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On the relationship between neurocognitive measures and olfactory dysfunction in COVID-19 patients with and without anosmia

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ABSTRACT

One of the predominant symptoms of the COVID-19 virus is the complete (anosmia) or partial (hyposmia) loss of smell. Anosmia may be a critical neurocognitive symptom because there is an empirically demonstrated association of anosmia with neurodegenerative diseases like Parkinson's disease, Alzheimer's disease, etc. The present study assessed the neurocognitive disorder patterns in recovered COVID-19 patients who either self-reported anosmia or its absence. Of the 60 adult participants (n = 32 males, n = 28 females; M_{age} = 20.78 years, range = 18–31 years), 15 reported COVID-19 induced anosmia, 15 reported COVID-19 without anosmia, and 30 reported not having contracted COVID-19. The participants were first administered a 10-item smell test, and analysis of variance revealed significantly better scores for the control group than the other two groups. Further, there was no significant difference in smell scores between the patients who self-reported anosmia or denied it. This statistical pattern was consistent across all neuropsychological tests: short- and long-term verbal memory, digit span, Trail Making, and a self-report 46-item neurocognitive scale. Regardless of the self-report of anosmia or denial, all thirty COVID-19 patients scored significantly poorer than the control group on all of the tests and neurocognitive scale. In summary, the self-report of anosmia appears to be unreliable, and the COVID-19 patients who were found to be anosmic on the initial objective smell test demonstrated poorer neuropsychological performance than controls.

1. Introduction

The Coronavirus Disease 2019 (COVID-19) virus is well known to negatively affect brain regions and their functions (e.g., Avula et al., 2020; Wu et al., 2020). Recent studies demonstrate many long-term psychological and neurological issues associated with COVID-19 symptoms and their severity (Helms et al., 2020; Li et al., 2020; Moriguchi et al., 2020; Nath, 2020). More than one-third of hospitalized COVID-19 patients have experienced severe neurological problems such as headaches, altered sensory experiences, ataxia, strokes, and seizures, and neurocognitive symptoms such as memory problems, inattention, executive function deficit, etc. (Mao et al., 2020; Pilotto et al., 2021). One common neurological symptom associated with COVID-19 is the complete loss of smell (anosmia) or partial loss of smell (hyposmia). Disturbances in olfactory function are known to have deleterious effects on the quality of life, emotional states, diminished pleasure in eating, and maintaining personal hygiene (Kollndorfer et al., 2017). However, one issue in current research on the effects of anosmia in COVID-19 patients is that some studies employ only self-reports of anosmia. For example, Klopfenstein et al. (2020) examined anosmia/hyposmia in 114 COVID patients, and 54 (47%) self-reported the loss of smell, lasting for an average of approximately 9 days. They reported that 80% of these patients self-reported recovery from anosmia by 2 weeks. Al-Zaidi and Badr (2020) examined 65 COVID-19 patients by questionnaire and found that 89% self-reported anosmia. Approximately 40% of these patients reported recovery from anosmia within 3 weeks. Again, however, the presence of anosmia and the recovery from anosmia were determined by self-report. Thus, it is the purpose of the present study to investigate neurocognitive symptoms in recovered COVID-19 patients who self-reported anosmia or a lack of anosmia and compare the two groups on an objective smell test measure compared to a group of participants who did not contract COVID-19 infection.

Moein et al. (2020) employed an objective measure of anosmia in 60 COVID-19 patients and found 59 of the 60 were determined to have some degree of anosmia, and 35 (58%) of these patients were completely or severely anosmic. Notably, only 35% of the patients reported any

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anosmic symptoms before their testing. Yadav et al. (2021) reported that only 18% of 152 COVID-19 patients self-reported the presence of anosmia upon hospitalization. Thus, the results of these two aforementioned studies not only highlight that self-reported anosmia grossly underestimates true symptoms of anosmia but also reinforce the importance of employing objective measures of olfactory dysfunction.

2. COVID-19, anosmia, and neurocognitive impairments

Considerable evidence suggests that the COVID-19 virus penetrates the olfactory epithelium, travels through the olfactory nerve to the olfactory bulbs, and then to the central nervous system (CNS). This process appears to initiate a cascade of inflammatory reactions in the CNS (cytokine storm) and then other organs in the body (Anwar et al., 2020; Aragão et al., 2020; Almeria et al., 2020; Li et al., 2020; Roozbeh et al., 2021). Structural brain abnormalities following a COVID-19 infection has been shown to be associated with ataxia, motor deficits, and altered mental status (e.g., Kumar et al., 2021). Autopsy reports of deaths due to COVID-19 appear to indicate neuronal degeneration, acute inflammation of cortical areas, encephalitis, epilepsy, stroke, and other diseases and brain insults (e.g., Avula et al., 2020; Helms et al., 2020; Mao et al., 2020; Wu et al., 2020). Anwar et al. suggested a neuroinvasive route of COVID-19 infection into the nerve cells primarily via the olfactory pathway. Alternatively, Li et al. suggested the role of cerebrospinal fluid in transporting the viral pathogens transnasally to the brain.

3. The purpose of the present study

This study investigated neurocognitive functions, specifically phonological storage capacity/verbal working memory, short- and long-term verbal memory, visual attention/task switching/processing speed/mental flexibility/executive functions, and general neurocognitive symptomatology, in recovered COVID-19 patients. We also compared their self-reported anosmia or a lack of anosmia to an objective smell test measure and compared their results to a group of participants who did not contract the COVID-19 virus.

4. Method

4.1. Sample and Procedure

Sixty participants ($n = 32$ males, $n = 28$ females; Mean age = 20.78 years, range = 18 to 31) were recruited by e-mail from the student community of the Indian Institute of Technology Gandhinagar (IITGN), India, with the prior approval by the IITGN's Institute Ethical Committee (IEC). The participants were 18 years or older and able to read English proficiently, and they did not report any pre-existing or co-morbid physiological, neurological, and/or psychiatric problems. The inclusion criteria also required the participant's absence of any specific prior condition of nasal problems or olfactory dysfunctions. Of the sixty participants, 15 reported that they had COVID-19 induced anosmia/hyposmia, 15 reported that they had COVID-19 without anosmia/hyposmia, and 30 reported that they had not ever contracted COVID-19. The mean length of time between the onset of the COVID-19 infection and laboratory neurocognitive testing was 64 days (range = 18–224 days).

First, the participants answered the demographic questions related to age, gender, level of education, medical conditions, and health status. Second, they underwent the 10-item objective smell test. Third, they were administered three neurocognitive laboratory measures – Wechsler Memory Scale, which measures both short and long-term verbal memory; Digit Span (forward and backward), which measures phonological acoustic memory and working memory; Trail Making Test measures attention and perceptual processing speed. Fourth, a self-report 46-item Neurocognitive scale was administered to the participants.

4.2. Instruments

Smell Test: The present study employed a 10-odorant objective smell test (odor identification), created by the authors and based upon a previously validated 10-item objective smell test (Tabert et al., 2005). Each item was answered on a four multiple-choice scale, where only one of the four choices was correct. Thus, the scores could range from 0 (complete anosmia) to 10 (no olfactory dysfunction). The ten odorants were: orange, strawberry, pineapple, saffron, vanilla, sandalwood, jasmine, rose, lemongrass, and lavender.

Short- and Long-Term Verbal Memory Test: Short- and long-term verbal memory was assessed by an Indian cultural version in English of Wechsler's Memory Scale (Wechsler, 2009), which is a reliable, valid, and well-established measure commonly used in neuropsychological assessment.

Digit Span Test: Phonological storage capacity and verbal working memory were assessed by the Digit Span subtest from Wechsler's Adult Intelligence Scale (Wechsler, 1997). The Digit Span Forward subscale requires a participant to repeat up to 10 digits Forward and is reported to be a measure of phonological acoustic memory. The Digit Span Backward subscale requiring the repetition of up to 9 digits Backward and is reported to be a measure of short-term verbal working memory.

Trail Making Test: Visual attention, task switching, speed of processing, mental flexibility, and executive functions were assessed by the Trail Making Test (Parts A & B; Reitan, 1956).

Neurocognitive Scale: A self-report, 46-item standardized Neurocognitive scale assesses five neuropsychological domains for Neurocognitive Disorder in the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-5*; American Psychiatric Association, 2013). The scale was appropriated from the Coolidge Axis II Inventory (CATI; Coolidge, 2021). The neuropsychological domains included: Inattention (9 items), e.g., I have difficulty paying attention; Executive Dysfunction (10 items), e.g., I fail to finish tasks, even when I have the ability to do them; Learning and Memory problems (10 items), e.g., I often forget to do things I am supposed to do; Receptive and Expressive language difficulties (7 items), e.g., People do not understand what I am trying to say; Perceptual-motor impairments (9 items), e.g., I have dizzy spells. All of the self-reported items were answered on a four-point scale ranging from *Strongly False* (1) to *Strongly True* (4). The CATI Neurocognitive scale has excellent internal reliability ($\alpha = 0.95$) and good evidence for its validity (Coolidge, 2021).

A sample of recovered COVID-19 patients with self-reported anosmia ($n = 15$), a sample of recovered COVID-19 patients without self-reported anosmia ($n = 15$), and healthy controls ($n = 30$) were recruited for the study. First, the participants answered the demographic questions related to age, gender, level of education, medical conditions, and health status. Second, they underwent the 10-item objective smell test. Third, they were administered three neurocognitive laboratory measures – Wechsler Memory Scale, which measures both short and long-term verbal memory; Digit Span (forward and backward), which measures phonological acoustic memory and working memory; Trail Making Test measures attention and perceptual processing speed. Fourth, a self-report 46-item Neurocognitive scale was administered to the participants.

5. Results

5.1. Smell Test

An analysis of variance (ANOVA) of the smell test mean scores revealed a significant difference among the three groups (self-reported anosmic COVID-19 patients, self-reported non-anosmic COVID-19 patients, and the control group), $F(2,59) = 78.51$, $p < .001$, with a large effect size ($\eta^2 = 0.75$). A Tukey's post hoc test ($p = .05$) revealed that the control group's mean smell test score ($M = 8.17$, $SD = 1.18$, range = 6 to 10 correct) was significantly greater than the anosmic ($M = 4.20$, $SD =$

1.52, range = 1 to 8 correct) and non-anosmic ($M = 3.80$, $SD = 1.27$, range = 1 to 5 correct) COVID-19 groups' means. However, there was no significant difference between the latter two groups' means. One implication of the latter finding is that the self-report of anosmia or non-anosmia in recovered COVID-19 patients is not a valid measure. Because of the invalidity of self-reported anosmia, the two recovered COVID-19 patient groups were combined for the subsequent statistical analyses. Table 1 presents the correlations between the 10-item objective smell test score and the laboratory measures of neurocognition and the self-reported Neurocognitive scale sum. As shown in Table 1, the smell test score was strongly and significantly correlated with all measures of neurocognition. These results preliminarily support the idea that higher degrees of anosmia are associated with higher levels of neurocognitive impairment.

The present study employed the criteria for severe to complete anosmia, which was extrapolated from the Moein et al. (2020) study. In our study, four items correct or less out of the 10-item smell test were indicative of complete or severe anosmia. We found that 21 of the 30 (70%) COVID-19 participants qualified for a diagnosis of complete or severe anosmia. The other nine participants in the present study would qualify for mild to moderate anosmia (range = 1 to 6 correct).

5.2. Neurocognitive laboratory measures

Independent samples *t* tests were conducted between the combined COVID-19 group ($n = 30$) and the control group ($n = 30$) on the three laboratory cognitive measures and their subscales. These results appear in Table 2. As shown in Table 2, the COVID-19 group scored significantly more poorly on all neurocognitive measures than the control group with large effect sizes.

5.3. Neurocognitive scale

An independent samples *t*-test between the combined COVID-19 group and the control group on the overall 46-item Neurocognitive scale score sum and its five domains revealed that the COVID-19 group self-reported significantly higher overall neurocognitive dysfunction than the non-COVID-19 control group (See Table 3). Further, the self-reported Neurocognitive scale had strong support for its convergent validity as all six laboratory measures had strong and significant correlations (absolute values) with the overall self-reported score. The median correlation between the Neurocognitive scale sum and the three laboratory measures and their subscales was $r = .62$ (range = 0.56 to 0.72). All five domains of the Neurocognitive subscales also produced significant correlations with the laboratory measures, and all had medium or strong relationships, with a median correlation of $r = 0.46$ (range $r = 0.36$ to 0.70).

Table 1
Correlations between the objective smell test score and the laboratory measures of neurocognition and the self-reported neurocognitive scale sum.

Neurocognitive Measures	Smell Test Score
Story Test Immediate Recall	.69*
Story Test Delayed Recall	.62*
Digit Span Forward	.62*
Digit Span Backward	.64*
Trail Making Test A	−.69*†
Trail Making Test B	−.82*†
Neurocognitive Scale Sum	−.78*†

*$p < .001$; † lower scores on these cognitive measures indicate better performance.
Note: These correlations were performed on the entire sample ($N = 60$).

Table 2
Independent Samples *t*-test Results Between the Combined COVID-19 Groups and the Control Group for the Three Laboratory Neurocognitive Measures and their Subscales.

Neurocognitive Measures	COVID-19 Group Mean & *SD*	Control Group Mean & *SD*	*t*	*p*	Cohen's *d*
Short-term Verbal Memory	19.27; ±2.65	23.73; ±1.14	8.47	<.001	2.91
Long-term Verbal Memory	17.60; ±3.41	22.37; ±1.29	7.16	<.001	2.16
Digit Span Forward	5.60; ±1.00	7.37; ±1.22	6.13	<.001	1.58
Digit Span Backward	4.83; ±1.05	6.50; ±1.04	6.16	<.001	1.06
Trail-Making Test Part A	77.18; ±16.28	48.88; ±9.68	8.18	<.001	−2.11
Trail-Making Test Part B	96.07; ±10.28	63.90; ±5.03	15.39	<.001	−3.97

Note: Cohen's *d* effect sizes are small ≥ 0.20, medium ≥0.50, large ≥ 0.80.

Table 3
Independent Samples *t*-test Results for the Five Neurocognitive Domains Between the Combined COVID-19 Groups and the Control Group.

Domains	COVID-19 Group Mean & *SD*	Control Group Mean & *SD*	*t*	*p*	Cohen's *d*
Inattention	17.47; ±3.78	12.27; ±2.42	6.34	<.001	1.64
Executive Dysfunction	23.27; ±4.34	14.23; ±3.09	9.28	<.001	2.40
Learning and Memory Problems	21.10; ±5.16	13.53; ±2.69	7.12	<.001	1.84
Receptive and Expressive Language Difficulties	14.00; ±3.65	9.33; ±2.09	6.08	<.001	1.57
Perceptual-Motor Impairments	20.23; ±4.29	14.53; ±2.39	6.36	<.001	1.64
Neurocognitive Sum	96.07; ±10.28	63.90; ±5.03	15.39	<.001	3.97

Note: Cohen's *d* effect sizes are small ≥ 0.20, medium ≥0.50, large ≥ 0.80.

6. Discussion

One of the important findings in the present study is that the recovered COVID-19 patients' self-reported anosmia or lack of anosmia did not appear to be valid. Both of these groups scored significantly lower than the control group on the 10-item objective smell test measure (with a large effect size), and there was no difference between those two groups' means. This result is consistent with the Moein et al. (2020) study who found that 98% of COVID-19 patients had objective olfactory dysfunction while only 35% of the patients reported olfactory deficits before their testing. They also found that 58% of their patients were either completely or severely anosmic. Yadav et al. (2021) also reported that only 18% of their COVID-19 patients self-reported the presence of anosmia upon hospitalization. As noted previously, 73% of the present sample of COVID-19 patients were completely or severely anosmic and 100% showed some degree of olfactory dysfunction. Preliminarily, our finding suggests that objective measures of anosmia be employed when determining olfactory dysfunction in COVID-19 patients. Additionally, the present smell test received preliminary support for its convergent validity as all three laboratory cognitive measures (with two subscales each) and the Neurocognitive scale sum strongly and significantly correlated with it. Again, these results support the idea that the degree of anosmia is linked to a variety of neurocognitive impairments.

From the results of the three laboratory neurocognitive measures, it was evident that the COVID-19 group (regardless of their self-reported

anosmia status) exhibited poorer short- and long-term verbal memory, reduced phonological storage and working memory, slower processing speeds, visual search problems, and impaired cognitive flexibility. Additionally, these findings were supported by the patient's self-reported neurocognitive dysfunction, and its five domains, which measured their attention, executive functions, learning and memory, receptive and expressive speech, and perceptual-motor abilities. Further, the self-reported Neurocognitive scale had strong support for its convergent validity as all six laboratory measures had strong and significant correlations with the overall self-reported score.

The present results are also consistent with studies that have found long-term neuropsychological dysfunction in COVID-19 patients (e.g., Helms et al., 2020; Li et al., 2020; Moriguchi et al., 2020; Nath, 2020; Pilotto et al., 2021; Rass et al., 2021). Overall, these results clearly demonstrate that neurocognitive deficits in COVID-19 patients, either objective laboratory measures or self-reported, are significantly and positively associated with the degree of anosmia. Again, future studies should not rely on a COVID-19 patient's self-report of anosmia but should employ objective smell measures. Finally, the self-report of neuropsychological dysfunction in COVID-19 patients did receive preliminary validity. It might also be of value to determine whether olfactory deficits associated with COVID-19 can be ameliorated and whether their amelioration results in cognitive improvements.

Limitations

The present study was conducted in English with a highly educated younger Indian sample, and thus, the results may be generalized only to English-fluent Indian participants. The study may also have limits to its generalizability due to its relatively small sample (30 COVID-19 patients and 30 controls). The study only administered three laboratory measures of neurocognition, and a broader array of neuropsychological tests should be employed in future studies. Also, we did not assess the participants' premorbid health conditions and/or comorbidities, which may have been critically important, particularly for the COVID-19 group. Finally, the study did not assess recovered COVID-19 patients with much longer durations of the virus, nor did the study analyze neurocognitive deficits as a function of the duration of the infection. It may also be useful for future studies to determine the degree of self-reported smell deficits compared to objective smell measures. In the present study, we employed only a 3-point scale, complete anosmia, partial anosmia, and no anosmia.

Author note

This article was based on a Master's thesis conducted by Madhumita Mahali at the Indian Institute of Technology Gandhinagar. We have no conflicts of interest.

Declaration of competing interest

The authors have no conflict of interest.

Data availability

Data will be made available on request.

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