Tracking trajectories of cognitive recovery in coma survivors using a validated battery of neuropsychological tests

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Abstract

Longitudinal cognitive outcomes of coma survivors are poorly characterized in the literature, contributing to a significant gap in clinical practice. This dissertation is part of a larger project which looks to address this gap by establishing neurophysiological evidence for the treatment of brain injury in intensive care unit survivors (NET-ICU). The NET-ICU study uses high-density electroencephalography (EEG) to uncover neurophysiological markers that predict recovery of cognitive functions. The focus of this dissertation is on the cognitive outcome measures and trajectories of cognitive recovery of the NET-ICU patients.

In Section 1, this thesis reviews the literature to identify the current status of cognitive research in coma survivors. This section reveals the inconsistencies across studies of cognition and identifies gaps in the literature. Section 2 describes a validation study of the neuropsychological testing battery Cambridge Brain Sciences (CBS). CBS is a suite of computerized tests of cognition that assess aspects of memory, attention, planning and reasoning. Two hundred healthy adults completed these tests at 19 timepoints across 3 months, mimicking the timepoints of a longitudinal study conducted in recovering ICU patients. This control study provides accurate learning curves associated with each of the 12 tests in the CBS battery against which recovering ICU patients can be compared in future studies. Finally, the last section of this thesis investigates the cognitive outcomes of a sample of ICU coma survivors. In this study, the CBS results from a sample of recovering ICU patients are compared to the trendlines identified in the control study described in Section 2.

This series of projects provides concrete outcome data that will be used in the NET-ICU study in conjunction with the EEG data collected in the acute post-injury phase in the intensive care unit to predict cognitive outcomes, with the aim of developing a more objective tool for clinical decision-making in acute settings.

Résumé

L’évolution cognitive longitudinale des survivants du coma est mal documentée dans la littérature, ce qui se rapporte à une lacune importante en pratique clinique. Cette thèse fait partie d'un projet d’envergure qui cherche à remédier à cette lacune en établissant des évidences neurophysiologiques pour le traitement des lésions cérébrales chez les survivants des unités de soins intensifs (NET-ICU). Dans l’étude NET-ICU, on utilise l'électroencéphalographie à haute densité (EEG) afin d’identifier des marqueurs neurophysiologiques qui prédisent la récupération des fonctions cognitives. Cette thèse a pour objectif de caractériser l’évolution sur le plan cognitif, ainsi que les trajectoires de récupération cognitive chez les patients NET-ICU.

La première section de cette thèse comporte une revue de la littérature, permettant d’établir l'état actuel de la recherche cognitive chez les survivants du coma. Cette section révèle les incohérences entre les études, ainsi que les lacunes présentes à travers les études s’intéressant à la cognition. La section 2 décrit une étude de validation de la batterie de tests neuropsychologiques « Cambridge Brain Sciences » (CBS). La batterie CBS est une suite de tests cognitifs informatisés qui permettent d’évaluer des aspects de la mémoire, de l'attention, de la planification et du raisonnement. Deux cents adultes en bonne santé ont complété ces tests à 19 reprises sur une période de 3 mois, reproduisant les temps de mesures d'une étude longitudinale menée auprès de patients en réadaptation après coma. Cette étude de contrôle nous permet de tracer des courbes d'apprentissage précises associées à chacun des 12 tests de la batterie CBS, auxquels les patients en réadaptation pourront être comparés dans le cadre d’études futures. Enfin, la dernière section de cette thèse investigue les résultats cognitifs d'un échantillon composé de survivants du coma. Dans cette étude, les résultats des tests CBS d'un échantillon de patients en réadaptation aux soins intensifs sont comparés aux courbes d’apprentissage identifiées dans l'étude de contrôle décrite à la section 2.

Cette série de projets fournit des données concrètes qui seront utilisées dans le cadre de l'étude NET-ICU en conjonction avec les données du EEG collectées dans la phase aiguë dans l'unité de soins intensifs pour prédire les résultats cognitifs à long terme, dans le but de développer un outil objectif pour aider avec les prises de décisions cliniques en milieu aigu.

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Contribution of Authors

In Chapter 1, Allison Frantz developed and refined the search strategy, screened and read the articles, analyzed the data, constructively interpreted the findings and wrote and edited the manuscript. Natalia Incio Serra[1] screened and read articles, analyzed the data, constructively interpreted findings, and wrote and edited the manuscript. Dr. Stefanie Blain-Moraes[1,2] contributed to the search strategy, interpreted the findings and edited the manuscript. Aracely Lopez Almendariz[2] contributed to the data analysis.

In Chapter 2, Allison Frantz designed the study, collected, analyzed, and interpreted the data, and wrote the manuscript. Dr. Emily Nichols[3] analyzed and interpreted the data. Dr. Adrian Owen[4,5,6] contributed to the conception and design of the study. Dr. Stefanie Blain-Moraes[1,2] helped in the design of the study and provided feedback and edits to the manuscript.

In Chapter 3, Allison Frantz collected, analyzed, and interpreted the data, and wrote the manuscript. Marie-Pier Besner[1] helped with data collection. The study described in Chapter 3 is part of a larger clinical trial designed by Dr. Stefanie Blain-Moraes[1,2] and Dr. Adrian Owen[4,5,6]. Dr. Stefanie Blain-Moraes[1,2] also edited the manuscript, helped interpret the data, and provided constructive feedback.

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Introduction

Individuals who have suffered a severe injury and undergone a prolonged period of unconsciousness typically require extensive hospitalization in intensive care units (ICU) to survive their injury and regain their cognitive functions. Advances in medical technology have allowed these patients to survive significantly longer in some industrialized countries, regardless of the patients' ability to recover consciousness or cognitive abilities (Claasen et al., 2021). Critical decision-making by healthcare providers in this acute setting has an incredible impact on patient survival and outcomes yet are typically made based solely on clinical judgment (Duclos et al., 2020). In fact, decisions regarding course of treatment and specific care goals are made based on behavioural responses, which are often missing in the early days of a patient's admission to intensive care, rather than objective and quantifiable markers. In other words, significant decisions about whether to pursue treatment are typically made when patients are in a pharmacologically-induced coma and therefore unamenable to a thorough cognitive or behavioural assessment due to partial of complete lack of responsiveness. There is thus a critical need for point-of-care systems that can be used at bedside to predict patient outcomes and recovery trajectories to inform clinical decision-making about treatment of unresponsive brain-injured patients in the ICU (Honarmand et al., 2019).

Currently, there are no known or accepted physiological, neurological, or behavioural markers that can be gathered at bedside which reliably determine an unresponsive patient's prognosis. Cutting edge techniques such as fMRI are not practical in an acute setting where patients are unlikely to be stable enough to undergo extensive imaging protocols (Weijer et al. 2016). Clinical electroencephalography (EEG) allows neurologists to identify pathological characteristics, but the EEG waveforms and spectral properties have limited prognostic value with respect to cognitive outcomes beyond predicting patient survival. Preliminary studies conducted by Stefanie Blain-Moraes' team have demonstrated the potential prognostic value of network features of continuous EEG. Instead of focusing on waveforms and spectral properties as is standard in current clinical practice, or on event-related information, Dr. Blain-Moraes has found that information flow networks in the brain such as functional connectivity and their changes in response to a perturbation (e.g. the administration or interruption of anesthesia) have heralded the return (or not) of patient consciousness (Blain-Moraes et al., 2017; Nadin et al.,

2020; Duclos et al., 2021). While promising, the full prognostic potential of these features has yet to be explored.

Our team has developed a study to address the needs outlined above and establish neurophysiological evidence for the treatment of brain injury in intensive care units using EEG and a validated battery of computerized neuropsychological tests (NET-ICU study) (Duclos et al., 2020). The NET-ICU study aims to bridge the gap between high-density EEG markers and long-term cognitive outcomes of brain-injured ICU patients. Specifically, this study aims to design and implement a point-of-care system that predicts outcomes of continuously-sedated, brain-injured patients in the ICU by: 1) developing a set of EEG techniques that can be recorded at the ICU bedside that robustly predict the recovery of consciousness and cognition and; 2) developing patient-accessible methods of measuring long-term cognitive outcomes in ICU survivors.

To attain these objectives, the NET-ICU study conducts high-density EEG recordings acutely in the ICU, between 24 hours and 7 days of a patient's admission to the unit. Patients must be in a pharmacologically-induced coma (continuously sedated) and have suffered a brain injury to be eligible. Brain activity is recorded using EEG for 10 minutes at resting state (under continuous sedation). The clinical team then interrupts sedation to carry out a standard-of-care neuro-behavioural assessment. Throughout this assessment, and for an additional 10 minutes, sedation is withheld and EEG activity is recorded. Sedation is then reinstated and a final 10-minute resting state EEG is recorded.

The use of EEG networks as a prognostic tool is only meaningful if they can be validated against a set of patient outcome measures that are sensitive to the dynamic and complex changes in cognitive functions across various domains. Currently, very little is known about the long-term outcomes of ICU survivors. While it is known that long-term cognitive impairments affect 40–100% of ICU survivors (Hopkins et al., 2005; Moulaert et al., 2009; Iwashyna et al., 2010; Wilcox et al., 2013; Honarmand et al., 2020), and affects people of all ages (Pandharipande et al., 2014), there is a lack of a systematic, patient-accessible method for accurately tracking cognitive recovery in these patients. In the absence of this cognitive recovery data, it is

unrealistic to attempt to characterize the prognostic value of any markers gathered in the ICU. Clinical assessment of cognitive outcomes has been historically difficult to collect due to the lack of a comprehensive, easy-to-administer, standardized battery of tests. Generally, assessment of cognitive function requires that patients attend a clinic where trained personnel administer standard cognitive batteries. These testing sessions can be hours in length, are inconvenient for patients given the required travel to clinics, are costly due to the need for specially trained administrators and are related to high rates of patient attrition. Therefore, there is a need for a comprehensive cognitive assessment battery that can be used for large-scale, multi-center, repeated assessment, natural history studies that measure cognitive function recovery trajectories of ICU patients (Honarmand et al., 2020).

Furthermore, there is a lack of consensus in the literature regarding assessment of cognition, both in terms of the measures used and the timing of assessment. Measures of cognitive function assess various cognitive domains (Turnbull et al., 2016), where each domain informs clinicians and researchers about different aspects of a patient's cognitive recovery. Without consistency across the literature regarding cognitive domain accessed by these tests, it is difficult to interpret short- and long-term cognitive outcomes across studies.

Over the last 25 years, a suite of computerized cognitive tests, Cambridge Brain Sciences (CBS), has been developed to assess aspects of memory, attention, planning and reasoning in health adults and patient populations (Owen et al., 1990, 1991, 1992, 1996, 2010; Bor et al., 2003; Hampshire et al., 2012). The tests have been validated in patients with anatomically-specific brain lesions (e.g., Owen et al., 1990, 1991), in neurodegenerative populations (e.g., Owen et al., 1992, 1993), in pharmacological intervention studies (e.g., Owen et al., 1996), and in neuropathological populations (e.g., Owen et al., 1998; Williams-Gray et al., 2007). The tests have recently been modified to allow participants to complete them online without the supervision of a trained specialist, creating the opportunity for these tests to be used in large-scale, low-cost studies of cognition in the general population (Hampshire et al., 2012; Wild et al., 2018). The CBS tests have been taken more than 10 million times and have created a normative database of over 75,000 participants. This suggests that web-based studies of cognition are not

only possible, but also provide a novel opportunity for assessing cognition in a way traditional methods cannot.

Recently, a pilot study in a small cohort of ICU patients demonstrated the feasibility of administering these tests in an acute setting (Honarmand et al., 2019). The study found that patients can not only self-administer these assessments, addressing one of the key issues of current standard cognitive measures, the tests were also able to identify key cognitive impairments in several domains. Taken with the evidence that these tests can be used in longitudinal online studies, this provides a sound argument for using these tests in larger studies of clinical populations and opens the possibility of feasibly tracking trajectories of cognitive recovery in brain-injured ICU patients.

This thesis will focus on identifying the gaps in the literature regarding cognitive assessments for ICU survivors, and will address the second objective of the NET-ICU study, namely, to characterize and test a patient-accessible method of measuring long-term cognitive outcomes and trace the recovery of cognitive functions in brain-injury ICU survivors. In Section 1, this thesis reviews the literature to identify the current status of cognitive research in coma survivors. This section reveals the inconsistencies across studies of cognition in this population and identifies significant gaps in the literature. Section 2 describes a validation study of the neuropsychological testing battery Cambridge Brain Sciences (CBS). While already validated as a cognitive testing tool, these tests have never been assessed at multiple timepoints longitudinally. In this control study, 167 healthy adults completed these tests at 19 timepoints across 3 months, mimicking the timepoints of the NET-ICU study. This control study provides accurate learning curves associated with each of the 12 tests in the CBS battery against which recovering ICU patients can be compared in future studies. Finally, the last section of this thesis investigates the cognitive outcomes of a sample of ICU coma survivors. In this study, the CBS results from a sample of recovering ICU patients are compared to the trendlines identified in the control study described in Section 2.

Chapter 1: Cognitive measures and testing timepoints in critical care patients following a period of unconsciousness: A literature review

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Abstract

Trajectories of cognitive recovery in brain-injured patients following a prolonged period of unconsciousness are poorly characterized. This is due in part to the lack of an agreed-upon best measure of cognition and a lack of consensus among experts regarding assessment of cognitive function. Differences exist in the literature in terms of cognitive tests, cognitive domains assessed, and timing of cognitive assessment. This review aims to characterize the inconsistences regarding tests of cognition and frequency of cognitive testing in studies of brain-injured patients recovering from coma. 996 articles were screened, and 134 articles were included for analysis. 133 unique tests and testing batteries were identified, providing evidence that there is no established "best test" of cognition. Further, differences were found in terms of method of administration, timing of assessments, and frequency of testing. Inconsistencies also emerged in the reporting of cognitive outcomes, with 7.5% of tests not reporting on the specific tests used to assess cognition, and 7.5% of tests not specifying the timing of cognitive assessments. Overall, this literature review brought to light the inconsistencies in cognitive assessment and reporting of cognitive assessment in brain-injured individuals post-coma, and exposed the need to establish an agreed-upon best cognitive testing tool that is practical, assessed various cognitive domains, and can be assessed longitudinally.

Introduction

Individuals recovering from a severe brain injury have unique and heterogenous trajectories of recovery. Critical care research is needed to trace these trajectories and examine the natural course of recovery in patients who have recovered from a prolonged period of unconsciousness. Primary outcomes of intensive care unit (ICU) survivors typically focus on functional outcomes and mortality (Udekwu et al., 2004; Jennett & Bond, 1975). However, 40-100% of patients requiring care in a ICUs subsequently exhibit cognitive impairment (Schlichter et al., 2020; Hopkins et al., 2005; Wilcox et al., 2013; Moulaert et al., 2009; Iwashyna et al., 2010) regardless of age at injury (Pandharipande et al., 2013). Despite this, most studies focused on cognitive outcome end points after critical illness have excluded patients with brain injuries (Turnbull et al., 2016).

Given the lack of focus on cognitive outcomes as primary measures, there is incredible variety within the literature regarding the outcome measures available. Firstly, tests of cognition can be used to diagnose individuals recovering from disorders of consciousness. One must consider whether these tests of diagnosis are similar to cognitive outcome tests and whether these two types of measures can be compared. Further, cognitive outcome tests differ substantially in the way that they are administered, the cognitive domain assessed, and the type of task performed (Gordon et al., 2004; Honarmand et al., 2020). Classic tests of cognition such as the digit span memory task require participants to recall numbers presented to them in a sequence orally or visually (Blackburn & Benton, 1957). Other tests, such as the Functional Independence Measure, require a trained administrator to examine a patient and determine their level of cognitive functioning based on clinical observation (Grey & Kennedy, 1993).

Besides, measures of cognitive function can assess various cognitive domains, including memory, executive functions, attention, language and learning, and others. Each of these domains informs clinicians and researchers about different aspects of a patient's cognitive recovery. However, the choice of the which cognitive domain to assess remains apparently a personal decision among physicians and researcher without further discussion. There is a lack of consensus in the literature available about which cognitive functions should be taken into consideration for the recovery of brain-injured patients.

Furthermore, non-conventional and non-behavioural assessments of consciousness are also sometimes considered assessments of an individual's cognitive functioning. Such tests include electroencephalography (EEG) measures of event-related potentials (ERPs) and somatosensory-evoked potentials (SEPs). ERPs and SEPs have the potential to predict a patient's recovery of consciousness by illustrating underlying cognitive functioning despite low or inexistent behavioural response (Hauger et al., 2017; Lew et al., 2006). While it is agreed that these measures can identify the capacity for cognition, these measures of cognition are hard to compare to the behavioural assessments of cognitive function and will therefore not be included in this review.

Another gap in the literature exists regarding the timing of cognitive assessments in critical care units in brain-injured patients. Trajectories of functional recovery of ICU patients are inconsistent, and cross-study comparisons are difficult due to differences in study design, definition of sequelae, neurocognitive tests administered, time to follow-up, patient population, and disease severity (Gordon et al., 2004). Currently, no reviews exist in the literature exploring the timing of cognitive assessments in ICU survivors. This makes it difficult for clinicians and researchers alike to determine when it is best to assess cognitive function in coma survivors. Additionally, it makes it impossible to draw conclusions from the literature as a whole if studies cannot be examined as a group with similar testing points.

The primary objective of this review is to determine the common practices for measuring cognitive outcomes of unresponsive brain-injured patients in intensive care units. This includes identifying the most commonly assessed cognitive domains and determining which cognitive measures access those domains. The secondary objective of this review is to identify other gaps in the literature regarding the frequency and timepoints of cognitive assessments in these patients. By painting a picture of literature's current state, we hope to reveal the trends and expose the inconsistencies in cognitive assessments of ICU and coma survivors. Ultimately, the research objectives of this literature review are to determine the cognitive outcome measures used in research of adult ICU survivors who have experienced a prolonged period of unconsciousness; and to identify gaps in the literature regarding frequency and timepoints of these cognitive assessments.

Methods

A search strategy was created by developing a concept map and taking into consideration brainstorming sessions with librarians and experts in the field of brain-injury and critical care. As experts agreed that patients in ICU have suffered a primary cardiac injury can have suffered a secondary brain injury, we chose to include articles of brain-injured patients as well as of post-cardiac-arrest patients. Three search concepts were identified within the study objectives: "unresponsiveness," "brain-injured," and "cognitive outcomes."

The search was conducted within the PubMed database in two separate searches. Search terms for both searches are included in Appendix 1. The initial search yielded 996 articles. After eliminating duplicates, 992 articles were included in the first round of screening. Articles were uploaded to the online systematic and literature review tool Rayyan. Reviewers were blinded to the inclusion decisions of others. During the initial screening process, two reviewers assessed titles and abstracts according to a team consensus. Articles were included if they met the following inclusion criteria:

1) papers must be primary research articles (no reviews, case studies, etc.);
2) articles must have been published in English;
3) participants must be primarily adults (some articles included a child subpopulation);
4) participants must have suffered a coma or other period of prolonged unconsciousness;
5) the methods must include some measure of cognitive function.

For the purposes of this review, only behaviour-based assessments of cognition were included (studies using only ERPs to assess cognition were excluded).

157 articles were included after the first round of screening. A second round of screening was performed, in which reviewers read entire articles to ensure they met inclusion criteria. Also during this round of screening, reviewers extracted information from included articles relating to cognitive tests, timing of testing, and frequency of assessments. Following this second and final round of screening, 134 articles were included for analysis. Measures of cognition were extracted from the articles and the number of occurrences of each measure was documented. We then categorized the tests by the target cognitive domain assessed. The cognitive domains included memory, attention, and processing speed, among others. Next, tests were separated according to how they are administered and scored. Finally, testing timepoints were extracted from the articles and plotted in bar graphs according to the baseline reference point (which differs across the literature). Articles were considered cross-sectional if they only tested cognition at one timepoint, while articles that had several follow-up assessment timepoints were considered longitudinal.

Results

Overall, 992 articles were identified, and 157 articles were included after the preliminary round of screening. Of those, 134 met the inclusion criteria and were selected for data extraction and analysis.

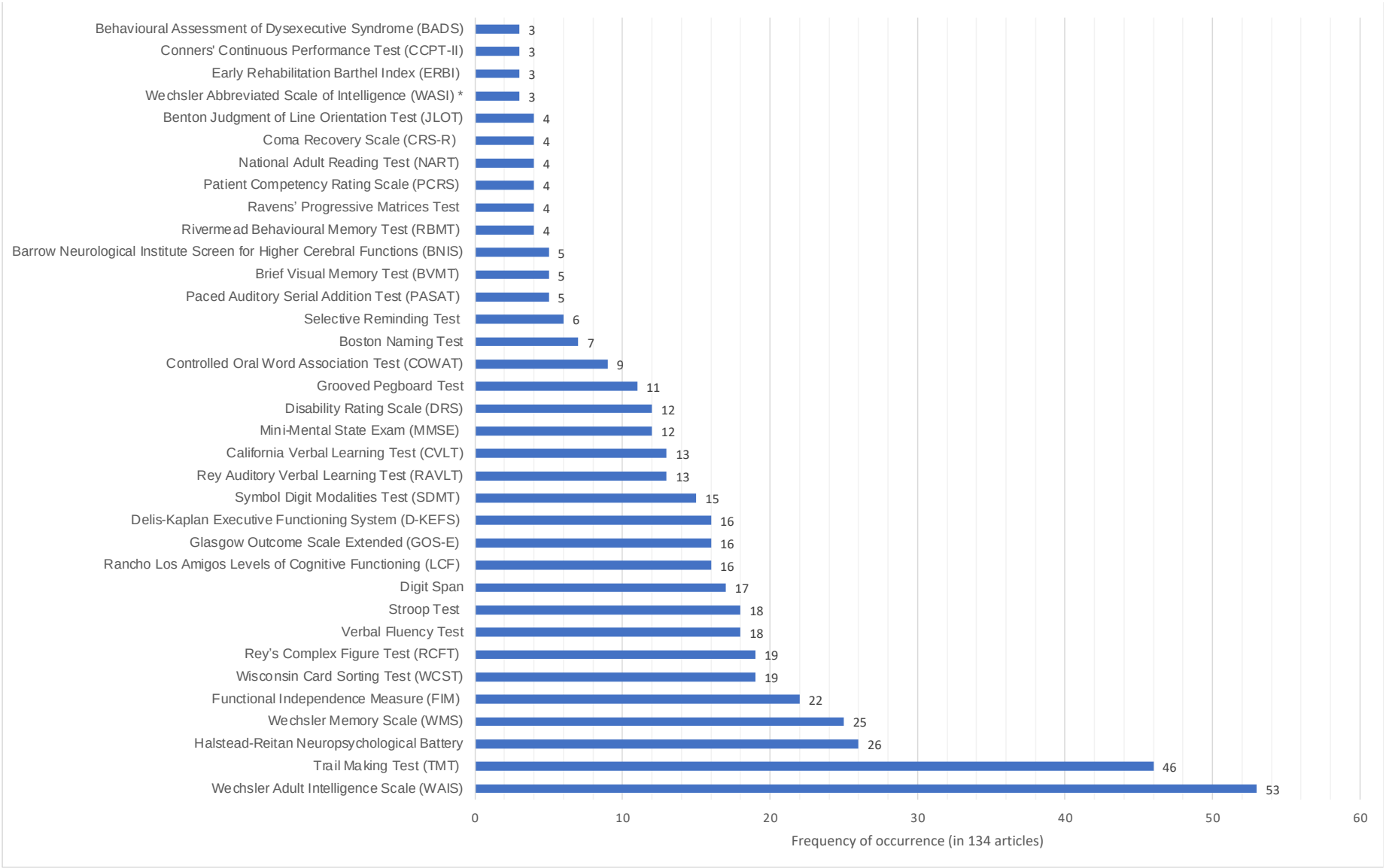
Measures of cognition

Measures of cognition were extracted from the articles and the number of occurrences of each measure was documented. A list of all tests identified in the review can be found in Appendix 2 133 unique tests and testing batteries were identified. Among these, 97 tests occurred in fewer than 3 articles. For the purposes of this review, only tests which appeared in 3 or more articles were included. A total of 36 cognitive tests or testing batteries were analyzed. A list of these tests, including descriptions and administration methods, is included in Appendix 3.

The trail-making test (TMT) was the most frequently used assessment, appearing in 46 articles (34.3%). Other popular cognitive measures included the Functional Independence Measure (FIM, 22 articles, 16.4%), the Wisconsin Card Sorting Test (WCST, 19 articles, 14.2%), the Stroop test (18 articles, 13.4%), the Glasgow Outcome Scale Extended (GOS-E, 16 articles, 11.9%), the Ranchos Los Amigos Levels of Cognitive Functioning (Ranchos LCF, 16 articles, 11.9%), and the Symbol-Digit Modality Test (SDMT, 15 articles, 11.2%). Figure 1.1 provides an overview of the most frequently used tests identified in our review of the literature.

The most commonly used cognitive testing batteries were the Weschler Adult Intelligence Scale (WAIS) which appeared in over 50 articles (37.3%), and the Weschler Memory Scale (WMS) which appeared in over 20 articles (14.9%). Only 23 studies (17.2%) included the entire WAIS battery, while 11 (8.2%) included the WMS in full. In general, most studies chose only a selection of subscales within the larger testing batteries to assess. All occurrences of subtests and full testing batteries are included in the table in Appendix 3.

Figure 1.1 *Frequency of occurrence of the 36 tests included for analysis*



Cognitive domains

While there appeared to be a wide range of tests assessed, we recognized that these tests fit into similar categories when sorted according to certain criteria. First, we categorized the tests by the target cognitive domain assessed (Table 1.1). The most frequently assessed cognitive domains were attention (10 tests, 138 occurrences), memory (11 tests, 130 occurrences) and executive function (5 tests, 76 occurrences). General "cognitive ability" (6 tests, 73 occurrences) was also a commonly assessed cognitive domain, with no further explanation regarding which cognitive domains are involved.

Table 1.1 *Tests of cognition*

Tests are listed alphabetically, along with the cognitive domains that they evaluate (including number of appearances of each test in a review of 134 articles). Cognitive domains are listed in the first column, with the number of tests evaluating that domain in brackets. The second column lists all tests that appeared 3 or more times in the review, with the number of appearances in brackets following the test name.

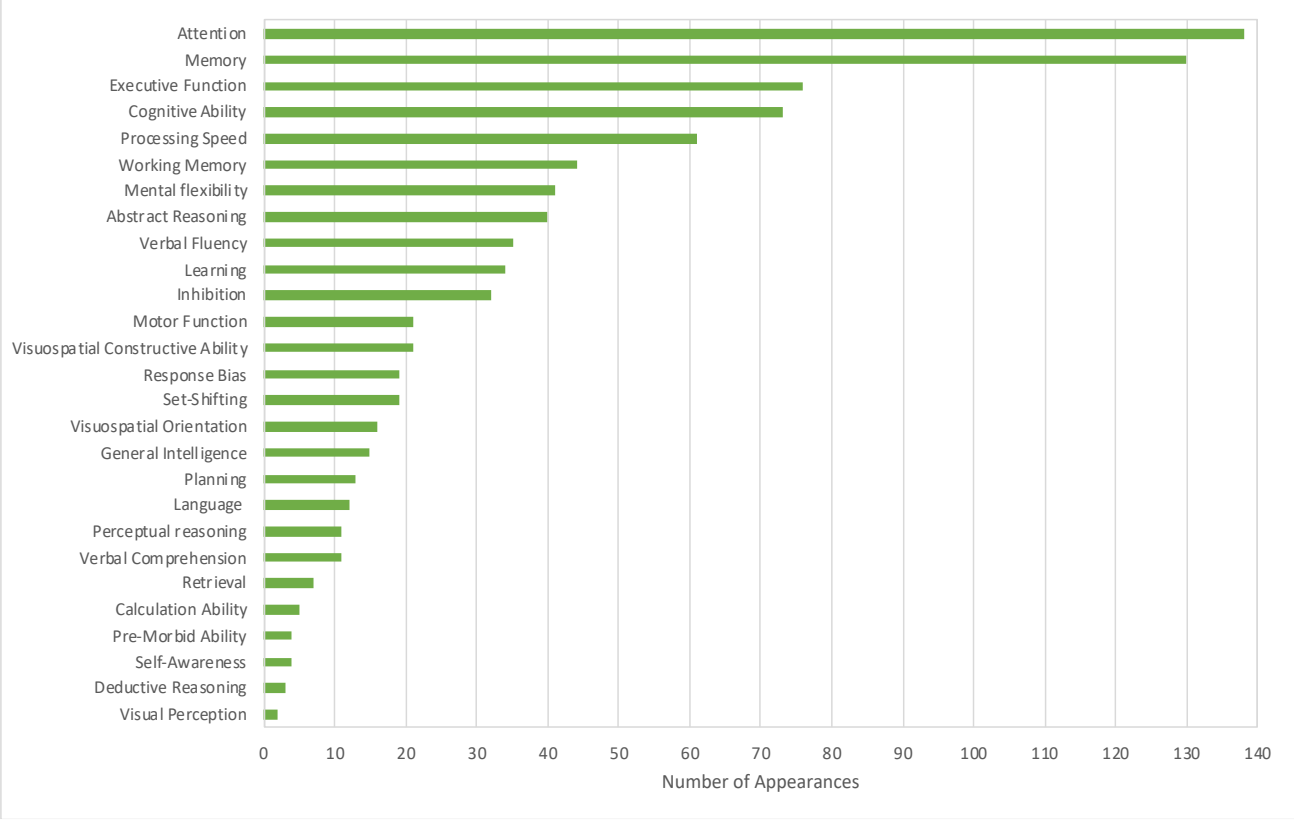
Domains (# of tests)	**Tests Included (# of appearances)**
Abstract Reasoning (5)	Category Test from HRNB (11), Proverb Test from D-KEFS (3), Raven's Progressive Matrices (4), Twenty Questions Subtest from D-KEFS (3), Wisconsin Card Sorting Test (19)
Attention (10)	Conner's Continuous Performance Test (3), Grooved Pegboard Test (11), Mini-Mental State Exam (12), Rey Auditory Verbal Learning Test (13), Rhythm Test from HRNB (7), Sorting Test from D-KEFS (3), Speech Sounds Perception Test from HRNB (6), Symbol Digit Modalities Test (18), Trail Making Test (46), Wisconsin Card Sorting Test (19)
Deductive Reasoning (1)	Word Context Test from D-KEFS (3)
Executive function (5)	Conner's Continuous Performance Test (3), D-KEFS (3), Grooved Pegboard Test (11), Rey Auditory Verbal Learning Test (13), Trail Making Test (46)
General Intelligence (2)	Raven's Progressive Matrices (4), Wechsler Adult Intelligence Scale-Revised (11)
Inhibition (3)	Colour-Word Interference Test from D-KEFS (7), Stroop Test (18), Tower Test from D-KEFS (7)

Learning (3)	California Verbal Learning Test (13), Rey Auditory Verbal Learning Test (13), Selective Reminding Test (8)
Memory (11)	Benton Visual Retention Test (2), Brief Visual Memory Test (5), California Verbal Learning Test (13), Digit Span (35), Mini-Mental State Exam (12), Rey Auditory Verbal Learning Test (13), Rey's Complex Figure Test (19), Rivermead Behavioural Memory Test (4), Selective Reminding Test (8), Tactual Performance Test from HRNB (8), Wechsler Memory Scale (11)
Mental Flexibility (5)	Design fluency from D-KEFS (3), Paced Auditory Serial Addition Test (5), Trail Making Test from D-KEFS (11), Wisconsin Card Sorting Test (19), Word Context Test from D-KEFS (3)
Motor Function (2)	Finger tapping Test from HRNB (10), Grooved Pegboard Test (11)
Perceptual Reasoning (1)	Wechsler Adult Intelligence Test-Revised from D-KEFS (11)
Planning (3)	Design Fluency from D-KEFS (3), Tower Test from D-KEFS (7), Zoo Map Test from BADS (3)
Processing Speed (5)	Paced Auditory Serial Addition Test (5), Rey's Complex Figure Test (19), Symbol Digit Modalities Test (18), Trail Making Test from HRNB (8), Wechsler Adult Intelligence Scale-Revised (11)
Response Bias (1)	Rey's Complex Figure Test (19)
Retrieval (1)	Boston Naming Test (7)
Self-Awareness (1)	Patient competency Rating Scale (4)
Set-Shifting (1)	Wisconsin Card Sorting Test (19)
Working Memory (4)	Sorting Test from D-KEFS (3), Wechsler Adult Intelligence Scale-Revised (11), Wechsler Memory Scale (11), Wisconsin Card Sorting Test (19)
Language (1)	Mini-Mental State Exam
Verbal Comprehension (1)	Wechsler Adult Intelligence Scale-Revised (11)

Figure 1.2 lists each of the cognitive domains illustrates their frequencies. The frequency was calculated by first calculating the number of appearances of each individual test, then associating

each test to the domain(s) that it assesses. Each value represents how often that domain was assessed across all articles and all tests analyzed.

Figure 1.2 *Bar graph illustrating the frequency of cognitive domains identified among 36 tests*



Tests were also separated according to how they are administered and scored. The most commonly used measures of cognition fit a similar type of administration model in which the tests are supervised by an examiner and are scored based on performance according to an instruction manual (Table 1.2). Interestingly, the tests of "general cognitive ability" fit a different model. These measures are administered by an examiner who either interviews the participant or observes participant behaviour and then provides a score based on their observations.

Table 1.2 *Tests of cognition sorted by method of administration*

Method of administration	**Tests**
Questionnaire completed by trained rater	MMSE
Trained examiner provides a score based on participant's abilities (gathered through interview or observation)	CRS-R, FIM, GOS-E, Ranchos LCF, ERBI
Test supervised by examiner, score based on time for performance	CTT, Grooved Pegboard, TMT, D-KEFS, HRNB (TMT, Tactual Performance Test), WAIS (Block Design)
Test completed on computer which generates score automatically	CCPT-II
Test supervised by examiner, score based on performance and instructions from rater's manual	BADS, JLOT, Boston Naming Test, BVMT, CVLT, COWAT, Digit Span, D-KEFS (Verbal Fluency, Design Fluency, Colour-Word Interference, Sorting Test, 20Q, Tower Test), HRNB (Category Test, Finger Tapping Test, Rhythm Test, Speech Sound Perception Test, Sensory Perceptual Test, Lateral Dominance), NART, PASAT, Raven's Progressive Matrices, RBMT, RAVLT, RCFT, Selective Reminding Test, Stroop Test, Verbal Fluency Test, WAIS (Similarities, Matrix Reasoning, Digit Span, Letter-Number Sequencing, Picture Completion, Arithmetic, Digit Symbol, Symbol Search), WCST, WMS (Spatial Addition, Design Memory, Symbol Span, Logical Memory, Verbal Paired Associates, Visual Reproduction)

Ten studies (7.5%) did not specify the tests used to assess cognition. In these cases, the articles described the cognitive measures using general terms such as "standardized neuropsychological

examination" (Fordyce et al., 1983), "other measures of attention, speed, and memory" (Dykmen et al., 1986) or even "no standardized set of tests used" (Trexler and Zappala, 1988).

Timing of assessments

Next, we assessed whether there were differences in the literature with regards to the time points at which cognition was assessed. We found inconsistencies across articles in terms of the timing of assessments as well as the reference frames for those testing timepoints. Studies assess cognition at various times relative to various milestones in injury progression and recovery. Further, timing of assessments differs in the literature depending on the chosen point-of-reference.

The most common milestone (or point-of-reference) was "time since injury" (Figure 1.3), with 74 out of 134 articles (55%) using this as the point of reference. Other time-points used as points-of-reference included 1) time since admission to rehabilitation centre (Figure 1.4), 2) time since discharge from rehabilitation centre, 3) time since admission to intensive care unit, 4) time since discharge from intensive care unit, and 5) time since intervention/treatment. These time-points are illustrated in Figure 1.5. 10 articles (7.5%) did not specify the exact timing of cognitive assessments. The y-axes in Figures 1.3, 1.4, and 1.5 indicate the time of assessment. In Figure 1.3, this time is depicted in days since injury. In Figure 1.4, some studies reported days since rehab admission while other studies did not provide specific timing, resorting instead of milestones such as "every 2 weeks between rehabilitation admission and discharge." Figure 1.5 does not show any values in days since all articles in this case only reported milestones as the timepoints for cognitive assessment.

Figure 1.3 *Bar graph illustrating number of follow-up assessments of cognition relative to the date of injury.*

Red bars indicate a timepoint being used as a first follow-up, orange bars indicate a second follow-up, amber bars indicate a third follow-up, and yellow bars indicate a fourth follow-up. This graph comprises data from 74 articles (55%) analyzed for the literature.

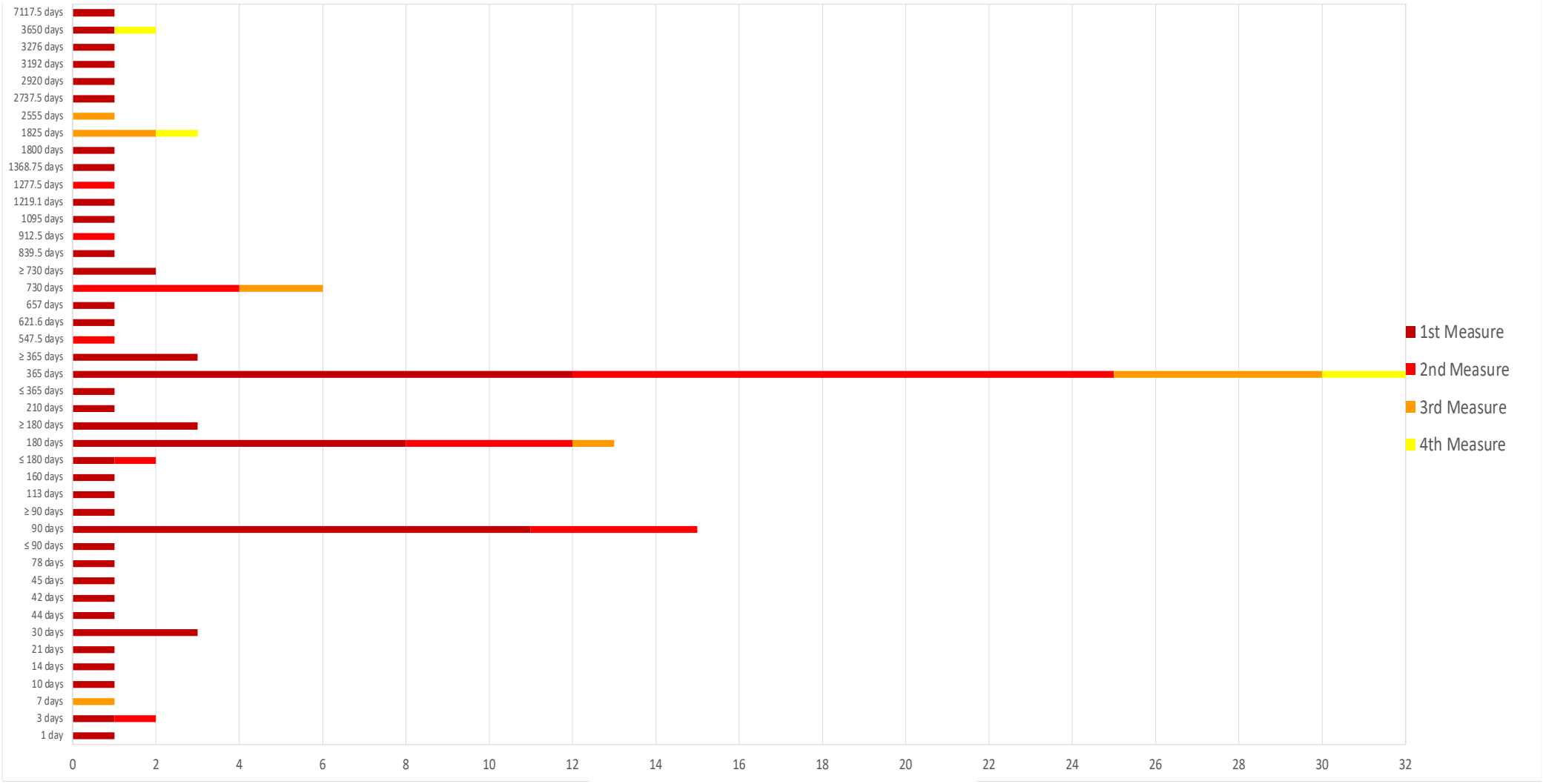


Figure 1.4 *Bar graph illustrating number of follow-up assessments of cognition relative to the date of rehabilitation centre admission*

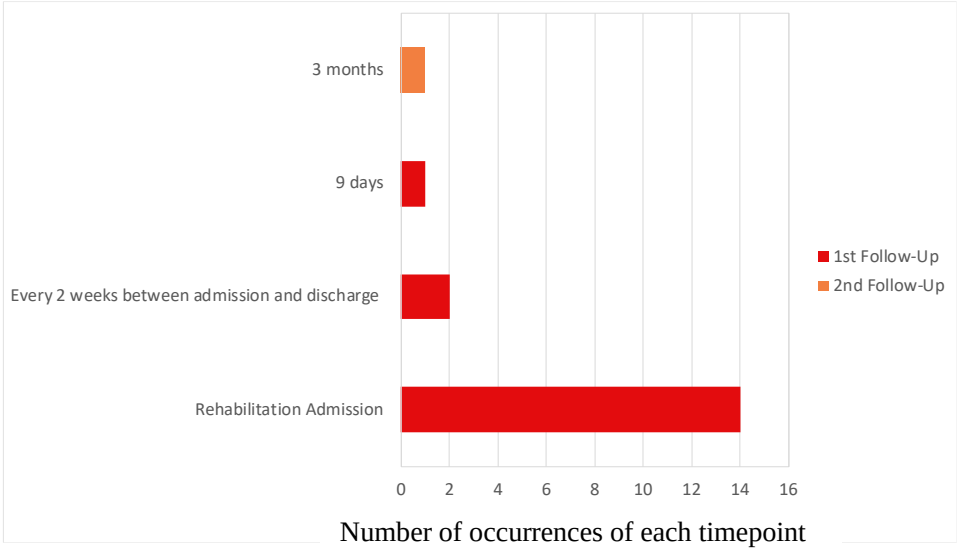
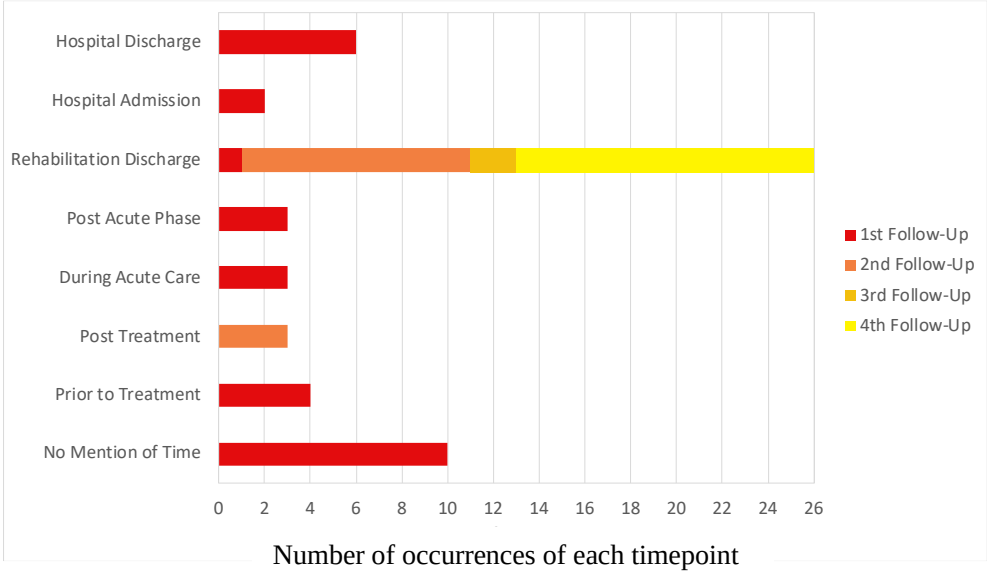


Figure 1.5 *Bar graph illustrating number of follow-up assessments of cognition relative to various timepoints*



Figures 1.3, 1.4 and 1.5 also illustrate whether a time-point was used for a first assessment or a follow-up assessment. The colours in the graph show that 74 articles assessed cognition at least once (red), 30 articles assessed cognition at least twice (orange), 12 articles had at least three timepoints (dark yellow) and 4 articles had 4 timepoints (light yellow). These colours thus illustrate the occurrence of repeated measures in the articles analyzed for this review. The majority of studies only tested cognitive outcomes at one time-point, illustrated by the high volume of red bars and low occurrence of other colours.

Among all studies, the most common time-points for assessing cognition were at 3 months, 6 months, and one year post-injury. 15 studies assessed cognition at 3 months post-injury: 11 studies assessed participants for the first time at 3 months; 4 studies assessed participants for the second time at 3 months. 13 studies assessed participants at 6 months post-injury, where 8 studies used this time-point as a first assessment, 4 studies used it for the second assessment, and 1 used it as a third assessment. 31 articles described cognitive assessments at 1-year post-injury: 11 studies tested participants for the first time at 1 year, 13 for the second, 5 for the third, and 2 for the fourth. No articles assessed participants at more than 4 time-points over the course of the study.

Discussion

This review brings to light three major trends in the literature examining the cognitive recovery of coma patients. First, there is no clear "best" test for measuring cognition in a post-coma population. Several tests were identified for use in assessing cognition in these populations, but no clear trends emerged regarding the most commonly used tests used or the cognitive domains targeted. Second, this review identified disparities across the literature with respect to the timing of cognitive outcome measures. Articles were inconsistent with their reporting of timing of assessments, reference-frames for study timepoints, and number of follow-up sessions. Finally, this review identified differences across the tests used to assess cognition and the methods of administration used for those tests. Specifically, tests of "general cognitive ability", among the most commonly used measures of cognition, fit a different administration model than the other most frequently used assessments. These findings are discussed in detail.

First, this review provides evidence for the lack of consistency across studies with regards to cognitive testing following coma. Specifically, this report failed to identify a "best practice" for assessing cognition. In fact, no two articles analyzed for this review had the same methods or timepoints for assessing cognition in patients recovering from a period of unconsciousness. Among the 134 articles analyzed, 133 unique tests or testing batteries were identified.

Despite the range of tests revealed in our initial analysis, we expected to identify similarities within the tests which allow researchers to compare them across studies. However, when categorized based on the cognitive domain assessed, there were no clear trends identified. Some domains did stand out, including attention, memory, executive function and general cognitive ability. However, few studies assessed all of these domains. No best practice emerged from this review with regards to which cognitive domains are most important to assess in a post-coma population. These findings illustrate a lack of consistency across the literature and identifies a need for a standard set of tests or a testing battery so that results can be compared across studies.

Next, we examined how frequently cognition is assessed. We found a lack of consistency in this area as well. First, the way in which follow-up timepoints are measured differs across studies. Just over half of the studies (74 studies, 55.2%) measured cognitive outcomes as a function of time since injury. However, numerous studies used alternate timeframes, including time since hospital discharge (6 articles, 4.5%), time since rehabilitation admission (17 articles, 9.8%), and time since intervention (7 articles, 5.2%). This makes it difficult to track trajectories of recovery across studies given the disparity in the literature.

Even when looking only at studies measuring cognition at timepoints following "time since injury," there was significant variation across articles. Figures 1.3, 1.4 and 1.5 illustrate how varied the timepoints are across studies. The numerous short bars on the bar graphs visually emphasize how different each study's methods are. In fact, the majority of timepoints (and bars) on the graph represent one single study, demonstrating a lack of consistency in the literature with regards to testing points. Once again, this makes it difficult to interpret single studies since they cannot be easily compared to the literature as a whole.

We also found that most articles only assess participants at one timepoint (57.4%). This suggests that the majority of studies do not assess cognition longitudinally and reveals that the majority of studies examine cognition as a single outcome point and not as a process evolving over time. If an article only assesses cognitive outcomes at one point during the recovery process, even if it is over 1 year after injury, it becomes difficult to predict trajectories of cognitive recovery following coma.

Finally, we examined the tests of cognition identified in our analysis and identified differences in the methods of administration of the tests. Some measures are completed entirely by the participant, while being supervised by an examiner and scored based on performance and a scoring manual. The majority of the most commonly used tests fit this model. However, several tests fit a different model. All of the tests targeting "general cognitive ability" (including the Functional Independence Measure, the Glasgow Outcome Scale, and the Ranchos Los Amigos Levels of Cognitive Functioning) are administered by an examiner who observes the participant's behaviour and provides a score based on their observations. This is an important distinction to make from other methods of administration, as this introduces the possibility of rater bias and other confounding factors.

It is important to define what "general cognitive ability" means in this review. It is evident that these measures assess cognition, as they all have subtests or sections dedicated to measuring the patient's level of cognitive functioning. However, as noted previously, these tests are different than other tests of cognitive function in their method of administration (i.e. formal or informal interviews and observations). Further, these tests do not assess any classic cognitive domains such as attention, executive function, or memory. Instead, they measure what they call "cognitive ability." For the purposes of this review, we included these tests as measures of cognition. They appeared in many articles of patients recovering from a period of unconsciousness and were sometimes used as a diagnostic tool to determine at what point patients' regained their cognitive functions. It is unclear whether these tests should be considered measures of cognition or not considering the fundamental differences they have with respect to the other most commonly used assessments.

Overall, general trends indicate that cognition is not measured as a primary outcome. Most studies either assessed cognition to meet secondary endpoints or as an outcome measure following an intervention. This review revealed the need for research looking directly at cognitive outcomes of individuals recovering from a period of unconsciousness. The recovery process from a coma is multi-dimensional and the research should reflect that: not only should functional outcomes be measured, but cognitive outcomes should also be considered.

There is also a need for longitudinal studies of cognitive recovery. There appears to be a lack of research surrounding the trajectories of recovery from coma. Further, there is a need for outcome measures that are sensitive to the dynamic changes in cognitive functions across multiple domains in coma survivors. Such measures have historically been difficult to gather due to a lack of comprehensive, easy-to-administer neurocognitive tests. The current standard tools require patients to attend a clinic where specially trained personnel administer standard cognitive batteries. This model has several limitations including the length of these testing sessions, patient inconvenience of traveling to clinic assessments, high costs associated with employing trained personnel, and high rates of patient attrition. As a result, traditional methods of comprehensive cognitive assessment cannot be used for a large-scale multi-center natural history study that requires repeated measurement of cognitive function within individual patients during their recovery. Additionally, there is a need for more consistency across the literature when it comes to testing cognition. The lack of consistency across articles makes it difficult to infer trends and predict outcomes in clinical populations.

This structured literature review was conducted following the recommended steps for scoping reviews, with guidance provided by a trained librarian from McGill University. Despite the measures taken to ensure scope, this is not a formal scoping or systematic review. Therefore, the findings in this study are meant to represent a picture of the literature but did not necessarily incorporate all articles. Further, our search was conducted within the parameters of only the PubMed database, whereas most scoping reviews include more databases. Additionally, our definition of "cognition" and what we consider to be "cognitive measures" may have influenced our screening process and influenced what articles were excluded due to their chosen cognitive testing tools. Further, author reports of the tests they used may have influenced our interpretation

of articles. Some tests of cognition exist as stand-alone tests while different versions of those same tests are included in various testing batteries. If articles did not report where their tests were taken from, it was difficult to determine whether two versions of the same test could be categorized together. This review included interventional articles, in which cognition was typically measured as secondary outcome. This could have influenced our results since these studies may have been looking for specific cognitive outcomes, and not studying natural trajectories of recovery. Finally, general publication bias influences what articles we were exposed to, and therefore our findings may represent current research practice and not true clinical practice.

Conclusion

This review unveils no major trends in the literature relating to assessments of cognition in brain-injured patients following a prolonged period of unconsciousness. In fact, findings from this review reveal incredible diversity across articles. First, no single test or testing battery was used significantly more often than others. Among 134 articles assessed for this review, 133 unique tests and testing batteries were identified. This demonstrates how inconsistent researchers are, even within a specific population of ICU survivors, when choosing a method of assessing cognition. Next, timing of assessments varied across articles. Not only was there disagreement in the literature regarding timepoints of assessments and frequency of follow-up assessments, but we also failed to find a consistent reference frame for assessing cognition. Some articles chose to assess cognition at various timepoints following “time of injury” while others chose to measure time relative to rehabilitation admission or some other timepoint in the patient’s recovery process. This makes it incredibly difficult to compare patient outcomes and trace cognitive recovery trajectories given the differing timelines.

Further research is necessary to identify best-practices for assessing cognition in these patients. Perhaps certain tests are more sensitive to cognitive deficits early in recovery, while other testing batteries may be more useful later in the recovery process. Future studies should examine the types of tests used at various timepoints and their benefits. Additionally, this review identified a need for longitudinal assessments of cognition in coma survivors. While there is evidence

supporting the notion that coma survivors suffer from cognitive impairments, there is a need for studies of the natural history of cognitive recovery in these patients.

Overall, there is a need for consistency in assessing cognition so we can form connections across articles and bridge gaps between research and clinical practice. Given the diversity in the literature identified in this review, there is a need for a systematic, comprehensive cognitive assessment battery that accesses numerous cognitive domains that can be used for large-scale, multi-center, repeated assessment studies in order to establish a standard practice to allow for researchers and clinicians alike to trace the cognitive recovery trajectories of patients recovering from coma.

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Chapter 2: A longitudinal validation study of the cognitive testing battery Cambridge Brain Sciences in healthy adults

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Preamble

In this study, we aim to establish learning curves associated with longitudinal repeated assessments of the Cambridge Brain Sciences (CBS) cognitive testing battery. Given the longitudinal nature of the study, we researched different recruitment platforms to ensure highest compliance and retention rates. One challenging aspect of longitudinal cognitive research is the dependency on reliable participants. Typically, longitudinal cognitive studies rely on university undergraduate students who participate in exchange for course credit, experience, or money. In an attempt to mitigate the recruitment of homogenous participant samples, online crowdsourcing platforms were introduced to academic research. Mechanical Turk (MTurk) is an online crowdsourcing platform hosted by Amazon.com Inc. Platforms such as MTurk make it easy for researchers to reach large numbers of participants through a distributed workforce who can take part in study tasks virtually (www.mturk.com). MTurk allows researchers to harness the collective intelligence, skills, and insights from a global workforce to increase data collection rates and accelerate analyses. Given the reputability of the platform and the services offered, we chose MTurk to host our large-scale, longitudinal control study.

Amazon offers support to researchers conducting longitudinal studies on their platform to help integrate research programs seamlessly into MTurk. The study team conducted extensive research and ran various practice trials in order to ensure best practices were employed for this study. The plan was for participants to enroll on MTurk using their email addresses, as is the norm for CBS studies. For repeated measures studies, the CBS platform contains a welcome page requiring participants to enter their names and email addresses. Reminders automatically generated by CBS are sent to participants by email at every trial timepoint (in this case, every day for 7 days, then every week for 3 months, for a total of 19 timepoints), an important feature for long-term participant retention.

On July 11th, 2020, the trial, titled “Put your brain to the test!,” went live on www.mturk.com. In less than one day, the trial was taken offline by Amazon for being in violation of the website’s terms of agreement. The issue was flagged as being a problem with a “completion code.” This completion code is necessary for participants to prove their completion of the entire 45-minute assessment. Upon investigation, it became clear that CBS was not automatically generating this

code as it was supposed to. This was an important issue as this completion code ensures participants get paid.

Impressively, in just 4 hours the study had recruited 254 participants. Despite being taken offline, this provided evidence for the usefulness of the online crowdsourcing platform. The ability to recruit such large numbers in such a short period of time is crucial for a time-sensitive longitudinal study such as this one. A phone call with Amazon's technological support team was set up for July 17, 2020. Simultaneously, the development team at Cambridge Brain Sciences was contacted to quickly fix the technological issues on that end. The goal was to resolve the CBS-related issues as quickly and efficiently as possible, while maintaining contact with MTurk's technical support team for assistance in assuring no other issues would arise.

During the meeting with MTurk tech support, the agent explained that MTurk's terms and conditions prohibit researchers from collecting any personal or identifiable information from the "Workers" (participants). While this was not the reason our study was taken down, this made it clear that it was highly likely our study would be flagged in the future if we continued collecting email addresses from participants. This presented its own set of challenges as CBS uses email addresses to generate automatic email reminders for participants to log in and complete each day's set of tests. Without email reminders, the risk of losing participants in a longitudinal study increases significantly (Patel et al., 2018). If removing the email component of CBS was required, we needed to find an alternative method of sending participants reminders. Mechanical Turk has an application programming interface (API) built into their platform. This API has certain conditions which theoretically allow a study to send automatic reminders to Workers directly through MTurk. We set up a second phone call with Amazon tech support to discuss API shortcuts and other potential solutions for this project. Our phone call took place on August 21, 2020. Despite this, after over a month of work, weekly (and sometimes daily) phone calls, and various obstacles, it became apparent that the API would not be a realistic solution given our goal of completing the study by end of 2020.

Next, we needed to go back to CBS and ensure that they were no longer requesting email addresses from participants. This took several weeks to sort through. We scheduled yet another

phone call with MTurk for September 21, 2020 to ask some final questions before relaunching the study. In this call, we inquired about the different methods of setting up our study. That is, we wanted to know if there was a way to set up our longitudinal study as one study, rather than create 19 identical studies (one for each timepoint). The technical support agent informed us that despite how the platform is advertised, MTurk is not well set up for longitudinal studies: the only way to set up our study was to create 19 individual timepoints, or HITs (i.e. Human Intelligence Tasks). Each HIT would be set to expire after 24 hours, at which point the following HIT would become "active." However, because Workers do not get notified when they "qualify" for a HIT, this still did not resolve the issue of participant notification. The MTurk employee reminded us that the only way to message Workers directly is through the API, which was not a reasonable solution for us.

Ultimately, we decided the most effective solution to get our study active in a time-effective manner would be to send all participants reminders manually using the "Bonus" system. Bonuses allow researchers to communicate with Workers who have taken part in their studies for as little as $0.01. Whereas there is no systematic method allowing for mass-communication outside of MTurk's API, the "Bonus" system allows researcher-participant communication otherwise not available on the Mechanical Turk platform.

Before re-launching the study, we reframed it to match MTurk's guidelines and terms of conditions more closely. We decreased our target recruitment goals to 250 participants, aiming to enroll all participants within the first day. In theory, this should help the study run seamlessly on the platform, since every day we would need to create a new HIT with new eligibility criteria based on the Workers who completed the prior day's assessment. We also planned to send out notifications to participants manually, using the Bonus system, to remind participants of follow-up assessments. Finally, we asked the CBS team to remove the page asking participants for their email addresses to keep in line with MTurk's policies on personal information.
On October 12, 2020, we launched the study on MTurk for the second time. Within one hour, the study was taken down. Although we were no longer requiring participants to enter their email addresses, the field was not completely removed from the CBS sign-in page. For that reason, it was flagged by Mechanical Turk as a violation of the terms and conditions of the site. In the one

hour the study was live on the platform, 86 Workers signed up, many of whom used their real email addresses.

Since some Workers enrolled using their real email addresses, they continued to receive reminders automatically generated by the CBS platform. Without any intervention from the study team, 30 participants from the two MTurk trials completed at least 15 of the 19 timepoints. Those participants who completed the trial were asked to complete a demographic questionnaire and were subsequently compensated.

Following the months of MTurk-related issues, we decided to pursue classic recruitment techniques through university platforms, social media, and word of mouth. The study is described in full below.

Abstract

Traditional comprehensive methods of cognitive assessment cannot be used for large-scale multi-center natural history studies that require repeated measurements of cognitive functions in individual brain-injured patients due to a variety of factors. Because of this, there is a need to validate an easy-to-administer, convenient battery of neuropsychological tests that can be used in clinical populations. The Cambridge Brain Sciences (CBS) neurocognitive battery of tests is a series of online tests that assess three distinct cognitive domains and has been modified to be completed online without formal supervision. This suggests that web-based studies of cognition are not only possible, but provide a novel opportunity for assessing cognition in ways traditional methods cannot. The present study aims to determine learning curves associated with each of the CBS battery's 12 tests when tested in healthy adults across repeated timepoints. Participants were assessed at 19 timepoints in a 3-month repeated measures protocol. Data for each test was plotted and linear mixed effects modelling was completed for both the linear and quadratic models for all 12 tests. 4 of the 12 tests did not show any learning associated with repeated assessment. The other 8 tests showed a quadratic effect and were associated with minimal learning. Overall, the practice effects for all 12 tests were found to be negligible, allowing for the use of the CBS tests in future longitudinal studies.

Introduction

Natural trajectories of recovery of individuals following a period of unconsciousness are poorly characterized in the literature (Duclos et al., 2020). Specifically, cognitive outcomes are inconsistently measured and are not commonly taken as primary outcome measures. This is partially due to a general focus on functional outcomes in intensive care unit (ICU) patients (Claassen et al., 2021), as well as a lack of a strong cognitive outcome measure that can be used in these populations (Honarmand et al., 2020).

Those with significant cognitive or physical disability cannot be evaluated by using traditional neuropsychological testing, and are thus typically excluded from such studies (Claassen et al., 2021). A strong cognitive outcome measure must be sensitive to the dynamic and complex changes in cognitive functions of a recovering ICU patient. Such measures have been historically difficult to gather due to a lack of comprehensive, easy-to-administer neurocognitive tests (Duclos et al., 2020). Standard cognitive measures typically require patients to attend a clinic where specially trained personnel administer the tests. This model has several limitations including the length of these testing sessions, patient inconvenience of traveling to clinics for assessment, high costs associated with employing trained personnel, and high rates of patient attrition. As a result, traditional methods of comprehensive cognitive assessment cannot be used for large-scale multi-center natural history studies that require repeated measurements of cognitive functions within individual patients throughout recovery (Honarmand et al., 2020).

The Cambridge Brain Sciences (CBS) neurocognitive battery of tests is a series of online tests developed by Dr. Adrian Owen over 25 years ago that assess three distinct cognitive domains. The tests have been validated in patients with anatomically-specific brain lesions (e.g., Owen et al., 1990, 1991), in neurodegenerative populations (e.g., Owen et al., 1992, 1993), in pharmacological intervention studies (e.g., Owen et al., 1996), and in neuropathological populations (e.g., Owen et al., 1998; Williams-Gray et al., 2007). The tests have recently been modified to allow participants to complete them online without the supervision of a trained specialist, creating the opportunity for these tests to be used in large-scale, low-cost studies of cognition in the general population (Hampshire et al., 2012; Wild et al., 2018). The CBS tests have been taken more than 10 million times and have created a normative database of over

75,000 participants. This suggests that web-based studies of cognition are not only possible, but provide a novel opportunity for assessing cognition in a way traditional methods cannot. Despite the enormous normative CBS database, no studies have been conducted in the same population longitudinally to determine expected learning curves and practice effects associated with each of the tests. The CBS testing battery cannot be used as a comparator in longitudinal studies of clinical populations until the practice effects associated with these tests have been well examined in a healthy population across multiple timepoints.

We designed this study to mimic the timepoints of a longitudinal outcomes study in brain-injured ICU patients recovering from coma (the NET-ICU study). The NET-ICU study follows patients recovering from a prolonged period of unconsciousness and evaluates their cognitive function daily while in ICU (typically approximately 1 week), and weekly for 3 months following hospital discharge. The current study tests cognitive function in healthy adults daily for 7 days, then weekly for 3 months.

In this study, we predicted that the cognitive testing battery "Cambridge Brain Sciences" would not be significantly associated with any long-term learning effects following a 3-month repeated measures protocol. The CBS tests have been shown to withstand learning and be objective measures of cognitive performance (Hampshire et al., 2012). Therefore, we hypothesized that participants would not show significant increases in their scores despite repeated assessments over a 3-month time period.

Methods

Participants

709 healthy participants were recruited using three recruitment platforms. First, the study was advertised on the crowdsourcing platform Mechanical Turk (MTurk), hosted by Amazon.com. Next, participants were recruited through various social media platforms associated with McGill University (e.g. McGill's Integrated Program in Neuroscience Facebook page). Finally, participants were identified through Western University's OurBrainsCAN network. Overall, 447 participants were enrolled on MTurk, 220 participants were enrolled through McGill's recruitment platforms, and 42 participants were enrolled on Western's OurBrainScan portal.

However, due to high attrition rates, only 167 participants completed the study. These high attrition rates are mostly attributed to technical difficulties which occurred on the Mechanical Turk platform. Due to these substantial technical difficulties, we sought alternative recruitment methods through McGill and Western, and the retention of 30 participants from MTurk was more than was anticipated following the aforementioned issues. Retention techniques including frequent reminders, reliable communication with study team members, and user-friendly data collection methods were employed to mitigate attrition risks (Hanna et al., 2014).

Inclusion criteria for this study required participants to be 1) 18 years of age or older; 2) speak English or French; and 3) have no pre-existing cognitive or neurological disorders. Participants were asked to complete a demographic questionnaire prior to starting the assessments. A member of the research team would then screen all questionnaires to ensure patient eligibility. Following this, participants were prompted to complete the Cambridge Brain Sciences testing battery at 19 timepoints over the course of 3 months. Timepoints for this study were once daily for 7 days, then once weekly for 3 months. In total, participants were asked to complete 19 timepoints. Only data from participants who completed the demographic questionnaire and at least 15 of the 19 timepoints were included for analysis. As of July 2021, only 89 participants met these requirements.

All participants provided informed consent prior to participation. The study was approved under 2 different ethics boards: first, by Western University's Health Sciences Research Ethics Board (#107976), and second by McGill University's Research Ethics Board (#A03-B20-21A). Recruitment was accomplished through postings on Amazon's Mechanical Turk, institutional social media advertisements (Facebook and Twitter) and word of mouth. Volunteers received $50 CAD as compensation for their participation in the study.

Demographic information collection

Once consent was provided, participants were asked to complete an online demographic questionnaire using the survey platform Survey Monkey (www.surveymonkey.com). A copy of the questionnaire can be found in Appendix 4. Survey responses were screened by a researcher to confirm participant eligibility.

Cognitive data collection

Data were collected using the Cambridge Brain Sciences (www.cambridgebrainsciences.com) online platform. Accuracy of online data has been found to be high (Ruano et al., 2016; Morrison et al., 2015; Di Rosa et al., 2015; Wesnes et al., 2017) and this particular platform has been used in multiple previous large-scale studies (Nichols et al., 2020; Owen et al., 2010; Hampshire et al., 2012). Upon reaching the website, participants were asked to enroll using a valid email address and a secure password. Due to the longitudinal nature of the study, participants were sent reminders to their email addresses to ensure minimal attrition rates. They were then asked to complete the 12 cognitive tests measuring a broad range of cognitive abilities including inhibition, selective attention, reasoning, verbal short-term memory, spatial working memory, planning and cognitive flexibility.

Cognitive tests

Digit Span is based on the verbal working memory component of the revised Wechsler Adult Intelligence Scale (WAIS-R; Wechsler, 1981). A sequence of digits is displayed one at a time. Participants must then repeat the sequence of digits by selecting them on the on-screen keyboard. The resulting score is the length of the longest digit sequence successfully remembered.

Double Trouble is a novel and challenging variant of the Stroop test (Stroop, 1935), a test of inhibition. A target word (either "RED" or "BLUE") is displayed on the screen in either the colour red or the colour blue. The participant must select the probe word that correctly describes the colour that the target word is drawn in. Participants have 90 seconds to complete as many trials as possible. A correct response increases the total score by 1 point, and an incorrect response decreases the score by 1 point.

Feature Match is based on classic feature-search tasks used to measure attentional processing (Treisman & Gelade, 1980). On each trial, two groups of items (n items in each group) are displayed beside each other. The groups are either identical in their contents and item positions or differ by just one item. Participants have 90 seconds to complete as many trials as possible, indicating whether the groups match. A correct response increases the final score by n, and the subsequent trial has groups of n + 1 items. If the response is incorrect, the total score decreases by n, and the next trial has groups of n – 1 items.

Grammatical Reasoning is based on Baddeley's 3-min grammatical-reasoning test (Baddeley, 1968). On each trial, a written statement regarding two shapes is displayed on the screen, and the participant must indicate whether the statement is true or false. The participant has 90 seconds to complete as many trials as possible. A correct response increases the total score by 1 point, and an incorrect response decreases the score by 1 point.

Monkey Ladder is based on a task from the nonhuman-primate literature (Inoue & Matsuzawa, 2007). Numbered boxes are displayed simultaneously at random locations within a grid. The numbers then disappear and participants must click the boxes in ascending numerical sequence. The test ends after three errors, and the resulting score is the length of the longest sequence successfully remembered.

Odd One Out is based on a subset of reasoning problems from the Cattell Culture Fair Intelligence Test (Cattell, 1949). Nine groups of coloured shapes are displayed in a grid. The features (colour, shape, number of items) define each group and are related to each other according to a set of rules. Participants must deduce the rules that relate these features and select the group with contents that do not correspond to those rules. They have 180 seconds to solve as many problems as possible, and the puzzles become progressively more difficult. A correct response increases the final score by 1 point, whereas an incorrect response decreases the score by 1 point.

Paired Associates is based on a test commonly used to assess memory impairments in aging clinical populations (Gould et al., 2005). Sets of boxes are displayed at random locations on a grid. The boxes open one after another to reveal an icon, after which they close. The icons are then displayed sequentially, and the participant must select the appropriate box. If the participant remembers all the icon–location pairs correctly, then the next trial will have one box more. If an error is made, the next trial will have one box less. The test ends after three errors. The participant's score is the maximum number of pairs successfully remembered.

Polygons is based on the Interlocking Pentagons task, a test of visuomotor ability often used for assessing age-related disorders (Folstein et al.,1975). Two overlapping polygons outlines are displayed on the left side of screen, and participants must indicate whether the shape to the right is identical to one of the two overlapping ones. A correct response increases the total score by the difficulty level, and the subsequent trial will be more difficult. Participants have 90 seconds to complete as many trials as possible.

Rotations is a task that measures the ability to spatially manipulate objects in mind (Silverman et al., 2000). On each trial, two groups of coloured squares (each with n squares) are displayed beside each other. The groups either are identical (when unrotated) or different, and participants must indicate whether the groups match. They have 90 seconds to complete as many trials as possible. A correct response increases the final score by n, and the subsequent trial has groups of n + 1 squares. If the response is incorrect, the total score decreases by n, and the next trial has groups of n – 1 squares.

Spatial Planning is based on the Tower of London task (Shallice, 1982), which is widely used to measure executive function. Numbered beads are positioned on a tree and must be rearranged into ascending numerical order. Participants have 3 minutes to solve as many puzzles as possible. A successfully completed puzzle increases the final score by (2 × minimum number of moves required – the number of moves made).

Spatial Span is based on the Corsi block-tapping task—a tool for measuring spatial short-term memory capacity. Sixteen purple boxes are displayed in a grid. A sequence of randomly selected boxes turn green one at a time. Participants must then repeat the sequence by clicking boxes in the same order. The test ends after three errors. The score is the length of the longest sequence successfully remembered.

Token Search is based on a test that is widely used to measure strategy during search behavior (Collins et al., 1998). A set of boxes, one of which contains a hidden green token, is displayed on a grid. Participants must find the token by clicking the boxes one at a time. Once found, the token is hidden within another box. The token will not appear within the same box twice, so the participant must search the boxes until the token has been found once within each box. An error is committed if the participant checks a box that has already been clicked while trying to find the token or if the participant checks a box that previously contained the token. The test ends after three errors. The resulting score is the maximum level completed.

Analysis

Data was cleaned and analyzed using the R statistical toolbox (Version 4.0.5, R Core Team, 2021). First, duplicate runs (which occur due to a browser refreshing or a participant going back on the webpage) were removed. Test scores were then filtered for outliers using the *replaceOuts* function in R. Due to the online nature of the study, we chose to exclude outliers as we could not

rule out cheating or other forms of untrustworthy data. Participants were removed if they had completed fewer than 15 of the 19 timepoints. We decided to include participants with some missing timepoints as we expect heterogeneity in the testing timepoints of our clinical populations and want this control study to be representative of that. Finally, timepoints were labelled based on how many days had passed since the first assessment to account for differences in time passed between timepoints.

Data was plotted using the *ggplot2* package in R for each of the tests by date of assessment to visualize learning curves and visually determine best fit models. Raw scores were used (as opposed to z-scored values) so as not to water down the effect of learning on scores. All tests were modelled using both linear and quadratic methods.

To test whether the effect of multiple repeated timepoints affected scores on each of the CBS tests, a linear mixed effects model was constructed that modeled the twelves test scores as repeated measures for each subject. Linear mixed effects models do not depend on limited assumptions about the variance-covariance and can accommodate missing data (Magezi, 2015). A major difficulty when conducting longitudinal studies and interpreting growth in outcomes is missing data points (Walker et al., 2019). In fact, missing data are almost unavoidable in longitudinal research because participants start late, drop out, or miss intervening test visits (Moeller et al., 2007). Classic statistical tests such as repeated-measures analysis of variance tests (ANOVA) exclude all individuals with any amount of missing data from the analysis. The linear mixed effects model has several advantages, specifically when considering longitudinal datasets (Krueger & Tian, 2004). Mixed effects modelling allows us to examine the condition of interest while also taking into account variability within and across participants and other effects simultaneously (Magezi, 2015).

The linear mixed effects model was generated using the *lmer* function in the R package *lme4*. The second-order polynomial expansion of the "timepoint" variable was included in the linear regression models to test for a quadratic effect. The linear mixed effects model was built with age and gender included as covariates of no interest. Test statistics and degrees of freedom were

calculated, along with *p*-values. A Satterthwaite adjustment was used to compute the degrees of freedom.

Results

Of the 709 participants who enrolled for the study, only 167 individuals completed the study and were included for analysis. Descriptive statistics for the participants who completed the study (i.e. finished at least 15 of the 19 timepoints) are shown in Table 2.1. The majority of participants were female (70.66%) and aged 18-29 years old (48.5%). Other demographic information collected includes highest level of education completed, country of origin, number of languages spoken, and handedness. For the purposes of this study, only age and gender were included as covariates of no interest in the linear mixed effects modelling.

Table 2.1 *Descriptive statistics for the group of participants included for analysis*

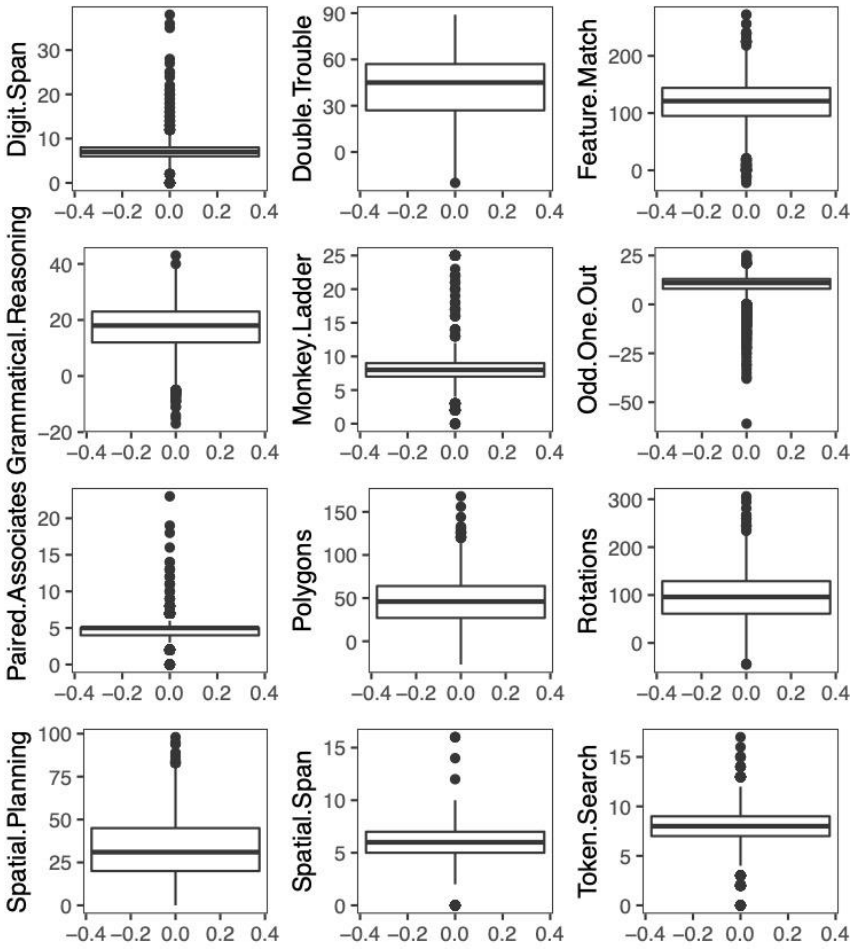
Variable	Participants (n = 167)
Gender	
Female	118 (70.66%)
Male	48 (28.74%)
Other	1 (0.6%)
Age (years)	
18-29	81 (48.5%)
30-39	27 (16.17%)
40-49	18 (10.78%)
50-59	17 (10.18%)
60 or older	24 (14.37%)
Highest education completed	
High school or equivalent	12 (7.19%)
Associate degree	8 (4.79%)
Some college but no degree	26 (15.57%)

Bachelor's degree	73 (43.71%)
Graduate degree	48 (28.74%)
Country of origin	
Canada	87 (52.10%)
United States of America	36 (21.56%)
India	16 (9.58%)
Brazil	4 (2.40%)
United Kingdom	3 (1.79%)
Other	21 (12.57%)
Number of languages spoken	
One	80 (47.90%)
Two	61 (36.53%)
More than two	26 (15.57%)
Handedness	
Right	154 (92.22%)
Left	13 (7.78%)

Distributions of scores for each individual test, including outliers, are illustrated in Figure 2.1. Given the presence of significant outliers, such as can be seen in Digit Span, we opted to remove outliers from our analysis. Specifically, in tests such as Digit Span, where we expect participants to score on average between 5 and 9 based on the evidence that humans can remember 7 +/- 2 items (Miller, 1956), scores over 30 are unrealistic and likely impossible. As this was an online study, cheating could not be ruled out and thus outliers were removed.

Figure 2.1 *Distribution of scores for participants on each of the 12 tests*

Medians are indicated by thick black horizontal lines. The first and third quartiles are marked by the lower and upper edges of the boxes, respectively. Lower and upper whiskers extend to the smallest and largest value, respectively, within 1.5 times the interquartile range. Outlying values beyond these ranges are plotted individually.



Regression parameters were calculated using linear mixed effects modelling for the effect of repeated testing timepoints on scores. Specifically, *t* tests were calculated using Satterthwaite approximations to degrees of freedom for both the effect of timepoint and the second-order polynomial of timepoint (shown in Table 2.2 as timepoint^2). Degrees of freedom differ across tests due to several factors including outlier removal and the inclusion of participants who had incomplete testing days.

All tests except Monkey Ladder, Paired Associates, Spatial Span, and Token Search, were significant with *p*-values <0.001. This means that there were significant differences in scores across time, thus illustrating the possibility of a practice effect. All tests showed a quadratic effect and were fitted to a quadratic model except Monkey Ladder ($\hat{\beta}$ = -1.256e^{-05}, p = 0.651), Paired Associates ($\hat{\beta}$ = -3.238e^{-05}, p = 0.149) , Spatial Span ($\hat{\beta}$ = -4.639e^{-05}, p = 0.05) , and Token Search ($\hat{\beta}$ = -5.655e^{-05}, p = 0.100), whose quadratic terms were non-significant. When looking at the linear model for those tests, Monkey Ladder ($\hat{\beta}$ = 0.00211, p = 0.346), Paired Associates ($\hat{\beta}$ = 5.915e^{-05}, p = 0.743), Spatial Span ($\hat{\beta}$ = 0.00448, p = 0.00188), and Token Search ($\hat{\beta}$ = 0.00289, p = 0.408) all had large *p*-values as well.

Positive and negative coefficient estimate ($\hat{\beta}$) values indicate the direction of the quadratic curve, where negative values refer to an inverted U-shape. All tests fitted to the quadratic model had negative $\hat{\beta}$ values, showing improvement of scores after day 1. Estimate values for all tests are considerably low (Table 2.2).

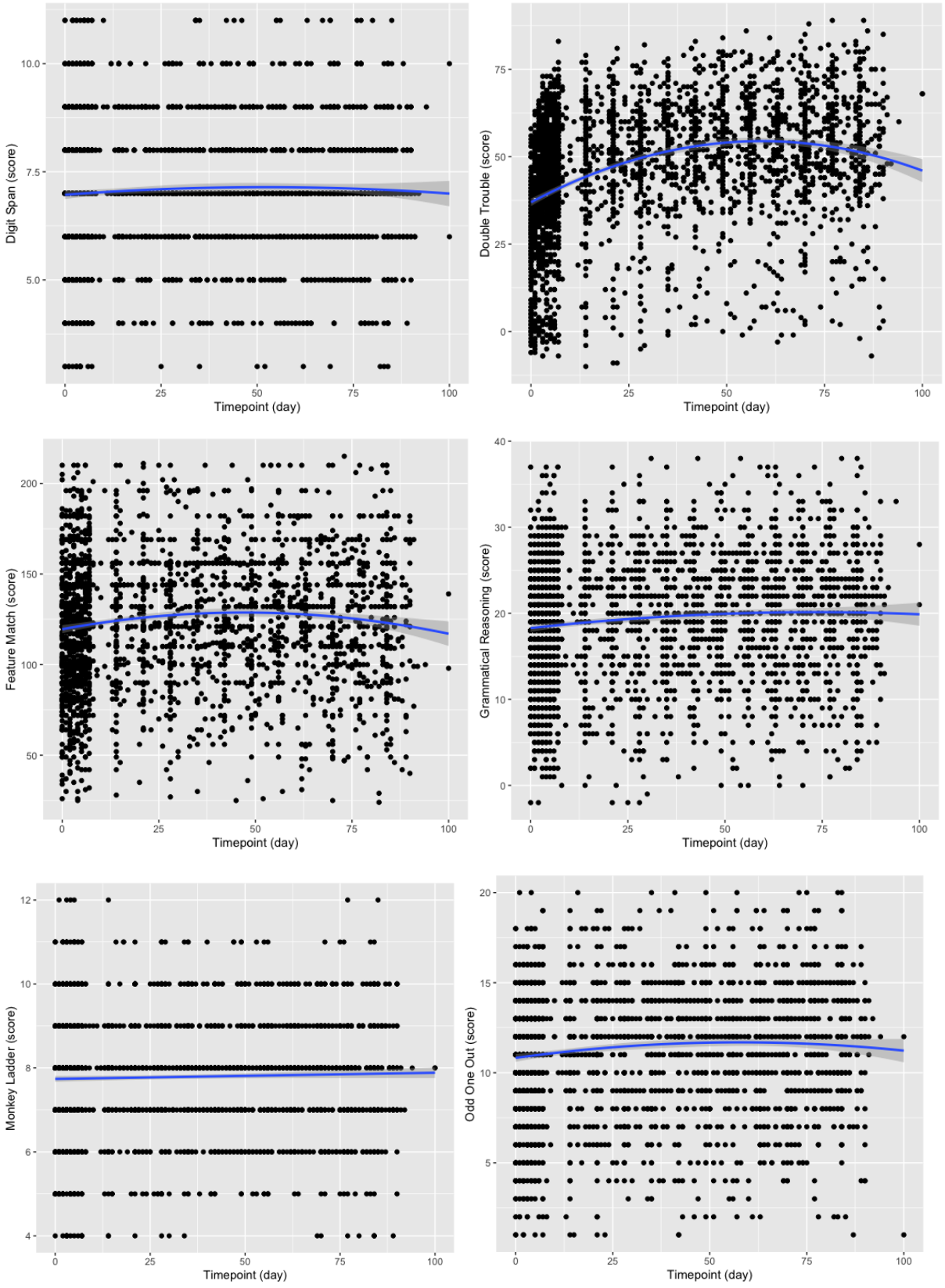
Table 2.2 *Regression parameters for linear mixed effects model of test scores by day of testing*

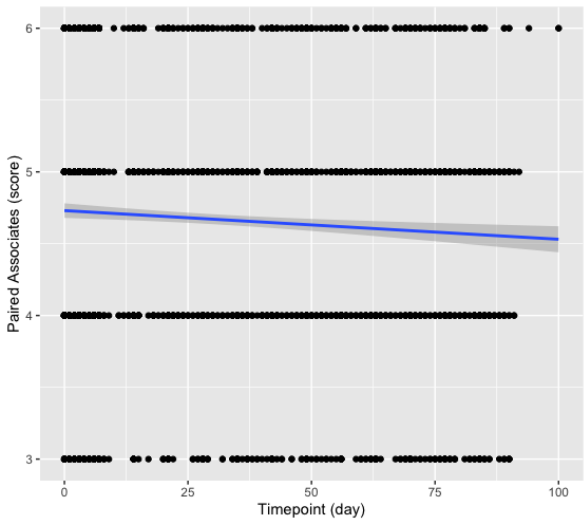
Effect	Test	Estimate	Standard Error	df	*t*-value	Pr (>|t|)
Timepoint	Digit Span	8.262e^{-03}	2.391e^{-03}	2719	3.456	<0.001***
	Double Trouble	0.578	0.0211	2772	27.359	<0.001***
	Feature Match	0.372	0.0642	2728	5.795	<0.001***
	Grammatical Reasoning	0.0553	9.054e^{-03}	2755	6.111	<0.001***
	Monkey Ladder	2.106e^{-03}	2.238e^{-03}	2728	0.941	0.346
	Odd One Out	0.0286	7.019e^{-03}	2722	4.079	<0.001***
	Paired Associates	5.915e^{-05}	1.807e^{-03}	2533	0.327	0.743
	Polygons	0.273	0.0457	2754	5.982	<0.001***
	Rotations	0.662	0.0753	2758	8.797	<0.001***

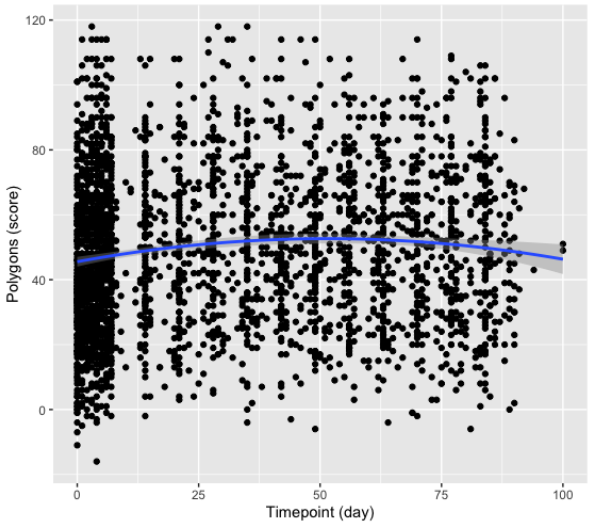
	Spatial Planning	0.472	0.0239	2761	19.72	<0.001***
	Spatial Span	$4.475e^{-03}$	$1.905e^{-03}$	2761	2.349	0.0188*
	Token Search	$2.289e^{-03}$	$2.768e^{-03}$	2758	0.827	0.408
$Timepoint^2$	Digit Span	$-8.734e^{-05}$	$2.968e^{-05}$	2719	-2.943	0.00328**
	Double Trouble	$-4.825e^{-03}$	$2.628e^{-04}$	2772	-18.359	<0.001***
	Feature Match	$-3.897e^{-03}$	$8.004e^{-04}$	2728	-4.869	<0.001***
	Grammatical Reasoning	$-3.935e^{-04}$	$1.127e^{-04}$	2755	-3.491	<0.001***
	Monkey Ladder	$-1.256e^{-05}$	$2.778e^{-05}$	2728	-0.452	0.651
	Odd One Out	$-2.379e^{-04}$	$8.272e^{-05}$	2722	-2.726	0.00645**
	Paired Associates	$-3.238e^{-05}$	$2.248e^{-05}$	2533	-1.440	0.149
	Polygons	$-2.679e^{-03}$	$5.690e^{-04}$	2754	-4.709	<0.001***
	Rotations	$-4.876e^{-03}$	$9.373e^{-04}$	2758	-5.202	<0.001***
	Spatial Planning	$-3.518e^{-03}$	$2.984e^{-04}$	2761	-11.788	<0.001***
	Spatial Span	$-4.639e^{-05}$	$2.371e^{-05}$	2761	-1.957	0.050
	Token Search	$-5.655e^{-05}$	$3.445e^{-05}$	2758	-1.642	0.100

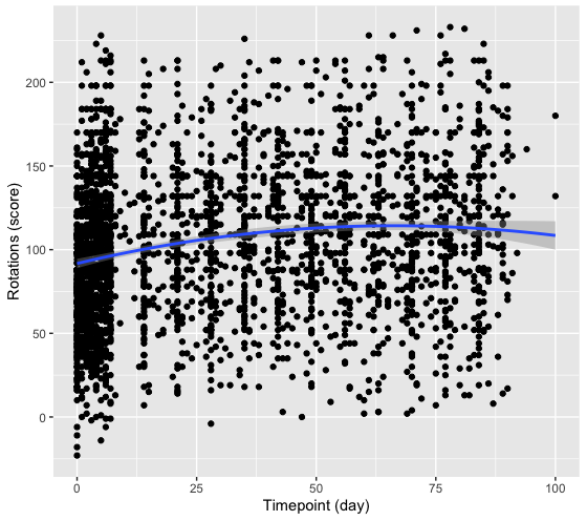
Scores for all participants who completed at least 15 assessments were plotted according to the day the tests were completed. Plots for each of the tests can be found in Figure 2.2. Slopes were plotted to fit either a linear or quadratic model, depending on the best fit of the data (Monkey Ladder, Paired Associates, Spatial Span, and Token Search were fitted to the linear model).

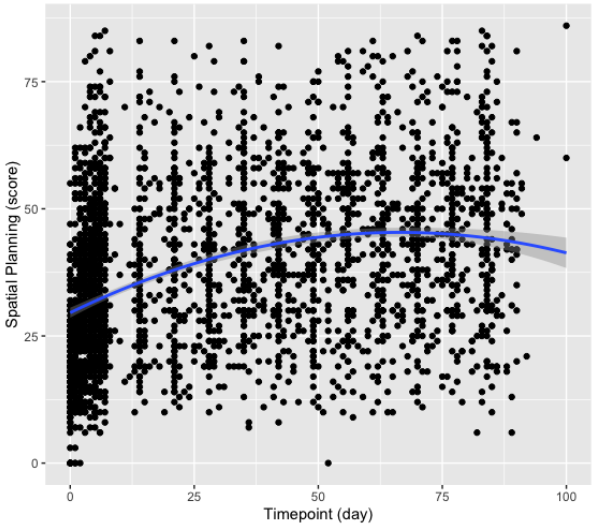
Figure 2.2 *Learning curves associated with each of the 12 CBS tests*

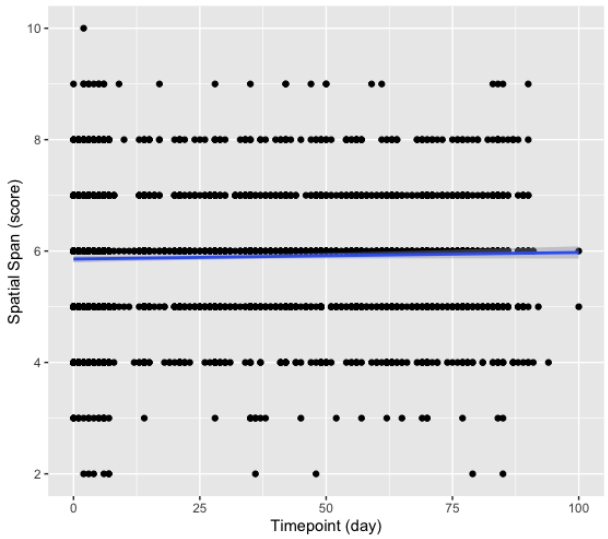


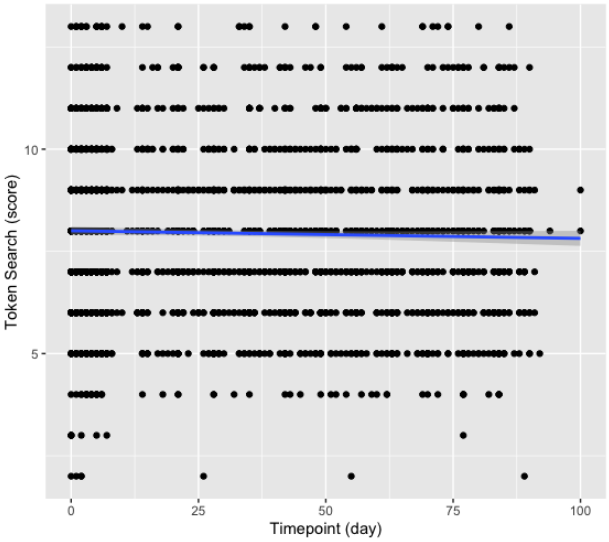

Paired Associates (score)
6
5
4
3
0
25
50
75
100
Timepoint (day)


Polygons (score)
120
80
40
0
0
25
50
75
100
Timepoint (day)


Rotations (score)
200
150
100
50
0
0
25
50
75
100
Timepoint (day)


Spatial Planning (score)
75
50
25
0
0
25
50
75
100
Timepoint (day)


Spatial Span (score)
10
8
6
4
2
0
25
50
75
100
Timepoint (day)


Token Search (score)
10
5
0
25
50
75
100
Timepoint (day)

Discussion

In this study, we provide evidence for negligible learning effects of the Cambridge Brain Sciences battery of neurocognitive tests in healthy adults when assessed at multiple timepoints over 3 months. We conducted cognitive testing in a healthy adult population at 19 timepoints over a 3-month period and traced learning curves for each of 12 tests in the CBS battery. When fitted to a quadratic model, coefficient estimates for all tests were negative (Table 2.2). A negative term means the curve fits an inverted U-shape, whereas a positive term means the curve will take a regular U-shape. In this case, it is intuitive that all $\hat{\beta}$ values are negative since we expect participants to improve from baseline (or stay the same) rather than get worse over time. 8 of 12 tests fit a quadratic model which implies that more improvement occurs in the early testing sessions when compared to the long-term learning effects. This makes sense for these tests, where participants may take the first few days to grasp an understanding of the tasks and develop techniques to succeed. However, in the long term, it still appears that the practice effects are minimal in all 12 tasks.

8 of the 12 tests had significant *p*-values when fitted to a quadratic model. Despite this strong significance, coefficient estimates were low for all tests (< 0.003) suggesting that even though scores may increase over time, these increases are on the order of < 0.003 points per testing day. These values indicate that the increase in scores observed over time is incremental and therefore learning over a longitudinal period is negligible.

4 of the 12 tests (Monkey Ladder, Paired Associates, Spatial Span, and Token Search) were shown to have a linear relationship with scores over time. This is consistent with the literature given that these are all tests of short-term or working memory. Scores for these tests range from 2 to 15, which is expected since humans are known to have a working memory capacity of, on average, 7 +/- 2 items (Miller, 1956).

Taken together, these results will allow future researchers to use the Cambridge Brain Sciences at repeated timepoints for longitudinal studies at least up to 3 months in length knowing that negligible practice effects are expected for all 12 tests. Not only is this useful for research in

healthy adults, but this also means that these tests can be used in longitudinal studies of clinical populations to track cognitive recovery.

This study provides strong evidence for negligible learning effects in a longitudinal cognitive study in healthy controls. However, there are several limitations to the presented work that should be noted. Firstly, attrition rates in this study are notably high. This is due in part to the longitudinal, online nature of the study. Furthermore, difficulties with the proposed recruitment platform Mechanical Turk (described in the chapter preamble) meant that a high number of individuals enrolled but only completed one timepoint. Following this, our study sample is not a perfect representation of the population. Our study team was intentional in participant recruitment, aiming to enroll a diverse and representative sample, but recruitment through university-affiliated platforms meant that we recruited a high number of young adults. Finally, a potential confound with our study population is the self-selection bias that is present when participants choose to enroll in an online study. While our research team tried to mitigate this bias by recruiting participants from various platforms in numerous settings, we cannot be sure the results will not be affected by this bias.

Conclusion

Accessible, online, reliable neurocognitive testing batteries are difficult to find as most are associated with some learning when tested at repeated timepoints. The Cambridge Brain Sciences testing battery has been validated for online use in healthy adults in many previous studies, but learning effects associated with the battery have never been testing longitudinally. The present study provides strong data to show minimal learning associated with all 12 tests when tested at multiple timepoints over a 3-month period.

The observed practice effects were minimal. The average increase in score was negligible and therefore learning effects are minimal at best. These established learning curves, minimal as they are, will allow future researchers to plot clinical data against them in order to track cognitive trajectories of patients.

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Chapter 3: Trajectories of cognitive recovery in individuals recovering from a prolonged period of unconsciousness: A feasibility study

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Abstract

Trajectories of cognitive recovery in individuals recovering from a severe brain injury are poorly characterized and need to be established. However, there are currently no strong cognitive testing battery that have been validated longitudinally that can be used to assess a brain-injured population recovering from coma in intensive care units (ICUs). Recently, the Cambridge Brain Sciences (CBS) testing battery has been validated in healthy adults longitudinally and was shown to have negligible practice effects. The current study is a feasibility study aimed at determining the possibility of measuring trajectories of cognitive recovery in a pilot sample of brain-injured ICU patients recovering from coma. Recruitment capability, evaluation of data collection procedures, ability of research team to manage protocol, and preliminary evaluation of participant responses to procedures were all recorded to determine the study's feasibility. Overall, recruitment numbers were high (with 100% of eligible participants enrolled), data collection procedures were refined and deemed feasible, the study team retained all but 2 participants (who were lost-to-follow-up due to the Covid-19 pandemic), and preliminary evidence showed that the CBS testing battery is sensitive to cognitive changes in ICU patients throughout the recovery process.

Introduction

Individuals recovering from a severe brain injury have unique and heterogenous trajectories of recovery, both functionally and cognitively. Primary outcomes of intensive care unit (ICU) survivors typically focus on functional outcomes and mortality (Udekwu et al., 2004; Jennett & Bond, 1975). However, 40-100% of patients requiring care in ICUs subsequently exhibit cognitive impairment (Schlichter et al., 2020; Hopkins et al., 2005; Wilcox et al., 2013; Moulaert et al., 2009; Iwashyna et al., 2010) regardless of age at injury (Pandharipande et al., 2013). Brain-injured ICU survivors are especially affected by post-injury cognitive impairment. Despite this, most studies focused on cognitive outcome end points after critical illness have excluded patients with brain injuries (Turnbull et al., 2016). Critical care research is needed to trace these trajectories and examine the natural course of recovery in patients who have recovered from a prolonged period of unconsciousness.

The current feasibility study is based on a larger clinical trial focused on establishing neurophysiological evidence for the treatment of brain-injured patients in intensive care units (referred to as the NET-ICU study). Briefly, the NET-ICU study aims to bridge the gap between high-density electroencephalography (EEG) markers and long-term cognitive outcomes of brain-injured ICU patients. Specifically, this study plans to design and implement a point-of-care system that predicts outcomes of continuously-sedated, brain-injured patients in the ICU by 1) developing a set of EEG techniques that can be recorded at the ICU bedside that robustly predict the recovery of consciousness and cognition, and 2) developing patient-accessible methods of measuring long-term cognitive outcomes in ICU survivors.

This study will address the second objective of the NET-ICU study and determine the feasibility of an easy-to-use series of cognitive tests to trace the recovery of cognition in brain-injury ICU survivors. Over the last 25 years, a suite of computerized cognitive tests, Cambridge Brain Sciences (CBS), has been developed to assess aspects of memory, attention, planning and reasoning in health adults and patient populations (Owen et al., 1990, 1991, 1992, 1996, 2010; Bor et al., 2003; Hampshire et al., 2012). The tests have recently been modified to allow participants to complete them online without the supervision of a trained specialist, creating the opportunity for these tests to be used in large-scale, low-cost studies of cognition in the general population (Hampshire et al., 2012; Wild et al., 2018). The CBS tests have been taken more than 10 million times and have created a normative database of over 75,000 participants. Recently, these tests have been shown to be associated with negligible practice effects, making them ideal for use in longitudinal studies of cognitive recovery (Chapter 2).

A pilot study in a small cohort of ICU patients demonstrated the feasibility of administering these tests in an acute setting (Honarmand et al., 2019). The study found that not only can patients self-administer these assessments, addressing one of the key issues of current standard cognitive measures, the tests were also able to identify key cognitive impairments in several domains. However, Honarmand et al.'s feasibility study excluded patients with brain injuries, omitting a key critical care demographic. Therefore, despite existing evidence that the CBS testing battery is feasible in an ICU population, there is a need to establish the feasibility of using these tests in brain-injured patients recovering from coma.

Methods

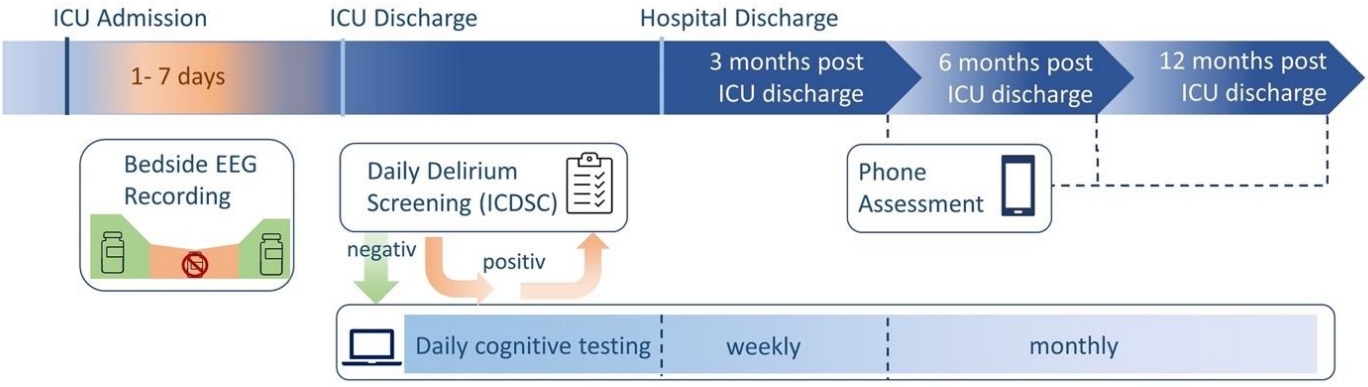
Participants

Participants for this study were recruited through the NET-ICU project. The NET-ICU study was reviewed and approved by the Research Ethics Board of the McGill University Health Centre (Project ID 2020-5972).

Inclusion criteria for this study were: 1) having suffered a brain injury (e.g. traumatic brain injury, anoxic brain injury, stroke, subarachnoid haemorrhage); 2) be at least 18 years of age or older; 3) having been hospitalized in the ICU; and 4) having been continuously sedated in the first 7 days in ICU. Participants were excluded if they did not speak English or French; have a history of pre-existing dementia or cognitive impairment; or are on contact precautions which require extraordinary disinfection protocols.

Once patients were identified and/or recruited in the ICU and reached the waking stage, they were screened daily for delirium by the clinical team (Figure 3.1). When a patient no longer exhibited signs of delirium, and showed clear understanding of their current situation, they were asked to provide written informed consent to participate, continue participating, or withdraw from the study.

Figure 3.1 *General timeline of overall NET-ICU study measures.*



Feasibility studies have 4 main goals (Orsmond & Cohn, 2015). In this study, we will aim to:

1) Evaluate recruitment capability and resulting sample characteristics;
2) Evaluate and refine data collection procedures and outcome measures, and evaluate the acceptability and suitability of the study procedures;
3) Evaluate the required resources and the ability of the study team to manage and implement the study procedures; and
4) Conduct a preliminary evaluation of participant responses to the study procedures

Cognitive data collection

Participants were asked to complete an abridged version of the Cambridge Brain Sciences (CBS) testing battery on a tablet or laptop. The battery of six tests takes approximately 20 minutes to complete and are designed to assess verbal and deductive reasoning, episodic memory, visuospatial working memory, and short-term memory.

In brief, the six tests used in the abridged version of the CBS battery are: *Odd One Out*, a test of reasoning problems based on the Cattell Culture Fair Intelligence Test (Cattell, 1949) lasting 90 seconds. *Grammatical Reasoning* is based on Baddeley's 3-minute grammatical reasoning test (Baddeley, 1968) lasting 90 seconds. *Digit Span* is a task based on the verbal working memory component of the WAIS-R intelligence test (Weschler, 1981). The test ends after the participant makes 3 mistakes. *Rotations* is a task that measures the ability to spatially manipulate objects in mind (Silverman et al., 2000) and participants have 90 seconds to complete as many trials as possible. *Paired Associates* is based on a test commonly used to assess memory impairments in aging clinical populations (Gould et al., 2005). Finally, *Monkey Ladder* is based on spatial tasks from non-human primate literature (Inoue et al., 2007). The tests are described in full in Chapter 2 of this thesis.

CBS testing occurred every day in the acute phase (while patients were in ICU), typically for approximately 1 week. Following hospital discharge, patients completed the tests on a weekly basis for 3 months. After this period, patients then completed tests once a month for up to 12 months post-injury.

Analysis

Data was first cleaned manually according to chart notes taken during data collection (removal of false scores, incomplete testing days, etc.). Next, patients were grouped according to the number of testing sessions that they completed. For the purposes of this paper, only participants who completed more than 1 week of testing were included for analysis. Analyses were conducted on individual patients, as each patient was expected to have a unique trajectory of recovery based on multiple factors (including age at injury, type of injury, length of coma, gender, etc.). Therefore, while participants were grouped together for illustrative purposes, each patient's data should be interpreted individually.

Data was cleaned and trajectories of recovery were plotted using the R statistical toolbox. First, individual test scores were plotted according to the days the scores were earned. Daily scores were connected using lines to clearly visualize participant score changes over time. Separate graphs were generated for each test. Trendlines from a study of healthy controls were plotted against the NET-ICU participant scores to visualize differences in slopes.

Results

Participant screening and recruitment was delayed for 9 months due to the Covid-19 pandemic, slowing potential enrollment rates. Despite this, 23 participants have been enrolled in the acute stage of the NET-ICU study to date. At the time of this dissertation, 12 individuals recovering from a brain-injury in ICU were identified and all 12 were enrolled in the cognitive outcomes portion of the NET-ICU study. Participants were followed by a member of the research team while in hospital. Upon discharge, the research team continued to complete cognitive testing with participants in person when possible. Retention techniques included in-person visits to patient homes, visits to rehabilitation centres, frequent phone-call follow-ups, and regular email reminders. Despite this, 2 participants voluntarily withdrew and 2 were lost-to-follow-up. One participant passed away after starting CBS testing. At the time of this dissertation, 7 participants were actively completing longitudinal cognitive testing. Descriptions of each of the participants and their involvement in the study can be found in Table 3.1.

Table 3.1 *Participant descriptions and demographic information for patients who completed cognitive testing in NET-ICU study*

Participant ID	Data points	Status	Description & notes
NET-ICU-005	5	Withdrawn	56yo female, suffered subarachnoid hemorrhage (SAH). CBS started in ICU 3 days after recovery of consciousness. Participant withdrew upon discharge from hospital, stating that she was too tired to complete the tests from home. Given the state of the ongoing pandemic, research team was unable to go to the patient's home to facilitate data collection.
NET-ICU-006	2	Withdrawn	54yo male, suffered cerebrovascualar accident (CVA) and stroke. Participant was lost-to-follow-up upon discharge from Montreal Neurological Institute, as he did not have a cell phone, home phone, or email address at which he could be reached.
NET-ICU-007	9	Active	67yo female with intracerebral hemorrhage (ICH) and intraventricular hemorrhage (IVH). This participant was followed for 1 week while she was at the Montreal Neurological Institute. The patient was lost-to-follow-up while she was at the rehabilitation institute due to pandemic research restrictions. Upon discharge to her home, CBS was restarted (after a 3-month gap).
NET-ICU-008	10	Active	56yo female who suffered an ICH. Given the ongoing Covid-19 pandemic, this participant only started CBS 41 days after recovery of consciousness. Following this initial delay, the participant was followed in hospital and continued to complete the tests regularly (monthly) upon discharge.
NET-ICU-009	15	Active	75yo female who experienced a brain abscess following pansinusitis. This participant started CBS early in the recovery process – because of this, the first week of data is incomplete due to patient fatigue and other recovery factors. In general, this patient completed CBS in the hospital for two weeks with the

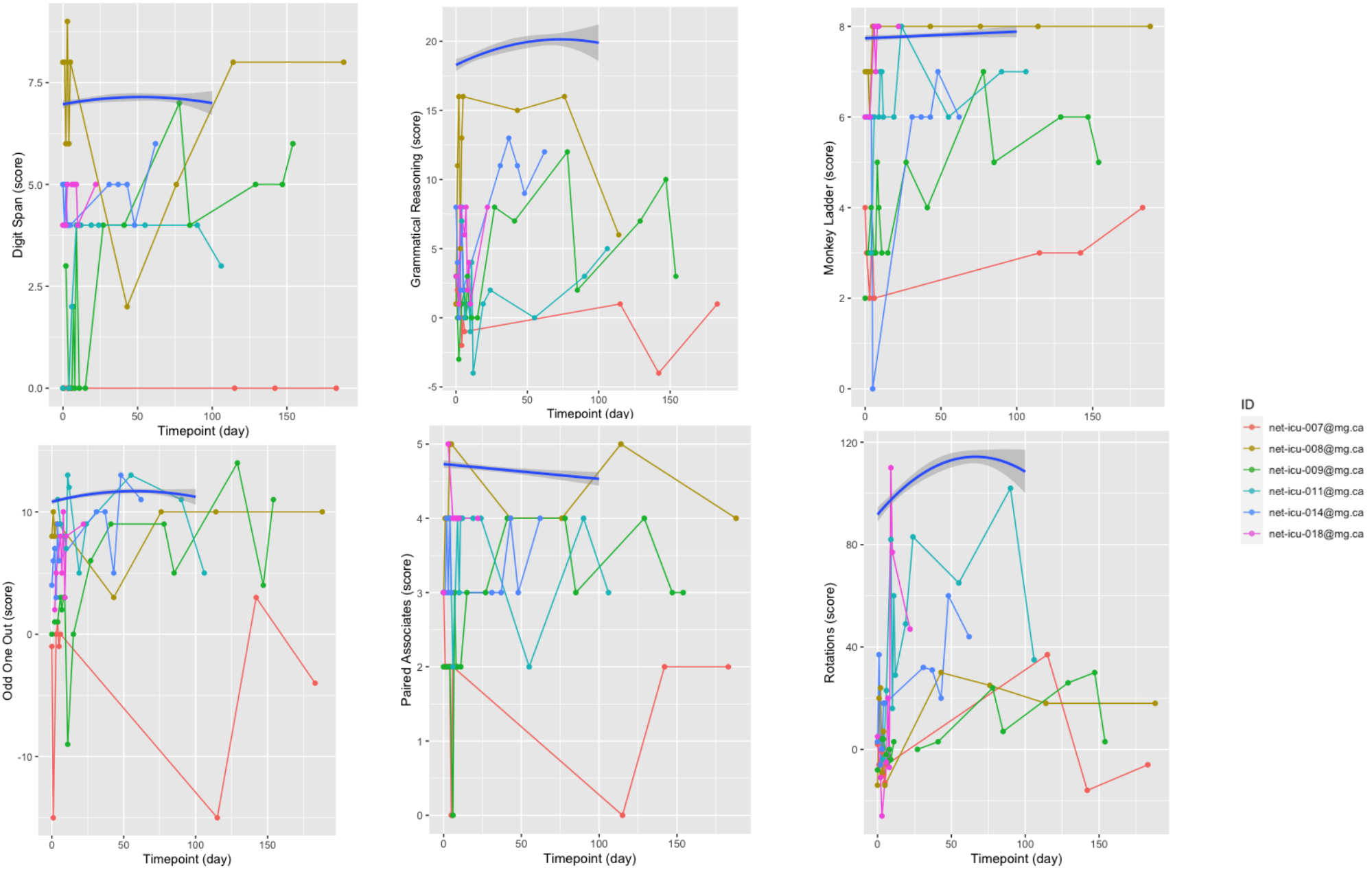
			assistance of a researcher, and continued with help from her family members and caregivers following discharge.
NET-ICU-010	5	Withdrawn	42yo male, suffered an intracerebral hemorrhage (ICH). First day of data collection was incomplete given participant's loss of interest. He completed 5 days of CBS in hospital but chose not to continue upon discharge (voluntary withdrawal).
NET-ICU-011	11	Active	51yo female who suffered a stroke. Despite initial lack of interest in the tests, which explains a lack of data in the first week of assessment, this participant completed CBS consistently in the hospital and in the rehabilitation centre with the help of a research team member. Gaps in data collection can be explained by pandemic visitor regulations at the rehab centre (Institut de Readaptation Gingras-Lindsay), which restricted research team access and thus delayed data collection.
NET-ICU-014	11	Active	82yo male who suffered a right M1 occlusion. This participant completed CBS with a member of the research team in the hospital for 1 week. Following a brief delay after discharge, he continued to complete CBS until the time this dissertation was written.
NET-ICU-016	2	Withdrawn	59yo female who experienced a severe myasthenia gravis exacerbation. This participant began completing CBS while in palliative care at the Royal Victoria Hospital in Montreal, and completed two days of testing before passing away.
NET-ICU-017	6	Withdrawn	27yo male who suffered a depressed skull fracture with bilateral hematoma following a bike accident. The participant completed cognitive testing in hospital for two weeks before being discharged. Upon discharge home, the participant voluntarily withdrew from the study.
NET-ICU-018	10	Active	23yo male who suffered a traumatic brain injury following an all-terrain vehicle accident. This participant began completing CBS testing as early as possible upon recovery of consciousness. With the help of a team member, he completed CBS daily in hospital

			and rehab institute. Upon discharge home, the participant was expected to continue. At the time this dissertation is being written, the participant has completed 10 timepoints in 30 days.
NET-ICU-020	6	Active	21yo male who experienced polytrauma including brain injury following a fall from significant height. Upon recovery of consciousness, CBS testing was started immediately. Data was collected daily for the first week. This participant was still completing his first month of testing at the time of this dissertation.

Data was plotted in R for each individual participant who completed more than 1 week of data collection and each participant's unique learning curves were traced. The slopes of each of those curves are shown in Figure 3.2.

In healthy controls, *Monkey Ladder* and *Paired Associates* showed no learning (Chapter 2). Therefore, any increases in scores seen in those tests should not be attributed to practice effects. The other 4 tests (*Digit Span, Grammatical Reasoning, Odd One Out,* and *Rotations*) showed minimal learning effects in the control study (cite). As this is a feasibility study, no formal analyses were run on the NET-ICU participant scores to compare them to the control study trendlines. However, plots were generated to visualize these differences and illustrate the ability to see recovery of cognition (or lack thereof) in patients recovering from a period of unconsciousness. Each of the plots considers the true scores for each participant on each of the tests. Although this is a feasibility study, and therefore scores will not be analysed using formal statistical testing, the true participant test scores are an important factor in providing evidence for the feasibility of these tests to measure cognition over time.

Figure 3.2 *CBS test scores for individuals recovering from coma. Scores are plotted against healthy control practice effects trends (illustrated as a thick blue line with standard error in grey)*



Discussion

The present study presents evidence for the feasibility of the tracking of cognitive trajectories in brain-injured patients recovering from a period of unconsciousness using the Cambridge Brain Sciences battery of tests. In order to deem the study feasible, 4 factors were considered.

Recruitment capability and sample characteristics: Despite a 9-month recruitment ban due to the Covid-19 pandemic and subsequent pandemic-related restrictions, 23 participants were enrolled into the NET-ICU study. Of those 23 participants, 12 were reached the waking stage and were eligible for cognitive testing. Of those 12 eligible participants, all were enrolled in NET-ICU longitudinal cognitive portion of the study, consisting of 100% enrollment rate.

Evaluation and refinement of data collection procedures: Retention techniques were developed to ensure minimal patient attrition rates and increased compliance rates. This included getting ethics approval at numerous local rehab hospitals, assisting patients with data collection in their homes, and training participants on the cognitive tasks prior to hospital discharge. Furthermore, data collection on the tablet was convenient and allowed for effective and efficient data collection.

The ability of the research team to manage study procedures: This was measured based on the ability of the research team to retain participants and get consistent data throughout the length of the study protocol. The convenience of the Cambridge Brain Sciences testing battery made the study very manageable for the research staff. Only 2 participants were lost to follow-up over the course of the study, and both can be attributed to pandemic-related travel restrictions and not a lack of ability on the research team's part.

Preliminary evaluation of participants responses to study procedures: The CBS testing battery was shown to be sensitive to the cognitive recovery trajectories of brain-injured patients recovering from coma. This was clear the differences observed between individual patient score trajectories over time when compared to the expected practice effects observed in healthy adults.

Despite a focus on retention techniques and increased compliance, this study still saw several participants voluntarily withdraw from the study (Table 3.1). If this study had not taken place amid a global pandemic, perhaps higher retention rates would have been possible, for example if the study team could make home visits or schedule frequent meetings with participants to complete testing sessions together. As the study is ongoing, the current study team should consider alternative methods of retaining participants. Such techniques could include setting up a weekly phone call or video call with the participant to touch base and ensure they have completed that week's testing or providing text-message reminders to participants rather than email reminders (which often end up in spam folders).

Conclusion

Trajectories of cognitive recovery in brain-injured individuals recovering from a prolonged period of unconsciousness are poorly characterized. There is a need to trace these trajectories using a validated battery of neurocognitive tests in order to address the gap in clinical practice. The present study provides evidence for the feasibility of using the Cambridge Brain Sciences neurocognitive battery of tests in order to trace these recovery trajectories. The proposed study was deemed feasible, with an enrollment rate of 100% for patients already enrolled in the NET-ICU study. Furthermore, our pilot study of the proposed procedures demonstrate that the CBS testing battery is sensitive to cognitive changes in brain-injured patients recovering from coma, and can be used in future studies to map and quantify trajectories of cognitive recovery in individuals recovering from coma.

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Discussion

This thesis aimed to characterize the trajectories of cognitive recovery in individuals recovering from a prolonged period of unconsciousness. First, we established the inconsistencies in the literature regarding cognitive testing a post-coma population and identified gaps in cognitive tests chosen, cognitive domains assessed, timing of assessments, and frequency of testing. Next, it was established that an easy-to-administer testing battery of cognitive testing was needed that can be used longitudinally in a brain-injured patients in intensive care units (ICUs). Since no reliable, fast, and effective batteries have been validated longitudinally to date, we validate the Cambridge Brain Sciences (CBS) neurocognitive testing battery in healthy adults at repeated timepoints to establish the learning curves associated with repeated assessments. Finally, the CBS battery was administered in a post-coma population to determine the feasibility of using these tests to trace trajectories of cognitive recovery following a prolonged period of unconsciousness and was shown to be feasible.

First, our literature review aimed to characterize the inconsistences regarding tests of cognition and frequency of cognitive testing in studies of brain-injured patients recovering from coma. 996 articles were screened, and 134 articles were included for analysis. 133 unique tests and testing batteries were identified, providing evidence that there is no established “best test” of cognition. Further, differences were found in terms of method of administration, timing of assessments, and frequency of testing. Inconsistencies also emerged in the reporting of cognitive outcomes, with 7.5% of tests not reporting on the specific tests used to assess cognition, and 7.5% of tests not specifying the timing of cognitive assessments. Overall, this literature review brought to light the inconsistencies in cognitive assessment and reporting of cognitive assessment in brain-injured individuals post-coma, and exposed the need to establish an agreed-upon best cognitive testing tool that is practical, assessed various cognitive domains, and can be assessed longitudinally.

Following this, it was clear that there was a need to validate an easy-to-administer, convenient battery of neuropsychological tests that can be used in clinical populations. The Cambridge Brain Sciences (CBS) neurocognitive battery of tests is a series of online tests that assess three distinct cognitive domains and has been modified to be completed online without formal supervision. This suggests that web-based studies of cognition are not only possible, but provide a novel

opportunity for assessing cognition in ways traditional methods cannot. Chapter 2 described a study aimed at determining the learning curves associated with each of the CBS battery's 12 tests when tested in healthy adults across repeated timepoints. Participants were assessed at 19 timepoints in a 3-month repeated measures protocol. Data for each test was plotted and linear mixed effects modelling was completed for both the linear and quadratic models for all 12 tests. 4 of the 12 tests did not show any learning associated with repeated assessment. The other 8 tests showed a quadratic effect and were associated with minimal learning. Overall, the practice effects for all 12 tests were found to be negligible, allowing for the use of the CBS tests in future longitudinal studies.

Finally, Chapter 3 described a feasibility study aimed at determining the possibility of measuring trajectories of cognitive recovery in a pilot sample of brain-injured ICU patients recovering from coma. Recruitment capability, evaluation of data collection procedures, ability of research team to manage protocol, and preliminary evaluation of participant responses to procedures were all recorded to determine the study's feasibility. Overall, recruitment numbers were high (with 100% of eligible participants enrolled), data collection procedures were refined and deemed feasible, the study team retained all but 2 participants (who were lost-to-follow-up due to the Covid-19 pandemic), and preliminary evidence showed that the CBS testing battery is sensitive to cognitive changes in ICU patients throughout the recovery process.

Thus, the problem of tracing trajectories of cognitive recovery in brain-injured individuals recovering from a period of unconsciousness was addressed in full in this thesis. The problem was identified and quantified in a thorough review of the literature. The need to establish an easy-to-administer testing battery that can be assessed longitudinally was determined. To resolve this, the CBS testing battery was validated in healthy adults and practice effects were quantified for all 12 tests in the neurocognitive testing battery. Finally, the CBS testing battery was shown to be sensitive to cognitive changes in brain-injured patients following a coma and pilot data allowed us to trace trajectories of cognitive recovery in the first longitudinal cognitive study in this clinical population.

The series of studies described in this thesis sets the stage for future researchers to map trajectories of cognitive recovery in individuals recovering from coma. The current dissertation is part of a larger clinical study (the NET-ICU study), focused on establishing neurophysiological evidence for the treatment of brain-injury in intensive care units by developing a set of EEG techniques that robustly predict recovery of consciousness and cognition and developing a patient-accessible method of measuring long-term cognitive outcomes in ICU survivors. The combined knowledge from this dissertation contributes directly to the NET-ICU project, providing the study with background information regarding testing of cognition, practice effects associated with the CBS tests, pilot data for the first 12 NET-ICU CBS participants, and analysis techniques for future CBS participants.

Limitations of this thesis

In addition to the limitations presented in Chapters 1, 2 and 3, several other limitations should be considered when interpreting the findings presented in this thesis. First, the cognitive domains identified in Chapter 1 were determined by the researchers conducting the study based on evidence from the literature. This process was conducted rigorously but is nonetheless subject to interpretation and the findings may not represent all cognitive domains accessed by each of tests. Next, the participant self-selection bias presented in Chapter 2 could influence the findings from that study and the study described in Chapter 3. Scores may not be representative of the population, which could affect the generalizability of the trendlines found in Chapter 2 and applied in Chapter 3. Furthermore, Chapter 3 presented data and descriptive statistics for each individual participant. We did not conduct formal statistics on each participant's data and therefore cannot make claims about individual participant's trajectories of cognitive recovery. Further analysis should be conducted on each participants' data to determine whether statistical differences are observed between the participant's scores and the slopes of the healthy control trendlines described in Chapter 2. General conclusions regarding the recovery of cognition in a post-coma population cannot be drawn from the findings of Chapter 3, as we did not present a large enough dataset to make those inferences. The study provided proof of feasibility, and further research should be conducted to draw more general conclusions about cognition in this clinical population.

Conclusion and Summary

Longitudinal cognitive outcomes of coma survivors are poorly characterized in the literature. Furthermore, there is a need to validate an easy-to-administer, convenient battery of neuropsychological tests that can be used longitudinally in clinical populations to effectively track the trajectories of cognitive recovery in brain-injured individuals following a period of prolonged unconsciousness. This thesis aimed to address these issues and provide the framework for the effective tracking of cognitive recovery trajectories in a post-coma clinical population. First, Chapter 1 provided evidence for the inconsistencies in the literature with regards to cognitive testing in terms of cognitive tests chosen, cognitive domains assessed, timing of assessment, and frequency of testing. From this, it was clear that no reliable, easy-to-administer, effective neurocognitive testing battery have been validated longitudinally to date. Therefore, in Chapter 2, we validated the Cambridge Brain Sciences (CBS) testing battery, an easy-to-administer series of tests, in healthy adults at repeated timepoints over a prolonged period of time to determine the practice effects and learning associated with these tests after repeated assessment. The testing battery was found to be associated with no practice effects in 4 of the 12 tests, and minimal learning was found in 8 of the 12 tests. The CBS tests were then administered in a post-coma population in Chapter 3, where we demonstrated the feasibility of using these tests to trace trajectories of cognitive recovery following a prolonged period of unconsciousness. The series of studies presented in this dissertation provide future researchers with the tools to effectively and reliably track trajectories of cognitive recovery in large-scale studies of individuals recovering from a prolonged period of unconsciousness.

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Appendix 1: Search terms for two separate searches used in the literature review on cognitive outcomes of coma-survivors

Table 1. *Search terms used in PubMed for literature review on cognitive outcomes of brain-injured patients following a period of unconsciousness. All terms in the table were included in the search. Concepts are separated into columns where each term in a column was separated by "OR" in the search and each column (concept) was separated by "AND". This search focused on patients with a primary brain injury (see Concept 1).*

Concept 1: Brain Injury	**AND**	*Concept 2*: Coma	**AND**	*Concept 3:* Cognition	**AND**
"brain injuries, traumatic" [MeSH Terms]		"coma" [MeSH Terms]		"cognition" [MeSH Terms]	
"craniocerebral trauma" [MeSH Terms]		"coma, post head injury" [MeSH Terms]		"cognitive disorders" [MeSH Terms]	
"severe traumatic brain injur*"[Title/Abstract]		"unconsciousness" [MeSH Terms]		"neurocognitive disorders" [MeSH Terms]	
NOT "concussion"		"unresponsiveness" [Title/Abstract]		"cognitive dysfunction" [MeSH Terms]	
NOT "mild traumatic brain injury"		"coma" [Title/Abstract]		"cognitive impairment" [Title/Abstract]	
		"non-responsive" [Title/Abstract]		"cognitive recovery" [Title/Abstract]	
				"cognitive deficit" [Title/Abstract]	

Table 2. *Search terms used in PubMed for formal literature review on the cognitive outcomes of brain-injured patients following a period of unconsciousness. All terms in the table were included in the search. Concepts are separated into columns where each term in the column was separated by "OR" in the search and concepts were separated by "AND". This search focused on patients with brain injuries secondary to cardiac arrest (Concept 1).*

Concept 1: Cardiac arrest	**AND**	*Concept 2*: Coma	**AND**	*Concept 3*: Cognition	**AND**
"heart arrest" [MeSH Terms]		"coma" [MeSH Terms]		"cognition" [MeSH Terms]	
"myocardial infarction" [MeSH Terms]		"coma, post head injury" [MeSH Terms]		"cognitive disorders" [MeSH Terms]	
"cardiac arrest" [Title/Abstract]		"unconsciousness" [MeSH Terms]		"neurocognitive disorders" [MeSH Terms]	
"myocardial infarction" [Title/Abstract]		"unresponsiveness" [Title/Abstract]		"cognitive dysfunction" [MeSH Terms]	
		"coma" [Title/Abstract]		"cognitive impairment" [Title/Abstract]	
		"non-responsive" [Title/Abstract]		"cognitive recovery" [Title/Abstract]	
				"cognitive deficit" [Title/Abstract]	

Appendix 2: Tests of cognition used in brain-injured patients following coma and the number of times these tests were used in 134 articles

Measure	Number of appearances
Addenbrooke's Cognitive Exam (ACE-R)	1
Adult memory and information processing battery (AMIPB)	1
Adult self-report scale (ASR)	1
Attentive matrices test	1
Barrow Neurological Institute Screen for Higher Cerebral Functions (BNIS)	5
Behavioural Assessment of Dysexecutive Syndrome (BADS)	3
Behaviour Rating Inventory of Executive Function - Adults (BRIEF-A) *	2
Benton Facial Recognition Test	1
Benton Judgment of Line Orientation Test (JLOT)	4
Benton Multilingual Aphasia Examination (MAE)	1
Benton Visual Discrimination Test	1
Benton Visual Retention Test	2
Beck Hopelessness Scale (BHS)	1
Boston Diagnostic Aphasia Examination (BDAE)	1
Boston Naming Test	7
Brief Psychiatric Rating Scale (BPRS)	1
Brief Post-Coma Scale (BPCS)	1
Brief Visual Memory Test (BVMT)	5
Buschke Selective Reminding Task	2
Cerebral Performance Categories (CPC)	1
Conners' Continuous Performance Test (CCPT-II)	3
Cognitive Capacity Screening Evaluation (CCSE)	1
Computer Assessment of Mild Cognitive Impairment (CAMCI)	1
Clinical Dementia Rating Scale (CDR)	1

Complex Figures Test (Medical College of Georgia version)	1
Cognitive Failures Questionnaire (CFQ) *	2
Cognitive Log (Cog-Log)	1
CogState	2
Cognitive Test for Delirium (CTD)	1
California Verbal Learning Test (CVLT)	13
Continuous Visual Memory Test (CVMT) *	2
Color Trails Test (CTT) *	2
Corsi Block Tapping Test	2
Controlled Oral Word Association Test (COWAT)	9
Continuous Performance Test	1
Coma Recovery Scale (CRS-R)	4
Confrontation Naming Test	1
CRECER Clinical Outcome Scale (CRECERCOS)	1
Daily Fatigue Impact Scale (DFIS)	1
Delis-Kaplan Executive Functioning System (D-KEFS)	3 full battery; 13 subtests only
Detroit Tests of Learning Aptitude (DTLA)	1
Differential Outcome Scale (DOS)	1
Digit Span	17
Digit Symbol Substitution Test (DSST)	1
Digit Symbol Modality Test (DSMT)	2
Disability Rating Scale (DRS)	12
Dot Cancellation Test	1
Dot Counting Test	1
“Draw-a-bicycle” test	1
D2 Test of Attention	2
Early Rehabilitation Barthel Index (ERBI)	3

Emotional Empathy Questionnaire (EEQ)	1
Executive Route Finding Test (EFRT)	1
Fame Judgment Task	1
Faux Pas Test	1
Frontal Assessment Battery at Bedside (FAB)	1
Facial Expressions of Emotion: Stimuli and Tests (FEEST)	1
Figure Connection Test (FCT)	1
Functional Independence Measure (FIM)	22
Geriatric Depressive Scale (GDS)	1
General Health Questionnaire (GHQ-28)	1
Glasgow Outcome Scale Extended (GOS-E)	16
Grooved Pegboard Test	11
Halstead-Reitan Neuropsychological Battery	4 full battery; 22 subtests only
Hospital Anxiety and Depression Scale (HADS) *	3
Hong Kong List Learning Test (HKLLT)	2
Hopkins Verbal Learning Test (HVLT)	2
Hundred Pictures Naming Test (HPNT)	1
Inglis Paired Associates Test	1
Intelligence Structure Test	2
Katz Adjustment Scale (KAS-R)	2
Lumos Labs NeuroCognitive Performance Test	1
Memory for Design Test (MFDT)	1
Multidimensional health locus of control (MHLC scale)	1
Mill Hill vocabulary scale	1
Mini-Mental State Exam (MMSE)	12
Minnesota Multiphasic Personality Inventory (MMPI)	2
Mnemonic Efficiency Battery (MEB)	1

Montreal Cognitive Assessment (MoCA)	1
National Adult Reading Test (NART)	4
Neurobehavioral Rating Scale - Revised (NRS-R)	1
Number Connection Test	2
Number Location Test	2
Object Memory Test	1
Orientation Log (O-Log)	2
Paced Auditory Serial Addition Test (PASAT)	5
Paired Associates Test	2
Paragraph Recall	1
Patient Competency Rating Scale (PCRS)	4
Peabody Picture Vocabulary	2
Persian Aphasia Test (PAT)	1
Prospective Memory Task	2
Psychomotor Vigilance Test	1
Rancho Los Amigos Levels of Cognitive Functioning (LCF)	16
Random Number Generation	1
Ravens' Progressive Matrices Test	4
Rivermead Behavioural Memory Test (RBMT)	4
Rey Auditory Verbal Learning Test (RAVLT)	13
Rey's Complex Figure Test (RCFT)	19
Rey 15-item Test	1
Recurring Figure Test (RFT)	1
Revised Internal External Scale (RIES)	1
Sustained Attention to Response Task (SART)	1
Screen for Higher Cerebral Functions (BNIS)	1
Selective Reminding Test	6
Sensory Tool to Assess Responsiveness (STAR)	1

Six Elements Test (SET)	1
Short Test of Mental Status (STMS)	1
Spatial Learning	2
Stroop Test	18
Supermarket test	1
Supervision Rating Scale (SRS)	1
Symbol Digit Modalities Test (SDMT)	15
Taylor Complex Figure	1
Test of Adult Word Finding (TAWF)	1
Test d'Evaluation de l'Attention (TEA) battery	1
Telephone Interview for Cognitive Status (TICS)	1
Token Test	2
Trail Making Test (TMT)	46
Unusual Views Test	1
Verbal Fluency Test	18
Visual Object and Space Perception Battery	2
Visual Discrimination	2
Visual Reaction Time	2
Visual Search Test	1
Wechsler Adult Intelligence Scale (WAIS)	23 full battery; 30 subtests only
Wechsler Abbreviated Scale of Intelligence (WASI)	3
Wechsler Memory Scale (WMS)	11 full battery; 14 subtests only
Wessex Head Injury Matrix (WHIM)	1
Western Neuro Sensory Stimulation Profile (WNSSP)	2
Wisconsin Card Sorting Test (WCST)	19
Wisconsin General Test Apparatus (WGAT) - adapted for humans	3

Appendix 3: Descriptions and administration methods for the 36 cognitive tests included in the literature review of patients recovering from coma

Measure	Subscale (if applicable)	Description	Administration	Freq.
Barrow Neurological Institute Screen for Higher Cerebral Functions (BNIS)		38-item test which examines 7 functions: language, orientation, concentration, visuospatial function, memory, affect, and self-evaluation of performance	Total score is sum of 7 sub-scores. Does not require training for clinicians	5
Behavioural Assessment of Dysexecutive Syndrome (BADS)	Zoo Map Test	Participants are given a map of a zoo and instructions of places they have to visit. Test of planning abilities (formulation and execution)	Scoring based on total number of errors and times taken to plan and execute the routes.	3
Benton Judgment of Line Orientation Test (JLOT)		Measures visuospatial judgment in brain-injured patients. The test examines the ability of a subject to estimate angular relationships between line segments by visually matching angled line pairs to 11 numbered radii forming a semi-circle.	Subjects are given a stimulus booklet and asked to match two angled lines to a set of 11 lines that are arranged in a semicircle and separated 18 degrees from each other. The complete test has 30 items.	4
Boston Naming Test		Neuropsychological assessment tool to measure confrontational word retrieval in individuals with aphasia or other language disturbance caused by stroke, Alzheimer's disease, etc.	60-item test, it aims to determine the extent of the subject's visual confrontation naming abilities. A 15-item short form and a multiple-choice version of the test can be used to retest comprehension of any words missed on the confrontation naming exercise.	7
Brief Visual Memory Test (BVMT)		Measure of visuospatial memory and memory abilities. Subjects are asked to look at six stimuli (geometric figures) and subsequently draw as many as possible in their correct location. A Delayed Recall Trial is administered after a 25-minute delay. Lastly, a Recognition Trial, in which the subject is asked to identify which of 12 figures were included among the original geometric figures.	Total administration time is 45 min approx.	5

Conners' Continuous Performance Test (CCPT-II)		Standardized, computerized instrument designed to assess different aspects of attention/executive functions.	Consists of 360 single letters presented one by one on a computer screen in 18 consecutive blocks of 20 trials. Respondents are asked to press a button every time a stimulus (letter) is presented, except for the letter "X." It takes 12 minutes to complete.	3
California Verbal Learning Test (CVLT)		Measures episodic verbal learning and memory, and demonstrates sensitivity to a range of clinical conditions.	The experimenter reads a list of 16 nouns aloud, at one-second intervals, in fixed order, over five learning trials. After each trial, the subject is asked to recall as many words as they can in any order (i.e., free recall). An interference list of words is used too and the test ends with a word recognition task. Total administration time is around 30 min.	13
Controlled Oral Word Association Test (COWAT)		Verbal fluency tasks evaluate the spontaneous production of words under restricted search conditions.	This test requires the individual to name as many words as possible that begin with a given letter. Sixty seconds are allotted for each letter. Administration takes around 5 minutes.	9
Coma Recovery Scale (CRS-R)		Used to assist with differential diagnosis, prognostic assessment, and treatment planning in patients with disorders of consciousness. It consists of 23 items that comprise six subscales addressing auditory, visual, motor, oromotor, communication and arousal functions.	Time to administer between 15 and 30 min.	4
Delis-Kaplan Executive Functioning System (D-KEFS)	*Whole battery	Standardized assessment of executive functions including flexibility of thinking, inhibition, problem solving, planning, impulse control, concept formation, abstract thinking, and creativity. It is composed of nine stand-alone tests that can be individually or group administered.	Administration of the full battery takes 90 minutes.	3
	Verbal fluency	Assess verbal behavioural productivity and cognitive flexibility.	Composed of three testing conditions: Letter Fluency,	5

			Category Fluency, and Category Switching.	
	Color-Word Interference Test (CWIT)	Measures multiple aspects of visual behavioral productivity and cognitive flexibility. DF evaluates visual productivity with and without distracting stimuli, and switching between stimuli		4
	Tower Test	Measures planning and reasoning in the spatial modality, impulsivity.		4
Digit Span				17
Disability Rating Scale (DRS)		This scale was developed as a measure of disability that would be applicable to individuals with moderate to severe traumatic brain injury at a wide range of functional levels from coma through community living. It has eight areas of functioning components: Eye Opening, Best Communication Ability, Best Motor Response, Cognitive Ability (Feeding, Toileting and Grooming, Level of Functioning and Employability.	The scale can be self-administered or scored through an interview with the participant or a family member.	12
Early Rehabilitation Barthel Index (ERBI)	-aka Barthel index	Ordinal scale used to measure performance in ADLs. Ten variables describing ADLs are scored. The Barthel Index measures the degree of assistance required by an individual for mobility and self-care.	Self-report (5 minutes) & direct observation (20 minutes)	3
Functional Independence Measure (FIM)	Motor and Cognitive subtest	Developed as a measure of disability for a variety of populations. 18-item 7-level ordinal scale intended to be sensitive to changes over the course of a comprehensive inpatient medical rehab program. Cognition subscale includes: comprehension, expression, social interaction, problem solving, memory	Each item is scored on a 7 point ordinal scale (by a rater). Takes approximately 30-45 minutes to administer.	22
Glasgow Outcome Scale Extended (GOS-E)		A test to classify global outcomes in TBI survivors. It is a “global scale for functional outcome that rates patient status into one of five categories: dead, vegetative, severe disability, moderate disability, and good recovery”	Use of the structured interview is recommended to facilitate consistency in ratings since this test isp rated by an examiner.	16
Grooved Pegboard Test		Manipulative dexterity test that contains 25 holes with randomly positioned slots and pegs which	Measures performance speed in a fine motor task.	11

		have a key along one side. Pegs must be rotated to match the hole before they can be inserted.		
Halstead-Reitan Neuropsychological Battery	Whole battery	The full HRNB includes: Weschler Intelligence Scale, Aphasia Screening Test, Trail-Making Test, Halstead Category Test, Tactual Performance Test, Seashore Rhythm Test, Speech Sounds Perception Test, Finger Tapping Test, Sensory Perceptual Examination, Lateral Dominance Examination	Used to evaluate the "condition and functioning of the brain, including etiology, type, localization and lateralization of brain injury." Administration of the full battery takes over 3 hours.	4
	Finger Tapping/Oscillation Test	Participant places hand on flat surface and uses 2 fingers on the same hand to tap two buttons, alternating.	Test that examines motor functioning (motor speed and lateralized coordination).	6
	Speech Sounds Perception Test	Measures a person's ability to match a spoken nonsense word containing double e (e.g. teeg) with its written counterpart		2
	Seashore Rhythm Test	Participant listens to a recording of pairs of rhythmic patterns and indicates whether they are the same or different.		3
	Tactual Performance Test	Participants are blindfolded and are asked to place wooden shapes into a formboard placed at a 45 degree angle.	Measures motor abilities and recall of motor stimuli, as well as nonverbal memory and other cognitive functions.	4
	Category Test	Participant is presented with 6 subtests - each has a different set of stimuli organized according to a specific principle, and each stimulus is associated with a particular number. Participants must choose a number and use feedback/response accuracy to solve each item.	Non-verbal problem-solving task that requires abstract reasoning, concept formation, and mental flexibility.	7
Mini-Mental State Exam (MMSE)	-	Scale used to measure cognitive impairment in older adults. It assesses different subsets of cognitive status including attention, language, memory, orientation, visuospatial proficiency.	Objective questions administered by a rater (10-15 minutes)	12
National Adult Reading Test (NART)		The test comprises 50 written words in English which all have irregular spellings, so as to test the participant's vocabulary rather than ability to apply pronunciation rules.	Used to estimate pre-morbid intelligence, because it assesses abilities that are thought to be spared following neurological injury.	4

Paced Auditory Serial Addition Test (PASAT)		Participants are given a number every 3 seconds and are asked to add the number they just heard to the number they heard before.	Used to assess capacity and rate of information processing and sustained and divided attention. This task involves working memory, attention, and arithmetic capabilities.	5
Patient Competency Rating Scale (PCRS)		Scale that aims to assess self-awareness following brain injury. Consists of 30 items that specify different tasks and functions in four domains (ADLs, behavioural and emotional function, cognitive abilities, and physical function).	Participant responds on a 5-point scale to each of the 30 items. An informant rating should be obtained from a relative or therapist.	4
Rancho Los Amigos Levels of Cognitive Functioning (LCF)		Describes the cognitive and behavioural patterns found in brain injury patients as they recover from coma. The scale consists of 8 levels. Each level is presented on the scale as a narrative form and the rater must decide which level best describes the patient's present behaviours.	The scale was based on the assumption that observation of the type, nature, and quality of a patient's behavioural responses can be used to estimate the cognitive level at which the patient is functioning.	16
Ravens' Progressive Matrices Test		Nonverbal test used to measure human intelligence. In each test item, subject is asked to identify the missing element that completes a pattern.	60 multiple choice questions. Measures reasoning ability.	4
Rivermead Behavioural Memory Test (RBMT)	14 subtests	Subtests include: First and second names (delayed recall): asked to remember names of people in photos Belongings (delayed recall): asked to remember what objects were hidden at the beginning of the test Appointments (delayed recall): when an alarm rings, participant has to answer specific questions Story (immediate & delayed) Picture recognition (delayed) Face recognition (delayed) Route (immediate and delayed): same as zoo map test Messages (immediate and delayed) Orientation Novel task (immediate and delayed): use different coloured pieces to make a shape as demonstrated by examiner	Assesses aspects of visual, verbal, recall, recognition, immediate and delayed everyday memory, prospective memory skills, ability to learn. It takes approx 30 minutes to complete.	4

Rey Auditory Verbal Learning Test (RAVLT)		Five presentations of a 15-word list are given, each followed by attempted recall. This is followed by a 15-word interference list (list B), followed by recall of list A. This test is succeeded by CVLT.	Evaluates short-term memory, rate of learning, interference, and other executive functions. Approximately 10-15 minutes required (plus 30 minute interval)	13
Rey's Complex Figure Test (RCFT)		Participants are asked to reproduce a complicated line drawing, first by copying it freehand and then drawing from memory.	Captures information about five cognitive domains: visuospatial recall memory, visuospatial recognition memory, response bias, processing speed, visuospatial constructional ability.	19
Selective Reminding Test		Test designed to measure verbal learning and memory through use of a list-learning procedure over multiple trials (participant is asked to remember a list of words; on next trial, participant is only reminded of missed words from previous trial). This test distinguishes short-term memory from long-term storage	Approximately 30 minutes.	6
Stroop Test	-	Test used to assess the ability to inhibit cognitive interference.	Objective measure, scored on speed and accuracy	18
Symbol Digit Modalities Test (SDMT)	-	Simple substitution task (where the examinee pairs specific numbers with geometric figures), sensitive to cognitive changes over time. *DSMT=DSST=SDMT	Scored on speed and accuracy (90 second task)	15
Trail Making Test (TMT)	Subtests A and B	Test in which participants must link numbers from 1-25 or numbers (1-12) and letters (A-L) in order.	Timed assessment. Reviewer must be present to correct if the participant makes a mistake.	46
Verbal Fluency Test	Animal, Vegetable, etc.	Short test of verbal functioning. Typically 2 tasks (category/semantic fluency and letter/phonemic fluency)	Scored on number of unique words	18
Wechsler Adult Intelligence Scale (WAIS)	*Full battery	IQ test, designed to measure intelligence and cognitive ability. Full scale IQ = Verbal IQ (verbal comprehension index + working memory index) + Performance IQ (perceptual organization index + processing speed index)		23 (+3)
	Block design	Test of perceptual organization index (within performance IQ subindex)		6

	Processing Speed Index (PSI)	Measures the speed of mental processing, using visual stimuli and graphomotor skills. Includes symbol search and digit symbol coding tasks. These tasks require attending to visual material, visual perception and organization, visual scanning, and hand-eye coordination.	Timed assessments	4
	Digit Span	Test of working memory within verbal IQ index		5
	Symbol Search	Test of processing speed within performance IQ index		1
	Digit Symbol Modalities Test (DSMT)	Test of processing speed within performance IQ index		3
	Similarities	Test of verbal comprehension within verbal IQ index		4
	Vocabulary	Test of verbal comprehension within verbal IQ index		2
	Letter-Number sequencing (LN)	Test of working memory within verbal IQ index		2
Wechsler Abbreviated Scale of Intelligence (WASI) *		Short form of the WAIS used to estimate intellectual functioning. 4 subtests: 2 verbal, 2 performance	Approximately 20 minutes in length	3
Wechsler Memory Scale (WMS)	*Full battery	Designed to be used WITH the WAIS. • WMS-IV is made up of seven subtests: Spatial Addition, Symbol Span, Design Memory, General Cognitive Screener, Logical Memory (I & II), Verbal Paired Associates (I & II), and Visual Reproduction (I & II)	A person's performance is reported as 5 index scores: auditory memory, visual memory, visual working memory, immediate memory, and delayed memory	11
	Digit Span	*has since been eliminated from WMS. Measures verbal STM		2
	Spatial Addition	Evaluates visual-spatial working memory using a visual addition task. The participant is shown two		-

		images with red and blue circles, and asked to add or subtract the locations of the circles.		
	Design Memory	Assesses memory for visual images in a grid (requiring memory of both visual and spatial information)		-
	Symbol Span	Assesses visual working memory. Uses novel visual stimuli (difficult to verbalize) and requires storage and manipulation functions.		-
	Logical Memory (I&II)	Participant is read a short prose passage and asked to recall as many details as possible both immediately and after delay.	Takes approximately 5 minutes to administer, but requires time for delay.	8
	Verbal Paired Associates (I&II)	Required to recall novel and semantically related word pairs after 20-30 minute delay. Measure of delayed cued recall for word associations		-
	Visual Reproduction (I&II)	Test of nonverbal delayed recall.		4
Wisconsin Card Sorting Test (WCST)		Stimulus cards are presented to the participant, who must match the cards (but are not told how). Test of "set-shifting" (ability to display flexibility in changing schedules of reinforcement)	Takes ~12-20 minutes to carry out. Generates scores of categories achieved, trials, errors, and perseverative errors.	19

Appendix 4: Demographic questionnaire for the longitudinal validation study of the cognitive testing battery Cambridge Brain Sciences in healthy adults

1. The purpose of this study is to measure the reliability of cognitive performance on the Cambridge Brain Sciences tasks. If you agree to participate, you will be asked to perform computer tasks that will assess different aspects of cognition. For example, you will be presented a series of numbers on a computer screen and asked to remember and reproduce the numbers that you see. If you would like to view the tasks before consenting, they can be found at http://www.cambridgebrainsciences.com/.Each session will take approximately 40 minutes. You will be asked to complete the tasks 19 times over the course of 12 weeks. You will be compensated $50 upon completion of all 19 assessments. The data that you provide will be anonymized; no information that identifies you will be retained for research purposes. There are no known risks to you of participating in this study. If you have any questions or require further information regarding this research project, you may contact Allison Frantz (biaptlabmcgill@gmail.com). If you would no longer like to participate, you may close this browser window now. If you agree to participate, please enter your study ID.
2. What is your gender?
    a. Female
    b. Male
    c. Other
3. Which category below includes your age?
    a. 18-29
    b. 30-39
    c. 40-49
    d. 50-59
    e. 60 or older
4. What is the highest level of education you have completed or the highest degree you have received?
    a. Less than high school degree
    b. High school degree or equivalent (e.g., GED)
    c. Some college but no degree
    d. Associate degree

    e. Bachelor degree
    f. Graduate degree
5. What is your combined household income?
    a. $0 to $9,999
    b. $10,000 to $24,999
    c. $25,000 to $49,999
    d. $50,000 to $74,999
    e. $75,000 to $99,999
    f. $100,000 to $124,999
    g. $125,000 to $149,999
    h. $150,000 to $174,999
    i. $175,000 to $199,999
    j. $200,000 and up
    k. Prefer not to answer
6. What is your country of origin?
7. How many languages are you fluent in?
    a. 1
    b. 2
    c. More than 2
8. What is your dominant hand?
    a. Left
    b. Right
9. Do you have any neurological conditions that might affect your ability to complete a battery of cognitive tasks?
    a. No
    b. Yes (please explain)
10. Do you have any learning disabilities that might affect your ability to complete a battery of cognitive tasks?
    a. No
    b. Yes (please explain)