The Combined Use of Neuropsychiatric and Neuropsychological Assessment Tools to Make a Differential Dementia Diagnosis in the Presence of “Long-Haul” COVID-19

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Abstract
The longer term neurocognitive/neuropsychiatric consequences of moderate/severe COVID-19 infection have not been explored. The case herein illustrates a complex web of differential diagnosis. The onset, clinical trajectory, treatment course/response, serial neuroimaging findings, and neuropsychological test data were taken into account when assessing a patient presenting 8 months post-COVID-19 (with premorbid attention-deficit hyperactivity disorder, diabetes mellitus, mood difficulties, and a positive family history of vascular dementia). Her acute COVID-19 infection was complicated by altered mental status associated with encephalopathy and bacterial pneumonia. After recovery from COVID-19, the patient continues to experience persisting cognitive and emotive difficulties despite an ongoing psychopharmacotherapy regimen (16 + years), psychotherapy (15 + sessions), and speech-language pathology SLP; 2 × week/for 12 weeks). The purpose of her most recent and comprehensive neuropsychological evaluation was to determine the presence/absence of neurocognitive disorder. The patient is a 62-year-old Caucasian woman. Cognitive screening was completed 3 months post-acute COVID-19 as part of an SLP evaluation, and a full neuropsychological evaluation was conducted 8 months post-COVID-19 recovery on an outpatient basis (in person). The patient had serial neuroimaging. Initial neurological evaluation during acute COVID-19 included unremarkable brain computed tomography (CT)/magnetic resonance imaging. However, follow-up CT (without contrast) revealed, in part, “asymmetric perisylvian atrophy on the left.”
Full neuropsychological evaluation at 8 months post-COVID-19 recovery revealed a dysexecutive syndrome characterized by language dysfunction and affective theory-of-mind deficit, consistent with dementia. There is need for careful use of differential diagnosis in COVID-19 patients with multiple risk factors that make them more susceptible to long-term neurological complications post-COVID-19. Differential diagnosis should involve multidisciplinary assessment (e.g., neuropsychology, SLP, neurology, and psychiatry).

Introduction

Although it is known that acute and post-acute cognitive and emotive dysfunction can occur with COVID-19 [1], the longer term neuropsychological manifestations of COVID-19 have not been fully characterized. The National Institute of Health and Care Excellence (NICE) in the UK has defined "long-haul" COVID-19 – as it has come to be known – as occurring when signs and symptoms continue or develop after acute COVID-19. This definition includes both "ongoing symptomatic COVID-19" and "post-COVID-19 syndrome." While "ongoing symptomatic COVID-19" refers to signs and symptoms of COVID-19 from 4 to 12 weeks, "post-COVID-19 syndrome" refers to signs and symptoms that develop during or after an infection consistent with COVID-19 that continue for more than 12 weeks (and are not explained by an alternative diagnosis). Long COVID-19 is thought to occur in approximately 10% of people infected. To better characterize long-haul COVID-19, the guidelines state the importance of multidisciplinary assessment by various professionals in different disciplines, including respiratory physicians, cardiologists, neurologists, general physicians (from primary care or rehabilitation medicine), neuropsychologists or neuropsychiatrists, occupational therapists, speech and language therapists, and dieticians.

Toward this aim of comprehensive assessment, Helms et al. [2] reported the neurological and neuropsychological characteristics of 58 consecutive COVID-19 patients and observed that 33% (15 of 45) of patients exhibited a dysexecutive syndrome at discharge, consisting of "inattention, disorientation, or disorganized movements in response to commands." Unfortunately, they did not report what actual neuropsychological tests were performed with patients to reach this conclusion. In separate studies, integrating neuroimaging and psychiatric data, short-term psychiatric dysfunction – including depression and psychosis – were reported in patients with COVID-19 [3–5]. Similarly, in yet another separate study, 65% of severe COVID-19 patients hospitalized in an intensive care unit (ICU; N = 58) experienced confusion, and 69% experienced agitation [6]. Regarding the neurological basis for the former finding, all 11 patients in the study who underwent perfusion neuroimaging were found to have bilateral frontotemporal hypoperfusion [2]. Additionally, in a separate magnetic resonance imaging (MRI) study of COVID-19, Kandemirli et al. [6] reported that 37% showed signal intensity abnormality accompanied by subcortical and deep white-matter signal intensity abnormality. Abnormalities involved the frontal lobe in 4 patients, the parietal lobe in 3 patients, and the temporal lobe in 1 patient. Guedji et al. [7] found orbitofrontal and limbic/paralimbic hypometabolism in COVID-19 patients versus matched controls.

Although the underlying neural mechanism for the observed functional changes is unknown, it has been speculated that COVID-19 can trigger an acute immune-mediated encephalopathy, which leads patients to experience neurocognitive and/or neuropsychiatric symptoms [5, 7, 8]. Specifically, COVID-19 can activate cytokines at the cellular level that cause injury to the blood-brain barrier (BBB). Via breaks in the BBB, cytokines are thought to penetrate the brain...
parenchyma, especially within the temporal lobes where the BBB is weaker. An association between such an immune response and the development of Alzheimer's disease has already been put forth [8]. However, regarding COVID-19, it is thought that the activated inflammatory response – with entry of blood material into the parenchyma – can result in seizures and/or encephalopathy. This total process is referred to as the "COVID-19 cytokine storm hypothesis."

Complicating matters in terms of isolating a causal link between COVID-19 infection and an onset of neurocognitive and/or neuropsychiatric symptomatology is the fact that it is also well known that critically ill patients in ICU settings in general (i.e., patients who suffer with multiple medical conditions and are on many medications) commonly develop delirium, memory loss, and slowed processing speed, and these symptoms can persist even after stabilization of their medical conditions [9]. As such, some researchers suggest that any decline in mentation among acutely ill patients with severe COVID-19 may not necessarily represent the action of a direct brain injury brought on by COVID-19 but could be attributable to the fact that these patients are critically ill. However, this reasoning is weakened by the finding that COVID-19 patients experience encephalopathy and delirium at a greater rate than would be otherwise expected for a patient in an ICU setting [5]. Furthermore, in a neuroimaging study, researchers [10] suggested that COVID-19 might disproportionately affect gray-matter volume in the frontal-temporal network in older adults infected, providing an anatomical and functional framework for understanding the expression of neuropsychiatric symptoms in COVID-19 patients.

Regardless of the exact underlying neurobiological cascade that may be triggered by COVID-19 acutely, infected patients that recover remain at increased risk for experiencing persistent cognitive difficulties, including a new onset or more rapidly progressing memory decline, inattention, and/or slowed processing speed [5]. Thus, some researchers suggest that such patients see a neurologist and/or undergo neurocognitive testing 6–8 months after recovery (i.e., if they are experiencing persistent cognitive issues, including slowness in processing information and/or poor attention) [5]. These researchers also hypothesized that patients with low scores in certain cognitive domains (e.g., processing speed vs. attention) may benefit from tailored cognitive rehabilitation services. Such treatment may maximize their chances of returning to their baseline level of cognitive capacity [5]. However, it is largely unknown whether engaging in cognitive rehabilitation would reduce risk for accelerated age-related cognitive decline later on.

There is already preliminary evidence that COVID-19 can result in longer term cognitive difficulties (i.e., up to 6 months post-COVID-19) [11]. For example, even mild COVID-19 patients can demonstrate persistent deficits in memory and heightened psychiatric symptomatology up to 6 months posttreatment [12, 13]. In addition, general cognitive decay (as measured by the Mini-Mental State Exam [MMSE]) was present in patients with severe COVID-19 who were entering the post-acute phase of illness (i.e., defined as clinical stability and complete weaning from sedative and antipsychotic medications) – on average 30 days post-COVID-19 diagnosis [14]. Similarly, cognitive decline was still persistent at the 2-month follow-up in 58.7% (out of 179 COVID-19 positive patients) of mild-to-severe COVID-19 patients, with 39.1% of those patients also showing psychiatric comorbidity (i.e., also at the 2-month follow-up) [15]. In particular, cognitive deficits were noted in attention and calculation (i.e., during a counting backwards task), short-term memory (i.e., during recall of 3 familiar words), constructional apraxia (i.e., when asked to copy a drawing of 2 intersecting pentagons), and written language (i.e., composing/writing a complete sentence) [15]. Results utilizing the Montreal Cognitive Assessment (MoCA) have been similar [13].

Studies employing more comprehensive neuropsychological testing also suggest persistent cognitive difficulties in some COVID-19 patients. For example, Méndez et al. [14] followed COVID-19-positive patients up to 2 months posthospital discharge, assessing cognitive and neuropsychiatric symptomatology. Their telephone-based test battery included verbal learning
and delayed recall, Animal Naming from the Controlled Oral Word Association Test, and Digit Span Backwards from the Wechsler Adult Intelligence Scale-III. They found that 58.7% of patients exhibited at least “moderate” neurocognitive decline, and 39.1% had psychiatric comorbidity. “Moderate” decline was defined as a score greater than two standard deviations below the population normative data in any single domain (i.e., verbal learning/memory, verbal fluency, or working memory) [14]. Furthermore, these researchers found that delirium during hospitalization and prior psychiatric diagnosis were associated with greater neurocognitive decline.

Further still, Zhou et al. [16] utilized an online iPad-based neuropsychological battery of tests that included the Trail Making Test, a symbol-digit transcription task, a continuous performance measure (Connors Continuous Performance Test [CPT]), and a forward and backward Digit Span Test. Comparing COVID-19-recovered patients (tested two to 3 weeks post-negative test) to age-, education-, and gender-matched controls, these researchers found that patients exhibited deficits in reaction time and sustained attention as assessed by the CPT. Finally, Whiteside et al. [17] utilized the most comprehensive neuropsychological battery to date in their case series based on their telephone-administered test battery. This group observed cognitive difficulties across 3 patients in the domains of verbal fluency and attention. This group proposed a three-stage model of cognitive dysfunction that corresponds to the three-stage NeuroCOVID model proposed by Fotuhi et al. [5].

Differential diagnosis is a major purpose for neuropsychological evaluation. The current case report centers on an individual with multiple premorbid risk factors (diabetes, attention-deficit hyperactivity disorder [ADHD], depression, and anxiety) who survived COVID-19 infection complicated by encephalopathy and an ICU stay. This patient reported persistent cognitive difficulties extending beyond the 6-month post-acute infection stage. The key concern for the neuropsychologist was to make a differential diagnosis between ongoing encephalopathy, onset of dementia (i.e., premorbid and independent of COVID-19 vs. perhaps being set in motion or hastened by COVID-19 infection), or exacerbation of preexisting neurocognitive (e.g., ADHD) and/or neuropsychiatric (anxiety/depression) and/or medical comorbidities (e.g., diabetes). Additionally, there was a question of whether the patient could return to work and general prognosis. This case describes a complex presentation of a constellation of cognitive and emotive symptoms that may increasingly represent what neuropsychologists will encounter in the outpatient neuropsychology clinic setting in the coming months/years.

**Case Presentation**

**Patient Demographics**

The patient is a 62-year-old Caucasian woman who completed four semesters of college (in a nursing program) but ultimately became a pharmacy technician. The patient has worked in the pharmacy field for 20 years total. The patient lives with her husband and has one adult daughter. Family neurological history is reportedly positive for dementia and stroke with associated aphasia. Current psychoactive medications include vitamin B12, Xanax/alprazolam, Neurontin/gabapentin, oxycodone and acetaminophen/Percocet, venlafaxine/Effexor XR, and melatonin. Prior diagnoses include high blood pressure, hyperlipidemia, sleep apnea, vitamin B12 deficiency, calcium deficiency, diabetes type 2, COVID-19 (recovered), depression, and anxiety.

**Reason for Referral**

A neuropsychological evaluation was conducted in order to clarify the patient’s current level of cognitive functioning in the context of recovery from COVID-19-related encephalopathy,
with persistence of cognitive-emotive symptoms 8 months posthospital discharge, with particularly worsening attention, poor short-term memory, and reduced executive functioning capacity. Cognitive screening with the Repeatable Battery for the Assessment of Neuropsychological Status Update® (RBANS Update) obtained while the patient was undergoing outpatient rehabilitation approximately 3 months prior to the full neuropsychological evaluation revealed extremely low immediate memory (SS = 69) but low average (SS = 89) delayed memory. The patient’s spouse reported at that time: “She’s always had bad attention, but it’s much worse now. She repeats herself and does not realize it. She tells me the same story over and over.” The patient indicated: “I write everything down,” and “I can be talking to you and completely zone out.” She also acknowledged some personality change: “I’ve turned into a really hateful person. I used to laugh a lot.”

**History of Presenting Concerns**

The patient reported no significant cognitive issues before contracting COVID-19 in the spring of 2020, except for a prior diagnosis of ADHD identified in early adulthood (i.e., college-age). At the time of the full outpatient neuropsychological evaluation, the patient had no memory for the course of her COVID-19-related hospital stay. She reported that her first memory after falling ill with COVID-19 is of being in the rehabilitation facility in July 2020. Note that this symptom (i.e., lack of awareness/memory/insight) has been reported in other case studies of acute COVID-19 (e.g., 17). See Figure 1 for a summary of her symptom course.

The patient was in her normal state of health until she began to run an increasingly high fever several days prior to her hospital admission. She did experience ageusia and anosmia. Her family eventually took her to a rapid COVID-19 testing site due to worsening symptoms. The patient has a vague memory of being in the parking lot of the testing site, but she does not recall being transported to the ER from the testing site. Once at the hospital, the patient was noted to be extremely combative and did not want to be admitted. She eventually ended up in the COVID-19 ICU because her oxygen level was very low (i.e., hypoxia), and she was running such a high fever. She was intubated. She was found to have superimposed bacterial pneumonia, and she was diagnosed with COVID-19-related encephalopathy. She was eventually
transferred to an inpatient rehabilitation hospital and then received rehabilitative services on an outpatient basis after that (she completed a brief cognitive screening as an outpatient during this time). She continued to carry the diagnosis of encephalopathy and was diagnosed with memory impairment, attention and concentration deficit, and cognitive communication deficit throughout the duration of rehabilitation services.

Medical records indicate that the patient experienced vague and then elaborate visual hallucinations while hospitalized, at first seeing a “white brick tunnel with light at the end,” which progressed to “people, cats, and dogs” that were not there. She further progressed to experiencing delusions along with visual hallucinations; e.g., she would save food to feed the imaginary animals. Further, she believed that her sister-in-law (who is childless in reality) had been in her hospital room with “her children” and that she, her sister-in-law, and the children, were all going on a trip to Disney. Psychiatry and neurology were consulted during her inpatient stay, and she was started on ZyPREXA/olanzapine (she discontinued use following discharge), and neuroimaging was obtained serially due to repeated concern for stroke.

**Neuroimaging**

Brain computed tomography (CT)/MRI in June 2020 during the acute stage of COVID-19 was interpreted as within normal limits. However, repeat CT testing in July in response to an abnormal neurological exam during the course of her inpatient stay revealed “mild parenchymal volume loss, particularly within the bilateral sylvian fissures. There is proportional dilation of the ventricles. No hydrocephalus.” Follow-up brain MRI 2 days later revealed “extensive patchy T2 FLAIR hyperintensities in the bilateral periventricular white matter.” Worsening encephalopathy led to repeat CT in mid-July and revealed “moderate diffuse cerebral atrophy with more prominent, asymmetric left perisylvian temporal and frontal lobe atrophy…background cerebral atrophy with asymmetric perisylvian atrophy on the left. Neurodegenerative disorder/dementia could be considered.”

**Premorbid Conditions/Comorbidities**

The patient has a history of back issues (with an onset before she contracted COVID-19) and a history of diabetes type 2. She suffered with lower back pain for approximately 10 years prior to her full outpatient neuropsychological evaluation, though without any surgery. However, her back pain was notable enough that it caused her to stop working approximately 10 years ago. At the time of the neuropsychological evaluation, the patient was walking with an assistive device. The patient also suffers with poorly controlled diabetes.

The patient had been treated for ADHD in the past with pharmacotherapy, though she was not taking any medication for this at the time of the neuropsychological evaluation. The patient indicated an “upset and irritable” mood. She indicated feeling overcome with anger at times, but at other times, her mood is “a lot better.” The patient had been participating in psychotherapy prior to contracting COVID-19 and had diagnoses of major depressive disorder and anxiety. She reported having a “hard time letting it out” in therapy initially but later gained from therapy as she indicated that her depression had gotten better, and she does not worry as much as she used to. She reported no recent change in her appetite. She does however experience significant daytime fatigue currently. She consumes up to two cans of caffeinated soda daily and has 1 cup of coffee daily. She denied alcohol use, and she quit smoking in 1985. She denied any other substance use.

The patient’s neurological history is notable for at least one prior incident resulting in a head injury but without loss of consciousness. Additionally, the patient suffers from sleep apnea (diagnosed several years ago). She uses a continuous positive airway pressure machine and reported poor sleep quality without it. Sensory functioning is notable for slight cataracts diagnosed in the past year and reduced hearing. The patient had tubes placed in her ears...
approximately 20 years ago due to recurrent ear infections. The right tube has fallen out. The patient denied any recent change in her sense of taste or smell, though she did experience ageusia and anosmia during the acute phase of her illness.

Current Neurocognitive Functioning (8 Months Post-COVID-19)
The patient underwent cognitive rehabilitation with a speech and language pathologist and a physical therapist at a major research university-affiliated rehabilitation hospital on an outpatient basis. The patient reported at the time of neuropsychological evaluation that her memory for recent events remains compromised in that “I can’t remember right now.” Specifically, she tends to forget her train of thought if she is interrupted. She cannot remember plans each day. She keeps a large wall calendar to note all appointments. The patient also continues to misplace items and sometimes places items in the wrong place, e.g., her spouse finds nonfood items in the refrigerator. Regarding attention, she reported that she forgets what she wants to say mid-sentence now. She also notices that she is tangential in conversation now. She also abandons tasks prematurely and forgets to complete them. She gets lost in the hospital when she has an appointment or when she is otherwise going somewhere new. However, her long-term memory remains intact. The patient is currently independent in terms of basic activities of daily living functions, but she requires help to accomplish most instrumental functions. For example, during the neurobehavioral status exam, the patient could not recall the names of her medications, but she was able to describe that she has to take 3–4 insulin shots per day.

Behavioral Observations the Day of Testing
The patient appeared alert, and spontaneous speech was fluent with normal prosody and rate, but word-finding difficulty was apparent. Receptive language was reduced; instructions were repeated on several tasks, and the patient appeared not to understand concepts at times. For example, she never figured out the concept of the Wisconsin Card Sorting Task, and it was discontinued after 30 min, and only one category sort. She also performed poorly on a sentence comprehension task, suggesting additional receptive language difficulties. Expressive language was also impacted as her single-word reading score was much lower than expected and notable for unusual pronunciations of words that she likely could easily sight-read in the past (e.g., “lamb” for “lame” and “trumpet” for “triumph”). Thought processes were coherent and of normal content, but she was quite tangential. Gross motor functions were very slow. Mood was euthymic and affect remained pleasant throughout the evaluation. The patient was cooperative with the interview and testing procedure. She appeared motivated to perform to the best of her abilities, and her score on one of two embedded performance validity measures was within expectation. Her performance on a standalone validity indicator was borderline (8/15 correct; when the cutoff for valid performance is 9 or above). When combined with her reliable Digit Span score, these results are suggestive of true difficulty in the domains of attention and learning, rather than suboptimal effort. Therefore, the present results were judged a valid reflection of her current level of cognitive-emotive functioning, with significant attentional and learning difficulties noted.

Test Data
Test data are presented in Table 1.

Testing Highlights

Intellectual Functioning
Taken together with demographic information (e.g., educational achievement and career trajectory), it is likely that the patient’s intellectual functioning fell at least within
Table 1. Descriptors are based on normative data and professional consensus [18], and are adjusted based on clinical judgment.

| Descriptor                          | Percentile rank   | Descriptor                          | Percentile rank   |
|-------------------------------------|-------------------|-------------------------------------|-------------------|
| Exceptionally high                 | 98 and above      | Low average/borderline elevated     | 9–24              |
| Above average                       | 91–97             | Below average/elevated              | 2–8               |
| High average                        | 75–90             | Exceptionally low/very elevated     | <2                |
| Average                             | 25–74             |                                     |                   |
| Estimated premorbid intellectual functioning | Age-adjusted standard score (percentile/grade equivalent) |                      |                   |
| WRAT-5 word reading                 | 77 (6th %tile/5.3) | Below average                       |                   |
| Current intellectual functioning    | Age-adjusted standard score/scaled score |                      |                   |
| WASI-II                             |                   |                                     |                   |
| Verbal Comprehension Index          | 80                | Low average                         |                   |
| Similarities                        | 6                 | Low average                         |                   |
| Vocabulary                          | 7                 | Low average                         |                   |
| Perceptual Reasoning Index          | –                 | –                                   |                   |
| Matrix reasoning                    | 4                 | Below average                       |                   |
| WAIS-IV                             |                   |                                     |                   |
| Working Memory Index                | 69                | Below average                       |                   |
| Digit Span                          | 4                 | Below average                       |                   |
| Arithmetic                          | 5                 | Below average                       |                   |
| Processing Speed Index              | 56                | Exceptionally low                   |                   |
| Symbol search                       | 2                 | Exceptionally low                   |                   |
| Coding                              | 2                 | Exceptionally low                   |                   |
| Academic                            | Age-adjusted standard score (percentile/grade equivalent) |                      |                   |
| WRAT-5 math computation             | 78 (7th %tile/3.8) | Below average                       |                   |
| Memory                              | Raw score         |                                     |                   |
| CVLT-3 (Standard)                   |                   |                                     |                   |
| Total trials 1–5 (list A)           | 22/80 (4-4-5-5-4) | Below average                       |                   |
| List B free recall                  | 2/16              | Low average                         |                   |
| Short-delay free recall             | 2/16              | Below average                       |                   |
| Short-delay cued recall             | 4/16              | Below average                       |                   |
| Long-delay free recall              | 5/16              | Low average                         |                   |
| Long-delay cued recall              | 4/16              | Below average                       |                   |
| Recognition hits                    | 12/16             | Low average                         |                   |
| False-positive errors               | 14                | Below average                       |                   |
| Intrusion errors (trials 1–5)       | 19                | Below average                       |                   |
| Forced choice recognition           | 16/16             | WNL                                 |                   |
Table 1 (continued)

| Descriptor | Percentile rank | Descriptor | Percentile rank |
|------------|-----------------|------------|-----------------|
| BVMT-R (form 1) | Raw score | Total learning (trials 1–3) | 4/36 (0-2-2) | Exceptionally low |
| delayed recall | 3/12 | Exceptionally low |
| Learning | 2 | Low average |
| Recognition hits | 6/6 | WNL |
| False-positive errors | 1 | Below average |
| Executive functioning | | WAIS-IV Digit Span | Scaled score (max. span) |
| Forward | 5 (5) | Below average |
| Backward | 6 (3) | Low average |
| Sequencing | 4 (4) | Below average |
| CPT-3 | T-score | Omissions | 55 | WNL |
| Commissions | 39 | WNL |
| Hit RT | 64 | Elevated |
| Hit RT SD | 56 | WNL |
| Variability | 50 | WNL |
| Detectability (d’) | 50 | WNL |
| Perseverations | 60 | Borderline elevated |
| Hit RT block change | 62 | Borderline elevated |
| Hit RT ISI change | 49 | WNL |
| Trail Making Test | Raw score (T-score) | Part A | 69 s, 2 errors (27) | Exceptionally low |
| Part B | 371 s, 2 errors (11) | Exceptionally low |
| COWAT verbal fluency | Raw score (T-score) | Exceptionally low |
| Letter fluency (FAS) | 17 (26) | | |
| Bicycle Drawing Test | 5/20 (34) | Below average |
| Clock Drawing Test | 8/10 | Below average |
| WCST | Raw score | Categories (trials) | 1 (discontinued at 94 trials/~30 min) | Exceptionally low |
| Perseverative responses | 60 | Exceptionally low |
| Failure to maintain set | 2 | Low average |
| Trials to complete first category | 83 | Exceptionally low |
| Language | Raw score (T-score) | BNT | 53/60 (41) | Low average |
| Complex Ideational Material (BDAE) | 8/12 (13) | Exceptionally low |
| COWAT verbal fluency | Category fluency (animals) | 9 (23) | Exceptionally low |
the low average range at some point in the past. Her poor single-word reading test score (i.e., the WRAT-5) is unexpected and thus likely represents true language decline rather than being a genuine indicator of her baseline intellectual functioning. Consistent with this hypothesis, estimation of additional aspects of intellect most susceptible to cognitive decline revealed significantly reduced working memory and processing speed, providing further evidence of significant intellectual decline relative to her core verbal reasoning capacity.

**Learning and Memory**

Overall, her ability to accumulate (i.e., learn) new visual and verbal information was compromised (e.g., look at her scaled score trajectory across the learning trials of the CVLT-3 in Fig. 2), but she did not show a rapid decay pattern after a delay. Recognition memory is adequate for visual information but is compromised for verbal information.
Attention, Processing Speed, and Executive Function

Basic attention is reduced, and her rote working memory is below average when no context is provided (i.e., Digit Span backward < Digit Span sequencing). These specific tests correlate with ability to manage finances [44]. Contextualized working memory in the form of rapid calculation via math word problems is below average. Processing speed is exceptionally low. She lost mental set across repeated trials of a complex problem-solving task (note that the WCST categories achieved significantly correlates with wages earned and hours worked) [45], and she struggled to represent time on a clock face (Fig. 3), drew a bicycle lacking several important parts (Fig. 4), she generated novel ideas very slowly, and performed below expectation in terms of rapid mental flexibility (see Fig. 5). Indeed, Trail B performance is known to correlate with driving ability [46]. All of these tasks call upon utilization of more than one executive operation. Finally, her sustained attention

Fig. 2. Patient’s CVLT-3 profile.

Fig. 3. Patient’s clock drawing.
capacity was poor on a CPT as her response speed was slow overall and slowed down even further (i.e., disproportionately) during later blocks of the task.

Language
Her performance across language measures suggests difficulty extracting meaning from verbal information presented in an auditory format.

Academic
The patient demonstrated below average calculation skill on a paper-and-pencil measure (WRAT-5 Math, Fig. 6), which certainly represents decline for this patient given her career in a technical field where she had to use mathematics frequently. This test is also correlated with financial ability in Alzheimer’s disease [47].

Mood, Social Cognitive Behavior, and Personality
On self-report mood measures, the patient’s pattern of responses indicated moderate depression currently and mild anxiety. In addition, her social cognitive functioning on a behavioral
The task is compromised in terms of reduced affective theory of mind, with her performance falling within the exceptionally low range. Finally, the patient endorsed items on separate self-report measures to indicate the presence of clinically meaningful apathy but normal hedonic tone.

**Diagnosis**

The patient meets criteria for major neurocognitive disorder due to multiple etiologies with behavioral disturbance (i.e., apathy and reduced social cognition) (i.e., ICD 10: F02.81).
General Summary/Discussion of Neuropsychological Test Results

The patient's neuropsychological profile is aberrant relative to neurotypical individuals her age and education level. Intraindividual inspection of her scores revealed intellectual decline most notable in the following domains (in order of severity, high to low): processing speed, working memory, and perceptual reasoning. Vocabulary knowledge was roughly consistent with expectation. Basic attention on a rote Digit Span task was below average, and her learning curve across a list-learning task was flat, with essentially no growth across five trials (of the same list). The same pattern emerged on a visual learning task across three trials. However, she is not amnestic; she did not show a pattern of rapid decay across a delay period (for visual nor verbal information).

Her prominent learning difficulties provide evidence for the presence of an overall dysexecutive syndrome, a supposition that is also supported by her performance on a complex problem-solving task (i.e., the WCST). She only deduced one category, and she lost mental set twice (and the task was ultimately discontinued after 30 min for lack of achievement). Furthermore, she was very slow to respond on a CPT and showed a significant decrement in her speed of performance during later blocks of this task (relative to early blocks). Additional features of a dysexecutive syndrome include: poor working memory on the WAIS-IV (she could only keep track of 3–4 bits of information accurately) and poor phonemic fluency. Finally, her executive-based visuoconstructive ability was poor on the clock-drawing task (e.g., the size difference between the hour and minute hand was not represented) and on the bicycle drawing task (i.e., several key elements were missing), suggesting significant abstraction-motor planning difficulties. Research indicates that executive dysfunction and dysexecutive behavior – which compose the “dysexecutive syndrome” – have both separable and common neuroanatomical and functional correlates. The common correlate is rostral prefrontal cortex activity bilaterally [48]. Her executive functioning deficits on formal testing and the numerous dysexecutive behaviors reported by the patient’s spouse and by the patient herself (e.g., worsened attention, losing her train of thought, being tangential in conversation, prospective memory difficulties, etc.) indicate anterior prefrontal cortex involvement.

Overall, then, these results indicate significant difficulty with learning, abstraction, attention, mental speed, and sustained focus, which is consistent with what the patient and her spouse reported (i.e., a dysexecutive presentation). However, importantly, language functioning was also an area of weakness. Both expressive (e.g., Complex Ideational Material) and receptive language (e.g., Animal Naming) were weaker than expected given her vocabulary knowledge. While her phonemic fluency difficulties implicate prefrontal pathology, her semantic language difficulties suggest some degree of temporal involvement. Specifically, moderately intense depressive symptoms, poor affective theory of mind, and clinically significant apathy (but normal hedonic tone) implicate primarily limbic structures, with spared functioning in certain reward-based striatal structures. Indeed, prior research indicates that affective theory-of-mind deficits in particular – which refer to a person’s ability to understand the feelings, emotions, and affective states of others [49] – as quantified by accuracy score on the Reading the Mind in the Eyes Test [50] – relates to activity in the limbic-paralimbic region.

Possible Etiological Factors

Applying all of this information to the present case, the white-matter changes observed on imaging could relate to her diabetes and/or history of head injury and ADHD. It is also important to note the potential effects of pain medication (e.g., Percocet) use on her cognitive presentation, which may be expected to affect her processing speed most prominently and
lead to a blunted/flat neurocognitive profile in general. Although she does demonstrate poor processing speed, this is not in isolation, and thus, pain medication is likely not the primary cause of her cognitive profile or the most parsimonious explanation for the peaks and valleys (variability) across her intraindividual neurocognitive pattern. Furthermore, although aspects of her test performance are consistent with premorbid ADHD, her attentional difficulties appear to be greater than that observed in this age-group with “typical” ADHD in isolation (i.e., a drastic worsening of attention over the course of weeks in an otherwise healthy adult ADHD patient is not expected). This finding is consistent with the budding research literature, e.g. [17].

Therefore, the nature of the onset of cognitive difficulties in tandem with the onset of COVID-19 symptoms and the fact that her cognitive functioning has not returned to baseline despite general recuperation/recovery from core respiratory and focal neurological symptoms (i.e., somnolence, hallucinations/delusions, and altered mental status) associated with the acute phase of COVID-19 suggest an ongoing process. A persistent low-level delirium due to encephalopathy versus an emergent neurodegenerative cause remained on the differential. Her cognitive pattern + serial neuroimaging implicate frontoparietal (i.e., given the presence of a dysexecutive syndrome, visuoconstructive, attentional, and mathematical difficulties), fronto-subcortical (i.e., given reduced processing speed, learning capacity, and ongoing emotive symptoms such as apathy and depression – with particular impact to limbic structures such as the amygdala and hippocampus but not the frontostriatal system given normal hedonic tone currently – a constellation that may be most associated with the onset and severity of COVID-19 infection) [7, 51], and temporoparietal junction dysfunction (e.g., evidenced most prominently by social cognitive and reduced expressive and receptive language dysfunction).

Given that none of the above-discussed premorbid/confounding factors explains the fact that she experienced not only worsening attention but also a new onset and persisting cognitive difficulties following COVID-19 infection (i.e., new onset memory difficulties, mood and social cognitive difficulties, and language difficulties), an alternative explanation was required. Indeed, consistent with prior reports [14–17], the patient’s neuropsychological exam confirms language, mathematical, socio-cognitive, and learning difficulties. The patient’s most recent neuroimaging findings indicate progressive, and now, asymmetrical cerebral atrophy (i.e., affecting the left perisylvian region slightly > right), along with patchy white matter hyperintensities bilaterally. This largely excludes ongoing encephalopathy as an appropriate explanatory variable. Instead, an active neurodegenerative process (possibly ignited or hastened by the initial encephalopathy) appears more probable. Specifically, a frontotemporal or atypical AD pathology seems most plausible [52], given specific and notable decline in learning, language/single-word reading, and calculation skill. Indeed, recent research proposes the existence of a temporoparietal junction subtype of AD [53]. Her most recent neuroimaging findings may be the strongest harbinger for the presence of an independent neurodegenerative process [54]. Also, note that the patient has a positive family history of neurodegenerative disease following stroke (characterized by aphasia), and this likely increased her risk for cognitive decline even without COVID-19.

Regarding the specificity of COVID-19 in this patient’s neuropsychological exam, the presence of a dysexecutive profile (which is strongly consistent with previous reports of the neuropsychological profile in COVID-19 patients) fits with what is known about the impact of COVID-19 on the brain. The idea that COVID-19 may alter fronto-subcortical circuitry in particular is supported by these data and other previous work, including neuroimaging studies that have consistently observed frontotemporal/fronto-subcortical dysfunction in COVID-19 patients. Specifically, in one study, all 11 COVID-19 patients who underwent perfusion neuroimaging were found to have bilateral frontotemporal hypoperfusion [2]. Additionally, in a separate MRI study of COVID-19 [6], researchers observed fronto-subcortical signal intensity abnormality in nearly 20% of COVID-19 patients. Guedji et al. [7] observed orbitofrontal and
limbic/paralimbic hypometabolism in COVID-19 patients versus matched controls. Again, these results provide evidence to support the idea that fronto-limbic disruption is a characteristic of this virus.

**Recommendations**

What the patient perceived as a “memory problem” turned out to be more so a language, working memory/attentional, and dysexecutive problem based on the results of psychometric testing. Given her history of COVID-19, the presence of a dysexecutive syndrome (with notable language difficulties on neuropsychological testing) and neuroimaging findings suggestive of atypical AD versus frontotemporal pathology; PET brain imaging was recommended to further interrogate a neurodegenerative diagnosis (e.g., to confirm or rule out a straightforward frontal-temporal pattern of hypoactivation consistent with what has been reported in COVID-19 patients who have undergone PET imaging [7]) versus an atypical AD pattern of hypoactivation (which would include more temporoparietal involvement [52]). In addition, continued speech and language therapeutic services were encouraged, with more direct focus on addressing the patient’s language difficulties (in addition to attentional, learning, and executive deficits). Referral to geriatric psychiatry or continued community-based psychotherapy was recommended to address ongoing mood symptoms in the context of her health issues. A behavioral approach to psychotherapy was recommended (as the most likely therapy orientation to be successful), given the patient’s reduced executive functioning. A trial of a cognition-enhancing medication (i.e., a stimulant or atypical stimulant and/or an anticholinesterase inhibitor) to address ongoing attentional, learning, daytime fatigue, and executive symptoms was also recommended. The patient was strongly encouraged to reduce her intake of caffeine. Given reported driving difficulties, cognitive flexibility difficulties, and processing speed difficulties on testing (e.g., Trail B), a formal driving evaluation was recommended. Given the patient’s pattern of difficulties, including math decline, attentional and executive difficulties, and the expected pattern of further decline, it was recommended that she refrain from returning to her job, at least not in a pharmacy technician role like the one she had in the past.

**Conclusion**

The strengths of this case report include the serial nature of cognitive and brain assessment (i.e., neuroimaging). The limitation of this case includes several premorbid conditions that each can affect brain health. Nevertheless, overall, these results provide further preliminary evidence for continuing to investigate the interaction between COVID-19 infection, detectability of cognitive decline, and emergent or accelerated progression of neurodegenerative disease. The timeline of neuropsychological evaluation of this patient, i.e., 8 months post-COVID-19 recovery, helps to solidify the hypothesis that COVID-19 may increase risk for neurodegeneration or increase manifestation/detectability of cognitive decline or actually speed up progression in neurodegenerative disease. The latter idea has been speculated on in the literature already [7, 15].

The pattern of cognitive-emotive deficits observed in this patient includes a dysexecutive syndrome with attentional and social cognitive deficits. The former is consistent with previous reports of acute and post-acute COVID-19 patients [17], but the latter is a novel finding that deserves further inquiry. This case also illustrates the need for caution in interpreting neuropsychological data in the midst of several overlapping differentials and correlating neuropsychological findings with serial neuroimaging data (when available). Specifically, this patient (based on neuroimaging, and also based on the patient’s pattern of symptom onset, and evolving cognitive and neuropsychiatric symptoms) demonstrated a traditionally accepted...
"neurodegenerative pattern" in addition to meeting the neuroCOVID stage III criteria [5]. However, this pattern may have been missed without a full neuropsychological evaluation and amidst the backdrop of her comorbid diagnoses, which otherwise “clouded” aspects of her neuropsychological profile and may have ultimately resulted in a less accurate conclusion (i.e., “inconclusive,” "primarily psychiatric-related," "vascular-related," etc. vs. major neurocognitive disorder).

In this vein, this case uniquely illustrates complex differential diagnosis and the potential confluence of several etiological risk factors contributing to the manifestation of a major neurocognitive disorder. It is this type of complex presentation (i.e., which calls for careful consideration of premorbid conditions and the differentiation between normal age-related cognitive change vs. cognitive decline, the neurobiology of COVID-19, and other factors such as vascular risk factors, premorbid psychiatric illness, and medication regimen) that is more likely to be observed in the outpatient neuropsychology clinic, and it will be essential to carefully evaluate/monitor these types of patients' neurocognitive and neuropsychiatric functioning over time. In fact, these results suggest that long-term follow-up of these patients may be necessary [17]. It is recommended that the neuropsychological battery used with these patients (at minimum) include executive, learning and memory, attention, processing speed, language, social cognitive, and mood measures to properly assess the patient’s degree of vulnerability/increased risk for neurodegenerative disease associated with COVID-19 infection.

**Statement of Ethics**

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. Ethical approval was not required or obtained for this study. The paper is exempt from Ethical Committee approval because all information is de-identified.

**Conflict of Interest Statement**

The author has no conflicts of interest to declare.

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**Author Contributions**

S.N. Light was solely involved in the inception, writing, and interpretation of all data presented in this case study.

**Data Availability Statement**

All data generated and analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.
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