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Assessing Neuropsychological Changes Post COVID-19 Infection Using The Global Neuropsychological Assessment

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ASSESSING NEUROPSYCHOLOGICAL CHANGES POST COVID-19 INFECTION USING THE GLOBAL NEUROPSYCHOLOGICAL ASSESSMENT

by

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This dissertation, submitted by Jeremy McAlpine Raines in partial fulfillment of the requirements for the Degree of Doctor of Philosophy from the University of North Dakota, has been read by the Faculty Advisory Committee under whom the work has been done and is hereby approved.

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Jeremy McAlpine Raines
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TABLE OF CONTENTS

LIST OF TABLES

Table Page

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ABSTRACT

COVID-19 is characterized by a respiratory syndrome with severity ranging from mild upper respiratory tract illness to severe interstitial pneumonia and acute respiratory distress syndrome. Although physical symptoms are most common in those infected with COVID-19, patients may present with several neuropsychiatric sequelae caused by direct central nervous system infection, neuroinflammation, and/or prolonged hypoxia encephalitis. Though extent literature on COVID-19 related cognitive decline is still in its infancy, it has been suggested neurological impairment is most common in those with severe symptom presentation, requiring hospitalization and among those who have experienced hypoxic events. In the current study, sixty-two healthy controls and sixty-two individuals previously infected with COVID-19 were administered the Global Neuropsychological Assessment (GNA), Hopkins Adult Reading Test, and Mental Status Exam-Telephone Version and completed a COVID-19 symptom questionnaire in a telehealth format. The GNA consists of subtests intended to measure learning and memory, attention, processing speed, language, executive functioning, and mood. Those previously infected with COVID-19 largely experienced benign symptom presentation, as only three required hospitalization and only two required intubation. Of the tests administered the two groups performances were only significantly different on the processing speed subtest of the GNA. However, multiple regression analysis revealed this difference was accounted for only by age, not COVID-19 diagnosis status. Examination of outliers in the COVID-19 group revealed those with relatively severe COVID-19 symptom presentation were not among the outliers on any GNA subtest. These results imply that individuals with a benign COVID-19 symptom presentation do not appear to be cognitively impacted as a result. These results are also promising regarding the clinical utility of the GNA as a clinical and research tool.

CHAPTER I

INTRODUCTION

The 2019 novel coronavirus (SARS-CoV-2 or COVID-19) is a new human coronavirus which was initially discovered December 2019 in Wuhan, China and has since spread with epidemic features around the world. As of November 12, 2022, over 635 million cases have been confirmed worldwide with over 97.8 million cases in the United States resulting in 6.61 million confirmed deaths worldwide and over 1.07 million deaths in the United States (World Health Organization, 2022). Although many have recovered, it is unclear at this time if non-fatal contraction of COVID-19 is a risk factor for neuropsychological decline after all other symptoms have abated. However, due to common psychological and neuropsychological sequelae, calls to action have been made to prepare the psychiatric community to equip itself with assessment tools to appropriately assess individuals infected by COVID-19 (Singh, 2020). The current study examines the results of a brief neuropsychological measure administered to individuals with a historical positive COVID-19 test and healthy controls.

COVID-19 Infection

Coronavirus disease (COVID-19) is the clinical syndrome associated with SARS-CoV-2 infection. COVID-19 is characterized by a respiratory syndrome with severity ranging from mild upper respiratory tract illness to severe interstitial pneumonia and acute respiratory distress syndrome (ARDS; Wang et al., 2020). COVID-19 belongs to the same *Betacoronavirus* genus as six previously identified coronaviruses which can infect humans (Desforges et al., 2019). Four of these previously identified viruses cause seasonal, predominantly mild respiratory illness. The other two coronaviruses, severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) previously led to major epidemics with deaths related to respiratory disease.

Human coronaviruses are single-stranded RNA viruses which can cause upper respiratory tract infections even in immunocompetent individuals (Lu et al., 2020; Desforges et al., 2019) and have been detected in the brain and cerebrospinal fluids in individuals affected by seizures, encephalitis, and encephalomyelitis (Bohmwald, 2018). Human coronavirus infections are not restricted to the respiratory tract, with RNA from two coronavirus strains (229E, OC43) detected in human brain autopsy samples from neurologically affected individuals and inter-neuronal propagation and axonal transport may even favor viral invasion of the CNS (Arbour et al., 2000; Dubé et al., 2020; Jarrahi et al., 2020; Talbot et al., 1994). Retrograde axonal transport has been demonstrated to cause rapid spread to the brain (Fodoullian er al., 2020), giving the virus an entry to the brain through endothelial cells lining the blood-brain barrier and through the vagus nerve (Lochhead & Thorne, 2012). Additionally, cytokine storm, an immune reaction to COVID-19, can activate brain glial cells, which can lead to delirium, depression, bipolar disorder, and obsessive compulsive disorder (Lochhead & Thorne, 2012).

Coronavirus Symptomatology

COVID-19 appears to be associated with less severe infections than SARS and MERS, though with a wider spread (Munster et al., 2020). SARS and MERS cause severe respiratory illness and studies have been conducted to examine the acute and post-illness psychiatric and neuropsychiatric outcomes of these diseases. Though direct comparisons between SARS, MERS, and COVID-19 has been cautioned due to chronic sequelae of COVID-19 and potential confounding factors being (Sommer & Bakker, 2020), it may still be useful to examine past literature related to SARS and MERS. Though uncommon, SARS has been detected in cerebrospinal fluid (CSF) and brain tissue at autopsy for individuals who experienced cases of encephalopathy with seizures (Hung et al., 2003; Lau et al., 2004). In adults with MERS, single-

digit cases have been reported of individuals with encephalomyelitis, cerebrovascular disease, and brainstem encephalitis (Algahtani et al., 2016; Arabi et al., 2015; Kim et al., 2017).

The most common presenting symptoms in early COVID-19 studies include fever, cough, sore throat, and labored breathing, though 81% of cases had mild symptoms and 1.2% of cases were asymptomatic (Petrosillo et al., 2020). Overall, COVID-19 appears to be different from SARS regarding clinical features. It is less lethal than MERS which is less closely related to SARS and COVID-19 in terms of phylogenetic and pathogenetic features (Petrosillo et al., 2020). Because COVID-19 has less lethal symptomatology than SARS and MERS, it can spread throughout the community more easily.

Although physical symptoms are most common in those infected with COVID-19, patients may present with several neuropsychiatric sequelae caused by direct central nervous system (CNS) infection, neuroinflammation, and/or prolonged hypoxia encephalitis (Steardo et al., 2020). An early study of individuals in Wuhan admitted to the hospital for COVID-19 infection showed 36% suffered neurological features, mostly consisting of dizziness and headache, but with some as severe as encephalitis (Mao et al., 2020). Other studies have reported additional common neurological symptoms including nausea, anosmia, aguesia, myalgia, confusion, disorientation, vomiting, encephalitis, and increased stroke risk (Dubé et al., 2020; Helms et al., 2020; Gane et al., 2020; Kotfis et al., 2020; Poyiadji et al., 2020; Talan, 2020; Yan et al., 2020). One retrospective report described encephalopathy or alterations in consciousness lasting greater than 24 hours in approximately one-fifth of individuals with COVID-19 (Chen et al., 2020). Some evidence of hypercytokinemia has been reported in hospitalized COVID-19 patients, which could lead to long-term post COVID-19 delirium, particularly in elderly patients (Yang et al., 2020). This can even occur in patients without nose block or other signs typically

seen in those with respiratory infections (Speth et al., 2020). The long-term neuropsychiatric effects following recovery from COVID-19 are currently unknown (Troyer et al., 2020). Although these symptoms may be due to systemic illness rather than a neurological syndrome, some patients had acute cerebrovascular disease or impaired consciousness concurrent with their illness (Mao et al., 2020). Neuropsychological symptoms may be proportionately rare, though with how widespread COVID-19 has become, a considerable number of individuals worldwide may be affected by neurological symptoms (Pleasure et al., 2020; Troyer et al., 2020).

In addition to medical and neuropsychiatric implications, there are several widespread psychiatric implications (World Health Organization, 2020; The Lancet Psychiatry, 2020). Individuals are impacted socially by following social distancing and quarantine suggestions and mandates (Lewnard & Lo, 2020; Brooks et al., 2020), which could cause psychological stressors amongst afflicted and non-afflicted individuals, including anxiety (Asmundson & Taylor, 2020), social isolation (Brooks et al., 2020), stress in health-care and other essential workers (Greenberg et al., 2020) and unemployment and financial difficulties (Chaves et al., 2018). Those afflicted may further suffer psychologically due to concern regarding their illness (Xiang et al., 2020), social stigma (Siu, 2008), and traumatic memories of their severe illness (Jones et al., 1998). Socially, this public health emergency has led even those who are unafflicted to exhibit vulnerabilities to loneliness, uncertainty, feelings of vulnerability to COVID-19 infection, economic difficulties, and career difficulties, which may lead to many being vulnerable to development of psychological disorders (Pfefferbaum & North, 2020).

Several psychological complications, such as depression, anxiety, and trauma-related symptoms have been associated with previous coronavirus pandemics, but it is uncertain whether these sequelae are related to the viral infections themselves or to the host immune response

(Troyer et al., 2020). Studies of healthcare workers during these pandemics suggest these psychiatric symptoms are associated with proximity to infected individuals (Kang et al., 2020, Lai et al., 2020, Lee et al., 2018, Lin et al., 2007), though no known studies in the literature have compared healthcare workers who have contracted coronaviruses during the pandemics to those who remained uninfected. Although data on COVID-19 survivors is inconclusive at this time, SARS survivors have been clinically diagnosed with PTSD (55%), depression (39%), pain disorder (36%), panic disorder (33%), and obsessive-compulsive disorder (16%), at 31-50 months post-infection (Lam, 2009). Conversely, only 3% of individuals studied had a pre-infection psychiatric diagnosis.

An extensive meta-analysis of 72 independent studies investigates acute and post-illness SARS and MERS cases (Rogers et al., 2020). During the acute phase of illness, approximately 42% reported insomnia, 36% reported anxiety, 38% of individuals reported impaired concentration or attention, 34% reported impaired memory, 33% reported depressed mood, 28% reported confusion, 29% reported emotional lability, 21% reported altered consciousness, 21% reported pressured speech, 8% reported euphoria, 7% reported aggression, and 2-5% reported irritability, auditory hallucinations, persecutory ideas, visual hallucinations, and suicidality.

Amongst those polled post-illness, 30% reported a frequent recall of traumatic memories, 24% reported emotional lability, 20% reported impaired concentration or attention, 19% reported impaired memory, 19% reported fatigue, 12% reported insomnia, 12% reported anxiety, 12% reported irritability, 11% reported depressed mood, and 1-5% reported unspecified psychotic symptoms, visual hallucinations, persecutory ideas, aggression, self harm, or confusion (Rogers et al., 2020). Most of these studies were performed in hospital settings, which necessitates

caution when generalizing any findings to COVID-19 cases (especially regarding those with mild symptoms).

Overall, neurological complications amongst individuals with SARS and MERS have been rare (Ellul et al., 2020). In a sample of 8096 individuals infected with SARS, 3 (0.04%) experienced CNS complications and 4 (0.05%) experienced PNS complications. In a sample of 2228 individuals infected with MERS, 5 (0.20%) experienced CNS complications and 4 (0.16%) experienced PNS complications. Similar trends are expected for those infected with COVID-19. However, with the number of cases worldwide now in the hundreds of millions, even a rarity among those who have been infected with COVID-19 may be of numerical significance to healthcare providers.

One key question regarding neurological symptoms manifesting as a result of COVID-19 is the mechanism by which such symptoms may occur (Ellul et al., 2020). Direct infection and inflammation to the CNS and PNS is thought to be possible through the olfactory bulb, as it is the only part of the CNS not protected by the dura and may explain the common anosmia in individuals infected with COVID-19. Further, this is the entry route by the herpes simplex virus which sometimes causes sporadic viral encephalitis (Solomon, 2009). However, unlike the herpes simplex virus, current data do not suggest COVID-19 is highly neurovirulent.

Perhaps more common than direct infection of the CNS or PNS is the indirect neurological complications resultant from COVID-19 related cerebrovascular disease. COVID-19 can cause damage to endothelial cells, which activates inflammatory and thrombotic pathways (Varga et al., 2020). Microvascular and macrovascular complications in the brain can be caused by endothelial dysfunction, which is a potential consequence of COVID-19 infection (Klok et al., 2020).

Respiratory Conditions

Considering coronaviruses are known to target the respiratory system in humans (Rothan & Byrareddy, 2020), previous research regarding the effects of chronic pulmonary diseases on cognition may be useful in informing research on cognition in COVID-19 patients. As several conditions affecting the flow of oxygenated blood to the brain have been demonstrated to incur neurological sequelae and symptoms in afflicted individuals, it is an important consideration when examining individuals who have been infected with COVID-19.

COVID-19 has been shown to access host cells through the ACE2 enzyme, which is present in the type II alveolar cells within the lungs (Letko et al., 2020). Cellular failure of lung-based type II alveolar cells has been linked to several pulmonary diseases (Beers & Moodley, 2017). As such, pneumonia has been reported as a frequent serious clinical manifestation of COVID-19 exposure with common symptoms including dry cough, dyspnea, and lung CT scans showing a 'ground-glass' opacity (Huang et al., 2020). Pneumonia has consistently been shown as the most frequent serious manifestation of COVID-19, as 20-40% of COVID-19 patients with pneumonia reported acute respiratory distress syndrome (Wang et al., 2020; Wu et al., 2020). In addition, lung abnormalities have been observed in otherwise asymptomatic patients (Shi et al., 2020) and reduced lung function and pulmonary fibrosis have been observed in individuals who have otherwise recovered from COVID-19 (Wang, et al., 2020).

Research has shown a bidirectional relationship between cognitive impairment and pneumonia, as the presence of either has been shown to increase the likelihood of the other in the same individual (Shah et al., 2013). Pneumonia has also been shown to increase the likelihood of dementia development in elderly patients (Tate et al., 2014). Even otherwise healthy younger adults without major medical comorbidities or other recent hospitalizations have substantially

increased risk of cognitive impairment after a single episode of pneumonia (Davydow et al., 2013; Girard et al., 2018), as well of risk of depression and functional impairment in activities of daily living (Davydow et al., 2013).

Acute respiratory distress syndrome (ARDS) has also been linked to acute and chronic changes in cognition. In one study, approximately 73% of intubated patients with ARDS and 52% of non-intubated patients reported experiencing delirium (Hsieh et al., 2015). Regarding chronic cognitive change, a meta-analysis cited ARDS-related deficits in attention, concentration, memory, or executive functioning in 70-100% of patients at discharge, with 46-78% one year later, 25-47% two years later, and approximately 20% five years later (Wilcox et al., 2013).

Research has shown individuals with Chronic Obstructive Pulmonary Disease (COPD) frequently report areas of cognitive dysfunction, including motor functioning, abstraction, executive functioning, learning and memory, processing speed, and working memory (Grant et al., 1982; Hansen et al., 2008; Prigatano et al., 1983). Although some studies have shown negligible or no cognitive deficits in patients with COPD (Fix et al., 1982, Kozora et al., 1999), impairment is common in those with hypoxemia and non-hypoxemic COPD (Prigitano et al., 1983). Fortunately, performance on language measures appear to be unaffected by COPD (Dodd et al., 2010). Studies which sought to compare patients with COPD to patients with Alzheimer's disease (AD) and healthy controls revealed less severe patterns of cognitive impairment in COPD patients compared to AD patients (Kozora et al., 1999; Morris et al., 2019). In studies of individuals with asthma, impairments in attention, processing speed, learning and memory, and visual-spatial functioning have been observed (Irani et al., 2017; Moss et al., 2005).

Neurological Effects of Viral Infection

Viral infections are common amongst humans and studies have found some can infect the central nervous system (CNS), which may cause neuropsychiatric deficits in cognitive, affective, behavioral, and perceptual domains (Arciniegas & Anderson, 2004; Dubé et al., 2005; Hinkin et al., 2001). Although not all viral infections can be expected to produce the same neurological results after infection, numerous examples exist of individuals with viral infections experiencing secondary psychological and neuropsychological symptoms. Several infectious diseases (e.g., HIV/AIDS, syphilis, Lyme disease, Prion disease, herpes simplex virus) have been demonstrated to be associated with neurological manifestations in infected individuals (Isaac & Larson, 2014**).** Previous outbreaks of influenza and other coronaviruses have revealed highly variable complications over the weeks following acute respiratory symptomatology, to even decades later even affecting those with in-utero exposure to a viral infection (Kepińska et al., 2020; Kim et al., 2017; Tsai et al., 2004). Previous influenza pandemics have left some patients with long-lasting neuropsychiatric symptoms, which implies the possibility that other viral infections on such a large scale could cause similar outcomes for some individuals (Kepińska et al., 2020).

Parkinson's disease was first described following the influenza pandemic of 1918 (Cheyette & Cummings, 1995). To date, literature has not described any direct association between PD and coronavirus. However, anti-coronavirus antibodies have been observed in the cerebrospinal fluid of individuals with PD (Fazzini et al., 1992). As neural and immune cells have been observed to serve as reservoirs of latent coronavirus, it is speculated that this coronavirus exposure could contribute to delayed neurodegenerative processes, though this will likely remain unclear for years in relation to COVID-19 (Desforges et al., 2019).

Previous respiratory viral pandemics suggest diverse types of neuropsychiatric symptoms can possibly arise as a result of viral infection, or even post-infection. Reports from 18th and 19th century suggest an increase of several common neurological symptoms, such as insomnia, anxiety, depression, mania, psychosis, suicidality, and delirium, were concurrent with widespread pandemics (Honigsbaum, 2013). During the 2009 influenza (H1N1; Manjunatha et al., 2011; Wu et al., 2014), 2003 SARS (Tsai et al., 2004), and 2012-2020 MERS (Kim et al., 2017) pandemics neuropsychiatric sequelae such as narcolepsy, seizures, encephalitis, encephalopathy, and Guillian-Barre syndrome were reported. Survivors of West Nile virus infection commonly reported fatigue, memory impairment, weakness, headache, joint pain, and balance problems, regardless of severity of infection (Carson et al., 2006). On neuropsychological testing deficits were defined as scoring two standard deviations below the mean compared to healthy controls. Of hospitalized patients, 40% had deficits in the dominant and nondominant hand on Finger Tapping Test and 29% had deficits on both hands on the Purdue Pegboard Test. Of non-hospitalized survivors, 15% had deficits on Wisconsin Card Sorting Test categories completed, 26% on Finger Tapping Test dominant hand, 45% on Finger Tapping Test nondominant hand, and 12% on both hands on the Purdue Pegboard Test.

Patients with advanced human immunodeficiency virus (HIV) have been observed to have comparable neurological impairment regardless of highly active antiretroviral therapy (HAART) treatment and monotherapy treatment (Cysique et al., 2004). In the monotherapy cohort, 41% of HIV+ individuals were shown to have neuropsychological impairments compared to 6% of healthy controls. In the HAART cohort, 39% of HIV+ individuals were shown to have neuropsychological impairments compared to 7% of healthy controls. Overall, the monotherapy cohort had a higher frequency of moderate impairment (2 standard deviations below the mean)

on digit span forward, verbal fluency, and a Rey figure copy and the HAART cohort had a higher frequency of moderate impairment on the oral version of the Symbol Digit Modalities test, and California Verbal Learning Test total word learning.

Neuropsychological Testing and COVID-19

Though research involving neuropsychological testing data is sparse some attempts have been made across the globe to assess post recovery cognitive functioning using objective measures. One study examined cognitive differences in the Trail Making Test (TMT), Sign Coding Test (SCT), Digit Span Test (DST), and the Continuous Performance Test (CPT) between 29 Chinese COVID-19 patients and 29 Chinese healthy controls (Zhou et al., 2020). The groups were not significantly different on age, gender, and education levels. The differences between the two groups were not significantly different on most measures, though COVID-19 patients performed significantly worse on CPT Part 2 Missing Number and CPT Part 3 Correct Number and Missing Number.

Almeria and colleagues (2020) observed 35 Spanish participants who had been infected with COVID-19. The average age of these patients was 47.6 (SD=8.9), 19 were female and 18 were male, and average educational achievement was 12.6 years (SD=4.6). The most common symptoms at onset of illness were fever (45.7%), cough (28.6%), fatigue (17.1%), headache (5.7%), and myalgia (2.9%). Neuropsychological measures administered to all participants 10-35 days after hospital discharge included the Test de Aprendiazaje Verbal España-Complutense (TAVEC), Wechsler Memory Scale-IV Visual Reproduction subtest (WMS-IV-VR), Digit Span Forward (DSF) and Backward (DSB), Letter and Numbers, TMT, Symbol Digit Modalities Test (SDMT), Stroop, Phonemic and Semantic Fluency, and Boston Naming Test from the NEURONORMA project (NN). Using the metric that a score of ≤ 30T is considered impaired,

impairment was observed in some participants on Semantic Fluency (11.4%), TMT-B (8.6%), DSB (8.6%), Phonemic Fluency (5.7%), SDMT (5.7%), TAVEC List Learning (5.7%), TAVEC Delayed Recall (5.7%), TMT-A (2.9%), Stroop (2.9%), Rey Copy (2.9%) and BNT (2.9%).

Another study of 57 COVID-19 infected individuals (64% of whom had preexisting cardiovascular or metabolic conditions) administered several neuropsychological measures at bedside a mean of 6.6 days after transfer to a COVID-19 rehabilitation unit. After admission for COVID-19, 88% had documented hypoxia respiratory failure, 77% were treated with intubation and mechanical ventilation, and 29% required a tracheostomy to wean off of ventilation. Participants were 75% male, 25% female with a mean age of 64.5 (SD=13.9). Although most participants were administered the measures in English (81%), a minority required translation and were administered the tests in Spanish (9%), Chinese (7%), or another language (3%). Participants were administered the Brief Memory and Executive Test (BMET), which has eight subtests including orientation, immediate word recall, delayed word recall, word recognition, rapid letter-number matching, motor speed, rapid letter sequencing, and letter-number switching. Mild impairment on testing was defined as greater than 1 standard deviation below the age-adjusted norms of the BMET and impairment was defined as greater than 2 standard deviation below the age-adjusted norms. At least mild impairment was observed on tasks of working memory (55%), set-shifting (47%), divided attention (46%), and processing speed (40%).

Méndez and colleagues (2020) examined a sample of 179 COVID-19 survivors two months after hospitalization. These patients were aged 22- to 81- years of age (mean=57) and close to half (49.7%) required respiratory support while hospitalized. On neurocognitive assessment, verbal learning, delayed verbal memory, semantic verbal fluency, and working memory were evaluated. In this sample, 38% evidenced moderate impairment and 11.2%

evidenced severe impairment in immediate verbal recall. Moderate impairment in delayed memory was observed in 11.8% of the sample, and severe impairment was observed in 2.8%. Regarding semantic verbal fluency, 34.6% had moderate deficits, whereas 8.4% had severe deficits. Working memory was moderately impaired in 6.1% of those examined and severely impaired in 1.1%. Based on these results, 58.7% of patients were determined to have met criteria for moderate neurocognitive impairment (as defined by at least moderate impairment on four or more neuropsychological tests) and 18.4% met criteria for severe neurocognitive impairment (as defined by severe impairment on four or more neuropsychological tests).

Neuropsychological Assessment

A detailed reconstruction of the patient's medical, social, cultural, intellectual, educational, and emotional past is an important part of any neuropsychological assessment (Hebben & Milberg, 2009). This is because many clinical issues assessed by a neuropsychologist occur across years of development and experience. Information regarding a person's functioning prior to the onset of an illness or event, as well as the possible etiological factors which may contribute to a patient's illness or performance on testing is paramount to proper diagnostic procedures and treatment recommendations. As such, the Global Neuropsychological Assessment contains a cover sheet which asks participants their age, sex, race, ethnicity, education level, English language proficiency, presence of several medical conditions, and history of medication use. Most common neuropsychological tests require detection of visual and hearing stimuli (Hebben & Milberg, 2009). As such the GNA cover sheet contains three short tasks to assess the client's vision, hearing, and ability to follow basic instructions.

A neuropsychological battery should consist of measures intended to assess arousal and attention, executive functions, intelligence/achievement, learning and memory, language ability,

visuospatial skills, sensory and motor skills, emotion, behavior and personality, and effort and compliance (Hebben & Milberg, 2009). The composite subtests of the GNA include a measure of all of the above mentioned neuropsychological constructs with the exception of intelligence and effort and compliance, which will be assessed using the Hopkins Adult Reading Test (HART) and the Mental Status Exam-Telephone Version (MSE-TV). Previous research has established convergent validity with measures commonly used in neuropsychological assessment with general patient and control samples (Carrol et al., 2019) and more recently with patients with Alzheimer's disease (Olson et al., 2022). The HART has been researched as a measure of premorbid intelligence (Schretlen, et al., 2009) and has been used as a calibrated factor in normative data (Schretlen et al., 2010). The MSE-TV is a brief measure screening measure of cognitive functioning (Nguyen-Louie et al., manuscript submitted 2020; see below).

CHAPTER II

METHOD

Apparatus and Measurements

The Global Neuropsychiatric Assessment (GNA) is a brief neurocognitive test battery with five alternate forms (Olson et al., 2022; Smerbeck et al., 2021). The test contains a face sheet and five brief subtests; Story Memory, Perceptual Comparison, Digit Span, Verbal Fluency and Switching, Spatial Span, and the Patient Health Questionnaire-4 (Kroenke et al., 2009). This assessment requires approximately 20 minutes to administer and is intended to assess cognitive domains of verbal learning and memory, processing speed, attention, language fluency, executive functioning, and mood. The face sheet asks several demographic and medical history questions and checks participant's vision, hearing, and ability to follow directions which are necessary for an accurate assessment. In the Story Memory task, examiners read a short story to participants twice and the participants are asked to recall details of the story after each reading and after an 5-10-minute delay. In the Perceptual Comparison task, participants are given a sheet with several pairs of symbols and asked to tell the examiner if the pairs are the same or different in a timed condition. In the Digit Span task, participants are read spans of numbers and asked to repeat them back to the examiner in either the same or backward order. In the Verbal Fluency task, participants are asked to name as many animals as possible in one minute. In the Verbal Switching task, participants are asked to name as many body parts and foods as they can, switching back and forth between these semantic categories for one minute. In the Spatial Span task, participants are asked to look at a grid with numbers placed in it, then from memory trace a path where the numbers were. The PHQ-4 is a brief mood questionnaire which asks the participant to answer four brief questions related to mood. A slightly modified version of the

standard GNA form was administered to accommodate a telehealth administration format. The Spatial Span subtest was not administered, and the Perceptual Comparison subtest and cover sheet tasks related to vision and ability to follow a command were administered through Microsoft Office PowerPoint slides on a shared screen.

Low scores on a brief screening battery, such as the Mini Mental State Exam (MMSE) may be indicative of deterioration of cognitive functioning (Hebben & Milberg, 2009). The Mental Status Exam-Telephone Version (MSE-TV) is a brief cognitive screen developed to be administered through telephone calls and performance on this test has been demonstrated to correlate significantly with performance on the MMSE (Nguyen-Louie, et al., submitted manuscript, 2020). This measure consists of eight brief tasks which assess temporal orientation, word-list learning and memory, attention, vocabulary, mental arithmetic, and fund of knowledge. Total scores are calculated as the sum of all items and range from 0-50. This test requires approximately 5 minutes to administer in person, over the telephone, or through a teleconference service. The MSE-TV has shown diagnostic value for discriminating healthy adults from neuropsychiatric patients (groups examined included intellectual disability, dementia, schizophrenia, affective disorders, and poor medical health) even after controlling for age, sex, race, and education ($M \pm SD$: 38.7 ±5.5 in controls, 29.5 ±7.8 in patients; $F_{8, 396} = 70.9$, $aR^2 = .59$, $p < .0001$; Nguyen-Louie, et al., submitted manuscript, 2020). In addition, patients with intellectual disability scored significantly lower than other diagnostic groups (ps < .05) and patients with dementia scored significantly lower than patients with overall poor medical health ($p = .03$).

The Hopkins Adult Reading Test (HART) is a 35-item, oral word-reading test with two equivalent forms designed to estimate premorbid abilities (Schretlen, et al., 2009). When

controlling for age, sex, race, and education level, form A (r=.780; p<.05) and form B (r=.779; p<.05) of the HART correlated significantly with WAIS-IV FSIQ in healthy controls. The HART has also been used as a covariate to calibrate normative data for FSIQ in the Calibrated Neuropsychological Normative System software portfolio (CNNS-SP; Schretlen et al., 2010) and was used for the same purpose in the current study. The HART typically takes less than five minutes to administer and was administered through the use of Microsoft Office PowerPoint slides on a shared screen.

A brief questionnaire was developed to determine participant's subjective account of their neuropsychological symptoms before their COVID-19 exposure, while experiencing symptoms, and after recovery. This resulted in a 44-item questionnaire which takes approximately five minutes to complete.

Procedure

Participants were recruited through social media platforms (e.g., Reddit, Twitter, Facebook) and word of mouth. Participants were identified as having a history of COVID-19 infection or as healthy controls. Participants with a history of COVID-19 infection were asked to show the examiner documentation of a positive molecular (nasal or throat swab), antigen (nasal or throat swab) or antibody/serology (blood sample) COVID-19 test from at least 14 days prior to participation in this study. Healthy controls were assumed to not have a history of COVID-19 infection if they denied a history of a positive test and did not personally suspect they had a history of infection. Participants were entered into a drawing to win one of two $100 Amazon gift cards.

The GNA, MSE-TV, HART, and COVID-19 symptom questionnaire were administered to all participants through the teleconference program, Zoom. During the Zoom session, verbal

informed consent was collected. Participants were notified their participation was voluntary and they had the option to stop at any time without penalty. Exclusion criteria at intake included individuals unable to provide verbal informed consent and individuals under the age of 18. Exclusion criteria after beginning testing included individuals who failed the audio, visual, or command screening items of the GNA and individuals with an unstable internet connection. Though additional participants were considered for exclusion at post hoc, dependent on MSE-TV performance or complex medical histories, the relatively small number of outliers in either group (see Table 5) and the lack of identifiable factors contributing to their performance led to the retention of all participants in the final analyses.

Anticipated Results

Due to the wide range of reported symptoms of COVID-19 and significant numbers of asymptomatic individuals with positive COVID-19 tests, it was anticipated mean scores on most measures would not differ significantly between those who recovered from COVID-19 and healthy controls. However, it was anticipated individuals with symptoms such as difficulty breathing, hypoxic events, or intubation experienced concurrent with COVID-19 infection may perform significantly lower on some measures of cognitive functioning. As it was not possible to accurately predict the number of individuals who may report any specific symptoms prior to data collection, these analyses were planned and conducted post-hoc.

Data Analysis

Independent samples t-tests were conducted to determine group differences (COVID-19 history and healthy controls) regarding age, sex, race, education level, and HART. A series of ANOVAs were conducted to determine potential cognitive deficits in individuals depending on their previous COVID-19 exposure. The independent variable was a dichotomous positive

COVID-19 test, dependent variables included all subtests of the GNA. Covariates included age, sex, and education.

Post-hoc analyses were conducted to determine if any history of cognitive symptoms, intubation history, or COVID-19 related hospital stay were related to lower performance on any cognitive measures. As severity and presentation of symptoms was inconsistent across recovered individuals, post-hoc analyses were conducted to determine which individuals in the COVID-19 group preformed lower on GNA subtests compared to the rest of the COVID-19 group (i.e., 2 standard deviations below the normative mean). These individuals were examined to determine which measured cognitive constructs they performed below expectations on, and which factors may predict or explain these deficits (e.g., length of illness, hospitalization, symptom presentation, age, education, HART).

A power analysis was conducted using G*Power (Buchner et al., 2017) to determine necessary sample size for this study. Power was calculated using the ANOVA, fixed effects, omnibus, one-way option. The set effect size was set at f =.25, as a medium effect size would be considered meaningful by the authors. Error probability was set to α = 0.05, and power was set to .80. With these parameters in place, the total sample size required was 124 participants.

CHAPTER III

RESULTS

Participants

Following IRB approval of the current study, participants were recruited through social media (e.g., Facebook, Reddit, Twitter) and word of mouth between March 2021 and June 2022. A total of 62 individuals who had a positive COVID-19 test at least 14 days prior to the date of their session and 62 healthy controls who did not suspect they had ever been infected with COVID-19 were recruited. Four individuals with a history of COVID-19 infection declined to participate due to a tendency toward excessive fatigue and the time demand of the study. Six potential healthy controls expressed interest in the study but did not participate due to uncertainty regarding past COVID-19 infection. Twenty-six individuals expressed initial interest in the study but did not schedule an appointment with an examiner or did not attend the scheduled appointment. Participants were asked if they had any history of various medical or cognitive concerns and diagnoses which may work as moderating factors. These included a history of dementia or Alzheimer's disease, Parkinson's disease, seizures or epilepsy, severe traumatic brain injury, intellectual disability, autism or other developmental disorder, schizophrenia or other psychosis, severe depression or anxiety, alcohol or drug addiction, HIV or AIDS, and diabetes.

For brevity, participants with a history of COVID-19 infection will be referred to as "COVID-19 participants". The 62 COVID-19 participants were aged 19 to 77 (mean = 44.44, *SD* = 13.39), 14 (22.58%) were cisgender males and 48 (77.42%) were cisgender females (Table 1). Racially, 54 (87.10%) identified as White, with a minority of participants identifying as Black (*n* = 3; 4.84%), Asian (*n* = 2; 3.23%), or Native American (*n* =1; 1.61%) and two participants

Table 1

Demographics of COVID-19 Participants and Healthy Controls

Variable	COVID-19 Participants	Healthy Controls	Comparison
Age (Mean; SD)	44.44 (13.39)	37.56 (12.13)	t (122) = 2.99*
Gender[a]			χ^2 (1) = 6.16*
Cisgender Female	48 (77.42%)	35 (56.45%)	
Cisgender Male	14 (22.58%)	27 (43.55%)	
Race			χ^2 (3) = 1.52
White	54 (87.10%)	53 (85.48%)	
Black	3 (4.84%)	2 (3.23%)	
Asian	2 (3.23%)	5 (8.06%)	
Native American	1 (1.61%)	2 (3.23%)	
Declined to Answer	2 (3.23%)	0 (0%)	
Ethnicity			χ^2 (1) = 1.03
Latine	1 (1.61%)	3 (4.84%)	
Non-Latine	61 (98.39%)	59 (95.16%)	
Education (Mean; SD)	16.18 (2.08)	15.77 (1.95)	t (122) = 1.12
English as Primary Language	62 (100%)	59 (95.2%)	χ^2 (1) = 3.07
Urban/Rural			χ^2 (1) = 2.07
Urban	34 (54.83%)	26 (41.94%)	
Rural	28 (45.16%)	36 (58.06%)	
Medical Diagnosis			
Dementia or Alzheimer's Disease	0 (0%)	0 (0%)	n/a
Parkinson's Disease	0 (0%)	0 (0%)	n/a
Seizures or Epilepsy	2 (3.23%)	0 (0%)	χ^2 (1) = 2.03
Severe Traumatic Brain Injury	2 (3.23%)	1 (1.61%)	χ^2 (1) = 0.34
Intellectual Disability	0 (0%)	0 (0%)	n/a
Autism	1 (1.61%)	0 (0%)	χ^2 (1) = 1.01
Schizophrenia	0 (0%)	0 (0%)	n/a
Severe Depression or Anxiety	30 (48.39%)	12 (19.35%)	χ^2 (1) = 11.67**
Alcohol or Drug Addiction	1 (1.61%)	1 (1.61%)	χ^2 (1) = 0
HIV or AIDS	1 (1.61%)	0 (0%)	χ^2 (1) = 1.08
Diabetes	5 (8.06%)	0 (0%)	χ^2 (1) = 5.21*

[a] No participants identified their gender as anything other than cis-gendered male or female. * p <.05, **p < .001.

(3.23%) declining to provide their racial identification. Comorbid diagnoses included a history of severe depression or anxiety (n =30; 48.39%), diabetes (n = 5; 8.06%), historical seizures or

epilepsy (*n* = 2; 3.23%), historical traumatic brain injury (*n* = 2; 3.23%), autism (*n* =1; 1.61%), historical alcohol or drug addiction (*n* =1; 1.61%), and HIV or AIDS (*n* = 1; 1.61%).

The 62 healthy control participants were aged 19 to 70 (mean = 37.56, *SD* = 12.13), 27 (43.55%) were cisgender males and 35 (56.45%) were cisgender females. Racially, 53 (85.48%) identified as White, with a minority of participants identifying as Black (*n* =2; 3.23%), Asian (*n* = 5; 8.06%), or Native American (*n* = 2; 3.23%). Comorbid diagnoses included a history of severe depression or anxiety (*n* =12; 19.35%), historical traumatic brain injury (*n* = 1; 1.61%), and historical alcohol or drug addiction (*n* =1; 1.61%).

Independent samples t-tests were conducted to determine if significant differences existed between the COVID-19 participants and healthy controls on age or education (Table 1). Before doing so, it was determined all dependent variables were measured on a continuous scale, the independent variable (COVID-19 diagnosis status) consisted of two categorical, independent groups, and independence of observations could be assumed. When these variables were checked for significant outliers, it was determined the control group had no outliers, but the COVID-19 group had one individual significantly older than the rest of the sample (aged 77), and 7 individuals with significantly less education than the rest of the sample (12 years). Although Shapiro-Wilk tests were significant regarding age for the control group and education for both groups, skewness and kurtosis were within normal limits (less than +1 and greater then -1) for age and education for both groups and will therefore be considered normally distributed for the purposes of this analysis. One-way ANOVA tests were conducted to determine homogeneity of variance of age and education in both groups. Levine's statistic indicated the assumption of homogeneity of variance was met for both age and education. An independent samples t-test indicated the COVID-19 group was significantly older than the control group with a medium

effect size (t = 2.99, p < .05, d = 0.54), but that both groups were approximately equal in educational attainment (t = 1.12, *ns*).

Chi-squared tests were conducted to determine if dichotomous variables were significantly different between the COVID-19 and control groups. As COVID-19 diagnosis status is measured as a categorical variable and all other analyzed variables consist of two or more categorical, independent groups, all assumptions have been met for chi-squared analyses. A chi-squared test indicated there were significantly more cis-gendered female participants in the COVID-19 group, compared to the control group χ^2 (1, n = 124) = 7.94, p < .05, φ = .22. Other background characteristics such as race, ethnicity, educational achievement, English as a primary language, and youth spent in an urban or rural environment were not significantly different between groups. Chi-squared tests indicated significantly more individuals in the COVID group had a historical diagnosis of severe depression or anxiety group χ^2 (1, n = 124) = 11.67, p < .001, φ = .31 and diabetes group χ^2 (1, n = 124) = 5.21, p < .05, φ = .21.

COVID-19 Sequelae

COVID-19 participants were asked about their history of respiratory complications and sequalae related to COVID-19 infection (Table 2). They were asked to dichotomously select (yes or no) if they required an emergency room (ER) visit, hospitalization, and/or intubation related to their COVID-19 infection. They were also asked to dichotomously select (yes or no) if they have any history of pneumonia, acute respiratory distress syndrome (ARDS), chronic obstructive pulmonary disease (COPD), asthma, and smoking. Severity of COVID-19 symptoms was relatively mild for this population, as 18 (29.03%) participants indicated they required an emergency room visit due to their COVID-19 infection, 3 (4.84%) indicated they required hospitalization, and 2 (3.13%) indicated they required intubation. Although 15 participants

Table 2

Frequency of COVID-19 Participants with Related Events and Symptoms

Variable	Frequency	Percentage
ER Visit	18	29.03%
Hospitalization	3	4.84%
Intubation	2	3.23%
Pneumonia (ever)	15	24.19%
Pneumonia (since COVID-19 infection)	4	6.45%
History of ARDS	3	4.84%
History of COPD	1	1.61%
History of Asthma	17	27.42%
History of Significant Smoking	17	27.42%
Stroke	0	0%
Brain Bleed	0	0%
Difficulty Concentrating, Remembering Things, or Solving Problems	27	43.55%
Shortness of Breath while Infected[a]	35	56.45%
Shortness of Breath at Assessment[a]	21	33.87%
Fever ≥ 100° while Infected[a]	22	35.48%
Fever ≥ 100° at Assessment[a]	3	4.84%
Significant Confusion while Infected[a]	25	40.32%
Significant Confusion at Assessment[a]	16	25.81%
Loss of Smell while Infected[a]	35	56.45%
Loss of Smell at Assessment[a]	15	24.19%
Loss of Taste while Infected[a]	32	51.61%
Loss of Taste at Assessment[a]	14	22.58%

[a] Endorsed as "Often" or "Almost Always"

indicated they had a lifelong history of pneumonia, only 4 (6.45%) indicated they had pneumonia concurrent with their COVID-19 symptoms. Length of time between positive COVID-19 test and participation in this study ranged between 21 and 551 days (mean = 258.94, SD = 136.56).

COVID-19 participants were also asked about thirty post-infection symptoms identified in the literature (Table 2). They were asked to identify the frequency of these symptoms on a four-point Likert-type scale (1 = "Almost Never", 2 = "Occasionally", 3 = "Often", 4 = "Almost Always") as they were before their COVID-19 infection, while actively infected, and as the time of testing. Of these symptoms 7 (shortness of breath for unknown reasons, fever at or greater

than 100 degrees, stroke, brain bleed, pneumonia, significant confusion, loss of smell, and loss of taste) were selected for analysis as the other inquired symptoms were not supported by literature to affect cognition or were otherwise assessed through the GNA.

Examination of GNA Subtests

The GNA, HART, and MSE-TV were completed by 62 COVID-19 participants and 62 healthy controls (Table 3). Before conducting independent samples t-tests, it was determined all dependent variables were measured on a continuous scale, the independent variable consisted of two categorical, independent groups, and independence of observations was established. All dependent variables were then examined for significant outliers. For the control group, one individual scored significantly higher than others (MSE-TV= 50) and three individuals scored significantly lower than others (MSE-TV =29 for all three). One individual scored significantly lower on the HART compared to others (HART=44). Five individuals scores significantly higher on the GNA Digit Span Backwards than others (DSB=8 for two participants, DSB=7 for three participants) and one scored significantly lower than others (DSB = 2). On Category Switches, one individual scored significantly higher than others (CS = 36). For the COVID-19 group, two individuals scored significantly lower than others on GNA Story Memory Total (SM=8 for both participants). Five individuals scores significantly higher on the GNA Digit Span Backwards than others (DSB= 7 for all five participants) and one scored significantly lower than others (DSB = 2). On Category Switches, one individual scored significantly higher than others (CS = 38). Neither group had any outliers on the Perceptual Comparison, Digit Span Forward, Animal Naming, or PHQ-4 subtests. To compensate for outliers, t-tests were conducted with and without outliers included.

Table 3

GNA[a] *Subtest Means and Standard Deviations*

	COVID-19 Participants		Healthy Controls		
Subtest	*n*	Mean (SD)	*n*	Mean (SD)	*t* (122)
Story Memory Total	62	18.35 (4.24)	62	19.06 (4.22)	0.93
outliers excluded	60	18.70 (3.85)	62	19.06 (4.22)	*t* (120) = 0.50
Story Memory Delay	62	9.24 (2.46)	62	9.56 (2.25)	0.76
log 10 transformed	62	0.95 (0.13)	62	0.97 (0.11)	0.93
Perceptual Comparison	62	30.44 (7.79)	62	33.35 (7.78)	2.09*
Highest Digit Span Forward	62	6.45 (1.28)	62	6.18 (1.40)	1.14
Highest Digit Span Backward	62	4.69 (1.15)	62	4.52 (1.24)	0.83
outliers excluded	56	4.54 (0.91)	56	4.30 (0.87)	*t* (110) = 1.38
Animal Naming	62	26.56 (5.41)	62	26.56 (5.66)	0.00
Category Switching	62	22.98 (5.14)	62	22.05 (5.36)	0.99
outliers excluded	61	22.75 (4.85)	61	21.84 (5.13)	*t* (120) = 1.02
PHQ-4	62	3.90 (3.16)	62	3.15 (2.43)	1.50
HART[b]	62	22.82 (4.41)	62	23.56 (5.12)	0.87
outliers excluded	62	22.82 (4.41)	61	23.79 (4.85)	*t* (121) = 1.15
MSE-TV[c] Total	62	38.34 (4.44)	62	39.29 (4.37)	1.20
outliers excluded	62	38.34 (4.44)	58	39.64 (3.57)	*t* (118) = 1.76

[a] GNA=Global Neuropsychological Assessment. [b]HART= Hopkins Adult Reading Test. [c]MSE-TV= Mental Status Exam-Telephone Version. * $p < .05$

Both groups were also checked for normal distribution using the Shapiro-Wilk test. The control group was demonstrated to have significant Shapiro-Wilk tests for Story Memory Delay, Digit Span Forward, Digit Span Backward, and PHQ-4 subtests. The COVID-19 group was shown to have significant Shapiro-Wilk tests on the Story Memory Total, Digit Span Forward, Digit Span Backward, or PHQ-4 subtests. However, except for Story Memory Delay in the control group, all variables with significant Shaprio-Wilks tests were within the normal range of skewness and kurtosis (less than +1 and greater than -1). Story Memory delay had low kurtosis in the control sample (-1.12), which was improved with a log 10 transformation (kurtosis=-.996) and was therefore analyzed with and without the log 10 transformation. Homogeneity of variance

was determined using Levine's test. It was determined that the PHQ-4 did not achieve homogeneity of variance, though all other analyzed tests did.

On the GNA Perceptual Comparison subtest, the healthy control group (Mean = 33.35; SD = 7.78) scored significantly higher than the COVID-19 group (Mean = 30.44; SD= 7.79), with a small effect size, $t = 2.09$, $p < .05$, $D = 0.37$). Significant differences were not observed amongst Story Memory Total, Story Memory Delayed, Highest Digit Span Forward or Backward, Animal Naming, Category Switching, and PHQ-4 subtests of the GNA, the MSE-TV, or the HART regardless of log10 transformation or exclusion of outliers (Table 3).

A series of multiple regression analyses was conducted to predict scores on the GNA subtests, MSE-TV, and HART from COVID-19 diagnosis status, gender, age, and education (Table 4). Before conducting these analyses, assumptions were checked. Assumptions of variable scales, independence of observations, and significant outliers are discussed above. Examination of scatterplots and partial regression plots evidenced linear relationships between the independent variables and dependent variables. Homoscedascity was established by examining the P-P plots of all dependent variables. The plots examined showed no strong evidence of heteroscedascity for any of the examined variables. Multicollinearity was examined using VIF scores. As no observed VIF scores were greater than 10, it was determined that no independent variable violated the assumption for any of the examined dependent variables.

As a group, COVID-19 diagnosis status, age, gender, and education statistically significantly predicted GNA Perceptual Comparison, F (4, 119) = 8.89, $p < .001$, $R^2 = .20$. Only age added statistically significantly to the prediction of performance on GNA Perceptual Comparison, $p < .001$. These variables also statistically significantly predicted GNA Animal

Table 4

GNA Subtest Multiple Regression Analyses to predict subtest scores from COVD-19 diagnosis status, gender, age, and education.

Subtest	*F* (4, 119)	R^2	Significant Predictors
GNA[a] Story Memory Total	.82	.03	None
outliers excluded	*F* (4, 117) = .70	.02	None
GNA Story Memory Delay	1.20	.04	None
log10 transformed	0.73	.02	None
GNA Perceptual Comparison	8.89***	.20	Age
GNA Highest Digit Span Forward	1.68	.05	Education
GNA Highest Digit Span Backward	1.62	.05	Education
outliers excluded	*F* (4, 107) = 0.55	.02	None
GNA Animal Naming	5.85***	.16	Age, Education
GNA Category Switching	3.05*	.09	Age, Education
outliers excluded	*F* (4, 117) = 2.82*	.09	Age, Education
PHQ-4	.77	.03	None
MSE-TV Total	3.11*	.10	Education
outliers excluded	*F* (4, 115) = 3.00*	.09	None
HART	6.56***	.18	Education
outliers excluded	*F* (4, 118) = 6.31***	.18	Education

[a] GNA=Global Neuropsychological Assessment. * p <.05, ** p <.01, *** p<.001

Naming *F* (4, 119) = 5.85, p <.001, R^2 = .16. Only age (p < .05) and education (p < .001) added statistically significantly to the prediction of performance on GNA Animal Naming.

As outliers were present for the Story Memory Total, and Category Switching tasks of the GNA, as well as the HART and MSE-TV, multiple regression analyses were conducted for these variables with and without outliers included. As a group, COVID-19 diagnosis status, age, gender, and education statistically significantly predicted GNA Category Switching *F* (4, 119) = 3.05, p <.05, R^2 = .09. Only age (p < .05) and education (p < .05) added statistically significantly to the prediction of performance on GNA Category Switching and exclusion of outliers did not significantly alter the interpretation of the results. These variables also statistically significantly predicted performance on the HART, *F* (4, 119) = 6.56, p <.001, R^2 = .18. Only education added

statistically significantly to the prediction of performance on GNA Perceptual Comparison, ($p <$ .001) and exclusion of outliers did not significantly alter the interpretation of the results.

COVID-19 diagnosis status, age, sex, and education also statistically significantly predicted performance on the MSE-TV, F (4, 119) = 3.11, $p <.05$, $R^2 = .10$. Only education added statistically significantly to the prediction of performance on MSE-TV, $p < .01$. With outliers excluded, these variables still statistically significantly predicted performance on the MSE-TV, F (4, 115) = 3.00, $p < .05$, $R^2 = .09$. However, with outliers excluded education no longer added statistically significantly to the prediction of performance on the MSE-TV. These variables did not statistically significantly predict GNA Story Memory Total (raw scores or log10 transformed scores), GNA Story Memory Delay, or PHQ-4. Of note, COVID-19 diagnosis status and gender did not add statistically significantly to the prediction of performance on any of the administered neuropsychological measures.

Outliers Among COVID-19 Participants

To determine if specific symptoms were indicative of poor performance on neuropsychological measures, each of the administered tests were analyzed for individuals who scored 2 standard deviations below the mean of the COVID-19 participant group (Table 5). Of note, no individuals who required an inpatient hospitalization (n = 3) or intubation (n = 2) as a result of COVID-19 infection scored below normal limits on any administered test. Only three individuals were considered a low performing outlier on any of the administered measures, one on GNA Highest Digit Span Backwards and two on GNA Story Memory Total (Table 5). The participant who scored significantly lower on the GNA Highest Digit Span Backwards (DSB=2) was a 36-year-old White male with 12 years of formal education. He reported a previous diagnosis of severe depression or anxiety, was not taking anti-depressant or anti-anxiety

Table 5

COVID-19 Group Outliers

Variable	Age	Sex	Education	Race	Notes
DSB[a]=2	36	Male	16	White	• Severe Depression or Anxiety • Not Prescribed Anti-Depressants • Not Prescribed Anti-Anxiety • PHQ-4=12 • Did not visit ER • Shortness of Breath • Fever >100 degrees • Significant Confusion
SM[b]=8	46	Female	12	White	• Severe Depression or Anxiety • Not Prescribed Anti-Depressants • Not Prescribed Anti-Anxiety • PHQ-4=9 • Visited ER • Shortness of breath • Significant confusion
SM=8	39	Female	16	White	• Severe Depression or Anxiety • Prescribed Anti-Depressants • Prescribed Anti-Anxiety • PHQ-4=6 • Did not visit ER • Shortness of Breath • Loss of Smell • Fever >100 degrees • Significant Confusion

[a]Digit Span Backwards. [b]Story Memory

medications at the time of testing and indicated severe depression and anxiety symptoms on a brief self-report measure (PHQ-4=12). This individual did not require an ER visit or inpatient hospitalization d his COVID-19 infection. However, he reportedly experienced shortness of

breath, a fever greater than 100 degrees Fahrenheit, and significant confusion while infected with COVID-19.

One participant who scored significantly lower on the GNA Story Memory Total (SM=8) was a 46-year-old Caucasian female with 12 years of formal education. She reported a previous diagnosis of severe depression or anxiety, was not taking anti-depressant or anti-anxiety medications at the time of testing and indicated severe depression and anxiety symptoms on a brief self-report measure (PHQ-4=9). This individual visited the ER but did not require an inpatient hospitalization as a result of her COVID-19 infection. She reportedly experienced shortness of breath and significant confusion in conjunction with her COVID-19 infection.

The other participant who scored significantly lower on the GNA Story Memory Total (SM=8) was a 39-year-old Caucasian female with 16 years of formal education. She reported a previous diagnosis of severe depression or anxiety and was prescribed anti-depressant and anti-anxiety medications at the time of testing. She indicated moderate depression and anxiety symptoms on a brief self-report measure (PHQ-4=6). This individual did not require an ER visit or inpatient hospitalization as a result of his COVID-19 infection. However, she reportedly experienced shortness of breath, loss of smell, a fever greater than 100 degrees Fahrenheit, and significant confusion while infected with COVID-19.

CHAPTER IV

DISCUSSION

In December 2019, COVID-19 was first discovered in humans in Wuhan, China and has become a worldwide pandemic, infecting millions and resulting in hospitalizations, death, and long-term side effects. Of interest, many individuals infected with COVID-19 reported long standing subjective cognitive symptoms even after recovery from COVID-19 infection. COVID-19 initially caused in-person neuropsychological assessments to be halted across the United States and the rest of the world. This called to attention a dearth of research involving neuropsychological testing measures which had been validated through a telehealth delivery method. The current study sought to not only offer evidence of the Global Neuropsychological Assessment's (GNA) utility as a telehealth measure, but to also determine if COVID-19 infection led to significant cognitive decline in otherwise healthy individuals.

Neuropsychological Results of Infected Individuals and Healthy Controls

Results of the current study revealed minimal differences on the HART, GNA, or MSE-TV between individuals previously infected with COVID-19 and healthy controls. The only significant differences observed between the groups was on a the GNA Perceptual Comparison subtest, which is intended to measure mental processing speed. However, multiple regression analysis revealed age, not COVID-19 infection status, was the only significant predictor of this change. Considering the COVID-19 group was significantly older than the healthy control group, this difference between groups should not be of concern to clinicians.

Although this lack of significant differences may be encouraging for those concerned about the cognition of those who have been previously infected by COVID-19, it should be noted the participants in the COVID-19 group mostly had benign symptom presentations. Research has

suggested neurological damage resultant from COVID-19 infection is most likely due to either hypoxic brain injury or immune system mediated damage to the CNS (Ahmad & Rathmore, 2020). However, in the current sample, 62 individuals previously infected with COVID-19 were recruited, including 18 (29%) who visited the ER due to their infection, and only 4 (6%) had pneumonia concurrent with COVID-19, 3 (5%) who were hospitalized and 2 (3%) who were intubated. Although a larger number had some symptoms which could have led to immune mediated damage to the CNS (e.g., 35% experienced a fever greater than 100º while infected, and 40% experienced significant confusion), these symptoms were typically not severe enough to require acute medical attention. In addition, four individuals contacted the study coordinator, but ultimately declined to participate, citing COVID-19 related chronic fatigue and the time commitment of the study. This may imply those with more severe and long-lasting symptoms may have self-selected to not participate in this study. Still, although concerns may still be present for individuals with severe symptomatology, the long-term effects of infection amongst those who required minimal medical attention appears to be minimal.

Symptom Presentation of Outliers

Though the COVID-19 group and healthy controls were not significantly different on any administered tests of cognition, some individuals in the COVID-19 group scored significantly lower (i.e., 2 standard deviations below the mean) than the rest of the COVID-19 group on individual measures. Two individuals performed lower than expected on GNA Story Memory Total and one individual performed lower than expected on GNA Digit Span Backwards. Among these three individuals, only one visited the ER due to their COVID-19 infection, and none of them required hospitalization or intubation. Although all three individuals reported significant confusion while infected with COVID-19, none continued to report this symptom at the time of

testing. However, all three reported a history of severe anxiety or depression with one in the moderate range of the PHQ-4 and two in the severe range. As these individuals had relatively mild symptom presentations related to COVID-19, these results are less likely to be related to their COVID-19 symptom history and are more possibly due to extant mood symptoms or are incidental findings.

Limitations

Several limitations exist in the current study. One significant limitation is the lack of testing for individuals who have not been infected with COVID-19. As an estimated 35% of individuals with infected with COVID-19 are asymptomatic (Sah et al., 2021), it is possible several participants from the control group may have had a history of COVID-19 infection and were never tested. An additional limitation is a lack of data regarding COVID-19 variants within the current study. As data collection began early after the discovery of COVID-19, data on specific variants, such as delta, omicron, ba4, or ba5 was not collected.

As data collected for the current study were from volunteers recruited from social media, symptom severity may have been a limited factor on an individual's willingness to participate. Four individuals contacted the primary investigator regarding the study, but declined to participate, as they felt their COVID-19 related fatigue was too limiting to fully engage with the evaluation. It is possible other individuals who have more severe post-COVID-19 symptoms may have been unwilling to participate with similar reasoning.

Strengths

Despite the above weaknesses, the current study has a number of strengths. As the spread of COVID-19 continues, there is now speculation that it is endemic (Klobucista, 2022) and a large percentage of individuals report cognitive decline post recovery. As such, it is important to continue

to collect data to improve our understanding of how COVID-19 may affect cognition. The current study provides valuable data to support diagnostic decision differentiation regarding patients who seek out a neuropsychological evaluation after COVID-19 exposure.

Another strength of the current study is the neuropsychological testing methodology. The COVID-19 pandemic disrupted traditional neuropsychological testing in an unprecedented way, which necessitated practices which were not researched with the same scientific rigor as more traditional clinical methodologies (Bilder et al., 2020). Although telehealth assessment was not unheard of, the validation of measures for use in this capacity were lacking. The current study represents an early step in the validation of the GNA for use in a telehealth format, which may be useful in the assessment of individuals who are unable or unwilling to attend appointments in person or for times when a public health crisis may force the closure of neuropsychology clinics.

Future Directions

As the current study provides evidence that the secondary symptoms of COVID-19 are more likely to impact cognition than COVID-19 infection itself, future studies should investigate the impact of specific severe symptoms such as hypoxic events and intubation. Future research which further differentiates the lingering symptoms of COVID-19 based on initial symptom severity could assist in diagnostic differentiation amongst those who have recovered from COVID-19, but may be experiencing unrelated cognitive symptoms. Future studies should continue to monitor COVID-19 variants for any evidence of the virus' ability to cross the blood-brain barrier. If such a variant were to exist, further studies should examine the effects on cognition of this variant compared to other variants and healthy controls.

In addition, further research could also continue to collect normative data on various measures for use with telehealth services. The utility of such services in the time of a pandemic

and to those who may not have easy access to a neuropsychological clinic in their local area is invaluable. However, with the current measures and data available, such assessments are limited in their utility.

Conclusions

Although subjective complaints of cognitive concerns after COVID-19 infection are common, the current study suggests a benign symptom presentation (i.e., individuals able to recover from home who have not had a hospital stay, hypoxic event, etc.) does not impact cognition long-term, at least among fairly young adults. This is unsurprising, as SARS-CoV-2 is not typically found postmortem in brain tissue, implying that any neurological injury is not caused by a direct viral attack on the brain in those infected with COVID-19 (Lee et al., 2020). However, even mild respiratory infection resultant from SARS-CoV-2 infection has been shown to cause multi-lineage cellular dysregulation and myelin loss in the brain (Fernández-Castañeda et al., 2022). These results should be encouraging for those who experience anxiety related to the long term cognitive effects of relatively benign COVID-19 symptom presentation.

The results are also promising for the utilization of a telehealth version of the GNA and the MSE-TV. As performance on this healthy sample produced few outliers on any measure and the results were normally distributed with the exception of the delayed memory task of the GNA. Although a comparison of in-person and telehealth administration would be more compelling, this study represents a first step to establishing this alternative format.

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