MRI-Based Analysis of Structural Brain Changes in Congenital Anosmia: Preliminary Report

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Introduction

Congenital anosmia (CA) is a rare lifelong absence of odor perception (~1 in 10,000). Beyond impaired quality of life, CA has been linked to structural brain changes in regions such as the prefrontal cortex and limbic system, and to compensatory functional activation in olfactory-related cortices. MRI has become essential for studying these alterations, revealing abnormalities like absent or hypoplastic olfactory bulbs and reduced gray matter volume in the bilateral olfactory sulci. However, prior studies remain limited, often small in size and focused only on olfactory regions, restricting generalizability. Thus, we applied whole-brain volumetric MRI to comprehensively assess gray matter (GM) and white matter (WM) alterations in CA.

Methods

Inclusion Criteria

Participants were included if they (1) had a history of absent smell since childhood, (2) showed anosmia confirmed by the phenyl ethyl alcohol (PEA) threshold test (score = –1), and (3) had MRI evidence of absent or hypoplastic olfactory bulbs. Controls with no olfactory dysfunction were randomly selected and matched by age (±2 years) and gender.

Exclusion Criteria

Excluded were individuals with secondary causes of anosmia (e.g., severe chronic rhinosinusitis, head trauma, tumors), anterior skull base/paranasal abnormalities, or MRI performed before age 20.

Participants

A total of 56 individuals were analyzed: 28 CA patients (16 women, 12 men; mean age 32.7) and 28 controls (14 women, 14 men; mean age 32.9). All underwent axial FLAIR MRI on either a Siemens 1.5T (n=51) or Philips 3T (n=5) scanner.

MRI & Processing

FLAIR sequences were chosen for GM and WM segmentation using SPM12. Volumes were quantified across 11 predefined brain regions (frontal, temporal, parietal, occipital, limbic, sub-lobar, midbrain, frontal–temporal, cerebellum–anterior/posterior, pons). Images were converted to NIfTI format (Neuroimaging Informatics Technology Initiative), segmented into GM, WM, and CSF, and thresholded at 0.5. Quality control was performed slice-by-slice. WFU_PickAtlas templates were applied to define lobar regions (11 areas).

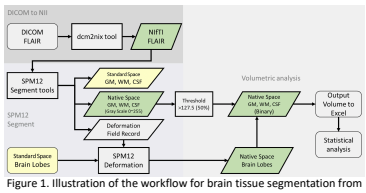

Figure 1. Illustration of the workflow for brain tissue segmentation from MR images using the methods available in SPM12.

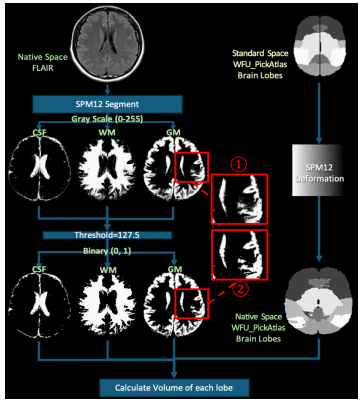

Figure 2. Illustration of the workflow for brain tissue segmentation from MR images using the methods available in SPM12. The red-outlined region (1) shows an enlarged view of the gray scale segmentation result, whereas in the lower panel, the red-outlined region (2) displays the corresponding binarized (thresholded) segmentation mask.

Result

Overall Brain Volumes

Patients with CA exhibited significantly smaller GM volumes compared to healthy controls (p< 0.001) but larger WM volumes (p = 0.015). When analyzed as percentages of total brain volume, the proportion of GM was also significantly reduced in patients with CA (p <0.001), whereas the proportion of WM was higher (p< 0.001)

	CA	Control	p-value
Volume			
Whole brain	1104.9±114.4(cc)	1184.8±158.4(cc)	.071
Gray matter	560.6±114.7(cc)	693.7±96.3(cc)	<.001
White matter	554.2±75.4(cc)	491.1±79.7(cc)	.015
Percentage			
Gray matter	50.45±7.22(%)	58.60±3.14(%)	<.001
White matter	49.55±7.22(%)	41.4±3.14(%)	<.001

CA: congenital anosmia.

Table 1. Comparison of whole brain volumes between patients with CA and healthy controls.

Gray Matter

We compared GM volumes across 11 brain regions between patients with CA and healthy controls. Patients with CA demonstrated significant GM reductions in the frontal (p < 0.001), temporal (p = 0.001), parietal (p < 0.001), sub-lobar (p = 0.001), occipital (p < 0.001), and midbrain (p = 0.006) regions.

Area	CA	Control	p-value
Frontal	131.9 ± 33.7 (cc)	173.7 ± 27.0 (cc)	< .001
Temporal	81.1 ± 18.4 (cc)	96.5 ± 14.1 (cc)	.001
Limbic	59.3 ± 8.9 (cc)	61.9 ± 9.1 (cc)	.422
Parietal	52.4 ± 15.2 (cc)	77.2 ± 12.4 (cc)	< .001
Sub-lobar	57.8 ± 9.7 (cc)	68.2 ± 10.2 (cc)	.001
Occipital	39.1 ± 13.0 (cc)	57.8 ± 8.9 (cc)	< .001
Midbrain	2.0 ± 0.5 (cc)	2.3 ± 0.4 (cc)	.006
Frontal-Temporal	0.206 ± 0.169 (cc)	0.177 ± 0.128 (cc)	.731
Cerebellum-Anterior	30.7 ± 4.5 (cc)	32.3 ± 4.6 (cc)	.287
Cerebellum-Posterior	37.1 ± 6.1 (cc)	39.0 ± 5.1 (cc)	.376
Pons	0.6 ± 0.3 (cc)	0.8 ± 0.2 (cc)	.098

CA: congenital anosmia

Table 2. Comparison of gray matter volumes between CA patients and healthy controls

White Matter

WM analysis revealed significantly larger volumes in patients with CA compared to healthy controls in the frontal(p = 0.027),temporal(p = 0.001),parietal(p< 0.001), and occipital(p< 0.001) regions. Notably, the difference in the frontal lobes did not remain significant after adjustment for multiple comparisons (adjusted p = 0.074)

Area	CA	Control	p-value
Frontal	152 ± 19.9 (cc)	139.2 ± 24 (cc)	.027
Temporal	71.5 ± 11.5 (cc)	60.8 ± 9.5 (cc)	.001
Limbic	48.3 ± 7 (cc)	48.3 ± 7.9 (cc)	.831
Parietal	75.8 ± 12.4 (cc)	61.9 ± 11.5 (cc)	<.001
Sub-lobar	79.6 ± 10.3 (cc)	77.9 ± 13 (cc)	.441
Occipital	58.7 ± 10.3 (cc)	41.9 ± 7.9 (cc)	<.001
Midbrain	9.7 ± 1.6 (cc)	10.6 ± 2 (cc)	.106
Frontal-Temporal	0.001 ± 0.002 (cc)	0.004 ± 0.009 (cc)	.106
Cerebellum-Anterior	7.3 ± 1.9 (cc)	7.7 ± 1.4 (cc)	.372
Cerebellum-Posterior	9.8 ± 2.7 (cc)	8.5 ± 2.7 (cc)	.098
Pons	9 ± 1.2 (cc)	9.3 ± 2 (cc)	.330

CA: congenital anosmia.

Table 3. Comparison of white matter volumes between CA patients and healthy controls

Discussion

This study used whole-brain volumetric MRI to examine structural changes in CA, extending analysis beyond classical olfactory regions. Patients with CA showed reduced GM and increased WM volumes, particularly in the frontal, temporal, parietal, occipital, sub-lobar, and midbrain regions. These alterations overlap with the frontoparietal control and multisensory integration networks, suggesting that lifelong olfactory deprivation may affect cognitive control and cross-modal processing. Our findings align with prior reports of reduced GM in orbitofrontal and insular cortices, while also supporting evidence of increased GM in regions such as the piriform cortices. Differences across studies likely reflect variations in MRI sequences (T1 vs. FLAIR), processing pipelines, and analysis methods. The observed WM increases may relate to altered synaptic pruning and myelination during early brain development, consistent with patterns reported in congenital visual or auditory deprivation.

Conclusion

This study, utilizing a whole-brain MRI approach, revealed significant structural brain alterations in patients with CA, characterized by a global reduction in GM volume and a corresponding increase in WM volume compared to healthy controls. These volumetric differences were predominantly observed in the frontal, temporal, parietal, occipital, and sub-lobar regions, suggesting a widespread impact of congenital olfactory deprivation on brain development beyond traditionally defined olfactory areas. The increased WM volumes, particularly in regions corresponding to GM reductions, might reflect compensatory mechanisms or altered developmental trajectories. Overall, the regional alterations in GM and WM observed in this study point toward a more generalized and complex neurodevelopmental impact of congenital anosmia than has been previously recognized. Future studies should employ subregional and clinical analyses, consider cognitive and experiential factors, and use multimodal neuroimaging to clarify CA's structural and functional impacts.