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Neurocognitive Outcome Following Recovery from Severe Acute Respiratory Syndrome – Coronavirus-1 (SARS-CoV-1)

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Abstract

Objective: Severe acute respiratory syndrome (SARS) is a highly contagious viral respiratory illness associated with hypoxia and dyspnea. Many of those who contracted and recovered from SARS during the 2002–2003 outbreak reported persistent physical, psychological, and cognitive difficulties. Here, we investigated the residual influences of SARS on cognition for a subset of healthcare professionals who recovered and were referred for neuropsychological evaluation through their workplace insurance. **Method:** Twenty-eight healthcare professionals were evaluated on neuropsychological and mood functioning approximately 1.5 years post-recovery from a severe respiratory illness. Test scores were compared with age-matched normative data, and correlations were examined between mood, self-report memory scales, subjective complaints (e.g., poor concentration, pain, fatigue), illness severity (i.e., length of hospitalization, oxygen use during hospital stay), and cognitive performance. **Results:** Participants performed within age expectations on the majority of cognitive measures including overall memory ability. Although processing speed was generally within normal limits, 43% showed significant speed–accuracy trade-offs favoring accuracy over maintaining speed. Deficits were observed on measures of complex attention, such as working memory and the ability to sustain attention under conditions of distraction. Participants endorsed poorer memory ability than same-age peers on a meta-memory measure and mild to moderate depression and anxiety symptoms. Objective test performance was largely uncorrelated with self-reports, mood, or illness severity, except for moderate correlations between complex attention and participants' subjective ratings of Everyday Task-Oriented Memory. **Conclusions:** These findings demonstrate specific long-term cognitive deficits associated with SARS and provide further evidence of the cognitive effects of hypoxic illnesses.

Keywords: SARS virus, SARS, Coronavirus, Acute respiratory illness, Hypoxia, Cognition

INTRODUCTION

Outbreaks of coronavirus are occurring with greater regularity, as indicated by three epidemics within the last two decades. Most recently, severe acute respiratory syndrome – coronavirus-2 (SARS-CoV-2) surfaced in December 2019 and developed into a worldwide pandemic of the clinical syndrome coronavirus disease 2019 (COVID-19). In this study, we focus on the SARS-CoV-1 (or SARS) outbreak of 2002–2003, which infected approximately 8100 people and claimed the lives of 774 people in 29 countries in under 5 months (WHO, 2015). SARS-CoV-1 initially presents with flu-like symptoms that, in some individuals, progress to life-threatening atypical pneumonia associated with dyspnea (difficult or labored breathing) and hypoxemia (deficient oxygenation of the blood; Kamps & Hoffman, 2004; Moldofsky & Patcai, 2011). Because the mechanism and route of transmission of SARS-CoV-1 were initially unknown, there was an early lack of containment of the disease within hospitals, which resulted in a disproportionate infection rate among healthcare professionals. In Toronto, Canada, where 273 cases

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were reported, healthcare professionals accounted for over 40% of those affected (Muller et al., 2006; Naylor et al., 2003).

Approximately 30–90% of those who survived SARS-CoV-1 experienced residual effects up to 7 years later, such as shortness of breath, chronic fatigue, nonrestorative sleep, muscle and joint pain, psychological disorders [e.g., depression, anxiety, and post-traumatic stress disorder (PTSD), and an overall reduced quality of health and life (Gardner & Moallef, 2015; Herridge et al., 2003; Lam et al., 2009; Moallef, Lueke, Gardner, & Patcai, 2021; Moldofsky & Patcai, 2011)]. A recent meta-analysis supports the neuropsychiatric presentation and revealed similarities among severe coronavirus infections [SARS-CoV-1, SARS-CoV-2 (or COVID-19), and Middle East Respiratory Syndrome (MERS); Rogers et al., 2020]. Importantly, individual factors such as hypoxia, chronic fatigue, pain, and mood can negatively affect cognition (Irani, Barbone, Beausoleil, & Gerald, 2017; Suhr, 2003). However, little is known about the cognitive profile associated with SARS-CoV-1 or with coronaviruses in general.

One recent study assessed cognitive functioning in a small group of patients that were hospitalized due to symptoms of COVID-19 and found declines in attention, memory, language, and praxis (Negrini et al., 2020); of note, the conclusions were clouded by a significant association between impairments and length of stay in the intensive care unit. Another study examined cognitive outcomes in 29 recovered COVID-19 patients using a digital iPad-based online neuropsychological assessment. The authors found a significant deficit in sustained attention compared to controls, according to subcomponents of a continuous performance test (CPT; Zhou et al., 2020). Several individuals who contracted SARS-CoV-1 reported problems with memory and attention after acute symptoms had receded, which raises the possibility that SARS-CoV-1 may have persistent effects on cognitive functioning (Chan, 2005; Sheng, Cheng, Lau, Li, & Chan, 2005). To date, there has been no investigation to objectively characterize the nature and degree of the subjectively reported persistent cognitive difficulties described by some SARS survivors.

As the neuropsychological outcome of SARS-CoV-1 has not been well studied, the mechanism responsible for cognitive and psychological changes is also poorly understood. Subjective cognitive changes are reported in many populations (cognitive aging, cancer, stroke, depressed mood); however, these can be weakly correlated with objective cognitive function and are often more strongly related to mood factors and/or fatigue related to illness (Burmester, Leathem, & Merrick, 2016; O'Farrell, MacKenzie, & Collins, 2013). The neuropsychological sequelae of SARS may very well result from various interacting factors (Rabinovitz, Jaywant, & Fridman, 2020). Hypothesized mechanisms contributing to changes in brain health in this group include indirect effects due to systemic complications (e.g., hypoxia; Ritchie, Chan, & Watermeyer, 2020), psychological trauma (Adhikari et al., 2011; Mak, Chu, Pan, Yiu, & Chan, 2009; Wing & Leung, 2012), as well as potential direct neural damage from the virus (Bohmwald, Gálvez, Ríos, & Kalergis, 2018).

Indeed, considering that one of the critical symptoms of SARS is hypoxemia, its effects may be similar to other hypoxic disorders. Complex attention (sustained, divided, and concentration during interference), mental processing speed, memory, and executive functioning is the most commonly impaired cognitive domains in several hypoxic disorders (see Schultz, Sepehry, & Greer, 2018 for a review), including sleep apnea (Sforza & Roche, 2012; Stranks & Crowe, 2016), chronic obstructive pulmonary disease (Riordan, Stika, Goldberg, & Drzewiecki, 2020; Schou, Østergaard, Rasmussen, Rydahl-Hansen, & Phanareth, 2012; Thakur et al., 2010), hypoxia due to stroke or heart attack (Kim, 2016), and other acute respiratory diseases such as acute respiratory distress syndrome (ARDS; Riordan et al., 2020; Mikkelsen et al., 2012) and hantavirus pulmonary syndrome (HPS; Hopkins, Larson-Lohr, Weaver, & Bigler, 1998). Furthermore, there is a complex relationship between the severity of hypoxia and cognition. For example, the degree of cognitive impairment among individuals with obstructive sleep apnea has been associated with the degree of oxygen deprivation in patients who experience hypoxia (Greenberg, Watson, & Deptula, 1987; Thakur et al., 2010). In addition to these cognitive effects, many hypoxic conditions are also associated with elevated symptoms of depression, anxiety, and PTSD (Kim, 2016; Mikkelsen et al., 2012; Sheng et al., 2005).

Given the scale of the ongoing COVID-19 pandemic, knowledge of long-term cognitive outcomes following infection from a respiratory virus such as SARS-CoV-1 would be useful for future resource planning of those recovering from coronavirus infection. Here, we report on data from neuropsychological and mood functioning that were collected from healthcare professionals approximately 1.5 years post-recovery from SARS-CoV-1. Based on past research investigating the cognitive consequences of other hypoxic illnesses (Kim, 2016; Mikkelsen et al., 2012; Schou et al., 2012; Thakur et al., 2010; see Schultz et al., 2018 for a review), we hypothesized that: (a) survivors of SARS would show impairments on neuropsychological measures of complex attention, memory, and processing speed; (b) survivors would perform normally on less complex measures of attention and memory; (c) degree of cognitive dysfunction would be associated with illness severity; and (d) survivors' subjective complaints would be weakly correlated (if at all) with their performance on objective cognitive measures.

METHOD

Participants

Thirty healthcare professionals from the Toronto area who were classified as having contracted SARS[1] were referred

[1]In 2002/3, there was "possible SARS" and "probable SARS", with criteria for each. Mild cases did not meet the criteria. There were also no criteria for a definitive diagnosis of "SARS;" "probable SARS" was the closest to this and all participants met these criteria (i.e., severe respiratory illness with likely exposure to a laboratory-confirmed case; CDC, 2003).

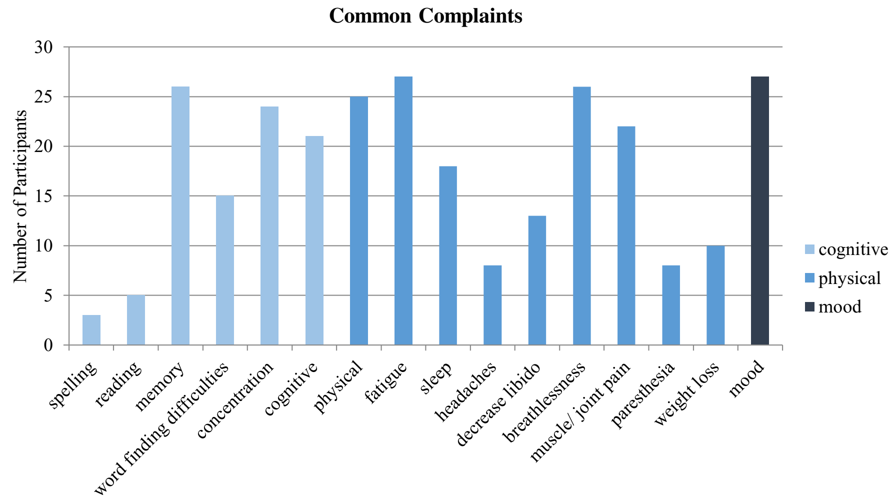

Fig. 1. Common difficulties reported by SARS patients 1.5 years post-recovery.
Common cognitive, physical, and mood complaints were reported by 28 healthcare professionals 1.5 years post-recovery from SARS.

for a neuropsychological evaluation at Baycrest Health Sciences from a provincial government agency SARS rehabilitation clinic at St. John's Rehabilitation Centre. All participants were fully employed healthcare workers, mostly nurses – all were midlevel socioeconomic status. At the time of testing, these healthcare workers were on a leave of absence. They were not dismissed from their employment. During the clinical interview, all participants spontaneously self-reported lingering cognitive, mood, and/or physical changes post-recovery when probed with open-ended questions. Fatigue, low energy, breathlessness, and pain were the most common physical complaints. Poor memory (particularly prospective memory), difficulty attending to complex tasks, and word-finding problems were the most common cognitive complaints (see Figure 1).

The neuropsychological evaluations were conducted to characterize each individual's cognitive profile, understand the personal impacts associated with having had the illness, and provide recommendations for practical strategies that might help minimize the impacts of reduced cognitive capacity. All participants consented to having their neuropsychological evaluation data analyzed as part of a research study to examine the effects of SARS on cognition. This research was conducted in accordance with the Research Ethics Board at Baycrest Health Sciences and St. John's Rehabilitation Hospital and in compliance with the Helsinki Declaration. This research is not under review elsewhere.

Of the 30 participants (28 female) who underwent neuropsychological assessment, data from 2 (females) were excluded due to poor proficiency in English. Specifically, they were non-fluent English speakers whose low FSIQ scores (< 70) were likely an underestimate of their true intellectual abilities. Demographic data for the remaining 28 participants are shown in Table 1. The vast majority of the participants were nurses (79%), and the rest were other interprofessional healthcare providers (e.g., orderlies, an ECG technician, respiratory therapist, paramedic, dietician, case manager, and a business project manager). All participants contracted the virus at their place of work. Testing was conducted approximately 1.5 years postinfection (in late 2004 to early 2005). Participants endorsed symptoms consistent with mild to moderate depression on the BDI-II ($M = 17.4$, with 10 participants falling in the moderate-to-severe range; Beck Depression Inventory-II; Beck, Steer, & Brown, 1996), and mild anxiety on the BAI ($M = 14.0$; Beck Anxiety Inventory; Beck & Steer, 1993).

Materials

The neuropsychological battery was selected based on knowledge of the brain regions most vulnerable to hypoxia and the cognitive processes these regions subserve, and consideration of cognitive skills most critical to the performance of health professionals' work-related duties, such as working memory. See Table 2 for the cognitive domains assessed and the specific tests administered.

Illness Severity

Illness severity was defined as length of hospital stay and whether or not oxygen was administered.

Data Analysis

Mean scaled scores (SS) were obtained for all neurocognitive measures using age-matched normative data. Scores within one standard deviation of the mean were considered average (i.e., $7 \leq SS \leq 13$), while those with SS greater than one standard deviation above or below the mean were classified as above average or below expectations, respectively. Pearson product-moment correlations were conducted to investigate whether the degree of memory complaint or depression and anxiety levels from self-report measures were significantly related to performance on the cognitive measures. Similarly, point-biserial correlations or Pearson

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Table 1. Demographic and psychometric data for SARS patients ($n = 28$)

Variable	Mean	*SD*	Range	%
Age, years	46.7	10.0	24–64	
Education, years	15.0	1.4	12–18	
Gender (females)				93
First language (English)				39
FSIQ	101.9	10.2		
Vocabulary	10.3	2.3		
Matrix Reasoning	10.3	2.4		
Length of Hospitalization	14.9	7.4	5–35	

FSIQ = Full-Scale Intelligence Quotient, estimated using the Wechsler Abbreviated Scale of Intelligence (WASI) Matrix Reasoning and Vocabulary subtests. We have hospital data for 27 of the 28 participants. Of these 27, all were hospitalized, 15 received oxygen, and 2 were in ICU.

Table 2. Neuropsychological test battery

Cognitive domain	Test
Orientation to time and place	WMS-III Orientation subtest
Estimated intellectual function	WASI Matrix Reasoning
	WASI Vocabulary
Simple and complex (executive) attention	DKEFS Trail Making Test
	DKEFS Stroop
	TEA Lottery subtest
	WMS-III Digit Span
	WMS-III Spatial Span
	Consonant Trigrams
	Ruff 2 & 7 Selective Attention Test
	PASAT
Language	Boston Naming Test; 60-item
	D-KEFS Verbal Fluency
Memory	WMS-III Logical Memory
	WMS-III Faces subtest
	RCFT
	CVLT-II
	Event and Time-Based Prospective Memory
Self-reported meta-memory	MAC-S revised
Self-reported mood status	Beck Depression Inventory (BDI-II)
	Beck Anxiety Inventory (BAI)

WMS-III = Wechsler Memory Scale – Third Edition; D-KEFS = Delis–Kaplan Executive Function System (Stroop = Color–Word Interference Test); TEA = Test of Everyday Attention; PASAT = Paced Auditory Serial Addition Task; RCFT = Rey–Osterrieth Complex Figure Test; CVLT-II = California Verbal Learning Test; MAC-S revised = Memory Assessment Clinic Self-Rating Scale; WASI = Wechsler Abbreviated Scale of Intelligence.

product-moment correlations were used to examine the relationship between severity of illness (i.e., duration of hospitalization and requirement of oxygen during hospital stay) and cognitive performance. Lastly, chi-square analyses were conducted to examine the relationship between relevant subjective complaints on the interview (i.e., attention, fatigue, and pain levels) and illness severity (i.e., duration of hospitalization and requirement of oxygen during hospital stay).

Of note, not all participants were administered the full complement of tests. This was a clinically informed decision to further streamline the battery for greater efficiency while examining the intended cognitive constructs that would aid in advising return to work decisions. Consequently, the following subtests had missing data (with a total number of participants in parentheses): TEA Lottery subtest ($n = 15$); PASAT test ($n = 25$); WMS-III Logical Memory and Faces subtests ($n = 17$); and MAC-S self-report ($n = 27$).

RESULTS

Orientation and Estimated Intellectual Function

All participants were oriented to time and place. Estimated general intellectual function was within the normal range (see Table 1), and performance on the Vocabulary and Matrix Reasoning subtests was equivalent (WASI; Wechsler, 1999).

Simple and Complex Attention

Performance was within normal limits on tasks of simple attention and processing speed (Figure 2). Specifically, performance was average for the DKEFS (Delis, Kaplan, & Kramer, 2001) Number and Letter Sequencing subtests, the Color Naming, and Word Reading subtests of the DKEFS Color–Word Interference Test, the WMS-III forward digit and spatial spans (Wechsler, 1997), the Ruff 2 & 7 Test including both automatic and controlled cancelation tasks' speed and accuracy ratings (Ruff et al., 1992), and the TEA Lottery subtest (Robertson, Ward, Ridgeway, & Nimmo-Smith, 1994). Working memory, as measured by the WMS-III backward digit and spatial spans, was within expectations. Overall, participants showed normal cognitive set shifting on the DKEFS Trail Making Test Switching subtest, Color–Word Interference Test, and fluency switching tasks.

Examination of the Ruff 2 & 7 Test revealed that nearly half the participants (43%) showed a significant speed–accuracy trade-off, in which they sacrificed speed to maintain accuracy. Other measures of complex attention showed evidence of mild deficit, particularly those that placed increased demands on working memory and are more vulnerable to distraction. Specifically, performance on tests of complex forms of attention, the PASAT (Gronwall, 1977) and Consonant Trigrams, was below expectations.

Language

Overall language performance was generally within expectations. Performance on the DKEFS verbal fluency tasks was within normal limits, both when participants were required to generate words beginning with particular letters as

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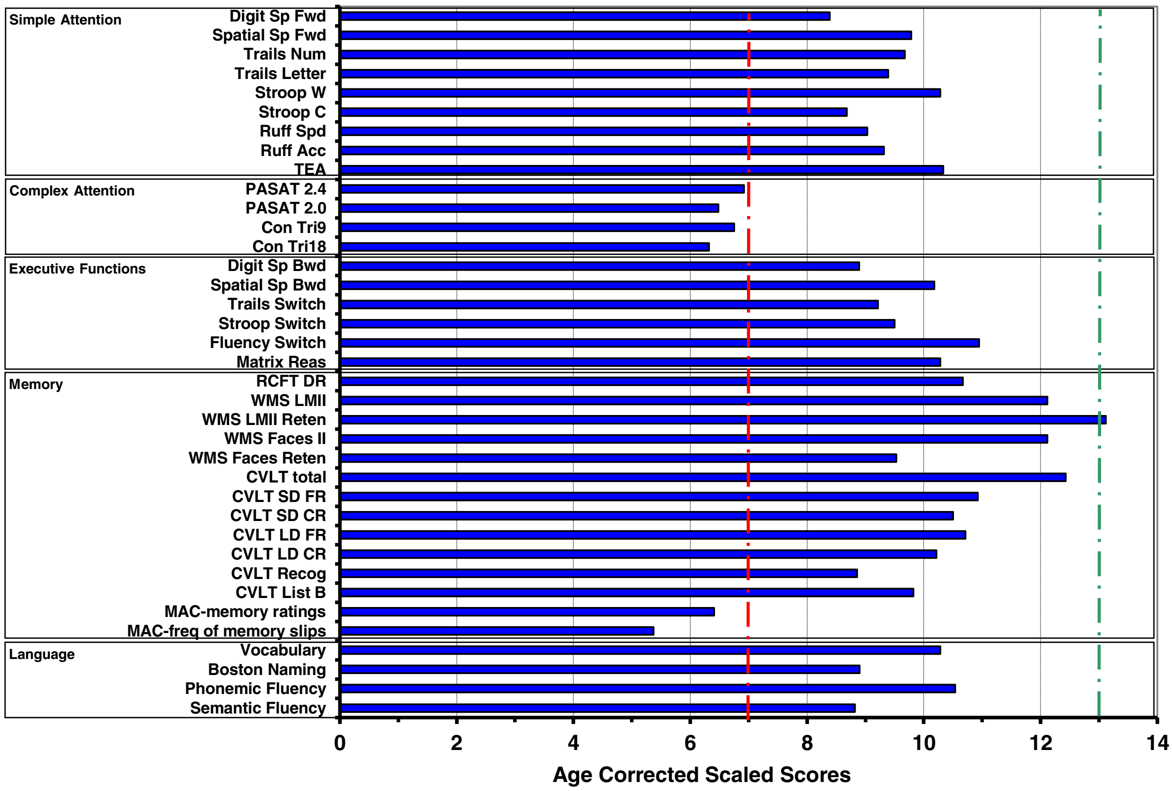

Fig. 2. Neurocognitive profile of SARS patients 1.5 years post-recovery.
Bars represent aggregate neuropsychological test scores from 28 SARS participants. Red dotted line = 1 standard deviation below the expected mean. Green dotted line = 1 standard deviation above the mean. Sp = span; Fwd = forward; Num = number; W = word; C = color; Spd = speed; Acc = accuracy; TEA = Test of Everyday Attention; PASAT = Paced Auditory Serial Addition Task; Con Tri = Consonant Trigrams; Bwd = backward; Switch = switching; Matrix Reason = Matrix Reasoning; RCFT DR = Rey–Osterrieth Complex Figure Test delayed recall; WMS = Wechsler Memory Scale; LM = Logical Memory; Reten = retention; CVLT = California Verbal Learning Test; SD = short delay; FR = free recall; CR = cued recall; LD = long delay; Recog = recognition; MAC-S = Memory Assessment Clinic Self-Rating Scale; freq = frequency.

well as specific categories. Although performance on the BNT (Kaplan, Goodglass, & Weintraub, 1983) was significantly below average, this test is a highly culturally bound measure of word-finding ability. To compensate for this, all participants were on average credited for four items that more than 20% of people with diverse cultural and linguistical backgrounds typically get incorrect (see Chen et al., 2014; Mariën, Mampaey, Vervaet, Saerens, & De Deyn, 1998; Roberts & Doucet, 2011; Tallberg, 2005); once doing so, their performance was within normal limits (SS = 8.9).

Memory

Performance was average to above average on most tests of memory, including immediate and delayed recall of the Rey–Osterrieth Complex Figure Test (Stern et al., 1994), delayed recall of the Logical Memory and Faces subtests of the WMS-III, all trials of the CVLT-II (Delis, Kramer, Kaplan, & Ober, 1987), and both time and event-based tasks of prospective memory (with percentage hits at 89% for time and 93% for event; Event and Time-Based Prospective Memory; Troyer & Murphy, 2007).

Performance on a memory ability task mediated by executive cognitive processes was impaired in up to 40% of participants. Specifically, proactive interference as measured by comparison of List B to List A Trial 1 recall on the CVLT-II was generally normal ($M = 8.96$, $SD = 3.04$). However, 29% of the sample showed significant proactive interference (i.e., 1.5 standard deviations below average), and 39% had scores (SS ≤ 7) one standard deviation or more below the average. Thus, despite normal performance on the learning trials, a number of participants had difficulty actively filtering out information that was no longer useful. Importantly, performance on the CVLT Forced Choice
was 99.5% on average (range: 94–100), and this is above the recommended cutoff of 87.5% for valid responding (Schwartz, Erdodi, Rodriguez, Ghosh, Curtain, Flashman, & Roth, 2016).

Self-Report Scales

On the MAC-S self-report measure, participants rated their memory as significantly lower than same-age peers and reported an increased frequency of memory problems.

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Table 3. Correlations between cognitive and mood ratings and complex attention measures

Self-report questionnaires	PASAT 2.4	PASAT 2.0	Consonant Trigrams (9s)	Consonant Trigrams (18s)	CVLT Proactive Interference
MAC-S Ability, *r* (*df*)	.36 (23)	.01 (23)	.20 (25)	.10 (25)	−.27 (25)
Everyday Memory	.48 (23)*	.18 (23)	.23 (25)	−.02 (25)	−.29 (25)
MAC-S Frequency, *r* (*df*)	.37 (23)	.30 (23)	.30 (25)	.07 (25)	.11 (25)
Everyday Memory	.52 (23)**	.44 (23)*	.24 (25)	−.16 (25)	−.06 (25)
Attention	.29 (23)	.16 (23)	.30 (25)	.25 (25)	.10 (25)
Depression (BDI-II), *r* (*df*)	−.16 (23)	−.39 (23)	.03 (26)	.01 (26)	.15 (26)
Anxiety (BAI), *r* (*df*)	.34 (23)	.22 (23)	−.04 (26)	−.00 (26)	.07 (26)
Length of Hospitalization, *r* (*df*)	.34 (22)	.18 (22)	.14 (25)	−.02 (25)	−.08 (25)
Oxygen Use, χ^2 (*df*)	−.13 (23)	−.17 (23)	−.03 (26)	−.17 (26)	.25 (26)

Pearson product-moment correlation coefficients between participants' self-ratings of memory and attention ability and frequency, as measured by the Memory Assessment Clinic Self-Rating Scale (MAC-S) questionnaire and their performance on complex attention measures (i.e., PASAT, Consonant Trigrams, and proactive interference on CVLT). Pearson correlation coefficients are also presented between the complex attention measures and participants' emotional state, as measured by the Beck Depression Inventory (BDI-II) and Beck Anxiety Inventory (BAI). Pearson correlation and point-biserial correlation coefficients between complex attention tasks and severity of illness (i.e., duration of hospitalization and oxygen use). Correlation coefficients significant at a .05 two-sided significance level ($p < .05$) were considered statistically significant.
*Statistically significant at $p < .05$.
** Statistically significant at $p < .01$.

However, overall self-ratings were not significantly associated with performance on any of the cognitive measures on which participants showed difficulty (i.e., PASAT, Consonant Trigrams, and the proactive interference measure on the CVLT-II), *r*s = .01–.37, *p*s = .067–.975 (see Table 3).

Given that some MAC-S items probe behaviors that have a greater attentional involvement (i.e., Everyday Task-Oriented Memory and Attention/Concentration subscales), these items may be more specifically related to the cognitive performance observed in the sample (see Crook & Larrabee, 1990). To explore this possibility, a second set of correlations was run with scores averaged from the Everyday Task-Oriented Memory subscale. A combined score of items comprising the Everyday Task-Oriented Memory *ability* factor of the MAC-S showed a medium-sized correlation with scores on the PASAT 2.4s. Similarly, the Everyday Task-Oriented Memory *frequency* factor showed medium to large correlations with performance on the PASAT 2.4s and PASAT 2.0s tasks. However, the Attention/Concentration factor itself was not significantly correlated with any of the more challenging complex attention tasks.

Depression and anxiety levels were uncorrelated with cognitive measures, *r*s = .01 – .39, *p*s = .054 – .962. Furthermore, depression and anxiety ratings were unrelated to each other, $r(26) = .19$, $p = .342$.

Subjective Complaints and Illness Severity

The most prominent cognitive complaints reported by participants on the interview included poor prospective memory, problems with concentration and distractibility, and word-finding difficulties (see Figure 1). Common physical complaints were breathlessness, muscle/joint pain, low energy (with decreased libido), fatigue, poor sleep, and weight loss (15–20 pounds). Overall, correlational analyses revealed that there was generally no significant relationship between subjective cognitive or physical complaints (i.e., problems with attention, fatigue, and pain) and illness severity (length of hospitalization, whether oxygen was given; see Table 4). However, there was a significant moderate relationship between self-reported reduced attention and duration of hospitalization.

Table 4. Correlations between illness severity and subjective complaints from interview

Subjective reports from interview	Length of hospitalization (*r*, *df*)	Oxygen use (χ^2, *df*)
Attention	−.38 (25)*	2.91 (26)
Fatigue	.02 (25)	1.20 (26)
Pain	−.12 (25)	1.26 (26)

Point-biserial correlation coefficients between duration of hospitalization and subjective cognitive and physical complaints were obtained from the clinical interview. Chi-square coefficients between oxygen use and subjective complaints were obtained from the interview. Coefficients significant at a .05 two-sided significance level ($p < .05$) were considered statistically significant.
*Statistically significant at $p < .05$.

Table 5. Mean scaled scores for attention switching tasks for individuals who received and did not receive oxygen

Cognitive measure	Oxygen received		Oxygen not received	
	M	*SD*	*M*	*SD*
DKEFS Verbal Fluency	9.5	4.1	12.6	3.29
DKEFS Trail Making Test	9.1	2.7	9.4	1.6
DKEFS Stroop	8.2	2.5	11.0	2.5

D-KEFS = Delis–Kaplan Executive Function System; Stroop = Color–Word Interference Test.

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An additional analysis was conducted to examine if oxygen status influenced test findings given that a subset (i.e., 15 of 28) of participants had received oxygen. The data revealed that oxygen status significantly affected performance on (two of three) attention switching tasks only. Individuals who had not received oxygen significantly outperformed individuals who had received oxygen on the Switching subtests of DKEFS Verbal Fluency, $t(26) = 2.16$, $p = .04$ and Stroop, $t(26) = 2.92$, $p = .007$, but not on the Trail Making Test, $t(26) = .37$, $p = .71$ (see Table 5 for each subtest's mean SS and standard deviations). Of note, participants' overall performance on switching tasks was within normal limits. Participants who received oxygen ($M = 19.9$, $SD = 7.5$, $n = 15$) also endorsed more symptoms of depression than those who did not receive oxygen ($M = 14.5$, $SD = 3.8$, $n = 13$), $t(26) = -2.35$, $p = .027$.

DISCUSSION

This study examined the persistent neuropsychological sequelae among survivors of SARS-CoV-1. Individuals who recovered from the illness showed chronic cognitive difficulties 1.5 years post-illness on tasks of complex attention and working memory that rely on executive thinking skills. Specifically, below-expected performance was observed on complex attention measures that required participants to either maintain concentration in the face of interference or ignore irrelevant but once salient information to accurately complete a task. Poor target/nontarget discrimination and deficits in filtering information is also consistent with executive dysfunction. Additionally, participants who received oxygen had poorer performance on most attention switching tasks, though their overall performance on these tasks was within normal limits.

Furthermore, approximately half of the participants exhibited slower processing speed when performing tasks that required controlled attention and concentration, which is suggestive of increased mental effort. Participants performed within normal limits on simple measures of attention and concentration, immediate and delayed memory, reasoning skills, visuospatial ability, and language. Although some participants endorsed word-finding difficulties, the cultural bias inherent in the measure used to evaluate confrontation naming limited interpretation of performance on this measure. Participants also endorsed poorer memory ability than same-age peers, and mild to moderate symptoms of depression and anxiety. Participants who received oxygen endorsed more symptoms of depression than those who had not received oxygen.

It is worth noting that because testing was conducted in a highly controlled environment, it is possible that functional difficulties could be worse during real-world day-to-day experiences. Indeed, participants' complaints about everyday attention-related memory slips were significantly correlated with one of the most challenging complex attention tasks given to them (i.e., PASAT). Arguably, complex attention, among other executive functions, is perhaps a more sensitive measure of real-world functioning. The importance of complex attention to daily functioning has been supported in a meta-analysis, which showed that executive function ability (including complex attention) is one of the most reliable predictors of return to work (among individuals with traumatic brain injury; Ownsworth & McKenna, 2004).

The cause of persistent cognitive symptoms in SARS survivors is not fully understood, but the evidence is highly suggestive of hypoxemia, or hypoxia-induced brain injury. Hypoxic injury has been shown to affect such cognitive domains as attention and vigilance, memory, and executive functions (see Schultz et al., 2018 for a review). Tests of sustained attention and memory are particularly sensitive to hypoxia, and there is a dose-dependent relationship between hypoxia and cognitive deficits (Stuss, Peterkin, Guzman, Guzman, & Troyer, 1997). The current findings of a relative weakness on tasks of vigilance and self-monitoring among SARS survivors suggest that brain regions involved in the control of executive attention are compromised.

The present observed executive deficits can be mapped to Stuss's theory of frontal lobe functioning that proposes a fractionation of processes: energization, monitoring, and task setting (Stuss, 2006; Henri-Bhargava, Stuss, & Freedman, 2018). According to this theory, energization (or activation) is mediated by the superior medial frontal lobe region and is important for response initiation and maintenance. Individuals with lesions in the superior medial frontal lobe are more likely to have slower reaction times on tasks that recruit significant brain resources (Stuss, 2006). Vigilance and monitoring are important processes of the right lateral frontal lobe, whereas increased errors are observed with lesions in the left lateral prefrontal cortex due to poor criterion setting (Stuss, 2006, 2011). In the present SARS-CoV-1 sample, participants' difficulty on a complex sustained attention task and slowed processing speed on another (possibly to maintain accuracy), was perhaps indicative of superior medial frontal lobe dysfunction. Indeed, this pattern of slowing is suggestive of difficulty maintaining alertness and is consistent with data on disrupted superior medial frontal lobe function (Stuss, 2006). The superior medial frontal lobe has been shown to be susceptible to dysfunction in hypoxic conditions (Rosenzweig et al., 2015). Furthermore, participants in the current study showed vigilance and monitoring errors on attentional tasks, which was suggestive of right lateral frontal lobe deficits.

Our results support recent research on the cognitive outcome of SARS-CoV-2, with the primary domain affected being complex attention (Zhou et al., 2020). The findings also provide converging evidence with the extant literature on the impact of hypoxic illnesses such as sleep apnea, chronic obstructive pulmonary disease (COPD), and ARDS on cognition (Hopkins et al., 2005; McMorris, Hale, Barwood, Costello, & Corbett, 2017; Mikkelsen et al., 2012; Schou et al., 2012; Sforza & Roche, 2012). Specifically, the cognitive sequelae of SARS were less severe than other hypoxic disorders, with mild deficits evident during complex attention and memory tasks only. Oxygen saturation levels were not available for all participants, and we were unable to determine if illness severity based on this factor correlated with performance on complex attention and memory tasks. Nonetheless, the data suggest a possible link between subjective reports of attentional errors and illness severity, as measured by duration of hospitalization. In addition, given the findings of reduced attention switching among the subset of participants who received oxygen, we speculate that the requirement of oxygen may represent an additional level of severity that is worth further investigation in future studies.

Importantly, the neurocognitive and mood-related difficulties found among the current sample were consistent with evidence from other studies on hypoxic illnesses (Gardner & Moallef, 2015; Moldofsky & Patcai, 2011; Mikkelsen et al., 2012; Schou et al., 2012; Sforza & Roche, 2012). The persistence of symptoms reported is in line with severe cases of influenza. That is, one study found that psychological impairment following recovery from H7N9 influenza persisted at 2 years (Chen et al., 2017), while another study found that a large proportion of individuals with H1N1 influenza were experiencing depression and anxiety, decreased quality of life, and an elevated risk of PTSD 1-year post-discharge (Luyt et al., 2012). Although the underlying mechanism for persistent symptoms following recovery from influenza is unclear, Luyt and colleagues proposed that significant respiratory distress leading to hypoxemia may be one possible contributor. Thus, it is reasonable to believe that hypoxemia is an important differential for the SARS-CoV-1 neurocognitive profile.

Another consideration is the direct effect of mood and physical complaints on cognition. Meta-analytic studies have revealed significant effects of depression across measures of attention, processing speed, encoding and retrieval memory, and executive functions (Rock, Roiser, Riedel, & Blackwell, 2014; Zakzanis, Leach, & Kaplan, 1998). Similarly, neurocognitive deficits that are commonly present in individuals with a history of chronic pain include memory, processing speed, and attention (Higgins, Martin, Baker, Vasterling, & Risbrough, 2018). The triad of physical, cognitive, and psychological symptoms seen in respiratory illnesses (Rogers et al., 2020; Riordan et al., 2020) are also found in clinical syndromes, such as post-concussion syndrome (PCS). Analogous to PCS, a number of moderating factors may influence the persistence of symptoms experienced by some SARS survivors, and also like PCS, it is unclear why some SARS survivors have ongoing symptoms and others do not (Marshall, 2020). PCS research suggests that full recovery may depend on such factors as injury severity, age, comorbidities, cognitive reserve prior to syndrome onset, presence of affective disturbance that prolongs and/or worsens symptoms, level of resiliency, environmental demands, and expectations (Cole & Bailie, 2016; Lezak, 2012). It is possible that similar factors influence recovery from SARS.

It is possible that the persistent effects of mild hypoxia-producing conditions, such as SARS-CoV-1, constitute a syndrome. There may be moderating factors related to vulnerability and resiliency that put individuals at risk of developing persistent symptoms, as well as those that relate to protracted rates of recovery. For example, psychological distress, PTSD symptoms, level of support, and amount of time given to recover before being required to return to normal daily activities could all be potential contributors. Furthermore, the specific environment (e.g., healthcare) and/or sociocultural aspects may represent an additional contextual element. Unfortunately, we were unable to address whether or not there are sex differences in the impact of SARS given that our sample was over 90% female working in a female-dominated profession (80% of our sample were nurses; see Statistics Canada, 2005 for gender-based employment data). To our knowledge, the results from other publications examining the health impacts of SARS on affected individuals have not reported gender differences.

Nonetheless, the experience for SARS survivors in Toronto was found to be more psychologically distressing than for those living in a nearby city where the outbreak was not as significant (Maunder et al., 2006). Indeed, Moallef and colleagues (2021) recently published findings from a 4- and 7-year follow-up of Toronto healthcare workers who had contracted SARS. Their data revealed that SARS can have chronic psychological effects, particularly among healthcare workers who had client-facing roles that exposed them to the virus. Of the healthcare workers who had contracted SARS, 78% were still experiencing clinically significant symptoms of PTSD (avoidance and hyperarousal scores were moderately related to adverse functioning), approximately 50% had clinically significant symptoms of depression and anxiety, and 69% scored in the clinically impaired range on a measure of overall well-being (Moallef et al., 2021).

Client-facing healthcare professionals had one of the lowest return-to-work rates among SARS survivors (Gardner & Moallef, 2015; Kwek et al., 2006; Moallef et al., 2021; Wu et al., 2009). Thirty percent of healthcare professionals who survived SARS-CoV-1 did not return to work, whereas others resumed on modified duties because they were unable to keep up with the multiple demands of their role in the workplace (Ngai et al., 2010). Most of the participants in our sample were nurses, a role for which complex attention and executive functions are critical to monitor, track, and carry out intended tasks. In our sample, approximately 64% of healthcare professionals were not working at the time of the assessment. Although this rate is high, the sample is likely biased given it is based on survivors with persistent cognitive complaints that affected their ability to return to functioning at their premorbid level within the work environment. Moallef and colleagues (2021) revealed that even 7 years postinfection, 66% of healthcare professionals were either unemployed or on disability.

Unfortunately, our study is limited by a relatively small sample size and lack of comparison group. Future studies examining neurocognitive outcomes will benefit from the inclusion of a larger sample and control group in order to replicate these findings and enhance generalizability. As stated earlier, another study limitation is our predominantly female sample, which precluded an examination of gender differences in the health impacts of SARS on affected individuals. Lastly, a worthy investigation is the degree of SARS-related hypoxic injury on neurocognitive sequelae, particularly complex attention. Unfortunately, we did not have oxygen saturation levels to examine this relationship. A longitudinal sample is warranted to explore gender differences and oxygen saturation levels among SARS survivors.

Nonetheless, the current findings provide objective evidence of cognitive deficiencies in SARS survivors who experience subjective difficulties post-recovery. Whereas, the current literature accounts for the long-term physical and psychological effects of SARS, our study points to the need to examine the prevalence and potential persistence of cognitive deficits associated with coronavirus and other severe infectious diseases. Indeed, the past outbreak of another coronavirus, MERS (Butler, 2015; Hilgenfeld & Peiris, 2013; WHO, 2013), and SARS-CoV-2, illustrate that similar-acting viruses do sporadically appear, which underscores the relevance of this research. The prediction of the long-term neuropsychological outcomes of coronavirus infections is especially important now given the large number of infections due to the current ongoing COVID-19 pandemic. Importantly, our interpretation of these findings is not based on causal inference, rather it is based on the discovery of an association between ongoing subjective and objective cognitive difficulties and having experienced probable SARS.

Neurocognitive assessments are necessary to ensure that accommodations are set in place for individuals to return to employment that is commensurate with their capacity. The cognitive effects of SARS beyond 2 years are unknown. However, other hypoxic conditions such as obstructive sleep apnea put patients at greater risk of developing mild cognitive impairment at a later age, and it has been suggested that its effects may be due to an acceleration of the aging process (Sforza & Roche, 2012). Early evaluation of individuals recovering from hypoxic conditions should assess physical, psychological, and neurocognitive functioning. It is with heightened awareness and comprehensive evaluation that we may identify symptoms that benefit from treatment, such as poor mood, sleep deprivation, and pain. Consequently, we can more effectively intervene with the goal of preventing, reversing, or reducing cognitive decline and improving the overall well-being of affected individuals.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this paper.

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