

# Slow but evident recovery from neocortical dysfunction and cognitive impairment in a series of chronic COVID-19 patients

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## ABSTRACT

Cognitive impairment is a frequent complaint in coronavirus disease-19 (COVID-19) and can be related to cortical hypometabolism on  $^{18}\text{F}$ -FDG PET at the subacute stage. However it is unclear, if these changes are reversible. **Methods:** We prospectively assessed Montreal Cognitive Assessment (MoCA) and  $^{18}\text{F}$ -FDG PET scans in 8 COVID-19 patients at the subacute (once no longer infectious) and chronic stages (approximately six months after symptom onset). The expression of the previously established COVID-19-related covariance pattern was analyzed at both stages to examine the time course of post-COVID-19 cognitive impairment. For further validation, we also conducted a conventional group analysis. **Results:** Follow-up  $^{18}\text{F}$ -FDG PET revealed a significant reduction of initial frontoparietal and, to a lesser extent, temporal hypometabolism that was accompanied by significant improvement in cognition. The expression of the previously established COVID-19-related pattern was significantly lower at follow-up and correlated inversely with MoCA performance. However, both  $^{18}\text{F}$ -FDG PET and cognitive assessment suggest a residual impairment. **Conclusions:** Although a significant recovery of regional neuronal function and cognition can be clearly stated, residuals are still measurable in some patients six months after manifestation of COVID-19. Given the current pandemic situation and tremendous uncertainty concerning the long-term effects of COVID-19, the present study provides novel insights of highest medical and socioeconomic relevance.

Key Words: COVID-19, cognition, neurology,  $^{18}\text{F}$ -FDG PET, Montreal Cognitive Assessment

## INTRODUCTION

As the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic proceeds, neurocognitive long-term consequences are frequently observed (1): follow-up investigations of coronavirus disease-19 (COVID-19) patients two to four months after symptom onset report, among others, impaired memory (20-34%) (2,3), disturbed concentration (20-40%) (2,3) and cognitive problems (36%) (4). These cognitive deficits in the chronic stage are now frequently referred to as ‘Long-COVID-syndrome’. Recently, we described impairment of frontoparietal cognitive functions accompanied by frontoparietal dominant cortical hypometabolism on  $^{18}\text{F}$ -FDG PET (as an established marker of neuronal function) in a relevant subset of subacute COVID-19 patients initially requiring inpatient treatment for non-neurological complications (5). By comparison of  $^{18}\text{F}$ -FDG PET scans of those subacute COVID-19 inpatients to a control sample using voxel-wise principal components analysis, we established a COVID-19-related spatial covariance pattern, the expression of which was tightly correlated with performance in the Montreal Cognitive Assessment (MoCA) (6). Frontal and, to a lesser extent, temporoparietal cortical hypometabolism, which improved during follow-up at 1 and 6 months, were also confirmed as major findings in the acute phase of COVID-19-related encephalopathy by a recent study of Kas et al. (7). Deviating from aforementioned results, Guedj et al. (8) reported a profile of hypometabolism in limbic/paralimbic regions extended to the brainstem and cerebellum in patients with ‘Long-COVID’ examined at about 3 months after symptom onset. Against this background, we investigated whether the frontoparietal hypometabolism might be a biological fingerprint of ‘Long-COVID-syndrome’ neurocognitive impairments. We re-assessed  $^{18}\text{F}$ -FDG PET and MoCA performance in eight patients presenting for a follow-up in the chronic stage approximately six months after symptom onset.

## **MATERIALS AND METHODS**

### **Standard Protocol Approvals, Registrations, and Patient Consents**

Patients were part of a prospective monocentric register (Neuro-COVID-19). The local ethics committee approved this study (EK 211/20) and all subjects gave written informed consent in accordance with the Declaration of Helsinki.

### **Study Design, Participants and Assessment of Cognitive Functions**

The register enrolled patients with reverse transcription polymerase chain reaction-confirmed SARS-CoV-2 infection, at least one novel neurological symptom developed under COVID-19 and required inpatient treatment in the Department of Internal Medicine of the University Hospital Freiburg between April 20, 2020 and June 10, 2020 (for details see Hosp and colleagues (5)). During the acute stage a total of 31 subacute COVID-19 patients were assessed for impaired cognitive functions with the MoCA (German, version 7.1) (6). 17 of these patients had undergone an <sup>18</sup>F-FDG PET examination at the subacute stage. Of those, eight patients underwent a second examination with <sup>18</sup>F-FDG PET and MoCA (German, alternative version 7.2) at the chronic stage of the disease and were included in this study. Eight patients refused further investigations (no more self-perceived complaints: n = 6; long traveling distance: n = 1; bad physical condition: n = 1) and one patient died.

Of note, the present population does not represent a so-called Long-COVID (typically defined by long-lasting, not exclusively neurological complaints at least 4 to 12 weeks after symptom onset (9)) since patients were enrolled into this prospective study based on at least one new neurological symptom at the subacute stage (on average  $37 \pm 19$  days after COVID-19 symptom onset) and then followed-up to investigate the reversibility of symptoms. In fact, 4/8 (50%) patients did not have any more self-reported cognitive deficits at the time of the second examination (Table 1).

The manifestation of cognitive deficits was further described by domain scores of the MoCA test as suggested by Nasreddine and colleagues (6) based on single item scores (Orientation: spatial and temporal orientation; Attention: digit span, letter A tapping, subtraction; Executive: Trail Making, abstraction, word fluency; Visuoconstructive: cube copying, clock drawing; Language: naming, sentence repetition; Memory: delayed word recall). The global MoCA test score was corrected for years of education (YoE; +1 point if  $\leq 12$  YoE). Domain-scores were not adjusted for YoE.

### **<sup>18</sup>F-FDG PET Imaging**

PET emission data were acquired on a fully digital Vereos PET/CT scanner (Philips Healthcare, The Netherlands) 50 minutes after injection of  $213 \pm 9$  MBq <sup>18</sup>F-FDG for 10 minutes. <sup>18</sup>F-FDG PET scans were spatially normalized to an in-house <sup>18</sup>F-FDG PET template in Montreal Neurologic Institute space, followed by a smoothing with an isotropic Gaussian kernel of 10 mm full width at half maximum. The topographic profile rating algorithm (10) was employed to derive each individual's pattern expression score (PES) of the previously established COVID-19-related spatial covariance pattern (5). For additional conventional analysis, a paired *t* test between the <sup>18</sup>F-FDG PET scans at the subacute and chronic stages was calculated after proportional scaling of individual voxel-wise <sup>18</sup>F-FDG uptake to white matter (given the obvious involvement of grey matter shown in previous study (5)). Voxel-wise two-sample *t* test was also applied to the <sup>18</sup>F-FDG PET scans of COVID-19 patients at the chronic stage compared to control cohort ( $n = 45$  age-matched control patients in whom a somatic CNS disease was carefully excluded, see previous report (5)) in order to explore whether hypometabolism still remains at the chronic stage of disease. All processing steps were implemented with an in-house pipeline in MATLAB (The MathWorks, Inc., Natick, Massachusetts, United States) and Statistical Parametric Mapping (SPM12) software ([www.fil.ion.ac.uk/spm](http://www.fil.ion.ac.uk/spm)).

## Statistical Analysis

Significance of differences between subacute and chronic stages for MoCA test scores and PES of COVID-19-related covariance pattern was assessed with paired  $t$  tests. Student's one-tailed  $t$  test was applied to test whether the PES in COVID-19 patients at the subacute stage was still significantly higher compared to the control cohort. Cohen's  $d$  was calculated for all pairwise comparisons. Strength of relationship between MoCA and PES of COVID-19-related covariance pattern was estimated within the stages by linear regression and across stages with a repeated measures correlation test (11). Statistical analyses were performed using R (<https://www.R-project.org/>).

## Data Availability

The data generated and analyzed during the current study are not publicly available but could possibly be provided by the corresponding author on reasonable request and upon approval of the local ethics committee.

## RESULTS

Demographics and patient characteristics are listed in Table 1. The eight patients presenting for a follow-up examination were not distinct from the rest of cohort at baseline examination (PES of COVID-19-related covariance pattern on  $^{18}\text{F}$ -FDG PET, MoCA, and age were not significantly different between groups, all  $p > 0.1$ ). MoCA-performance significantly improved over time from a mean ( $\pm$  standard deviation) global score of  $19.1 \pm 4.5$  (maximum 30 points) at the subacute stage to  $23.4 \pm 3.6$  at the chronic stage ( $d = 0.97$ ,  $p = 0.03$ , table 1), which is however still below the frequently used cut-off value for detection of cognitive impairment ( $<26/30$ ). Five of eight patients still were below this threshold (6). MoCA domain scores showed that orientation and attention were almost unimpaired at the chronic stage, but revealed persistent deficits in visuoconstructive and executive functions and, especially, memory (Table 1). As previously shown (5), the PES of the COVID-19-related pattern (Fig. 1, panel A) in the subacute COVID-19 patients was significantly higher compared to the control cohort

(44.3 vs. -11.3;  $d = 1.84$ ,  $p = 6 \times 10^{-6}$ ). COVID-19 patients had significantly lower mean PES at the chronic than at the subacute stage ( $6.8 \pm 32.6$  vs.  $44.3 \pm 33.1$ ;  $d = 1.06$ ,  $p = 0.002$ ), although still at trend-level higher in comparison to the control cohort (6.8 vs. -11.3;  $d = 0.60$ ,  $p = 0.06$ ) (Fig. 1, panel B). Exploratory correlation analysis revealed a significant relationship between cognitive assessment (MoCA global score adjusted for YoE) and PET ( $R^2 = 0.39$ ,  $p = 0.01$ ; i.e., lower PES was associated with better cognitive performance) over the subacute and chronic stages (Fig. 1, panel C). Moreover, changes in cognition (MoCA) seem to be associated with change in PES, which, however, failed to attain statistical significance in the present small sample ( $r = -0.54$ ,  $p = 0.16$ ,  $n = 8$ ). No significant correlation was found between changes of PES and MoCA on one side and time to follow-up examinations on the other.

Averaged  $^{18}\text{F}$ -FDG PET images of the COVID-19 patients at both stages and the regions that showed a significant increase of regional glucose metabolism at the chronic compared to the subacute stage ( $p = 0.01$ , false-discovery rate (FDR)-corrected, corresponding to  $\{T\} > 5.31$ ) are displayed in Fig. 2. Group analysis using SPM revealed a wide-spread increase of  $^{18}\text{F}$ -FDG uptake in frontoparietal and, to a lesser extent, temporal neocortical regions at the chronic stage compared to the subacute stage. No regions with significant decrease of glucose metabolism were identified. Voxel-wise comparison of chronic-stage patients to the age-matched control cohort confirmed the presence of a remaining neocortical hypometabolism in COVID-19 patients even at the chronic stage at an exploratory statistical threshold ( $p = 0.005$  corresponding to  $\{T\} > 2.68$ ; no significant cluster at  $p = 0.01$ , FDR-corrected; Fig. 2).

## DISCUSSION

In the present follow-up study, we demonstrate essential reversibility of decreased neocortical glucose metabolism assessed by  $^{18}\text{F}$ -FDG PET accompanied by an improvement of cognitive functions in COVID-19 patients from the subacute to the chronic stage after a SARS-CoV-2 infection. The expression of the previously established COVID-19-related spatial covariance pattern at the chronic stage was

significantly reduced compared to the subacute stage. However, in comparison to a control cohort, chronic COVID-19 patients still exhibited a slightly higher pattern expression (at trend-level) and residual hypometabolism indicating a shift towards normal levels, but no definite return. Although we observed a significant improvement in the cognitive screening test (MoCA), the average performance was still within the range of mild cognitive impairment (6). This slow but evident recovery provides fundamental and novel insights into the pathophysiology of cognitive deficits associated with COVID-19.

Recent neuropathological examinations of patients who died from COVID-19 due to non-neurological causes shed light on potential pathophysiological mechanisms underlying the sustained cortical hypometabolism and impairment (12): SARS-CoV-2 RNA or proteins could be detected in 53% of patients with a predominance for caudal brainstem and cranial nerves highlighting the known neuroinvasive propensity of human Beta-Coronavirus clades (13,14). However, major histopathological findings were astrogliosis, microglia activation and mild infiltration by cytotoxic T lymphocytes with an emphasis on brainstem and cerebellum (12) that were unrelated to the presence of SARS-CoV-2. Therefore, these changes are more likely caused by a systemic inflammatory response or cytokine release (15). As the cortical grey matter is largely spared from damage and inflammatory changes (5,12), the reduced glucose metabolism is likely secondary, e.g. as a consequence of a functional decoupling from aminergic brainstem nuclei (16,17). This inflammation-triggered process could have outlasted the acute infection and only partly recovered over the contemplated period of six months. Of note, changes in cognition (MoCA) seem to be associated with change in PES although this observation failed to attain statistical significance ( $r = -0.54$ ,  $p = 0.16$ ). We did not observe an association between changes of PES and MoCA on one hand and time to follow-up examinations on the other. This may also be due to the limited number of subjects and relatively narrow and late time range of follow-up examinations. Still, the regions with residual hypometabolism are those with the most prominent decreases during the acute stage and may thus take a longer period to fully recover. Consequently, the slow reversibility of post-COVID-19 cerebral hypometabolism and cognitive impairment described in the present study would be in

accordance with a lasting perturbation of cortical function caused by a subcortical peri-inflammatory process as correlate of the ‘Long-COVID-syndrome’.

The comparison of the present study to other studies employing  $^{18}\text{F}$ -FDG PET for assessment of COVID-19-associated metabolic deficits is hampered by various factors. For instance, Guedj et al. (8) reported a cohort of patients examined at highly variable time points (about 1 to 5 months after COVID-19, on average  $96 \pm 31$  days). Given the apparent time dependency of cognitive and metabolic changes, such pooling of patients at presumably different stages precludes a comparison to studies of selected time points like ours. Moreover, given the obvious alterations in cortical metabolism observed in our cohort and the study by Kas et al. (7), the use of cortical regions for count rate normalization of PET data appears problematic. In fact, this is why we selected an approach (i.e., principal components analysis) that does not require an a priori definition of a reference region. Such factors (among others) might led to discordant results and contra-intuitive findings like decreasing glucose metabolism with longer time after first COVID-19 symptoms (8), which is in contrary to both, the study from Kas et al. (7) and ours. In turn, the latter studies are in good agreement with each other, showing a slow, though not (yet) complete recovery of cortical metabolism over six months. Still, a detailed comparison of these two studies is complicated by the initial inclusion criteria: Patients were prospectively enrolled in our cohort when presenting with at least one new neurological symptom and underwent  $^{18}\text{F}$ -FDG PET for further diagnostic work-up if  $\geq 2$  new symptoms were present (5). Kas et al. (7) report the analysis of  $^{18}\text{F}$ -FDG PET scans in 7 patients with COVID-19-related encephalopathy with new-onset cognitive impairment. Moreover, initial disease severity was different in both studies (for instance, 3/7 or 43% of patients reported by Kas et al. (7) needed mechanical ventilation opposed to 2/8 or 25% in the present study). Finally, Kas et al. (7) also conducted an assessment by a comprehensive cognitive test battery but no direct association to PET data was reported.

A limitation of the present study is the small sample size with only eight out of 17 initial patients receiving a follow-up  $^{18}\text{F}$ -FDG PET and MoCA examination. Obviously, patients with actual cognitive

complaints are more likely to adhere to a follow-up program than subjectively healthy patients. In fact, six patients declined follow-up with reference to the lack of self-perceived complaints, whereas only four out of eight patients denied cognitive impairments in our actual sample. However, this “selection bias” is inherently linked to the major finding of the present study of slow but evident recovery of cognitive impairment. In addition, the selection of the initial cohort (only inpatient, but not dominant ICU treatment) limits generalizability of our findings (especially to outpatients, representing the majority of COVID-19 patients). Furthermore, there may be premorbid conditions or risk factors rendering subgroups of patients particularly susceptible for COVID-19-associated cognitive impairments. No obvious factors were identified in the present prospective single-center study (including the initial sample) (5). However, future larger, population-based studies are needed to address this question.

## **CONCLUSION**

Given the current pandemic situation and still tremendous uncertainty concerning the long-term sequelae of COVID-19, the present study provides novel insights of highest medical and socioeconomic relevance. We provide evidence of longer lasting metabolic and accompanying cognitive deficits after COVID-19. Although a significant recovery of regional neuronal function and cognition can be clearly stated, residuals are still measurable in some patients six months after manifestation of COVID-19. In consequence, post-COVID-19 patients with persistent cognitive complaints should be presented to a neurologist and possibly allocated to cognitive rehabilitation programs.

## **DISCLOSURE**

The authors declare they did not receive any funding for this study. PTM received honoraria from GE (presentation, consultancy) and Philips (presentation). All declared interests are outside of the submitted work.

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## **KEY POINTS**

**QUESTION:** Are cognitive impairment and associated cortical hypometabolism reversible after six months post COVID-19?

**PERTINENT FINDINGS:** We now prospectively examined the course of cognitive impairment and cortical hypometabolism in eight patients with COVID-19-associated deficits at the subacute until the chronic stage. <sup>18</sup>F-FDG PET revealed reversibility of initial frontoparietal and, to a lesser extent, temporal glucose hypometabolism that was accompanied by significant improvement in cognition. The expression of the previously established COVID-19-related covariance pattern was significantly lower at the follow-up and correlated inversely with MoCA performance.

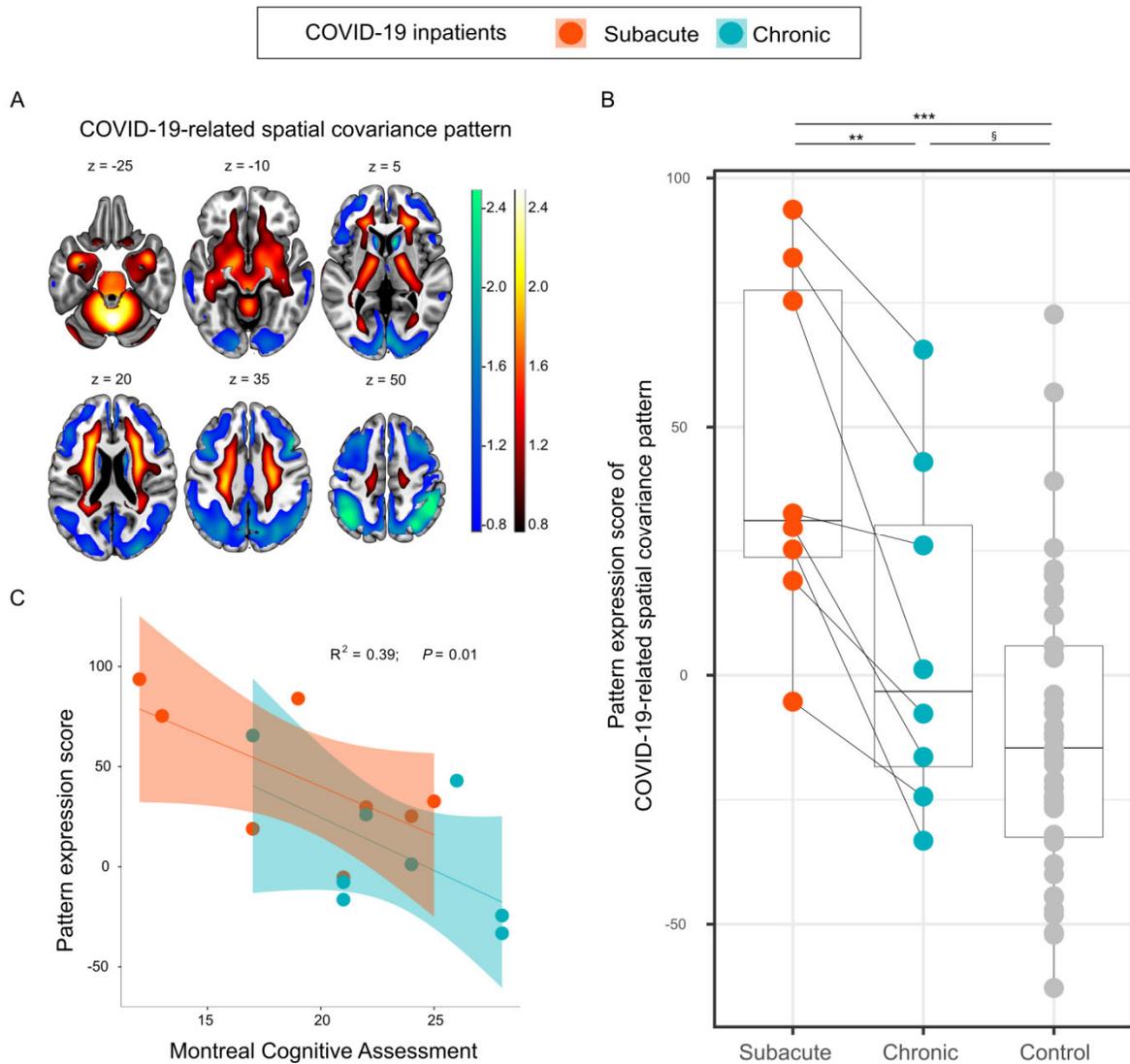
**IMPLICATIONS FOR PATIENT CARE:** While significant recovery of regional neuronal function and cognition can be clearly stated, residuals are still measurable even six months after manifestation of COVID-19. Post-COVID-19 patients with persistent cognitive complaints should be presented to a neurologist and possibly allocated to cognitive rehabilitation programs.

## REFERENCES

1. Honigsbaum M, Krishnan L. Taking pandemic sequelae seriously: from the Russian influenza to COVID-19 long-haulers. *Lancet*. 2020;396:1389-1391.
2. Halpin SJ, McIvor C, Whyatt G, et al. Postdischarge symptoms and rehabilitation needs in survivors of COVID-19 infection: A cross-sectional evaluation. *J Med Virol*. 2021;93:1013-1022.
3. Garrigues E, Janvier P, Kherabi Y, et al. Post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19. *J Infect*. 2020;81:e4-e6.
4. van den Borst B, Peters JB, Brink M, et al. Comprehensive health assessment three months after recovery from acute COVID-19. *Clin Infect Dis*. 2020;In press.
5. Hosp JA, Dressing A, Blazhenets G, et al. Cognitive impairment and altered cerebral glucose metabolism in the subacute stage of COVID-19. *Brain*. 2021;In press.
6. Nasreddine ZS, Phillips NA, Bedirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*. 2005;53:695-699.
7. Kas A, Soret M, Pyatigorskaya N, et al. The cerebral network of COVID-19-related encephalopathy: a longitudinal voxel-based 18F-FDG-PET study. *Eur J Nucl Med Mol Imaging*. 2021.
8. Guedj E, Campion JY, Dudouet P, et al. (18)F-FDG brain PET hypometabolism in patients with long COVID. *Eur J Nucl Med Mol Imaging*. 2021:1-11.
9. Excellence NifHaC. COVID-19 rapid guideline: managing the long-term effects of COVID-19: NICE guideline [NG188]. <https://www.nice.org.uk/guidance/ng188>. Accessed 18 December, 2020.
10. Spetsieris PG, Eidelberg D. Scaled subprofile modeling of resting state imaging data in Parkinson's disease: methodological issues. *Neuroimage*. 2011;54:2899-2914.
11. Bakdash JZ, Marusich LR. Repeated measures correlation. *Front Psychol*. 2017;8:456.
12. Matschke J, Lutgehetmann M, Hagel C, et al. Neuropathology of patients with COVID-19 in Germany: a post-mortem case series. *Lancet Neurol*. 2020;19:919-929.
13. Desforges M, Le Coupanec A, Dubeau P, et al. Human coronaviruses and other respiratory viruses: underestimated opportunistic pathogens of the central nervous system? *Viruses*. 2019;12.

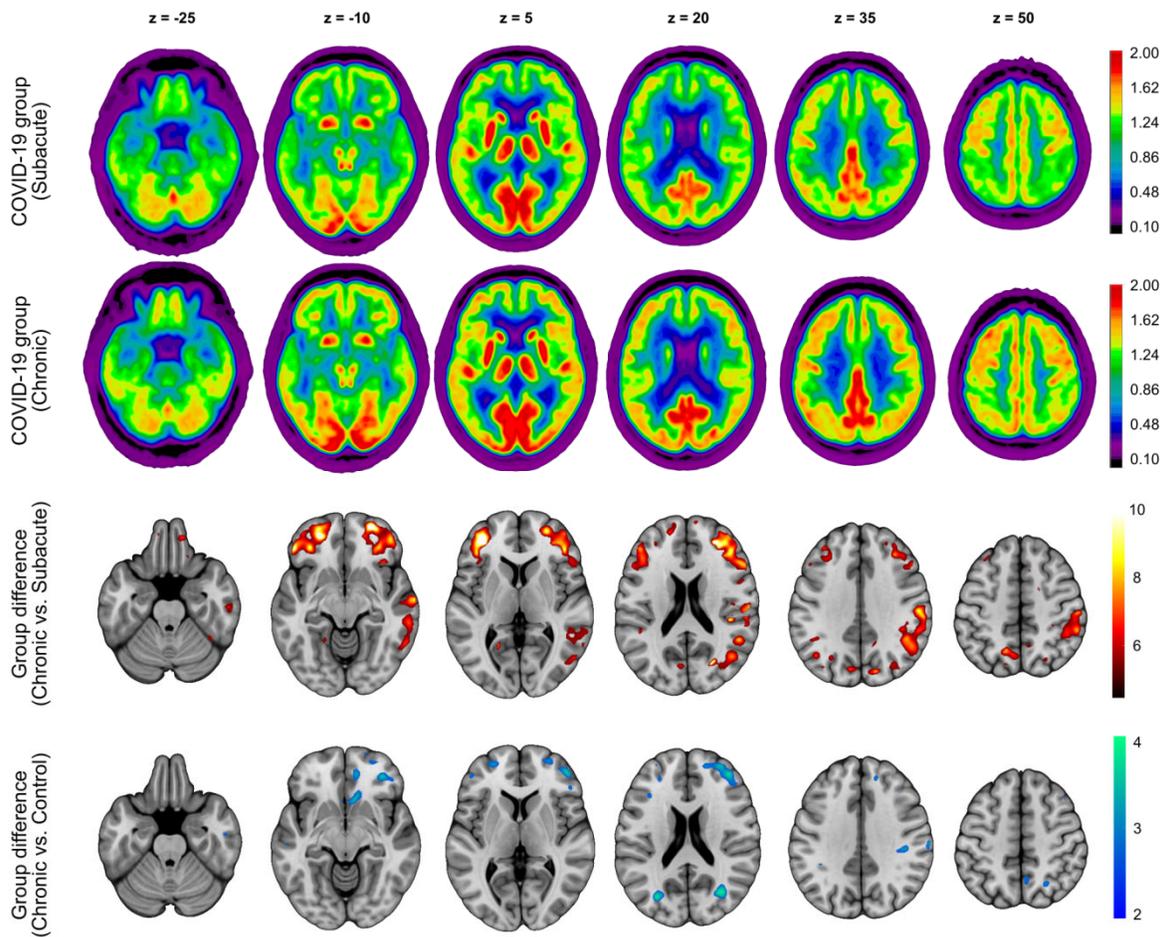
- 14.** Dube M, Le Coupanec A, Wong AHM, Rini JM, Desforges M, Talbot PJ. Axonal transport enables neuron-to-neuron propagation of human coronavirus OC43. *J Virol.* 2018;92:e00404-00418.
- 15.** Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet.* 2020;395:1033-1034.
- 16.** Bekar LK, Wei HS, Nedergaard M. The locus coeruleus-norepinephrine network optimizes coupling of cerebral blood volume with oxygen demand. *J Cereb Blood Flow Metab.* 2012;32:2135-2145.
- 17.** Bosch OG, Wagner M, Jessen F, et al. Verbal memory deficits are correlated with prefrontal hypometabolism in (18)FDG PET of recreational MDMA users. *PLoS One.* 2013;8:e61234.

# FIGURES



**FIGURE 1. Expression of the COVID-19-related spatial covariance pattern.** **A:** COVID-19-related spatial covariance pattern of cerebral glucose metabolism established in Hosp and colleagues (5) overlaid onto an MRI template. Voxels with negative region weights are color-coded in cool colors, and regions with positive region weights in hot colors (neurologic orientation, i.e., left image side corresponds to patients' left body side; numbers denote axial (Z) position in mm). **B:** The pattern expression score (PES) of the COVID-19-related spatial covariance pattern is lower in COVID-19 patients at the chronic stage compared to the subacute stage, but still at trend-level higher compared to the control cohort. Boxplots (grey) as well as individual values for COVID-19 patients (colored) and the control cohort (grey) are displayed. Repeated measures for each patient are connected by the line. \*\*\*  $p < 0.001$  (two-sample  $t$  test;

see previous study (5)); \*\*  $p < 0.005$  (two-tailed paired  $t$  test); §  $p = 0.06$  (one-tailed two-sample  $t$  test). C: Association between the PES and the Montreal Cognitive Assessment score adjusted for years of education. Each dot represents an individual patient's data; the lines (shaded areas) correspond to the fit of a linear regression (95% confidence interval) for each disease stage separately ( $p = 0.07$  and  $0.12$  for the subacute and chronic stage, respectively). Repeated-measures  $R^2$  and  $P$  value represent the correlation between variables with both stages pooled.



**FIGURE 2. Result of the  $^{18}\text{F}$ -FDG PET group analysis.** First and second row: Transaxial sections of group averaged, spatially normalized  $^{18}\text{F}$ -FDG PET scans in COVID-19 patients at the subacute and chronic stages ( $n = 8$ ; initially requiring inpatient treatment for non-neurological complications). Third and fourth rows: Results of a statistical parametric mapping analysis. Third row illustrates regions that show significant increases of normalized  $^{18}\text{F}$ -FDG uptake in COVID-19 patients at the chronic compared to the subacute stage (paired  $t$  test,  $p < 0.01$ , false discovery rate-corrected). Fourth row depicts regions that still show significant decreases of normalized  $^{18}\text{F}$ -FDG uptake in COVID-19 patients at the chronic stage compared to the age-matched control cohort (two-sample  $t$  test,  $p < 0.005$ ). SPM T values are color-coded and overlaid onto an MRI template. Images are presented in neurologic orientation, i.e., left image side corresponds to patients' left body side; numbers denote axial (Z) position in mm

## TABLES

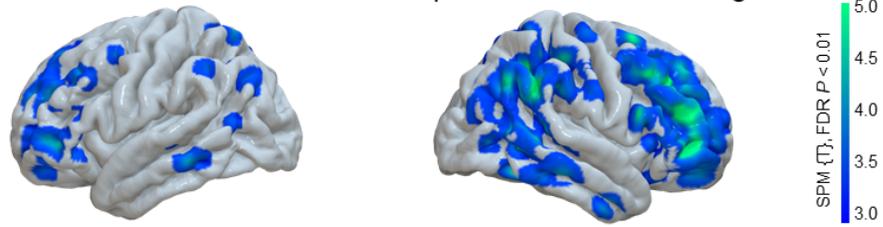
**TABLE 1.** Patient demographic and basic clinical characteristics and results of the Montreal Cognitive Assessment.

<b>Demographic data</b>	
Age (years)	66.00 (14.23) [39 - 89]
Gender (male / female)	6 (75%) / 2 (25%)
Years of education (YoE; years)	12.63 (2.74) [9 - 18]
Delay symptom onset - 1th exam (days)	28.50 (14.63) [13 - 61]
Delay symptom onset - 2nd exam (days)	160.13 (46.79) [113 - 233]
Delay 1st PET - 2nd PET (days)	123.13 (39.61) [87 - 196]
Self-reported persistent cognitive deficits	4 (50%)
<b>Characteristics of initial inpatient treatment</b>	
Reduced general condition	2 (25%)
Bacterial pulmonary superinfection	2 (25%)
Kidney failure	3 (37.5%)
Ischemic stroke	1 (12.5%)
Required ICU treatment	2 (25%)
<b>Montreal Cognitive Assessment (MoCA) corrected for YoE</b>	
MoCA 1st exam	19.13 (4.51) [13 - 25]
MoCA 2nd exam	23.38 (3.60) [17 - 28]
Δ MoCA (2nd exam - 1st exam)	4.25 (4.20)
<b>MoCA Domain Scores</b>	
Orientation (max. 6)	6.00 (0.00) [6]
Attention (max. 6)	5.13 (0.83) [4 - 6]
Language (max. 6)	3.88 (1.96) [1 - 6]
Visuoconstructive functions (max. 4)	3.13 (0.99) [2 - 4]
Executive functions (max. 4)	2.50 (1.07) [1 - 4]
Memory (max. 5)	2.25 (2.12) [0 - 5]

Data are given as N (%) (nominal data) or mean (SD) [range] (continuous data)

## Graphical Abstract

Extensive cortical hypometabolism accompanying marked cognitive impairment was detected in 15 COVID-19 inpatients at the acute stage.



Cortical dysfunction and cognitive impairment improved, but did not completely resolve in 8 patients re-assessed at six-month follow-up.

