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Cognition and Behavioral Outcome in Children and Adolescents with Previous ECMO Treatment: A Case Series with Neuroimaging Correlates

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ECMO Treatment: A Case Series with Neuroimaging Correlates

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ABSTRACT

Cognitive and Behavioral Outcome in Children and Adolescents with Previous ECMO Treatment: A Case Series with Neuroimaging Correlates

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Extra-corporeal membrane oxygenation (ECMO) is a life-saving procedure for patients in respiratory or cardiac distress. Prior studies have demonstrated several known risks to the procedure, such as hypoxia, stroke, and other neurological complications (Cheng et al., 2014) that can lead to temporary or permanent deficits in motor abilities, developmental trajectory, academic abilities, and cognition (Glass et al., 1995). Although several studies have investigated morbidity and mortality rates of pediatric ECMO patients, few have looked at cognitive deficits, and even fewer at magnetic resonance imaging in relation to neuropsychological outcome and behavioral, emotional, or social functioning. The aims of this study were to investigate cognitive ability and behavioral functioning in a group of ECMO-treated patients compared to a normative sample, and to examine brain morphometry in hippocampal regions as they relate to cognitive outcome.

Participants for this study were recruited from Primary Children's Hospital in Salt Lake City, UT. The total number of participants recruited was 8 (63% female; M age at testing = 16.75, SD = 4.5), and all participants were at least 1 year post-ECMO procedure (M=5.6 years; SD=2.1) for acute respiratory or cardiac illness. Neuropsychological testing was completed using the NIH Toolbox Cognition Battery. Scores were compared to normative data for age to investigate potential impairment in multiple cognitive domains. Each participant and the parent or guardian of minor participants completed brief questionnaires measuring executive functioning, behavior, and social skills, namely The Behavior Rating Inventory of Executive Functioning, The Behavioral Assessment System for Children, Second Edition, and the Social Skills Improvement System Rating Scales. Six of the participants also underwent MR imaging to obtain measures of cortical thickness in the frontal areas of the brain, as well as hippocampal and total intracranial volume. Performance results on the NIH Toolbox Cognition Battery was impaired in over half of the tested individuals who underwent ECMO as children. Attention, executive function, processing speed, and visual memory were well below the expected range for age in the majority of participants. Crystallized intelligence tasks, such as vocabulary, were in the average to above average range for most participants, likely indicating normal baseline functioning. Self- and informant report revealed variable results across participants, with various behavioral, emotional, and social difficulties reported in the group. Bilateral hippocampal volume was positively correlated with scores on tasks of episodic and working memory, though further study with a larger sample and control group is warranted. Preliminary MRI data for cortical thickness and volume of frontal regions are presented. Interpretation of results, limitations, and future directions are discussed.

Keywords: ECMO, children, pediatric, cortical thickness, executive functioning, NIH Toolbox

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Cognitive and Behavioral Outcome in Children and Adolescents with Previous ECMO Treatment: A Case Series with Neuroimaging Correlates

Extra-corporeal membrane oxygenation (ECMO) is a life-saving procedure that has been shown to increase survival rates in individuals in severe pulmonary and cardiac distress (Glass, Miller, & Short, 1989). The primary goal of ECMO is to oxygenate the blood and remove carbon dioxide outside of the body in order to sustain heart and/or lung function (Graber, Quillinan, Marrotte, McDonagh, & Bartels, 2015). This can be accomplished using two types of ECMO, veno-venous (VV), in which cannulation is drained from a vein and pumped back through the right atrium, or veno-arterial (VA), in which cannulation bypasses the heart and venous blood is pumped into arterial circulation (Graber et al., 2015). Typically, VV ECMO is used for respiratory disorders such as acute respiratory distress syndrome (ARDS), while VA ECMO is utilized when a patient requires heart support for acute or chronic cardiac disease (e.g. myocardial infarction, myocarditis, or while waiting for transplant). It is estimated that in the past 25 years, more than 30,000 children have undergone ECMO, most often for severe respiratory failure (Paden, Conrad, Rycus, & Thiagarajan, 2013). Although technology is continuously improving, mortality remains high (Aubron et al., 2013). Outcome can be partially explained by factors independent of ECMO (e.g., nature and severity of illness), but there are also several known risks and complications for the procedure, such as bleeding, infection, embolism, and limb ischemia (Aubron et al., 2013). Infections in particular are common during ECMO, with up to 45.1% of patients contracting infection at some point during the procedure, and up to 89.4% of these being bloodstream infections, which are associated with poor outcome in children (Sun et al., 2010). Additionally, neurological complications resulting from embolism are likely underestimated and can negatively impact prognosis (Aubron et al., 2013). Despite these serious risks, very few studies have investigated long-term evaluations or follow-ups to monitor the effects of ECMO on patients who underwent the procedure as an infant or child. Further, the majority of available reports and statistics merely confirm morbidity and mortality rates, and do not examine the potential neurocognitive, behavioral, or social consequences of the procedure. Since the introduction of ECMO in 1975, there have been several known risks to the procedure, such as hypoxia and temporary or permanent deficits in motor abilities, developmental trajectory, academic abilities, and cognition (Benjamin et al., 2013; Cooper et al., 2013; Glass et al., 1995; Guerra et al., 2015).

Neuropsychological Findings in ECMO

Current literature suggests that an increased risk of neurologic complications during ECMO can lead to significant cerebral sequalae following the treatment. Risnes et al. (2006) found that over half of the studied ECMO patients had some form of neurocognitive impairment or abnormality, as evidenced by either MRI scan, neuropsychological testing, or both. ECMO-treated patients were found to have lower scores in spatial ability, verbal skills, and reasoning compared to a control group, which did not improve with age (IJsselstijn & van Heijst, 2014). Interestingly, the children treated with ECMO had average IQ scores, though overall lower than the control group (96 and 115, respectively), yet they still were at a greater risk for school failure (Madderom et al., 2013; IJsselstijn & Heijst, 2014; Rais-Bahrami, Wagner, Coffman, Glass, & Short, 2000). Clinical behavioral problems, hyperactivity, inattention, and somatic complaints were also reported at a higher rate by both parents and teachers of ECMO-treated children (Hanekamp et al., 2006; Madderom et al., 2013; Rais-Bahrami et al., 2000).

Additionally, hypoxia in infancy has been shown to lead to hippocampal atrophy and therefore memory problems later in life (Cooper et al., 2013). Diffuse atrophy in other brain regions is suspected given hypoxic damage is typically diffuse and can impact many cognitive functions, even when oxygen desaturation levels are mild (Bass et al., 2004; McMorris, Hale, Barwood, Costello, & Corbett, 2017). However, because baseline measures are typically not available for patients post-procedure, it is often difficult to differentiate how adverse neurological effects are attributed specifically to the procedure rather than to the pre-existing medical conditions for which the ECMO was employed. In fact, Graber et al. (2015) suggest that chronic neurocognitive dysfunction is common in patients who have spent time in the intensive care unit (ICU), citing anywhere from 25-78% of patients reporting cognitive decline. Specific to ECMO therapy, Cheng et al. (2014) conducted a meta-analysis totaling 20 studies and 1866 patients post-ECMO procedure, finding that 5.9% of patients suffered from stroke and 13.3% had other neurological complications. Similar results have been shown by others, reporting significant neurological events (e.g. stroke) or impairments (Mateen et al., 2011; Guttendorf, Boujoukos, Ren, Rosenzweig, & Hravnak, 2014; Aubron et al., 2013), including cerebral radiologic findings (Risnes et al., 2006). Deficits may be due to contributory factors such as inflammation, hemodilution (decreased cell concentration in the blood), embolism, hypoperfusion (shock), or genetic predisposition (Graber et al., 2015). Further, as ECMO is commonly used in instances of cardiac arrest that are otherwise non-responsive to usual resuscitative techniques (Cheng et al., 2014), cognitive impairment may also be observed as it relates to initial arrest. In a study investigating cognitive functioning in cardiac arrest survivors four years after arrest, Buanes et al. (2015) found short-term memory impairment in more than 25% of participants. Similar results have yielded impaired verbal memory deficits for patients with even brief hypoxic periods (Stamenova et al., 2018).

Neuroimaging Findings in Pediatric Brain Injury

To our knowledge, there is no current literature using volumetric measurement of brain structures to assess potential damage in children who have undergone ECMO. However, other forms of neuroimaging identify neural abnormalities present in ECMO-treated infants. For example, von Allmen et al. (1992) found neuroimaging abnormalities in 78% of the studied ECMO-treated neonates, with major lesions associated with poor neurodevelopmental outcomes. Other studies show similar results, citing intracranial hemorrhage and infarction as major contributory factors in long-term functional deficits (van Heijst, Amerik, & IJsselstijn, 2014; Vaucher, Dudell, Bejar, & Gist, 1996). Studies assessing gray and white matter changes in other pediatric populations, such as epilepsy and traumatic brain injury (TBI), have promising results. In a recent meta-analysis of 20 independent studies totaling 291 children with TBI and 465 healthy controls, it was found that axonal damage was increased in most white matter tracts in the short-term, post-TBI (i.e. tracts had greater myelination and low diffusivity immediately following the injury), with significantly decreased anisotropy in the medium- to long-term (i.e. more diffuse water flow indicating potential damage; Roberts, Mathias, & Rose, 2014). Additionally, Wilde et al. (2011) found that decreased white matter integrity of the frontal lobes was associated with longer reaction times on an item recognition task in a sample of children with TBI. Because previous studies involving pediatric patients both with ECMO treatment and other acquired brain injuries have shown physiological and psychological symptoms, it is probable cerebral abnormalities exist in white and gray matter brain regions.

Cortical Thickness

Cortical thickness is a measurement that detects inner and outer surfaces of the cortical gray matter, and calculates the thickness as the distance between these two surfaces (Macey et al., 2018). This can be detected using magnetic resonance imaging (MRI) and software that quantifies cortical thickness and sub-cortical volumes (Yadav et al., 2017). In an adult brain, reduced cortical thickness is a marker that may indicate injury severity, though this is less studied in pediatric brains that are still developing and maturing (Bigler et al., 2016). Cortical changes have been shown in several pediatric populations following brain injury or illness. In a sample of pediatric patients suffering from obstructive sleep apnea (OSA), Macey et al. (2018) found regions of both cortical thinning and cortical volume increases, likely indicating disruption in the typical neuronal development processes in a maturing brain. Specifically, significant cortical thinning was present in the superior frontal, ventral medial prefrontal, and superior parietal cortices, with thickening in the bilateral precentral gyrus, mid-to-posterior insular cortices, left central gyrus, and right anterior insula cortex (Macey et al., 2018). Similar studies involving pediatric OSA reveal additional alterations of cortical matter and neurochemicals, including changes in the limbic system, subcortical, and brainstem regions, which heavily influence cognition and mood (Philby et al., 2017; Macey et al., 2002; Macey et al., 2008; Kumar et al., 2014; Yadav et al., 2014). This is particularly relevant to the current study, as OSA is characterized by intermittent hypoxia similar to what is observed in children who have undergone ECMO treatment. The frontal lobe has been shown to be vulnerable to hypoxic injury and can incur atrophy in several areas, particularly in the superior frontal, and to a lesser degree in the middle frontal, and medial orbitofrontal areas of the brain (Philby et al., 2017; Chan et al., 2014; Macey et al., 2002). Similarly, diffuse injury sustained in traumatic brain injury shows decreased gray and white matter volumes in the frontal lobe (Wilde et al., 2005). These hypoxic episodes may cause a disruption of typical neuronal maturation, and lead to volume reduction or other abnormalities during cortical development (Macey et al., 2018). Studies involving patients with cyanotic heart disease have yielded similar results. Cyanotic heart disease refers to a congenital defect that changes the way blood flows through the heart and lungs, bypassing the lungs to receive oxygen, and causing non-oxygenated blood to be distributed to the rest of the body. This causes decreases in oxygen levels in the body and can have severely negative ramifications on the patient. This is particularly relevant to our current study, as patients with cyanotic congenital heart disease can cause instances of hypoxemia, for which many undergo ECMO treatment (Imamura et al., 2004). Children with congenital cyanosis have been found to have global gray matter volume reduction, particularly in the basal ganglia, as well as decreased cortical thickness in the frontal, parietal, and temporal lobes when compared with healthy controls (Salama et al., 2016). This is especially salient to our study, as brain volume loss also correlated with levels of oxygen saturation, which is a concern both prior to and during ECMO. Changes in cortical thickness have been recognized in multiple other pediatric clinical samples including TBI, HIV, Autism, and even learning disabilities and ADHD (Dennis et al., 2017; Yadav et al., 2017; Moore, D'Mello, McGrath, & Stoodley, 2017; Stoodley, 2014), indicating that it is a reliable and valid measure for distinguishing gray matter changes in the cortices. In the current study, we specifically investigated cortical thickness and gray matter changes in the frontal regions of the brain and hippocampus based upon previously studied regions of interest in brain-injured pediatric populations, which are discussed below.

Association Between Neuroimaging and Cognition

Neuroimaging has been an increasingly valuable tool for detecting brain abnormalities, as well as identifying neural networks and activity during both resting states and physically or cognitively-demanding tasks (Schroeder, Weiss, Procissi, Disterhoft, & Wang, 2016). This allows investigation of individual differences in brain-behavior relationships and the neural underpinnings of cognition and behavior (Vuoksimaa et al., 2016). MRI scanning and processing gives us the ability to focus on brain characteristics such as gray and white matter volumes, cortical thickness, size, and shape, and their interactions with variables such as gender, age, and cognitive performance (Watson et al., 2016). Lesion studies and functional and resting state imaging show a strong link to anatomy and specific cognitive functions (Allen, Tranel, Bruss, & Damasio, 2006). Using regions of interest (ROIs) mapping, research has identified regional correlates for different cognitive domains, enabling the ability to predict which functional abilities are likely to be affected by brain damage (Vuoksimaa et al., 2016).

As noted in previous sections, the hippocampus is particularly vulnerable to oxygen deprivation, whether by direct hypoxia or ischemic injury (i.e., reduction in blood flow). Research investigating hippocampal damage in relation to neuropsychological testing reveals a correlation between gray and white matter volume and anterograde and retrograde memory tests in a group of anoxic patients (Allen et al., 2006). Studies investigating cognition following brain injury report similar markers of underlying neuropathology and cognitive function (Oehr & Anderson, 2017; Dennis et al., 2017). Attentional aspects of executive function are associated with the dopaminergic system and activation in the frontoparietal network, cerebellum, cingulate gyrus, and the ventral striatum (Xuan et al., 2016). Studies investigating the neuroimaging correlates of executive functioning found associations in the frontal, parietal, and cerebellar lobes with well-known and standardized neuropsychological measures such as the Trail Making Test, Stroop, Digit Span, and Wisconsin Card Sorting Test (Nowrangi, Lyketsos, Rao, & Munro, 2014). Thus, given the hypothesis that children with ECMO may sustain diffuse and widespread hypoxic damage, it is suspected that multiple cognitive domains—primarily memory, executive functioning, and attention—may be negatively impacted.

Significance of Study

Although several studies have investigated morbidity and mortality rates of pediatric ECMO patients, few have examined specific cognitive profiles, and even fewer have incorporated magnetic resonance imaging in relation to neuropsychological outcome with behavioral, emotional, or social functioning. Because ECMO is most commonly administered to infants and young children, there are very few studies investigating cognitive and behavioral effects in school-aged children and adolescents, particularly following a prolonged period after treatment. This is an important contribution to the long-term cognitive picture and potentially gives insight into how ECMO may affect the developing brain over time. Additionally, to our knowledge, there is no existing literature that specifically assessing MR-based metrics of brain morphology, which may help detect potentially atypical neuronal development processes in a maturing brain and how it may relate to cognitive outcomes.

Specific Aims and Hypotheses

The overarching aims of this project were to investigate cognitive ability and behavioral functioning in a group of ECMO-treated patients compared to a normative sample, and to examine cortical thickness and hippocampal volume as they relate to cognitive outcome. Specifically, there are two primary research aims for the project:

- **Specific Aim 1:** Evaluate cognitive ability and behavioral functioning in a group of young ECMO-treated patients compared to a normative sample.
    - *Hypothesis 1a:* ECMO subjects will demonstrate significantly poorer performance on measures of cognition, including attention, processing speed, immediate and delayed memory, and executive function relative to the normative sample.

  - *Hypothesis 2b:* ECMO subjects and their parent/guardian will endorse significantly higher rates of behavioral problems, hyperactivity, inattention, and somatic complaints on subjective measures, relative to the normative sample.

- **Specific Aim 2:** Relate hippocampal volume and cortical gray matter integrity to cognitive outcome following ECMO in children with acute respiratory and cardiac illness or injury.
  - *Hypothesis 2a:* ECMO subjects will have significantly decreased hippocampal volume compared with published normative data.
  - *Hypothesis 2b:* Hippocampal volume will correlate with decreased performance on measures of memory.

Method

Study Design and Procedure

The current project is a series of case studies that was compared against published norms and healthy reference groups. Participants were evaluated at the BYU MRI Research Facility in a single visit. Trained research personnel conducted an informed consent interview and a screening for MRI contra-indications. Structural scans and a resting state functional scan were obtained. For specifications regarding scanning protocol and acquisition, please see below. Status was checked between each scan, and the participant was free to communicate with us at any time during the scan. The entire protocol lasted approximately 30 minutes, and each participant had the option of watching a movie or listening to music to decrease likelihood of movement as well as sustain attention during the scan. Afterward, participants were taken to a private testing room in the MRI Research Facility where they completed a battery of neuropsychological tests; total testing time was less than 1 hour. Participants and/or their parent/guardian completed self- and parent-report questionnaires during and after neuropsychological testing. Following testing, participants were compensated for their time. Total participation time was no more than 2 hours.

Patient Eligibility

The current study investigated the cognitive and behavioral effects of patients who received either veno-venous or veno-arterial ECMO as children or adolescents for acute respiratory and cardiac illness. Due to electronic medical record constraints, we were only able to recruit patients who received ECMO in the last decade.

Inclusion criteria

Participants were included if they received ECMO within the past 10 years, were between the ages of 5-18 at the time of the procedure, and were at least 6 months post-discharge. Inclusion criteria includes ECMO for acute pulmonary illness and acute cardiac illness.

Exclusion criteria

Participants were excluded if ECMO treatment was due to chronic or congenital defects that could potentially confound current cognitive functioning. Participants were also excluded if ECMO was administered before the age of 5, as ECMO in infants is typically due to severe and chronic illness that may independently influence functioning.

Recruitment and Study Duration

Subjects were recruited through Primary Children's Hospital by identifying former patients using the medical record database. Twenty-two potential subjects were identified via electronic medical records as meeting inclusion criteria for the study. They were mailed a postcard inviting them to participate in the study, with a follow-up letter approximately 2-3 weeks following mailing. In total, 10 subjects requested more information, 2 of whom opted out of participation due to scheduling conflicts. Eleven subjects did not respond, and one was deceased, making a total of 8 participants. After the subjects contacted us by phone or email expressing interest, a time was set up to review eligibility and obtain consent. Healthy control subjects were not recruited at this time. Comparison data was used from previously published material and norms for each measure.

Consent

Consent was obtained from all subjects prior to participation, and in the case of minors or dependent adult participants, from the appropriate legal guardian. Participants received a copy of the signed consent form, with an assent form provided to those 12-17 years of age. All participants were compensated for their time at the completion of testing.

Participant Demographics

The total number of participants recruited was 8 (63% female; M age at testing = 16.75, SD = 4.5). Neuropsychological testing and questionnaires detailing behavioral, emotional, and social functioning were completed by all participants. Of the 8 participants, 2 (one male and one female) were excluded from the MRI portion of the study due to metal located in their bodies (bullet fragments and pacemaker). Each patient's electronic medical record was reviewed to collect the following data: diagnosis of medical condition requiring ECMO placement, date of ECMO, whether they required VA or VV catheterization, and number of days on ECMO. For a complete summary of demographic variables, see Table 1.

Table 1

Patient Characteristics

Demographic	(*n*=8)
Gender (Female)	5 (62.5%)
Age at testing	16.75 (4.5)
Age at ECMO	10.63 (4.2)
Time since ECMO (years)	5.75 (1.98)
Length of time on ECMO (days)	10.25 (11.1)
Handedness (Right)	6 (75%)
Medical Diagnosis	
Cardiac Illness	3 (37.5%)
Respiratory Illness	5 (62.5%)
ECMO Type	
Veno-arterial (VA) only	4 (50%)
Veno-venous (VV) only	3 (37.5%)
Veno-venous to Veno-arterial	1 (12.5%)
Ethnicity	
Caucasian	8 (100%)

Assessment Battery

Cognitive measures. The NIH Toolbox Cognition Battery was used to assess the domains of executive function, processing speed, attention, memory, and language. The NIH Toolbox is an iPad administered cognitive battery that has demonstrated developmental sensitivity across the lifespan as well as excellent reliability and convergent validity (Zelazo et al., 2013; Weintraub et al., 2013; Akshoomoff et al., 2014; Bauer & Zelazo, 2014). Although the NIH Toolbox Cognition Battery was originally developed for and validated in the general population, it has promising implications for clinical and research utility, and has demonstrated construct validity by replicating the 5-factor structure (reading, vocabulary, episodic memory, working memory, executive functioning/processing speed) in a sample of participants with acquired brain injury (Tulsky et al., 2017). Specific tasks within the battery are listed below. For summary descriptions of subtests, composite tests, and scoring, see Table 2.

NIH Toolbox Cognition Battery

(a) Processing Speed: NIH Toolbox Pattern Comparison Processing Speed Test. This test measures speed of processing by asking participants to discern whether two side-by-side pictures are the same or not.

(b) Executive and Attention Function: NIH Toolbox Flanker Inhibitory Control and Attention Test and the Dimensional Change Card Sort Test. In the Flanker Test participants are required to focus on a given stimulus while inhibiting attention to other stimuli. Sometimes the peripheral stimuli are in the same direction as the target and sometimes they are in the opposite direction. In the Dimensional Change Card Sort Test Participants are asked to match a series of bivalent test pictures (e.g., yellow balls and blue trucks) to the target pictures, first according to one dimension (e.g., color) and then, after a number of trials, according to the other dimension (e.g., shape).

(c) Working Memory: NIH Toolbox List Sorting Working Memory Test. This test requires immediate recall and sequencing of different visually and orally presented stimuli. Pictures of different foods and animals are displayed with accompanying audio recording and written text (e.g., "elephant"), and the participant is asked to say the items back in size order from smallest to largest, first within a single dimension (either animals or foods, called 1-List) and then on two dimensions (foods, then animals, called 2-List).

(d) Episodic Memory: NIH Toolbox Picture Sequence Memory Test. The participants are asked to recall the sequence of pictures demonstrated over two learning trials; sequence length varies from 6-18 pictures, depending on age.

(e) Language: NIH Toolbox Picture Vocabulary Test and Oral Reading Recognition Test. In the Picture Vocabulary test the respondent is presented with an audio recording of a word and four photographic images on the computer screen and is asked to select the picture that most closely matches the meaning of the word. In the Oral Reading Recognition Test a word is presented on the screen and the participant is asked to read the word as accurately as possible.

Table 2

NIH Toolbox Cognition Battery Subtests

Subtest Name	**Test Description**	**Scoring Implications**
Crystallized Composite	Measures previously learned abilities that are generally intact following acquired brain injury.	Composite score comprises of Picture Vocabulary and Oral Reading Recognition subtest scores. Higher score indicates better functioning.
Picture Vocabulary	Measures receptive vocabulary. Participants are asked to select the picture that best matches the word. Task is administered in a computer-adaptive format.	Score reflects the number of correct responses; higher score indicates better functioning.
Oral Reading Recognition	Measures verbal knowledge. Participants are asked to read and pronounce letters and words.	Score reflects number of letters and words correctly pronounced; higher score indicates better functioning.
Fluid Composite	Measures ability to reason and solve novel problems, independent of prior learned knowledge. Fluid intelligence is generally more sensitive to acquired brain injury.	Composite score comprises of Flanker Inhibitory Control and Attention, List Sorting, Dimensional Charge Card Sort, Pattern Comparison, and Picture Sequence subtest scores. Higher score indicates better functioning.
Flanker Inhibitory Control and Attention	Measures executive functioning, primarily inhibitory control. Participant must focus on given stimulus while inhibiting attention to the stimuli flanking it.	Score reflects combination of accuracy and reaction time; higher score indicates better performance.
List Sorting Working Memory	Measures working memory. Participant is asked to recall and accurately sequence orally and visually presented stimuli.	Score reflects correct items for one- and two-list versions (maximum 28); higher score indicates better performance.
Dimensional Change Card Sort	Measures cognitive flexibility and attention. Participants are required to match a series of bivalent pictures.	Score reflects combination of accuracy and reaction time; higher score indicates better performance.
Pattern Comparison Processing Speed	Measures speed of mental processing. Participants are asked to discern between two pictures in a timed task to determine whether the images are the same or different.	Score reflects total number of correct items (maximum 130) completed in 90 seconds; higher score indicates better performance.
Picture Sequence Memory	Measures episodic memory. Participants are asked to reproduce a picture sequence briefly displayed on the screen from memory.	Scores reflect number of correctly identified adjacent pairs over two trials; higher score indicates better performance.

Behavioral, Social, and Emotional Measures

Each participant was asked to fill out self-report forms for the appropriate age levels of available measures. For participants under the age of 18 or dependent adult participants, the parent or guardian was also asked to fill out 3 brief questionnaires for emotional, behavioral, and social functioning: the Behavior Assessment System for Children, Second Edition (BASC-2), the Behavior Rating Inventory of Executive Function (BRIEF), and the Social Skills Improvement System (SSIS). Each measure was administered in a standardized manner and scored with age and gender adjusted norms. Each measure is described briefly below.

The *Behavior Assessment System for Children, Second Edition (BASC-2)* is a questionnaire developed to evaluate the behavior and self-perception of children and adolescents (Reynolds & Kamphaus, 2004). It was designed as a screening tool for classification of emotional and behavioral disorders in children, as well as identification of differential diagnoses. Specifically, the BASC-2 is intended to look at both adaptive and maladaptive behaviors and identify the likelihood of emotional and behavioral diagnoses common in childhood (Chee Soon, 2007). Clinical subscales of the BASC-2 identify potential difficulties in the areas of aggression, anxiety, attention problems, conduct problems, and learning problems compared to a normative sample (Chee Soon, 2007). For the current study, we administered the BASC-2 Self-Report of Personality (SRP) for all participants, and the BASC-2 Parent Rating Scale (PRS) to parents or guardians of participants under the age of 18. The SRP has forms for three age levels: child (ages 8-11), adolescent (ages 12-21), and young adult (ages 18-25). This measure is comprised of True/False questions and a 4-point response scale (*Never, Sometimes, Often, Almost Always)*. The PRS measures adaptive skills and problem behaviors in the home environment. Similarly, the PRS is formatted into child and adolescent forms and uses a 4-point Likert scale (Reynolds &

Kamphaus, 2004). Each form takes approximately 20-30 minutes to complete. Raw scores are converted into T-scores which are used to indicate scores that warrant further attention, clinically. T-scores that are 59 and below are considered "Average"; T-scores of 60-69 are considered "At Risk", indicating behavior that may warrant clinical attention; and T-scores of 70 and above are considered "Clinically Significant" and indicate a level of maladjustment that warrants clinical attention (Schraegle & Titus, 2017). There has been research demonstrating the BASC-2 as a well-established assessment tool with reliability and validity in pediatric clinical populations (Reynolds & Kamphaus, 2004; Guilfoyle, Wagner, Smith, & Modi, 2012; Bender, Auciello, Morrison, MacAllister, & Zaroff, 2008).

The BASC-2 measures of behavior and emotion that were of interest in the current study were internalizing problems (anxiety, depression, and somatization), and externalizing problems (hyperactivity, aggression, and conduct problems). We also looked at the BASC-2 Adaptive Skills Composite (ASC) as a measure of social functioning, which is described in the section below. These scales have been shown to be a sensitive screening and identification measure of psychological symptoms in children with multiple medical conditions of childhood and adolescence including mild traumatic brain injury (mTBI), epilepsy, and pediatric multiple sclerosis populations. Literature has also shown a strong correlation between clinically significant behavior problems and cognitive functioning in these populations, including higher rates of anxiety, depression, and more psychosocial problems including isolation and low self-esteem (Guilfoyle et al., 2012). As noted above, there are no known studies utilizing the BASC-2 in pediatric ECMO populations. However, research completed in similarly relevant samples indicate its utility for detecting emotional and behavioral changes in other pediatric health populations (Burnett et al., 2018). In the previously mentioned study investigating outcomes of dexamethasone-treated children, significant differences were found for the Behavioral Symptoms Index and Adaptive Skills, with the dexamethasone-treated children having more difficulty than the group of healthy controls (Crotty et al., 2012).

Social Skills Measures

The *Social Skills Improvement Scale (SSIS)* is a multi-rater, targeted assessment of student social skills, problem behaviors, and academic competence that can affect relations with peers and teachers and performance in the school setting. The measure consists of teacher, student, and parent rating forms to obtain comprehensive information regarding the student's functioning in the school, home and community. Forms are available for three developmental levels: preschool, kindergarten through 6th grade, and grades 7 through 12. The measure takes approximately 10-25 minutes to complete (Crowe, Beauchamp, Catroppa, & Anderson, 2011). It has been shown to have good reliability and validity as a comprehensive assessment tool for measuring social skills (Gresham & Elliot, 2008). The SSIS evaluates the following domains:

a) Social Skills: includes subdomains of communication, cooperation, assertion, responsibility, empathy, engagement, and self-control.
b) Competing Problem Behaviors: includes subdomains of externalizing behavior, bullying, hyperactivity/inattention, internalizing, and Autism Spectrum.
c) Academic Competence: includes subdomains of reading achievement, math achievement, and motivation to learn.

The SSIS, along with its former version, the Social Skills Rating System (SSRS), is one of the most popular measures of social functioning due to its broad applicability, availability for wide age range, and user-friendly format (Crowe et al., 2011). While this specific measure has not been used with ECMO-treated patients, other measures such as the Child Behavior Checklist

(CBCL) and the Vineland Adaptive Behavior Scales have looked at aspects of social skills with varied results, finding that children with previous ECMO treatment had learning difficulties and were at significant risk for impaired social and adaptive functioning (Parish, Bunyapen, Cohen, Garrison, & Bhatia, 2004; Rais-Bahrami et al., 2000; Madderom et al., 2013). However, there is a general consensus amongst the literature that ECMO samples tend to be significantly heterogeneous, and results tend to vary with no clear and distinguishable pattern that indicate clear functional deficits (Rais-Bahrami et al., 2000).

The scales of interest included in the current study were the Social Skills Scale on the Parent and Student Forms. The Social Skills Scale is a composite of a broad array of prosocial behaviors, and includes the following subscales (Gresham & Elliott, 2008):

a) Communication (e.g., making eye contact when talking, saying “please” and “thank you”)
b) Cooperation (e.g., following rules, completing tasks without bothering others)
c) Assertion (e.g., asking for help when needed, speaking up when there is a problem)
d) Responsibility (respecting others’ property, behaving even when unsupervised)
e) Empathy (e.g. comforting others, relating to others’ feelings)
f) Engagement (e.g., making friends, introducing oneself to others, joining activities)
g) Self-Control (e.g., acting appropriately when upset, staying calm when teased)

As indicated previously, we also used the BASC-2 Adaptive Skills Composite (ASC) as a measure of social functioning, including the following scales: Adaptability, Activities of Daily Living, Functional Communication, Social Skills, Leadership, and Study Skills. This composite was chosen due to its breadth in identifying areas commonly impacting social functioning. As described in Reynolds & Kamphaus (2004), this composite “summarizes appropriate emotional expression and control, daily living skills inside and outside the home, and communication skills as well as prosocial, organizational, study and other adaptive skills" (p. 67). The scales that comprise this composite, as outlined by Reynolds & Kamphaus (2004) are summarized below.

a) Adaptability scale: assesses one's ability to adjust to change, or shift from task to task. (E.g., how quickly the child recovers following a setback, or how easily they can be soothed when upset.)

b) Activities of Daily Living scale: assesses adaptive-behavior deficits. (E.g., safety behaviors, routine-following, organization.)

c) Functional Communication scale: assesses ability to communicate and express ideas clearly to others. (E.g., ability to communicate via telephone.)

d) Social Skills scale: measures interpersonal social functioning. (E.g., encouraging and offering to help others, congratulating others, saying "please" and "thank you".)

e) Leadership scale: assesses competencies in the community and school settings. (E.g., joining clubs or social groups, problem-solving in group setting, giving good suggestions, decision-making.)

f) Study Skills scale: assesses school integration and adaptation. (E.g., analyzing a problem before solving it, achievement motivation, note-taking capabilities.)

Executive Functioning Self-Report Measure

Executive functioning consists of cognitive and behavioral skills including processes involved in planning, initiation, and execution of goal-oriented behavior (El-Ad & Lavie, 2005). The *Behavior Rating Inventory of Executive Function (BRIEF)* is an 86-item questionnaire that measures executive functioning such as planning and organization, attention, initiation, problem-solving, and emotional regulation skills. Each participant was asked to fill out self-report forms for the appropriate age level. For participants under the age of 18 or dependent adult participants, the parent or guardian was asked to fill out the parent/caregiver form. Each form takes approximately 10-15 minutes to complete (Gioia, 2000). Literature on the BRIEF indicates that the measure can identify individuals with behavioral difficulties and impaired executive functioning with high validity and reliability (Gioia, 2000). No known research has examined the BRIEF in a pediatric ECMO population. However, executive dysfunction has been shown in pediatric populations with obstructive sleep apnea, sleep-disordered breathing, and attempted hangings, all of which are characterized by hypoxic and/or ischemic injury similar to what we may see in ECMO-treated patients. Deficits in these studies were seen in processing speed, attention, working memory, and problem solving (El-Ad & Lavie, 2005; Quan et al., 2006; Zabel, Slomine, Brady, & Christensen, 2005).

This study utilized the BRIEF to measure executive abilities, with a particular interest in attention and processing speed, in children who have undergone ECMO treatment. Data analyses utilized the Behavioral Regulation Index (BRI) and the Metacognition Index (MI) on parent and self-report. The BRI measures cognitive flexibility and the ability to mentally shift-set, as well as regulate emotions and behaviors through appropriate inhibitory control (Gioia, 2000). The MI measures the ability to plan, organize, initiate, and self-monitor while actively problem-solving in multiple contexts (Gioia, 2000).

Image Acquisition

All MRI scans were acquired on a 3.0T Siemens TIM-Trio MRI scanner at the BYU Magnetic Resonance Imaging Research Facility. We used a 32-channel, receive-only, RF head coil. Structural scans were sagittal 3D MPRAGE T1-weighted images with 1x1x1 mm isotropic resolution (echo time = 2.26 ms, repetition time = 1900 ms, flip angle = 9, field of view = 250 mm, matrix = 256x160, slice thickness = 1.0 mm, number of slices = 160). Scans were acquired according to standard protocols.

Image Analysis

Cortical reconstruction and volumetric segmentation was performed with the FreeSurfer image analysis suite, which is documented and freely available for download online (http://surfer.nmr.mgh.harvard.edu/). The technical details of these procedures are described in prior publications (Dale, Fischl, & Sereno, 1999; Fischl, Liu, & Dale, 2001; Fischl et al., 2002; Han et al., 2006; Jovicich et al., 2006; Reuter, Schmansky, Rosas, & Fischl, 2012). Briefly, this processing includes motion correction and averaging (Reuter, Rosas, & Fischl, 2010) of multiple volumetric T1 weighted images, automated Talairach transformation, segmentation of the hippocampus, (Fischl et al., 2002), tessellation of the gray matter white matter boundary, automated topology correction (Fischl et al., 2001; Segonne, Pacheco, & Fischl, 2007), and surface deformation to optimally place the gray/white and gray/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class (Dale et al., 1999; Dale & Sereno, 1993; Fischl & Dale, 2000). Once the cortical models are complete, a number of procedures can be performed for further data processing and analysis including parcellation of the cerebral cortex into gyral and sulcal units (Desikan et al., 2006; Fischl et al., 2004). This method uses both intensity and continuity information from the entire three-dimensional MR volume to produce representations of cortical thickness, calculated as the closest distance from the gray/white boundary to the gray/CSF boundary at each vertex on the tessellated surface (Fischl & Dale, 2000). Procedures for the measurement of cortical thickness have been validated against manual measurements (Kuperberg et al., 2003; Salat et al., 2004). FreeSurfer morphometric procedures have been demonstrated to show good test-retest reliability across scanner manufacturers and across field strengths (Han et al., 2006; Reuter et al., 2012). For the current study, skull stripping and boundary identification were performed automatically by the program and then manually checked to ensure inclusion of all brain matter. For example, manual edits were required for instances in which the automatic calculation identified gray matter edge in the skull region. Other corrections included minor boundary issues to the pial matter and less frequently, the white matter. There were four bilateral, hypothesis-driven gray matter ROIs for this study: superior frontal, rostral middle frontal, caudal middle frontal, and medial orbitofrontal. ROIs were identified using the Desikan-Killiany atlas (Desikan et al., 2006) within FreeSurfer.

Results

Neuropsychological Data Cleaning

Normative standards corrected for demographic were used to detect deviations from expected performance levels as outlined by Casaletto et al. (2015). In regards to the self- and parent-report questionnaires, data were screened for invalid responses including overly negative or inconsistent responses, along with missing values and data entry errors. Built-in validity measures demonstrated valid profiles for each participant, with the exception of one raised ‘l scale’ on the BASC-2 self-report, indicating that this participant had a tendency to give an extremely positive self-representation and should be interpreted with caution. Self-report scores were compared with parent-report scores on similar questions and domains, and were determined to be similar in nature; therefore, we consider responses to be an accurate representation of all participants.

Table 3 describes the classification for all scales, using the guidelines depicted in the publisher’s manuals for each measure (Reynolds & Kamphaus, 2004; Gioia, Isquith, Guy, &

Kenworthy, 2000; Gresham & Elliot, 2008; Weintraub et al., 2013). Wechsler classification for standard scores was used for the NIH Toolbox and SSIS interpretation (Weiss, Saklofske, Prifitera, & Holdnack, 2006).

Table 3

Score Classification by Measure

BASC-2 Scale and Composite Score Classification		
T-Score Range	Adaptive Scales	Clinical Scales
70 and above	Very high	Clinically Significant
60-69	High	At-Risk
41-59	Average	Average
31-40	At-Risk	Low
30 and below	Clinically Significant	Very Low
BRIEF Scale and Composite Score Classification		
T-Score Range	Scale Classification	
70 and above	Clinically elevated	
65-69	Moderately elevated	
60-64	Mildly elevated	
41-59	Average	
NIH Toolbox and SSIS (Wechsler Standard Score Classification)		
Standard Score	Scale Classification	
130 and above	Very Superior	
121-129	Superior	
111-120	High Average	
90-110	Average	
80-89	Low Average	
70-79	Borderline	
69 and below	Impaired	

Participant 1

History and Background

Participant 1 was a 12-year-old, right-handed, Caucasian female who received veno-venous ECMO at the age of 5. She was initially admitted for pneumonia, which then progressed to respiratory failure. Total length of time on ECMO was 7 days. At the time of testing, she was 6 years post-procedure. Qualitative MRI inspection for Participant 1 was within normal limits with no gross abnormalities.

Neuropsychological Functioning

Performance on the NIH Toolbox Cognition Battery revealed strengths in several areas, with superior range scores in vocabulary, working memory, and oral reading. She showed relative weakness in areas of inhibitory control and attention and picture sequence memory, though still scoring in the average range. Overall, crystallized intelligence was in the superior range (SS = 134), and fluid intelligence was in the high end of the average range (SS = 115). Total Composite Score for cognitive functioning was in the superior range (SS = 130).

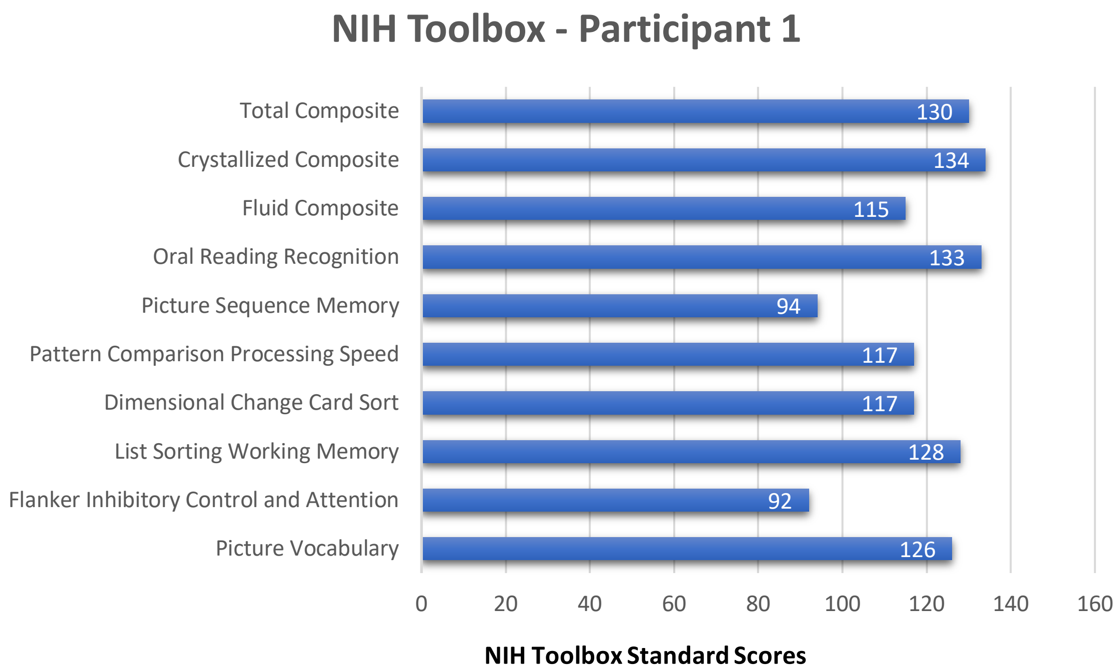

Figure 1. NIH Toolbox Scores for Participant 1.

Behavioral, Emotional, and Social Functioning

On the BRIEF Self-Report, Participant 1 rated her own functioning in the average range across all domains and was within normal limits for behavioral regulation, metacognition, and global executive functioning. In contrast, the BRIEF Parent Form revealed a mildly elevated Metacognition Index, moderately elevated Global Executive Composite, and clinically significant Behavioral Regulation Index. This implies that Participant 1 may have difficulty with inhibitory control, emotional modulation, and set-shifting, but suggests that her ability to cognitively self-manage tasks and monitor performance is generally intact.

On the BASC-2 Self-Report, Participant 1 similarly rated her behavioral and emotional functioning in the average range, while the Parent Report revealed mild elevations in Attention Problems and Behavioral Symptoms. Scores on the Internalizing Problems scale fell within the

At-Risk range, with elevations in depressive and somatic symptoms.

On the SSIS Student Report, Participant 1 scored in the average range for both Social Skills and Problem Behaviors, implying that she perceives herself as having socially acceptable learned behaviors used to promote positive interactions. Notably, she rated herself on the higher end of average for Social Skills (SS = 113), while her parent rated her significantly lower on the same scale (SS = 86), though still in the average range. Parent report for Problem Behaviors was within the expected limits, indicating that Participant 1 is not demonstrating significantly more problem behaviors than others her age.

Table 4

Participant 1 Behavioral, Emotional, and Social Scores

	BRIEF Self Report T-Scores	**BRIEF Parent Form T-Scores**
Behavioral Regulation Index	47	72
Metacognition Index	43	63
Global Executive Composite	45	67
	BASC-2 Self Report T-Scores	**BASC-2 Parent Report T-Scores**
School Problems	50	-
Inattention/Hyperactivity	41	-
Emotional Symptoms Index	43	-
Internalizing Problems	44	64
Attention Problems	41	60
Externalizing Problems	-	53
Adaptive Skills	-	50
Behavioral Symptoms Index	-	60
	SSIS Student Report Standard Scores	**SSIS Parent Report Standard Scores**
Social Skills	113	86
Problem Behaviors	95	106

Participant 2

History and Background

Participant 2 was a 19-year-old, left-handed, Caucasian male with a history of Down syndrome and associated developmental delay and history of learning disorder. He was originally admitted to the Emergency Department for H1N1 influenza at the age of 15, which then progressed to acute respiratory distress syndrome with deconditioning and left pneumothorax. He initially received veno-venous ECMO, which was later converted to veno-arterial. Total length of time on ECMO was 7 days. At the time of testing, he was 3 years post-procedure. Due to history of developmental and learning delays, Participant 2 was not able to complete subjective measures of behavioral, emotional, and social functioning. Subjective measurements for the current assessment are limited to parent report. Qualitative MRI inspection for Participant 2 was notable for significant atrophic changes including enlarged ventricles, thinning in the corpus callosum, and hippocampal atrophy, which are consistent with cerebral changes found in patients with Down Syndrome.

Neuropsychological Functioning

Participant 2 demonstrated broad impairment across most neuropsychological domains. He showed relative strength in areas of crystallized intelligence including picture vocabulary, oral reading, and picture sequence memory, though scores were still well below the expected level given his age. Relative weakness was demonstrated in areas of fluid intelligence, with impairment in processing speed, executive function, and attention. Overall, crystallized intelligence (SS = 61), fluid intelligence (SS = 34), and Total Composite Score for cognitive functioning (SS = 39) were all in the impaired range. Notably, due to patient's history of Down

Syndrome, premorbid levels of functioning were likely also impaired, given the prevalence of mild to moderate intellectual disability in patients with this disorder.

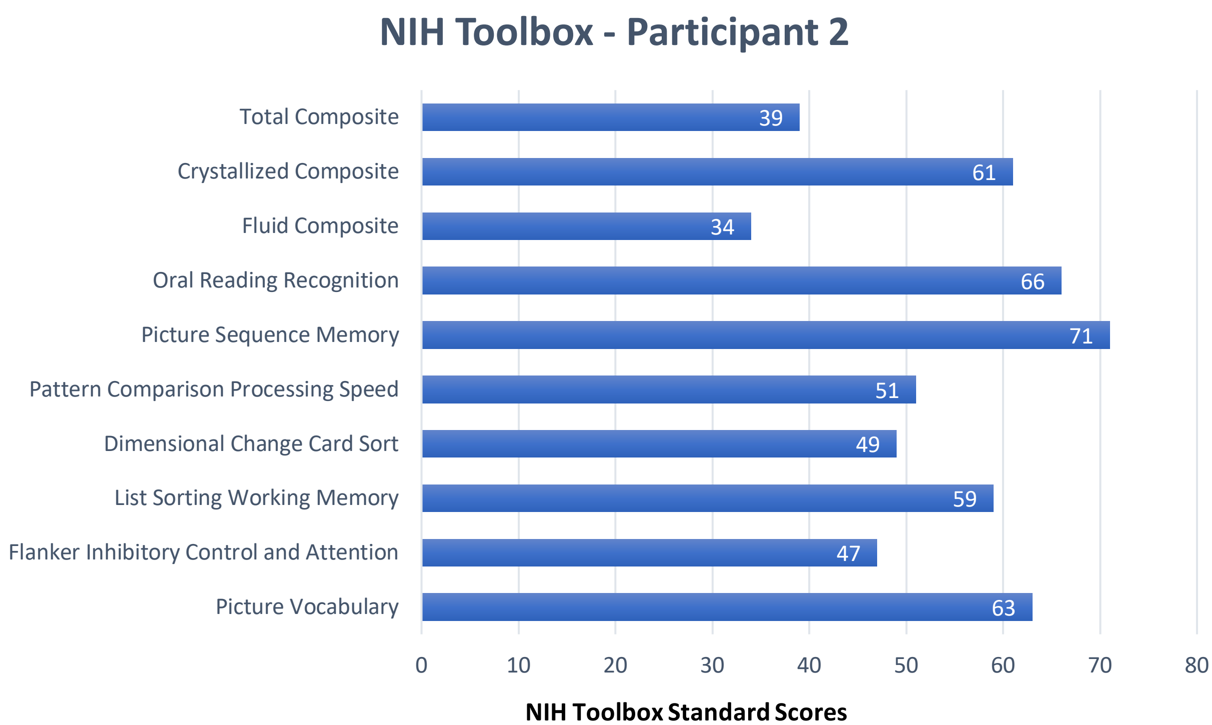

Figure 2. NIH Toolbox Scores for Participant 2.

Behavioral, Emotional, and Social Functioning

The BRIEF Parent Form revealed a significantly elevated Metacognition Index and Global Executive Composite, while his Behavioral Regulation Index was within the average range. This indicates that while Participant 2 generally has appropriate self-regulation and emotional control, he has difficulty with cognitive self-management, performance monitoring, and problem-solving, and may have overall difficulty with multiple areas of executive function.

The BASC-2 Parent Report revealed a Behavioral Symptoms Index in the At-Risk range, with scores on the Externalizing Problems in the Clinically Significant range, with elevations in hyperactivity, conduct problems, aggression, atypicality, and withdrawal. Adaptive Skills were rated well below average, indicating difficulty with social skills, leadership ability, activities of daily living, and functional communication.

On the SSIS Parent Report, Social Skills were well below average (SS = 64), indicating difficulty with prosocial skills. Problem Behaviors were significantly elevated (SS = 133), indicating difficulty with a broad array of behaviors that may interfere with an individual's social skill development.

Table 5

Participant 2 Behavioral, Emotional, and Social Scores

	BRIEF Parent Form T-Scores
Behavioral Regulation Index	57
Metacognition Index	76
Global Executive Composite	70
	BASC-2 Parent Report T-Scores
Internalizing Problems	46
Attention Problems	58
Externalizing Problems	70
Behavioral Symptoms Index	67
Adaptive Skills	30
	SSIS Parent Report Standard Scores
Social Skills	64
Problem Behaviors	133

Participant 3

History and Background

Participant 3 was a 22-year-old, right-handed, Caucasian male who received veno-venous ECMO at the age of 14 for respiratory failure following an accidental gunshot wound to the stomach. Total length of time on ECMO was 2 days. At the time of testing, he was 8 years post-procedure. Because this participant had bullet fragments remaining in his stomach, he was unable to participate in the MRI portion of testing. Due to patient's age, SSIS and parent report forms were not administered.

Neuropsychological Functioning

Participant 3 demonstrated average performance in most cognitive domains, with particular strength in the area of processing speed, and relative weakness in picture sequence memory. Scores in oral reading, vocabulary, attention, working memory, and executive functioning were all in the average range compared to same-aged peers. Overall, crystallized intelligence (SS = 95), fluid intelligence (SS = 104), and Total Composite Score for cognitive functioning (SS = 99) were all in the average range.

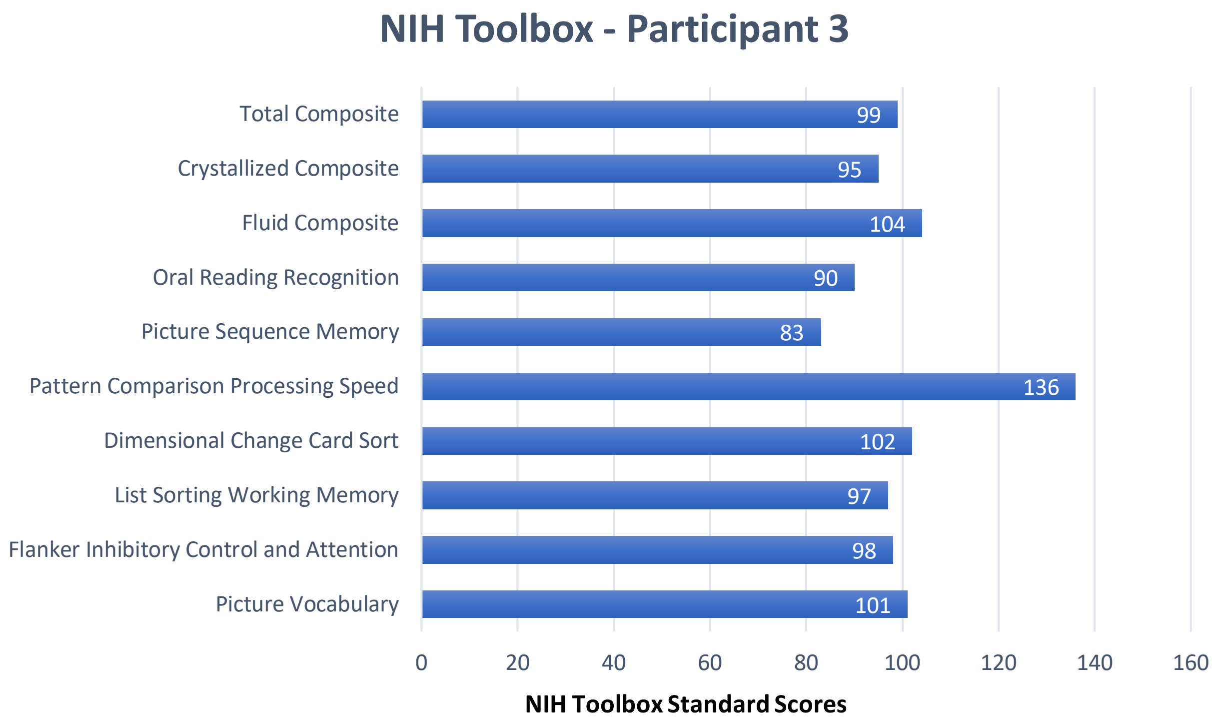

Figure 3. NIH Toolbox Scores for Participant 3.

Behavioral, Emotional, and Social Functioning

On the BRIEF Self-Report, Participant 3 rated his functioning in the average range across all domains and was within normal limits for behavioral regulation, metacognition, and global executive functioning, indicating intact overall executive functioning.

On the BASC-2 Self-Report, results were variable, with average scores in Internalizing Problems and Attention Problems, At-Risk scores in Interpersonal Relations, Inattention/Hyperactivity Composite, and Personal Adjustment Composite, and below average scores on the Emotional Symptoms Index. In particular, Participant 3 showed significantly elevated scores in somatization, hyperactivity, and sensation seeking.

Table 6

Participant 3 Behavioral and Emotional Scores

	BRIEF Self Report T-Scores
Behavioral Regulation Index	53
Metacognition Index	53
Global Executive Composite	53
	BASC-2 Self Report T-Scores
Inattention/Hyperactivity Composite	69
Emotional Symptoms Index	37
Internalizing Problems	47
Attention Problems	53
Interpersonal Relations	66
Personal Adjustment Composite	69

Participant 4

History and Background

Participant 4 was a 21-year-old, right-handed, Caucasian female who received veno-arterial ECMO at the age of 13 for acute respiratory distress syndrome. Total length of time on ECMO was 6 days. At the time of testing, she was 8 years post-procedure. Due to patient's age, SSIS and parent report forms were not administered. Qualitative MRI inspection for Participant 4 was within normal limits with no gross abnormalities.

Neuropsychological Functioning

Participant 4 demonstrated average performance in most cognitive domains, with particular strength in the area of processing speed, and relative weakness in attention and inhibitory control. Scores in oral reading, vocabulary, picture sequence memory, working memory, and executive functioning were all in the average range compared to same-aged peers. Overall, crystallized intelligence (SS = 98), fluid intelligence (SS = 102), and Total Composite Score for cognitive functioning (SS = 100) were all in the average range.

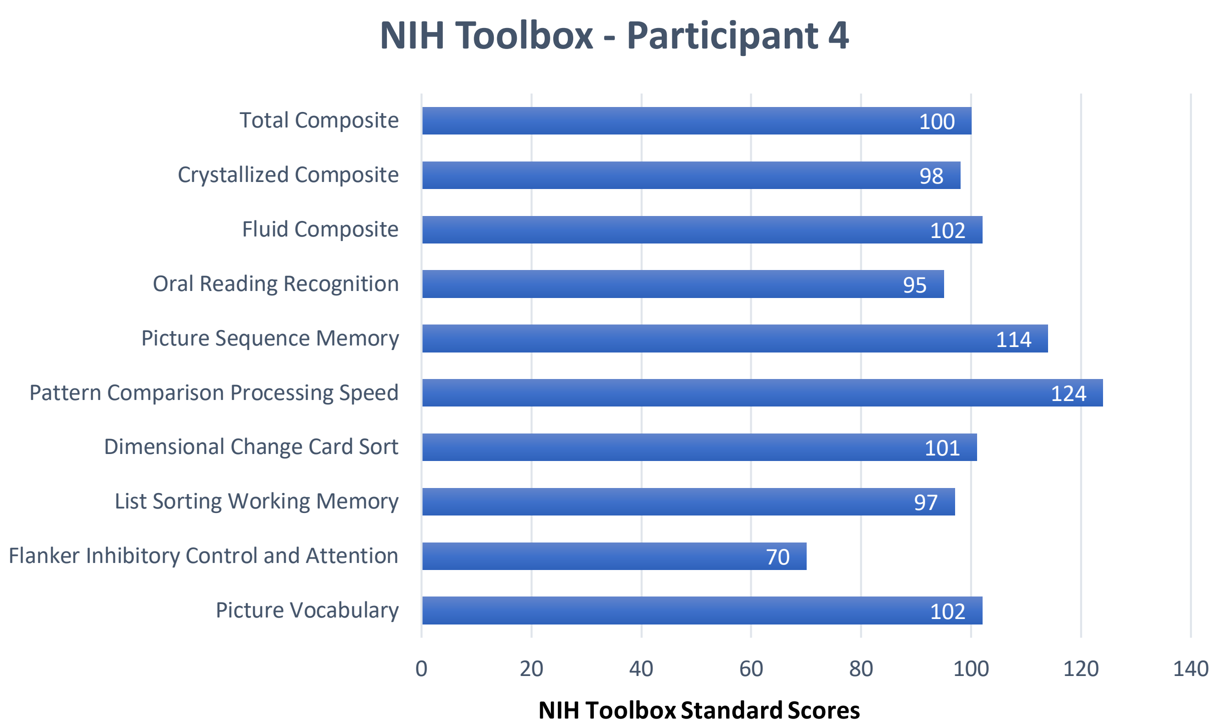

Figure 4. NIH Toolbox Scores for Participant 4.

Behavioral, Emotional, and Social Functioning

On the BRIEF Self-Report, Participant 4 rated her functioning in the average range across all domains and was within normal limits for behavioral regulation, metacognition, and global executive functioning, indicating intact overall executive functioning.

Similarly, on the BASC-2 Self-Report, Participant 4 rated herself in the average range across all areas, reporting typical functioning in attention, emotional, and interpersonal skills.

Table 7

Participant 4 Behavioral and Emotional Scores

	BRIEF Self Report T-Scores
Behavioral Regulation Index	53
Metacognition Index	44
Global Executive Composite	47
	BASC-2 Self Report T-Scores
Inattention/Hyperactivity Composite	48
Emotional Symptoms Index	52
Internalizing Problems	50
Attention Problems	50
Interpersonal Relations	55
Personal Adjustment Composite	51

Participant 5

History and Background

Participant 5 was a 21-year-old, right-handed, Caucasian female who received veno-arterial ECMO at the age of 15 for myocarditis and cardiogenic shock. Notably, at discharge, she had also been formally diagnosed with anoxia. Total length of time on ECMO was 8 days. At the time of testing, she was 6 years post-procedure. Due to patient's age, SSIS and parent report forms were not administered. Qualitative MRI inspection for Participant 5 was notable for history of right basal ganglia stroke.

Neuropsychological Functioning

Performance on the NIH Toolbox Cognition Battery revealed variable performance with relative strength on tasks of crystallized intelligence, such as picture vocabulary and oral reading, though scores in these areas were still in the average range. She showed relative weakness in areas of fluid intelligence including inhibitory control and attention, processing speed, and picture sequence memory, with scores in the impaired to borderline impaired range. Executive functioning and working memory were in the average range. Overall, crystallized intelligence was in the average range (SS = 108), and fluid intelligence was in the borderline impaired range (SS = 71). Total Composite Score for cognitive functioning was in the low end of the average range (SS = 88).

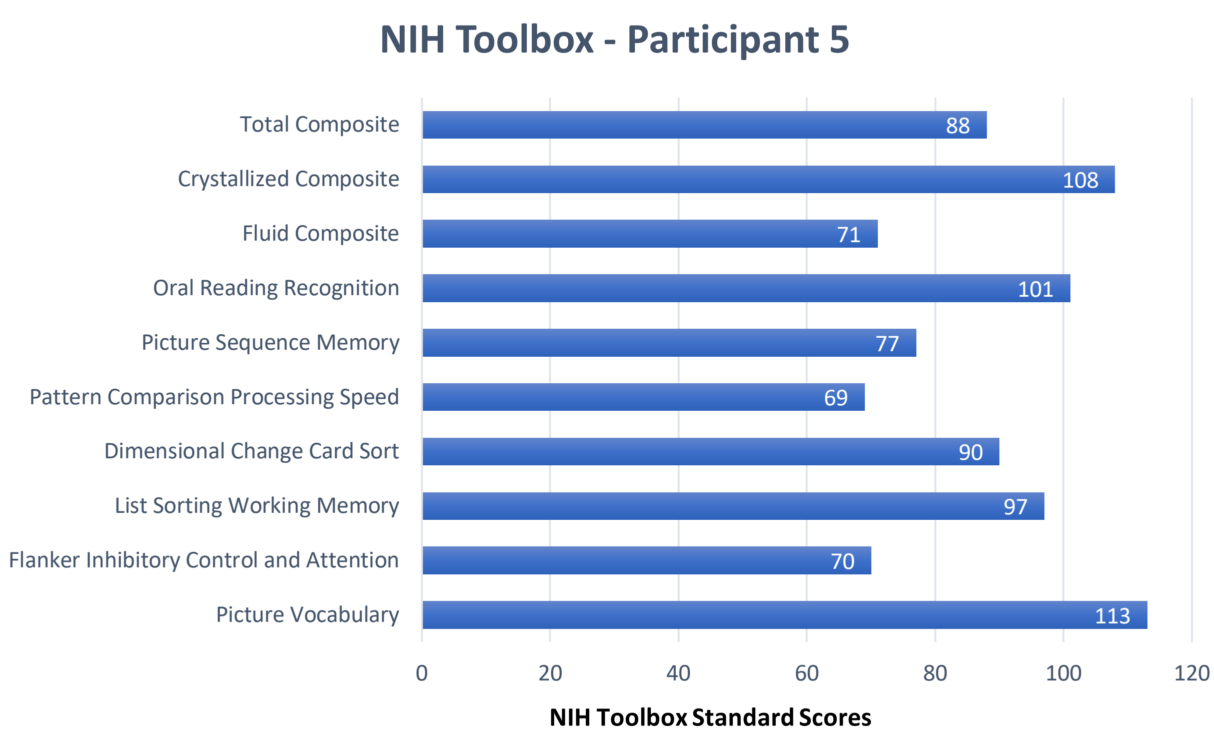

Figure 5. NIH Toolbox Scores for Participant 5.

Behavioral, Emotional, and Social Functioning

On the BRIEF Self-Report, Participant 5 rated her functioning in the clinically significant range across all domains and scores were elevated in the areas of behavioral regulation, metacognition, and global executive functioning, indicating concerns with cognitive set-shifting, emotional control, initiation and the ability to self-monitor, and working memory.

On the BASC-2 Self-Report, results were variable, with average scores in Attention and Hyperactivity, significantly elevated scores in Emotional Symptoms and Internalizing Problems, and below average scores in Interpersonal Relations and the Personal Adjustment Composite. In particular, Participant 5 showed significantly elevated scores in social stress, anxiety, depression, sense of inadequacy, somatization, and locus of control. Scores were mildly elevated in the area of alcohol abuse.

Table 8

Participant 5 Behavioral and Emotional Scores

	BRIEF Self Report T-Scores
Behavioral Regulation Index	74
Metacognition Index	70
Global Executive Composite	73
	BASC-2 Self Report T-Scores
Inattention/Hyperactivity Composite	53
Emotional Symptoms Index	81
Internalizing Problems	79
Attention Problems	50
Interpersonal Relations	24
Personal Adjustment Composite	24

Participant 6

History and Background

Participant 6 was an 11-year-old, right-handed, Caucasian male who received veno-arterial ECMO at the age of 5 for cardiomyopathy. Total length of time on ECMO was 10 days. At the time of testing, he was 5 years post-procedure. Qualitative MRI inspection for Participant 6 was notable for enlarged right, lateral ventricle.

Neuropsychological Functioning

Performance on the NIH Toolbox Cognition Battery revealed variable performance with relative strength on tasks working memory and vocabulary, with scores in the superior range. He showed relative weakness in multiple domains including inhibitory control and attention and executive functioning, which were in the borderline impaired range, and processing speed and picture sequence memory, with scores in the low average range. Oral reading was in the average range. Overall, crystallized intelligence was in the average range (SS = 111), and fluid intelligence was in the borderline impaired range (SS = 78). Total Composite Score for cognitive functioning was in average range (SS = 93).

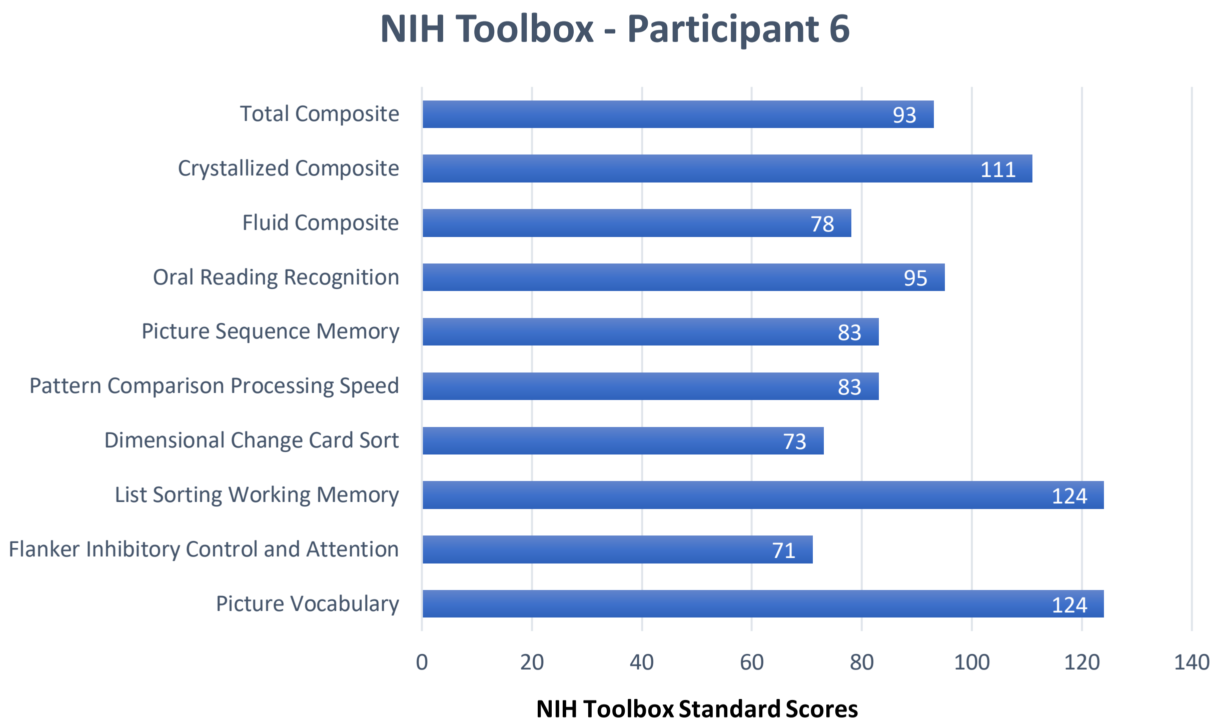

Figure 6. NIH Toolbox Scores for Participant 6.

Behavioral, Emotional, and Social Functioning

On the BRIEF Self-Report and Parent Form, Participant 6 and his parent/guardian both rated his functioning in the average range across all domains and were within normal limits for behavioral regulation, metacognition, and global executive functioning, indicating that overall executive functioning is generally intact.

On the BASC-2 Self-Report, Participant 6 similarly rated his behavioral and emotional functioning generally in the average range, with the exception of the School Problems scale, which was in the At-Risk range with elevated scores in Attitude Towards School. BASC-2 Parent Report were average across all areas, indicating typical emotional and behavioral functioning.

On the SSIS Student Report, Participant 6 scored in the high end of the average range for Problem Behaviors (SS = 113), but below average in Social Skills (SS = 79), indicating difficulty with socially acceptable learned behaviors and positive interactions. Conversely, his parent rated him significantly lower on the Problem Behavior scale (SS = 93), though still in the average range, with much higher parent scores in Social Skills (SS = 114).

Table 9

Participant 6 Behavioral, Emotional, and Social Scores

	BRIEF Self Report T-Scores	**BRIEF Parent Form T-Scores**
Behavioral Regulation Index	62	49
Metacognition Index	54	50
Global Executive Composite	59	49
	BASC-2 Self Report T-Scores	**BASC-2 Parent Report T-Scores**
School Problems	67	-
Inattention/Hyperactivity	56	-
Emotional Symptoms Index	51	-
Internalizing Problems	48	46
Attention Problems	58	43
Externalizing Problems	-	51
Adaptive Skills	-	55
Behavioral Symptoms Index	-	50
	SSIS Student Report Standard Scores	**SSIS Parent Report Standard Scores**
Social Skills	79	114
Problem Behaviors	113	93

Participant 7

History and Background

Participant 7 was a 13-year-old, left-handed, Caucasian female who received veno-arterial ECMO at the age of 10 following an episode of cardiac arrest, during which she also struck her head. Total length of time on ECMO was 5 days. At the time of testing, she was 3 years post-procedure. Because this participant has a pacemaker, she was unable to participate in the MRI portion of testing.

Neuropsychological Functioning

Participant 7 demonstrated broad impairment across most neuropsychological domains. She showed a relative strength in picture vocabulary, though scores were still in the low average range. Relative weakness was demonstrated in areas of fluid intelligence, particularly processing speed, which was severely impaired. Attention, working memory, and executive function were in the impaired range, while oral reading and picture sequence memory were in the borderline impaired range. Overall, crystallized intelligence (SS = 72), fluid intelligence (SS = 32), and Total Composite Score for cognitive functioning (SS = 42) were all in the impaired range.

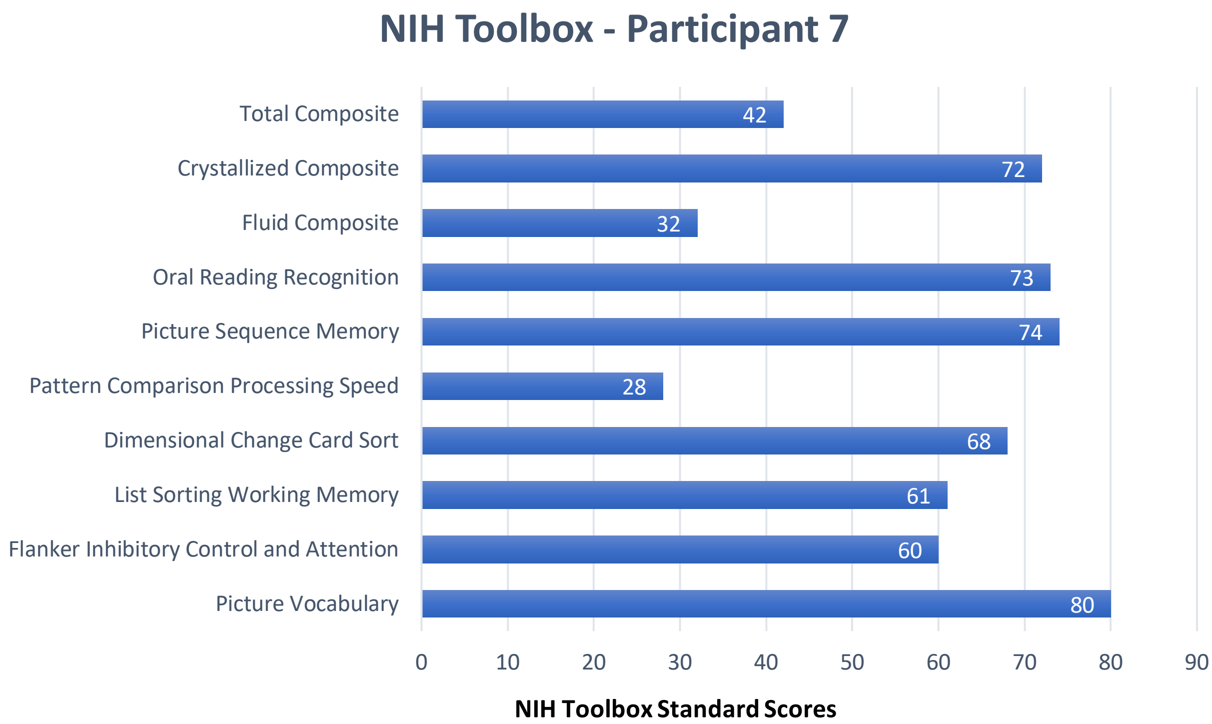

Figure 7. NIH Toolbox Scores for Participant 7.

Behavioral, Emotional, and Social Functioning

On the BRIEF Self-Report and Parent Form, Participant 7 and her parent/guardian both rated her functioning in the average range across all domains and were within normal limits for behavioral regulation and global executive functioning, with a slight elevation in metacognition (T = 66).

On the BASC-2 Self-Report, Participant 7 similarly rated her behavioral and emotional functioning generally in the average range, with the exception of the School Problems and Attention Problems scales, which were slightly below the expected range. BASC-2 Parent Report were average across all areas, indicating typical emotional and behavioral functioning.

On the SSIS Student Report, Participant 7 scored in the high average range for Social Skills (SS = 119), and average in Problem Behaviors. SSIS Parent Report indicated average scores for both Problem Behaviors and Social Skills.

Table 10

Participant 7 Behavioral, Emotional, and Social Scores

	BRIEF Self Report T-Scores	**BRIEF Parent Form T-Scores**
Behavioral Regulation Index	49	60
Metacognition Index	56	66
Global Executive Composite	53	65
	BASC-2 Self Report T-Scores	**BASC-2 Parent Report T-Scores**
School Problems	36	-
Inattention/Hyperactivity	43	-
Emotional Symptoms Index	43	-
Internalizing Problems	53	56
Attention Problems	38	50
Externalizing Problems	-	42
Adaptive Skills	-	49
Behavioral Symptoms Index	-	56
	SSIS Student Report Standard Scores	**SSIS Parent Report Standard Scores**
Social Skills	119	100
Problem Behaviors	95	111

Participant 8

History and Background

Participant 8 was a 15-year-old, right-handed, Caucasian female who received veno-venous ECMO at the age of 8 for bilateral pneumonia that progressed to acute respiratory distress syndrome. Total length of time on ECMO was 37 days. At the time of testing, she was 7 years post-procedure. Qualitative MRI inspection for Participant 8 was within normal limits with no gross abnormalities.

Neuropsychological Functioning

Participant 8 demonstrated average performance in most cognitive domains, with particular strength in the area of picture sequence memory, and relative weakness in attention and inhibitory control. Scores in vocabulary, picture sequence memory, working memory, and processing speed were all in the average range compared to same-aged peers. Oral reading and executive functioning were on the low end of the average range. Overall, crystallized intelligence (SS = 97), fluid intelligence (SS = 91), and Total Composite Score for cognitive functioning (SS = 93) were all in the average range.

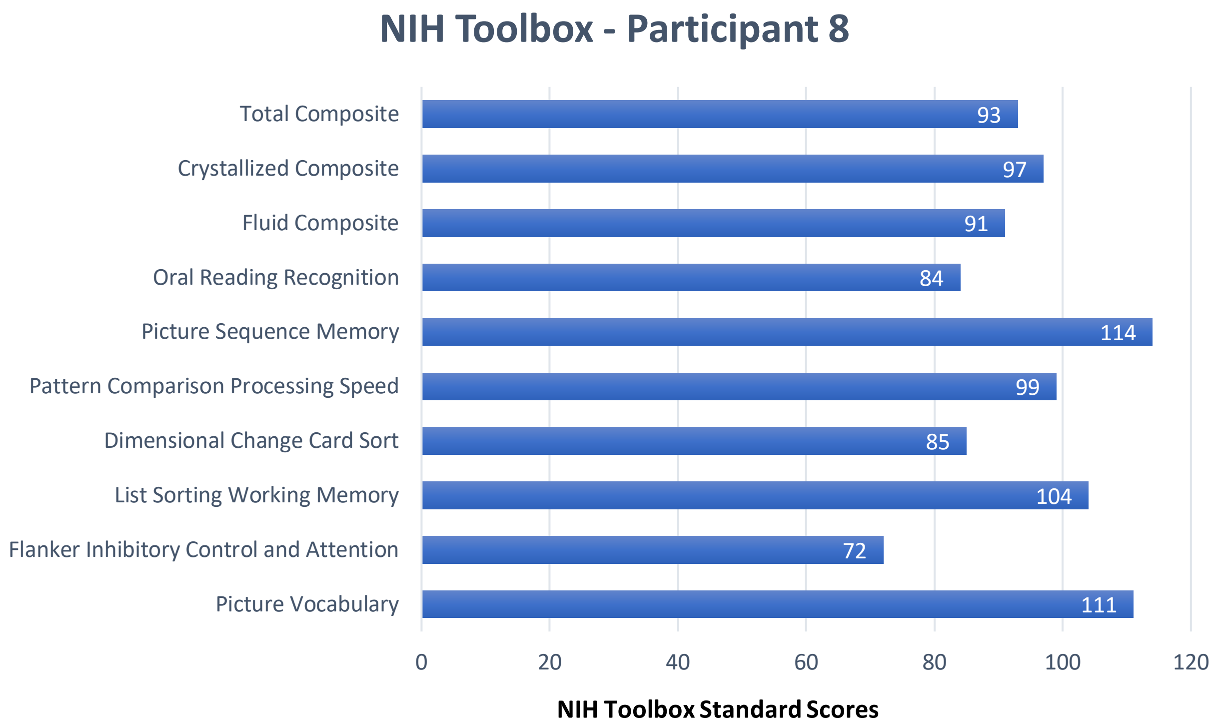

Figure 8. NIH Toolbox Scores for Participant 8.

Behavioral, Emotional, and Social Functioning

On the BRIEF Self-Report, Participant 8 rated her own functioning in the average range across all domains and was within normal limits for behavioral regulation, metacognition, and global executive functioning. In contrast, the BRIEF Parent Form revealed a moderately elevated Global Executive Composite and clinically significant Behavioral Regulation Index. Metacognition was within expected limits. This implies that Participant 8 may have difficulty with inhibitory control, emotional modulation, and set-shifting, but suggests that her ability to cognitively self-manage tasks and monitor performance is generally intact.

On the BASC-2 Self-Report, Participant 8 similarly rated her behavioral and emotional functioning in the average range, while the Parent Report revealed elevations on the Internalizing

Problems scale, with elevations in depressive and somatic symptoms. Additionally, although the parent report Adaptive Skills composite scores was on the low end of the average range (T = 41), individual subscales revealed an adaptability score well below average (T = 26), indicating that she may encounter some difficulty adjusting to changes in her environment.

On the SSIS Student Report, Participant 8 scored in the average to high average range for both Social Skills and Problem Behaviors, implying that she perceives herself as having socially acceptable learned behaviors used to promote positive interactions. Notably, she rated herself in the high average for Social Skills (SS = 119), while her parent rated her significantly lower on the same scale (SS = 85), though still in the average range. Parent report for Problem Behaviors was within the expected limits, indicating that Participant 8 is not demonstrating significantly more problem behaviors than others her age.

Table 11

Participant 8 Behavioral, Emotional, and Social Scores

	BRIEF Self Report T-Scores	**BRIEF Parent Form T-Scores**
Behavioral Regulation Index	40	76
Metacognition Index	42	57
Global Executive Composite	40	65
	BASC-2 Self Report T-Scores	**BASC-2 Parent Report T-Scores**
School Problems	42	-
Inattention/Hyperactivity	48	-
Emotional Symptoms Index	52	-
Internalizing Problems	56	77
Attention Problems	52	53
Externalizing Problems	-	59
Adaptive Skills	-	41
Behavioral Symptoms Index	-	63
	SSIS Student Report Standard Scores	**SSIS Parent Report Standard Scores**
Social Skills	119	85
Problem Behaviors	101	108

Group Results

Neuropsychological Outcome

Neuropsychological results are reported for all subjects excluding Participant 2, given his known premorbid history of developmental delay and learning disorder associated with his medical condition. Notably, Participant 7 also had significantly low scores on cognitive measures, but it is unclear whether she had premorbid difficulties or whether she is experiencing decline due to her medical condition or ECMO treatment. Therefore, results are reported but should be interpreted with caution as we do not have pre-ECMO data indicating significant change. Neuropsychological outcome revealed patterns in functioning among participants who have undergone ECMO treatment. Performance was at least one SD below the mean (M=100; SD=15) when compared with the normative sample in nearly half of the participants for multiple tasks, and at least 1.5 SD below the mean in at least a third of participants. Scores were at least one SD below the mean in 71% of participants on a task of inhibitory control; 57% on a task of visual memory; 43% on tasks of executive function and processing speed; and 29% on a task of oral reading. Scores were at least one and a half SD below the mean in 71% of participants on a task of inhibitory control; and 29% were impaired on tasks of visual memory, executive function, processing speed. Nearly half of the participants showed broad impairment in tasks of fluid intelligence, whereas crystallized intelligence was generally intact. See Figure 9 for neuropsychological functioning divided by individual NIH subtest and index scores.

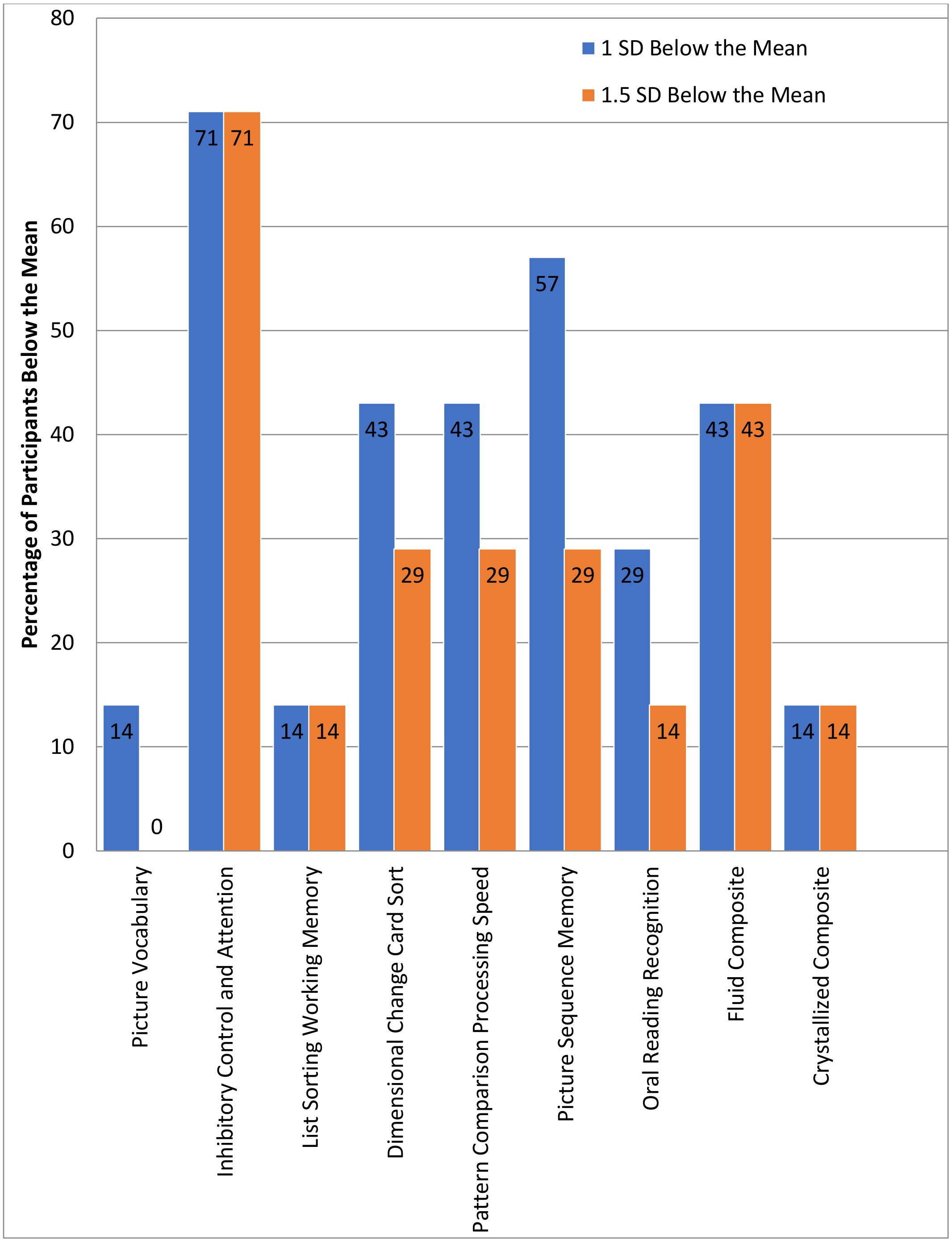

Figure 9. Percentage Impaired by NIH Toolbox Subtest and Index Scores Compared to Normative Sample.

As noted above, crystallized intelligence was in the average range in most participants (M = 102, SD = 18.8). Conversely, fluid intelligence was variable, and was below the expected level in half of the participants (M = 84.7, SD = 27.8). Total composite scores indicate average to above average overall functioning in 6 of the 7 participants (M = 92.14, SD = 26.10). See Figure 10 for participants' individual scores on these indices.

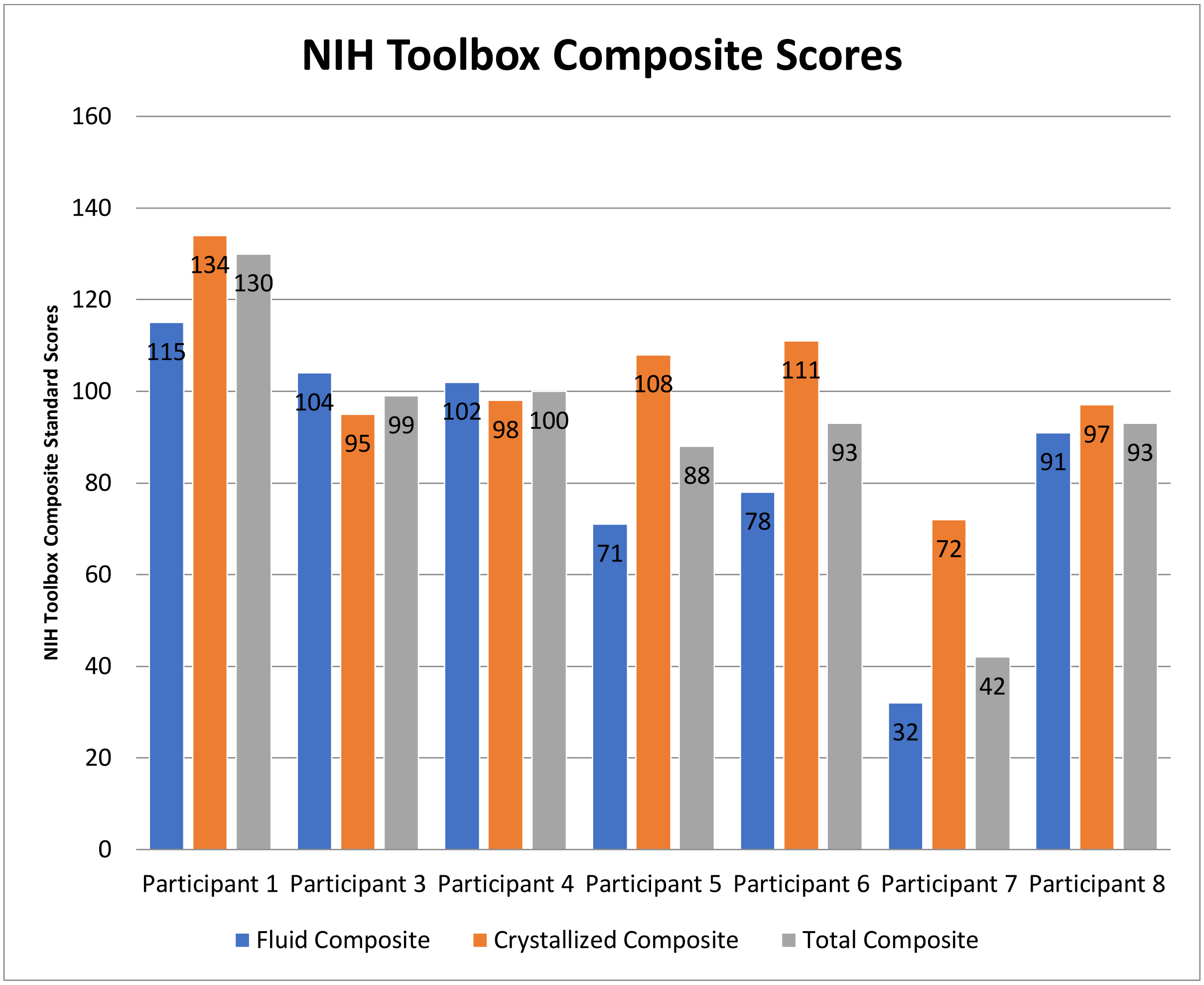

Figure 10. Individual Standard Scores on NIH Toolbox Indices**.** Scores between 85-115 are considered average.

Executive Functioning Measures

On the BRIEF Self Report, the Behavioral Regulation Index (BRI) was in the average range in most participants (M = 54, SD = 11.1), as was the Metacognition Index (MC) for the group (M = 51.7, SD = 9.9), and the Global Executive Composite (GEC) (M = 52.9, SD = 10.9). Conversely, parent report was variable, with an overall higher BRI (M = 62.8, SD = 11.1) and MC (M = 62.4, SD = 9.8), though still in the average range. GEC for the group was on the higher end of the average range (M = 63.2, SD = 8.2). However, when examining individual T-scores, GEC was at a Clinically Significant level (T = 65 or above) in four of the five participants whose parent or guardian completed a form. See Figures 11 and 12 for participants' individual scores on these indices.

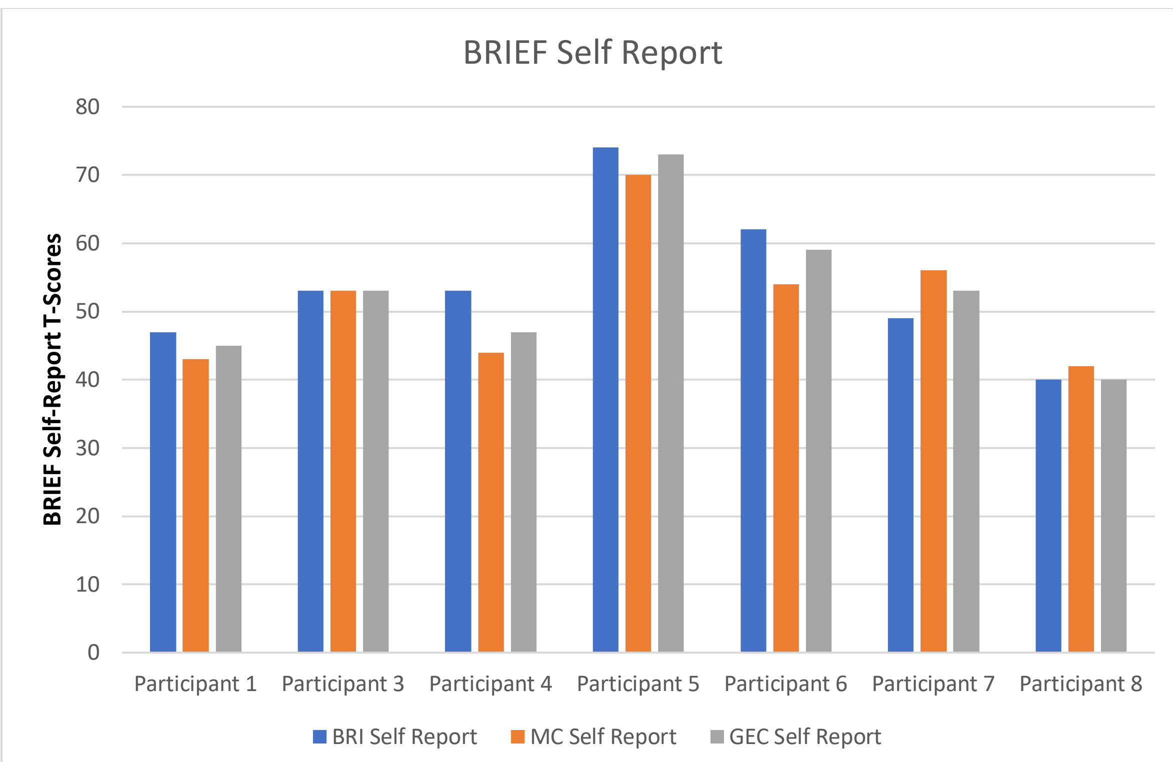

Figure 11. BRIEF Self Report Group T-Scores

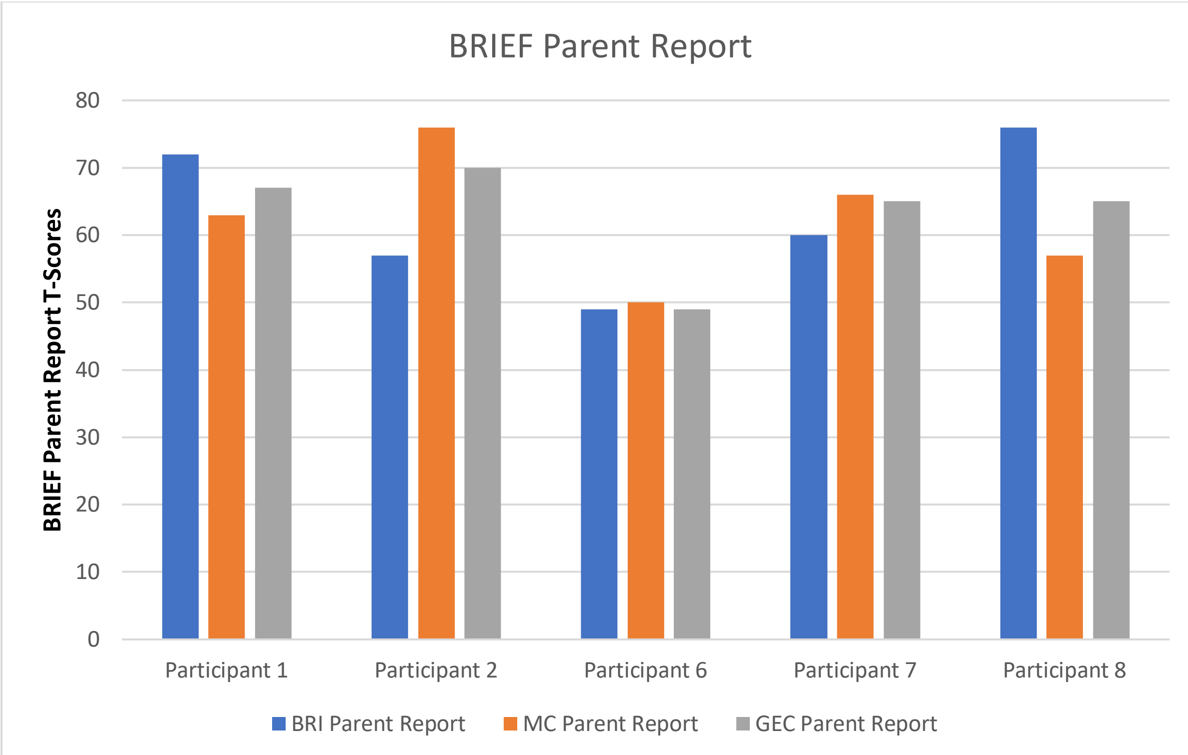

Figure 12. BRIEF Parent Report Group T-Scores

Behavioral and Emotional Functioning

On the BASC-2 Self Report, the Internalizing Problems Composite was in the average range in most participants (M = 53.9, SD = 11.8), as was the Inattention/Hyperactivity Composite for the group (M = 51.1, SD = 9.4), and the Emotional Symptoms Index (M = 51.3, SD = 14.3). On the parent report for those participants under the age of 18 or otherwise dependent, the Externalizing Problems Index was in the average range for the group (M = 55, SD = 10.4), as were Internalizing Problems (M = 57.8, SD = 13.1) and the Behavioral Symptoms Index (M = 59.2, SD = 6.5), though the latter two scales were on the higher end of average and nearer the At-Risk category. Attention Problems Index on Parent Report was in the average range for the group (M = 52.8, SD = 6.8). However, when looking at individual reports, parent-reported T-scores were at an At-Risk or Clinically Significant level in three of the five participants on the Behavioral Symptoms Index, and two of the five on Internalizing Problems. See Figures 13 and 14 for participants' individual scores on these indices.

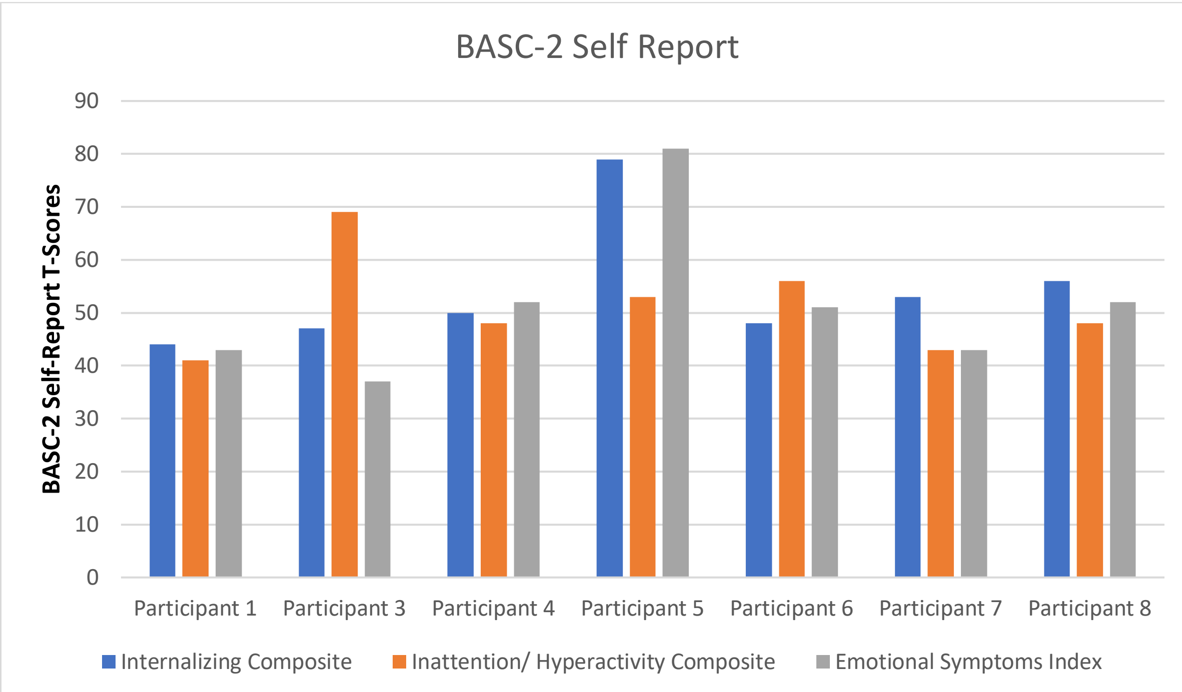

Figure 13. BASC-2 Self Report Group T-Scores.

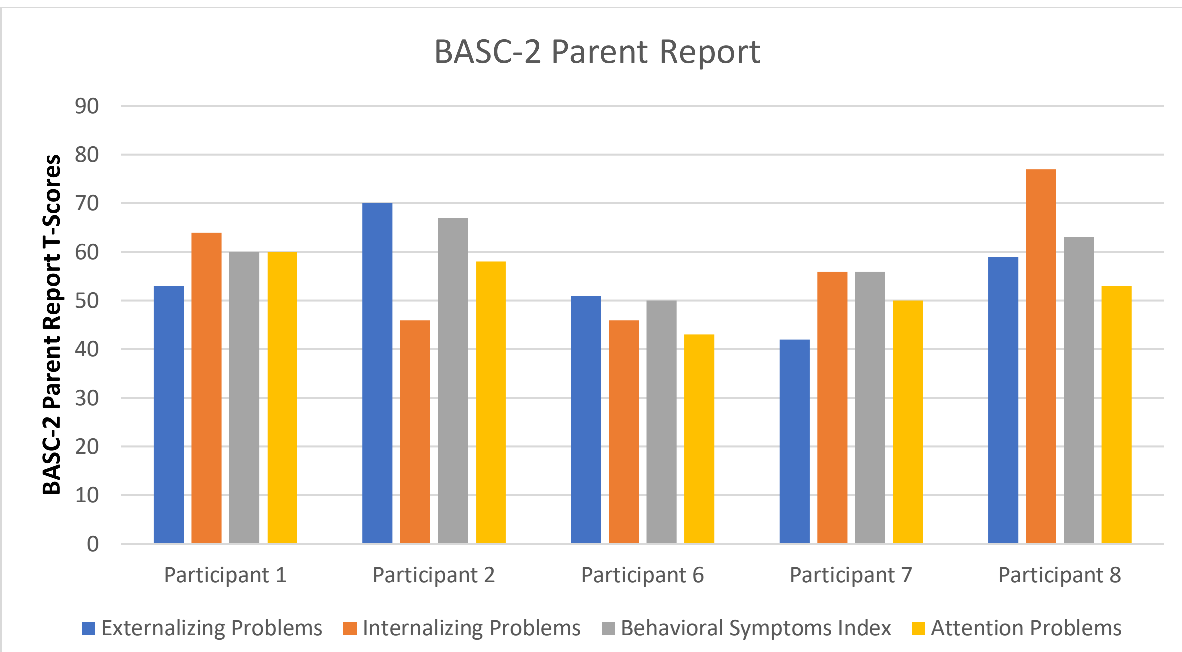

Figure 14. BASC-2 Parent Report Group T-Scores.

Social Functioning

On the SSIS Student Report, the Social Skills Composite was in the average range (M = 107.5, SD = 19.2), as was the Problem Behaviors Index for the group (M = 101, SD = 8.5). On the parent report for those participants under the age of 18 or otherwise dependent, the Social Skills Composite was in the low end of the average range for the group (M = 89.8, SD = 18.7), and Problem Behaviors were in the average range (M = 110.2, SD = 14.5). Individual scores reveal that generally, the participants and their parents/guardians perceive appropriate and developed social skills with the same or fewer problem behaviors compared to their peers. See Figures 15 and 16 for participants' individual scores on these indices.

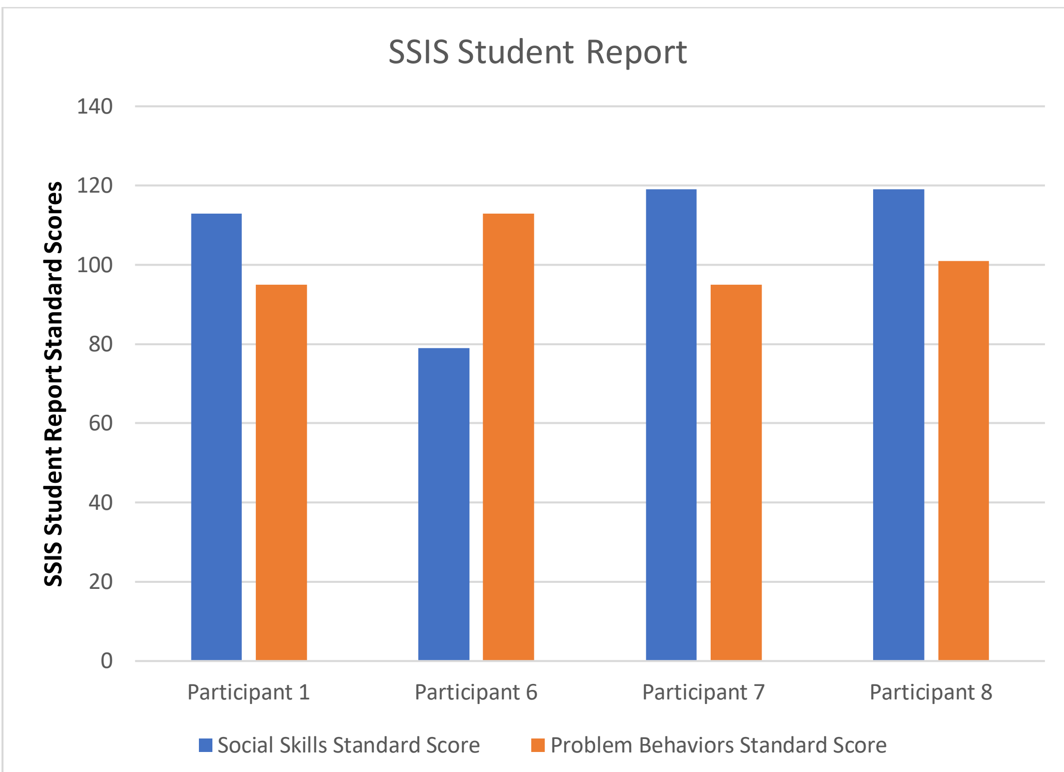

Figure 15. SSIS Student Report Group Standard Scores.

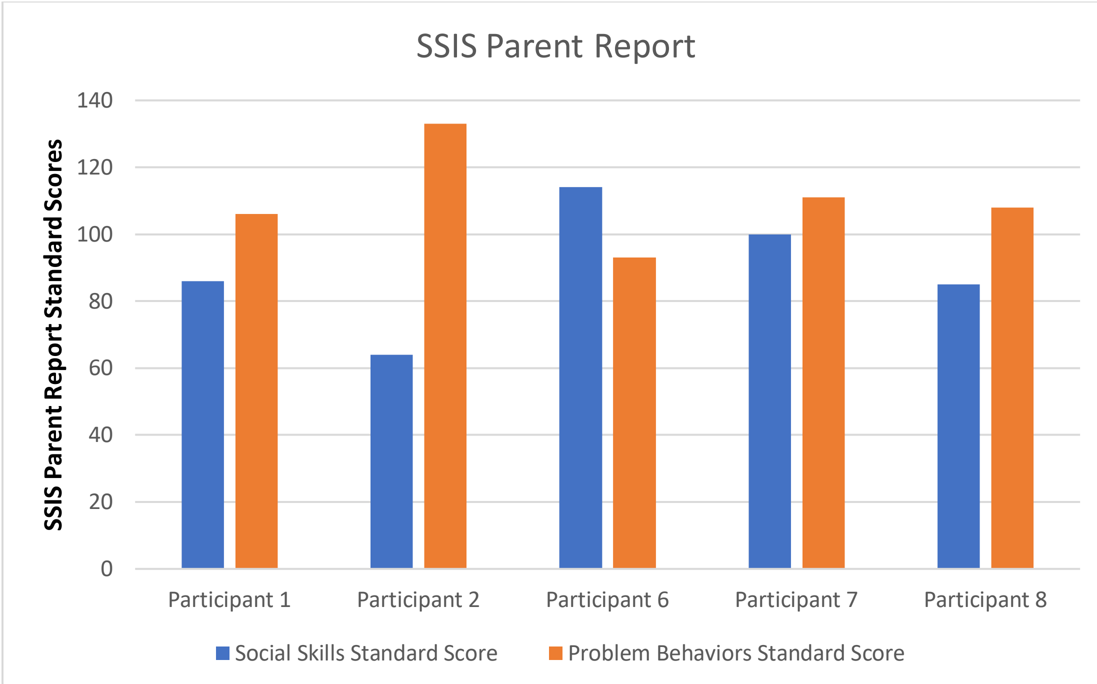

Figure 16. SSIS Parent Report Group Standard Scores.

Hippocampal Volumes

Hippocampal volume was also measured using the FreeSurfer image analysis suite, which provides segmentation of subcortical volumes. Results revealed average right hippocampal volume for the group was 4308.03 mm^3 (SD = 564.31) and 4305.08 mm^3 (SD = 500.33) for the left hippocampus (see Figure 17). Hippocampal volume was corrected for total brain size using total intracranial volume by calculating a proportion value (O'Brien et al., 2011; Seidman et al., 1999; Goldstein et al., 1999) (See Table 12). Recent literature measuring hippocampal volume in healthy control participants report much higher average values. For example, Al-Amin, Zinchenko, & Geyer (2018) investigated hippocampal subfield volume in 553 datasets from normally developing individuals ranging in age from 7-21 years. Mean bilateral hippocampal volume was 6802.95 (SD = 693.49), which is significantly higher than our current sample. Conversely, Hoogman et al. (2017) performed a meta-analysis involving 1436 controls from 23 sites (age range 4-63 years) and revealed average hippocampal volume of 4163.7, which is more representative of our current sample, though there was much more variability in subjects.

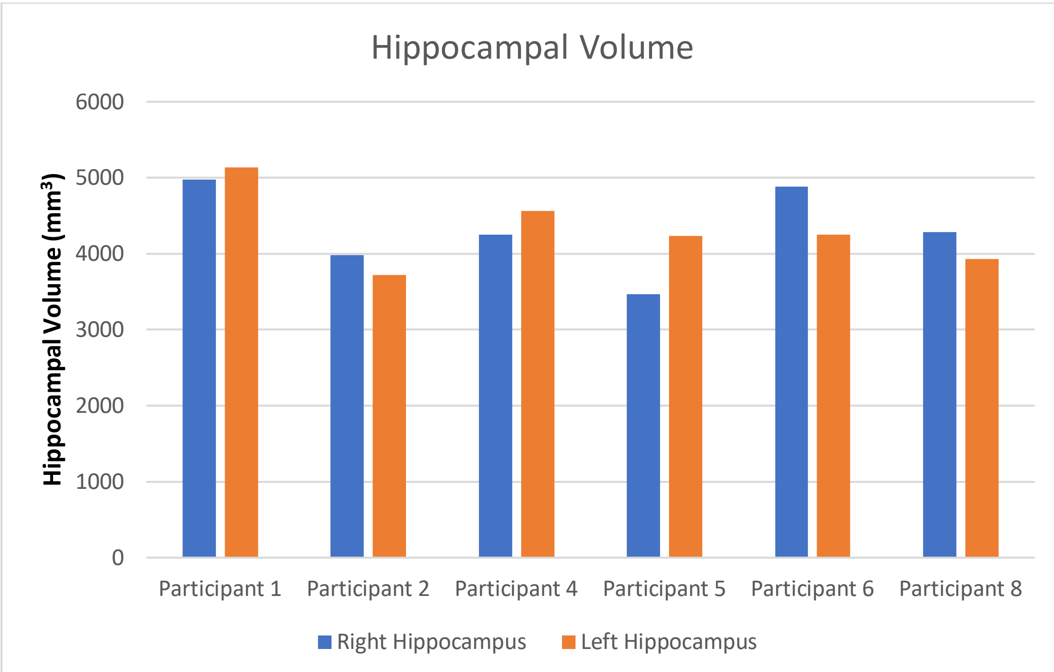

Figure 17. Raw Hippocampal Volume.

Table 12

Total Intracranial Volume and Hippocampal Volume Corrected for Head Size (cm^3)

	Total ICV	Left Hippocampus	Proportion	Right Hippocampus	Proportion	Mean Hippocampus	Proportion
Participant 1	1629.09	5.1371	0.0032	4.9777	0.0031	5.06	0.0031
Participant 2	1473.22	3.7184	0.0025	3.9811	0.0027	3.85	0.0026
Participant 4	1625.27	4.5616	0.0028	4.2537	0.0026	4.41	0.0027
Participant 5	1493.02	4.2307	0.0028	3.468	0.0023	3.85	0.0026
Participant 6	1594.54	4.2534	0.0027	4.8806	0.0031	4.57	0.0029
Participant 8	1343.40	3.9293	0.0029	4.2871	0.0032	4.11	0.0031

Hippocampal and Cognitive Correlations

Our next aim involves correlations between volumetric measurement and cognitive outcome. As hypothesized, results indicate an association, though not statistically significant, between bilateral hippocampal volume and memory, with the strongest associations between bilateral hippocampus volume and working memory performance (right hippocampus r = 0.69; left hippocampus r = 0.71) and weaker, but still positive associations between bilateral hippocampus volume and episodic memory performance (right hippocampus r = 0.27; left hippocampus r = 0.28).

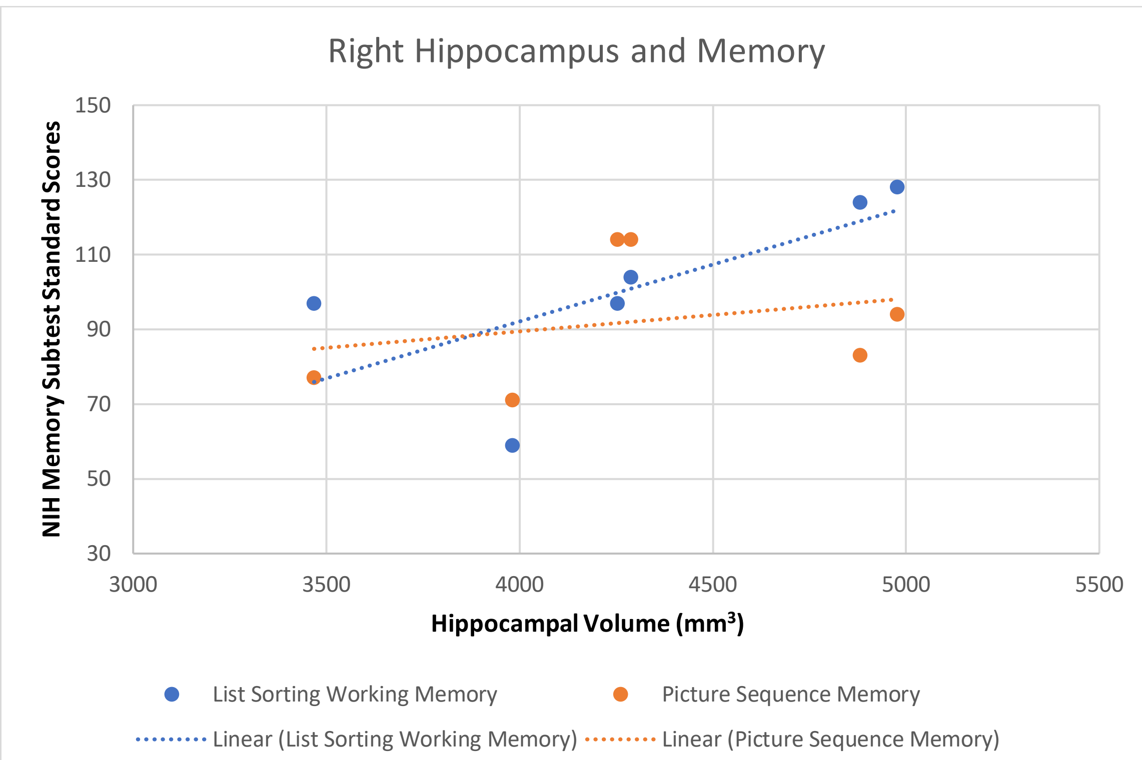

Figure 18. Association between right hippocampus and memory. Right hippocampus and working memory correlation r = 0.69, p = 0.13; right hippocampus and episodic memory correlation r = 0.27, p = 0.60.

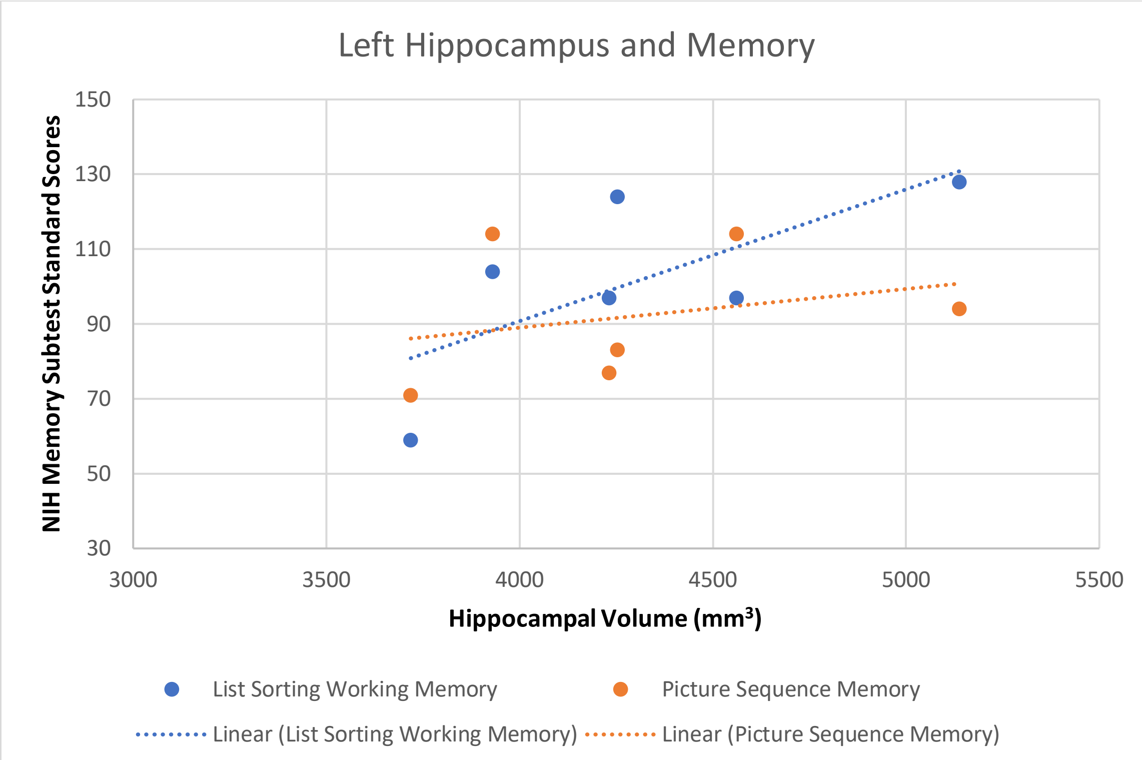

Figure 19. Association between left hippocampus and memory. Left hippocampus and working memory correlation r = 0.71, p = 0.11; left hippocampus and episode memory correlation r = 0.28, p = 0.59.

Cortical Thickness

Cortical reconstruction and volumetric segmentation were estimated using the FreeSurfer image analysis suite (Dale et al., 1999) in four, hypothesis-driven bilateral regions. As cortical thickness control data was not available at the time for quantitative comparison, preliminary data for our sample is reported in Table 13 for future exploratory purposes.

Table 13

Cortical thickness measures (in mm)

Region of Interest	*Mean*
Right superior frontal	2.94 (SD = 0.24)
Left superior frontal	2.92 (SD = 0.23)
Right rostral middle frontal	2.48 (SD = 0.17)
Left rostral middle frontal	2.50 (SD = 0.15)
Right medial orbitofrontal	2.63 (SD = 0.2)
Left medial orbitofrontal	2.54 (SD = 0.21)
Right caudal middle frontal	2.64 (SD = 0.25)
Left caudal middle frontal	2.74 (SD = 0.25)

Discussion

The overall aim of this pilot study was to investigate cognitive outcome, behavioral changes, and measurement of hippocampal volume (with exploration of cortical thickness in frontal regions) in adolescents and young adults who have undergone ECMO treatment as children for acute cardiac or respiratory illness. There is currently very little research detailing cognitive outcome following ECMO, and even less that examines cognition in relation to brain integrity. Because there are frequent complications prior to and during the ECMO procedure, such as stroke, hypoxia, and cardiac arrest (Risnes et al. 2006, Cheng et al., 2014), there is a likelihood that these children will experience significant disadvantages following medical discharge, such as poor developmental trajectory, impaired academic abilities, and cognitive deficits (Cooper et al., 2013; Glass et al., 1995). Therefore, for the current study, we hypothesized that measures of cognition would be lower than their same-aged peers, particularly in the areas of attention, processing speed, and executive function, as is commonly seen in frontal lobe injury and more diffuse axonal injury observed in hypoxia. This hypothesis was supported to some degree, as scores were at least one standard deviation below the mean in 75% of the participants for attention, 50% of the participants for processing speed, and 50% of the participants for executive functioning. Although there is no gold standard for defining a minimum clinically important difference (MCID) for cognitive measures, literature suggests that anywhere from 0.5 – 1.5 standard deviations below the mean (moderate to large effect size) can be clinically meaningful (Norman, Sloan, & Wyrwich, 2003; Jaeschke, Singer, & Guyatt, 1989; Wang et al., 2017). Therefore, given our current results, we can estimate that the majority of our participants are experiencing clinically meaningful impairment in at least one domain. Notably, we do not have pre-ECMO data detailing premorbid levels of cognitive functioning, and are estimating prior cognition using crystallized intelligence measures. Additionally, although the NIH Toolbox is quite comprehensive in its assessment of cognition, it does not include a measurement of verbal memory, which is an important factor in neuropsychological evaluation, particularly in relation to hippocampal functioning (Nagel et al., 2006; Johnson, DeMatt, & Salorio, 2009). Future analysis of cognition in this population should include verbal memory tasks to obtain a more complete picture of functioning.

Although there is no current research to our knowledge involving internalizing or externalizing problems specifically in children who have undergone ECMO, literature has linked behavioral and emotional problems commonly seen in children with neurological disorder with the composite scores of the BASC-2. Results from objective measures of emotional, behavioral, and social functioning were more variable across participants and between self- and parent report. Surprisingly, very few difficulties with inattention, behavioral problems, and internalizing symptoms were reported by participants and their parents, though there was some variability between subjects. Interestingly, on the SSIS, the student- and parent report tended to be contradictory, as students tended to perceive their social skills to be quite high and problem behaviors low, while their parents/guardians endorsed the opposite: higher rates of problem behaviors and lower social skill abilities. Though discrepancies between self- and informant reports are common, very little is known about the cause of these differences. It is suggested that multiple factors may contribute to this, such as differences in how informants interact with the child, differences in perspectives of the informants when rating problem behavior, context-based observations, and perhaps even psychometric differences between self- and informant report measures (De Los Reyes & Kazdin, 2005). Regarding contextual variation of behavior, it is suggested that children and adolescents in particular may demonstrate behavior, specifically problem behavior to a greater degree in certain contexts more than others (e.g., at home vs. with friends), which may explain up to a quarter of the variability of discrepancies of self- vs. informant report (Vierhaus, Rueth, & Lohaus, 2018). In addition, it could also be related to limited insight on the part of these participants regarding their social functioning or even minimization. Prior studies have found similar differences in children and adolescent following traumatic brain injury (Stancin et al., 2002) as well as many other neurologic injuries (Powell & Voeller, 2004) that occur during childhood and likely affect development.

Additionally, we predicted hippocampal volume reductions in ECMO relative to age-matched controls, which would correlate with decreased memory scores, as the literature demonstrates that the hippocampus is particularly vulnerable to hypoxic or anoxic episodes (Caine & Watson, 2000). Due to the absence of age- and sex-matched controls for the current study, the hypothesis cannot be fully assessed at this time. Based on recent literature, we have varied numbers for hippocampal volumes in healthy individuals; however, due to our small sample size, numbers cannot be interpreted in a meaningful way when compared to a large database of varied ages. However, preliminary data suggests that hippocampal volume in our clinical sample may be average to below average in comparison to healthy individuals. Additionally, there was an association between both episodic and working memory and total bilateral hippocampal volume, though slightly stronger for working memory, which supports the idea that hypoxic episodes prior to or during ECMO may impact hippocampal functioning, which in turn produces memory deficits .

Finally, we predicted that cortical thickness in the frontal lobe, particularly bilateral superior frontal, rostral middle frontal, caudal middle frontal, and medial orbitofrontal, would be decreased for our sample in comparison with a control group. Unfortunately, for the current study, control data could not be obtained for cortical thickness and meaningful analysis and interpretation could not be performed at this time. However, this preliminary data will be a useful contribution to the literature as we obtain age- and sex-matched control data for cortical thickness analysis in the near future. Based on prior research in similar populations, we expect to see cortical thinning in the frontal areas of the brain when compared with healthy controls (Macey et al., 2018).

Due to our small sample size, qualitative analysis of each subject's data becomes quite important and useful, particularly in a population such as ours that has limited or minimal research. Literature regarding case series suggests that neuropsychological case study is an empirical procedure that can help provide a better understanding of symptom presentation and its causes (Towgood, Meuwese, Gilbert, Turner, & Burgess, 2009). Case studies are becoming an increasingly accepted method to understanding cognitive deficits in many neurological populations, and investigating general associations for shared cognitive functions (Caramazza, 1986; Towgood et al., 2009; Rapp, 2011; Dell, Martin, & Schwartz, 2007). Though there was some variation between participants, we are able to see general trends in the data such as broad impairment in attention, overall decreases in fluid intelligence, and various behavioral, emotional, or social difficulties. Positively, most participants had intact crystallized intelligence, indicating strong cognitive reserve which is predictive of positive recovery and ability to compensate for deficits (Stern, 2002). Notably, we had a wide variable in age range in the current study, with participants ranging from age 11 to 22, with age at time of ECMO ranging from 5-15. Therefore, developmental differences in cognition between participants should be carefully considered. Research suggests that the young brain is particularly vulnerable to cerebral insult and axonal injury, and may be more susceptible to swelling and disrupted cerebral blood flow (Wilde et al., 2005) than a mature brain. Additionally, changes in the brain take place during development, including increasing white and gray matter volumes in the frontal and parietal cortex in older children and adolescence (Blakemore & Choudhury, 2006). Research has shown poorer performance on tasks of executive function and less efficient frontal lobe activation, as well as increased impulsive behavior and poor decision making in adolescents, compared to adults (Blakemore & Choudhury, 2006). Therefore, it is anticipated that associated cognition would look significantly different in our younger participants than our young adults, both due to age at the time of injury and to cerebral and cognitive changes associated with normal development.

Limitations

Due to this study's small sample size, results should be interpreted with caution and replication studies should be completed. Ideally, control subjects will be recruited in future studies and more meaningful analysis and interpretations can be made regarding the association between morphometry and cognitive outcome. Additionally, due to the broad range of ages of our participants and differences in factors such as diagnosis, length of time on ECMO, length of time since the procedure, and likely varying oxygen levels during hospitalization, it is likely not beneficial to make inferences based on our current data. However, although the overall sample size for this study is small and we have quite a heterogenous group of subjects, qualitative data can be an important contribution to the field, particularly in populations and subject matters that have not been previously investigated, such as ours. It will be beneficial for future research to include a larger sample size to examine group differences on various levels not explored in this study. Further study including comparison to a group of healthy controls is warranted to evaluate potential long-term effects of childhood ECMO on cognition.

Conclusions

Cognitive and behavioral difficulties exist in adolescents and young adults who underwent ECMO as children. Performance on the NIH Toolbox Cognitive battery was impaired in over half of the tested individuals. Attention, executive function, processing speed, and visual memory were well below the expected range for age in the majority of participants. Crystallized intelligence tasks, such as vocabulary, were in the average to above average range for most participants, likely indicating normal baseline functioning. On self-report measures, participants generally rated their behavioral, emotional, and social functioning within the average range, while their parents endorsed various difficulties in attentional and behavioral problems, social skills, and emotional regulation. This implies that parents or caregivers may be identifying more difficulties in daily life, and can be important contributors to neuropsychological assessment. Another contribution of this study was the use of the NIH Toolbox, which appears to be sensitive to the cognitive sequelae of ECMO and may be useful in a clinical context.

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