Untreated if Unrecognized: Subjective Cognitive Decline Following COVID-19, in a Heterogeneous International Sample

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Abstract

Introduction: Previous literature has reported that COVID-19 is associated with cognitive decline, and specifically executive dysfunction in severe patients. However, the literature is not yet clear on the landscape of cognitive functioning in less severe COVID-19 patients. Furthermore, most studies have relied upon objective measures of cognition. The present study focusses on subjective measures of executive functioning, and assesses mild to severe disease severity groups to identify the relationship between subjective executive dysfunction and disease severity. **Methods:** The full sample (N = 203) consisted of a healthy control group (n = 71) and a COVID-19 group (n = 131). The COVID-19 group disease severity was assessed using a self-report measure. A newly developed online test battery called CoCo-19 was used, which contained several existing questionnaires. This study focused specifically on the BRIEF-A, as a measure of executive functioning. A mixed-model ANOVA was used followed by multiple one-sided planned t-tests to explore the direction of the data. Furthermore, the Generalized Anxiety Disorder-7 (GAD-7) questionnaire and the Beck's Depression Inventory (BDI) were identified as covariates because executive dysfunction has been associated with both anxiety and depression. **Results:** The COVID-19 group showed significantly more executive dysfunction than the control group ($t(191) = 4.881$, $p < .000$, $d = .741$). All severity groups scored significantly differently from each other on the BRIEF-A, with exception of the control group and the mildest severity group. Thus, BRIEF-A scores increased with increasing symptoms severity. Exploratory analyses additionally found effects for sex and age on BRIEF-A scores. **Conclusion:** The current study has found that COVID-19 patients experience significantly more executive dysfunction than healthy controls. Our results have indicated that increased COVID-19 severity is associated with increased subjective executive dysfunction, even showing increased impairments in mild

disease severity compared to healthy controls. Our findings implicate that more sensitive assessment might be necessary in relatively less severe patients, in order to identify subclinical yet functionally limiting cognitive dysfunction.

Keywords: COVID-19, SARS-CoV-2, executive functioning, cognition, subjective measures

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Subjective Cognitive Decline Following COVID-19, in a Large International Sample

In December 2019, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) emerged in Wuhan, China. The disease associated with the outbreak and infection from this novel coronavirus was named Coronavirus Disease 2019 (COVID-19) by the World Health Organization (WHO). Due to the spread of SARS-CoV-2 and the burden of COVID-19 cases, the outbreak was declared a public health emergency and a pandemic. Currently, more than one and a half year after the outbreak was declared a pandemic, long-term effects of SARS-CoV-2 infection are becoming clearer. Among these effects, research clearly suggests the possibility of cognitive dysfunction in patients recovering from COVID-19 (Riordan et al., 2020; Almeria et al., 2020; Zhou et al., 2020). These long-term cognitive sequelae are recently referred to as "long COVID" or "post COVID-19-syndrome" in the media. The aim of the current study is to further analyze the relationship between COVID-19 severity and cognitive sequelae in the post-acute phase.

There is reason to assume neurological involvement in SARS-CoV-2 infections, since some neural cells are identified to have ACE-2 receptors which are susceptible to the virus (Iadecola, 2020). Three routes of infiltration of the virus into the central nervous system (CNS) were comprehensively listed by Iadecola et al. (2020); crossing a weakened blood-brain barrier; infiltration via immune cells; and through the olfactory nerves. The infiltration of the virus can unleash a dysregulated immune response, which in turn can have a delayed effect on the CNS (Iadecola et al., 2020). In addition, systemic factors such as lung damage and respiratory failure (Iadecola et al., 2020), systemic inflammation (Zhou et al., 2021; Iadecola et al., 2020), and a hyper coagulate state (Gibson, Qin & Puah, 2020) are associated with some of the most frequent and harmful complications of infection. In another study, neurological symptoms (e.g., dizziness,

headache, impaired consciousness) were observed in COVID-19 patients, which were more severe in patients with a severe infection (Mao et al., 2020). As SARS-CoV-2 is a virus that targets the respiratory system, reviews on similar diseases were conducted.

Neuropsychological Sequelae

Literature on other coronaviruses and respiratory disease shows a strong implication towards a significant potential for cognitive sequelae following SARS-CoV-2 infection. In a review of literature on acute and chronic pulmonary disease, Riordan et al., (2020) set expectations for the current SARS-CoV-2 virus based on previous neuropsychological findings. The literature suggests that among other domains of cognitive functioning, chronic memory impairment is especially associated with Acute Respiratory Distress Syndrome (ARDS) (Riordan et al., 2020). ARDS is observed in 42% of COVID-19 patients with pneumonia (Gibson, Qin & Puah, 2020), and is characterized by a difficulty in breathing, shallow and quick breathing, hypoxemia and pulmonary edema among other symptoms. Indeed, hypoxia and hypoxemia seem to be the main factors at the root of cognitive dysfunction in ARDS and pneumonia patients (Riordan et al., 2020). In a meta-analysis and systematic review of 72 studies on coronavirus infections (i.e., SARS and MERS), studies reveal the potential of a decline in executive function (EF) as a consequence of viral infections in addition to the mentioned memory impairments (Rogers et al., 2020). These initial findings point towards more severe respiratory disease (i.e., ARDS) being associated with more severe cognitive impairment. However, other findings regarding disease severity and cognitive outcome are mixed.

In an observational series of 58 COVID-19 patients with ARDS, 33% developed a dysexecutive syndrome (inattention, disorientation, poorly organized movement) after discharge from the hospital (Helms et al., 2020). In one of the first studies on the cognitive aspects of

COVID-19, the data suggests that in non-hospitalized patients' cognitive impairments are mild but measurable (Zhou et al., 2020). In that study, a significant decline was found on sustained attention only in COVID-19 patients compared to matched controls, measured via online neuropsychological tests. Likewise, in a mild- to moderate severity COVID-19 sample of 18 patients, sub-clinical cognitive dysfunction was uncovered on memory, attention and concentration (Woo et al., 2020). Similarly, in a non-hospitalized COVID-19 sample, executive dysfunction was found at least 98 days after acute COVID-19 symptoms (Hellmuth et al., 2021). Important in this study, is that cognitive deficits were not uncovered by common screening tools (e.g., MMSE, MoCA), but only using extensive neuropsychological testing. These findings underline the need for further investigations on cognition and COVID-19, including various methods of conceptualizing cognitive deficits. Deficits that are not uncovered by common objective screening tools or that are deemed sub-clinical, might still affect subjective functioning.

Jaywant et al. (2021) found that 57 COVID-19 patients of varied severities recovering from hospitalization commonly exhibit impairments in attention and executive functions. These functions were analyzed using (sub)scores on the Brief Memory and Executive Test. Impairments were found on working memory, divided attention, and set shifting. These findings could not be explained by other chronic medical factors in the sample, suggesting these effects can be attributed to more severe COVID-19. However, it was noted that not all findings of cognitive dysfunction could be generalized to milder forms of COVID-19, since no comparator group was available (Jaywant et al., 2021). In the study by Woo and colleagues (2020), an exploratory analysis was done on predictors for observed subjective cognitive dysfunction in mild to moderate COVID-19 patients. It was found that disease severity did not predict cognitive

outcome, albeit this implication was severely limited by their sample size (N = 18) (Woo et al., 2020).

Given the mixed and limited findings from previous research, further analyses on the relationships of cognitive outcome and disease severity in COVID-19 patients is warranted. Not all studies have found that increased disease severity is associated with increased cognitive complaints, likely due to the heterogeneity in measurement instruments and limited samples. Further assessing the relationship of severity and cognition seems especially relevant in the case of executive functioning, given these functions are at the base of many tasks encountered in daily life (Miyake et al., 2000; Snyder et al., 2015).

Executive Functions

As was noted by Helms et al. (2020), one-third of 58 severe COVID-19 patients developed executive dysfunction in their sample. Accordingly, in a case description of 13 inpatients with COVID-19, all patients exhibited lowered executive functions even with normal scores on further cognitive performance tests (Beaud et al., 2020). Executive dysfunction is therefore an aspect of cognition that is possibly affected post-infection.

Executive functions (EF) are a collection of self-regulatory functions involved in memory, attention and planning. They can be considered core components of self-regulation and self-control abilities, and therefore have broad implications for daily life (Snyder et al., 2015). The current study is following the model by Miyake et al. (2000), on a conceptualization of EF processes as a unity and diversity model. In their work, EF have been conceptualized as broadly consisting of shifting, inhibition and updating. In this model, these three core functions have separable and differential (i.e., diversity) contributions to complex executive tasks (i.e., unity). As mentioned above, executive functions are at the base of many cognitive functions which are

essential for effective functioning in daily life. It is for that reason and its possibly broad societal implications, executive dysfunction is at the focus of our investigation.

Subjective and Objective Measures

Assessing subjective measures of executive functioning is relevant because subjective complaints might still significantly influence the daily life functioning of patients (Hohman et al., 2011; Burmester et al., 2016). Moreover, as was shown in previous literature, objective measures might not be sensitive enough for less severe dysfunctions that nonetheless can subjectively impact daily life functioning. Therefore, subjective measures for EF might present a more accurate picture of functional cognitive impairments in our non-clinical sample.

The Present Study

The current research aims to identify whether (potentially sub-clinical) executive dysfunctions are associated with COVID-19 in a large sample. Furthermore, we want to clarify whether the experienced executive dysfunction is related to the COVID-19 disease severity in our sample. To do so, the current study will compare different severity groups and use subjective cognitive measures of executive functioning. Exploratory analyses will be carried out to identify other possibly relevant relationships related to cognitive functioning and COVID-19.

Taken together, we hypothesize the following:

H1: COVID-19 patients will report worse subjective executive functioning than the healthy control group.

H2: Increased subjective disease severity is associated with worse subjective executive functioning (worse = reporting more difficulty than a milder severity group).

Methods

Sampling and Participants

In this online study, a total of 288 participants (mean age between 30 – 39) were recruited. This original sample consisted of 56 male and 222 female participants, with one participant falling into the "other" category. Within this sample, 174 participants declared having had COVID-19, and a healthy control group of 114 participants declared never having had COVID-19.

Recruitment

Recruitment of all groups was done using convenience sampling, by posting on social media (Instagram, LinkedIn, Facebook), and by distribution of the questionnaire via acquaintances. On Facebook, a large (+/- 21.000 members) Dutch group about recovering COVID-19 patients was utilized to spread the questionnaire. In addition to social media, flyers were distributed among general practitioners, medical staff in a hospital and via other health care professionals that distributed the flyers among their patients. Internationally, the study was spread via general practitioners and acquaintances, most notably in Germany, Mexico, and Spain.

Inclusion and Exclusion Criteria

Participants were excluded from the analyses if; they did not give their informed consent; if their completion time was unreasonably low (i.e., only logging in for a few seconds, then closing the questionnaire) or if informed consent was not answered. In addition to this, participants who showed no valid responses on the BRIEF-A were excluded from the analysis: a negativity score ≥ 4, infrequency score ≥ 3 or inconsistency score ≥ 8 (Isquith et al., Interpretive Report, 2006).

Importantly, participants who did not fully complete the questionnaire were not automatically excluded from the analysis. Given the nature of the subject being studied (i.e.,

cognitive dysfunction; lack of concentration; fatigue), and the length of the questionnaire (>60 min), we cannot expect all participants to have completed the questionnaire entirely. Therefore, if all incomplete responses were to be deleted automatically, a bias towards less severely ill patients could be created.

Assessment of Validity and Filtering

Incomplete responses were individually assessed for validity. In an attempt to minimize this bias, all participants who gave informed consent and at least completed the questionnaire until the final BRIEF-A question were included into the main analysis. Due to this filtering, there was not controlled for psychological variables in the main analyses for the reason that those items were presented near the end of the questionnaire. Unless mentioned otherwise, this filter was applied in order to minimize the chance of filtering out the participants with major concentration or attention problems. Additional analyses were carried out in which covariates were included.

Final Sample

After the exclusion criteria were applied, the actual sample consisted of N = 203 participants (n = 45 male and n = 157 female). Within this sample, 131 participants declared having had COVID-19, and a healthy control group of 72 participants stated never having COVID-19. The sample included 99 Dutch, 101 German and three Spanish speaking participants. The largest age groups within this sample were ages between 18 and 29 (n = 70; 34.5%), and ages between 50 and 64 (n = 65; 32.0%). Within this sample, 45 participants suffered comorbid health issues: 26 from psychological, neurological or psychiatric issues and were under medication. 24 participants indicated being overweight, and seven participants indicated suffering from diabetes. Further demographics are summarized in Table 1.

Table 1

Sociodemographic Characteristics of the sample

Characteristic	COVID-19 diagnosed		Healthy control		Full sample	
	n	%	*n*	%	*n*	%
Gender						
Female	111	84.7%	46	63.9%	157	77.3%
Male	19	14.5%	26	36.1%	45	22.2%
Age ranges (in years)						
18 – 29	35	26.7%	35	48.6%	70	34.5%
30 – 39	21	16.0%	8	11.1%	29	14.3%
40 – 49	30	22.9%	4	5.6%	34	16.7%
50 – 64	44	33.6%	21	29.2%	65	32.0%
65 >	1	.8%	4	5.6%	4	2.0%
COVID-19 diagnosis [a]	131	100%	.	.	131	64.5%
COVID-19 symptoms [a]	122	93.1%	.	.	122	93.1%
Highest completed education						
Middle school or lower	39	29.7%	14	19.5%	53	26.1%
Bachelor's degree	34	26.0%	25	34.7%	59	29.1%
Master's degree or postgraduate	40	30.5%	19	26.4%	59	29.1%
Studied but no diploma	17	13.0%	14	19.4%	31	15.3%
Employment						
Unemployed	11	8.5%	4	5.6%	15	6.4%
Student	13	9.9%	21	29.2%	34	16.7%
Employed						
1 – 39 hrs	76	58.0%	20	27.8%	96	47.3%
40+ hrs	20	15.3%	12	16.7%	32	15.8%
Self-employed	9	6.9%	8	11.1%	17	8.4%
Retired	1	0.8%	7	9.7%	8	3.9%
Previous psychological disorder [a]	18	13.7%	5	6.9%	23	11.3%
Intake of medication for (psychological) disorder [a]	18	13.7%	8	11.1%	26	12.8%

Note. $N = 203$.

[a] Reflects the number and percentage of participants answering "yes" to this question.

The Ethics Committee of the Department of Psychology at the University of Groningen has approved this research project. Informed consent was obtained from all participants of the study, before the questionnaire was presented. Participants who did not give their consent or who did not enter a response, were excluded from the analyses. Participants were not (financially or otherwise) compensated for their participation in the current study.

Test battery

For this project, a set of psychological, neuropsychological, adapted as well as new self-report measures was compiled into an online test battery which was named "Groninger Neuropsychological COVID-19 Test battery Cognitive Complaints (CoCo-19)" using Qualtrics. The questionnaire was divided into five thematic parts: demographics, functional outcome, neuropsychological, personality, psychological. As was mentioned above, the total completion time of the questionnaire was around 60 minutes. In designing the questionnaire, an effect of fatigue and/or lack of concentration was taken into account. Therefore, the most relevant neuropsychological questionnaires were included near the beginning of the questionnaire.

Procedure

When participants entered the Qualtrics link, a choice between five languages was presented. After selecting their preferred language, the objective of the study was presented followed by asking for informed consent. Following informed consent, demographics were assessed. Besides age, gender, living situation, pre-existing conditions and medication intake, participants were asked whether they had been diagnosed with COVID-19. If participants indicated having been diagnosed with COVID-19, further questions were asked about date of diagnosis, inpatient stay, severity of the disease and related medication intake. Medication intake was not further specified in the questionnaire.

Measures of COVID-19 severity

From the participants who indicated having been diagnosed with COVID-19 in our sample, 122 (93.1%) indicated experiencing symptoms that they judged were typical for COVID-19. Moreover, 7 (5.3%) participants reported being hospitalized follow their COVID-19 diagnosis. Interestingly, 60 (45.8%) participants reported making use of medications for their COVID-19 symptoms.

As a measure of severity in our analyses, subjective disease progression severity and experienced subjective impairment of daily activities were measured. Participants could rate their disease progression severity (i.e., "Please rate the severity of your disease course.") on a slider from 1% – 100%. Additionally, experienced interference on daily life activities (i.e., "Overall, when these symptoms were at their worst, did they interfere with your daily activities?") was also rated on a slider from 1% – 100%. The latter variable was retroactively added to the questionnaire, which results in only a small number of participants in our sample being shown this question (n = 24). The severity groups were coded into 4 groups (0 = *Control,* 1 = *Benign,* 2 = *Mild,* 3 = *Severe*), using cut-off scores <31 as mild and scores >74 as severe.

Comparisons between hospitalized versus non-hospitalized patients were to be analyzed in the original research design. However, due to the small number of hospitalized participants in the final sample (n = 8), this idea was abandoned. Hospitalization was initially to be used as an objective measure for disease severity, and to be compared to healthy and non-hospitalized participants on subjective cognitive measures.

Self-reports on Executive functions

The Behavior Rating Inventory of Executive Functioning for Adults (BRIEF-A) was utilized to assess subjective executive functioning (EF) in daily life (Roth, Isquith & Gioia,

2005). The BRIEF-A consists of 75 items, which are subdivided into 9 subscales. Furthermore, these subscales can be summed to form three larger scales; Global Executive Composite (GEC); Metacognition Index (MI); Behavioral Regulation Index (BRI). The Global Executive Composite is a grand summary score of all items, and reflects general executive functioning. A higher score indicates more difficulty in general EF. The Metacognition Index is comprised of five subscales; Initiate; Working Memory; Plan/Organize; Task Monitor; and Organization of Materials. Finally, the Behavioral Regulation Index is comprised of four subscales; Inhibit; Shift; Emotional Control; and Self-monitor. In addition to these clinical scales, the BRIEF-A includes three validity scales; Negativity; Infrequency; and Inconsistency. All items on the BRIEF-A are scored on a three-point Likert scale (*1 = never, 2 = sometimes, 3 = often*). A higher score on the scales of the BRIEF-A indicate poorer subjective EF performance. In this study, there will be focused on the Global Executive Composite, since it is most informative of general EF difficulty (Roth, Isquith & Gioia, 2005). The Behavioral Regulation Index and Metacognition Index scales are included for completeness. A summary of Cronbach's Alpha of the BRIEF-A scales in this study are found in Table 3.

Table 3

Summary and description of the BRIEF-A subscales in the current study

Scales	Description	Cronbach's Alpha
Global Executive Composite (GEC)	Overarching summary score of all scales	.960
Metacognition Index (MI)	Reflecting ability to initiate, problem-solve, sustain WM, plan and organize problem solving ideas, monitor success or failure and organizing materials and environment	.940
Initiate		
Working Memory		
Plan/Organize		
Task Monitor		
Organization of Materials		
Behavioral Regulation Index (BRI)	Capturing ability to maintain regulatory control of behavioral and emotional responses	.901
Inhibit		
Shift		
Emotional Control		
Self-monitor		

Controlling for Psychological variables

As was noted by meta-analyses by Snyder et al. (2015), EF are related to psychological and psychiatric disorders. In their analysis, Snyder and colleagues found that depressed participants experienced impairments on all-round EF (d = 0.39 – 0.70, N = 7.707). Furthermore, in another paper by Snyder et. al. (2014) it was pointed out that anxiety has an effect on EF, but in a separate mechanism to depression. Importantly for the current research, elevated depression and anxiety are regularly observed in COVID-19 studies (Rogers et al., 2020; Zhang et al., 2020; Alonso-Lana et al., 2020; Liguori et al., 2020). Depression and anxiety

have shown to be elevated in COVID-19 patients as well as in the general public, with a trend towards higher scores for COVID-19 patients (Zhang et al., 2020). It seems therefore that the current pandemic situation brings elevated depression and anxiety, in addition a psychological effect of contracting COVID-19. Due to the differential but significant effects of anxiety and depression on EF, Snyder et al. (2015) argue controlling for both factors to take their effects into account. In our study, controlling for these psychological factors might offer a clearer picture of the effects of COVID-19 itself. To do so, Beck's Depression Inventory (BDI) and General Anxiety Disorder-7 (GAD-7) were used to control for these effects. The BDI (Beck et al., 1961) assesses depressive symptoms either since the COVID-19 diagnosis, or for the past week for healthy controls. The BDI includes 21 questions, which can be answered on four response options. A sum score was created for all items in the questionnaire, with a higher score indicating more frequent and severe depressive symptoms. Cronbach's Alpha for the BDI was .892 in the current study.

The GAD-7 (Spitzer et al., 2006) was used to assess the frequency of general anxiety symptoms in participants. The GAD-7 includes seven items, measuring symptoms either since their COVID-19 diagnosis or for the past two weeks for healthy controls. The items can be answered using a four-point Likert scale (0 = *Never,* 2 = *Multiple days,* 3 = *More than half of the days,* 3 = *Almost every day*). A sum score was created for all items of the GAD-7, with higher scores indicating more frequent general anxiety symptoms. Cronbach's Alpha was .544 in the current study, and was deemed poor. This however, could be due to the short length of the questionnaire (Tavakol & Dennick, 2011), which could underestimate alpha. A correlation matrix revealed some items indeed correlated poorly. A subsequent analysis on Cronbach's Alpha if certain items were deleted, showed Alpha could be increased to .664 if one item were to

be deleted. This showed one item to be particularly inconsistently scored in our sample. Since the GAD-7 scale is widely validated (Tiirikainen et al., 2019), it was still included into our analyses.

Statistical Design

In order to test whether executive functioning is reduced in COVID-19 patients, and are related to severity, a mixed model ANOVA will be used, with BRIEF-A scales as the within-subject factors and severity groups as between-subject factors. In order to analyze the individual differences between the groups, one-sided planned independent-samples T-tests is planned. All severity groups including the healthy control group, were compared to each other on BRIEF-A scores. To check if assumptions are met, Q-Q plots and Levene's test of equality of error variances will be used.

In additional analyses, standardized z-scores of the BDI and GAD-7 scales were entered as covariates into the ANOVA. To further explore these covariates, the same procedure using one-sided planned independent-samples T-tests was used with the BDI and GAD-7 as test variables. In all mentioned analyses, p-values below 0.05 were judged significant. Data was separately imported from Qualtrics for every language, and was merged in SPSS. IBM SPSS Statistics version 27 (IBM SPSS Statistics, New York, NY, United States) was used for performing statistical analyses.

Results

COVID-19 severity and executive functions

As a first analysis to test our main hypothesis, the relationship between the subjective disease severity and scores on EF scales were assessed. Participants who indicated being diagnosed with COVID-19 scored significantly higher on all summary scores of the BRIEF-A

compared to healthy controls. In our first mixed ANOVA analysis a significant interaction effect for EF and severity group was found, with a large effect size [$F(3.427, 214.766) = 13.719$, $p < .000$, $\eta_p^2 = .180$]. This indicates at least one significant difference between the four severity levels (control, benign, mild and severe) and the scores on the BRIEF-A scales (GEC, MI and BRI). See Figure 1 for a visual representation of the effects of severity and EF.

To explore the use of including theoretically supported covariates, correlations with anxiety and depression and the dependent variable EF were computed. Indeed, the BDI correlated significantly with the BRIEF-A GEC $r(191) = .637$, $p < .000$, as did the GAD-7 $r(191) = .497$, $p < .000$. Therefore, scores BDI and GAD-7 were included as covariates into the ANOVA. Consistently, the interaction between EF and severity groups remained significant, with a reasonable effect size [$F(3.705, 211.204) = 4.753$, $p < 0.01$, $\eta_p^2 = .077$]. See Figure 2 for a visual representation of the effects of severity and EF, while controlling for the effects of depression and anxiety.

Table 2

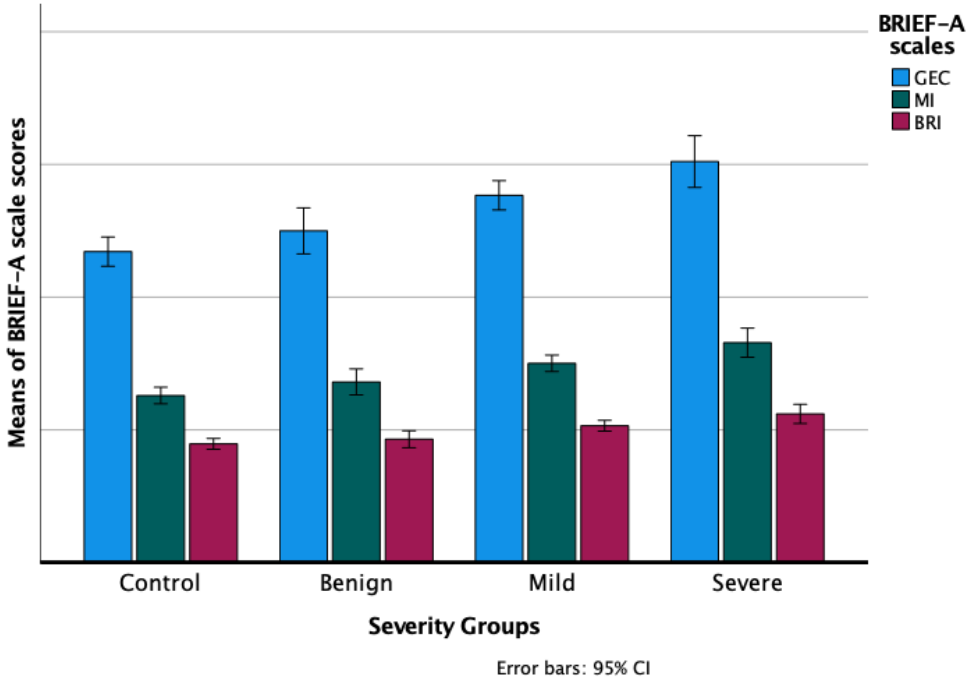
BRIEF-A Descriptive Statistics Excluding Covariates

	Control (*n* = 66)	Benign (*n* = 29)	Mild (*n* = 71)	Severe (*n* = 26)
Scale	*M* ± *SD*	*M* ± *SD*	*M* ± *SD*	*M* ± *SD*
GEC	117.79 ± 26.87	123.90 ± 23.18	137.34 ± 23.33	150.23 ± 22.48
MI	63.35 ± 15.21	67.45 ± 13.27	74.40 ± 13.30	82.54 ± 12.24
BRI	44.95 ± 9.74	46.14 ± 8.43	51.37 ± 8.73	55.65 ± 9.80

Note: GEC = Global Executive Composite; MI = Metacognition Index; BRI = Behavioral Regulation Index. There was not controlled for the covariates (anxiety and depression).

Figure 1

BRIEF-A subscale scores across severity groups excluding covariates



Note: Plot of mean scores on BRIEF-A subscales for the different severity groups, without controlling for covariates anxiety and depression. GEC = Global Executive Composite; MI = Metacognition Index; BRI = Behavioral Regulation Index.

Table 3

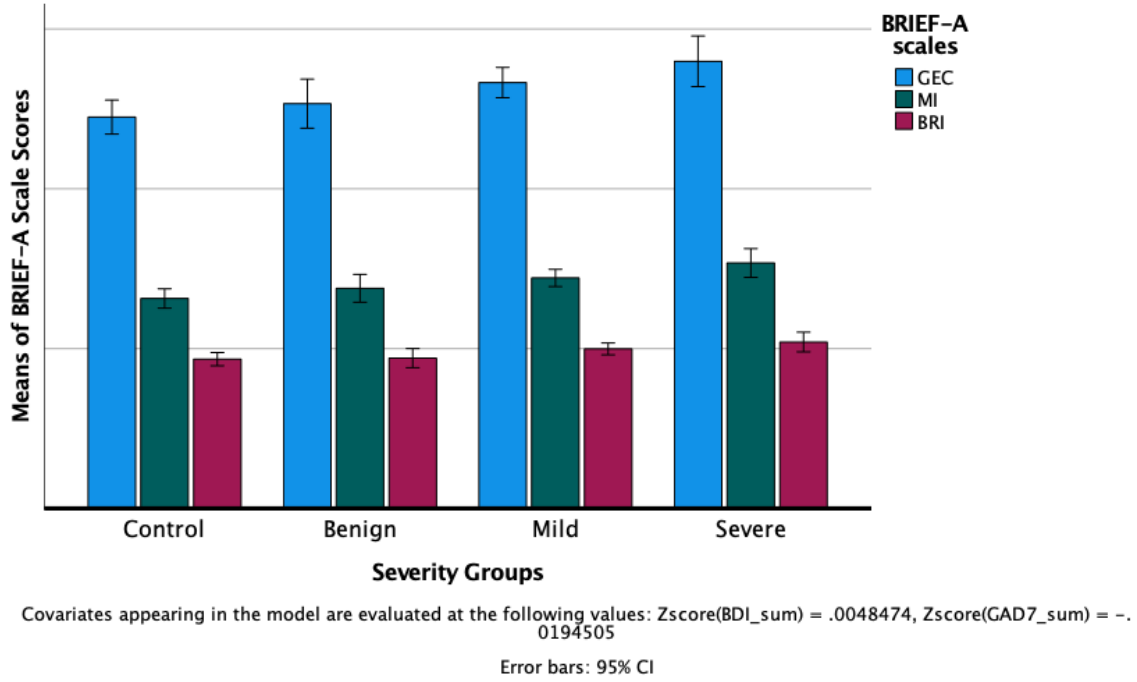
BRIEF-A Descriptive Statistics Including Covariates

	Control (*n* = 57)	Benign (*n* = 26)	Mild (*n* = 68)	Severe (*n* = 26)
Scale	*M* ± *SD*	*M* ± *SD*	*M* ± *SD*	*M* ± *SD*
GEC	115.72 ± 25.17	120.08 ± 20.20	137.50 ± 22.62	150.23 ± 22.48
MI	62.00 ± 13.99	65.27 ± 11.90	74.47 ± 12.81	82.54 ± 12.24
BRI	44.40 ± 9.46	44.77 ± 7.12	51.40 ± 8.52	55.65 ± 8.88

Note: GEC = Global Executive Composite; MI = Metacognition Index; BRI = Behavioral Regulation Index. For these mean scores, there was controlled for the covariates (anxiety and depression).

Figure 2

BRIEF-A subscale scores across severity groups including covariates



Note: Plot of mean scores on BRIEF-A subscales for the different severity groups, while controlling for the covariates anxiety and depression. GEC = Global Executive Composite; MI = Metacognition Index; BRI = Behavioral Regulation Index.

The statistically significant interaction effects were further analyzed using planned independent-samples T-tests. Severity groups were compared to each other on EF scores in order to assess differences between the control group and benign, mild and severe severity groups.

Importantly, the control group (M = 136.62, SD = 24.65) differed significantly from the COVID-19 group (M = 117.79, SD = 26.87) on the BRIEF-A GEC: $t(191) = 4.881$, $p < .000$, $d = .741$. Further significant differences were found between the severe (M = 150.23, SD = 22.48) and benign (M = 123.90, SD = 23.18) severity groups on the BRIEF-A GEC: $t(53) = 4.267$, $p < .000$, $d = 1.152$. Additionally, the same pattern of significant differences was found for the MI and BRI subscales. Smaller, but significant differences were also found when comparing the severe group with the mild group (M = 136.83, SD = 23.55) on the BRIEF-A GEC: $t(96) = 2.515$, $p = .007$, $d = .575$. Accordingly, significant differences between the mild and severe groups were also found on the MI and BRI subscales. The benign (M = 123.90, SD = 23.18) and mild groups were compared (M = 136.83, SD = 23.55), and were judged to score significantly different on the BRIEF-A GEC: $t(99) = -2.508$, $p < .01$, $d = -.552$. Congruently with previous comparisons, significant differences between the benign and mild groups were also found on the MI and BRI subscales. Finally, the control group (M = 117.787, SD = 26.868) was compared with the lowest severity (benign) group, which did not significantly differ from each other on the BRIEF-A GEC: $t(94) = -1.062$, $p = .145$, $d = -.237$. Table 4 contains a summary of the T-tests that were performed on the different severity groups and the BRIEF-A GEC scores, with its associated effect sizes

Table 4

T-scores, p-values and effect sizes of planned t-tests of BRIEF-A GEC scores

Groups	*t*	*p*	*Cohen's d*	*Relative size*
Control vs. COVID-19	4.881	<.000*	.741	Fairly large
Benign vs. Severe	4.267	<.000*	1.152	Large
Benign vs. Mild	-2.508	<.01*	-.552	Medium
Benign vs. Control	-1.062	.145	-.237	Small
Severe vs. Mild	-2.508	<.01*	-.552	Medium

Note: **p* = <0.05. Summary of planned one-sided T-tests of GEC scale scores between different severity groups, including relative effect sizes. GEC = Global Executive Composite. Effect sizes were judged using Cohen's (1992) guidelines.

Exploratory analyses: executive domains, age and sex

For exploratory analyses, EF were further subdivided into the domains of shifting, inhibition and working memory. There was no significant interaction effect found for the different domains and the severity groups, indicating that separate BRIEF-A scale scores did not depend on disease severity. However, visual inspection of the data did indicate a trend towards increased scores (thus, increased difficulties) for the higher severity groups. Next, as was expected, no significant differences between the hospitalized and non-hospitalized groups were found on the three summary scales of the BRIEF-A. This is most likely due to a very limited hospitalized group (n = 5).

In order to further analyze effects of the covariates entered in the previous ANOVA model, a mixed ANOVA was conducted with BDI and GAD-7 as dependent variables, and the

severity groups as between-subjects factors. Indeed, a significant interaction between BDI and GAD-7 and the severity groups was found [$F(3, 174) = 6.732$, $p < .000$, $\eta_p^2 = .104$]. Our data did show a positive, relationship between symptom severity and depression and anxiety. Thus, symptoms of anxiety and depression increased with increasing symptom severity.

Furthermore, a significant interaction was found between age category and BRIEF-A scores [$F(4.51, 210.78) = 4.343$, $p < .01$, $\eta_p^2 = .085$]. Using T-tests, we found that the group between 18 and 29 ($M = 120.250$, $SD = 23.96$) differed significantly from the 30 to 39 group ($M = 137.69$, $SD = 27.10$) on the BRIEF-A GEC: $t(91) = -3.121$, $p < .01$, $d = -.699$. However, the group between 30 and 39 did not differ significantly from the 40 to 49 group ($M = 138.81$, $SD = 28.03$) on the BRIEF-A GEC: $t(60) = -.161$, $p = .437$. This indicates that our youngest age group experienced less executive dysfunction than both older age groups, which did not differ from each other.

As a final analysis, the effects of sex were analyzed using independent samples T-tests in order to check whether females scored significantly different than males on the BRIEF-A GEC. Based on the literature, we expected differences between men and women on experienced complaints (Regitz-Zagrosek, 2012; Liguori et al., 2020). Indeed, when comparing males ($M = 115.577$, $SD = 26.772$) and females ($M = 131.919$, $SD = 30.070$) on BRIEF-A GEC mean scores, a significant difference was found: $t(236) = 3.543$, $p = <.000$, $d. = .556$. Thus, in our sample, females experienced significantly more executive dysfunction than males. The explanatory analyses identified variables that have a mutual influence on each other, which are therefore argued to be included into further research on the topics of COVID-19 and EF.

Discussion

Main analyses

The aim of the current study was to increase the understanding of the cognitive sequelae following COVID-19, with the specific question how disease severity influences these adverse effects on cognition. In order to answer this question, COVID-19 diagnosed patients were subdivided into three levels of severity and were assessed on their executive functioning. For this study, we looked into subjective measures of executive functioning. This is of value, because subjective cognitive complaints can possibly impact daily life functioning (Hohman et al., 2011; Burmester et al., 2016), even though traditional objective measures may not detect impairments (as seen in e.g., Hellmuth et al., 2020; Woo et al., 2020). Executive functioning is at the base of many tasks in daily life, which is why this study focused on the effects of COVID-19 on EF. A summary scale of the BRIEF-A was used, to give a general indication of executive dysfunction in the different severity groups. Long term cognitive sequelae following COVID-19 have recently been highlighted in the media, presented as “long-COVID” and “Post-COVID-syndrome”. Our study therefore aims to extend the knowledge surrounding these sequelae and discuss its implications for research and patients, given the public relevance in this pandemic. In the following paragraphs, the results on our main analyses will be discussed, interpreted and embedded in the literature.

Our results show support for both our hypotheses which stated that COVID-19 patients experience more EF difficulty, and that more severely ill participants consistently experience more difficulty with EF in their daily life. These findings should be taken into account in the management of recovering, severe (sub-clinical) COVID-19 patients. Our large, heterogeneous and international sample shows that all severity groups have different degrees of difficulty with

executive functioning. The highest severity group experienced significantly more executive dysfunction than both the mild, benign and control group. Additionally, our findings seem to imply that not only the most severe COVID-19 cases present with cognitive decline, but that dysfunction is also experienced among milder patients. Our data therefore agrees with a very similar study conducted by Goërtz et al. (2020), which also showed that mild non-hospitalized COVID-19 patients experience symptoms in the sub-acute phase. With this, we have highlighted that patients who may not be expected and identified as having executive dysfunction due to their relatively mild disease course, may still experience difficulty in executive functioning in daily life. The medium and large effect sizes (see table 4) in our analyses implicate that these effects bear practical relevance in addition to statistical significance.

Importantly however, no significant differences between healthy controls and benign COVID-19 patients were found on subjective executive functioning. This finding is in contrast with Amalakanti et al. (2020), which found that even asymptomatic COVID-19 patients do show cognitive decline. Their study is however limited by a small sample of patients (n = 93), and used objective measures. The discrepancy in our results can be due to lack of standardization and specificity in our definition of severity, as will be discussed further in our limitations. Our data seems to indicate that COVID-19 does not result in executive dysfunction in the majority of infected people, given that the disease course has shown to be asymptomatic or mild in the majority of cases (Shoaib et al., 2020). In addition to the main analyses mentioned in the previous paragraphs, exploratory analyses on EF, age and psychological factors will now be discussed. This will be followed by the limitations and implications of the current study.

Exploratory analyses

The statistically significant differences that were found on summary scales of the BRIEF-A translated over into the Behavioral Regulation Index and the Metacognition Index across all groups. This seems to indicate that COVID-19 severity does not target either the behavioral or cognitive aspect of EF in our sample, but affects EF as a whole. This is in line with prior research, that associated executive dysfunction with COVID-19 (e.g., Helms et al., 2020; Almeria et al., 2020; Woo et al., 2020; Mazza et al., 2021). When EF is further subdivided however (i.e., shifting; inhibition; WM, following Snyder et al., 2015; Miyake et al., 2000), no statistically significant differences were found between the severity groups. This implies that the disease does not target specific EF domains depending on its severity. Although not statistically significant, the trend does suggest more difficulty in these domains for the high and mild severity group. Notably, a main effect was observed for the subdivided EF functions in our analyses. This seems to indicate that the separated EF functions do measure separate dimensions, which is in line with the diversity model of EF as postulated by Miyake et al. (2000).

In addition, our data suggests an effect for age on the severity of subjective EF difficulty. The youngest age category in our sample (18-29 years) indicated significantly less EF dysfunction than older age groups (age 30 and up), which did not differ from each other. This seems to indicate younger patients (under 30 years of age) are less cognitively impacted by COVID-19 than older patients. This finding underlines the importance of protecting older, thus more vulnerable, individuals in society from getting infected by SARS-CoV-2. Although our participants were questioned about their EF experiences in the past month, we cannot distinguish between normal decline or other factors that may impact functioning, and the effects of COVID-19. For instance, Fergusun et al. (2021) pointed out that some declines in EF already appear between the ages of 30 and 40. Accordingly, large meta-analysis on age effects of EF in young

adults and older adults reported significant differences on EF (Maldonado et al., 2020). These studies point out the importance of including a middle-aged group into studies to give a more accurate and complete picture of effects, which our data appears to correspond with. In order to reduce possible age-related bias in the interpretation of effects on EF, these findings could be taken into account.

Furthermore, psychological factors were analyzed to assess whether the severity groups experienced depression and anxiety. Indeed, the high and mild severity groups experienced significantly more depression and anxiety symptoms than the benign and control groups. This shows a positive relationship between experiencing COVID-19 symptoms and experiencing depression and anxiety, however, bidirectionality cannot be ruled out. Given that there is no significant difference on depression and anxiety between the control and benign group, our data might indicate that socio-cultural factors or effects of being infected itself are not sufficient to cause anxiety or depressive symptoms. However, we have only assessed differences between groups, while other studies have shown elevated depression and anxiety symptoms in the general population during the pandemic (Gasteiger et al., 2021). From our data we can tell that severe disease is associated with more depression and anxiety. This highlights the need for psychological assistance and support for patients that were more severely ill, even when they were not hospitalized.

It should be taken into account in our sample, that some participants were not able to fill out the questionnaire entirely due to a lack of cognitive resources related to their COVID-19 infection. Because the study aims to assess patients that presumably suffer from cognitive difficulty, we can expect that a bias is formed due to the most severely affected participants not being able to complete the questionnaire due to cognitive limitations. In our sample, this could

have resulted in an underestimation of the severity in the population. Additionally, this could be an explanation for our small hospitalized sample, given that the study was spread among hospitalized patients. Further efforts to obtain reliable self-reported data from even the most severely cognitively impaired patients should be undertaken in research of a similar nature.

Limitations

Further limitations of the current study entail that our sample was affected by a possible bias in gender, given that there were more females than males in our analyses (175 females and 45 males). This bias is even larger in the COVID-19 group, see Table 1. This could potentially have influenced our results, seen as there are differences in health and disease management between sexes (Regitz-Zagrosek, 2012). Indeed, in our exploratory analyses significant differences between sexes were found on experienced EF difficulties. If the disease is managed more effectively by either sex, perhaps less subjective problems are experienced. Additionally, multiple studies showed that a severe COVID-19 course was more prevalent among men (Jin et al., 2020; Vahidy et al., 2021). Effects for sex were lost in our analyses, since there was not accounted for the bias towards women in our sample. Further research should take into account effects for sex on COVID-19 outcomes (Meng et al., 2020; Gebhard et al., 2020; Vahidy et al., 2021).

Moreover, the disease severity scale that was relied upon heavily in the current study, is not an ideal measure and is prone to individual rating differences. COVID-19 diagnosed participants were asked to rate their disease progression severity from 0 to 100. Cut-off points were chosen to separate the severity groups from this scale. It was however not defined in the questionnaire what values correspond to which disease symptoms. Individual differences in severity ratings are therefore likely, regardless of actual objective disease symptom severity (e.g.,

two individuals suffering from the same disease symptom, might give different severity ratings). However, as there is great publicity surrounding COVID-19 and its severe cases, perhaps many participants place their own symptoms into the same context. Support groups, such as the Facebook group that was utilized to spread our questionnaire, offer further context to which our participants could relate their symptoms. Another possibility is that participants underestimate their symptomatology because they do not want to come across as "complainers", due to the formation of norms in these support groups (Visser et al., 2016). Taken together, our rating scale cannot completely be relied upon and requires a more objective measure of severity. A distinction between hospitalized and non-hospitalized patients can offer such an objective measure in the current design, but this requires a larger sample size for ample power.

Finally, the BRIEF-A as was used in this study normally includes an informant form (Roth et al., 2005), to counteract the beforementioned social bias. This informant form was however not included in the current study, which limits the BRIEF-A reliability in our study. The resulting loss of information and potential bias is the result of technical restrictions, given this study was based on an online questionnaire.

Implications

The current results add to the knowledge on the cognitive sequelae of COVID-19 infection, specifically on subjective executive dysfunction in relation to disease severity. We have shown that non-hospitalized patients, even with mild symptoms, experience subjective cognitive decline. Given most of the COVID-19 patients follow a mild disease course, our data shows that many people might suffer from unrecognized cognitive deficits. This long-term cognitive decline after COVID-19 is recently much discussed in the media and in literature as "long COVID", or even "post-COVID-19-syndrome" (Goërtz et al., 2020), which indicates its

relevance in this phase of the pandemic. The significant results of the current study highlight the presence of subjective and possible hard-to-detect cognitive complaints in recovered mild to severe COVID-19 patients, and shows support for the existence of a "post-COVID-19-syndrome". Based on these findings, it is suggested to not solely focus on severely ill patients in research and practice, but to not ignore less severe patients and assess them using sensitive or subjective measures when they seek help. Apart from its implication for clinical practice and research, results from our analyses show that even mild COVID-19 can result in executive dysfunction which could then influence functioning in daily life. Potentially, this finding has implications for individuals in environments with high cognitive demands in their daily lives or work. In these individuals, perhaps even a small decline in cognition after a mild infection might limit functioning if cognitive demands are not met. The medium to large effect sizes found for the effects in this study show its relevance in practice (see table 4), in addition to its statistical significance. Further research on the topic of COVID-19 severities, more accurate or objective conceptualizations of disease severity should be utilized to account for variability in severity ratings. Furthermore, this study has shown support for taking into account depression, anxiety and age as factors that influence EF and COVID-19. Further research that relies upon subjective measures should control for these factors, to minimize their effects on the measurements.

To conclude, in our large heterogeneous sample we identified a group of non-clinical, recovered COVID-19 patients that could require healthcare due to their experienced executive dysfunction, which they might not yet receive. In mild- and non-hospitalized patients, their executive dysfunction is often not uncovered by common screening measures, while it is still impacting their daily life functioning. More extensive neuropsychological screening could be

necessary in order to identify healthcare requirements in patients who seek help, even in those who were mild to severely ill, but not necessarily hospitalized.

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Appendix

BRIEF – A

1. I have tantrums

2. I make careless mistakes

3. I am poorly organised

4. I have difficulty concentrating (household, reading, working)

5. I am tapping my fingers and rocking my knees

6. I must be reminded to start a task, even if I want to do it

7. My cupboard is untidy

8. I have difficulty moving from one task to another

9. I am overwhelmed by big tasks

10. I forget my name

11. I have difficulties with tasks that consist of several steps

12. I overreact emotionally

13 I do not notice when I do something that makes others feel bad before it is too late

14. I have difficulties getting ready for the day

15 I have difficulty setting priorities

16. I have difficulty sitting still

17. In the middle of a task, I forget what I am actually doing

18 I do not check my work for errors

19 I have emotional outbursts because of trivialities

20 I spend a lot of time at home

21 I start tasks without having the right material (e.g., ingredients for cooking)

22. I have difficulties to accept other ways of solving problems (work, friendship, tasks)

23 I speak in the wrong moment

24 I misjudge how easy or difficult a task will be

25 I have problems getting started

I have problems in tackling new tasks without help from others

26. I have trouble staying on the same topic when speaking

27. i get tired

28. I react more emotionally to situations than my friends

29. I have problems waiting my turn

30. people say that I am badly organised

31. I lose things (keys, money, purse, homework)

32. I have problems finding other solutions when I am stuck with a problem

33 I overreact to small problems

34 I do not plan ahead

35. I have a short attention span

36. I make inappropriate sexual remarks

37. if people seem to be angry with me, I don't understand why

38. I have difficulty counting to three

39 I have unrealistic goals

40. I leave the bathroom untidy

41 I make mistakes through carelessness

42 I am quickly emotionally upset

43. I take decisions that cause me difficulties (legal, financial, social)

44. it bothers me when I have to deal with change

45. I have difficulties getting excited about things

46 I easily forget tasks

47 I have good ideas, but I can't put them down on paper

48. I make mistakes

49. I have problems to start a task

50. i say something without thinking

51 My anger is intense but ends quickly

52. I have problems completing tasks (household, work)

53 I start things at the last minute

54. I have difficulty completing tasks without help

55. people say I get easily distracted

56. I have problems to remember things, even for a few minutes (instructions, phone numbers)

57. people say that I am too emotional

58 I rush through tasks

59. i get angry

60 I leave my home untidy

61 I am upset by unexpected changes in my daily routine

62 I have difficulty thinking about what I can do with my free time

63 I do not plan tasks in advance

64. people say that I don't think before I act

65. I have problems finding things in my room, cupboard, or desk

66. I have problems organising activities

67 After having had a problem, I do not get over it easily

68 I have problems doing more than one thing at a time

69. my mood changes frequently

70 I do not think about consequences before I do something

71 I have problems organising my work

72 I quickly get upset about little things

73 I am impulsive

74. I do not clean up after myself

75. I have problems completing my work