Magnetic Resonance Spectroscopy Findings of Brain Olfactory Areas in Patients with COVID-19 Related Anosmia: a Preliminary Comparative Study

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Abstract

Objectives: COVID-19 infection is commonly associated with olfactory dysfunctions, but the basic pathogenesis of these complications remains controversial. This study seeks to evaluate the value of magnetic resonance spectroscopy (MRS) in determining the molecular neurometabolite alterations within the main brain olfactory areas in patients with COVID-19 related anosmia. Methods: In a cross-sectional study, seven patients with persistent COVID19 related anosmia (mean age: 29.57 years) and seven healthy volunteers (mean age: 27.28 years) underwent MRS in which N-acetyl-aspartate (NAA), choline (Cho), creatine (Cr) and their ratios were measured in the anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (DLPFC), orbitofrontal cortex (OFC), insular cortex (IC) and ventromedial prefrontal cortex (VMPFC). Data were analyzed using TARQUIN software (version 4.3.10), and the results were compared with an independent sample T test and non-parametric Mann-Whitney test based on the normality of the MRS data distribution. Results: The mean duration of anosmia before imaging was 8.5 months. MRS analysis elucidated a significant association between MRS findings within OFC and COVID-19 related anosmia (Pdisease<0.01), and NAA was among the most important neurometabolites (Pinteraction=0.006). Reduced levels of NAA (P<0.001), Cr (P<0.001) and NAA/Cho ratio (p=0.007) within OFC characterize COVID-19 related anosmia. Conclusions: This study emphasizes that MRS can be illuminating in COVID-19 related anosmia and indicates a possible association between central nervous system impairment and persistent COVID-19 related anosmia.

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Running title: MRS Findings in COIVD-19 related Anosmia

Abbreviations

- Magnetic resonance spectroscopy: MRS
- N-acetyl-aspartate: NAA
- Choline: Cho
- Creatine: Cr
- Anterior cingulate cortex: ACC
- Dorsolateral prefrontal cortex: DLPFC
- Orbitofrontal cortex: OFC
- Insular cortex: IC
- Ventromedial prefrontal cortex: VMPFC
- central nervous system: CNS
- region of interest: ROI

- Iran smell identification test: Ir-SIT
- Volume of interest: VOI
- single-voxel spectroscopy: SVS

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Methods: In a cross-sectional study, seven patients with persistent COVID19 related anosmia (mean age: 29.57 years) and seven healthy volunteers (mean age: 27.28 years) underwent MRS in which N-acetyl-aspartate (NAA), choline (Cho), creatine (Cr) and their ratios were measured in the anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (DLPFC), orbitofrontal cortex (OFC), insular cortex (IC) and ventromedial prefrontal cortex (VMPFC). Data were analyzed using TARQUIN software (version 4.3.10), and the results were compared with an independent sample T test and non-parametric Mann-Whitney test based on the normality of the MRS data distribution.

Results: The mean duration of anosmia before imaging was 8.5 months. MRS analysis elucidated a significant association between MRS findings within OFC and COVID-19 related anosmia ($P_{disease}<0.01$), and NAA was among the most important neurometabolites ($P_{interaction}=0.006$). Reduced levels of NAA ($P<0.001$), Cr ($P<0.001$) and $^{NAA}/_{Cho}$ ratio ($p=0.007$) within OFC characterize COVID-19 related anosmia.

Conclusions: This study emphasizes that MRS can be illuminating in COVID-19 related anosmia and indicates a possible association between central nervous system impairment and persistent COVID-19 related anosmia.

Key Points

- Magnetic resonance spectroscopy provides valuable data to identify the basic pathogenesis of various central nervous system disorders such as COVID-19.
- Orbitofrontal Cortex neurochemical dysfunction is significantly associated with persistent COVID-19 induced anosmia.
- N-acetyl-aspartate within the orbitofrontal cortex was significantly lower in patients with persistent COVID-19 related anosmia comparing normal volunteer participants ($P<0.001$).
- According to the results, NAA was among the most important neurometabolites ($P_{interaction}=0.006$).
- The main findings of this study could shed light on future studies to find more specific pharmacologic or nonpharmacologic treatments based on MRS findings.

Keywords

Magnetic Resonance Spectroscopy; Neuroimaging; Olfaction; COVID-19; Anosmia

Introduction

Magnetic resonance spectroscopy (MRS) is a non-invasive quantitative imaging technique with a high impact on diagnosing and managing central nervous system (CNS) disorders. MRS can assess regional levels of metabolites based on chemical alterations. Generally, N-acetyl aspartate (NAA), choline (Cho), creatine (Cr), and their ratios are the most common metabolites of the brain that are detected by MRS [1].

In the last years, COVID-19 infection had been a common cause of olfactory dysfunction. Although most of these anosmic patients will eventually improve within a few months, a considerable number of patients will develop prolonged smell loss more than two years after diagnosis [2,3]. Overally, olfactory disorders could be classified as conductive sensory-neural or due to a central nervous system impairment [4]. Until now, the basic

pathogenesis of these complications remains controversial, and evidence suggests that the main pathogenesis of anosmia can probably depend on CNS dysfunction[5]. The most important current discussions in COVID-19 related anosmia are the controversies about the biochemical basis of these pathologies, diagnosis, and treatment [6]. Therefore, using advanced CNS imaging to fill the lack of knowledge in the context of COVID-19 related anosmia and introduce more sensitive and specific methods for diagnosis is reasonable. Importantly, understanding the basic pathogenesis of the anosmia can potentially shed light on further trials to find a cure [7].

This study seeks to investigate the neurometabolic alterations in the brain structural regions associated with the olfaction process in cases with COVID-19 related anosmia. In this light, single-voxel spectroscopy was performed on five regions of interest (ROI), including anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (DLPFC), insular cortex (IC), orbitofrontal cortex (OFC), and ventromedial prefrontal cortex (VMPFC) in the right hemisphere [8-11].

Materials and methods

2.1 Participants

The strengthening of the reporting of observational studies in epidemiology (STROBE) statement was used for reporting the study. Between October 2021 and October 2022, two groups were included in the study to investigate MRS data in cases with COVID-19 related anosmia and those with normal olfactory function.

The exclusion criteria for both groups were as follows: (i) history of neurological, psychiatric, sino-nasal disorders, sinus or olfactory disorders; or (ii) current Symptoms of a rhinovirus Infection. (iii) any evidence may suggest other possible pathophysiology for the anosmia in two anosmic groups.

Normal healthy volunteers with an age between 18-60 were considered as group 1 and included in the study if they had no exclusion criteria. All healthy controls underwent the Iran smell identification test (Ir-SIT) to confirm normal olfactory function.

COVID-19 related anosmia patients (Group 2) were recruited based on the following criteria: (i) COVID-19 infection and subsequent anosmia; (ii) documented positive SARS-CoV-2 tests (direct antigen detection or reverse transcriptase-polymerase chain reaction) on nasopharyngeal swab specimen before the onset of anosmia; (iii) persisting the anosmia for at least three months; (iv) fulfillment of criteria for anosmia based on Ir-SIT; [12] (v) excluding all possible pathological etiologies by CT-scan and structural MRI; and (vi) age between 18-60 years.

Institutional review board (IRB) approval and patient informed consent was obtained. All the visits, physical examinations, and MRS acquisitions were performed concerning health protocols against COVID-19.

2.2 Iran smell identification test (Ir-SIT)

Iran Smell Identification Test (Ir-SIT) is a Modified Version of the University of Pennsylvania Smell Identification Test (UPSIT) for the Iranian Population [13]. The cut point for the anosmia was 9. A score between 10-13 and 14-18 is considered severe and mild microsomia, respectively. A score between 19-24 indicates that the participant has a normal olfactory function. Patients with COVID-19 related anosmia were completely anosmic. All participants in the control group were utterly normosmic (Table 1).

2.3 MRS protocol

Clinical evaluation was performed at a 1.5 Tesla Siemens scanner using an eight-channel receive-only head coil. A conventional 3-dimensional brain image (sagittal T1 MPRAGE, TR/TE = 1800/3.5, the field of view (FOV) = 256 ×2 56 × 160 mm3, Resolution = 1 × 1 × 1 mm3) as a reference image for the volume

of interest (VOI) positioning was performed for all patients before MRS sequence. For single-voxel spectroscopy (SVS), MRS was obtained using a point-resolved spectroscopy (PRESS) sequence. Four $2\times2\times2$ cm^3 voxels were located on the ACC, DLPFC, IC, and VMPFC. One $2\times2\times1$ cm^3 voxel was located at OFC to accurately estimate cerebral cortex neurometabolites concentration and to prevent the effect of surrounding bone tissue on the spectroscopy. The voxels were carefully placed to avoid the subcutaneous fat, skull, vasculature, arachnoid space, and cerebrospinal fluid. Manual shimming was performed for all acquisitions. The parameters were set as TR/TE=1500/135 and NEX=128. Six saturation bands were placed around the VOI to suppress the outer volume signals. The average time for each MRS duration was 25 ± 2 minutes (5 minutes for each region).

2.4 MRS data processing

Data were pre-processed by the administration of a water removal algorithm for the reference offset of 4.65 ppm to remove the residual water signals. SVS raw data were fitted using TARQUIN (version 4.3.10)[14]. Targeted approaches selected a predefined group of metabolites such as NAA, Cho, and Cr for peak fitting and metabolite concentration. The metabolite ratios of NAA to Cr ($^{NAA}/_{Cr}$), NAA to Cho ($^{NAA}/_{Cho}$), and Cho to Cr ($^{Cho}/_{Cr}$) were measured by dividing the metabolite values in the same spectrum for each ROI.

2.5 Statistical analysis

Statistical analyses were performed using SPSS version 26. Shapiro-Wilk test was used to determine the normality of MRS data distribution, including absolute and relative values of neurometabolites. The relative values of neurometabolites were calculated by dividing the arbitrary unit (au.) levels of NAA/Cr, NAA/Cho, and Cho/Cr.

Parametric independent t-test and non-parametric Mann-Whitney test were carried out for the comparison of quantitative variables with and without normal distribution between groups. Repeated measured ANOVA was used to determine the effect of the ROI and spectroscopic data on the anosmia as well as the interaction between MRS data in different brain regions. P values less than 0.05 were considered as significant.

Results

3.1 Clinical characteristics

Considering the risk of exposure to COVID-19 in the hospital, the cost and time of data acquisition and spectroscopy, we included only seven healthy volunteers in the study as control group (4 males and 3 females; mean age: 27.28, range: 20-38; Ir-SIT mean score: 20.1). Seven patients (4 males and 3 females; mean age: 29.57 years. range: 18–41; Ir-SIT mean score:7.5) met the inclusion criteria in COVID-19 related anosmia. The Mean duration of anosmia before the imaging was 8.5 months in these patients. Demographic characteristics relating to participants are summarized in table 1.

3.2 MRS results

As illustrated in Figure 1A, the NAA level within OFC (p=0.001) and VMPFC (p=0.026) detected by MRS in patients with COVID-19 related anosmia was significantly lower than the control group. Interestingly, anosmic patients exhibited a lower NAA level than the control group in all ROI (Table 2).

As opposed to NAA, there was no significant difference between groups for Cho levels. Nonetheless, as represented in Figure 1B, a diffuse non-significant decrease of Cho level in anosmic patients compared to the control group was observed (Table 2).

As reflected in Figure 1C, there was a significant reduction of Cr level within OFC in anosmic patients comparing the control group (P=0.001) (Table 2).

$^{NAA}/_{Cho}$ ratio within OFC was significantly different between groups (P=0.007) (Figure 1D) (Table 2).

We found no significant differences in$^{NAA}/_{Cr}$ or$^{Cho}/_{Cr}$ ratios among the two groups (Figure 1E and Figure 1F) (Table 2).

Our results demonstrated a significant association between OFC neurometabolite impairment and COVID-19 related anosmia ($P_{disease}$<0.001) (Figure 2). Repeated measured ANOVA analysis revealed that the interactions of NAA ($P_{interaction}$=0.006) and Cr ($P_{interaction}$=0.043) within OFC were significantly different between the two groups (Tables 2).

Gnuplot of Tarquin e*x* amples shown in Figure 3 has provided a visual display of the distribution of brain neurometabolites of the OFC spectroscopy in each group.

Discussion

Two processes can disrupt the sense of smell: conductive olfactory deficit and sensorineural olfactory deficit. Processing of the olfaction starts in the olfactory sensory neurons of the nasal olfactory epithelium. From there, efferent information travels through the olfactory tract to the primary olfactory cortex and subsequently to the secondary olfactory centers, including the insular cortex (IC), orbitofrontal cortex (OFC), thalamus, hippocampus, and anterior cingulate cortex (ACC)[11,15]. Therefore, the central olfactory system is closely interconnected with limbic structures and olfactory memory processes [15]. Furthermore, the limbic loop of the basal ganglia, including the ACC, ventromedial prefrontal cortex (VMPFC), and dorsolateral prefrontal cortex (DLPFC), has a critical role in olfactory processing [9,15]. These parts of the brain are also involved in olfactory memory[16]. Interestingly, literature has emphasized that right hemisphere structures play a more prominent role in olfaction[8-11].

4.1 Loss of smell sensation in the setting of COVID-19 infection

Relatively high occurrence of COVID-19 related anosmia led us to use magnetic resonance spectroscopy (MRS) to compare brain MRS data in normal control volunteer participants and patients with COVID-19 related anosmia [2]. To the best of our knowledge, only one study had utilized MRS to evaluate olfactory dysfunction in a variety of causes, including head injury (4 patients), post-viral (5 patients), and idiopathic causes (9 patients). Nevertheless, none of them were COVID-19 induced anosmia [17].

We performed five single voxel spectroscopies in ACC, DLPFC, VMPFC, IC, and OFC in the right hemispheres as the ROI to compare neurometabolite concentrations in normal volunteer participants and patients with COVID-19 related anosmia. The main findings of the study show that orbitofrontal cortex neurochemical dysfunction is significantly associated with COVID-19 induced anosmia, and the most critical neurometabolite was NAA.

We have observed that COVID-19 related anosmic patients present a diffuse reduction of NAA, Cr, and Cho levels in most brain regions, comparing the control group, especially in OFC. However, these findings were significant only for the NAA and Cr levels and $^{NAA}/_{Cho}$ ratio within OFC and NAA levels within VMPFC.

There are limited data on radiographic practice on patients with post-infectious olfactory loss, which lead to some controversies. Previously, Kollndorfer et al. reported gray matter volume reduction in the right orbitofrontal cortex in patients with post-infectious olfactory loss [10].

It is well known that loss of sense of smell after COVID-19 infection is much more common than previous reports of post-infectious olfactory loss before the COVID-19 pandemic. Moreover, COVID-19 related anosmia is less related to inflammation, rhinorrhea, or other obstructive mechanisms[18]. A few radiological studies

(e.g., MRI, Diffusion tensor imaging and olfactory functional magnetic resonance spectroscopy) have indicated that the main pathology in COVID-19 related olfactory dysfunction is better justified by central nervous system dysfunction[19].

Contrary to our results, Ho et al. suggest that COVID-19 infection may not have a role in frontotemporal cortex function because of the relatively normal oxyhemoglobin area under the curve (AUC) in COVID-19 related anosmic patients comparing the healthy control group[20]. In our opinion, normal oxyhemoglobin AUS based on the functional near-infrared spectroscopy (fNIRS) study could not rule out biochemical changes in neuronal damage [20].

Overall, the findings of this study suggest that olfactory dysfunction in patients with COVID-19 related anosmia is significantly associated with central nervous system impairment. Since the NAA originates from mitochondria, it can reflect neuronal integrity and viability; the significant decrease of NAA and $^{NAA}/_{Cho}$ in the OFC in COVID-19 related anosmia strongly suggests regional neuronal OFC impairment in the context of persistent COVID-19 anosmia. The second significant alteration in our patients was a reduction of Cr levels within OFC. Cr works as an indirect intermediator of cellular energy and previous studies have shown its reduction following nerve injuries[1]. Although this cellular dysfunction emphasized the hypothesis that impairment of OFC function is significantly associated with permanent anosmia, these results could not answer a controversy about the cause-and-effect relationship between brain neurometabolite dysfunction and COVID-19 related anosmia.

Finally, it should be noted that the results of recent clinical trials that did not achieve significant improvement from intranasal corticosteroids raise the property of central nervous system mechanisms for COVID-19 related anosmia [21-23].

4.2 Limitations and comments of the study

The small number of patients is certainly a major limitation of our study, but this is a well-designed preliminary study. Another limitation of our study was the nature of our scanner. More powerful scanners and multivoxel spectroscopy can detect extra metabolites such as Myo-inositol, glutamate, glutamine, glutathione, gamma-aminobutyric acid, and lactate.

Despite the limitations of this study, we believe that the MRS is a valuable advanced neuroimaging technique and could provide very important landmarks in the diagnosis, treatment and follow-up of patients with anosmia.

Interestingly, as MRS provides valuable, quantifiable data, it would be possible to build a predictive score based on future longitudinal studies and neural network to predict the outcomes of patients with acquired anosmia.

According to a suggestive origin of injury in patients with COVID-19 related anosmia, pharmacologic or nonpharmacologic therapies in order to increase NAA levels using electroconvulsive therapy, cognitive behavioral therapy, and physical exercise or short-course pharmacological therapies with lithium, valproate, or antipsychotics could be tried in these patients as they can lead to a widespread increase in brain NAA levels [24,25].

Conclusions

MRS is an exciting and novel approach to evaluating prolonged olfactory dysfunction after COVID-19 related anosmia. However, it is still not entirely clear that abnormalities in the CNS are the cause or the result of olfactory loss due to COVID-19. We believe further neuroimaging studies and clinical trials could answer some controversies about the cause-and-effect relationship between the neurometabolic alterations within OFC in COVID-19 anosmia.

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Tables

Table 1

Demographic data of included cases in each group. Group 1: healthy volunteer cases; Group 2: COVID-19 induced anosmia cases; M: Male; F: Female; C: case; Iran Smell Identification Test (Iran-SIT) Score (anosmia=0-9, severe microsmia=10-13, mild microsmia=14-18, normosmia=19-24); sum: summation.

Table 2

Magnetic resonance spectroscopy results from all regions of interest and main statistical findings of this study. NAA: N-Acetyl Aspartate; Cho: Choline; Cr: Creatine; ACC: Anterior Cingulate Cortex; DLPFC: Dorsolateral Prefrontal Cortex; OFC: Orbitofrontal Cortex; IC: Insular Cortex; VMPFC: Ventromedial Prefrontal Cortex. *P value < 0.005 considers significant.

Figure Legends

Figure 1

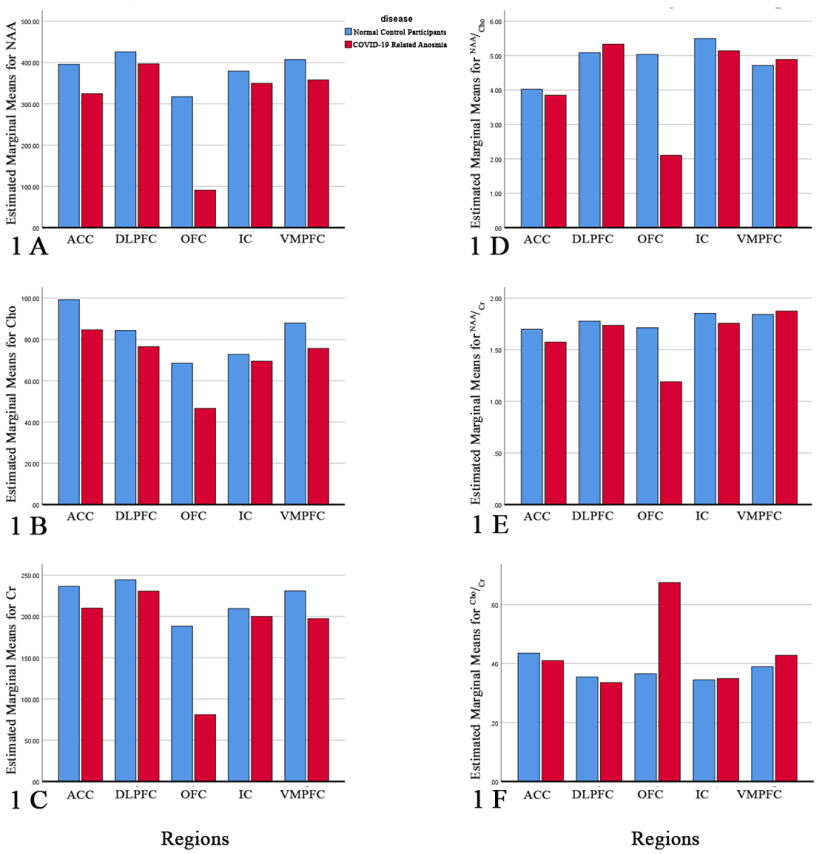
The difference in the Magnetic Resonance Spectroscopy (MRS) data between groups for each region of interest (ROI) including Anterior Cingulate Cortex (ACC), Dorsolateral Prefrontal Cortex (DLPFC), Orbitofrontal Cortex (OFC), Insular Cortex (IC), and Ventromedial Prefrontal Cortex (VMPFC). Blue color is related to healthy control volunteers (group1); Red color is related to COVID-19 related anosmia patients (group2); (A): Estimated marginal means of N-Acetyl Aspartate (NAA); (B) Estimated marginal means of Choline (Cho); (C): Estimated marginal means of Creatine (Cr); (D): Estimated marginal means of NAA/Cho ratio; (E): Estimated marginal means of NAA/Cr ratio; (F): Estimated marginal means of Cho/Cr ratio.

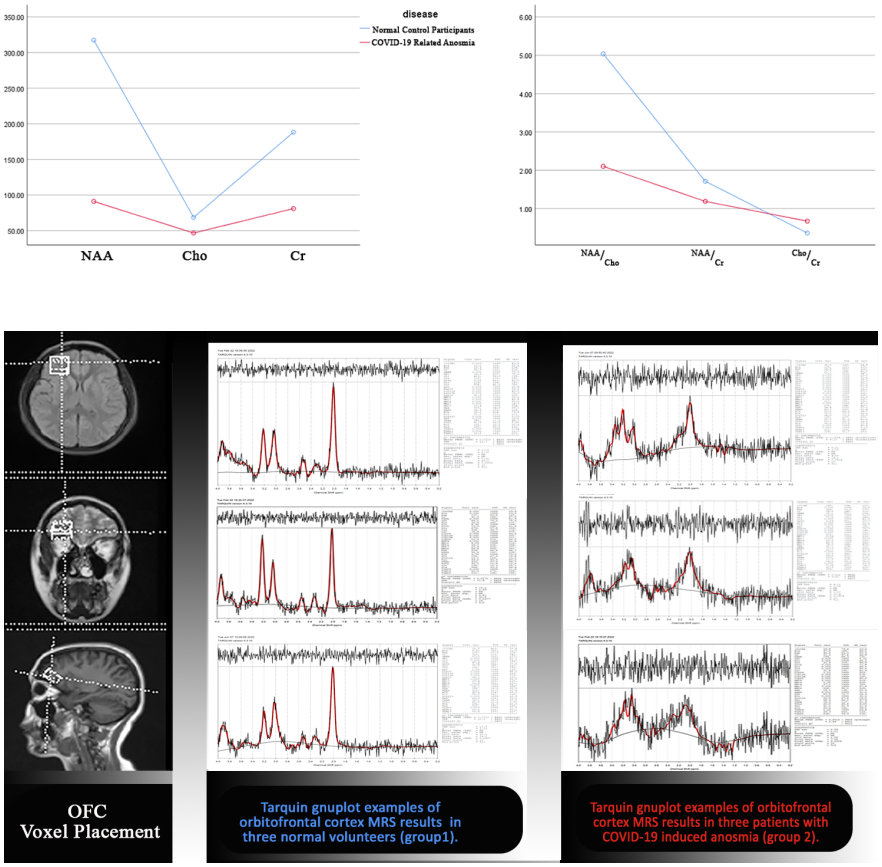
Figure 2

Comparison of MRS results within the orbitofrontal cortex between the healthy control group (group 1; the Blue line) and COVID-19 related anosmia patients (group 2; the Red line). N-Acetyl Aspartate (NAA), Choline (Cho), Creatine (Cr). Based on Repeated Measured ANOVA analysis, OFC neurometabolite impairment was significantly associated with COVID-19 related anosmia ($P_{disease} < 0.001$).

Figure 3

Voxel placement within Orbitofrontal Cortex (OFC) and examples of Tarquin Gnuplot results.





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