision, olfaction alone conveys important information about the environment. The olfactory system not only serves to detect potential dangers, such as smoke, dust or gas, but also influences our social behaviour and well-being (Stevenson, 2010). Therefore, one may postulate that olfaction has an enhanced ecological value for blind individuals as olfactory stimuli provides for them crucial information about their surroundings that vision cannot signal or corroborate. Consequently, olfactory inputs might be processed more efficiently leading to supra-performances among blind individuals, a phenomenon known as behavioural compensation and well established for the other remaining senses (Frasnelli et al., 2011; Voss et al., 2010). It was suggested that these behavioural compensations are mediated by changes in (1) primary cortex of the visual and spared modalities and (2) polymodal association and (for a review, see Bavelier & Neville, 2002). However, one may also stipulate that the strong relationship between vision and olfaction described above could restrain any compensation benefits among blind individuals. Existing literature concerning blind individuals' olfactory abilities is highly conflictual, but according to the recent meta-analysis of Sorokowska et al. (2019), individuals living with visual impairment show no positive effects on the most commonly tested olfactory tasks, namely, odour detection thresholds, olfactory discrimination, or on free identification abilities. Although this may lead one to conclude the olfactory function is unchanged in blind individuals, the picture may be more complex, notably if the tasks themselves present a higher level of difficulty, a phenomenon that was previously shown in blind individuals within other modalities (Alary et al., 2008; Simon et al., 2002). More specifically, during a wine odour categorization task (Manescu et al., 2018), early-blind individuals presented lower scores compared with sighted controls, suggesting the importance of previous visual experiences in the formation of internal representations of complex odours, such as wines. On the other hand, congenitally blind individuals outperformed controls in an odour localization task but not in identification tasks (Manescu et al., 2021). This result is in line with the notion of improved spatial abilities for non-visual modalities in early-blind participants (Battal et al., 2020) and suggests that some components of olfactory objects (e.g. trigeminal components) may be processed differently among blind individuals. The presence of enhanced, equal and even decreased olfactory abilities among blind individuals raises numerous questions, in particular the integrity of their olfactory cortical structures.

The olfactory pathway connects the olfactory epithelium in the nose with (1) the OB (the relay station between peripheral and central structures of the olfactory system) and then (2) the primary [piriform cortex (PC) and adjacent areas] and secondary olfactory cortex (including OFC and insular cortex). Morphometric measures of these structures are generally positively associated with olfactory abilities (Frasnelli et al., 2010; Hummel et al., 2015; Seubert et al., 2013). More specifically, OB volume varies as a function of olfactory sensitivity and is decreased in patients with olfactory disorders (i.e. sinunasal, post-infectious and post-traumatic olfactory loss; Mueller et al., 2005; Rombaux et al., 2006a, Rombaux et al., 2006b; Yousem et al., 1999; Yousem et al., 1996) and may increase during olfactory training (Negoias et al., 2017) and recovery from an olfactory disorder (Gudziol et al., 2009; Haehner et al., 2008). Because most causes of olfactory dysfunction, such as sinunasal, post-infectious and possibly post-traumatic olfactory dysfunction are the result of damages peripheral to the OB, OB volume is strongly determined by bottom-up mechanisms. In addition to this, top-down mechanisms are involved as suggested by the effect of unilateral olfactory training on the contralateral OB (Negoias et al., 2017).

The effect of olfactory loss and restoration extends beyond the OB and results in structural alterations in higher-order brain areas. For example, patients with olfactory loss exhibit a decrease in grey matter volume across the primary and secondary olfactory cortex (Bitter, Brüderle, et al., 2010; Bitter, Gudziol, et al., 2010; Han

et al., 2017; Yao et al., 2014), although surgical treatment for chronic rhinosinusitis re-establishes olfactory function and leads to an increase of grey matter volume within olfactory processing areas (Whitcroft et al., 2018). Furthermore, olfactory training is associated with an increase in grey matter volume and cortical thickness of central olfactory processing areas (Al Aïn et al., 2019; Gellrich et al., 2018).

Despite the established link between olfactory ability and the morphology of olfactory cortical structures, the literature regarding cerebral morphological alterations of the olfactory system among blind is very scarce. To our knowledge, only two studies have explored this theme: a mouse model (Touj et al., 2020) and a human study (Rombaux et al., 2010). Interestingly, both studies found that compared with sighted subjects, blind subjects presented significantly larger OB as well as better olfactory performances. Although these findings support the hypothesis that blindness modulates the OB volume and olfactory abilities, a few considerations and methodological issues hamper the generalizability of these results. First, even if animal studies give the opportunity to control environmental factors, generalization of results to human species should be done with caution, in particular with rodents who have lower visual acuity than primates (Prusky et al., 2002), make extensive use of their whiskers (Diamond et al., 2008) and sense of smell (Uchida & Mainen, 2003; von Heimendahl et al., 2007) when exploring their environment and presented a different organization and composition of the OB (Lane et al., 2020). Second, to thoroughly evaluate morphological alterations of the olfactory system, one should use standardized olfactory tasks, such as the Sniffin' Stick (Hummel et al., 1997). Third, due to the differences in performance between CB individuals and those who lost their sight later in life (Leporé et al., 2010), it is very important to take this into account and provide a detailed description of the blind group (i.e. age at and cause of blindness onset and presence of light perception). Finally, cortical alterations beyond the OB should also be investigated to have a better understanding of the impact of blindness on the olfactory system.

The remarkable ability of the brain to reorganize itself is primarily expressed within a limited time period during early development (Hensch, 2005; Knudsen, 2004)—although the cortex does retain some plasticity throughout the lifespan of an individual (de Villers-Sidani et al., 2010; Mishra et al., 2014; Voss et al., 2017). Previous research in sensory deprivation did not always categorize participants with respect to the onset age of privation. The division of blind individuals is important from a theoretical perspective because early visual loss results in significantly more robust changes in the cortical structures supporting the processing of the remaining senses than for late-onset loss of sight (Collignon et al., 2013; Leporé et al., 2010; Maller et al., 2016; Park et al., 2009). However, brain alterations seen in blind individuals are often associated with divergent morphology in terms of cortical thickness, surface area and grey matter density (Jiang et al., 2009; Park et al., 2009). Therefore, studying congenitally blind individuals using a combination of complementary morphological measures will help to disentangle morphological alterations found in the olfaction processing areas following visual deprivation.

In the present study, we aimed to determine whether congenitally blind individuals exhibited morphological alterations in olfactory processing areas. Specifically, we measured OB volumes using volumetric planimetry as well as cortical density and thickness in the primary (PC, amygdala) and secondary (OFC, insula, temporal poles, anterior cingulate cortex (ACC), hippocampal–parahippocampal complex, thalamus, caudate nucleus, putamen, pallidum) olfactory cortices (Fjaeldstad et al., 2017). In addition, we assessed olfactory performance: odour thresholds for each nostril, odour discrimination, cued odour identification, and odour memory. We hypothesized that individuals with early blindness exhibit (1) altered OB volumes and (2) altered cortical density and thickness in olfactory brain areas and (3) that the olfactory performances are correlated with alterations in olfactory brain structures.

2 | MATERIAL

2.1 | Participants

Sixteen congenitally blind [CB; age mean (M) = 52.56, standard deviation (SD) = 13.226, level of education M = 13.25, SD = 3.225, 8 women, 2 smokers] and sixteen matched (age, gender, level of education, manual dominance and smoking habits) sighted individuals (controls; age M = 53.50, SD = 11.41, level of education M = 14.69, SD = 2.27, 8 women, 2 smokers) participated in our study. All CB participants were affected by total blindness (absence of light perception) as a result of bilateral ocular or optic nerve alterations from birth. Further detailed descriptions of blind individuals can be found in Table 1. Except for blindness, all subjects were healthy and without olfactory disorders and without a medical history of neurological or psychiatric problems. Participants were instructed not to eat or drink anything besides water 1 h prior to the experiment. The study was approved by the Multicentric Research Ethics Board of the

TABLE 1 Characteristics of blind participants

Participant	Age	Sex	Education (years)	Handness	Smoking	Residual visual perception	Onset	Cause of blindness
B01	66	M	14	R	No	Diffuse light	0	Congenital cataracts
B02	28	M	16	R	Yes	No	0	Congenital microphthalmia
B03	61	F	8	R	No	No	0	Retinopathy of prematurity
B04	69	M	14	R	No	No	0	Rubella virus during pregnancy of the mother
B05	50	M	16	L	No	Diffuse light	0	Retinal detachment
B06	47	M	11	R	No	No	0	Retinopathy of prematurity
B07	51	F	16	R	No	No	0	Retina dysplasia
B08	32	M	14	R	No	No	0	Retinopathy of prematurity
B09	63	F	14	R	No	No	0	Retinopathy of prematurity
B10	54	M	10	R	No	No	0	Retinopathy of prematurity
B11	55	M	16	L	Yes	No	0	Affected by thalidomide treatment
B12	63	F	16	R	No	No	0	Leber congenital amaurosis
B13	66	F	7	R	No	No	0	Retinopathy of prematurity
B14	36	F	11	R	Yes	No	0	Retinal detachment
B15	37	M	18	R	No	Diffuse light	0	Leber congenital amaurosis
B16	63	F	11	R	No	No	0	Congenital toxoplasmosis

"Regroupement Neuroimagerie du Québec" [CMER RNQ 11-12-007]. All participants gave their written informed consent prior to inclusion.

2.2 | Assessment of olfactory functions

Psychophysical testing of olfactory function was performed with the Sniffin' Sticks battery (Hummel et al., 1997) based on pen-like odour dispensers. To present an odour, the pen's cap was removed by the experimenter for approximately 3 s, and the tip of the pen is placed approximately 2 cm in front of the nostril. All subjects (CB and controls) were blindfolded with an eye mask to prevent visual identification of the odour-containing pens. In addition to the usual testing, including odour threshold, odour discrimination and odour identification, we assessed odour perception and odour recognition memory.

1. Odour thresholds for each nostril were determined for phenyl ethyl alcohol (PEA, a rose-like odour) diluted in propylene glycol, with altogether 16 numbered dilutions, number 1 representing the strongest and number 16 the weakest odour. Odours were presented in triplets pens, with one pen among each triplet containing diluted PEA and two containing only propylene glycol, serving as blanks. Employing a 3-alternative forced-choice (3-AFC) paradigm, subjects had to identify the smelling pen among each triplet. Thresholds were determined using a single staircase technique: two successive correct identifications of the odour-containing pen or one incorrect response triggered a reversal of the staircase to the next higher or the next lower dilution step, respectively. Seven reversals had to be obtained (Hummel et al., 1997). Odour thresholds were determined as the average dilution of the last four staircase reversals for each nostril. The first nostril tested was counterbalanced across participants.
2. Odour discrimination (Hummel et al., 1997) was evaluated by presenting the subjects 16 triplets of odorants, of which two pens were the same and one was different. The subject's task was to indicate which pen of the triplet smelled differently. The discrimination scores were the count of correctly identified pens.
3. Odour identification (Hummel et al., 1997) was determined by presenting the subjects 16 pens containing different and common smells (e.g. orange, cinnamon,

onion, banana, lemon or fish). The subjects' task was to identify the odourant out of a list with four verbally presented descriptors in a forced-choice procedure (4-AFC). The identification scores were the count of correctly identified pens. The scores of each test, which could vary between 0 and 16, were summed into a total threshold, discrimination and identification (TDI) score. Higher scores indicate better performance.

4. To assess odour perception, following each presentation in the odour identification score, participants were instructed to rate the odorant in terms of pleasantness on a scale ranging from 1 to 7 (1 being *very unpleasant* and 7 being *very pleasant*) and intensity on a scale ranging from 1 to 5 (1 being *not intense* and 5 being *very intense*).
5. Finally, for the odour recognition memory task, we used eight randomly selected target pens that had been already presented to participants during the identification test and eight additional pens from the extended version of the Sniffin' Sticks test battery (Haehner et al., 2009). Therefore, 16 pens (eight target odours) were presented, and subjects were asked whether they smelled the odour before (i.e. during the identification test). Target and distractor odours were randomly selected at the onset of the study, used for all participants, and a random presentation order was pre-defined for every participant. Following each pen presentation, subjects were instructed to rate their degree of certainty about their answer on a scale ranging from 1 to 5 (1 being *not certain* and 5 being *very certain*).

2.3 | Whole-brain MRI image acquisition and OB image acquisition

Whole-brain magnetic resonance imaging was performed using a 3-T Prisma Fit system (Siemens, Erlangen, Germany) with a 32-channel phased-array head coil. Anatomical data were acquired using a T1-weighted three-dimensional (3D) magnetization-prepared rapid acquisition gradient echo sequence (MPRAGE) with the parameters: voxel size $1 \times 1 \times 1$ mm^3; repetition time (TR) = 2300 ms; echo time (ET) = 2.26 ms; inversion time (TI) = 900 ms; field of view (FoV) = 256; 176 contiguous slices of 1 mm thickness.

OB images were obtained using a focused acquisition paradigm (Yousry et al., 2000). Accordingly, coronal, fast spin-echo T2-weighted sequence covering the anterior and middle segments of the skull base was acquired with the following parameters: TR = 6100 ms; TE = 83 ms; voxel size $0.2 \times 0.2 \times 2$ mm^3, flip angle 150°, in total 29 contiguous slices of 2 mm thickness with no intergap.

3 | DATA ANALYSIS AND STATISTICS

3.1 | Behavioural data

Data were analysed using the software SPSS for Windows (Statistical Package for the Social Sciences, Version 25.0, SPSS Inc., Chicago, IL, USA). Statistical significance was set at $p < 0.05$, and Bonferroni corrections were applied for multiple comparisons. Data were assessed for normality and parametric or non-parametric tests used as appropriate. Unless otherwise specified, data are given as mean (SD).

3.2 | OB volumetric analysis

Using the OB acquisitions, manual planimetry was performed to measure OB volume using ImageJ software (available from https://imagej.net/). The surface area of the left and right OB was drawn manually on each coronal slice and calculated (surface in mm^2). The pronounced diameter change in transition from bulb to tract was used as the distal demarcation of the OB. The surface area of each slice was then summated and multiplied by slice thickness (2 mm) to obtain a volume in cubic millimetres. Previous studies using this approach of calculating and analysing OB volume have been shown to be reliable and accurate (Mueller et al., 2005; Yousem et al., 1997). OB measurements of all participants were performed twice by the same experimenter (CCL). The results from both measurements were averaged for further statistical analysis. The difference of the two measurements ranged from 65 to 66 ($M \pm SD = 65.86 \pm 15.4$) mm^3 for the left OB and from 62 to 63 ($M \pm SD = 62.9 \pm 16.7$) mm^3 for the right OB. For reliability purposes, interclass correlation coefficients for these data were calculated using a single-measurement, absolute-agreement, two-way mixed-effects model (ICC left OB = 0.973 with 95% confidence interval = 0.945–0.986, $p = 0.001$; ICC right OB = 0.991 with 95% confidence interval = 0.981–0.996, $p = 0.001$). A second rater (SM) measured OB volumes of all participants for the purpose of calculating the inter-rater correlation using also a single-measurement, absolute-agreement, two-way mixed-effects model

(IRC left OB = 0.970 with 95% confidence interval = 0.932–0.986, $p = 0.001$; IRC right OB = 0.989 with 95% confidence interval = 0.978–0.995, $p = 0.001$). Over all participants, the volume of the right OB (62.9 ± 16.7 mm^3) was comparable with the left OB (65.8 ± 15.3 mm^3, $t(31) = -1.972$, $p = 0.058$).

3.3 | Preprocessing

Preprocessing was performed using the CAT12 toolbox (available from http://www.neuro.uni-jena.de/cat/) implemented in SPM12 and MATLAB (MathWorks, Natick, MA, USA). According to SPM priors and to examine for obvious motion artefacts, a careful visual inspection of the T1 images was performed. These images were first segmented into white matter (WM), cerebrospinal fluid (CSF) and grey matter (GM). The classification of voxels was done depending on the grey steps and the classification of the surrounding voxels. Subsequently, these segmented GM images were spatially normalized in the customized template in standardized anatomical space using Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL).

3.4 | Cortical thickness

CAT12 uses a projection-based thickness (PBT) approach that uses tissue segmentation to estimate the white matter distance and projects the local maxima (equal to the cortical thickness) to other grey matter voxels by using a neighbour relationship described by the white matter distance (Dahnke et al., 2012). This results in separate cortical thickness data for the left and right hemispheres. This cortical thickness data were finally resampled and smoothed using a 15-mm FWHM kernel.

3.5 | Voxel-based morphometry

Cortical density was defined as the relative concentration of grey matter within a voxel. Voxel-based morphometry (VBM) data were resampled and smoothed using an 8-mm FWHM kernel. Each participant's data were entered in a second-level analysis. For all VBM analyses, we included total intracranial volume ['TIV', summated GM, WM and CSF volume (Ashburner & Friston, 2000)] as a 'nuisance covariate' during model specification in order to remove variance related to this global parameter of brain morphometry. An absolute grey matter threshold of 0.2 was applied to avoid possible edge effects between different tissue types (Delon-Martin et al., 2013; Han et al., 2017).

3.6 | Region of interest analysis

We were interested in morphometric measures of brain regions known to be relevant to olfaction and have a priori hypotheses regarding these relevant areas. Therefore, we performed a region of interest (ROI) analysis. We chose to base our ROIs from the merged functional and structural olfactory network map defined by Fjaeldstad et al. (2017). Our defined ROIs included bilateral areas of the primary and secondary olfactory cortex; primary (PC, amygdala) and secondary (OFC, insula, temporal poles, ACC, hippocampal–parahippocampal complex, thalamus, caudate nucleus, putamen, pallidum). ROIs were created within the WFU-PickAtlas software (available from http://fmri.wfubmc.edu/software/PickAtlas). The Montreal Neurological Institute (MNI) coordinates were used to report significant voxels. To control for the Type I error rate, we applied the Bonferroni correction by dividing the probability α (0.05) by the number of ROIs used (11) ($p_{corrected} = 0.0045$) (Croy et al., 2016; Delon-Martin et al., 2013).

3.7 | Relation between behaviour and imaging

We were interested in whether differences in morphometric measures were related to other factors, such as psychophysical test scores and subjective measures of olfaction perception. Using the MarsBaR toolbox for SPM (available from: http://marsbar.sourceforge.net/), only significant GM and thickness voxel clusters within the a priori ROIs were extracted to determine whether differences in morphometrics were correlated with behavioural measures. We also performed a correlation analysis between OB volume and GM volume (GM extracted densities from a priori ROIs as described) for both groups separately.

4 | RESULTS

4.1 | Psychophysical measurement

Psychophysical test scores and subjective evaluation of odours by both groups are shown in Table 2 and are illustrated in supplementary Figures S1 and S2. Correlation matrices among demographic variables, psychophysical

olfactory tests and subjective evaluations of the odours are provided in supplementary Tables S1–S3. Participants of the CB group did not differ from the control group in any olfactory task or subjective ratings of odours.

4.2 | Brain imaging

4.2.1 | OB volumetric measures

Congenitally blind individuals had significantly smaller OB volume bilaterally compared with sighted individuals (Table 3 and Figure S3).

4.2.2 | Cortical thickness

No significant differences were found within the pre-specified ROIs between blind individuals and controls.

TABLE 2 Psychophysical olfactory test and subjective evaluation of the odours

	Early blind group	Control group
'Sniffin' sticks' score		
Best nostril threshold (T)	9.19 (3.11)	10.20 (3.23)
Left nostril threshold	7.03 (3.04)	8.94 (4.12)
Right nostril threshold	8.20 (3.51)	9.16 (3.18)
Discrimination (D)	11.69 (2.09)	11.94 (2.52)
Identification (I)	12.50 (1.27)	12.44 (1.55)
Olfactory memory (OM)	11.56 (1.75)	11.13 (3.14)
T + D + I	33.38 (3.91)	34.58 (4.18)
Subjective score		
Pleaseantness of I odours	5.22 (1.08)	4.94 (0.86)
Intensity of I odours	4.12 (0.86)*	3.62 (0.39)*
Certainty of OM odours	4.17 (0.53)	3.93 (0.58)

Note: Results shown as mean (SD).
*Indicates statistically significant difference.

4.2.3 | VBM

Controlling for TIV, there were significant increases in GM density within the left temporal pole and the right ACC of blind individuals. In contrast, there was significant reduction in GM density among blind individuals within the left hippocampal–parahippocampal complex and both sides of the OFC (Table 4 and Figure 1). There were no other significant voxels within the pre-specified ROIs.

4.3 | Correlation between behavioural and brain measures

The olfactory threshold on the right nostril correlated with right OB volumes ($r = 0.500$, $p_{corrected} = 0.004$), but we did not observe any other significant correlation between psychophysical scores and OB volumes. Especially, we did not observe any group difference.

With regard to GM density, we observed a negative correlation between pleasantness ratings and left OFC GM density (−26, 21, −24) in the control group ($r = -0.710$, $p_{corrected} = 0.002$), but no other psychophysical score was correlated to GM density in any of the significant clusters within the a priori ROIs, in any group.

We were also interested in whether OB volume was related to GM density. As shown in Table 5, we found numerous positive correlations between OB volume and GM density within the significant clusters in the left temporal pole, left insula and orbitofrontal cortex (Figure 2) for the blind group, whereas only the left OB correlated with the left temporal pole for the control group.

5 | DISCUSSION

In the present study, we show morphological changes across multiple regions of the extended olfactory system in congenitally blind individuals, including the OB and higher-order processing centres. These alterations were not associated with any difference in psychophysical measures.

TABLE 3 OB volume in mm^3

	OB volume			
	Early blind group	Control group	*T* scores	*p*-values
Left	59.63 (15.69)	71.96 (12.53)	2.46	0.020
Right	57.00 (16.64)	68.71 (15.07)	2.09	0.046
Combined L + R	116.63 (30.98)	140.67 (26.61)	2.35	0.025

Notes: Results shown as mean (SD). *T* scores and associated *p*-values are shown.

TABLE 4 Alterations in GM volume of blind individuals within a priori ROIs

Regions	Side	MNI coordinates			*T* score
		X	Y	Z	
Anterior cingulate cortex	R	9	47	26	2.87
Temporal pole	L	−50	18	−30	3.54
Hippocampal–parahippocampal complex	L	−33	−38	−8	3.02
Orbitofrontal cortex	R	12	17	−24	3.70
	R	39	30	−15	3.07
	L	−26	20	−21	2.86
	L	−26	21	−24	3.15
	L	−32	38	−11	3.37

Notes: Results thresholds $p < 0.0045_{corr}$. Results controlled for TIV. Coordinates are expressed in MNI space.

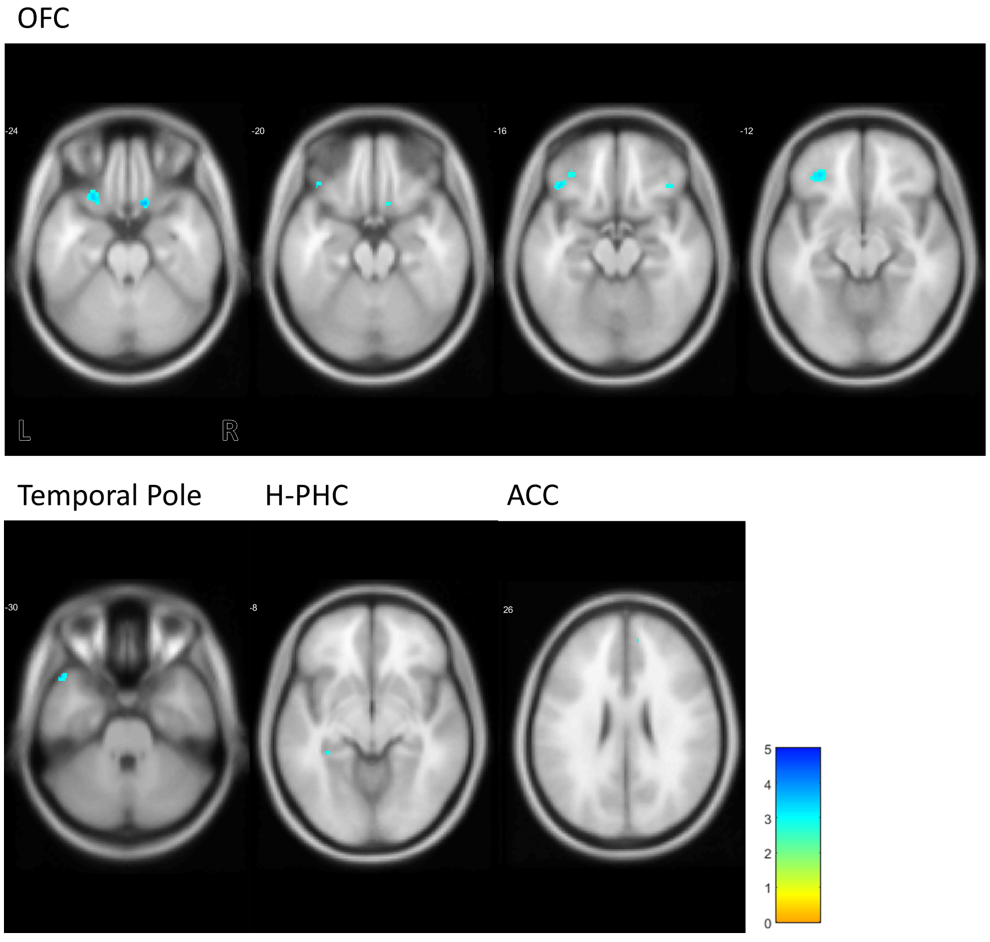

FIGURE 1 Transverse sections showing significant voxels from ROI analysis in secondary olfactory regions (*T* score scale to bottom right). Threshold set to $p < 0.0045_{corr}$. ACC, anterior cingulate cortex; H-PC, hippocampal–parahippocampal complex; OFC, orbitofrontal cortex. Y coordinate shown in top left corner, expressed in MNI space. Side according to neurological convention, as shown in top left panel

Our findings suggest that early blindness leads to a volume reduction of the OB. These results contrast with earlier findings of blind individuals exhibiting significantly larger OB than sighted individuals (Rombaux et al., 2010). Unfortunately, the authors did not furnish complete description of the composition of their early blind group (i.e. cause of blindness, age of onset, gender and age at the testing), which makes it difficult to pinpoint the reasons for this marked difference. In our study, we provided details about every congenitally blind individual included in order to offer the possibility to replicate our results easily. Moreover, we carefully paired every blind participant with a comparable sighted control not solely based on age and gender but also on level of education, smoking habit and manual dominance, variables potentially related with olfaction function and/or

TABLE 5 Statistically significant correlations between significant ROI GM clusters and OB volume

	Significant correlations			
			OB volume	
ROIs	**OB**	**Early-blind group**	**Control group**	**Both groups**
Temporal pole				
(−50, 18, −30)	Left	$r = 0.703$, $p = 0.002$	$r = 0.624$, $p = 0.010$	$r = 0.610$, $p = 0.001$
	Right			$r = 0.460$, $p = 0.008$
	L + R	$r = 0.668$, $p = 0.005$		$r = 0.521$, $p = 0.002$
Orbitofrontal cortex				
(−26, 20, −21)	Left			$r = 0.482$, $p = 0.005$
	L + R			$r = 0.435$, $p = 0.013$
(−26, 21, −24)	Left			$r = 0.497$, $p = 0.004$
	L + R			$r = 0.457$, $p = 0.008$
	Left	$r = 0.635$, $p = 0.008$		$r = 0.589$, $p = 0.001$
(−32, 38, −11)	Right			$r = 0.411$, $p = 0.012$
	L + R			$r = 0.549$, $p = 0.001$
	Left	$r = 0.626$, $p = 0.009$		$r = 0.504$, $p = 0.003$
(12, 17, −24)	Right	$r = 0.638$, $p = 0.008$		$r = 0.501$, $p = 0.003$
	L + R	$r = 0.712$, $p = 0.002$		$r = 0.525$, $p = 0.002$
	Left			$r = 0.460$, $p = 0.008$
(39, 30, −15)	L + R			$r = 0.440$, $p = 0.012$

Notes: Pearson's and Spearman's correlation coefficients (r) and associated p-values with Bonferroni correction ($p_{corrected} = 0.0167$) are shown.

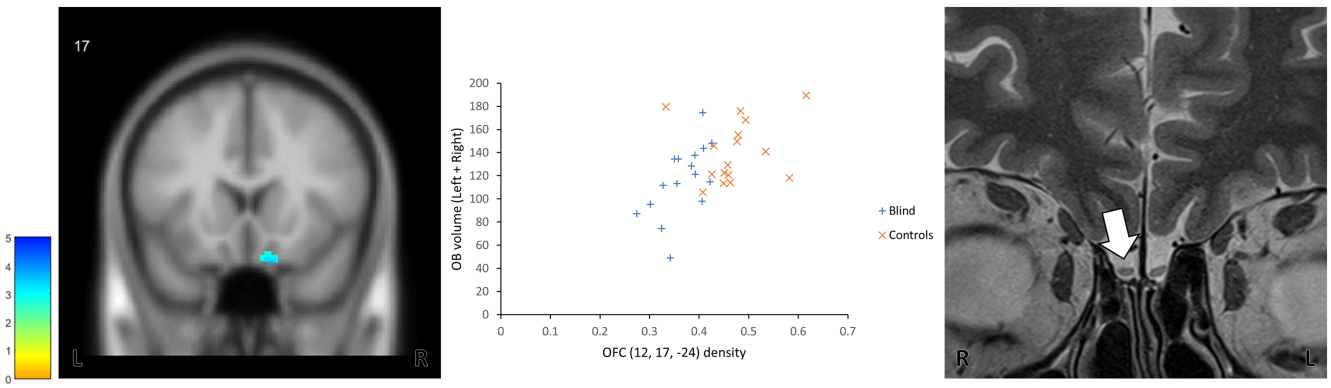

FIGURE 2 Scatterplot showing significant correlation ($r = 0.525$, $p = 0.002$) between change in total OB volume (y-axis, mm^3) and GM density (x-axis) within the significant OFC cluster (12, 17, −24). Left coronal T1 section = OFC cluster (y coordinate shown in top left corner, scale bar showing T score to left of image), right coronal T2 image = bilateral OB in a participant (white arrow showing right OB—please note neurological siding convention in left coronal T1 image and radiological siding convention in right coronal T2 image, as marked)

OB volumes (Fornazieri et al., 2019; Frye et al., 1990; Hummel et al., 1998; Orhan et al., 2012; Schriever et al., 2013; Zatorre & Jones-Gotman, 1990). Numerous studies highlight OB plasticity and the importance of olfactory input in modulating its volume (Mueller et al., 2005; Rombaux et al., 2006a, 2006b; Yousem et al., 1999). In fact, most studies evaluating OB volumes interpret changes in OB volume as the result of alterations of peripheral input (for review, see Huart et al., 2013). However, in recent years, diverse evidence showed that top-down processes are also involved in OB plasticity (Huart et al., 2013; Hummel et al., 2013; Negoias et al., 2017). There is no reason to suspect peripheral olfactory input to be altered in blindness. This is in line with the results of Sorokowska et al. (2019) meta-analysis, where blind and sighted individuals had

similar olfactory psychophysical performances. Consequently, our results support the hypothesis that OB volume modulation is possible in the absence of peripheral alteration. Future studies should also examine the integrity of peripheral olfactory system in order to rule out the possibility that OB volume is influenced by peripheral alterations.

Usually, OB volume is positively correlated with olfactory performance, and smaller OB volume is associated with a reduction in olfactory function, in both healthy (Buschhüter et al., 2008; Huart et al., 2013; Nguyen et al., 2016; Seubert et al., 2013; Turetsky et al., 2000; Yousem et al., 1999) and unhealthy individuals (Nguyen et al., 2011; Rombaux et al., 2009; Thomann et al., 2009). However, despite having a smaller OB, blinds individuals exhibited olfactory scores comparable with their sighted counterparts. This lack of any association between OB size and olfactory performance is in line with the earlier report, which, despite finding larger OB in blind individuals, did not observe any significant correlation between OB volume and olfactory identification/discrimination (Rombaux et al., 2010). In addition, our study lends further support to the notion that blind people do not have superior olfactory discrimination abilities compared with the sighted (Sorokowska et al., 2019).

The structural alterations we observed in congenital blindness stretch beyond the OB. For instance, bilateral OFC shows reduced GM in congenitally blind individuals. This region is part of the secondary olfactory cortex and receives cortico-cortical input from the PC. Its main functions include affective and experience-dependent odour percept encoding (Anderson et al., 2003; Gottfried et al., 2002; Zou et al., 2016) as well as multimodal sensory integration (Gottfried & Dolan, 2003). Typically, OFC thickness and olfactory performance scores are positively correlated (Frasnelli et al., 2010; Seubert et al., 2013). To illustrate, OFC volume is increased in perfumers, possibly due to an olfactory experience-dependent structural reorganization (Delon-Martin et al., 2013). Two explanations for reduced OFC GM density in blind individuals can be put forward. First, (1) the more complex olfactory behaviours usually associated with the OFC might be carried out, at least in part, by the visual cortex, as the occipital cortex plays an important role in the processing of the preserved sensory modalities in early blind individuals (for a review, see Frasnelli et al., 2011). In fact, the occipital cortex of blind individuals might act as a multimodal high-tier area, able to participate in more demanding processes (Büchel, 2003; Voss et al., 2010). In line with this, blind individuals recruit their occipital areas during an olfactory detection task (Beaulieu-Lefebvre et al., 2011). Second, (2) the OFC may not act as a visual–olfactory integration centre in early blind individuals, as it does in sighted individuals. More specifically, functional neuroimaging studies have identified activations of this region in response to congruent odour–visual presentations (Gottfried & Dolan, 2003). Furthermore, as the perceived congruency between a colour and odour pairing increases, the higher the activity in the OFC in sighted individuals (Österbauer et al., 2005). In primates and rodents, it has been shown that the OFC receives afferent inputs form both the POC and higher-order visual areas and also contains populations of bimodal neurons that are responsive to both olfactory and visual stimulation (Öngür & Price, 2000; Rolls & Baylis, 1994). Because OFC density appears to be experience dependent (Delon-Martin et al., 2013; Whitcroft et al., 2018), its relative underuse in congenital and early blindness, because of the two possibilities exposed above, may thus result in reduced density.

Additionally, the left temporal pole also had a reduced GM density in blind individuals. Both temporal poles are involved in olfactory processing (Jones-Gotman & Zatorre, 1993; Lötsch et al., 2016; Rausch et al., 1977; Royet et al., 2000) and receive input from the PC, amygdala and OFC. Their main role in olfactory processing is to assign emotional valence to sensory stimuli (Olson et al., 2007). One could therefore speculate that blind individuals process the emotional valence of odours differently. Although we did not observe any group difference for the evaluation of subjective odour pleasantness, one study has provided some support for this hypothesis (Iversen et al., 2015). Consequently, future neuroimaging studies should include odorant hedonic as a covariable when comparing odor processing in blind and sighted participants. In contrast to these two structures, we found that the ACC exhibited higher GM in congenitally blind individuals. The ACC plays a key role in attention (Botvinick, 2007; Pessoa, 2008), and it responds to the pleasantness of odours (De Araujo et al., 2005). Our results might relate to higher olfactory awareness of blind adults (Beaulieu-Lefebvre et al., 2011) and stronger reactions to odours in different situations in blind children (Ferdenzi et al., 2010). Ideally, future studies should therefore control or evaluate the impact of this factor by assessing olfactory awareness of individuals participating in their study. This could be done via the completion of a simple questionnaire (Odor Awareness Scale; Smeets et al., 2008).

Despite our best efforts, this study has some limitations. First, our study has relatively small groups of participants; it is therefore possible that individual variations might influence the results. However, behavioural results are coherent with the meta-analysis of Sorokowska et al. (2019) showing no superiority of blind individuals in olfactory tasks. Second, due to the relatively small sample

size, we did not consider multivariate covariance in morphometric features among our ROIs (Carmon et al., 2020). Therefore, it is possible that although morphometric measures (cortical thickness/density) are identical for both groups in a given olfactory region, they are differently correlated with the same measure in other cortical regions. Group differences in interregional correlations of morphometric features would then suggest differences in brain development and its organization across groups. Future studies should therefore include larger sample sizes that allow for multivariate analyses to specifically investigate interregional correlations to improve our understanding of experience-dependent plasticity in the context of visual deprivation. Future studies should also use state-of-the-art analyses techniques such as principal component analysis to investigate the variables that explain individual variability across the population (e.g. blindness onset, blindness duration, cause of blindness). This would allow us to better understand variables that influence the integrity of the olfactory system among blind individuals as well as olfactory abilities. In order to do so, studies need to be appropriately powered, a recurrent problem when investigating blind individuals. We therefore suggest that researchers use standardized measures for both olfactory evaluation and brain imaging. This will eventually enable the community to merge data sets in order to achieve required sample sizes for advanced data analysis.

To sum, we show structural differences in the extended olfactory system of congenitally blind individuals that are not restricted to peripheral brain structures such as OB, but extend well beyond them, including the temporal poles and OFC.

CONFLICT OF INTEREST

The authors declare no competing interests.

ETHICS STATEMENT

The study was approved by the Multicentric Research Ethics Board of the "Regroupement Neuroimagerie du Québec" (CMER RNQ 11-12-007); all participants gave their written informed consent in agreement with the ethical principles for research involving human subjects (Declaration of Helsinki).

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/ejn.15758.

DATA AVAILABILITY STATEMENT

Due to data-privacy protection issues, the collected MRI and behavioural datasets cannot be made available in public repositories. In particular, public sharing was not requested in the proposal for the Ethical Committee (CMER RNQ), and participants were not explicitly asked for their permission. The pseudo-anonymized dataset will be stored on a server, and the corresponding author can provide access to the data upon reasonable requests.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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