# Does COVID-19 Infection Accelerate Age-Related Cognitive Decline?

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## Introduction

- Similar neuroimaging abnormalities are reported in post-COVID patients and patients with Alzheimer's Disease (AD).
- COVID-19 and AD also share genetic vulnerabilities and have similar cognitive profiles (e.g., memory impairment, mental fatigue, anosmia, etc.).
- These findings raise the concern that COVID may cause or accelerate cognitive decline and increase the risk that older patients will develop Alzheimer's disease.

## Methods

Here we report preliminary results of ongoing normative data collection for the California Cognitive Assessment Battery (CCAB). Self-reported COVID histories were recorded from 798 older participants (mean age 65.8 years), including 282 COVID+ participants who had recovered from COVID infection prior to enrollment. In addition, 310 participants were longitudinally tested beginning in 2022 with 6- and 18-month retest scores reported here. The effects of COVID on cognitive performance were assessed with 18 verbal and 14 non-verbal subtests of the CCAB. For each subject, an omnibus z-score was produced by averaging across 120 individual test z-scores at enrollment, and again at 6- and 18-month retest in the longitudinal test sample. Omnibus z-scores were then analyzed with two models: a "conventional" (AEG) model using age, education, and gender as regressors, and a "comprehensive" (C-) model using 8 demographic predictors (see Table 1).

## Results

| Factor | C-model | AEG model |
|---|---|---|
| *Age* | 0.00 | 0.00 |
| *Education* | 0.00 | 0.00 |
| *Gender* | 0.00 | 0.00 |
| *Vocabulary* | 0.00 | 0.51 |
| *Race (ref: white)* | -0.01 | 0.34 |
| *Computer use* | 0.00 | 0.18 |
| *SES* | 0.00 | 0.17 |
| *Daily medications* | 0.00 | -0.20 |
| Latino | -0.08 | 0.01 |
| GAD | -0.09 | -0.15 |
| GDS | -0.06 | -0.09 |
| FS20 | -0.02 | -0.10 |
| Comorbidities | 0.01 | -0.10 |

Table 2. Pearson correlations of demographic factors with C-model and AEG-model omnibus z-scores. The C-model incorporated the 7 factors shown in italics (including three factors for race). AEG scores were strongly influenced by vocabulary, race, and other factors in the C-model. C-model predictors also reduced the influence of factors outside both models (e.g., hours reading).

## Results

| Domain | Severity | PASC+ |
|---|---|---|
| Episodic Memory | -0.15 | -0.12 |
| Language | -0.13 | -0.14 |
| Speech | -0.15 | -0.12 |
| Executive Function | -0.10 | -0.12 |
| Speed | -0.03 | -0.08 |
| Non-verbal | -0.02 | -0.05 |

Table 3. Pearson correlations of COVID severity and continued PASC+ symptoms with scores in different cognitive domains and modalities. Each score combines 15-25 different individual test z-scores from 798 subjects

| Group | 6-month | 18-month |
|---|---|---|
| COVID+ | 0.41* | 0.10 |
| COVID- | -0.07 | -0.03 |
| N (+ : -) | 39:239 | 51:149 |

Table 4. Omnibus z-scores at retest relative to predicted scores based on omnibus z-scores at enrollment and other predictors. COVID+ indicates a participant reporting a COVID infection occurring between enrollment and either the 6- or 18-month retest session. 97.35% of participants were vaccinated against COVID.

## Results

| Group | n | Age | Edu | %female | Vocab | %white | Daily meds | SES | Comp use | AEG-Z | C-Z | AEG-MCI | C-MCI |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| COVID+ | 282 | 61.91 | 8.60 | 59.93% | 34.13 | 25.89% | 2.07 | 3.44 | 4.32 | -0.10* | 0.02 | 8.18%* | 7.14% |
| COVID- | 516 | 67.93 | 8.79 | 50.39% | 36.92 | 45.16% | 2.46 | 3.66 | 4.31 | 0.06 | -0.01 | 6.67% | 6.81% |
| HOSP | 8 | 67.75 | 7.13 | 37.50% | 30.53 | 37.50% | 3.38 | 3.29 | 1.88 | -0.70* | -0.42 | 12.07%* | 12.39%* |
| PASC+ | 29 | 62.07 | 8.45 | 82.76% | 33.98 | 27.59% | 3.48 | 2.21 | 4.17 | -0.30* | -0.34* | 10.40%* | 10.25%* |

Table 1. Demographic predictors in the Comprehensive (C-) model. Up to 8 factors were included in the C-models for different test scores. The COVID+ population differed demographically from the COVID-population in all factors except Education (Edu) and Computer-use (C-use). Daily meds = daily prescription medications. C-z, and AEG-z: Mean omnibus z-scores averaged over 120 individual test scores using different scoring models. AEG-MCI, and C-MCI: The percentage of all test scores that fell within the MCI range (z-score < -1.5). HOSP: patients previously hospitalized for COVID. PASC+: Participants with unresolved Long-COVID symptoms at the time of testing. * = p <0.05.

## Summary

- <u>DEMOGRAPHIC DIFFERENCES BETWEEN COVID+ AND COVID-POPULATIONS</u> (Table 1). Table 2 shows correlations of C- and AEG-model scores with these factors. The C-model factored out the contributions of demographic factors distinguishing COVID+ and COVID- populations.
- <u>COVID EFFECTS WERE SEEN WITH CONVENTIONAL SCORING MODELS</u>. COVID+ patients had lower omnibus z-scores than COVID-patients when using the AEG model ($t(794) = -2.15, p<0.02$; Table 1), and performed worse in every cognitive domain and test modality; see Table 3.
- <u>COVID DID NOT CAUSE SUSTAINED COGNITIVE IMPAIRMENT WITH A MORE COMPREHENSIVE SCORING MODEL</u>. Differences between omnibus z- scores of COVID+ and COVID- participants disappeared when using the C-model ($t(281) = 0.35, NS$), as did significant COVID effects on cognitive domains and modalities. The effect of incidental COVID infections in already-enrolled participants was analyzed at 6 (N=39) and 18-months post-enrollment (N=51). No COVID-related impairment was seen. Infections prior to 6-month retest were paradoxically associated with improved 6-month omnibus scores ($t(49) = 2.74, p < 0.01$), but no effects were observed for infections prior to the 18-month retest ($t(90) = 0.95, NS$).
- <u>SEVERE INFECTIONS PRODUCED IMPAIRMENT</u>. Infection severity (WHO criteria) correlated with omnibus C-model ($r = -0.12, t(796) = -3.41, p < 0.001$) and AEG-model z-scores ($r = -0.09, t(796) = -3.41, p < 0.001$).
- <u>UNRESOLVED SYMPTOMS OF LONG COVID PRODUCED IMPAIRMENT</u>. Patients with unresolved Long-COVID symptoms (PASC) showed significantly reduced omnibus z-scores and greater incidence of performance in the MCI range (see Table 1).
- <u>COVID IMPACTS VERBAL MORE THAN NON-VERBAL ABILITIES</u>. Initial disease severity and current PASC symptoms both had minimal effects on Speed and non-verbal measures, and the largest effects on episodic memory, language, and speech (see Table 3).

## Discussion

- Preliminary results suggest that severe COVID infections requiring hospitalization result in significant cognitive deficits, across cognitive domains
- In contrast, mild infections and post-inoculation "breakthrough" infections do not have significant cognitive effects, when analyzed using a comprehensive model.
- Traditional models may overstate cognitive effects of COVID by failing to include important demographic factors
- Unresolved "long COVID" symptoms impair cognitive performance.

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