

## Morphological changes in secondary, but not primary, sensory cortex in individuals with life-long olfactory sensory deprivation

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### ABSTRACT

Individuals with congenital sensory deprivation usually demonstrate altered brain morphology in areas associated with early processing of the absent sense. Here, we aimed to establish whether this also applies to individuals born without a sense of smell (congenital anosmia) by comparing cerebral morphology between 33 individuals with isolated congenital anosmia and matched controls. We detected no morphological alterations in the primary olfactory (piriform) cortex. However, individuals with anosmia demonstrated gray matter volume atrophy in bilateral olfactory sulci, explained by decreased cortical area, curvature, and sulcus depth. They further demonstrated increased gray matter volume and cortical thickness in the medial orbital gyri; regions closely associated with olfactory processing, sensory integration, and value-coding. Our results suggest that a lifelong absence of sensory input does not necessarily lead to morphological alterations in primary sensory cortex and extend previous findings with divergent morphological alterations in bilateral orbitofrontal cortex, indicating influences of different developmental processes.

### 1. Introduction

The notion that the human brain is plastic and undergoes morphological as well as functional alterations in response to changes in experienced demands is widely accepted (Buonomano and Merzenich, 1998; Lindenberger et al., 2017). One of the more drastic changes in demands on the brain is undoubtedly the loss of a sensory modality, comprising a complete lack of input from the lost sense combined with altered demands on the remaining senses. Indeed, visual sensory deprivation has repeatedly been linked to both structural and functional cerebral reorganizations with often profound changes in regions normally focused on the processing of the absent sense, often in primary sensory cortex (for reviews see Bavelier and Neville, 2002; Frasnelli et al., 2011; Merabet and Pascual-Leone, 2010). In contrast, few studies have investigated the

potential plastic effects of complete olfactory sensory deprivation (anosmia, for a review see Reichert and Schöpf, 2018) and reports on cerebral reorganization in individuals with lifelong (congenital) anosmia is particularly rare.

Although the brain exhibits plasticity throughout life, it is strongest early in life when even brief periods of sensory deprivation can make it difficult, if not impossible, to gain normal abilities even if the sensory loss is reversed and normal sensory input established (Collignon et al., 2015; Guerreiro et al., 2016; Hyvärinen et al., 1981; Wiesel and Hubel, 1965). Thus, in comparison to individuals who have gone through normal sensory development, individuals with a congenital or very early acquired complete sensory deprivation would be expected to demonstrate pronounced patterns of cerebral reorganization. In addition, studying individuals with an isolated congenital sensory deprivation (i.e., a

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congenital sensory deprivation not related to additional symptoms) has the advantage of isolating plastic effects of the sensory deprivation, whereas individuals with an acquired sensory loss constitute a much more heterogeneous group where variability in the age at which the sense was lost, the duration of the sensory loss, the direct cause of sensory loss (as in the case of traumatic brain injury, which might in itself cause reorganization of the brain), and perceptual abilities before sensory loss likely affect sensory loss-related cerebral reorganization (Jiang et al., 2015; Noppeney et al., 2005; Voss and Zatorre, 2012). Individuals with isolated congenital sensory deprivation hence constitute a good model for increasing our understanding of the adaptiveness the human brain possesses.

Both congenital and acquired visual sensory deprivation have repeatedly been linked to atrophy in form of decreased gray matter volume in areas related to visual processing, specifically within primary visual cortex (Bridge et al., 2009; Jiang et al., 2015; Noppeney et al., 2005; Pan et al., 2007; Ptito et al., 2008). The gray matter volume decreases are, however, associated with divergent underlying morphology: the atrophy in congenital blindness is accompanied by a thickening of the visual cortex (Bridge et al., 2009; Hasson et al., 2016; Jiang et al., 2009; Park et al., 2009), whereas the atrophy in individuals with acquired sensory loss has been linked to either a cortical thinning or a lack of cortical thickness alterations (Jiang et al., 2009; Park et al., 2009; Voss and Zatorre, 2012). The fact that divergent underlying morphology may cause similar volumetric results emphasize the importance of not solely relying on one measure of morphological changes.

Despite the established link between olfactory ability and the morphology of olfactory cortical structures such as the olfactory bulb, piriform (commonly referred to as primary olfactory) cortex, and orbitofrontal cortex (OFC; commonly referred to as secondary olfactory cortex; Lundström et al., 2011), which generally indicates a positive correlation between volume and ability (Frasnelli et al., 2010a; Hummel et al., 2015; Seubert et al., 2013b), the only consistent finding in the study of cerebral morphological reorganization in individuals with isolated congenital anosmia (ICA) is the absence, or hypoplasia, of the olfactory bulbs and olfactory tracts, accompanied by a significant decrease in olfactory sulcus depth (Abolmaali et al., 2002; Huart et al., 2011; Yousem et al., 1996). With the exception of a case study (Yao et al., 2013), there are to the best of our knowledge only two studies that have investigated whether individuals with ICA display cerebral alterations beyond the olfactory bulb and olfactory sulcus in a statistical manner: one by Frasnelli et al. (2013) and one by Karstensen et al. (2018). Both studies indicate that individuals with ICA have increased gray matter volume in primary olfactory cortex (piriform cortex), albeit in opposite hemispheres. Although morphological alterations within primary sensory cortex are in agreement with the visual loss literature, the increase in gray matter volume reported in individuals with ICA contrasts the atrophy in both congenital and acquired blindness. In addition to primary olfactory cortex, alterations within secondary olfactory (orbitofrontal) cortex are reported by both Karstensen and Frasnelli: the former finds a volume decrease around the left posterior olfactory sulcus, and although the latter finds no evidence in support of volumetric alterations in OFC, an increase in cortical thickness in bilateral anteromedial OFC is reported. Albeit the overlap between reported results from the two studies is small, the failure of exact replication does not suggest inaccurate results, but indicates that the sample sizes (11 and 17 individuals with ICA in Karstensen and Frasnelli, respectively) are likely not large enough to gain sufficient statistical power to detect small effect sizes. This is not a unique problem. Sample sizes in studies of congenital sensory deprivation, independent of sensory modality explored, are typically small (undoubtedly a consequence of the scarcity of these conditions) and it is uncommon to include more than 20 patients.

In the present study, we aimed to determine whether cerebral morphological alterations beyond the olfactory bulb and olfactory sulcus depth are present in individuals with congenital anosmia. Structural magnetic resonance imaging data was collected for 34 individuals with

ICA (analyzed for 33, see methods) and 34 normosmic controls, matched in terms of age, sex, and education. First, we determined potential group differences in whole-brain gray matter volume using voxel-based morphometry (VBM) for voxel-wise comparisons. Thereafter, to assess possible underlying mechanisms of the VBM results, we determined potential differences in cortical thickness, surface area, and curvature between individuals with ICA and controls. Based on past findings indicating that both congenital blindness and ICA leads to alterations in cortical thickness and/or gray matter volume within early processing areas of the missing sense, we hypothesized that individuals with ICA would demonstrate an increase in gray matter volume within piriform cortex and OFC.

## 2. Materials and methods

### 2.1. Participants

A total of 68 participants were enrolled in the study: 34 individuals with isolated congenital anosmia (ICA, congenital anosmia unrelated to specific genetic disorders, such as Kallmann syndrome) and 34 controls, matched in terms of sex, age, and educational level (Table 1). Inclusion criteria for the ICA group was a self-reported lifelong lack of olfactory perception and thorough questioning failing to reveal any known underlying condition causing the anosmia (such as head trauma), and for the control group a self-proclaimed functional sense of smell (subsequently tested). In addition, 24 out of the 34 individuals with ICA had received a diagnosis from a physician. Of the 34 ICA individuals, 27 lacked bilateral olfactory bulbs, 3 individuals had identifiable (albeit very small) bulbs, and the presence of bulbs in the remaining 4 was non-determinable due to the limited spatial resolution of 1 mm<sup>3</sup> (assessed by J. N. L.). Participants were recruited and tested at two different sites: 46 participants (23 ICA) in Stockholm, Sweden, and 22 (11 ICA) in Wageningen, the Netherlands; the matched control was always tested at the same site as the individual with ICA. One individual from the ICA group was removed from analysis after visual inspection of the images due to abnormal anatomy, leaving a final sample of 33 individuals with ICA and 34 controls. All participants provided written informed consent and the study was approved by the ethical review boards in both Sweden and in the Netherlands.

### 2.2. Procedure

#### 2.2.1. Olfactory screening

Olfactory function was assessed with the full Sniffin' Sticks olfactory test (Burghart, Wedel, Germany), a standardized test consisting of three subtests with individual scores: odor detection threshold (T), odor quality discrimination (D), and 4-alternative cued odor quality identification (I), together yielding the combined TDI-score. Mean TDI scores on the Sniffin' Stick olfactory performance test were 10.9 (SD = 2.3, range: 7-15) and 35.4 (SD = 3.8, range: 28.5-42.5) for ICA and controls, respectively (Table 1), with all individuals in the ICA group demonstrating olfactory

**Table 1**  
Descriptive statistics per experimental group.

	ICA (n = 33)	Control (n = 34)
Age (years)	34.2 (12.9)	34 (12.1)
Female	21	22
Education (years)	14.1 (2.6)	14.1 (1.7)
TDI	10.9 (2.3)	35.4 (3.8)
Threshold	1.2 (0.5)	8.7 (3.2)
Discrimination	4.9 (1.6)	13.5 (1.6)
Identification	4.8 (1.5)	13.4 (1.3)
Left olfactory sulcus depth (mm)	4.9 (3.3)	8.6 (2.3)
Right olfactory sulcus depth (mm)	5.8 (3.6)	8.8 (2.3)

Values presented as mean (standard deviation). ICA = Isolated congenital anosmia, TDI = combined score from the Sniffin' Sticks olfactory sub-tests.

scores below the limit for functional anosmia (TDI cut-off at 16.0; Oleszkiewicz et al., 2019).

### 2.2.2. Image acquisition

Imaging data was acquired on two 3T Siemens Magnetom MR scanners (Siemens Healthcare, Erlangen, Germany). At the Swedish site, data was acquired on a Prisma scanner using a 20-channel head coil and in the Netherlands, a Verio scanner with a 32-channel head coil. The scanning sequence protocols were identical at both sites.

T<sub>1</sub>-weighted images with whole-brain coverage were acquired using an MP-RAGE sequence (TR = 1900 ms, TI = 900 ms, TE = 2.52 ms, flip angle = 9°, voxel size = 1 mm<sup>3</sup>, 176 slices, FoV = 256 mm) and T<sub>2</sub>-weighted images with whole-brain coverage were acquired using a SPACE sequence (TR = 3200 ms, TE = 405 ms, voxel size = 1 mm<sup>3</sup>, 224 slices, FoV = 256 mm). For detailed scanning protocols, see <https://osf.io/t4r9a/>. Additional functional imaging data, not reported here, were collected after the anatomical images in the same testing session.

### 2.3. Image processing

All images were visually inspected to ensure high image quality with absence of unwanted artifacts before inclusion. In addition, quantitative assessment of T<sub>1</sub>-weighted image quality was done using the CAT12 toolbox (Gaser and Dahnke, 2016) implemented in SPM12 (Wellcome Trust Centre for Neuroimaging, UCL; <http://www.fil.ion.ucl.ac.uk/spm/>), placing all images in the good or excellent quality categories (mean composite quality measure (IQR) = 87.39, SD = 2.77, range 82.42–91.88).

Three types of measures were extracted. Volumetric measures to assess potential effects of ICA on cortical and subcortical gray matter volume; surface based measures to assess potential mechanisms of cortical volumetric results; olfactory sulcus depth to support clinical diagnosis of ICA and to replicate past findings of differences in olfactory sulcus depth between ICA and control individuals (Abolmaali et al., 2002; Huart et al., 2011; Yousem et al., 1996).

#### 2.3.1. Volumetric measures

Voxel-based morphometry (VBM, Ashburner and Friston, 2000) analysis was done using SPM12 in MATLAB 2016a (The MathWorks, Inc., Natick, Massachusetts, USA). T<sub>1</sub>-weighted images were segmented into gray matter, white matter, and cerebrospinal fluid in native space using unified segmentation (Ashburner and Friston, 2005). The three tissues were used to compute total intracranial volume for each participant. The gray and white matter were further used as input to a diffeomorphic image registration algorithm to improve inter-subject alignment (DARTEL, Ashburner, 2007). DARTEL implements an iterative process in which gray and white matter from all subjects are aligned, creating an increasingly accurate average template for inter-subject alignment. The template and individual flow fields from DARTEL were then used to spatially normalize gray matter images to MNI space with 12 parameter affine transformations. The normalized gray matter images were modulated with the Jacobian determinant of the deformation fields and smoothed with a 6 mm full-width at half maximum isotropic Gaussian kernel. The relatively small kernel was chosen to optimize the discovery of group differences in piriform cortex, a small area at the junction between frontal and temporal cortex.

#### 2.3.2. Surface based measures

Surface based measures were used to calculate cortical thickness, surface area, and underlying white matter curvature. The T<sub>1</sub>-weighted images were processed using FreeSurfer ver. 6.0 (Dale et al., 1999); <http://surfer.nmr.mgh.harvard.edu/>). The processing pipeline is described in detail elsewhere (Fischl and Dale, 2000), but, in short, the image processing included removal of non-brain tissue, Talairach transformation, segmentation of subcortical white matter and gray matter, intensity normalization, tessellation of the boundary between gray and white matter, automated topology correction, and surface deformation to find

the gray/white matter boundary and the gray matter/cerebrospinal fluid boundary. Cortical thickness, area, and mean curvature of the gray/white matter boundary was calculated at each vertex point on the tessellated surface in native space. Thereafter, individual surfaces were aligned to an average template and smoothed (5 mm full-width at half maximum surface based Gaussian kernel chosen to optimize analysis in piriform cortex) to enable statistical comparisons between the subject groups. FreeSurfer data was pre-processed through the HiveDB database system (Muehlboeck et al., 2014).

#### 2.3.3. Olfactory sulcus depth

Two independent raters, blind to participant group, measured the depth of the olfactory sulci in the plane of the posterior tangent through the eyeballs, according to the method proposed by Huart et al. (2011). In short, on the first slice towards the posterior where the eyeballs were no longer seen on the T<sub>2</sub>-weighted MR images, a line measuring the depth of the olfactory sulcus was drawn, using the Multi-Image Analysis GUI (Mango version 4.0.1; Research Imaging Institute, UTHSCSA <http://ric.uthscsa.edu/mango>). There was a high agreement between the two raters' measurements (intraclass correlation coefficient of 0.88). Sulci defined as outliers (sulci for which the two initial raters' measurements differed more than 2 standard deviations from the mean difference; in total one sulcus in three individuals and both sulci in three individuals) were assessed by an additional observer. Olfactory sulcus depth was defined as the obtained mean measure, independent of the number of raters.

### 2.4. Statistical analysis

#### 2.4.1. Volumetric measures

To compensate for individual differences in intracranial volume when comparing gray matter volume between groups, the pre-processed, normalized gray matter images were proportionally scaled with total intracranial volume (Ashburner, 2015). Furthermore, the images were masked with a threshold of 0.15 to avoid inclusion of non-gray matter voxels. Voxel-wise differences in gray matter volume between groups were estimated with independent sample *t*-tests with age, sex, and scanning site as nuisance covariates. The tests were corrected for multiple comparisons with a family-wise error (FWE) corrected significance level of  $p < .05$ .

#### 2.4.2. Surface based measures

To investigate whether potential volumetric differences can be explained by differences in cortical thickness, surface area, or curvature, vertex-wise values were compared between groups using a general linear model with age, sex, and scanning site as nuisance covariates. Correction for multiple comparisons was done based on a false discovery rate (FDR) of  $< .05$  and group differences surviving this threshold were defined as significant. If no vertex survived this threshold, a more liberal threshold of  $p < .001$ , uncorrected, was used to explore the full extent of potential differences; highlighted in text when used.

#### 2.4.3. Olfactory sulcus depth

To assess differences between the two groups in olfactory sulcus depth, a repeated measures analysis of variance (rmANOVA; within subject factor Hemisphere, between subject factor Group) was used; effect size estimates are reported as partial eta-squared ( $\eta_p^2$ ). Potential group differences in olfactory sulcus depth were thereafter investigated for the right and left olfactory sulcus separately using Welch's *t*-test. Effect size estimates are given by Cohen's *d*.

### 2.5. Data availability

The conditions of our ethical approval does not permit public archiving of raw data from this study (however, tables, in manuscript reported results, as well as additional control analyses, are available at

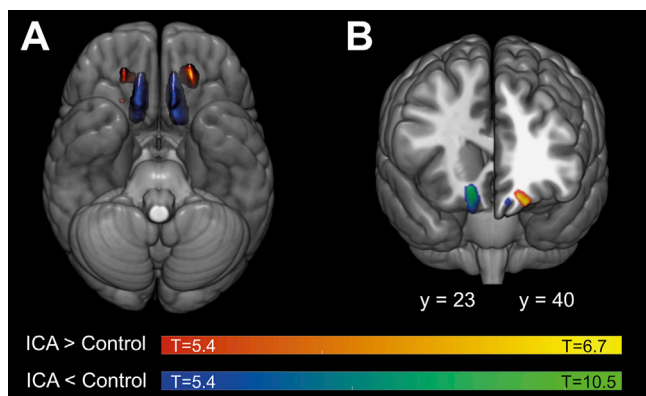
<https://osf.io/t4r9a/>). Anonymized data is available upon request for individuals with an explicit research purpose. Access is granted by the corresponding author or principal investigator (M.G.P., J.N.L.).

### 3. Results

#### 3.1. Altered morphology within the orbitofrontal cortex in congenital anosmia

To explore volumetric alterations, voxel-wise tests of group differences in gray matter volume were performed in a VBM analysis. Five clusters passed the FWE-corrected significance level of  $p < .05$ . All of the significant clusters were located in the OFC: two demonstrating gray matter atrophy in the ICA group around the bilateral olfactory sulci, two clusters demonstrating a gray matter volume increase in the ICA group centered around the bilateral medial orbital gyri (the latter located anterolateral to the aforementioned two clusters of gray matter atrophy), and an additional cluster of increased volume in the right posterior orbital gyrus, which will not be further discussed due to its minor size (Fig. 1, Table 2).

In opposition to our initial hypothesis, no significant group differences in gray matter volume within piriform (primary olfactory) cortex were demonstrated at an FWE-corrected significance level of  $p < .05$ . Given our specific hypothesis, two additional steps were taken. First, to confirm that the lack of group differences were not simply an effect of an excessively conservative statistical threshold, the significance level was altered to  $p < .01$ , uncorrected. Even at this liberal statistical threshold, no significant group differences in either left or right piriform cortex could be detected (data available at <https://osf.io/t4r9a/>). Second, to investigate whether there is statistical evidence in support of the lack of group differences, mean gray matter volume within the piriform cortex was extracted based on the region of interest from Zhou et al. (2019) using MarsBaR toolbox (version 0.44, <http://marsbar.sourceforge.net/>). Equivalence testing between groups was performed using the two one-sided tests procedure for equivalence testing using the TOSTER R package (Lakens, 2017) implemented in R (version 3.6.1, <https://www.r-project.org/>). The gray matter volume within both right and left piriform cortex were statistically equivalent between group within the equivalence bounds we have 80% power to detect (corresponding to an effect size of  $d \geq 0.6$ ; the test yielding the highest p-value in the right and left hemisphere, respectively:  $t(62.7) = 2.16, p = .017$ ;  $t(61.8) = 2.33, p = .012$ ), indicating that it is unlikely that there are real statistical differences between groups.



**Fig. 1. Groups differences in gray matter volume.** Gray matter volume differences displayed on MNI152-template. Individuals with isolated congenital anosmia (ICA) demonstrate gray matter volume atrophy in the bilateral olfactory sulci as well as gray matter volume increases in bilateral medial orbital gyri. **A** Results displayed on an inferior view of a transparent brain to reveal full extent of clusters. **B** Results displayed on an anterior view with coronal section at  $y = 23$  (right hemisphere) and  $y = 40$  (left hemisphere). All results are displayed at the statistical level of  $p < .05$ , FWE-corrected.

**Table 2**

Results from volumetric measures.

Region	Hemisphere	$x^a$	$y^a$	$z^a$	Cluster size <sup>b</sup>	$t^c$	$p^d$
<i>ICA &lt; Control</i>							
Olfactory sulcus <sup>1</sup>	L	-12	21	-16	2185	10.5	<.001
Olfactory sulcus <sup>2</sup>	R	13	19	-13	2135	9.7	<.001
<i>ICA &gt; Control</i>							
Medial orbital gyrus <sup>3</sup>	L	-21	39	-21	532	6.7	.001
Medial orbital gyrus <sup>4</sup>	R	17	39	-14	244	6.0	.006
Posterior orbital sulcus, middle branch	R	22	24	-11	8	5.5	.04

ICA – isolated congenital anosmia. <sup>1–4</sup> Clusters used in correlation analysis presented in Table 4. <sup>a</sup> Coordinates derived from MNI152. <sup>b</sup> Cluster size has unit mm<sup>3</sup>. <sup>c</sup>  $t$ -value for peak voxel in cluster <sup>d</sup>  $p$ -value for peak voxel, FWE-corrected. Regions are identified based on ‘Atlas of the Human Brain’ (Mai et al., 2015).

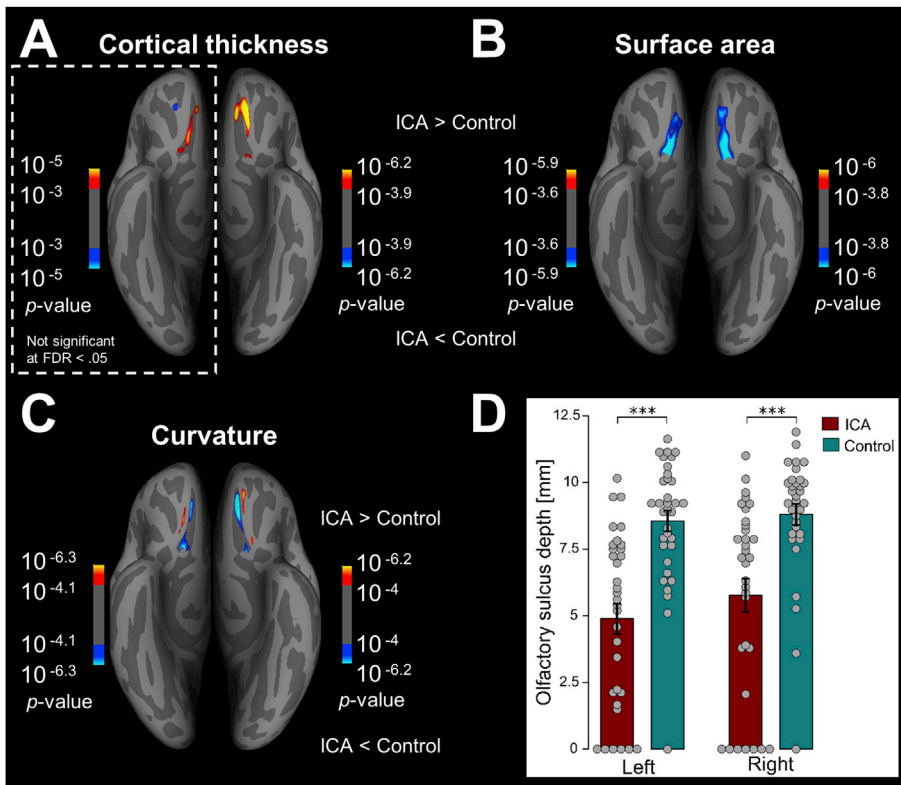
To investigate whether the gray matter volume alterations demonstrated within the ICA group could be further explained by alterations in cortical thickness, surface area, or curvature, these measures were compared vertex-wise between groups. The cortical thickness analysis demonstrated a thickening of the left medial orbital gyrus and anterior olfactory sulcus in the ICA group (Fig. 2A, Table 3); however, no group differences in cortical thickness were found in the right hemisphere when using the designated statistical cut-off (FDR < .05). When applying a more liberal threshold ( $p < .001$ , uncorrected), clusters similar to the ones in the left hemisphere were revealed in the right hemisphere, i.e., a cortical thickening around the olfactory sulcus in the ICA group (Fig. 2A). In addition to altered gray matter volume and cortical thickness in the OFC, the ICA group further demonstrated decreased surface area along the bilateral olfactory sulci (Fig. 2B, Table 3) accompanied by decreased curvature around the same orbitofrontal areas: the bilateral olfactory sulci and medial orbital gyri (Fig. 2C, Table 3), all at an FDR threshold of < .05. Furthermore, a small cluster of increased curvature was demonstrated in the left superior temporal sulcus along with additional minor clusters with few vertices surviving our predefined threshold that were identified but not further discussed (Table 3).

#### 3.2. Decreased olfactory sulcus depth in individuals with congenital anosmia

Finally, we assessed potential differences between individuals with ICA and normosmic controls in olfactory sulcus depth with a rmANOVA. Individuals with ICA demonstrated significantly more shallow olfactory sulci as compared to controls, main effect of Group:  $F(1,65) = 23.7, p < .001, \eta_p^2 = 0.267$ ; ICA mean = 5.3 mm, SD = 3.4 mm; Control mean = 8.7 mm, SD = 2.3 mm. Furthermore, a difference of depth in the right, as compared to left, olfactory sulcus was demonstrated, main effect of Hemisphere:  $F(1,65) = 9.0, p = .004, \eta_p^2 = 0.120$ ; however, no significant interaction between Group and Side was present,  $F(1,65) = 2.8, p = .098, \eta_p^2 = 0.042$ . The decrease in olfactory sulcus depth for the ICA group was demonstrated for the left olfactory sulcus,  $t(57.6) = 5.28, p < .0001, d = 1.3$ , as well as for the right olfactory sulcus,  $t(54.3) = 4.11, p < .001, d = 1.01$ ; Fig. 2D and Table 1.

#### 3.3. Relationships between olfactory sulcus depth and morphology results

Both volumetric and surface based analysis revealed structural group differences in bilateral medial OFC, mainly in, or in close proximity to,



**Fig. 2. Group differences in surface based measures and olfactory sulcus depth.** In A-C results are displayed on the inferior view of an inflated brain. Displayed results are corrected for multiple comparisons based on a false discovery rate (FDR) < .05, except for the right hemisphere in figure A. A Differences in cortical thickness with warm colors indicating cortical thickness increases in individuals with Isolated Congenital Anosmia (ICA) as compared to normosmic controls. Individuals with ICA demonstrate a significant increase in cortical thickness in the left medial orbital gyrus/olfactory sulcus. No significant group differences were demonstrated in the right hemisphere at FDR < .05; differences in the right hemisphere displayed  $p < .001$  for visual comparison. B Group differences in surface area demonstrate a significantly decreased area for individuals with ICA along the bilateral olfactory sulci. C Group differences in curvature. Significant differences demonstrated in bilateral olfactory sulcus and bilateral medial orbital gyrus; all indicating a lower absolute value of curvature for individuals with ICA, i.e., larger radii of curves (FreeSurfer's convention of curvature is negative for gyri and positive for sulci, warm colors indicate ICA > Control). D Mean olfactory sulcus depth (error bars indicate standard error) overlaid with individual values and separated by hemisphere and group. Individuals with Isolated Congenital Anosmia (ICA) demonstrate a significant decrease in bilateral olfactory sulci compared to matched controls. \*\*\* indicating  $p < .001$ .

the olfactory sulci. Based on these results, we assessed whether the volumetric and surface based group differences were linked to the group difference in olfactory sulcus depth by means of Pearson's correlation coefficient analyses. For each individual, mean gray matter volume was computed for each of the four large significant clusters. Similarly, mean cortical thickness was computed for the large significant cluster in the left hemisphere, mean surface area for the two significant clusters, and mean curvature was computed in the three largest significant cluster in left OFC and the three largest significant clusters in right OFC (all clusters used for correlation analysis marked in Tables 2 and 3). Pearson's correlation coefficients were computed between each of these structural measures and the olfactory sulcus depth in the corresponding hemisphere, with Bonferroni correction applied for number of tests of each type of structural measure (4 for volume, 2 for area, 6 for curvature). To avoid that the large demonstrated differences between groups would influence the correlations, the Pearson's correlation coefficients were computed within each group separately. Both the ICA and control group demonstrated significant negative correlation between olfactory sulcus depth and cortical thickness, as well as between olfactory sulcus depth and curvature, in the left medial orbital gyrus (Table 4). Furthermore, the curvature in the neighboring cluster in the left anterior olfactory sulcus correlated with olfactory sulcus depth in the control (but not ICA) group, whereas corresponding cluster in the right hemisphere (anterior olfactory sulcus) correlated with olfactory sulcus depth in the ICA group. Significant correlations between sulcus depth and surface area in the olfactory sulci were demonstrated, with exception for the left sulcus in the ICA group. Additionally, the gray matter volume cluster along the right olfactory sulcus correlated with the olfactory sulcus depth in the ICA, but not control, group. No other correlations between gray matter volume and olfactory sulcus depth were significant (Table 4).

#### 4. Discussion

We can here demonstrate that individuals with isolated congenital anosmia (ICA) have a significantly altered morphology in bilateral

medial orbitofrontal cortex (OFC), a multimodal region including areas often referred to as secondary olfactory cortex, but in contrast to our hypothesis, show no evidence of alterations within piriform cortex (primary olfactory cortex). Specifically, individuals with ICA demonstrated morphological alterations, compared to normosmic individuals, in and around the olfactory sulci, encompassing gray matter volume atrophy stretching along the olfactory sulci towards the medial orbital gyri, likely linked to the decreased sulcus depth, surface area, and curvature of the olfactory sulci. Moreover, gray matter volume and cortical thickness increases were demonstrated in the medial orbital gyri of individuals with ICA. These divergent results in neighboring cortical areas indicate that the cerebral reorganization related to a life-long olfactory sensory deprivation cannot be explained by a simple morphological mechanism applied to all olfactory-related cerebral areas, but rather, that the plasticity is area- or network-dependent.

The morphological reorganization demonstrated by individuals with ICA was restricted to orbitofrontal cortex, without any indications of morphological alterations in the piriform cortex. This lack of reorganization in primary sensory cortex is in disagreement with the previous studies on individuals with congenital anosmia (Frasnelli et al., 2013; Karstensen et al., 2018) as well as the larger literature on congenital visual sensory deprivation (Bridge et al., 2009; Hasson et al., 2016; Jiang et al., 2009; Park et al., 2009). Albeit the lack of alterations in piriform cortex are contradictory to our own hypothesis, we argue that the results are reliable. The results are based on a comparably large sample of individuals with congenital sensory deprivation and clear morphological reorganization was indicated by both volumetric and the individual surface based measures in medial orbitofrontal areas; measures that failed to find differences in piriform cortex. This lack of observable group differences remained also when applying a liberal statistical threshold uncorrected for multiple comparisons, and equivalence tests indicated that the gray matter volume within the piriform cortices were equal between groups (within the bounds detectable with the, in this context, large sample size). We can thereby conclude that it is unlikely that ICA leads to macroscopically detectable morphological alterations in piriform

**Table 3**  
Results from surface based measures.

Region	Hemisphere	x <sup>a</sup>	y <sup>a</sup>	z <sup>a</sup>	Cluster size <sup>b</sup>	p <sup>c</sup>
<b>Cortical Thickness</b>						
<i>ICA &gt; Control</i>						
Medial orbital gyrus <sup>5</sup>	L	-15	35	-22	171	10 <sup>-10</sup>
Posteromedial orbital lobule	L	-16	8	-16	12	10 <sup>-4.4</sup>
<b>Area</b>						
<i>ICA &lt; Control</i>						
Olfactory sulcus <sup>6</sup>	R	14	16	-13	343	10 <sup>-8.4</sup>
Olfactory sulcus <sup>7</sup>	L	-14	9	-16	251	10 <sup>-9</sup>
<b>Curvature</b>						
<i>ICA &lt; Control</i>						
Olfactory sulcus <sup>8</sup>	L	-12	37	-20	77	10 <sup>-12</sup>
Olfactory sulcus <sup>9</sup>	R	16	10	-15	56	10 <sup>-6.6</sup>
Medial orbital gyrus <sup>10</sup>	L	-14	42	-22	35	10 <sup>-5.9</sup>
Olfactory sulcus <sup>11</sup>	R	15	33	-19	34	10 <sup>-6.3</sup>
Superior temporal sulcus	L	-55	-43	7	22	10 <sup>-4.7</sup>
Olfactory sulcus <sup>12</sup>	L	-16	10	-16	16	10 <sup>-5.8</sup>
Medial orbital gyrus <sup>13</sup>	R	14	25	-25	15	10 <sup>-5.6</sup>
Medial/posterior orbital gyrus	L	-17	15	-22	9	10 <sup>-5.2</sup>
Medial/posterior orbital gyrus	R	16	17	-23	2	10 <sup>-4.2</sup>

ICA – isolated congenital anosmia. <sup>5–13</sup> Clusters used in correlation analysis presented in Table 4. <sup>a</sup> Coordinates derived from MNI305. <sup>b</sup> Cluster size has unit mm<sup>2</sup>. <sup>c</sup> p-value for peak vertex in cluster, uncorrected but surviving FDR < .05. <sup>d</sup> ICA < Control indicates that individuals with anosmia have a lower *absolute* curvature, i.e., a higher radius of curvature. FreeSurfer's convention of curvature is negative for gyri and positive for sulci, which means some of these contrasts are positive and some negative (see Fig. 2C). Regions are identified based on 'Atlas of the Human Brain' (Mai et al., 2015).

cortex. Support for the lack of alterations in piriform cortex demonstrated in the current study can be found in the rodent literature. Experimental removal of the olfactory bulb at postnatal day one, leading to a removal of the afferent input to the piriform cortex and analogous with congenital or extremely early sensory deprivation, resulted in minor to no alterations in thickness of the piriform cortex (Friedman and Price, 1986; Westrum and Bakay, 1986). In contrast, bulb ablation at a later point in time, analogous with a later acquired sensory deprivation, resulted in significant decreases in piriform thickness. Nonetheless, it should be noted that we are in this study limited by the spatial resolution of the methods used and that the lack of morphological changes in piriform cortex does not necessarily indicate that no functional or cytoarchitectonic reorganization occurs in individuals with ICA. The piriform cortex is a small structure with complex folding and to firmly establish that a lifelong lack of olfactory perception does not alter its structure, neuroimaging studies with higher spatial resolution and, if possible, post-mortem analyses of the cytoarchitecture are needed to definitively demonstrate a lack of structural changes in piriform cortex in congenital anosmia.

Why are clear morphological changes in the primary sensory cortex of the absent sense reported in congenital blindness but not evident in congenital anosmia? There are a number of possible mechanisms. Piriform cortex differs in a number of ways from our other primary sensory cortices: piriform cortex consists of paleocortex and not neocortex,

**Table 4**  
Correlations between listed clusters and olfactory sulcus depth in corresponding hemisphere.

Region	Hemisphere	ICA		Control	
		r	p	r	p
<b>VBM</b>					
Olfactory sulcus <sup>1</sup>	L	.28	.109	.31	.072
Olfactory sulcus <sup>2</sup>	R	.52	.002 **	.25	.16
Medial orbital gyrus <sup>3</sup>	L	.12	.491	-.24	.166
Medial orbital gyrus <sup>4</sup>	R	.06	.726	-.31	.066
<b>Cortical thickness</b>					
Medial orbital gyrus <sup>5</sup>	L	-.51	.003 **	-.59	2.7·10 <sup>-4</sup> ***
<b>Area</b>					
Olfactory sulcus <sup>6</sup>	R	.43	.013*	.39	.023*
Olfactory sulcus <sup>7</sup>	L	.28	.111	.42	.013*
<b>Curvature</b>					
Olfactory sulcus <sup>8</sup>	L	.24	.172	.50	.003 *
Olfactory sulcus <sup>9</sup>	R	.36	.040	.00	.981
Medial orbital gyrus <sup>10</sup>	L	-.5	.003 *	-.63	6.3·10 <sup>-5</sup> ***
Olfactory sulcus <sup>11</sup>	R	.65	3.9·10 <sup>-5</sup> ***	.12	.485
Olfactory sulcus <sup>12</sup>	L	.3	.087	-.24	.168
Medial orbital gyrus <sup>13</sup>	R	-.32	.072	-.06	.745

ICA – isolated congenital anosmia, r – Person correlation coefficient, asterisks mark Bonferroni corrected significance levels corresponding to \* p < .05, \*\*p < .01, \*\*\*p < .001. <sup>1–13</sup> cluster numbers corresponding to the ones in Tables 2 and 3.

peripheral input does not pass through thalamus before reaching piriform cortex, and piriform cortex is involved in more complex processing than what is commonly associated with primary sensory areas (Gottfried, 2010), suggesting that it might be better labeled as odor association cortex (in fact, it has been suggested that the olfactory bulb, rather than the regions the bulb projects to, could be considered as primary olfactory cortex (Haberly, 2001)). These clear structural and functional differences between primary olfactory and primary visual cortex might help explain the divergent effects of congenital olfactory and congenital visual sensory deprivation on the respective primary sensory cortices. The lack of input to the piriform cortex from the olfactory bulb might be partially compensated for processing of trigeminal stimuli, which also lead to an activation of the piriform cortex (Albrecht et al., 2010), or by input from downstream regions, such as the amygdala, OFC, and insula; indeed, plasticity in piriform cortex has been suggested to be highly affected by descending inputs (Strauch and Manahan-Vaughan, 2017). However, although the above mentioned factors have the potential of contributing to the lack of observed morphological alterations of piriform cortex, they are speculative. To provide mechanistic explanations to the lack of morphological alterations, studies establishing not only the cytoarchitecture but also the functional role of the piriform cortex in individuals with ICA are called for.

Our results demonstrate that the OFC of individuals with ICA has a distinctly different morphology than that of normosmic individuals. Although it is evident that this cortical reorganization is strongly related to the congenital sensory deprivation, the results are in their nature insufficient to conclude how these anomalies emerged. One hypothesis is that individuals with ICA are born with an abnormality in the cortical folding of the medial OFC, manifested as a cortical flattening around the olfactory sulci and medial orbital gyri, linked to the absence, or hypoplasia, of the olfactory bulbs and tracts. The olfactory bulbs and tracts reside in the olfactory sulci and the projection of the olfactory tracts is suggested to play an important role in the formation and deepening of the olfactory sulci during early development (Abolmaali et al., 2002; Huart et al., 2011; Turetsky et al., 2009). A congenital abnormal cortical folding could explain the decreased olfactory sulcus depth, decreased area, and

decreased curvature in olfactory sulci and medial orbital gyri, as well as the gray matter volume atrophy in the olfactory sulci, as a natural consequence of the decreased surface area. However, a decrease in cortical surface area in the pericalcarine sulci (visual cortex) in congenitally blind individuals has been described by Park et al. (2009), suggesting that the decreased olfactory sulcus depth in individuals with ICA might not be exclusively caused by a congenital abnormal anatomy linked to small or absent olfactory bulbs and tracts, but, similar to the blind, be a consequence of atypical development caused by a lack of sensory input. In addition, although the theory of congenital abnormal cortical folding in individuals with ICA provides a potential explanation of the gray matter volume atrophy and corresponding surface based measures, it cannot explain the gray matter volume increases in the medial orbital gyri in a straightforward way. By taking the proposed function of these cortical areas into account, other possible explanations of the cortical reorganization emerge.

The medial OFC is alongside the piriform cortex considered vital for olfactory processing (Gottfried, 2006; Lundström et al., 2011; Seubert et al., 2013a) and the cortical regions in which the individuals with ICA demonstrated cortical thickness and gray matter volume increases show a substantial overlap with areas repeatedly implicated in olfactory processing (for reviews see Gottfried and Zald, 2005; Seubert et al., 2013a). Considering that these orbitofrontal areas are important for olfactory processing, the cortical increases displayed by individuals with ICA can presumably be caused by the fact that these areas have never received olfactory input. In contrast, individuals with acquired olfactory sensory loss tend to demonstrate cortical volume decreases in the OFC (Bitter et al., 2010; Yao et al., 2017). Although these morphological consequences of olfactory sensory deprivation might seem contradictory, similar results have repeatedly been demonstrated in blind individuals, with a thickening of visual cortex of congenitally blind and a thinning of those with acquired blindness (Park et al., 2009; Voss and Zatorre, 2012). In addition, the demonstrated cortical volume and thickness increases reported here are an extension of Frasnelli et al. (2013) report of increased cortical thickness in the OFC of individuals with ICA. Cortical increases as a result of a lack of sensory processing might seem counter intuitive and the mechanisms behind these morphological alterations are not yet fully understood. One of the main theories proposed to explain the cortical increases in congenitally blind individuals (Jiang et al., 2009; Park et al., 2009), as well as in individuals with ICA (Frasnelli et al., 2013), is that the complete lack of sensory input to a cortical area normally devoted to the processing of the missing sensory modality alters normal postnatal development. Specifically, the absent input results in a lack of the typical sensory input-driven synaptic pruning of redundant connections. The exact mechanisms of these results need to be addressed using animal models.

Although the OFC undoubtedly is important for olfactory processing (Li et al., 2010), it is a much more multimodal area than the visual areas showing cortical thickness increases in congenitally blind. The key functions of the OFC is often put in the context of value encoding, including, but by no means limited to the olfactory domain (Gottfried and Zelano, 2011; Kringsbach and Rolls, 2004; Van den Bosch et al., 2014), with direct stimulation of human OFC eliciting not only olfactory but also somatosensory, gustatory, and emotional experiences (Fox et al., 2018). Specifically, the OFC is relevant for the processing and integration of information from different sensory modalities, receiving olfactory, gustatory, somatosensory, visceral, visual, and auditory input (Kringsbach and Rolls, 2004; Ongür and Price, 2000; Rolls, 2005), and the medial OFC has been suggested to be of high importance for food consumption (Price, 2008; Rolls, 2005). If we consider the medial OFC as a multimodal rather than predominantly olfactory processing area, it can be argued that alterations in gray matter volume and cortical thickness are not, as previously argued, caused by a lack of synaptic pruning due to absent olfactory input but, to the contrary, related to increased (compensatory) processing of the non-olfactory functions of the OFC. This argument lines up well with data demonstrating a positive relation between cortical

thickness in visual cortex and performance on auditory tasks in blind individuals (Voss and Zatorre, 2012), but seems less plausible when considering that individuals with congenital olfactory deprivation demonstrates similar, or even impaired, performance in the remaining chemical senses (Frasnelli et al., 2007; Frasnelli et al., 2010b; Gagnon et al., 2014). To find support for either theory, the specific functions of the orbitofrontal areas demonstrating structural reorganization in individuals with ICA need to be further investigated, preferably using functional neuroimaging methods, to delineate whether the structural reorganization in individuals with ICA is accompanied by altered function and connectivity.

The posterior tips of the large clusters of decreased gray matter volume demonstrated along the bilateral olfactory sulci in individuals with ICA show a minor overlap with the anterior part of the anterior olfactory nucleus, a region which, together with the piriform cortex, olfactory tubercle, and subregions of the entorhinal cortex and amygdala, receives direct input from the olfactory bulb (Gottfried, 2006). This overlap could be interpreted as an indication of reorganization in this early olfactory area. Although this cannot be ruled out, the slight overlap is likely resulting from the clearly altered morphology of the olfactory sulci rather than a specific reorganization of the anterior olfactory nucleus. Furthermore, the volumetric reorganization of primary olfactory (piriform) cortex previously reported (Frasnelli et al., 2013; Karstensen et al., 2018) indicate volume increases and not atrophy, as demonstrated here.

In addition to the clear reorganization in the orbitofrontal cortex, confirmed with both volumetric and surface based methods, individuals with ICA demonstrated a small but statistically significant cluster of altered curvature in the left superior temporal sulcus. The superior temporal sulcus is, along with the intraparietal sulcus and the prefrontal cortex, one of the classical cortical multisensory integration areas (Ghanzafar and Schroeder, 2006; Stein and Stanford, 2008). Although the group difference in the superior temporal sulcus is restricted to the curvature measure, it is noteworthy that a recent study demonstrated that individuals with ICA showed enhanced audio-visual integration performance; an effect that was interpreted as compensatory abilities due to the sensory deprivation (Peter et al., 2019). Whether the deviating anatomy in the superior temporal sulcus demonstrated here is in fact related to the proposed compensatory processing of multisensory stimuli in individuals with ICA previously reported should be investigated using functional neuroimaging techniques.

In line with previous studies, we could further demonstrate that individuals with ICA have a significantly decreased olfactory sulcus depth, as compared to matched normosmic individuals (Abolmaali et al., 2002; Huart et al., 2011; Karstensen et al., 2018; Levy et al., 2013; Yousem et al., 1996). The shallow olfactory sulcus depth in individuals with ICA is thought to be related to the complete lack of, or hypoplasia of, olfactory bulbs, often accompanied by small or absent olfactory tracts (Abolmaali et al., 2002; Yousem et al., 1996); structures located in the olfactory sulci. The olfactory sulcus depth has been suggested to be an indicator of congenital anosmia (Abolmaali et al., 2002; Huart et al., 2011), an idea supported by the fact that a difference in olfactory bulb size, but *not* in olfactory sulcus depth, is found between individuals with acquired anosmia and controls (Rombaux et al., 2010). It is, however, important to note that even though there are significant group differences between individuals with ICA and normosmic individuals, the use of olfactory sulcus depth of a certain value as a tool to diagnose olfactory dysfunction does not allow for an unambiguous diagnose, as there is overlap between groups in sulcus depth.

The restricted spatial distribution of the cortical alterations in individuals with ICA, combined with the established decrease in olfactory sulcus depth, begs the question whether there is a direct relationship between the olfactory sulcus depth and surrounding cortical morphology. Although the correlation analyses of olfactory sulcus depth and surface area indicate that a shallower olfactory sulcus is associated with a decreased surface area in the sulcus in question, and strong support for a relation between the sulcus depth and both cortical thickness

and curvature in the left medial orbital gyrus was demonstrated, the other correlation measures yielded mainly non-significant results. This ambiguity could partly be related to the fact that the sulcus depth is measured at one specific location, and the underlying morphology is likely more strongly related to areas in close proximity to that location. Other specific measures, such as maximum sulcus depth (Weiss et al., 2020) or sulcus length (Takahashi et al., 2013), could potentially provide additional information. These measures have, however, not shown to differ between individuals with life-long anosmia and controls (Abolmaali et al., 2002). Nonetheless, the fact that significant correlations could be demonstrated between olfactory sulcus depth and all types of cortical measures could be interpreted as support for the hypothesis of congenital abnormal cortical folding. However, this is speculative and needs to be validated by evidence from developmental studies.

Because ICA is a rare condition, data collection was done at two different locations to enable the inclusion of more individuals. Although efforts were made to equalize the conditions between the two sites (both sites had 3T Siemens scanners and implemented identical scanning sequence protocols), a 20-channel head coil was used at one site whereas a 32-channel coil was used at the other. Both the 20-channel and 32-channel head coils demonstrate low test-retest variability on a 3T Siemens scanner (Yan et al., 2020) and, importantly, the matched control and individual with ICA were always scanned at the same site. The balanced design means that the difference between scanning sites that potentially remains after the correction by including scanner as a nuisance covariate in the analyses would increase within group variance rather than between group variance, potentially reducing or masking very weak group differences. We do, however, argue that the advantages of an increase in sample size made possible by this multisite study far exceeds the disadvantage of increased variability.

## 5. Conclusions

The current study investigates whole-brain gray matter morphology in individuals with ICA and demonstrates substantial cortical reorganization beyond the olfactory bulb and olfactory sulcus depth. Strikingly, no morphological reorganization within piriform (primary olfactory) cortex is demonstrated. The lack of morphological alterations in primary sensory areas indicate that the cortical reorganization mechanisms at play when a sensory system is absent is sensory modality dependent. All morphological alterations, except for a small region in the superior temporal sulcus, are restricted to the orbitofrontal cortex, and indicate areas of atrophy as well as increases in individuals born without the olfactory sense. These alterations could potentially be due to a combination of congenital abnormal morphology and a sensory deprivation-dependent plastic reorganization occurring during development. These clear findings of morphological changes motivate future studies of their functional and behavioral relevance.

## Declaration of competing interest

The authors have no conflict of interest to report.

## CRediT authorship contribution statement

**Moa G. Peter:** Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing - original draft, Visualization, Project administration. **Gustav Mårtensson:** Software, Formal analysis, Investigation, Writing - review & editing. **Elbrich M. Postma:** Investigation, Resources, Writing - review & editing. **Love Engström Nordin:** Methodology, Writing - review & editing. **Eric Westman:** Methodology, Writing - review & editing, Supervision. **Sanne Boesveldt:** Resources, Writing - review & editing. **Johan N. Lundström:** Conceptualization, Methodology, Resources, Writing - review & editing, Supervision, Funding acquisition.

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