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Cognition and Memory Following COVID-19 in a Large Community Sample

Adam Hampshire, Ph.D.[1], **Adriana Azor, Ph.D.**[1], **Christina Atchison, Ph.D.**[2,3], **William Trender, M.Res.**[1], **Peter J. Hellyer, Ph.D.**[4], **Valentina Giunchiglia, M.Sc.**[1], **Masud Husain, Ph.D.**[5], **Graham S. Cooke, Ph.D.**[3,6,7], **Emily Cooper, M.A.**[2,3], **Adam Lound, M.Sc.**[2,3], **Christl A. Donnelly, Ph.D.**[2,8,9], **Marc Chadeau-Hyam, Ph.D.**[2,10], **Helen Ward, Ph.D.**[2,3,6], **Paul Elliott, Ph.D.**[2,3,6,10,11,12]

[1]Department of Brain Sciences, Imperial College London, London, UK

[2]School of Public Health, Imperial College London, London, UK

[3]National Institute for Health Research Imperial Biomedical Research Centre, London, UK

[4]Centre for Neuroimaging Sciences, Institute of Psychiatry Psychology and Neuroscience, King's College London, London, UK

[5]Nuffield Dept Clinical Neurosciences & Department of Experimental Psychology, University of Oxford, Oxford, UK

[6]Imperial College Healthcare NHS Trust, London, UK

[7]Department of Infectious Disease, Imperial College London, London, UK

[8]Department of Statistics, University of Oxford, Oxford, UK

[9]Pandemic Sciences Institute, University of Oxford, Oxford, UK

[10]MRC Centre for Environment and Health, School of Public Health, Imperial College London, London, UK

[11]Health Data Research UK London at Imperial, London UK

[12]UK Dementia Research Institute at Imperial, London UK

Abstract

Background—Cognitive symptoms post-COVID are well-recognized, but it is unclear whether objectively measurable cognitive deficits exist and, if so, how long they persist.

Correspondence to: Adam Hampshire; Paul Elliott.

Correspondence to: Professor Adam Hampshire (for NEJM communications), Burlington Danes Building, Imperial College London, 160 Du Cane Road, London, UK W12 0NN, Phone: +44 (0)20 7594 7993, a.hampshire@imperial.ac.uk or Professor Paul Elliott, School of Public Health, Imperial College London, White City Campus, 80–92 Wood Lane, London, UK W12 0BZ, Tel: +44 20 7594 3328, Fax: +44 20 7262 1034, p.elliott@imperial.ac.uk .

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Methods—Of 800,000 adults from the **RE**al-time **A**ssessment of **C**ommunity **T**ransmission (**REACT**) study in England, 141,583 started (112,964 completed) an online assessment of cognitive function ("Cognitron"). We estimated a global cognitive factor (G) across eight tasks. We hypothesized that people with persistent symptoms (≥12 weeks) post-COVID had objectively measurable global cognitive deficits, and secondarily, that there were executive and memory impairments in such participants, especially those reporting recent poor memory or "brain fog."

Results—In multiple regression (similarly on propensity score matching), recovered mild COVID-19 cases showed small deficits in global cognition relative to uninfected-unconfirmed participants (-0.23SD 95% Confidence Interval (CI), -0.33 to -0.13). Deficits were larger for participants with unresolved persistent symptoms post-COVID (-0.42SD 95% CI, -0.53 to -0.31), infection during Wildtype- or Alpha-variant periods vs. later variant periods (-0.17SD 95% CI, -0.13 to -0.20), and among hospitalized vs. non-hospitalized cases (-0.35SD 95% CI, -0.49 to -0.20). Memory, reasoning and executive tasks were the most sensitive (unresolved persistent symptom group, -0.20SD to -0.33SD) and correlated weakly with recent symptoms including poor memory and "brain fog." No adverse events were reported during this observational study.

Conclusions—Participants with resolved persistent symptoms post-COVID appeared to recover objectively measured cognitive functions to a similar degree as shorter-duration cases, although mild COVID-19 was still associated with small cognitive deficits post-recovery. Longer-term persistence of cognitive deficits and any clinical implications remain uncertain.

So-called "brain fog" and poor memory have been implicated in post-COVID syndromes, leading to suggestions that COVID-19 may have lasting cognitive consequences.[1–7] However, objective data on cognitive performance are largely lacking, and it is unclear how long such deficits might persist, and, if so, which functions are most vulnerable. Our primary study hypothesis was that there are measurable cognitive deficits post-COVID that scale with covariates of illness duration and severity; secondarily we speculated that objective impairments of executive and memory functions would be observable in people with prolonged symptoms, especially poor memory or "brain fog." [8–10] We addressed these hypotheses by analyzing cognitive task performance data[9,11] obtained in the Real-time Assessment of Community Transmission (REACT) cohort in England.[12–14]

Methods

Study Population and Design

SARS-CoV-2 infection in England was tracked in our study cohort from May 1, 2020 to March 31, 2022[12–15] using a randomly selected community sample of 3,099,386 adults (≥18 years); 2,494,309 (80.5%) consented to be recontacted and allow National Health Service (NHS) data linkage. Between August 1 and December 30, 2022 we invited a sub-sample of 800,000 (32.1%) to complete a follow-up survey[7] and cognitive assessment (Supplementary Appendix, Fig. S1, Table S1). Participants were required to have a self-reported test with confirmed or suspected COVID-19 and symptoms persisting ≥12 weeks (n=52,501); a test for SARS-CoV-2 that was positive by polymerase chain reaction (PCR) (n=13,482); unvaccinated status and test positive for SARS-CoV-2 IgG antibodies using an at-home Lateral Flow Immunoassay (LFIA) device (n=85,757);[16] or were selected randomly from the remaining REACT participants (n=648,260).

Cognitive Assessment

Participants undertook eight computerized online tasks from the "Cognitron" battery[11,17] in fixed order on their personal devices. Cognitive domains, implicated in post-COVID syndromes,[9,18–20] were spatial problem solving, semantic reasoning, executive function, crystalized intelligence, impulsivity, working memory, and immediate- and delayed-recognition memory (Fig, S1, Supplementary Methods 1). Each task resulted in a primary accuracy-based score, as well as secondary scores, e.g., response times or error types.

History of SARS-CoV-2 infection and COVID-19

We categorized participants into six SARS-CoV-2 illness-duration groups,[7] excluding N=10,701 with onsets <12 weeks prior to survey completion (illness duration not yet known). Categories 2-6 required a positive PCR or LFIA test or self-report positive test--

No-COVID: uninfected/unconfirmed SARS-CoV-2 infection

Asymptomatic: SARS-CoV-2 infection without symptoms

Resolved short COVID <4 weeks: symptoms resolved within 4 weeks

Resolved short COVID ≥4 to <12 weeks: symptoms resolved within 4-12 weeks

Resolved persistent symptoms post-COVID: symptoms lasted ≥12 weeks

Unresolved persistent symptoms post-COVID: symptoms ≥12 weeks and ongoing.

We estimated infection date from symptom onset or for asymptomatic infections from date of a positive SARS-CoV-2 test.

We used the UK dominant strain at the time of infection to assign variant period: Wildtype, before December 1, 2020; Alpha, December 1, 2020 to April 30, 2021; Delta, May 1, 2021 to December 15, 2021; Omicron, December 16, 2021 onwards.[21] We considered persons vaccinated for COVID-19 if ≥14 days prior to infection. We used NHS data linkage to classify three hospital attendance groups: accident and emergency (A&E), hospital admitted or intensive care unit (ICU).

Statistical Analyses

To assess responder bias, we compared characteristics of people who did or did not access and complete the cognitive assessment.

Data Preprocessing—We used linear regression to adjust task performance scores for age, sex, ethnicity, education, index of multiple-deprivation (quintiles),[7,22] and pre-existing health conditions (Table S2), followed by rank transformation to a normal distribution (N=141,582). We used factor analysis to obtain the global cognitive score (G) from the summary scores for participants who completed all eight tasks (N=112,964).

Test of Primary Hypothesis—Using linear regression, we first examined whether global cognition G differed by infection date in 100-day blocks for single COVID-19 episodes

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(N=58,104). We reran this analysis adjusting for time-varying factors: illness duration and hospital attendance as proxies of severity, variant period and vaccine doses (none, one, >one) ≥14 days pre-infection as potential mediators of severity.

We used multiple linear regression including with stepwise selection (unfixed) to identify covariates and two-way interactions that contributed to explaining G; criteria for inclusion or exclusion of terms (two independent analyses) were based either on frequentist F statistics (add if $p<0.001$, remove if $p>0.1$ for change in sum-of-squared errors), or the Bayesian Information Criteria (add if <0, remove if >0.01); these selected identical terms.

We used propensity score matching[23] (Table S3) to further account for potential confounding. Propensity scores were matched using fixed-widths on the probability scale; widths were adjusted downward until the mean difference in propensity scores between contrasted groups was minimized (<0.1SD) while maximizing retained group sizes.

Tests of Secondary Hypothesis—With terms selected in the stepwise regression, we performed linear regression on individual task summary scores for participants completing all tasks, and at least one task.

We estimated mean differences in G for presence vs. absence of symptoms that were reported as part of the COVID-19 illness (N=56,002), then for recent symptoms that participants associated with their COVID-19 episode in the unresolved persistent symptom group (N=2,580).

We estimated mean differences by specific task among people reporting poor memory or ‘difficulty thinking or concentrating (“brain fog”)’ during the past two weeks for (N=2,580) above; those in whom symptoms had resolved (N=53,422) and the No-COVID group (N=46,261).

We conducted sensitivity analyses by inclusion-exclusion of specified subsets of the sample to evaluate their influence on the results.

Study Oversight and Implementation

Study design: PE, HW, CA and AH. Data collection: REACT team, IPSOS and H2 Cognitive Designs. Analyses: AH using MATLAB version R2022a. First draft: AH and PE, who vouch for the integrity of data and analyses. Editing and decision to publish: all authors. Ethics approval: South Central-Berkshire B Research Ethics Committee (IRAS IDs: 298404, 259978, 283787 and 298724). Joint data controllers: Imperial College London and Department of Health and Social Care. A public advisory panel regularly reviewed study materials, processes and results: https://www.imperial.ac.uk/medicine/research-and-impact/groups/react-study/react_pag/ Views expressed here are the authors’ and do not necessarily reflect those of the funders.

Results

Questionnaire and Cognitive Test Response

Of 276,840/800,000 respondents (34.6%) undertaking the questionnaire, 141,583 (51.1%) started the cognitive battery (at least one task) and 112,964 (79.8%) completed all eight tasks (Fig. S1, Table S4). Compared to the base population (800,000) those doing the cognitive assessment were slightly more likely to be female, of white ethnicity and slightly less likely to be from the youngest age groups or most deprived areas (Table S4a). People reporting poor memory or “brain fog” were slightly more likely to participate across all groups including No-COVID (Table S4b). People recruited with a record of persistent symptoms were more likely to respond (16.6%) than the random sample (14.3%) or those with a positive test in REACT (11.4%), but among responders, there was no differential non-completion by demographics or other variables (Table S4c). Despite these biases, the large sample size means that adequate numbers are available by demographic group (e.g., age, sex, ethnicity, region, deprivation) to provide meaningful data broadly generalizable to those groups (Table S4d).

Primary Analyses

Participants with one COVID-19 episode early in the pandemic showed greater decrements in G ($p<0.001$) than those with later onsets. This association attenuated after adjusting for proxies and mediators of illness severity, although residual performance decrements remained for those infected during the first wave (Fig. 1, Table S5).

We found a downward shift in the distribution of G relative to No-COVID for participants infected during early variant periods (Wildtype and Alpha), with longer illness durations and attending hospital. This resulted in elevated probabilities of scoring below -2 SD (moderately impaired, Table S6).

On multiple regression (Tables S7 and S8), the stepwise procedure selected variant period, illness duration and hospital attendance as covariates explaining variability in G, but no two-way interactions. The largest associations (Fig. 2) were for the unresolved persistent symptom group vs. No-COVID (-0.42SD 95% CI, -0.53 -0.31) and hospital attendance vs. no hospital attendance (e.g., ICU -0.35SD 95% CI, -0.49, -0.20).

When stratified by variant period, relative to No-COVID, illness duration was associated with deficits in G in graded fashion; mean G was lower for unresolved persistent cases (Wildtype - 0.32SD, Alpha -0.33SD, Delta -0.26SD, Omicron -0.16SD) from all variant periods. For short duration resolved cases, G was lower in early (Wildtype -0.12SD, Alpha -0.12SD) but not later (Delta -0.04SD, Omicron 0.020SD) variant periods (Fig. S2, Table S9).

Propensity Score Matching—Grouping participants by illness-duration and variant period then individually propensity score matching each group to No-COVID for demographics, preexisting conditions and recent poor memory or “brain fog” symptoms, produced similar effect-size estimates to the primary regression analyses (Fig. S2, Table S10). When matching hospital attendance groups, additionally controlling for variant period,

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to either No-COVID, or those with SARS-CoV-2 who did not seek medical assistance, also gave similar findings (Table S11). Matching vaccinated with unvaccinated groups for demographics, pre-existing conditions and variant period showed a small cognitive advantage for multiple vaccinations (Table S12) (1 dose=0.08SD, 2+ doses=0.15SD). Matching people who initially had two AstraZeneca vs. two Pfizer vaccines showed a negligible scaled difference in G (Table S12) (-0.07SD). Matching people with repeat vs. single COVID-19 episodes showed a small cognitive disadvantage (-0.11SD), but this attenuated (-0.02SD) when additionally matching for variant period, illness duration and hospital attendance (Table S13).

Secondary Analyses

We observed similar associations to the primary regression model when analyzing individual tasks, both for participants completing all tasks (N=102,263) and those completing at least one task (max N=141,583). Memory, executive function and reasoning showed the largest deficits in the unresolved persistent symptom group; this pattern was similar for hospital attendance, but was disproportionately greater for visuospatial deficits in the ICU group (2D Mental Manipulation, Fig. 3, Table S14).

We found small associations between specific task scores and reporting poor memory or “brain fog” in the past two weeks. In the unresolved persistent symptoms group, decrements in G for people with these symptoms included: Verbal Analogical Reasoning Accuracy (-0.16/-0.20SD), Spatial Working Memory Span (-0.19/-0.15SD) and Immediate Memory Accuracy (-0.16/-0.21SD). The resolved symptoms group showed a similar profile but with smaller effect sizes (-0.003 to -0.14SDs, correlation of absolute effect sizes across tasks: poor memory r=0.81, “brain fog” r=0.76). These associations were all negligible (<0.1SD) for No-COVID (Fig. 4, Table S15, S16).

There were small associations between G and specific symptoms. In all participants >=12 weeks since infection, associations of G with symptoms from their acute COVID-19 episodes included face swelling, leg swelling, numbness/tingling, feet blisters/sores and chest pain, ranging from -0.43SD to -0.24SD (Fig. S3A, Table S17). For unresolved persistent cases, associations of G with recent (past 2 weeks) symptoms included severe fatigue, fever, dizziness, numbness/tingling, poor memory, chest pain, appetite loss and mood swings, ranging from -0.33SD to -0.21SD (Fig. S3B, Table S17).

Sensitivity Analyses

Excluding people who were vaccinated prior to their most severe COVID-19 episode (Table S18); were in the No-COVID group (Table S19); did/did not report poor memory or “brain fog” in the past two weeks (Table S20); or had unknown education level (Table S21), gave similar findings to the primary regression analyses. Treating 6,643 suspected but not confirmed COVID-19 cases as a separate illness-duration category did not materially alter model estimates (Table S22). Adding a covariate for people who sought non-hospital medical assistance showed small cognitive deficits (-0.12SD) (Tables S6 & S11). Stratifying by whether participants completed the whole assessment and evaluating their performance on the first task only (Immediate Memory) showed similar associations (Table S23).

Discussion

In this large community-based study, we found that COVID-19 was associated with longer-term objectively measurable cognitive deficits. The ~-0.2SD difference in global cognition (G) for resolved mild cases vs. the No-COVID group classifies as “small” by Cohen’s effect sizes;[24] this would equate to -3 points on a standard 15-point IQ scale. People with unresolved persistent symptoms had an additional ~-0.2SD mean difference with a downward shift in the distribution. This was most evident at the distribution extreme,[25] giving 2.4 times the probability of performing below the moderately impaired cut-point (-2SD) relative to No-COVID. Being treated in ICU was associated with larger cognitive differences relative to No-COVID (-0.63SD, equivalent to -9 IQ points), and 3.6 times the probability of being below -2SD; this aligns with previous findings of medium-large scale cognitive deficits in critical care cases.[2,26,27]

Multiple findings indicate that the association between COVID-19 and cognitive deficits attenuated as the pandemic progressed. We found milder cognitive deficits for recent variant periods, a small cognitive advantage for those with two or more vaccinations and minimal impact of repeat COVID-19 episodes. Furthermore, the cognitive deficits observed in first-wave infections coincided with peak health service strain and lack of proven effective treatments at that time, while the probability of hospitalization has progressively reduced.[28] That the resolved persistent symptoms group had comparable global cognitive deficits to shorter-duration groups suggests that those with unresolved persistent symptoms may achieve a level of cognitive recovery.[20]

Our assessment comprised tasks designed to measure distinct aspects of cognitive performance that associate with different brain systems.[17] The memory, reasoning and executive tasks were among the most sensitive to COVID-19-related cognitive differences.[9,10,26] Here, performance on these tasks differed with illness severity. It also correlated (albeit weakly) with recent poor memory or “brain fog,” for resolved and unresolved symptoms groups, but not No-COVID, highlighting that while these symptoms are imprecise, they can reflect objectively-measurable deficits. Poorer memory performance was characterized by reduced accuracy at encoding rather than accelerated forgetting, pointing to medial temporal lobe mechanisms, such as hippocampal neurogenesis[29,30] and functional interactions with frontoparietal attentional systems.[31] Coherently, increased medial temporal lobe inflammation,[32,33] accelerated atrophy[30,34] and disturbed functional dynamics have been reported following COVID-19.[35,36]

While previous, often under-powered, studies have offered contradictory evidence for associations between mental health and cognitive deficits post-COVID,[5,37,38] we were powered to detect small associations with high confidence. Our results confirmed associations with mood-swings and fatigue, but also with a variety of other symptoms. Therefore, it is likely that multiple underlying factors contribute to cognitive deficits in post-COVID conditions. This heterogeneity is exemplified by the distinct cross-task profile of impairments in ICU cases, who additionally experience cognitive consequences associated with critical care.[39]

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Contrary to some reports, e.g., from Long COVID clinics,[40] infection during the Delta period was associated with better cognitive performance than Alpha or Wildtype. Delta occurred in a highly vaccinated population; additionally, participants in our study were recruited via community-based random sampling, including more asymptomatic and milder cases than hospital or clinic-based studies, but excluding the most severe cases (e.g., deaths).

This study had certain limitations, which included reliance on subjective reporting to identify people with persistent symptoms. The relationship of our results to the Long COVID literature is complicated due to a lack of established defining criteria for post-COVID syndromes. Consequently, we focused on symptoms persisting ≥12 weeks and did not depend on a diagnosis of Long COVID, which may require clinical assessment (e.g., in Long COVID clinics). In the absence of baseline pre-infection cognitive data, we could not assess cognitive change and the observational nature of the data means we could not infer causality.

Our calculation of G included adjustment of raw performance scores for demographics and pre-existing health conditions. Nonetheless, given the observational nature of the data, it is possible that some residual confounding remained. Consequently, in addition to standard regression analyses, we applied propensity score matching[23] as an alternative approach to address confounding. Our analyses closely matching to selected individuals for potentially confounding variables, e.g., from the No-COVID group, produced a highly-consistent pattern of results.

Any study requiring active participant engagement has a degree of self-selection bias. Here, the most severely impaired may not have been able or willing to undertake a cognitive assessment. Additionally, certain groups including females and those of white ethnicity were slightly over-represented in our sample, while younger people and those from most deprived areas were under-represented; however, the sample size meant that all sectors of society were represented and contributed meaningful data to the findings.

In summary, we found objectively measurable cognitive deficits that may persist for a year or more post-COVID, although participants with persistent symptoms that resolved may expect to recover similar cognitive function to milder cases. Early variant period, longer illness duration and hospital attendance had the strongest associations with global cognitive deficits. The implications of longer-term persistence of cognitive deficits and clinical relevance remain unclear and warrant ongoing surveillance.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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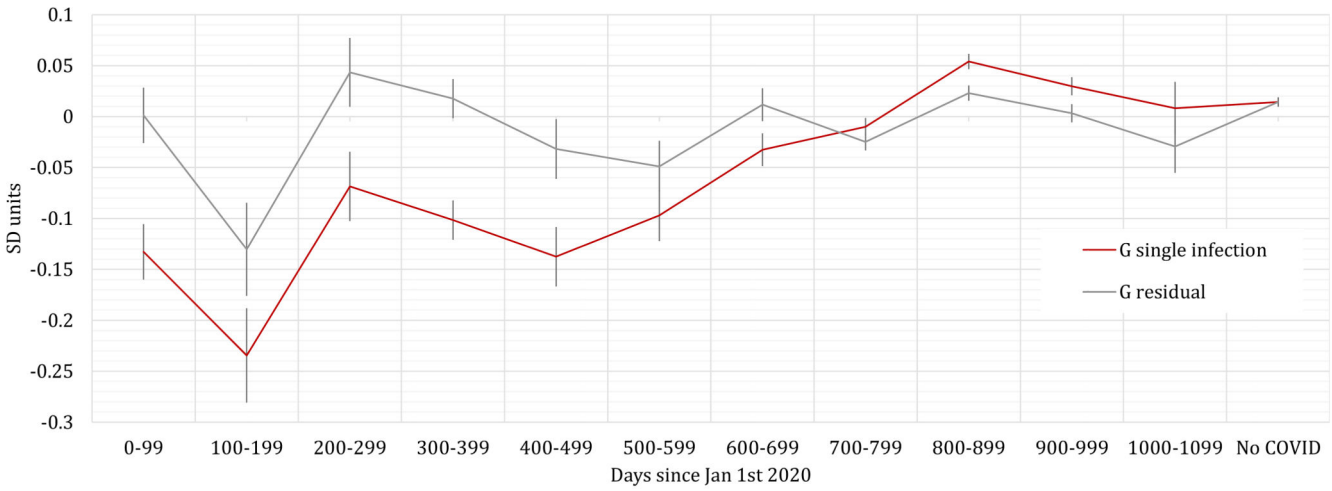

Figure 1. Association of Global Cognitive Scores with Infection Date

Mean global cognitive scores by date of infection for participants with single infections. Red is before and black is after factoring out time-varying covariates that are proxies and likely mediators of COVID-19 severity: illness duration, hospital attendance, SARS-CoV-2 variant period and vaccination status.

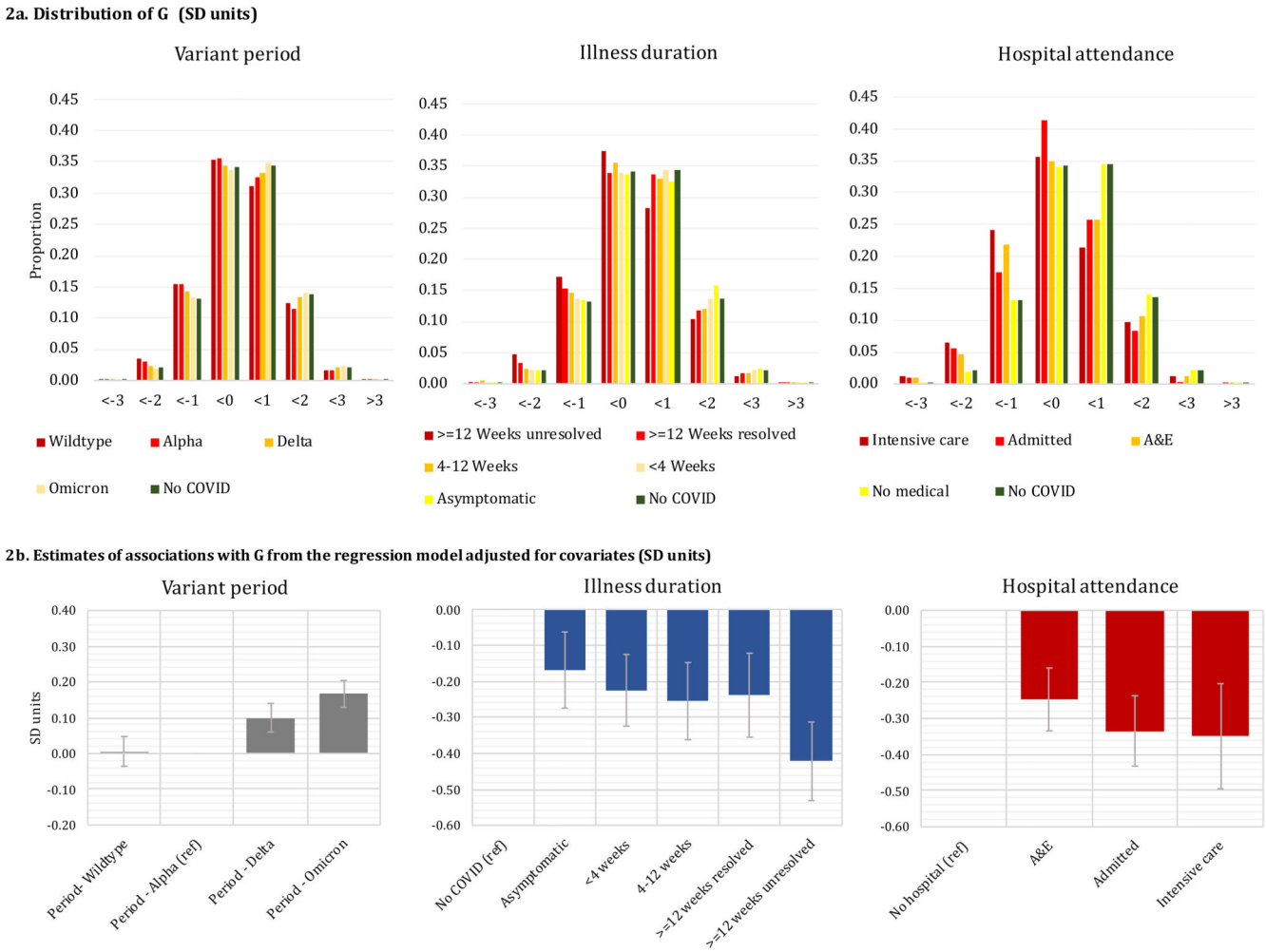

Figure 2. Association of Global Cognitive Score G with SARS-CoV-2 Variant Period, Illness Duration and Hospital Attendance

2a. Probability distributions of G scores within discrete ranges for with SARS-CoV-2 variant period (left), illness duration (middle) and hospital attendance (right). Note compared to the No-COVID group, shift in distributions to left with higher frequency of moderate impairment (<-2SD) and lower frequency of superior performance (>2SD). Distributions are adjusted for age, demographics and pre-existing conditions but not other covariates. **2b** Results of stepwise multiple regression on G adjusted for sociodemographic variables and pre-existing conditions and including all selected covariates simultaneously in the model. Ref=reference category in the model for each displayed covariate. Error bars show the 95% confidence interval. SD Units=standard deviation of global cognitive performance (G), A&E= Accident and Emergency.

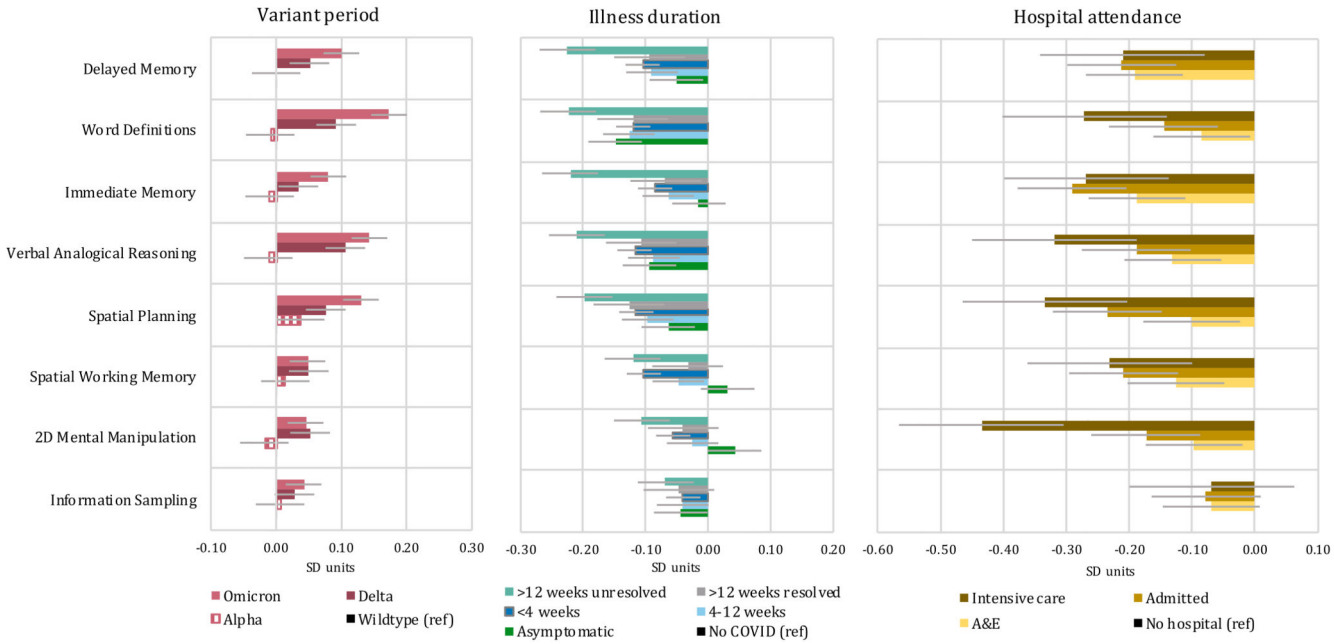

Figure 3. Performance of Specific Tasks in Relation to SARS-CoV-2 Variant Period, Illness Duration and Hospital Attendance

Associations from the multiple regression analyses of individual task summary scores with SARS-CoV-2 variant period (left), illness-duration (middle) and hospital attendance (right) simultaneously. Ref = reference categories for each covariate within the same multiple linear regression model. SD = standard deviation units, A&E= Accident and Emergency. Error bars show the 95% confidence interval. Higher score = better performance.

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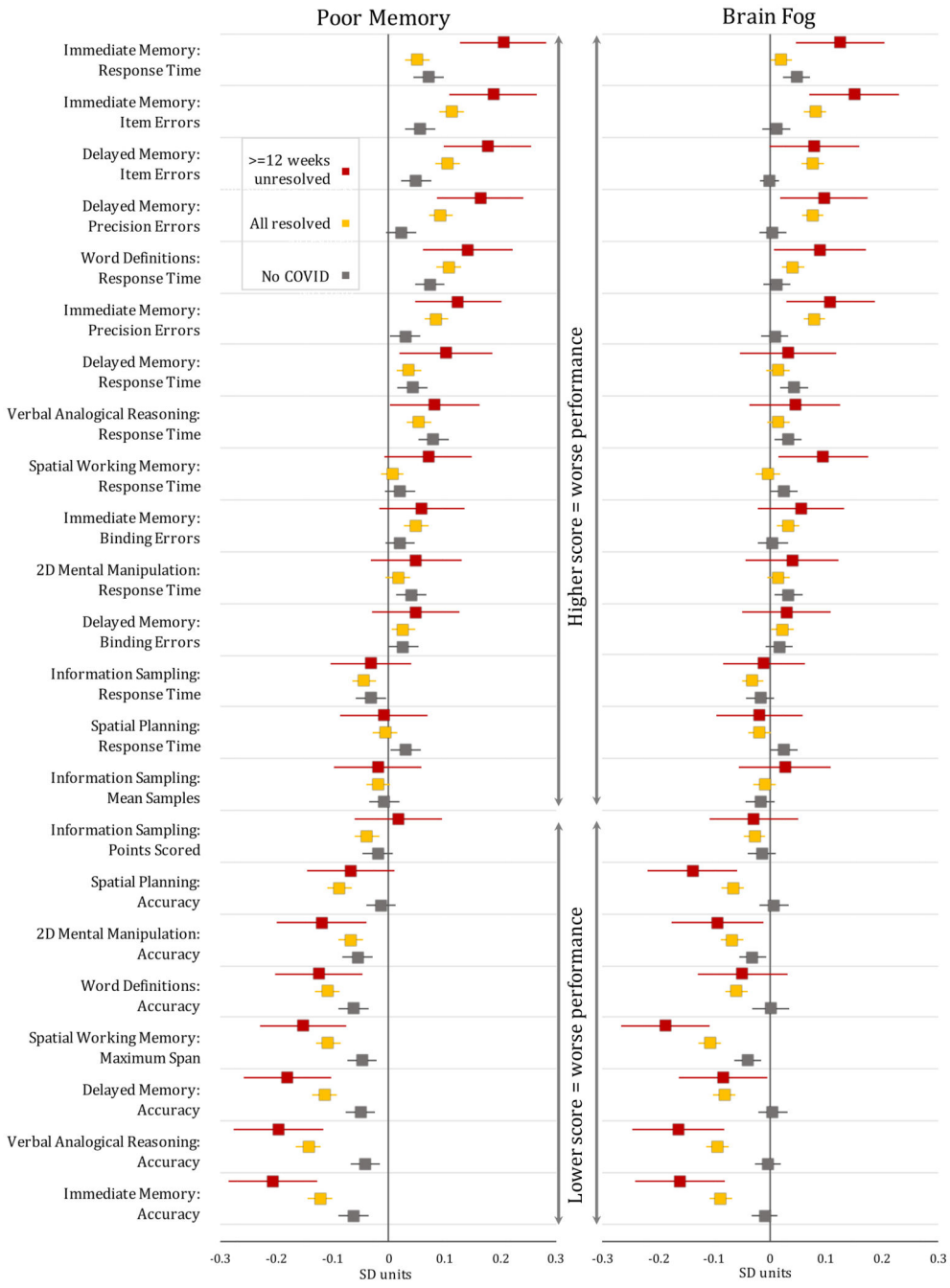

Figure 4. Associations of Subjective and Objectively Measured Cognitive Deficits

Associations of specific cognitive task performance measures with experiencing poor memory or “brain fog” in the past two weeks. Decrements in performance are greater for the unresolved persistent symptoms group, with a similar pattern among those with resolved symptoms. The largest decrements in performance were for persistent symptom cases in the memory (Immediate and Delayed Memory, Spatial Working Memory) reasoning (Verbal

Analogical Reasoning) and executive (Spatial Planning) tasks. SD is standard deviation difference in mean cognitive performance. Error bars report the 95% confidence interval.

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