Trajectories of chemosensory and cognitive functions up to 1.5 years after acute COVID-19

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Abstract

There is an increasing recognition of neurological manifestations from SARS-CoV-2 infection. Quantifications of such manifestations and their long-term dynamics in the general infected population are of essence in understanding the health and socioeconomic burden of neurological complications of COVID-19. Through rigorous empirical testing of over 800 volunteers, we present here repeated cross-sectional and longitudinal data that depict the trajectories of chemosensory functions, cognitive performances and depressive symptoms up to 1.5 years after acute COVID-19 in discharged patients with respect to non-infected controls. Overall, deficits in smell, taste and chemesthesis slowly resolved within about a year of discharge. Concerningly, cognitive impairments – independent of elevated depressive symptoms and evident even in those with nonsevere disease – showed no sign of improvement over time. In people over 50 years, COVID-19 was associated with a substantially increased risk for mild cognitive impairment. Our findings urge for cognitive and emotional interventions targeting COVID-19 convalescents.

Introduction

In December 2019, the first cases of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), were identified in Wuhan, China. The outbreak of COVID-19 has become a global pandemic, affecting over 280 million confirmed patients worldwide by December 2021. Symptoms of COVID-19 vary among different individuals, yet smell loss – potentially resulting from the expression of SARS-CoV-2 entry genes in the olfactory epithelium¹ – is common and serves as a valuable indicator of COVID-19^{2,3}. Taste and chemesthesis, which synergize with smell to create our perception of food flavor, are reportedly compromised independently of smell in some patients⁴. In addition, SARS-CoV-2 appears to exploit the neural-mucosal interface in the olfactory mucosa as a port of entry into the central nervous system, and subsequently induce neuroinflammatory response and cause microvascular injury and infarction in various regions in the brain^{5–7}. Some patients develop significant neurological and neuropsychiatric complications including impaired consciousness, new-onset psychosis, neurocognitive syndrome, and affective disorders^{7–9}. These, together with reports that certain symptoms like fatigue and muscle weakness linger for months and even a year after acute infection^{10,11} and that COVID-19 is associated with increased risks of neurological and psychiatric abnormalities on the population level¹², raise concerns over COVID-19's long-term toll on chemosensory functions, cognitive performance, as well as psychological wellbeing.

To date, psychophysical data on the recovery of chemosensory functions after acute COVID-19 have been scarce and scattered. Several studies assessed smell and taste abilities with self-report questionnaires or simple self-administered tests and the findings seem inconsistent^{13–16}. Whereas olfactory impairment is considered a potential prodromal marker for cognitive decline^{17,18}, there has been limited empirical research on the cognitive consequences of COVID-19 in the general infected population, let alone the long-term effect. Here we present and compare rigorous empirical data obtained from patients after

hospital discharge and age-matched controls so as to depict the recovery trajectories of olfactory, gustatory, and trigeminal functions, and to characterize the impacts of COVID-19 on various cognitive domains as well as mood state up to 1.5 years after acute COVID-19.

Results

Data collection spanned from 2020 to 2021. A total of 819 individuals in decent health volunteered for the study in 2020, including 474 discharged patients with symptomatic COVID-19, 26 with asymptomatic COVID-19, and 319 controls (Figure 1). For those with COVID-19, initial testing was performed 3 to 173 days (within 6 months, 90% interval: 45-155 days) after discharge. 5 symptomatic patients and 19 controls were excluded for reasons outlined in Figure 1. We focused our analyses on the remaining 469 symptomatic patients, subdivided into 94 severe (82 severe, 12 critical) cases and 375 nonsevere (170 mild, 205 moderate) cases ¹⁹, and 300 controls. Their demographic and lifestyle characteristics are summarized in Table 1 and underlying conditions in Table S1. Consistent with earlier reports ²⁰, significantly fewer COVID-19 patients were regular smokers (8.1% vs. 33.7%, $\chi^2_1 = 80.75$, $p < 0.001$) or drinkers (11.5% vs. 27.7%, $\chi^2_1 = 32.61$, $p < 0.001$) as compared with controls. More patients than controls reported that they had been taking medication for hypertension (16.8% vs. 8.0%, $\chi^2_1 = 12.34$, $p < 0.001$), hyperlipidemia (2.8% vs. 0.3%, $\chi^2_1 = 6.09$, $p = 0.014$), or digestive problems (2.1% vs. 0.3%, $\chi^2_1 = 4.20$, $p = 0.040$). Most of the patients and controls completed all 9 tests (see Procedures): odor threshold, odor discrimination (Table S2), odor identification (Table S3), gustatory function, trigeminal function, Montreal Cognitive Assessment (MoCA) ^{21,22}, go/no-go task (inhibitory control, Figure S1A) ²³, task-switching task (cognitive flexibility, Figure S1B) ²⁴, and the short form Beck Depression Inventory (BDI-SF) ²⁵. The valid response rate for a test was 96.4% on average. 75 of the patients were retested for odor threshold, odor discrimination, and/or taste identification – tasks that are less susceptible to practice effects or seasonal changes – 1 to 7 months after the initial evaluation, out of which 64 were retested once and 11 were retested twice for odor threshold and discrimination. Another 68 of the patients were followed up about 1 year after the initial evaluation, roughly 1.5 years after hospital discharge. Together with 53 newly enrolled COVID-19 patients who had been discharged for about 1.5 years, they were assessed for the following measures in 2021: odor identification, trigeminal function, MoCA, BDI-SF, as well as the generalized anxiety disorder 7-item scale (GAD-7) ²⁶.

Table 1
Characteristics of enrolled COVID-19 patients and controls in the initial evaluation in 2020.

	COVID-19 Cases (N = 469)		Controls (N = 300)
	Severe (N = 94)	Nonsevere (N = 375)	
Age, No. (%)			
≤ 39 yr.	10 (10.6%)	68 (18.1%)	85 (28.3%)
40 – 49 yr.	10 (10.6%)	76 (20.3%)	49 (16.3%)
50 – 59 yr.	38 (40.4%)	113 (30.1%)	87 (29.0%)
60 – 69 yr.	30 (31.9%)	103 (27.5%)	63 (21.0%)
≥ 70 yr.	6 (6.4%)	15 (4.0%)	16 (5.3%)
Female sex, No. (%)	55 (58.5%)	231 (61.6%)	187 (62.3%)
Regular smoker, No. (%) ^a	7 (7.4%)	31 (8.3%)	101 (33.7%)
Regular drinker, No. (%) ^a	13 (13.8%)	41 (10.9%)	83 (27.7%)
Education, mean (SD), yr. ^a	12.5 (3.6)	12.4 (3.2)	12.0 (3.3)
Length of hospital stay, median (SD), d.	25 (15.5)	17 (12.3)	
Time since discharge, No. (%)			
≤ 7 wk. (min. 3 d.)	24 (5.1%)		
8 – 11 wk.	98 (20.9%)		
12 – 15 wk.	130 (27.7%)		
16 – 19 wk.	75 (16.0%)		
20 – 23 wk.	133 (28.4%)		
≥ 24 wk. (max. 173 d.)	9 (1.9%)		
^a Lifestyle and demographic factors that differed between the patients and controls in one or more age groups. Their effects were statistically accounted for in subsequent analyses.			

Based on the control data, age, sex, education, smoking, and drinking significantly contributed to performances on one or more of the chemosensory and cognitive tests (Table S4). Incidences of chronic diseases other than hypertension (13.4%) were low (< 5%) in our sample and none significantly affected performances. To quantify the impacts of COVID-19, we stratified the data by age group and compared the performances of the COVID-19 patients with those of the controls of the same age group, adjusted for the effects of significant confounders including education, smoking and/or drinking whose distributions

differed between the patient and control groups (Table 1). Specifically, we standardized the continuous dependent data of all participants, adjusted for the significant confounders, based on the distributions of the bootstrapped control data per age group by z-transformation, so that for any given continuous dependent variable, the average z score of the controls fell around 0, whereas that of the patients reflected their relative standing with respect to matched controls (see Statistical analyses). Data from the 26 asymptomatic individuals (10 males, mean age $\pm$ SD = 45.6 $\pm$ 13.4 years) were separately analyzed in the same manner and presented in Figure S2.

Impaired olfactory, gustatory, and nasal trigeminal functions in discharged COVID-19 patients. Out of the 469 symptomatic patients, who were tested within 6 months (mean $\pm$ SD = 105.4 $\pm$ 37.4 days) of hospital discharge, 45.2%, 50.5%, and 70.4% subjectively reported they experienced losses of smell, taste, and appetite, respectively, when they had COVID-19. Many believed they had fully recovered by the time of testing: only 29.2%, 27.7%, and 20.5% of them considered their sense of smell, sense of taste, and appetite, respectively, to be poorer than before they contracted COVID-19, and only 19.4% rated their sense of smell to be below average. Their performances on the chemosensory tests, however, revealed a different picture (Figure 2A). Comparisons of the normalized z-scores between the patients and controls, which factored out the effects of significant demographic and lifestyle confounders and allowed direct comparisons to be made across tests, showed that these discharged patients performed significantly worse than the controls on odor threshold ($\Delta z = -0.56$, $t_{694.7} = -7.09$, $p < 0.001$), discrimination ($\Delta z = -0.32$, $t_{681.2} = -4.07$, $p < 0.001$), and identification ($\Delta z = -0.36$, $t_{760.7} = -3.69$, $p < 0.001$), with odor threshold (i.e., olfactory sensitivity) being the most impaired numerically ($F_{1.9, 861.4} = 5.40$, $p = 0.006$). Their overall olfactory function, as indexed by the mean of the z-scores for threshold, discrimination, and identification, was 0.41 SD below that of the controls ($t_{748.9} = -7.27$, $p < 0.001$, Cohen's $d = 0.52$). They also showed less differentiation of odor valence and rated the 18 odorants used in the odor identification test (Table S3) as more similar in valence ($t_{753} = -2.21$, $p = 0.027$). The pattern was found in those with an odor identification accuracy above 88% as well ($\geq 16/18$, $t_{483} = -2.08$, $p = 0.038$) and hence was unlikely a mere reflection of poor differentiation of odor quality. Eight patients, all aged below 40 years, reported signs of parosmia: 5 noted things smelled similarly unpleasant — stinky, metallic, or ammonia-like; 3 noted several specific odors smelled different from before, like coffee, cola, milk, or celery. Impairments of gustatory and trigeminal functions were likewise apparent. The discharged patients scored 0.44 SD below the controls on taste identification ($t_{735.7} = -4.61$, $p < 0.001$, Cohen's $d = 0.33$), and were particularly poor at identifying sourness ($B = -1.25$, $p < 0.001$) and saltiness ($B = -0.79$, $p = 0.012$) (Figure 2A inset), the two tastes mediated by ion channels, presumably due to reduced sensitivities (reflected in intensity ratings) to acid ($\Delta z = -0.25$, $t_{727} = -3.35$, $p = 0.001$) and salt ($\Delta z = -0.29$, $t_{723} = -3.46$, $p = 0.001$). Their nasal trigeminal sensitivity (indexed by ethanol lateralization accuracy) fell 0.32 SD below that of the controls ($t_{705} = -3.86$, $p < 0.001$, Cohen's $d = 0.30$). These adverse impacts of COVID-19 on olfactory function ($p < 0.001$), taste identification ($p = 0.014$), and nasal trigeminal sensitivity ($p = 0.019$) held true for patients who considered their sense of smell to be at least average and their sense of smell, sense of taste, and appetite to be as good as or better than before they caught COVID-19, which underscores the

necessity of objective testing in evaluating chemosensory functions. Moreover, smell loss appeared to persist after viral clearance even in asymptomatic individuals, and significant impairment of olfactory function was evident in our small sample of 26 discharged asymptomatic individuals ($\Delta z = -0.31$, $t_{319} = -2.30$, $p = 0.022$, Figure S2).

Table 2

Contributions of disease severity and time since discharge to chemosensory functions, cognitive performances and depressive state within 6 months of hospital discharge. The regression analyses on the raw data included demographic and lifestyle factors as additional regressors, see also Table S5. Numbers in square brackets: lower and upper bounds; B: unstandardized regression coefficient.

	Severity (severe vs. nonsevere)		Days since discharge	
	B (95% CI)	p	B (95% CI)	p
Chemosensory functions				
Odor threshold [0-20]	-0.93 (-1.85, -0.02)	<i>0.046</i>	0.02 (0.008, 0.03)	<i><0.001</i>
Odor discrimination [0-10]	-0.07 (-0.50, 0.36)	0.75	-0.001 (-0.005, 0.004)	0.76
Odor identification [0-18]	-0.71 (-1.34, -0.08)	<i>0.028</i>	0.001 (-0.006, 0.008)	0.76
Taste identification [0-5]	-0.13 (-0.30, 0.04)	0.12	0.003 (0.001, 0.004)	<i>0.006</i>
Trigeminal lateralization [0-10]	0.07 (-0.35, 0.49)	0.74	0.007 (0.003, 0.01)	<i>0.002</i>
Cognitive performances				
MoCA [0-30]	-0.28 (-0.98, 0.42)	0.44	-0.001 (-0.008, 0.007)	0.89
Go/No-go d'	-0.09 (-0.29, 0.11)	0.38	-0.001 (-0.003, 0.001)	0.46
Switch cost, ms.	-4.56 (-53.83, 44.70)	0.86	0.47 (-0.07, 1.00)	0.085
Depressive state				
BDI-SF [0-39]	1.25 (0.05, 2.44)	<i>0.041</i>	-0.02 (-0.03, -0.003)	<i>0.017</i>

Impaired cognitive functions and elevated depressive symptoms in discharged COVID-19 patients. More alarmingly, impairments in several domains of cognition were evident in the discharged COVID-19 patients (Figure 2A). They were overall 0.26 SD below the controls on MoCA ($t_{749} = -3.19$, $p = 0.001$, Cohen's $d = 0.24$), a brief test developed to detect mild cognitive impairment (MCI) ^{21,22}, and performed significantly worse than the controls on items pertaining to alternation (cognitive flexibility) ($B = -0.70$, $p < 0.001$), language ($\Delta z = -0.24$, $t_{677.4} = -3.05$, $p = 0.002$), memory ($\Delta z = -0.16$, $t_{749} = -2.07$, $p = 0.039$), and marginally so on items pertaining to visuospatial ability ($\Delta z = -0.15$, $t_{676.4} = -1.86$, $p = 0.063$) (Table S4). In addition, they exhibited heightened impulsivity (decreased inhibitory control, d' , $\Delta z = -0.17$, $t_{724} = -2.08$, $p = 0.038$) -- despite reacting more slowly than the controls ($t_{502.7} = -2.69$, $p = 0.007$) -- in the go/no-go task and increased switch cost ($\Delta z = 0.19$, $t_{685.8} = 2.09$, $p = 0.037$) in the task-switching task, which, along with the reduced performance on the MoCA alternation item, pointed to compromised executive function.

The gap in MoCA scores was wider for individuals aged 50 years and over ($\Delta z = -0.33$, $t_{377.1} = -3.15$, $p = 0.002$): 55.1% of the older patients fell below the recently recommended cutoff of 25 for MCI²⁷, as opposed to 41.9% in the age-matched controls, the difference being 13.2% ($\chi^2_1 = 7.25$, $p = 0.007$). Whereas caution has been suggested in applying a specific MoCA cutoff score and the cutoff of 25 was likely associated with a high rate of false positives in our sample^{28,29}, it was clear that COVID-19 was associated with impairments in alternation/cognitive flexibility ($p < 0.001$), memory ($p = 0.011$), language ($p = 0.036$), and visuospatial ability ($p = 0.032$), and substantially increased the risk for MCI in those 50 years and older. Note that the patients were otherwise in decent health and, like the controls, had no history of dementia, stroke, or neurotraumatic, neurodegenerative, or neuropsychiatric diseases (see inclusion criteria).

Depression was also common in the discharged COVID-19 patients, who on average scored 0.37 SD above the controls on BDI-SF ($t_{751.4} = 4.36$, $p < 0.001$; Figure 2A) – a reliable measure of depressive symptoms²⁵. 16.8% of them met the screening criterion (≥ 10) and 7.7% met the diagnostic criterion for depression (≥ 14)³⁰, as compared with 8.0% and 3.0% in the controls, $\chi^2_1s = 12.34$ and 7.26 , $ps < 0.001$ and $= 0.007$, respectively. Depression has been linked with deficits in olfaction and cognition^{31,32}. Indeed, we observed significant negative correlations between the normalized z-scores for BDI-SF and those for olfactory function and MoCA in both the patients ($r_{458} = -0.21$ and $r_{457} = -0.15$, $ps < 0.001$ and $= 0.002$, respectively) and the controls ($r_{295} = -0.21$ and $r_{294} = -0.15$, $ps < 0.001$ and $= 0.010$, respectively), indicating that the aforementioned impacts of COVID-19 were partly mediated by the elevated depressive symptoms in the patients. Critically, however, after partialling out the influence of depression level (BDI-SF), the adverse effects of COVID-19 remained significant for olfactory function (overall: $F_{1,750} = 34.21$, $p < 0.001$; threshold: $p < 0.001$, discrimination: $p = 0.001$, identification: $p = 0.007$), taste identification ($F_{1,735} = 15.80$, $p < 0.001$), nasal trigeminal sensitivity ($F_{1,704} = 11.78$, $p = 0.001$), MoCA ($F_{1,748} = 6.41$, $p = 0.012$ for all participants; $F_{1,451} = 5.83$, $p = 0.016$ for those 50 years and older), task switch cost ($F_{1,694} = 4.41$, $p = 0.036$), and marginally significant for inhibitory control ($F_{1,723} = 2.75$, $p = 0.098$). In other words, pathological factors specific to COVID-19 and independent of depressive symptoms associated with COVID-19 significantly impair chemosensory and cognitive functions, and the impacts last long after viral clearance. On the other hand, with the effect of depression level statistically accounted for, the patients' z scores for olfactory function remained significantly correlated with those for MoCA ($r_{446} = 0.26$, $p < 0.001$) and inhibitory control ($r_{440} = 0.17$, $p < 0.001$), corroborating the link between olfactory dysfunction and cognitive impairment¹⁷. Further inspection indicated that the correlations were driven by odor discrimination and identification (combined z scores, $rs = 0.26$ and 0.18 , respectively, $ps < 0.001$), which tap into higher levels of olfactory processing, rather than odor threshold ($rs = 0.14$ and 0.037 , $ps = 0.003$ and 0.43 , respectively).

Slow and steady recovery of basic chemosensory but not cognitive functions independent of disease severity. We wondered whether the observed adverse impacts of COVID-19 were related to disease severity and whether they would diminish over time. As an initial step, we performed multiple regressions

on the raw patient data collected within 6 months of hospital discharge, firstly using severity, days since discharge, as well as age, sex, education, smoking and drinking as the regressors (Tables 2 and S5), and then introducing BDI-SF score as an additional regressor to partial out the effect of depressive state. Results showed that the patients with severe COVID-19 performed worse than those with nonsevere COVID-19 on odor threshold ($\beta = -0.091$, $p = 0.046$) and identification ($\beta = -0.10$, $p = 0.028$), and suffered from a more severe depressive state ($\beta = 0.093$, $p = 0.041$). The differences in smell became marginally significant after controlling for depression level ($0.05 < ps < 0.09$). On the other hand, basic chemosensory functions like odor threshold ($\beta = 0.16$, $p < 0.001$), taste identification ($\beta = 0.13$, $p = 0.006$) and nasal trigeminal lateralization ($\beta = 0.15$, $p = 0.002$) improved steadily over time; these improvements persisted after adjusting for depression level ($ps < 0.009$). No significant effect of disease severity or days since discharge was detected for measures of cognitive functions including MoCA score, inhibitory control in the go/no-go task, and switch cost in the task-switching task. We next compared the normalized performances of the patients, classified by disease severity and time since discharge, respectively, and those of the controls, so as to further dissect and characterize the roles of severity and time (Figure 2A and B).

Various serious central neurological manifestations including stroke and psychosis have been reported in COVID-19 patients who developed acute respiratory distress syndrome and were admitted to intensive care units⁷. In our original sample of 469 symptomatic patients, only 12 (2.56%) had critical COVID-19. Although we did not detect statistically significant differences in cognitive functions between those with severe (severe and critical) and nonsevere (mild and moderate) COVID-19, this did not rule out the possibility that patients with critical disease are more prone to cognitive decline. What was striking, however, was that cognitive impairments were evident in those who had nonsevere COVID-19, no underlying health conditions, and were on average tested 106.2 days (> 3 months, $SD = 36.7$ days) after hospital discharge -- After partialling out the influence of depression level, they still scored significantly lower on MoCA ($\Delta z = -0.20$, $F_{1,557} = 5.05$, $p = 0.025$) and exhibited reduced inhibitory control ($\Delta z = -0.22$, $F_{1,536} = 5.57$, $p = 0.019$), as well as compromised olfactory ($\Delta z = -0.32$, $F_{1,554} = 24.04$, $p < 0.001$), gustatory (taste identification: $\Delta z = -0.34$, $F_{1,544} = 9.53$, $p = 0.002$) and nasal trigeminal functions (lateralization: $\Delta z = -0.24$, $F_{1,523} = 6.75$, $p = 0.010$), relative to the controls. The gap in MoCA score was again more pronounced for individuals aged 50 years and over ($\Delta z = -0.32$, $F_{1,295} = 6.21$, $p = 0.013$).

More concerning was that cognitive functions, unlike basic chemosensory functions, showed no sign of improvement over time. The patients tested on week 20 or more (mean = 151.4 days ≈ 5 months) significantly outperformed those tested within 11 weeks of discharge (mean = 58.9 days ≈ 2 months) on odor threshold ($\Delta z = 0.54$, $t_{261} = 3.78$, $p < 0.001$), taste identification ($\Delta z = 0.49$, $t_{222.5} = 2.52$, $p = 0.012$) and nasal trigeminal lateralization ($\Delta z = 0.31$, $t_{237} = 2.19$, $p = 0.030$), but not on MoCA ($t_{251} = -0.37$, $p = 0.71$), inhibitory control ($t_{246} = -0.059$, $p = 0.95$), or task switch cost ($t_{235} = 1.44$, $p = 0.15$). Meanwhile, their performances on odor threshold ($\Delta z = -0.34$, $t_{235.8} = -2.90$, $p = 0.004$), discrimination ($\Delta z = -0.30$, $t_{432} = -2.83$, $p = 0.005$), and identification ($\Delta z = -0.35$, $t_{190.3} = -2.28$, $p = 0.024$) still fell below those of the controls. That is, full recovery was not attained for all chemosensory functions by 5 months of discharge.

We went on and examined data collected after a longer period of recovery. In the subset of 75 patients (52.3 ± 10.3 years) with retest data for odor threshold, odor discrimination, and/or taste identification, 74.7% and 56.8% showed improvements in odor threshold and discrimination, respectively, over the initial test, and 73.7% of those who initially misidentified at least one tastant showed an improvement in taste identification. 66 were retested around 9 months (275.9 ± 23.2 days) after discharge. By then, their performances on these chemosensory tasks were overall comparable to those of the controls (odor threshold: $t_{363} = 1.58$, $p = 0.12$; odor discrimination: $t_{361} = 0.44$, $p = 0.66$; taste identification: $t_{74.4} = -1.21$, $p = 0.23$; Figure 2B and C), although one 46-year-old woman remained anosmic (mild case, threshold = 0, discrimination at chance) and one 62-year-old woman (severe case) failed to recognize bitter, salty, and umami, out of the five basic tastes. 11 were retested twice for odor threshold and discrimination, once 118.7 ± 23.6 days (~ 3.9 months) and once 272.0 ± 26.1 days (~ 8.9 months) after discharge. Data from their initial (80.7 ± 26.9 days or ~ 2.6 months after discharge) and follow-up tests (Figure S3) partially echoed the patterns seen in Figure 2B (leftmost panel) and suggested that the recovery of olfactory sensitivity was steady and relatively faster in the first few months following acute COVID-19, whereas that of olfactory discrimination was a more heterogeneous process.

68 patients (58.3 ± 6.4 years) were retested for odor identification, trigeminal lateralization, cognitive function, and mood state about a year (13.8 ± 0.7 months) following the initial test – roughly 1.5 years (17.0 ± 0.8 months) after hospital discharge (Figure 2C). 50.7% and 53.2% of them showed improvements in odor identification and nasal trigeminal sensitivity, respectively. There was however no improvement in MoCA score ($t_{64} = -0.67$, $p = 0.51$) or depressive symptoms ($t_{67} = 0.008$, $p = 0.99$). Poor performance on MoCA ($t_{341} = -5.17$, $p < 0.001$) and an elevated level of depression ($t_{60.4} = 3.30$, $p = 0.002$) were also evident in an independent group of 53 COVID-19 patients (34 females, 59.5 ± 7.4 years) enrolled about 1.5 years (17.2 ± 0.9 months) after hospital discharge. Collectively, these 121 patients, mostly nonsevere cases (81.8%) and over 50 years (94.2%), scored 0.68 SD above the controls on BDI-SF ($t_{153.1} = 4.01$, $p < 0.001$) and 0.54 SD above the patients tested at 5 months (20-23 weeks) after discharge ($t_{199.9} = 2.90$, $p = 0.004$). 24.0% of them met the screening criterion (≥ 10 on BDI-SF) and 14.0% met the diagnostic criterion for depression (≥ 14 on BDI-SF)³⁰, whereas 14.0% met the criterion for general anxiety disorder (≥ 10 on GAD-7)²⁶. A recent cohort study¹¹ noted a similar pattern – that depression or anxiety was more frequently reported at 12 months than 6 months following acute COVID-19. There was a strong correlation between levels of depression (BDI-SF) and anxiety (GAD-7) ($r_{121} = 0.75$, $p < 0.001$), in line with the documented high comorbidity of depressive and anxiety disorders³³. After controlling for the effect of mood state, no statistically significant difference was detected between the patients and controls in olfactory identification ($p = 0.37$) or trigeminal lateralization ($p = 0.63$). Nonetheless, the patients still fell 0.43 SD below the controls on MoCA ($F_{1,406} = 13.70$, $p < 0.001$), which pointed to a worrisome long-lasting toll of COVID-19 on cognitive abilities.

Discussion

The current study provides repeated cross-sectional and longitudinal empirical data that jointly characterize the trajectories of chemosensory and cognitive functions up to 1.5 years after acute COVID-19 in patients discharged from hospital with respect to matched controls. Through rigorous psychophysical testing, behavioral assessment and careful control of confounding factors, we found that the impairments of smell, taste, and chemesthesis lingered for several months after viral clearance and gradually resolved within a year or so for most patients. Concerningly, cognitive impairments were present even in those with nonsevere disease and showed no sign of improvement over time. Depressive symptoms also remained heightened at 1.5 years after discharge. These findings complement recent reports on the medium- and long-term outcomes of physical conditions (e.g., fatigue, lung function, exercise capacity) in COVID-19 survivors after hospitalization^{10,11}, and add to the understanding of the health consequences of and dynamics of recovery from COVID-19.

Chemosensation first occurs in sensory epithelia in the nose and mouth, where the initial targets of SARS-CoV-2 infection have been identified⁴. In parallel, a loss of smell and/or taste is the most prevalent and discriminative neurological symptom of COVID-19 that appears early in the disease process^{3,34}. Contrary to earlier claims that olfactory and gustatory impairments typically resolve within 1 or 2 months from symptom onset^{13–15}, our results showed that the COVID-19 patients tested between 2 to 6 months (mean: 3.7 months) after discharge significantly fell below the controls on all measures of chemosensory functions including odor threshold, odor discrimination, odor identification, taste identification, and nasal trigeminal sensitivity ($p \leq 0.001$), revealing a much slower recovery process than previously recognized. The observed time courses of recovery differed significantly from those of smell deficits caused by common cold³⁵ and likely involved recruitments of stem cells in the olfactory epithelium and the taste buds. Notably, the trajectories of odor discrimination and odor identification, which engage more complex olfactory and cognitive processing³⁶, diverged from that of odor threshold and showed less prominent recovery over time (Figure 2B and Figure S3). Moreover, not all basic tastes were equally affected. Significant impairments were found in the identifications of sour and salty but not sweet, bitter, or umami (Figure 2A inset). Whether this has to do with the pattern of expression of angiotensin-converting enzyme 2 (ACE2) — the entry receptor for SARS-CoV-2³⁷ — in different types of taste cells awaits further research³⁸. In addition, a loss of nasal trigeminal sensitivity, though less noticed, was common, and its recovery followed a course similar to those for the detections of odorants (odor threshold) and tastants (taste identification) (Figure 2B). Whereas how SARS-CoV-2 influences chemesthesis remains elusive, the pattern of recovery seems to hint at a peripheral rather than central mechanism.

The proportion of COVID-19 patients with CNS manifestations was originally estimated to be small based on data from epidemics caused by other coronaviruses like severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS)³⁹. Several subsequent studies suggested that neurocognitive impairments are not rare in COVID-19 survivors or limited to those with critical disease^{40–42}, but it was unclear whether this is coincidental, due to hypoxia, or a reflection of elevated depressive symptoms that adversely affect cognitive performances³¹. Here, along with mood disturbances, we identified cognitive impairments involving memory, language and executive function in discharged

COVID-19 patients who were otherwise in decent health and had no history of dementia, stroke, or neurotraumatic, neurodegenerative, or neuropsychiatric diseases (Tables 1 and S1). 10.3% of them (nonsevere cases: 68.5%) complained about cognitive decline/memory loss since contracting COVID-19 without being asked about it. The adverse cognitive impacts remained after partialling out the effect of depression level, even in those with nonsevere disease and no underlying health conditions, and persisted to 1.5 years after discharge. Our results thus indicated a causal link between COVID-19 and long-term cognitive losses in the general infected and symptomatic population. Neuroinflammation plausibly contributes to the cognitive sequelae. By way of the olfactory mucosa, SARS-CoV-2 could invade brain capillary endothelial cells via ACE2 receptors and induce neuroinflammatory responses that lead to thrombi and CNS damage^{43,44}. Sustained endotheliopathy appears to be common after acute COVID-19⁴⁵. Additionally, the choroid plexus has been shown to relay peripheral inflammation to brain microglia, astrocytes and neurons, which can also cascade into disruptions of synaptic signaling in upper-layer cortical circuitry and ultimately cognitive processing⁴⁶.

Although symptoms varied from individual to individual, on the group level, COVID-19 was associated with an elevated level of depression, a 10-15% (0.2-0.4 SD) drop in percentile ranking on the distribution of MoCA scores independent of demographic background and mood state, and a substantially increased risk of MCI for people over 50 years. Given the unprecedented scale of the pandemic, these consequences pose a pressing need for cognitive and emotional interventions targeting COVID-19 convalescents.

Methods

Participants. Initial testing of discharged COVID-19 patients was performed in Wuhan between April 25 and August 8, 2020. We enrolled all laboratory-confirmed and/or clinically diagnosed patients aged 16 years and over who had been discharged from hospital within 6 months, met the following criteria and volunteered for participation: (1) no history of dementia or neurotraumatic, neurodegenerative, or neuropsychiatric diseases; (2) no history of nasal injury or tumor in the nose, mouth, or pharynx; (3) no respiratory allergy or upper respiratory infection at the time of testing; (4) literate. Those who met the following additional criteria were invited for cognitive assessments: (5) normal or corrected-to-normal vision and hearing; (6) no history of stroke or brain surgery. The patients were subdivided into severe (severe and critical) and nonsevere (mild and moderate) cases based on WHO guidelines¹⁹. Control participants were recruited from local residential communities during the same period using the same set of criteria. They self-reported to have never had COVID-19 and tested negative for COVID-19 antibodies (the testing was performed when no COVID-19 vaccine was available). A subset of the COVID-19 patients was subsequently retested once or twice for odor threshold, odor discrimination, and/or taste identification, tasks that are not susceptible to practice effects or seasonal changes, 1 to 7 months after the initial evaluation. Another subset of the patients was followed up about 1 year after the initial evaluation. Along with an independent group of COVID-19 patients enrolled roughly 1.5 years after discharge using the aforementioned inclusion criteria, they were assessed in the summer of 2021 for odor identification, nasal trigeminal sensitivity, cognitive function, and mood state. All provided informed

consent to participate in procedures approved by the Institutional Review Board at Institute of Psychology, Chinese Academy of Sciences (H20007).

Procedures. Participants were individually assessed by a trained psychologist or physician in a well-ventilated room. They first completed a structured questionnaire that collected data regarding demographic and lifestyle characteristics, medical history, subjective olfactory ability, and for COVID-19 patients, clinical history related to COVID-19. Eligible participants were then administered a battery of chemosensory and cognitive tests as well as the short form Beck Depression Inventory (BDI-SF) ²⁵, as detailed below (Figure 1). Those assessed in 2021 also filled out the generalized anxiety disorder 7-item (GAD-7) scale, a brief self-report scale that identifies probable cases of general anxiety disorder and measures its severity ²⁶.

Olfactory function. Odor threshold was assessed using 20 concentrations of eugenol, a non-trigeminal compound with a distinctive odor ⁴⁷, dissolved in propylene glycol, paired with blanks containing only the solvent. The concentration series was obtained by two-fold serial dilution from 4% v/v (step 1). Threshold was determined using a standard seven-reversal staircase procedure ⁴⁸, and was expressed in binary dilution steps. Odor discrimination was assessed with 10 odor triplets, each comprising one target and two identical distractors (Table S2). Participants, blindfolded, were asked to pick the odd one out. The target and distractors were single compound odorants with various levels of structural and perceptual similarities in 9 triplets and binary odor mixtures in different proportions in 1 triplet. Odor identification was assessed with 18 items from the Chinese Smell Identification Test ⁴⁹ (Table S3). For each odorant, participants made a forced choice of its name from four options and also rated its valence on a 7-point Likert scale, with 7 representing very pleasant. All odorants were presented in identical felt-tip pens. Each odor presentation lasted ~2 s. There was a minimum interval of 30 s in between two trials to eliminate olfactory adaptation.

Gustatory function. Taste identification was assessed with five taste solutions presented once each in random order — sweet: 15% m/m sucrose, sour: 0.18% m/m acetic acid, salty: 1% m/m sodium chloride, bitter: 1 mM quinine sulfate, and umami: 1.2% m/m monosodium glutamate, dissolved in distilled water at room temperature. In each trial, 1 ml of a taste solution was applied to the center of the tongue with a 1 ml disposable transfer pipet, after the mouth was rinsed with distilled water for 20 s. Participants tasted it within the oral cavity and selected a descriptor from “sweet”, “sour”, “salty”, “bitter”, and “umami”. They also rated its intensity on a 7-point Likert scale, with 7 representing very intense.

Trigeminal function. Nasal trigeminal sensitivity was assessed in a lateralization task with ethanol (25% v/v in distilled water) and distilled water. In each trial, participants were instructed to hold breath while the experimenter carefully placed the tips (~1.5 cm) of two cotton swabs, soaked with ethanol and distilled water, respectively, into the two nostrils. They then inhaled through the nose and indicated which nostril sensed ethanol. The cotton swabs were immediately removed and discarded after the inhalation. There were 10 trials, with a minimum interval of 30 s in between.

Montreal Cognitive Assessment (MoCA). The MoCA is a brief 30-point test that assesses various cognitive functions including memory, language, visuospatial ability, attention, alternation (cognitive flexibility), abstraction (concept formation), and orientation to time and space²¹. A Chinese version of MoCA²² was used.

Go/No-go task. The go/no-go paradigm assesses inhibitory control. The visual stimuli were two simple shapes, a disk and a square, presented black-on-gray on a computer display. One was designated as go stimulus and the other as no-go stimulus (balanced across participants). A central fixation cross ($\sim 0.2 \times 0.2^\circ$) was displayed throughout the task. Each trial (Figure S1A) began with a shape stimulus ($\sim 2 \times 2^\circ$) appearing for 200 ms at a random location $1-1.5^\circ$ away from fixation, followed by a blank screen for an interval of 800–1300 ms. Participants were to press the spacebar as soon as the go stimulus appeared and to withhold response when the no-go stimulus appeared. A correct response (hit or correct rejection) would trigger the next trial; an incorrect response would trigger a warning. Specifically, if a response was registered for a no-go trial (false alarm), the words “wrong response” would immediately appear for 500 ms; if no response was registered for a go trial (miss), the words “no response” would appear for 500 ms. In these cases, the next trial would start 1 s after the warning disappeared. There were 100 trials per block, with 70 go trials and 30 no-go trials in random order. Each participant performed 2 blocks of the task, after completing 20 practice trials. D-prime (d') served as the dependent variable of interest.

Task-switching task. The task-switching paradigm assesses cognitive flexibility. In each trial (Figure S1B), participants viewed a blank screen for 1 s, followed by a digit ($\sim 1.1 \times 1.7^\circ$), 1, 2, 3, 4, 6, 7, 8, or 9, presented centrally for 350 ms. They then pressed one of two buttons as accurately and quickly as possible to indicate whether the presented digit was (a) odd or even or (b) smaller or larger than 5. The task (a or b, each in 50% of the trials) was cued by the color of the digit (green or yellow), which could differ (switch trial) or not differ (repeat trial) from that in the previous trial. A correct response would trigger the next trial. An incorrect response would trigger a warning – the word “error” displayed for 500 ms – and the next trial would start after the warning disappeared. There were 51 trials per block, including 25 switch trials and 25 repeat trials, presented in a pseudorandomized order. Each participant completed 2 blocks of the task (102 trials total) after being familiarized with the task rules in a short practice session. Switch cost, the difference in reaction time between switch and repeat trials, served as the primary dependent variable of interest.

Short form Beck Depression Inventory (BDI-SF). The BDI-SF²⁵ is a 13-item multiple-choice inventory that measures the severity of depression.

The above tests were administered in the following order in the initial evaluation: odor threshold, BDI-SF, odor identification, MoCA, go/no-go task, odor discrimination, task-switching task, gustatory function, and trigeminal function. The order was designed to eliminate chemosensory adaptation and cognitive fatigue. A few (Figure 1) subjectively rejected one or more of these tests.

Statistical analyses. Table S4 summarizes the primary dependent variables in the above tests and their respective demographic and/or lifestyle confounders, as identified by stepwise regressions on the data from the control participants that included age (age group), sex, education (years of education), smoking (regular smoker or not) and drinking (regular drinker or not) as the regressors. Since the continuous dependent variables were on largely different scales, we standardized them to facilitate comparisons. Specifically, we stratified the patient and control data by age group and statistically partialled out the effects of significant confounders whose distributions differed between the patient and control groups, respectively (Table 1). Put differently, we statistically held such confounders (i.e., education, smoking or drinking, see Table S4) fixed (at sample mean years of education, not a regular smoker, not a regular drinker, respectively) across all patients and controls. We then employed a standard bootstrapping method to estimate the means and SDs of the dependent variables for controls in each age group, which allowed us to individually normalize the data of all participants (adjusted for the significant confounders) according to their respective age groups by z-transformation. Consequently, for any given continuous dependent variable, the average z score of the control participants fell around 0, whereas that of the patients reflected their relative standing as compared to matched controls. We first performed independent sample t tests to compare these standardized continuous dependent variables between patients and controls. The results were also verified with univariate ANOVAs on the raw data – For a continuous dependent variable, group (patient vs. control) served as the key fixed factor; significant confounders for that variable (Table S4) like age, education, sex, smoking and/or drinking were included as covariates and/or fixed factors. For dichotomous dependent variables, we performed logistic regressions on the raw data with these regressors. To examine the extent to which depressive state contributed to the differences between patients and controls, we further conducted univariate ANOVAs on the standardized data that included BDI-SF score as a covariate. Next, to probe whether the influences of COVID-19 were related to disease severity and whether they would diminish over time, we analyzed the raw patient data with multiple regressions, firstly using severity (severe vs. nonsevere), time since discharge (in days), age, sex, education, smoking and drinking as the regressors, and then adding BDI-SF as an additional regressor. For the subset of patients with retest data, we used paired sample t tests to compare their performances over time. All statistical tests were two-sided.

Data Availability

The data that support the findings of this study are available within the paper and its supplementary information files.

Declarations

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Author contributions

Kepu Chen, Fei Gu, Yuli Wu, Yanqing Wang, Bin Zhou and Wen Zhou conceived and designed the study; Xiaoyue Chang, Kepu Chen and Kaiqi Yuan conducted the study; Xiaoyue Chang and Yuting Ye analyzed the data and interpreted the results under the supervision of Wen Zhou. Wen Zhou wrote the manuscript with inputs from all authors.

Competing interests

The authors declare no competing interests.

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Figures

Figure 1

Flowchart of participants.

Figure 2

Chemosensory functions, cognitive performances, depressive state and their trajectories over time in COVID-19 patients discharged from hospital with respect to uninfected controls. (A) Overall, along with elevated depressive symptoms, the patients demonstrated significant impairments in smell, taste, chemesthesis as well as cognitive functions involving language, memory and executive control at the initial evaluation conducted within 6 months of hospital discharge. Gray bars represent the means of the

normalized z-scores across all symptomatic patients. Brown, red and green dots represent the means for severe cases, nonsevere cases and controls, respectively. Inset, radar plot showing identification accuracies for the five basic tastes in the patients (red) versus the controls (green). (B) Slow yet steady improvements over time were observed for basic chemosensory functions but not cognitive performances or depressive state. Filled and open red markers respectively represent the mean z-scores of the patients tested at about 9 months and 1.5 years after hospital discharge. Asterisks indicate significant improvements over time within 6 months of discharge (Table 2). (C) Split violin plots comparing the distributions of the normalized z-scores for odor threshold, odor discrimination, odor identification, taste identification, nasal trigeminal lateralization, MoCA, or BDI-SF in the same subset of patients (individual dots) between the initial evaluation (roughly 3 months after discharge, gray-shaded area) and follow-up test at about 9 months (red-shaded) or 1.5 years (unshaded) after discharge. ‡, $p \leq 0.001$ for those who misidentified at least one tastant at the initial evaluation. Error bars, SEMs; *, $p < 0.05$; **, $p < 0.01$; ***, $p \leq 0.001$; †, $p < 0.1$.

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