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Original Research

Preliminary Findings on Cognitive Dysfunction in University-Educated Patients After Mild COVID-19 Disease

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COVID-19;
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Abstract *Objective:* To investigate cognitive functioning in patients with higher education having post COVID-19 condition.
Design: Prospective cohort study.
Setting: Outpatient rehabilitation clinic.
Participants: Patients (N=38; mean age, 48.5y; 71% women) at the Cognitive Post COVID-19 Clinic at Danderyd University Hospital in Stockholm, Sweden, who sought health care because of self-experienced cognitive problems. All had at least 4 years of university education and an initially mild infection (ie, most were not hospital admitted, none were admitted to intensive care).
Interventions: Not applicable.
Main Outcome Measures: Cognitive test performance assessed with a comprehensive neuropsychological test battery including Information, Matrix Reasoning, Coding, and Digit Span from Wechsler's Adult Intelligence Scale-IV, Buschke Selective Reminding Test, Rey Complex Figure Test, Ruff 2&7, Color-Word Interference Test, Verbal Fluency, and Trail Making Test. The mean time between the infection and the assessment was 18 months.
Results: Cognitive deficits were evident on tests of verbal learning and memory (Buschke Selective Reminding Test) and selective attention (Ruff 2&7). Approximately 50% of the participants had scores lower than 1 SD below the mean in the norm group on the measures of verbal learning and memory. When estimated premorbid cognitive functioning was accounted for, deficits were suggested in most cognitive domains.

List of abbreviations: PCC, post COVID-19 condition; PCR, polymerase chain reaction.
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Conclusions: Post COVID-19 condition seems to be associated with cognitive deficits, even in patients with high education and an initially mild infection.

The World Health Organization declared COVID-19 a pandemic in March 2020. Globally, since then, 770 million persons have been infected with SARS-CoV-2, the virus causing COVID-19. In Sweden, almost 3 million cases are confirmed.[1] It is being increasingly recognized that some patients report symptoms longer than initially expected after COVID-19. Symptoms persisting longer than 3 months after the infection have been suggested to be named post COVID-19 condition (PCC) by the World Health Organization.[2]

Common symptoms are cognitive dysfunction and fatigue.[2] Neuropsychological studies have revealed a variety of cognitive dysfunctions in patients with PCC,[3-6] also in patients not treated in an intensive care unit.[7] However, as with many conditions lacking objective biomarkers, it is debated to what degree the symptoms reported can be attributed to other conditions and/or premorbid functioning. This is a relevant question because most symptoms of PCC are nonspecific. Similarly, as performance on neuropsychological tests vary in the general population,[8] low premorbid cognitive functioning must be ruled out in order to attribute cognitive dysfunctions to an injury or disease, such as COVID-19.

Here, we minimized the risk of low premorbid cognitive functioning influencing the results by investigating cognitive functioning in university-educated patients with PCC. We aimed to investigate if patients with PCC had lower cognitive functioning than (A) their estimated premorbid cognitive functioning and (B) the population (norm group) mean.

Methods

Eligible patients at the Cognitive Post COVID-19 Clinic at Danderyd University Hospital in Stockholm, Sweden, with self-reported cognitive problems persisting ≥3 months after an initially mild infection (ie, no care in intensive care unit). For the present study, only those with a university education (≥4y) were included. The infection was confirmed with a polymerase chain reaction (PCR) test, anti-bodies, or otherwise very likely, which was determined by the physician at the first visit. The persistence of the symptoms was also assessed at the first visit (ie, it was determined that the symptoms experienced at the visit had their onset shortly after an infection with typical SARS-CoV-2 symptoms). Testing was not available in Sweden during the first wave (spring 2020) for patients with milder infections. The study was approved by the Ethics Committee in Sweden (ref no. 2021-03907) and all participants gave written informed consent to participate in the study.

A comprehensive neuropsychological battery was administered in the chronic phase, by licensed psychologists, measuring estimated premorbid functioning,[9] memory, attention, processing speed, and executive functioning (table 1). Raw scores were converted to T scores (mean, 50±10 in the norm group). Norms from the test manufacturer were used and were corrected according to age and/or sex and/or education (Scandinavian norms for the WAIS-IV subtests and international norms for the other tests). Scores lower than T20 were set to T20 (to comply with the norm range of most tests, which is T20-T80).

Most test scores had nonnormal distributions and 1-sample Wilcoxon signed rank tests were used to investigate if the test scores were significantly different from (A) estimated premorbid functioning based on a composite score of the hold-tests Information and Matrix Reasoning, tests considered largely insensitive to brain injury or disease[9] and (B) the population mean of T50. Additionally, the percentage of patients scoring 1 and 2 SDs below the mean was calculated. Uncorrected *P* values are reported in table 1 and it is indicated whether the difference was significant at $P<.05$ (2-sided) after Benjamini-Hochberg correction for multiple comparisons (false discovery rate). Missing data were handled by pairwise deletion and the number of participants in each analysis is specified in table 1. No analysis had more than 3 missing data points.

Results

During the inclusion period, 38 participants meeting inclusion criteria were enrolled (mean age, 48.5±8.5y; 71.1% women). Confirmed infection (PCR test or antibodies prevaccination) was found in 25 (65.8%) participants. The infection period was from January 9, 2020, to February 15, 2021. The mean time between infection and assessment was 18 months (range, 6-31mo). At the time of the assessment, 78.9% were on part- or full-time sick leave. Before the infection, none of the patients were unemployed. Common occupations were physicians, civil engineers, economists, and managers.

Corrected for multiple comparisons, the patients scored significantly lower than the composite score of estimated premorbid cognitive functioning (T61.6) on measures of processing speed (eg, Coding), attention (eg, Digit Span Forward), working memory (eg, Digit Span Backwards), verbal learning and memory (eg, Buschke Selective Reminding Test), visual memory (Rey Complex Figure Test), and executive functioning (eg, Color-Word Interference Test; Trail Making Test). On the measure of Phonetic Verbal Fluency, the scores were significantly higher than estimated premorbid functioning (table 1). As Ruff 2&7 provides education-corrected norms, no comparisons between the scores on this test and estimated premorbid cognitive functioning were performed.

When compared with the normative mean (T50), the patients scored significantly lower on verbal learning, memory, and attention. Around 50% of the participants had scores <T40 (1 SD below the mean) and 30% had scores <T30 (2 SD below the mean) on measures of verbal learning and memory, contrary to normal distribution where around 16% of the population is expected to have scores <T40 and around 2% <T30. On several measures, the scores were significantly

Table 1 Results on neuropsychological tests

Test and Measures	n	Median (IQR)	Mean (SD)	*P* Value ≠T50.0*	*P* Value ≠T61.6†	n (%) <T40	n (%) Expected <T40‡	n (%) <T30	n (%) Expected <T30‡
WAIS-IV									
Information	38	60.0 (56.7-66.7)	59.5 (7.9)	**<.0001**§	-	0 (0)	6.0 (15.7)	0 (0)	0.8 (2.1)
Matrix	38	66.7 (60.0-70.0)	63.7 (8.8)	**<.0001**§	-	0 (0)	6.0 (15.7)	0 (0)	0.8 (2.1)
Composite	38	61.7 (60.0-65.0)	61.6 (5.4)	-	-	-	-	-	-
Coding	38	50 (46.7-60.0)	52.7 (9.9)	.2540	**.0001**§	1 (2.6)	6.0 (15.7)	0 (0)	0.8 (2.1)
Digit span									
Forward	38	56.7 (46.7-60.0)	53.3 (10.6)	.0336	**.0001**§	4 (10.5)	6.0 (15.7)	0 (0)	0.8 (2.1)
Backwards	38	53.3 (46.7-60.0)	54.4 (11.5)	**.0232**§	**.0003**§	3 (7.9)	6.0 (15.7)	0 (0)	0.8 (2.1)
Buschke Selective Reminding Test									
Total recall	36	40.5 (22.5-47.0)	37.5 (13.6)	**<.0001**§	**<.0001**§	17 (47.2)	5.7 (15.7)	11 (30.6)	0.8 (2.1)
CLTR	36	35.5 (25.0-45.0)	36.5 (12.5)	**<.0001**§	**<.0001**§	21 (58.3)	5.7 (15.7)	13 (36.1)	0.8 (2.1)
Delayed recall	35	43.0 (29.0-52.0)	40.2 (13.5)	**.0021**§	**<.0001**§	16 (45.7)	5.5 (15.7)	9 (25.7)	0.7 (2.1)
RCFT									
Immediate recall	36	49.0 (40.0-58.5)	49.1 (14.2)	.6598	**<.0001**§	8 (22.2)	5.7 (15.7)	2 (5.6)	0.8 (2.1)
Delayed recall	37	50.0 (41.0-58.0)	48.6 (13.6)	.7228	**<.0001**§	7 (18.9)	5.8 (15.7)	4 (10.8)	0.8 (2.1)
Recognition	36	53.5 (45.5-59.0)	52.0 (10.9)	.1393	**<.0001**§	4 (11.1)	5.7 (15.7)	1 (2.8)	0.8 (2.1)
Ruff 2&7									
Automatic speed	38	50.0 (44.0-57.0)	49.5 (11.0)	.9768	-	6 (15.8)	6.0 (15.7)	2 (5.3)	0.8 (2.1)
Automatic accuracy	38	55.0 (53.0-57.0)	53.9 (4.2)	**<.0001**§	-	1 (2.6)	6.0 (15.7)	0 (0)	0.8 (2.1)
Controlled speed	38	45 (39.0-52.0)	44.8 (9.4)	**.0026**§	-	10 (26.3)	6.0 (15.7)	2 (5.3)	0.8 (2.1)
Controlled accuracy	38	52.5 (47.0-60.0)	51.8 (9.2)	.1023	-	4 (10.5)	6.0 (15.7)	2 (5.3)	0.8 (2.1)
Color-Word Interference Test									
Color naming	38	50.0 (43.3-50.0)	46.5 (9.6)	.0971	**<.0001**§	5 (13.2)	6.0 (15.7)	3 (7.9)	0.8 (2.1)
Color reading	38	50.0 (46.7-56.7)	50.0 (7.9)	.4939	**<.0001**§	2 (5.3)	6.0 (15.7)	1 (2.6)	0.8 (2.1)
Interference	38	50.0 (46.7-63.3)	50.4 (9.6)	.5928	**<.0001**§	4 (10.5)	6.0 (15.7)	1 (2.6)	0.8 (2.1)
Switching	38	51.7 (46.7-60.0)	50.3 (10.0)	.4822	**<.0001**§	4 (10.5)	6.0 (15.7)	2 (5.3)	0.8 (2.1)
Verbal Fluency									
Phonetic	38	71.7 (46.7-76.7)	66.1 (12.7)	**<.0001**§	**.0175**§	1 (2.6)	6.0 (15.7)	0 (0)	0.8 (2.1)
Semantic	38	70.0 (56.6-76.7)	65.1 (13.1)	**<.0001**§	.0542	1 (2.6)	6.0 (15.7)	0 (0)	0.8 (2.1)
Switching	38	63.3 (56.7-70.0)	62.3 (9.7)	**<.0001**§	.5084	0 (0)	6.0 (15.7)	0 (0)	0.8 (2.1)
Trail Making Test									
Visual scanning	38	58.3 (56.7-63.3)	58.2 (5.2)	**<.0001**§	**.0042**§	0 (0)	6.0 (15.7)	0 (0)	0.8 (2.1)
Numbers	37	56.7 (50.0-63.3)	55.5 (9.7)	**.0006**§	**.0030**§	1 (2.7)	5.8 (15.7)	1 (2.7)	0.8 (2.1)
Letters	38	60.0 (53.3-60.0)	55.4 (10.0)	**.0025**§	**.0027**§	3 (7.9)	6.0 (15.7)	1 (2.6)	0.8 (2.1)
Switching	37	56.7 (53.3-60.0)	54.4 (7.0)	**.0013**§	**<.0001**§	2 (5.4)	5.8 (15.7)	0 (0)	0.8 (2.1)
Motor	37	60.0 (56.7-63.3)	57.8 (8.0)	**<.0001**§	.0494	1 (2.7)	5.8 (15.7)	1 (2.7)	0.8 (2.1)

NOTE. Tscores are age-corrected for all tests. Buschke Selective Reminding Test is in addition corrected for sex and Ruff 2&7 is corrected for education.

Abbreviations: CLTR, Consistent Long Time Recall; IQR, interquartile range; RCFT, Rey Complex Figure Test; WAIS-IV, Wechsler's Adult Intelligence Scale-IV.

* Significantly different from the population mean (T50) using 1-sample Wilcoxon signed rank tests.

† Significantly different from the mean of the hold-tests Information and Matrix (Composite: T61.6) using 1-sample Wilcoxon signed rank tests. This is an estimate of premorbid cognitive functioning.

‡ The number of participants who should have scores below T40 or T30 based on a normal distribution.

§ Significant with Benjamini-Hochberg correction for multiple comparisons (27 measures).

higher than T50, as expected considering estimated premorbid cognitive functioning (table 1).

Thus, the most significant deficits were found in verbal memory. To minimize the risk that this was caused by non-representative norms, we recalculated these scores with age-, sex-, and education-corrected norms on the Buschke Selective Reminding Test, published in 2019.[10] With these norms, the mean total recall was T37.0±12.5 (58% performing <T40), the mean Consistent Long Time Recall was T38.3±11.3 (55.6% performing <T40), and the mean delayed recall was T38.0±14.0 (51.4% performing <T40).

Discussion

This study revealed significant memory dysfunctions after an initially mild SARS-CoV-2 infection, in line with previous studies reporting memory dysfunction after mixed severity COVID-19.[3-6] However, our findings are novel in at least 2 aspects. First, because the mean time between the infection and the assessment was 18 months (ie, longer than most previous reports), these dysfunctions appear to be particularly persistent for some patients. Second, as identified dysfunctions were present in patients with higher education, it is implausible that the results represent poor premorbid cognitive functioning.

When compared with estimated premorbid functioning, dysfunctions were evident not only in memory, but in most cognitive domains. The brain pathologies associated with COVID-19 are still indefinite, but it is reasonable to assume that they are diffuse in nature (ie, not affecting specific parts or structures of the brain exclusively). Therefore, it is likely that COVID-19 affects several cognitive domains with profound variability between patients, as seen in other conditions with a diffuse pathophysiology, such as concussion.[11] When estimated premorbid cognitive functioning was considered, our results support such heterogeneous and diffuse effect on cognitive test performance in PCC.

Most previous studies on COVID-19 have used a screening instrument, such as the Montreal Cognitive Assessment,[6] to assess cognitive test performance. These instruments are not sensitive to subtle cognitive dysfunction, or more severe dysfunction in patients with a higher premorbid cognitive functioning. Our findings stress the importance of a comprehensive neuropsychological assessment when investigating patients with a high premorbid cognitive level, as most patients in the present study probably would pass a screening instrument.

Study limitations

This study has limitations. First, the patients were self-selected with extensive self-reported post-COVID-19 symptoms, and consequently not representative for the typical patient with SARS-CoV-2. Secondly, the study lacked a control group. Thus, some of the differences in test results might be caused by differences between norm groups (ie, in neuropsychology, norms are sometimes considered "liberal" when they can be suspected to give T scores higher than they really should and "conservative" when they give lower T scores). However, by only including patients with higher education, we minimized the risk of a mean premorbid cognitive functioning below T50. Further, to explore how different norms affected results on memory, we performed follow-up analyses using another norm group, finding similar results. Unfortunately, specific Swedish norms do not exist for most of the test used, with the exception of the WAIS-IV subtests. Third, not all participants had an infection confirmed with a PCR test or antibodies. However, because both the availability and people's willingness of testing have varied substantially during the pandemic, such a criterion would likely bias the cohort.

Conclusions

This study demonstrated profound cognitive deficits in patients with PCC. Most were still on sick leave months to years after the infection, highlighting the urgent need to develop symptom-based rehabilitation interventions and psychological support for this large group of previously high-functioning persons.

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References

1. World Health Organization (WHO). WHO coronavirus (COVID-19) dashboard. Available at: http://covid19.who.int/. Accessed August 16, 2023.
2. Soriano JB, Murthy S, Marshall JC, Relan P, Diaz JV. A clinical case definition of post-COVID-19 condition by a Delphi consensus. Lancet Infect Dis 2022;22:e102–7.
3. Birberg Thornberg U, Andersson A, Lindh M, Hellgren L, Divanoglou A, Levi R. Neurocognitive deficits in COVID-19 patients five months after discharge from hospital. Neuropsychol Rehabil 2022 Oct 14. [Epub ahead of print].
4. Ariza M, Cano N, Segura B, et al. Neuropsychological impairment in post-COVID condition individuals with and without cognitive complaints. Front Aging Neurosci 2022;14:1029842.
5. Llana T, Zorzo C, Mendez-Lopez M, Mendez M. Memory alterations after COVID-19 infection: a systematic review. Appl Neuropsychol Adult 2022 Sep 15. [Epub ahead of print].
6. Biagianti B, Di Liberto A, Nicolò Edoardo A, et al. Cognitive assessment in SARS-CoV-2 patients: a systematic review. Front Aging Neurosci 2022;14:909661.
7. Voruz P, Jacot de Alcàntara I, Nuber-Champier A, et al. Frequency of abnormally low neuropsychological scores in post-COVID-19 syndrome: the Geneva COVID-COG Cohort. Arch Clin Neuropsychol 2023;38:1–11.
8. Binder LM, Iverson GL, Brooks BL. To err is human: "abnormal" neuropsychological scores and variability are common in healthy adults. Arch Clin Neuropsychol 2009;24:31–46.
9. Levi Y, Rassovsky Y, Agranov E, Sela-Kaufman M, Vakil E. Cognitive reserve components as expressed in traumatic brain injury. J Int Neuropsychol Soc 2013;19:664–71.
10. Thielen H, Verleysen G, Huybrechts S, Lafosse C, Gillebert CR. Flemish normative data for the Buschke Selective Reminding Test. Psychol Belg 2019;59:58–77.
11. Karr JE, Areshenkoff CN, Garcia-Barrera MA. The neuropsychological outcomes of concussion: a systematic review of meta-analyses on the cognitive sequelae of mild traumatic brain injury. Neuropsychology 2014;28:321–36.