Unilaterally disrupted structural and functional connectivity of the fronto-limbic system in idiopathic hypogonadotropic hypogonadism

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Abstract
Objective: Idiopathic hypogonadotropic hypogonadism (IHH) is rare and can either be associated with normal or defective olfactory sensation, classified as normosmic IHH (nIHH) or Kallmann syndrome (KS). We do not yet understand the central processing pathways in the olfactory system. We aimed to compare the resting-state structural and functional connectivity (FC) of olfactory neural pathways in patients with IHH. We hypothesized that alterations of structural connectivity and FC may exist in the olfactory cortex pathways in IHH patients.

Design: Structural and functional connectivity data results between two groups were analyzed.

Patients: Twenty-five IHH patients (13 nIHH patients and 12 KS patients) were recruited from the Department of Endocrinology and were assessed. A total of 25 age-matched healthy male controls were recruited from the community.

Measurements: All subjects underwent diffusion tensor imaging and functional magnetic resonance imaging (fMRI) scans. Structural and functional connectivity data analyses were then performed. Pearson’s correlation analyses were performed to investigate the correlations between the fractional anisotropy (FA) value and FC strength, showing significant differences among the three groups separately.

Results: Compared with the HC group, FA value in the right uncinate fasciculus (UF) decreased significantly in the IHH group. The olfactory cortex FC values of the right gyrus rectus, orbitofrontal cortex (OFC) and right middle temporal gyrus in the IHH group were decreased compared with those in the HC group. Moreover, there were significant negative correlations between right UF FA and olfactory cortex-FC to both the gyrus rectus and OFC within the HC group (p < .05).

Conclusion: Our findings suggest that alterations of structural and FC support the presence of neurobiological disruptions in IHH patients, particularly a specific structural-functional asymmetry disruption may exist in the olfactory cortex pathways in IHH patients.

Keywords
functional connectivity, idiopathic hypogonadotropic hypogonadism, Kallmann syndrome, olfactory cortex, structural connectivity
INTRODUCTION

Idiopathic hypogonadotropic hypogonadism (IHH) is a sporadic genetic disorder. The clinical features are total or partial lack of pubertal development and infertility due to complete or partial absence of gonadotropin-releasing hormone (GnRH)-mediated release of follicle-stimulating hormone and luteinizing hormone in individuals with otherwise normal anterior pituitary anatomy and function. IHH can either be associated with a normal or defective olfactory sensation, classified as normosmic IHH (nIHH, 40%) or Kallmann syndrome (KS, 60%), respectively. GnRH is the key central regulator of the reproductive axis. During fetal development, GnRH neurons located in the olfactory epithelium need to pass through the olfactory tract, to migrate to the hypothalamus and perform their normal physiological functions. Indeed, human embryo cytogenetic examination found that olfactory nerve fascicles were unable to penetrate the forebrain in KS patients; thus, the migration of GnRH neurons was blocked. However, the olfactory-mediated brain function in IHH has not been further verified.

An increasing number of neuroimaging articles on the olfactory system have significantly contributed to the localization of the olfactory cortex. However, localization of the olfactory cortex has also presented significant challenges to the scientific community. Over the last 30 years, technological developments in neuroimaging have facilitated progress in particular. The structural alterations of the rhinencephalon in KS patients have been well confirmed through magnetic resonance imaging (MRI).

Resting-state functional connectivity (rsFC) measures the temporal coherence of the spontaneous neural activity of spatially distinct regions and is commonly measured using blood-oxygenation-level-dependent (BOLD) functional MRI (fMRI). Diffusion tensor imaging (DTI) provides measurements to investigate the integrity of white matter (WM) architecture in vivo. Some human neuroimaging studies have combined rsFC and DTI, to elucidate the functional and structural connectivity between brain regions and show neurobiological-related abnormalities.

On this basis, we explored the olfactory neural pathways through combing rsFC and DTI to examine the olfactory processing mechanism of IHH patients.

MATERIALS AND METHODS

Subjects and clinical evaluation

All patients were recruited from the Department of Endocrinology and age-matched healthy male controls were recruited from the community. A complete laboratory endocrine examination was obtained for each patient. The Smell Identification Test was performed to evaluate olfactory function. ‘Testicular volume was evaluated with a Prader orchidometer’. Clinical symptoms and signs of hypogonadism, as well as data from clinical reports, indicating normal or defective olfactory function, were used as the diagnostic criteria for KS or nIHH.

MRI scans and laboratory tests were performed. Exclusion criteria for all participants in our control group included the following: (1) any history of prematurity and other endocrine diseases, (2) any psychiatric diseases or neurological disorders, (3) a history of neurosurgery or head trauma with a loss of consciousness ≥5 min, (4) medication history that may affect the central nervous system and (5) any MRI contraindications. This study was approved by the medical research ethics committee and was in accordance with the Declaration of Helsinki. All participants provided written informed consent.

MRI acquisition

We performed MRI scans by using a GE Signa HDX 3.0T MR scanner with a standard 8-channel head coil. Thin-Section (1 mm) coronal three-dimensional (3D) time-of-flight spoiled gradient-recalled acquisition and 3D fast imaging employing steady-state acquisition were acquired for rhinencephalon evaluation. At least two neuroradiologists were blinded to evaluate the olfactory sulci and bulbs independently. If there were different opinions, consensus should be reached after discussion. fMRI scans were obtained using a gradient echo planar imaging (EPI) sequence aligned to the anterior and posterior commissure plane with the following scan parameters: echo time (TE) = 30 ms, repetition time (TR) = 2000 ms, matrix = 64 × 64, flip angle = 90°, field of view (FOV) = 240 × 240 mm, 35 slices of 3 mm, and no gap, scan time = 6 min, 40 s. DTI used a single short spin-EPI sequence with the following parameters: TE = 85.4 ms, TR = 17,000 ms, matrix = 120 × 120, FOV = 240 × 240 mm, 65 contiguous slices of 2 mm, 25 noncollinear directions (b = 1000 s/mm²), together with an axial acquisition without diffusion weighting (b = 0), voxel size = 2.0 × 2.0 × 2.0 mm³, scan time = 7 min, 39 s. Three-dimensional, high-resolution, T1-weighted images were collected using a 3D fast spoiled gradient-echo sequence with the following parameters: TR/TE = 7.1/3.2 ms, image matrix = 240 × 240, FOV = 240 × 240 mm², 176 contiguous slices of 1 mm without gap, voxel size = 1.0 mm³. The subjects were to close their eyes but remain awake throughout the scan.

MRI data processing and analysis

FMRI data processing

Resting-state fMRI data preprocessing included disposing the first 10 time points, slice timing, head motion correction and normalization to the Montreal Neurological Institute (MNI) template (resampling voxel size = 3 × 3 × 3 mm³), followed by spatial smoothing (full width at half-maximum = 6 mm). Subjects with excessive motion (head motion > 3 mm or head rotation > 3°) were excluded. Preprocessing of REST involves filtering the time series of each voxel (bandpass filtering, 0.01–0.08 Hz) to reduce the effects of low-frequency drifts and high-frequency physiological noise. Linear
regression was performed for the head motion parameters, white matter signal, cerebrospinal fluid signal, and global mean signal to eliminate the influence of the nuisance covariates.

2.3.2 | Definition of regions of interest (ROIs)

We selected the bilateral olfactory cortex as the seed ROI based on the definition of the automated anatomical labelling (AAL) template contained in DPABI (resampling voxel size = 3 × 3 × 3 mm³). For each ROI, the BOLD time series of the voxels within the ROI were averaged to generate the reference time series for this ROI. An entire brain mask was created using the normalized T1-weighted high-resolution images of all participants, which were stripped using BrainSuite2 (http://brainsuite.usc.edu). Only voxels within this mask were further analysed.

For each subject, the mean time course for the olfactory cortex ROI was calculated by averaging the time course for all voxels within the hippocampus ROI. Correlation analysis was carried out between the seed ROI and the entire brain in a voxel-wise manner using REST. Correlation coefficients were then transformed to z-values using the Fisher r-to-z transformation to improve normality.

2.3.3 | DTI data processing

PANDA software (Pipeline for Analysing brain Diffusion imAges 1.2.3 http://www.nitrc.org/projects/panda/), a fully automated programme for processing brain diffusion images, was used to process the DTI images, which synthesizes procedures in FSL (http://fsl.fmrib.ox.ac.uk/fsl), MRicron (http://www.mccauslandcenter.sc.edu/mricro/mricron/) and Diffusion Toolkit (http://www.nmr.mgh.harvard.edu/%7Erpwang/dtk). The following steps were used to preprocess images: converting DICOM files into NIfTI images, estimating the brain mask with b = 0 images, cropping images, correcting for the eddy-current effect, averaging acquisitions, calculating DTI metrics and generating diffusion metrics such as DTI-fractional anisotropy (FA) and DTI-mean diffusivity (MD) for statistical analysis. The individual images of the diffusion metrics were transformed from native space to standard MNI space by spatial normalization (voxel size = 1 × 1 × 1 mm³).

2.4 | Statistical analysis

Normal distribution assumption was checked by means of Kolmogorov–Smirnov and Shapiro–Wilk tests. Demographic and clinical data were analysed using Student’s t tests (for age and body mass index [BMI]) with a significant threshold of p < .05. The statistical software was Statistical Package for the Social Sciences (SPSS) version 22.0.

Two-group (IHH and healthy control [HC]) analyses of FC and FA, MD values were performed by DPABI software in SPM8 using two sample T test. Gaussian random-field correction was performed for multiple comparisons and the significance threshold was set at corrected p < .05, corresponding to a threshold of 594 and 352 contiguous voxels with p < .01 for FC and FA values, respectively. For each cluster with significant two-group difference, FC and FA values were extracted. The fine anatomical localization of statistical results was acquired based on the AAL template.

We performed Pearson’s correlation analyses to investigate the correlations between the FA value and FC strength in the significant regions. SPSS software, version 20.0 (SPSS Inc), was used to perform statistical analysis of clinical and demographical variables. All statistical thresholds were set at p < .05.

3 | RESULT

3.1 | Demographic and clinical characteristics

Twenty-five patients with an average age of 18.29 ± 1.36 years, ranging from 15.95 to 21.43 years of age, were assessed. All patients were males. We found no significant differences in age and BMI between the IHHs and HCs (p > .05). The demographics and clinical data of participants were shown in Table 1. In addition, the details of the 25 patients (12 KS and 13 nIHH patients) are all displayed in Table 2.

3.2 | FC findings

Compared with the FC strengths of the HC group, the olfactory cortex FC strengths in the bilateral dorsolateral prefrontal cortex (DLPFC), gyri recti, orbitofrontal cortex (OFC), angular gyri, post-central gyri, right middle temporal gyrus, inferior parietal lobule, precentral gyrus, supramarginal gyrus and left precuneus were significantly decreased in the IHH group (p < .05, corrected; shown in Figure 1 and Table 3).

| Characteristic   | HC       | IHH      | T     | p    |
|------------------|----------|----------|-------|------|
| Number           | 25       | 25       | -     | -    |
| Age (years), mean ± SD | 18.42 ± 1.45 | 18.29 ± 1.36 | 0.347 | 0.73 |
| Male/female      | 25/0     | 25/0     | -     | -    |
| BMI              | 22.02 ± 1.08 | 22.6 ± 1.71 | -1.54 | 0.132 |
| Handedness (R/L) | 23/2     | 23/2     | -     | -    |

Notes: Data are presented as mean ± SD. Abbreviation: BMI, body mass index; HC, healthy control; IHH, idiopathic hypogonadotropic hypogonadism; L, left; R, right.

*p < .05 was considered statistically significant.
**TABLE 2** Main clinical and demographic features in IHH patients

| Subjects no. | Age (year) | Bone age | Height (m) | Weight (kg) | BMI | Handedness | Olfactory function | MRI abnormalities | Testosterone (nmol/L) | FSH (IU/L) | LH (IU/L) | TV (ml) | Clinical diagnosis |
|--------------|------------|----------|------------|-------------|-----|------------|-------------------|-------------------|---------------------|-------------|------------|---------|------------------|
| 1            | 19.49      | >17      | 1.73       | 70.2        | 23.46 | Right      | Normal            | Normal            | 3.19                | 0.61        | 0.71       | 1.70    | nIHH             |
| 2            | 18.05      | 16       | 1.7        | 68.8        | 23.81 | Right      | Anosmia           | bOB hypoplasia    | 1.21                | 0.43        | 0.68       | 1.39    | KS               |
| 3            | 20.08      | -        | 1.76       | 78.2        | 25.25 | Right      | Normal            | Normal            | <0.69               | 0.18        | <0.10      | 0.83    | nIHH             |
| 4            | 17.76      | 16       | 1.66       | 64.1        | 23.26 | Right      | Normal            | Normal            | 3.02                | 1.01        | 0.76       | 4.35    | nIHH             |
| 5            | 19.16      | 16       | 1.68       | 67.3        | 23.84 | Right      | Anosmia           | bOB hypoplasia    | <0.69               | 0.57        | <0.10      | 0.97    | KS               |
| 6            | 19.14      | -        | 1.76       | 60.5        | 19.53 | Right      | hyposmia          | rOB hypoplasia    | 2.43                | 0.92        | 0.60       | 2.23    | KS               |
| 7            | 16.41      | 16       | 1.62       | 52.3        | 19.93 | Left       | Anosmia           | bOB hypoplasia    | 2.45                | 0.83        | 1.0        | 2.18    | KS               |
| 8            | 21.43      | -        | 1.75       | 69.4        | 22.66 | Right      | Normal            | Normal            | <0.69               | 0.34        | 1.15       | 1.43    | nIHH             |
| 9            | 17.90      | 16       | 1.72       | 72.4        | 24.47 | Right      | Normal            | Normal            | 0.90                | 0.90        | 0.83       | 3.12    | nIHH             |
| 10           | 16.71      | 16       | 1.63       | 62.8        | 23.64 | Right      | Anosmia           | bOB aplasia       | 1.21                | 0.86        | 0.78       | 3.10    | KS               |
| 11           | 19.08      | >17      | 1.69       | 58          | 20.31 | Right      | Normal            | Normal            | 0.98                | 0.65        | 0.74       | 3.39    | nIHH             |
| 12           | 18.55      | >17      | 1.76       | 70.2        | 22.66 | Right      | Normal            | Normal            | <0.69               | 0.72        | 0.65       | 1.23    | nIHH             |
| 13           | 21.17      | >17      | 1.68       | 59          | 20.90 | Right      | Normal            | Normal            | 2.63                | 0.94        | 0.85       | 4.05    | nIHH             |
| 14           | 16.95      | 16       | 1.65       | 63.5        | 23.32 | Right      | Normal            | Normal            | 1.89                | 0.45        | 0.58       | 2.84    | nIHH             |
| 15           | 17.18      | >17      | 1.61       | 58.6        | 22.61 | Left       | hyposmia          | bOB hypoplasia    | <0.69               | 0.94        | 0.86       | 0.83    | KS               |
| 16           | 17.70      | 16       | 1.65       | 67.4        | 24.76 | Right      | Anosmia           | bOB aplasia       | 2.31                | 0.34        | 0.57       | 3.93    | KS               |
| 17           | 18.13      | >17      | 1.73       | 69.5        | 23.22 | Right      | Anosmia           | bOB hypoplasia    | 1.87                | 0.45        | 0.64       | 3.23    | KS               |
| 18           | 18.70      | >17      | 1.75       | 72.3        | 23.61 | Right      | hyposmia          | IOB hypoplasia    | 1.34                | 0.91        | 0.95       | 2.32    | KS               |
| 19           | 19.07      | -        | 1.71       | 59          | 20.18 | Right      | Anosmia           | bOB hypoplasia    | <0.69               | 0.54        | <0.10      | 0.68    | KS               |
| 20           | 18.15      | 16       | 1.81       | 76.7        | 23.41 | Right      | Normal            | Normal            | 2.32                | 0.86        | 0.65       | 2.86    | nIHH             |
| 21           | 18.14      | >17      | 1.73       | 72.5        | 24.22 | Right      | Anosmia           | bOB hypoplasia    | <0.69               | 0.72        | 0.84       | 2.75    | KS               |
| 22           | 15.95      | 14       | 1.63       | 63.5        | 23.90 | Right      | Normal            | Normal            | 0.74                | 0.76        | 0.98       | 3.13    | nIHH             |
| 23           | 18.22      | 16       | 1.68       | 57.3        | 20.30 | Right      | Normal            | Normal            | <0.69               | 0.97        | 0.71       | 2.92    | nIHH             |
| 24           | 16.45      | 16       | 1.62       | 67.4        | 21.72 | Right      | Normal            | Normal            | 1.30                | 0.74        | 0.68       | 3.30    | nIHH             |
| 25           | 17.91      | 16       | 1.76       | 62.4        | 20.14 | Right      | Anosmia           | bOB aplasia       | <0.69               | 0.93        | 0.45       | 3.95    | KS               |

Abbreviations: BMI, body mass index; bOB, bilateral olfactory bulbs; FSH, follicle-stimulating hormone; HH, hypogonadotropic hypogonadism; IHH, idiopathic hypogonadotropic hypogonadism; lOB, left olfactory bulb; MRI, magnetic resonance imaging; rOB, right olfactory bulb; TV, testicular volume; --, not available.
3.3 | WM integrity findings

Compared with the HC group, the FA value in the right uncinate fasciculus (UF) and anterior limb of internal capsule decreased significantly in the IHH group ($p < .05$, corrected). Other regions did not differ between the two groups (Figure 2). There was no statistically difference of MD values between two groups.

3.4 | Correlation analyses

There were significant negative correlations between right UF FA values and olfactory cortex FC to both the gyrus rectus and OFC within the HC groups ($r = -.403; p = .04$). However, there was no significant correlation within the IHH group ($p > .05$).

4 | DISCUSSION

We have reported significant structural and functional disruption unilaterally at the right junction of the fronto-limbic system in IHH patients. The results may indicate that a specific structural-functional asymmetry exists in the olfactory cortex pathways in IHH patients.

Our results revealed that the olfactory cortex FC values of the bilateral gyri recti and OFC, which were close to the olfactory bulbs...
and symmetrically clustered in the frontal basal regions, changed in IHH patients. The OFC, which is the key region of the olfactory system, is considered to be not only deeply involved in olfactory processing, such as odour recognition and olfactory memory, but also involved in the integration of cognition and emotion in decision-making processes. Therefore, olfactory perception is considered to be integrated by the OFC with input from many cortical and subcortical areas responsible for basic sensory processing, as well as integrated with cognition apart from sensory input alone. Previous meta-analysis research based on voxel-coordinate mapping localized the regions of the OFC that respond to olfactory stimuli bilaterally near the orbital transverse sulci. More recently, further study has established that damage in these regions may lead to a loss of the ability to consciously perceive odours, although the early sensory pathways are intact.

Olfactory afferents, especially from olfactory tracts, not only connect with the olfactory cortex but also interact with the limbic system (including the amygdala, hippocampus, lateral hypothalamus and parahippocampal gyrus) to form memory and learning mechanisms. This study also found significant alterations of olfactory cortex FC in IHH patients in the bilateral DLPFC, angular gyri, postcentral gyri, right middle temporal gyrus, inferior parietal lobule, precentral gyrus, supramarginal gyrus and left precuneus. This finding suggests that these regions may represent shared neural pathways for psychopathophysiology.

We indicate that abnormalities in brain connectivity in the neuropathophysiology of IHH, which may lead to corresponding clinical manifestations. In addition, a variety of specific neurologic disorders have been illustrated in IHH. These findings suggest that FC abnormalities in IHH patients may provide new clues to reveal the underlying pathophysiological mechanisms in these disorders. A growing number of reports have found that olfactory disorders are associated with cognitive function, which has been identified as an extensive structural or functional abnormality in the brain.

In this study, a decreased FA value of the UF was detected in IHH patients. The commonly used metric of DTI is FA. FA quantifies the directionality of constrained water diffusion in the brain tissue, and reveals widespread changes in tissue microstructure. Decreased FA may represent abnormal fronto-temporal white matter integrity via the olfactory pathway. DTI has been used to investigate IHH patients in a few studies, and the reduced FA value in brain regions that correspond to the olfactory system has been revealed. The UF connects the anterior part of the temporal lobes and the inferior frontal lobes (via the olfactory pathway). It is the major fibre tract originating from the temporal lobe lateral to the amygdala and hippocampus, passes through the temporal stem and has a characteristic hooked shape as it curves upward into the extreme and external capsule to continue into the orbital gyrus. The UF has a suggested decision-making role that is mediated by dopaminergic mechanisms.

The most attractive findings in this study were the unilateral disruption of rsFC in the right olfactory cortex-prefrontal cortex and decreased FA of UF, which linked the two regions within the IHH group. The results provide critical evidence that reveal the disruption of structural connectivity—FC in the right fronto-limbic system unilaterally, which complements and extends previous data implicating these areas in olfactory processing. We suggest a structural and functional specialization of the right fronto-limbic system, also consistent with earlier behavioural findings. Note also that this asymmetry occurs in the secondary olfactory cortex. This asymmetry may be a common feature of the organization of lateral-asymmetric perceptual systems, suggesting that hemispheric specialization is generally associated with higher-order processes rather than initial sensory analysis.

We inferred a negative correlation between the structural connectivity and FC in the right olfactory pathway. The mechanisms of the anatomical–functional relationship in the olfactory neural system have remained vague until now. It has been reported that structural abnormalities might disrupt the corresponding FC in the neural system. The negative correlation between structural connectivity and FC may reflect a compensatory mechanism in the HC group; enhanced FC may have complemented lower structural connectivity to maintain the...
balance of olfactory pathways (fronto-limbic system). The compensatory mechanism may have been destroyed in the IHH group, leading to an imbalanced pathway. This finding provides primary evidence that damaged structural-functional relationships may play an essential role in the neuropathophysiology of IHH.

This study has some limitations. First, as a rare disease, the sample size is relatively small, so the results should be interpreted cautiously, and a study with a larger sample should be performed to investigate the olfactory pathway and the comparison of KS and nIHH further. Second, our seed ROI was selected from an open-access anatomical atlas without detailed subregions. However, our selection was in accordance with previous reports that statistically localized the human olfactory cortex. Reproducibility and standardization in our study protocol still made some sense. Third, the idea that handedness reflects asymmetries in terms of structural and functional brain organization has been tested many times. In our research, we selected the handedness-matched HCs to avoid the effects. Along with other indicators such as BMI, age, it still needs to be carefully discussed (although minimal impact). In our future work, we will validate and investigate the reproducibility of the present findings.

5 CONCLUSION

In conclusion, we implicate the involvement of a multiregional model of cerebral cortex integration in olfactory development and pathophysiology. These findings suggest that structural connectivity and FC abnormalities in IHH patients may provide new clues to reveal the underlying pathophysiological mechanisms in these disorders. We have reported significant structural-functional disruption unilaterally at the right junction of the fronto-limbic system in IHH patients in the present study. The results may indicate that a specific structural-functional asymmetry exists in the olfactory cortex pathways in IHH patients.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data available on reasonable request to the corresponding author.

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