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Executive deficits after SARS-CoV-2 infection: A cross-sectional population study

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ABSTRACT

Importance: Despite the major implications of executive deficits in day-to-day functioning, few studies have investigated this in post-acute sequelae of SARS-CoV-2 infection using standardized measures that differentiate between aspects of executive function.

Objective: Examine whether SARS-CoV-2 infection is associated with deficits in executive functions and if so, investigate the duration of this association.

Design, Setting, and Participants: The present research has a cross-sectional design and uses data from the Norwegian Covid-19 Cohort study. The current cohort (n = 8102) completed the Behavior Rating Inventory of Executive Function- Adult Version (BRIEF-A) electronically between April 2021 and September 2021. During the assessment, 4183 of the included participants had a prior positive polymerase chain reaction test (PCR) for SARS-CoV-2 and 3919 were untested or had a confirmed negative PCR test.

Exposure: Laboratory-confirmed SARS-CoV-2 infection.

Main outcomes and measures: Executive functions were measured using the BRIEF-A, a self-report questionnaire comprising 75 items within nine theoretically and empirically distinct clinical scales. All participants self-reported on demographical variables and comorbidity. Information on sex and age was derived from the personal identification number, and vaccination status was obtained from the Norwegian Immunization Registry (SYSVAK).

Results: Participants with a positive SARS-CoV-2 status reported executive deficits in everyday life above the clinical threshold (T-score \geq 65) more often than non-infected controls (383 vs. 225). Specifically, the SARS-CoV-2 positive status group indicated significantly more deficits related to metacognition, with the greatest difference demonstrated for working memory. This difference remained when adjusting for various demographic factors and comorbidities, with significantly greater odds of reporting above the clinical threshold following SARS-CoV-2 infection, as observed on the global executive composite score 6–12 months after infection (OR 1.97; 95% CI 1.51 to 2.55).

Conclusions: Our study confirms more perceived executive deficits following SARS-CoV-2 infection compared to non-infected controls, with metacognitive aspects being the most affected. These findings shed light on the potential functional difficulties that individuals may encounter during the post-acute phase of SARS-CoV-2 infection and may guide further development of targeted interventions addressing metacognitive domains of executive functioning.

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1. Introduction

As of February 2024, the World Health Organization (WHO) has reported over 700 million cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and approximately 7 million deaths worldwide (Organization, 2024). Globally, an estimated 400 million patients who recovered from SARS-CoV-2 infection experience persistent symptoms, often referred to as "long COVID" or post-acute sequelae of SARS-CoV-2 (PASC) (Altmann et al., 2023/10). These prolonged symptoms affect day-to-day functioning beyond the initial acute period (Lancet, 2023; Soriano et al., 2022; Thaweethai et al., 2023). Despite numerous studies on PASC, the complexity of its clinical presentation (e.g., heterogeneity within the study population) and limitations in study design have led to inconsistent characterizations (Galderisi et al., 2024). Nonetheless, cognitive impairment is considered one of the most onerous consequences following SARS-CoV-2 infection, characterized primarily by deficits in executive functions (Thaweethai et al., 2023; Perrottelli et al., 2022; Cecchetti et al., 2022/07; Douaud et al., 2022; Davis et al., 2023/03).

Executive functions encompass advanced interrelated cognitive functions or processes responsible for controlling and guiding lowerlevel functions (i.e., by regulating top-down processes of behavior, emotion, and cognition) (Diamond, 2013; Lezak et al., 2012). These functions include self-regulation domains, such as the ability to inhibit prepotent responses, monitor or shift problem-solving strategies, hold information "online" during problem-solving (working memory), initiate behavior, and plan and organize one's behavior. Importantly, executive functions are not only limited to cognition but are also involved in emotionally and behaviorally mediated aspects of control (Miyake et al., 2000). Executive functions are critical to nearly all aspects of an individual's everyday functioning, including professional environments and social relationships, and long-term implications of executive deficits can be devasting.¹¹Thus, it is urgent to identify which aspects of executive functions that are predominately affected in the post-acute phase of infection.

Although cognitive deficits, including executive deficits, have been described as one of the most frequent features of PASC, (Hampshire et al., 2024; Ellingjord-Dale et al., 2024; Becker et al., 2023/11) assessing executive functions poses a major challenge due to its multidimensional and dynamic nature (Lezak et al., 2012). Thus, most studies that have identified executive deficits following SARS-CoV-2 infection have relied on suboptimal assessment methods, including coarse dementia screeners and concise self-report measures not differentiating between the various components of executive function (Crivelli et al., 2022). Consequently, the estimated prevalence of executive deficits following SARS-CoV-2 infection has varied significantly due to the between-study heterogeneity regarding the methods and assessments, ranging from 6% to 80% (Galderisi et al., 2024; Becker et al., 2023/11). Yet, there is a lack of in-depth characterization and ecologically valid assessment of executive deficits, encompassing various aspects of executive functions, in individuals with confirmed SARS-CoV-2 infection.

The present study investigates executive deficits following SARS-CoV-2 infection by utilizing the gold standard of self-reports for assessing executive functioning in daily life, the Behavior Rating Inventory of Executive Function- Adult Version (BRIEF-A¹⁸). In contrast to the highly structured test environment, the BRIEF-A is ecologically valid. This term refers to how accurately test performance reflects real-world functioning, and therefore, BRIEF-A provides enhanced prognostic value to everyday functioning (Bulzacka et al., 2013; Franzen and Wilhelm, 1996). A clear advantage of the BRIEF-A is its ability to measure executive deficits across various patient populations and is therefore expected to capture potential alterations following SARS-CoV-2 infection (Roth et al., 2005; Løvstad et al., 2016). The current study aims to describe executive deficits following SARS-CoV-2 infection. We also aim to clarify the association between SARS-CoV-2 infection and executive deficits, as well as investigate the duration of

this association.

2. Methods

This cross-sectional study was approved by the Regional Research Ethics Committee (REK 124170) as part of the Norwegian COVID-19 Cohort study (clinical.trials.gov identifier: NTC04320732). Results are reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies (von Elm et al., 2007).

2.1. Study design and participants

The Norwegian COVID-19 Cohort Study began recruiting participants across Norway using social media, personal invitations, and media coverage starting March 27, 2020 (Søraas et al., 2021). Eligible participants signed an online consent form. In April 2021, BRIEF-A was distributed to a subset of the main cohort, comprising 14,039 individuals. Of this subset, 50% had a confirmed positive result for SARS-CoV-2 via real-time polymerase chain reaction (rt-PCR) tests, as recorded in the Norwegian Surveillance System for Communicable Diseases. The remaining participants tested negative or had not been tested at the time. The BRIEF-A questionnaires were completed from April 27, 2021, to September 29, 2021. Out of those invited, 9218 (66%) participants responded. Among the 9218 respondents in the subsample, 1116 were excluded before analysis due to incomplete BRIEF-A submissions (n = 658), age ineligibility (n = 2), or exceeding the standardized threshold for the BRIEF-A validity scales (n = 456) (Roth et al., 2005) (Fig. 1).

3. Measures

3.1. Demographics and comorbidity

All participants self-reported their highest level of education attained, ethnicity, and comorbid chronic disorders. Comorbidity was evaluated by self-reports of one, two, or more than three chronic conditions, including heart disease, hypertension, lung disease, asthma, diabetes, and cancer, among others, or by past treatment with immunosuppressants. Information on sex and age was derived from the personal identification number.

3.2. Executive functions

Daily-life executive functions were measured using BRIEF-A, a 75item standardized questionnaire. The participants rated how often they have considered certain behaviors posing a problem to them during the past six months on a three-point Likert scale (never = 1; sometimes = 2; or often = 3). The BRIEF-A questionnaire yields a Global Executive Composite (GEC) score in addition to two Composite Index scores, the Behavioral Regulation Index (BRI, subscales Inhibit, Shift, Emotional Control and Self-Monitor), and the Metacognition Index (MI, subscales Initiate, Working Memory, Plan/Organize, Task Monitor and Organization of Materials). For instance, within MI, 8 items make up the subscale of Working memory. An example of an item developed to capture perceived on-line representational memory is "I forget instructions easily".

Raw scores were transformed into age-corrected *T*-scores (M = 50; SD = 10) based on the United States' normative data. The clinical cutoff score is $T \ge 65$, and the recommended cutoff values for the validity scales are Negativity >6, Infrequency >3, and Inconsistency >8 (Roth et al., 2005). Participants with more than one validity scale above the cutoff values were excluded (Roth et al., 2005). BRIEF-A has excellent psychometric properties with one-month test-retest reliability of 0.82–0.93 for all subscales (Roth et al., 2005; Waid-Ebbs et al., 2012). In the present study, Cronbach's alfa at baseline was 0.92 for GEC.

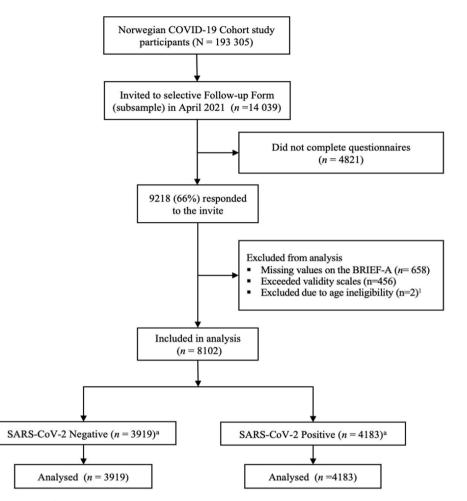


Fig. 1. Flow Diagram. ¹According to the BRIEF-A conversion table in the BRIEF-A professional manual (Roth et al., 2005).

3.3. SARS-CoV-2 status

Positive SARS-CoV-2 status required a confirmed positive real-time polymerase chain reaction (rt-PCR) test in any accredited Norwegian clinical microbiology laboratory before completing BRIEF-A (Brunvoll et al., 2023). The data was obtained from the Norwegian Health Register 'MSIS' (Reporting System for Infectious Diseases). Non-infected controls include those who were registered with a confirmed negative PCR test or were untested when the BRIEF-A was administered. Vaccination status was obtained from the Norwegian Immunization Registry (SYSVAK).

3.4. Statistical analysis

The gathered data was described using mean and standard deviations (SD) for continuous variables and with counts and percentages for categorical variables. Independent sample t-tests were applied for continuous variables and the Chi-Square test for categorical variables to investigate differences in demographical characteristics and comorbidity between participants with a confirmed history of SARS-CoV-2 and non-infected controls. For our primary adjusted analyses, we used 12 logistic regressions to estimate the association between SARS-CoV-2 status and executive deficits in each domain of BRIEF-A (GEC, BRI, MI, and all subscales). The exposure was a combination of COVID-19 vaccination status and time from acute SARS-CoV-2 infection. The reference level was never testing positive for SARS-CoV-2 regardless of vaccination status, the other category levels were not vaccinated before infection which occurred 0-90 days, 91-182 days, 183-365 days, 366 days, and vaccinated before positive SARS-CoV-2 test. The regression models were adjusted for age, sex, education level, and comorbidities.

Linear regression models were also used to estimate risk differences in each BRIEF-A domain, controlling for the same covariates as described. In secondary analyses, we compared unadjusted odds of executive deficits in participants with a confirmed history of SARS-CoV-2 vs. controls. The primary analyses were run in 20 imputed datasets, which were created using multivariate imputation by chained equations (van Buuren and Groothuis-Oudshoorn, 2011). A complete case analysis was also run as a sensitivity analysis. To investigate potential selection bias, an additional sensitivity analysis was performed where the primary analysis was rerun in two strata: (1) people who were vaccinated before 2021-07-01 and (2) people who were not vaccinated before 2021-07-01. All statistical analyses were performed using R Statistical Software (version 4.2.2 R Foundation for Statistical Computing, Vienna, Austria) using two-sided p-values and a 0.05 significance level.

4. Results

The demographic characteristics of our final sample of 8102 participants (4183 with a positive SARS-CoV-2 status and 3919 non-infected controls) are outlined in Table 1. In terms of sex and highest level of education attained, the non-infected controls were numerically similar to the participants with positive SARS-CoV-2 status, however, chisquared tests were significant likely due to large sample sizes. The positive SARS-CoV-2 participants reported fewer chronic comorbidities than non-infected controls. Overall, most participants were women (66%) and of European ethnicity (96%–98%). Age ranged from 18 to 90 years (Table 1).

Table 1

Demographics of the study sample.

Characteristics	Total (N = 8102) ^a	Non-infected controls (n = 3919) ^a	Positive SARS-CoV-2 status (n = 4183) ^a	p- value ^{c b}
0			4103)	
Sex Female	5310 (66)	2568 (66)	2742 (66)	>0.9
Male	2792 (34)	1351 (34)	1441 (34)	
Age	(0.1)			< 0.001
Mean (SD)	49(14)	51 (14)	46 (13)	< 0.001
18–29	779 (9.6)	259 (6.6)	520 (12)	
30–39	1475 (18)	645 (16)	830 (20)	
40–49	1903 (23)	866 (22)	1037 (25)	
50–59	2099 (26)	996 (25)	1103 (26)	
60–69	1268 (16)	742 (19)	526 (13)	
70–79	526 (6.5)	370 (9.4)	156 (3.7)	
80–90	(0.3) 52 (0.6)	41 (1)	11 (0.3)	
Highest level of education attained	8085	11 (17	11 (0.0)	< 0.001
Primary and/or lower secondary school (7–10 yrs)	268 (3.3)	158 (4.0)	110 (2.6)	
Upper secondary school (12 yrs)	1557 (19)	764 (20)	793 (19)	
Higher education	6235 (77)	2984 (76)	3251 (78)	
Other	25 (0.3)	6 (0.2)	19 (0.5)	
Missing	17	7	10	
Ethnicity	7977			< 0.001
European	7727 (97)	3806 (98)	3921 (96)	
Asian	145 (1.8)	37 (1.0)	108 (2.6)	
African	30 (0.4)	4 (0.1)	26 (0.6)	
Other	75 (0.9)	33 (0.9)	42 (1.0)	
Missing Comorbid chronic disorders ^b	125 7698	39	86	<0.001
None	5540	2652 (70)	2888 (74)	
One	(72) 1709	877 (23)	832 (21)	
Two	(22) 365 (4.7)	202 (5.3)	163 (4.2)	
Three or more chronic comorbidities	(4.7) 84 (1.1)	58 (1.5)	26 (0.7)	
Missing Time since SARS-CoV-2	405	130	274	< 0.001
infection prior to completing the BRIEF-A				<0.001
Non-infected controls	3919	3919 (100)	-	
0-90 days	(48) 532	-	532 (13)	
91–182 days	(6.6) 1470	-	1470 (35)	
102 26E dama	(18)		800 (10)	
183–365 days =>366 days	809 (10) 1264 (16)	-	809 (19) 1264 (30)	
Vaccinated prior to	(16) 108	_	108 (2.6)	
SARS-CoV-2 infection	(1.3)		100 (2.0)	
Vaccination prior to completing the BRIEF-A	3185 (39)	1646 (42)	1539 (37)	<0.001

^a n (%).

^b One or more of these chronic conditions: heart disease, hypertension, lung disease, asthma, diabetes, cancer, and others, or treated with immunosuppressants.

^c Pearson's Chi-squared test; Wilcoxon rank sum test.

4.1. Group differences across BRIEF-A

Overall, the mean T-scores were in the range of 44-54 across all indexes and subscales for the SARS-CoV-2 positive and non-infected controls, which is below the recommended clinical cutoff score of T >65 (Roth and Gioia, 2005) (eTable 1 in Supplement 1). When comparing the proportion of participants scoring above the clinical cutoff, there were significantly more participants with clinically elevated scores in the positive SARS-CoV-2 status group across all scales (Fig. 2; eTable 2 in Supplement 1). Specifically, 383 participants (9.2%) in the SARS-CoV-2 positive status group reported a clinically elevated Global Executive Composite (GEC) score, as opposed to 225 (5.7%) in the non-infected group. The greatest difference is observed for the Metacognitive Index with 503 (12%) scoring in the clinical range in the positive group, compared to 282 (7.2%) in the non-infected group. Within the Metacognitive Index (MI), the Working memory subscale displays the greatest difference with 784 (19%) reporting in the clinical range in the positive group, compared to 420 (11%) for non-infected controls. Additionally, for the initiate subscale, a significantly higher proportion of SARS-CoV-2 positive participants report difficulties in the clinical range (699; 17%), compared to the non-infected group (446; 11%) (Fig. 2; eTable 2 in Supplement 1).

4.2. Executive deficits following SARS-CoV-2 infection

Participants with a positive SARS-CoV-2 status displayed higher odds of reporting clinically relevant executive deficits than the non-infected controls when adjusting for age, sex, education and comorbidities. The exposure was a combination of days since SARS-CoV-2 infection and vaccination status before SARS-CoV-2 infection.

The statistically significant deficits in executive functions following SARS-CoV-2 infection are numerically largest between six months and a year following infection with an odds ratio [OR] of 1.97; [95% CI = 1.51, 2.55] for GEC. During the same period, positive SARS-CoV-2 participants displayed greater odds of reporting impaired ability to regulate behavior and emotional responses as opposed to non-infected controls (BRI, OR: 2.10; 95% CI: 1.55, 2.85), with the highest odds ratio observed for the self-monitoring subscale (OR: 2.38; 95% CI: 1.62, 3.49). Yet, metacognition was the predominantly affected domain (MI, odds ratio [OR]: 2.03; 95% confidence interval [CI]: 1.60, 2.57). Within MI, working memory displayed the greatest odds ratio [OR]: 2.14; 95% confidence interval [CI]: 1.75, 2.62 (Fig. 3).

The statistically significant increase in absolute risk of reporting executive difficulties following SARS-CoV-2 infection is numerically the highest between six months to one year after infection when compared to non-infected controls. In this period, the risk of reporting executive deficits is 5 percentage points higher (GEC, [RD]: 0.05; 95% [CI]: 0.03, 0.07; eTable 5 in Supplement 1). The absolute risk of reporting meta-cognitive difficulties is 6 percentage points higher at six months to a year after infection (MI, [RD]: 0.06; 95% [CI]: 0.04, 0.09), as opposed to 4 percentage points on executive components related to behavioral regulation (BRI, [RD]: 0.04; 95% confidence interval [CI]: 0.02, 0.06; eTable 5 in Supplement 1).

From a temporal perspective, the risk of reporting deficits in executive functioning increases after the acute phase of SARS-CoV-2 infection. For GEC, immediately after 90 days following infection, the risk difference is 2 percentage points and increases to 3 percentage points between 91 and 182 days after infection. From six months to one year after infection, the risk difference is 5 percentage points; after the first year has passed, it drops down to 2 percentage points. Infection after vaccination did not significantly differ from the reference group (eTable 5 in Supplement 1). The complete case analysis presented similar associations to the imputed analysis (Fig. 3 and eTable 3 in

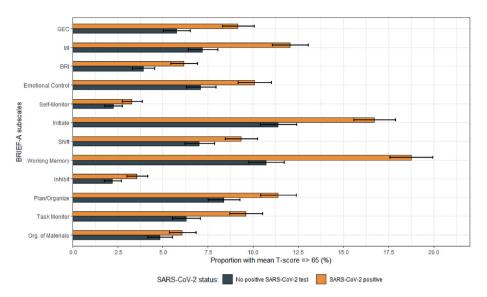


Fig. 2. Proportion (%) of participants scoring above the clinical cut-off on BRIEF-A.

Supplement 1). Stratified analyses run within early vaccinated people (eTable 4 in Supplement 1) and within non-early vaccinated people (eTable 4 in Supplement 1) gave similar associations to the imputed analyses (Fig. 3).

5. Discussion

The present study investigated executive functions utilizing BRIEF-A in a large, population-based cohort of participants with confirmed SARS-CoV-2 infection and non-infected controls. Our study shows that (1) the frequency of executive deficits is significantly higher in SARS-CoV-2 infected participants than in non-infected controls, especially with regard to working memory and the ability to initiate (metacognitive components of executive function); (2) deficits within the metacognitive domain are associated with COVID-19 and the association displays changes over time since initial SARS-CoV-2 infection.

The between-group differences in the extent of executive deficits do not become evident until the cut-off scores are applied ($T > 65^{18}$). These findings are consistent with previous research implying that most patients recover from COVID-19 and return to their baseline state of functioning following the acute phase of SARS-CoV-2 infection (Davis et al., 2023/03). Still, the lack of major group differences on mean T-scores suggests that it is necessary to utilize the BRIEF-A cut-off scores to detect those who develop clinical and treatment-demanding executive deficits following SARS-CoV-2 infection. Here, the SARS-CoV-2 positive group displayed more frequent clinically relevant executive deficits across all aspects of executive functioning captured by the BRIEF-A, with the highest frequency observed in the metacognitive domain, indicating that particularly difficulties with the ability to initiate, plan, and cognitively self-manage tasks and monitor performance, in addition to online representational memory, characterize executive deficits following SARS-CoV-2 infection. These findings are in line with previous research on executive deficits following SARS-CoV-2 infection, but also on previous research on post-viral cognitive sequela (Becker et al., 2023/11; Øie et al., 2022).

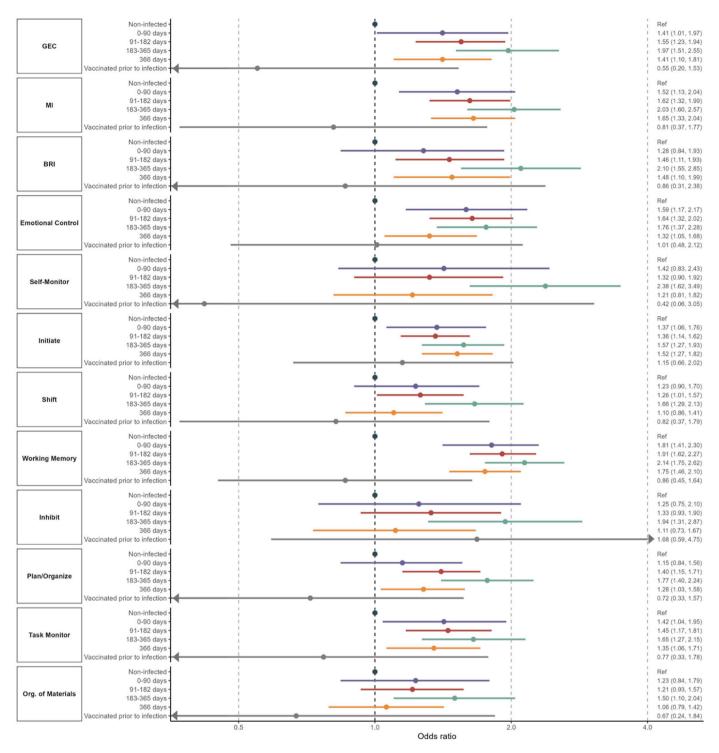
In the post-acute phase of COVID-19 (>3 months after initial SARS-CoV-2 infection) (Organization, 2024), various factors are associated with a higher risk of developing persisting symptoms, including sex, age, education, socioeconomic status, pre-existing mental health conditions, as well as initial SARS-CoV-2 symptoms and psychosocial stress due to global lockdown (Davis et al., 2023/03; Cavaco et al., 2023; Schulte-braucks et al., 2023/04; Subramanian et al., 2022/08; Whitaker et al., 2022/04; Zeng et al., 2023/01; Selvakumar et al., 2023; Rai et al., 2023/01; Selvakumar et al., 2023; Rai et al.,

2022). However, the direction of associations has been inconsistent, for instance, the association between initial SARS-CoV-2 symptoms and later manifestation of cognitive impairment and executive deficits have been found across all initial symptom severities, ranging from mild to severe cases during the acute phase of COVID-19 (Becker et al., 2021; Hall et al., 2022/05; Hampshire et al., 2021/09; Jaeger, 2018; Jaywant et al., 2021/12; Ariza et al., 2023). Comorbidities, including fatigue and mental health conditions, have also been found to not account for the extent of cognitive deficits in the post-acute phase of SARS-CoV-2 (Zhao et al., 2024).

In the present study, the participants with a history of SARS-CoV-2 infection displayed an increased risk of COVID-19-associated executive deficits even after adjusting for potential confounders, similar to previous research (Ellingjord-Dale et al., 2024; Becker et al., 2023; Hall et al., 2022). Moreover, in our study sample, COVID-19-associated executive deficits became more pronounced 3 months to a year after SARS-CoV-2 infection. As such, executive deficits may not follow the characteristic course of other acute SARS-CoV-2 symptoms (e.g., fever, cough, shortness of breath, muscle or body aches, headache, fatigue) with elevated symptom load in the acute phase with subsequent significant improvements observed over time (Cheetham et al., 2023). Our findings of a temporal increase in executive deficits accord with previous research (Davis et al., 2023/03). It is possible that these deficits do not peak until after six months to a year post-infection due to the time needed to experience and become self-aware of potential alterations in one's day-to-day functioning. However, the temporal increase may also be a result of different viral strains. Moreover, recent research findings have similarly illustrated that perceived memory function may worsen, persisting up to 36 months following infection (Ellingjord-Dale et al., 2024).

It is not possible to draw definitive conclusions about the impact of vaccination from this study due to the limited power of our analyses (i. e., small sample size of participants who were vaccinated before contracting SARS-CoV-2). Prior research has indicated that vaccination only provides partial protection in the post-acute phase of COVID-19 and may not by itself optimally reduce prolonged health implications, including executive deficits (Al-Aly et al., 2022/07).

A strength of the current study is the use of a robust, standardized measurement to assess the multidimensional construct of executive function following SARS-CoV-2 infection. The current study also provides data on the BRIEF-A in a large, population-based sample, and to our knowledge, the largest non-US population-based comparison group to date. Available normative data on the BRIEF-A is based on and limited



Time since SARS-CoV-2: 🔶 366 days 🔶 183-365 days 🔶 91-182 days 🔶 0-90 days 🔶 Non-infected

Fig. 3. Adjusted odds ratios of executive deficits above the clinical cutoff ($T \ge 65$) in positive SARS-CoV-2 status group vs. non-infected controls.

to US validation data with a normative mean of T = 50 and a clinical cutoff score of T = 65. Previous studies using healthy controls have indicated the US norms underestimate the level of executive deficits in Norway (Løvstad et al., 2016). However, healthy comparison groups may not represent the variations observed in the general population (Kukull and Ganguli, 2012). The current study has a mean *T*-score of 47.4 for the participants with a negative SARS-CoV-2 status, indicating that when using a population-based comparison group instead of a highly selected healthy comparison group, the threshold based on US

normative data may be more adequate across cultural contexts than first anticipated.

6. Limitations

A limitation of the current study is its cross-sectional design, which does not allow for causal inferences or conclusions regarding the temporal trajectories of executive deficits following SARS-CoV-2 infection. Future studies may consider alternative approaches such as longitudinal

S. Buer et al.

studies that track changes over time to investigate temporal relationships. We also recommend future studies to consider investigating fatigue and mental health conditions as potential effect modifiers and whether COVID-19 associated fatigue is a mediating factor for executive deficits. Another limitation of the current study is that we were not able to investigate the effect of different virus variants on executive deficits due to the limited date range of the proportion of the sample size testing positive for SARS-CoV-2 in the current sample.

Furthermore, BRIEF-A is not by itself a diagnostic tool and to provide a more comprehensive executive function assessment in clinical and research settings other sources of information (e.g., clinical interviews, informants, and performance-based neuropsychological tests measuring executive functions) should also be included. Additionally, potential biases may interfere with and impact response style (e.g., contextual factors, the extent of self-awareness, psychological distress, and notably, the knowledge of having had COVID-19), which also can skew responses in self-reported measures (Løvstad et al., 2016). When relying on self-report instruments for assessing post-COVID-19 cognitive dysfunction, it is important to emphasize the fact that the correspondence between self-report and performance-based measures of cognition, and in particular executive function, is typically low (Becker et al., 2023). This discrepancy can be attributed to the properties of the measure applied (Hagen et al., 2023), and it has been suggested that self-report typically measures success or goal pursuit in daily life, while assess efficiency performance-based tests in structured optimal-performance settings (Orfei et al., 2022; Toplak et al., 2013).

7. Conclusion

The findings of this study include robust associations between SARS-CoV-2 infection and working memory impairment, specifically online representational memory, alongside novel associations with other metacognitive executive functions critical to manage daily life, such as the ability to initiate, plan, and monitor performance. An implication of this may be to increase the awareness in public health of executive dysfunction for individuals recovering from SARS-CoV-2 infection. Future studies should investigate the efficacy of a standardized cognitive rehabilitation intervention, specifically targeting the metacognitive aspects of executive function after SARS-CoV-2 infection. Moreover, BRIEF-A does appear to be a sensitive instrument for capturing executive function deficits post- SARS-CoV-2 infection and may be recommended as part of a broader assessment of executive deficits in further clinical and research settings.

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Role of the funder/sponsor

The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

CRediT authorship contribution statement

S. Buer: Writing – review & editing, Writing – original draft, Visualization, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **B.I. Hagen:** Writing – review & editing, Supervision, Methodology, Conceptualization. **A. Søraas:** Writing – review & editing, Validation, Supervision, Project administration, Funding acquisition, Data curation. **R.A. White:** Writing – review & editing, Visualization, Validation, Methodology,

Formal analysis. R. Bø: Writing – review & editing, Methodology, Conceptualization. M. Ellingjord-Dale: Writing - review & editing, Resources, Project administration, Data curation. M.S. Istre: Writing review & editing, Project administration, Data curation. S.H. Brunvoll: Writing - review & editing, Project administration, Data curation. A. Lerdal: Writing - review & editing, Resources. N.I. Landrø: Writing review & editing, Methodology, Conceptualization. A.B. Nygaard: Writing - review & editing, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. J. Stubberud: Writing - review & editing, Supervision, Resources, Project adminis-Methodology, tration. Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

Dr. Søraas reported being an employee and shareholder at Age Labs outside of the submitted work. No other disclosures were reported.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2024.100857.

References

- Al-Aly, Z., Bowe, B., Xie, Y., 2022. Long COVID after breakthrough SARS-CoV-2 infection. Nat. Med. 28 (7), 1461–1467. https://doi.org/10.1038/s41591-022-01840-0.
- Altmann, D.M., Whettlock, E.M., Liu, S., Arachchillage, D.J., Boyton, R.J., 2023. The immunology of long COVID. Nat. Rev. Immunol. 23 (10), 618–634. https://doi.org/ 10.1038/s41577-023-00904-7.
- Ariza, M., Cano, N., Segura, B., et al., 2023. COVID-19 severity is related to poor executive function in people with post-COVID conditions. J. Neurol. 270 (5), 2392–2408. https://doi.org/10.1007/s00415-023-11587-4.
- Becker, J.H., Lin, J.J., Doernberg, M., et al., 2021. Assessment of cognitive function in patients after COVID-19 infection. JAMA Netw. Open 4 (10), e2130645. https://doi. org/10.1001/jamanetworkopen.2021.30645.
- Becker, Vannorsdall, T.D., Weisenbach, S.L., 2023. Evaluation of post–COVID-19 cognitive dysfunction: recommendations for researchers. JAMA Psychiatr. https:// doi.org/10.1001/jamapsychiatry.2023.2820.
- Becker, Lin JJ., Twumasi, A., et al., 2023. Greater executive dysfunction in patients post-COVID-19 compared to those not infected. Brain Behav. Immun. 114, 111–117. https://doi.org/10.1016/j.bbi.2023.08.014.
- Brunvoll, S.H., Nygaard, A.B., Fagerland, M.W., et al., 2023. Post-acute symptoms 3-15 months after COVID-19 among unvaccinated and vaccinated individuals with a breakthrough infection. Int. J. Infect. Dis. 126, 10–13. https://doi.org/10.1016/j. ijid.2022.11.009.
- Bulzacka, E., Vilain, J., Schürhoff, F., Méary, A., Leboyer, M., Szöke, A., 2013. A self administered executive functions ecological questionnaire (the behavior rating inventory of executive function - adult version) shows impaired scores in a sample of patients with schizophrenia. Ment. Illness 5 (1), e4. https://doi.org/10.4081/ mi.2013.e4.
- Cavaco, S., Sousa, G., Gonçalves, A., et al., 2023. Predictors of cognitive dysfunction oneyear post COVID-19. Neuropsychology. https://doi.org/10.1037/neu0000876.
- Cecchetti, G., Agosta, F., Canu, E., et al., 2022. Cognitive, EEG, and MRI features of COVID-19 survivors: a 10-month study. J. Neurol. 269 (7), 3400–3412. https://doi. org/10.1007/s00415-022-11047-5.
- Cheetham, N.J., Penfold, R., Giunchiglia, V., et al., 2023. The effects of COVID-19 on cognitive performance in a community-based cohort: a COVID symptom study biobank prospective cohort study. EClinicalMedicine 62, 102086. https://doi.org/ 10.1016/j.eclinm.2023.102086.
- Crivelli, L., Palmer, K., Calandri, I., et al., 2022. Changes in cognitive functioning after COVID-19: a systematic review and meta-analysis. Alzheimers Dement 18 (5), 1047–1066. https://doi.org/10.1002/alz.12644.
- Davis, H.E., McCorkell, L., Vogel, J.M., Topol, E.J., 2023. Long COVID: major findings, mechanisms and recommendations. Nat. Rev. Microbiol. 21 (3), 133–146. https:// doi.org/10.1038/s41579-022-00846-2.

- Diamond, 2013. Executive functions. Annu. Rev. Psychol. 64, 135–168. https://doi.org/ 10.1146/annurev-psych-113011-143750.
- Douaud, G., Lee, S., Alfaro-Almagro, F., et al., 2022. SARS-CoV-2 is associated with changes in brain structure in UK Biobank. medRxiv. https://doi.org/10.1101/ 2021.06.11.21258690, 2021.06.11.21258690.
- Ellingjord-Dale, M., Brunvoll, S.H., Søraas, A., 2024. Prospective memory assessment before and after covid-19. N. Engl. J. Med. 390 (9), 863–865. https://doi.org/ 10.1056/NEJMc2311200.
- Franzen, M.D., Wilhelm, K.L., 1996. Conceptual Foundations of Ecological Validity in Neuropsychological Assessment. *Ecological Validity of Neuropsychological Testing*. Gr Press/St Lucie Press, Inc, pp. 91–112.
- Galderisi, S., Perrottelli, A., Giuliani, L., et al., 2024. Cognitive impairment after recovery from COVID-19: frequency, profile, and relationships with clinical and laboratory indices. Eur. Neuropsychopharmacol 79, 22–31. https://doi.org/10.1016/j. euroneuro.2023.11.001, 2024/02/01/.
- Hagen, B., Landrø, N.I., Hoorelbeke, K., Lau, B., Stubberud, J., 2023. Characteristics associated with the discrepancy between subjective and objective executive functioning in depression. Appl. Neuropsychol Adult. 30 (5), 567–576. https://doi. org/10.1080/23279095.2021.1969398.
- Hall, P.A., Meng, G., Hudson, A., et al., 2022. Cognitive function following SARS-CoV-2 infection in a population-representative Canadian sample. Brain Behav. Immun. Health 21, 100454. https://doi.org/10.1016/j.bbih.2022.100454.
- Hall, P.A., Meng, G., Hudson, A., et al., 2022. Cognitive function following SARS-CoV-2 infection in a population-representative Canadian sample. Brain, Behavior, & Immunity - Health 21, 100454. https://doi.org/10.1016/j.bbih.2022.100454.
- Hampshire, A., Trender, W., Chamberlain, S.R., et al., 2021. Cognitive deficits in people who have recovered from COVID-19. EClinicalMedicine 39, 101044. https://doi. org/10.1016/j.eclinm.2021.101044.
- Hampshire, A., Azor, A., Atchison, C., et al., 2024. Cognition and memory after covid-19 in a large community sample. N. Engl. J. Med. 390 (9), 806–818. https://doi.org/ 10.1056/NEJM0a2311330.
- Jaeger, J., 2018. Digit symbol substitution test: the case for sensitivity over specificity in neuropsychological testing. J. Clin. Psychopharmacol. 38 (5), 513–519. https://doi. org/10.1097/jcp.00000000000941.
- Jaywant, A., Vanderlind, W.M., Alexopoulos, G.S., Fridman, C.B., Perlis, R.H., Gunning, F.M., 2021. Frequency and profile of objective cognitive deficits in hospitalized patients recovering from COVID-19. Neuropsychopharmacology 46 (13), 2235–2240. https://doi.org/10.1038/s41386-021-00978-8.
- Kukull, W.A., Ganguli, M., 2012. Generalizability: the trees, the forest, and the lowhanging fruit. Neurology 78 (23), 1886–1891. https://doi.org/10.1212/ WNL.0b013e318258f812.
- Lancet, T., 2023. Long COVID: 3 years in. Lancet 401 (10379), 795. https://doi.org/ 10.1016/S0140-6736(23)00493-2.
- Lezak, M.D., Howieson, D.B., Bigler, E.D., Tranel, D., 2012. Neuropsychological Assessment. OUP, USA.
- Løvstad, M., Sigurdardottir, S., Andersson, S., et al., 2016. Behavior rating inventory of executive function adult version in patients with neurological and neuropsychiatric conditions: symptom levels and relationship to emotional distress. J. Int. Neuropsychol. Soc. 22 (6), 682–694. https://doi.org/10.1017/s135561771600031x.
- Miyake, A., Friedman, N.P., Emerson, M.J., Witzki, A.H., Howerter, A., Wager, T.D., 2000. The unity and diversity of executive functions and their contributions to complex "Frontal Lobe" tasks: a latent variable analysis. Cognit. Psychol. 41 (1), 49–100. https://doi.org/10.1006/cogp.1999.0734.
- Øie, M.G., Rødø, A.S.B., Bølgen, M.S., Pedersen, M., Asprusten, T.T., Wyller, V.B.B., 2022. Subjective and objective cognitive function in adolescent with chronic fatigue following Epstein-Barr virus infection. J. Psychosom. Res. 163, 111063 https://doi. org/10.1016/j.jpsychores.2022.111063.
- Orfei, M.D., Porcari, D.E., D'Arcangelo, S., Maggi, F., Russignaga, D., Ricciardi, E., 2022. A new look on long-COVID effects: the functional brain fog syndrome. J. Clin. Med. 11 (19) https://doi.org/10.3390/jcm11195529.

- Organization, W.H., 2024. WHO Coronavirus (COVID-19) Dashboard > Deaths [Dashboard]. World Health Organization. https://www.who.int/europe/newsroom/fact-sheets/item/post-covid-19-condition. (Accessed 21 February 2024).
- Perrottelli, A., Sansone, N., Giordano, G., et al., 2022. Cognitive impairment after postacute COVID-19 infection: a systematic review of the literature. Pers. Med. 12. https://doi.org/10.3390/jpm12122070, 2070.
- Rai, S.N., Tiwari, N., Singh, P., et al., 2022. Exploring the paradox of COVID-19 in neurological complications with emphasis on Parkinson's and alzheimer's disease. Oxid. Med. Cell. Longev. 2022 (1), 3012778 https://doi.org/10.1155/2022/ 3012778.
- Roth, R.M., Gioia, G.A., 2005. Behavior Rating Inventory of Executive Function–Adult Version. Psychological Assessment Resources Lutz, FL.
- Roth, R., Isquith, P., Gioia, G., 2005. Behavior Rating Inventory of Executive Function -Adult Version (BRIEF-A), vol. 20.
- Schultebraucks, K., Blekic, W., Basaraba, C., et al., 2023. The impact of preexisting psychiatric disorders and antidepressant use on COVID-19 related outcomes: a multicenter study. Mol. Psychiatr. https://doi.org/10.1038/s41380-023-02049-4
- Selvakumar, J., Havdal, L.B., Drevvatne, M., et al., 2023. Prevalence and characteristics associated with post–COVID-19 condition among nonhospitalized adolescents and young adults. JAMA Netw. Open 6 (3), e235763. https://doi.org/10.1001/ jamanetworkopen.2023.5763.
- Søraas, A., Bø, R., Kalleberg, K.T., Støer, N.C., Ellingjord-Dale, M., Landrø, N.I., 2021. Self-reported memory problems 8 Months after COVID-19 infection. JAMA Netw. Open 4 (7), e2118717. https://doi.org/10.1001/jamanetworkopen.2021.18717.
- Soriano, J.B., Murthy, S., Marshall, J.C., Relan, P., Diaz, J.V., 2022. A clinical case definition of post-COVID-19 condition by a Delphi consensus. Lancet Infect. Dis. 22 (4), e102–e107. https://doi.org/10.1016/s1473-3099(21)00703-9.
- Subramanian, A., Nirantharakumar, K., Hughes, S., et al., 2022. Symptoms and risk factors for long COVID in non-hospitalized adults. Nat. Med. 28 (8), 1706–1714. https://doi.org/10.1038/s41591-022-01909-w.
- Thaweethai, T., Jolley, S.E., Karlson, E.W., et al., 2023. Development of a definition of postacute sequelae of SARS-CoV-2 infection. JAMA 329 (22), 1934–1946. https:// doi.org/10.1001/jama.2023.8823.
- Toplak, M.E., West, R.F., Stanovich, K.E., 2013. Practitioner review: do performancebased measures and ratings of executive function assess the same construct? JCPP (J. Child Psychol. Psychiatry) 54 (2), 131–143. https://doi.org/10.1111/jcpp.12001.
- van Buuren, S., Groothuis-Oudshoorn, K., 2011. Mice: multivariate imputation by chained equations in R. J. Stat. Software 45 (3), 1–67. https://doi.org/10.18637/jss. v045.i03.
- von Elm, E., Altman, D.G., Egger, M., Pocock, S.J., Gøtzsche, P.C., Vandenbroucke, J.P., 2007. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Ann. Intern. Med. 147 (8), 573–577. https://doi.org/10.7326/0003-4819-147-8-200710160-00010.
- Waid-Ebbs, J.K., Wen, P.S., Heaton, S.C., Donovan, N.J., Velozo, C., 2012. The item level psychometrics of the behaviour rating inventory of executive function-adult (BRIEF-A) in a TBI sample. Brain Inj. 26 (13–14), 1646–1657. https://doi.org/10.3109/ 02699052.2012.700087.
- Whitaker, M., Elliott, J., Chadeau-Hyam, M., et al., 2022. Persistent COVID-19 symptoms in a community study of 606,434 people in England. Nat. Commun. 13 (1), 1957. https://doi.org/10.1038/s41467-022-29521-z.
- Zeng, N., Zhao, Y.-M., Yan, W., et al., 2023. A systematic review and meta-analysis of long term physical and mental sequelae of COVID-19 pandemic: call for research priority and action. Mol. Psychiatr. 28 (1), 423–433. https://doi.org/10.1038/ s41380-022-01614-7.
- Zhao, S., Martin, E.M., Reuken, P.A., et al., 2024. Long COVID is associated with severe cognitive slowing: a multicentre cross-sectional study. eClinicalMedicine, 68doi. https://doi.org/10.1016/j.eclinm.2024.102434.