Long-Term Executive, Behavioral, and Environmental Functions after Pediatric Traumatic Brain Injury (TBI)

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I. Introduction

This project provides a unique opportunity to use an existing database that prospectively followed adolescents who sustained a TBI to evaluate long-term transitional outcomes, thereby allowing us to understand how these children are functioning in young adulthood. Executive function and behavioral deficits are among the most common impairments following pediatric TBI. These impairments affect both school and home functioning; however, the progression of these deficits and their emerging effect on functioning in young adulthood are less understood. This study provided an opportunity to evaluate these longer-term outcomes.

Seemingly similar injuries lead to differential outcomes. Environmental factors are often related to outcomes after injury. Individual factors also likely effect outcomes, specifically genetic effects may explain, in part, these differential outcomes. Catecholamine gene polymorphisms affect cognitive and behavioral functioning; however, the association of catecholamine polymorphisms with executive, behavioral, and psychosocial functioning after pediatric TBI has not been explored in depth. Understanding the relationship of these polymorphisms to executive and behavioral functioning after TBI could lead to identification of individuals who are at significant risk of impairments. Additionally, by examining how family and social environment moderate recovery, we could predict individuals who will recover successfully.

Findings from this study will potentially provide a foundation for individualizing prognosis and interventions to address the executive function and behavioral consequences of adolescent TBI as they relate to cognitive, behavioral, and psychosocial functioning.

II. Executive Summary

<u>Background</u>

Pediatric TBI is a significant cause of morbidity in children (M. Faul, Xu, Wald, & Coronado, 2010). Many of the impairments sustained after pediatric TBI are related to emerging

executive and behavioral dysfunction. These difficulties in organization, planning, problem solving, and self-regulation contribute to problems related to the transition to functional independence, especially related to educational and vocational outcomes (Donders & Warschausky, 2007; Massagli et al., 1996; Taylor, 2004; Taylor et al., 2008; Todis & Glang, 2008). Multiple factors have been shown to play a role in recovery after TBI, including injury severity, age at injury, family environment, and other psychosocial factors (Klonoff et al., 2006; Massagli et al., 1996; Taylor, 2004; Taylor et al., 2008). Additionally, although previous research is extremely limited, individual characteristics, specifically genetics, are also likely to play a role in the recovery process (Kurowski, Martin, & Wade, 2012; Thomas W. McAllister, 2010).

Participants

Participants were recruited from a previously completed multi-center (Cincinnati, OH, Cleveland, OH, Denver, CO, and Rochester, MN), randomized clinical trial comparing Counselor-Assisted online Problem Solving (CAPS) to access to internet resources related to brain injury (Internet Resource Comparison; IRC). For the long-term follow-up of the proposed EMS project, participants were recruited from the Cincinnati and Cleveland, OH sites initially. The Denver site was added later to help with recruitment of additional participants. One hundred twenty-two participants with moderate to severe TBI were initially eligible for participation in the study. A total of 47 participants were recruited for the long-term follow-up study. Thirty-seven participants completed both the long-term behavioral and psychosocial follow-up questionnaires and genetic portion of the study and 10 completed only the genetic portion.

Methodology

This was a long-term longitudinal cohort study that examined functional outcomes of children with moderate and severe TBI who completed a prior randomized controlled study

evaluating the effectiveness of online-problem solving therapy. The overarching objectives of the EMS project were threefold 1) identify predictors of long-term functioning following adolescent TBI, specifically during the transitional period; 2) characterize the relationship of polymorphisms in catecholamine-related genes to neuropsychological, executive, behavioral, and psychosocial functioning after adolescent TBI; 3) characterize the influence of catecholamine polymorphism on the effectiveness of a problem-solving intervention in improving behavioral and psychosocial functioning. The primary outcomes of this study were the measures of psychosocial, executive, and behavioral functioning at least 24 months post injury.

Conclusion

Building upon a large prospective cohort and excellent institutional resources, this project provides novel information about transitional outcomes after adolescent TBI and begins to evaluate the relationship of genes to mental health outcomes and treatment response following adolescent TBI. Findings from this project will serve as a foundation for larger projects that will work towards individualizing prognosis and management after TBI.

III. Information/Qualifications – Principal and all co-investigators

Principle Investigator – *Brad G Kurowski, MD, MS* – Dr. Kurowski is an Assistant Professor of Pediatric Physical Medicine and Rehabilitation (PM&R) at Cincinnati Children's Hospital Medical Center (CCHMC) and the University of Cincinnati College of Medicine. He has successfully obtained a NIH-sponsored K-12 grant exploring the association of catecholamine-related polymorphisms with recovery from early childhood TBI. The same techniques used in his K-12 grant were used in this study of adolescents with TBI, which allowed for efficient collection of data to ensure timely analysis and dissemination of findings. He has also been working closely with Shari Wade, PhD (co-investigator) to examine the combined role of

psychosocial factors, environmental factors, genetics, and injury-specific factors in recovery after pediatric TBI.

Co-Investigator – *Shari L. Wade, PhD* – Dr. Wade is a tenured Professor at CCHMC. She has published more than 100 peer-reviewed articles related to recovery from pediatric TBI. Dr. Wade's expertise in neurocognitive and psychosocial parameters related to recovery from pediatric TBI is integral to successful completion of this project. Her expertise in behavioral and family outcomes and social environmental moderators of recovery complements and augments Dr. Kurowski's strengths and the strengths of the other co-investigators.

Co-Investigator – *H. Gerry Taylor, PhD* – Dr. Taylor is a Professor of Pediatrics at Case Western Reserve University. He is a pediatric neuropsychologist with a strong record of federally-funded investigations of the childhood sequelae of early brain insults. He has authored nearly 200 peer-reviewed publications and has given hundreds of presentations at local, national, and international meetings.

Co-Investigator – *Terry Stancin, PhD* – Dr. Stancin is a Professor of Pediatrics, Psychiatry and Psychology at Case Western Reserve University School of Medicine and Head of Pediatric Psychology at MetroHealth Medical Center. She has participated in pediatric TBI outcome and intervention research for more than 20 years and has numerous peer-reviewed publications and presentations at local, national, and international meetings.

Co-Investigator – *Michael Kirkwood, PhD,* is an Associate Professor, Department of Physical Medicine and Rehabilitation; Children's Hospital Colorado, University of Colorado School of Medicine. He is a board-certified clinical neuropsychologist. He has extensive clinical and research experience working with children and families faced with traumatic brain injury. He has been on the rehabilitation staff at The Children's Hospital (Denver/Aurora) since 2001, founded its Mild TBI management program, and has participated in or directed a variety of federally- and state-funded research projects focused on childhood TBI over the last decade. He has authored multiple peer-reviewed articles and book chapters on pediatric TBI and has

presented about childhood brain injury throughout Colorado, as well as nationally and internationally.

IV. A review of the literature related to the project topic

Pediatric TBI is a significant cause of morbidity in children (M. Faul et al., 2010). Many of the impairments sustained after pediatric TBI are related to emerging executive and behavioral dysfunction. These difficulties in organization, planning, problem solving, and self-regulation contribute to problems related to the transition to functional independence, especially related to educational and vocational outcomes (Donders & Warschausky, 2007; Massagli et al., 1996; Taylor, 2004; Taylor et al., 2008; Todis & Glang, 2008). Many factors have been shown to play a role in recovery after TBI, including injury severity, age at injury, family environment, and other psychosocial factors (Klonoff et al., 2006; Massagli et al., 1996; Taylor, 2004; Taylor et al., 2008). Additionally, although previous research is extremely limited, individual characteristics, specifically genetics, are also likely to play a role in the recovery process (Thomas W. McAllister, 2010).

Transitional outcomes: Many of the deficits sustained after TBI are cognitively related. They commonly include word finding difficulties and other language disorders; memory deficits; and difficulties with executive functioning, including disorganization and slowness in completing tasks, poor concentration or attention, and impaired problem-solving skills.(Taylor, 2004) Furthermore, academic performance and school readiness are often impaired after pediatric TBI (Glang, Todis, et al., 2008; Glang, Ylvisaker, et al., 2008; Todis & Glang, 2008; Todis, Glang, Bullis, Ettel, & Hood, 2011; Ylvisaker et al., 2005). Pre-injury factors, including age at injury, education status, and location of injury are important factors in educational, vocational, and social outcomes after TBI.(Klonoff et al., 2006). Participation in and quality of postsecondary education are generally poor for individuals with a moderate to severe pediatric TBI (Todis &

Glang, 2008). However, improved access to services and internal factors, specifically motivation, are associated with better educational outcomes (Todis & Glang, 2008). Earlier (age 6-12 years) compared to later (age 16-20 years) age at injury is associated with poorer higher-level cognitive skills, social integration, and a lower likelihood of driving during the transitional age period (Donders & Warschausky, 2007). Optimizing management and services during the transitional period after pediatric TBI may be essential to optimizing functional independence.

Environmental Factors: Environment plays a role in the recovery from pediatric TBI. Impairments after TBI are related to multiple factors, including age of injury, severity of injury, and time post-injury; however, there is often differential recovery in individuals with very similar brain injuries (Massagli et al., 1996; Taylor, 2004; Taylor et al., 2008). Several environmental factors, including family functioning, are known to moderate the effects of injury severity on cognitive and social recovery after pediatric TBI (Yeates et al., 1997). Socioeconomic resources, social supports, and better family functioning buffer or reduce the adverse effects of severe TBI on executive functions and social problem solving skills (Yeates et al., 2004). These findings suggest that there is a complex interplay among injury characteristics, individual factors, and environmental factors that influence recovery from TBI. Genetic factors are also likely to significantly affect the recovery process (Kurowski et al., 2012; Thomas W. McAllister, 2010). Genes or genetic inheritance increase or decrease the risk of many complex diseases; however, it is the interaction between the environment and genetics that often determines the final outcome or phenotype. A genetic predisposition to certain cognitive or behavioral problems could explain some of the observed variability in outcomes after TBI. Better characterization of genetic factors associated with recovery from TBI could also provide insight into the complex pathophysiology of recovery and identify possible targets for interventions to improve recovery. Additionally, investigations considering the interaction between individual

(i.e., genetic) and environmental influences involved in recovery are essential to better understand the trajectory of recovery, which would allow improved identification of individuals at risk for poorer recovery. The ultimate goal is to optimize services and interventions to maximize recovery and functional independence following pediatric TBI.

Cognitive, behavioral, and psychosocial interventions and moderators of treatment effects: A significant amount of effort is put into cognitive, behavioral, and psychosocial rehabilitative interventions after TBI. However, studies evaluating the effectiveness of these interventions specific to the management and recovery after pediatric TBI are scarce. There is a need to develop well designed studies to assess the efficacy of these interventions and to evaluate the long-term effects (Rees, Marshall, Hartridge, Mackie, & Weiser, 2007; Slomine & Locascio, 2009). Additionally, family factors, as noted above, play an important role in the recovery process and the role of family interventions should also be evaluated. The needs of the family change throughout a child's recovery after pediatric TBI (S. Wade, Drotar, Taylor, & Stancin, 1995; S. L. Wade, Taylor, Drotar, Stancin, & Yeates, 1996), therefore, interventions will likely need to be modified throughout the course of recovery. Since the proposed study plans to build on an ongoing randomized controlled study that is evaluating the efficacy of a family-based problem-solving intervention, Counselor-Assisted Problem Solving (CAPS), it is a unique opportunity to add important information to the literature. It will allow better characterization of the long-term efficacy of the intervention, provide an opportunity to elucidate the effects of environmental and individual factors on the intervention's efficacy, and will be a novel opportunity to assess the role of genetics related to long-term outcomes and treatment effects.

Pathophysiology and recovery related to genetics: The pathophysiology of TBI is complex and there are a myriad of potential genes related to recovery (Jordan, 2007; Thomas W. McAllister, 2010). Genes related to healing after the initial injury, the inflammatory cascade, plasticity, and neural recovery are all potentially involved in the recovery process. Likely, there

is interaction among multiple genes during this process. Since catecholaminergic systems are susceptible to injury and altered regulation after TBI (Kobori, Clifton, & Dash, 2006; T. W. McAllister, 2009; T. W. McAllister, Flashman, Sparling, & Saykin, 2004) and they are associated with neural recovery through effects on brain-derived growth factor (Guillin et al., 2004; T. W. McAllister, 2009), catecholamine-related genes are attractive targets for evaluation. Catecholamine-related genes are associated with neurocognitive outcomes after adult TBI (T. W. McAllister et al., 2004; McIntosh, 1994) and disorders of regulation and attention in childhood such as attention deficit hyperactivity disorder (ADHD) (Prince, 2008). Moreover, catecholaminergic mechanisms play an important role in attention and memory function in the prefrontal cortex (T. W. McAllister, Flashman, McDonald, & Saykin, 2006) and they are integral to the modulation of memory, attention, and executive function after TBI (T. W. McAllister et al., 2004; McIntosh, 1994). Thus, catecholamine-related genes might influence aspects of memory, attention, and executive function after TBI through the modulation of catecholamine systems. Genetic differences could explain, in part, variance in cognitive and behavioral recovery after pediatric TBI.

Some of the more commonly studied catecholamine genes that have been linked to attention, executive function, and behavior impairments include the dopamine receptor, dopamine transporter (DAT), catechol-O-methyltransferase (COMT), and adrenergic receptor alpha-2a (ADRA2A) genes. The dopamine receptor genes have been implicated in cognitive dysfunction related to adult TBI, ADHD, schizophrenia, and addiction (Abdolmaleky, Thiagalingam, & Wilcox, 2005; Doehring, Kirchhof, & Lotsch, 2009; Esposito-Smythers, Spirito, Rizzo, McGeary, & Knopik, 2009; Ettinger, Joober, R, & O'Driscoll G, 2006; Gelernter et al., 1997; Kang, Palmatier, & Kidd, 1999; Lung, Chen, & Shu, 2006; T. W. McAllister et al., 2008; T. W. McAllister et al., 2004; T. W. McAllister et al., 2005; Rommelse et al., 2008; Waldman & Gizer, 2006). The DAT genes have been implicated in outcomes related to ADHD and adult

TBI.(Doehring et al., 2009; Liao et al., 2009; Wagner et al., 2007; Xu et al., 2009). COMT has been implicated in outcomes after adult TBI and as a marker of risk for schizophrenia, ADHD, and addiction (Abdolmaleky et al., 2005; Doehring et al., 2009; Halleland, Lundervold, Halmoy, Haavik, & Johansson, 2009; Lipsky et al., 2005; Noble, 2003; Omidvar et al., 2009). The ADRA2A gene has been implicated in cognitive dysfunction in ADHD (Doehring et al., 2009). Overall, catecholamine-related genes are associated with cognitive and behavioral impairments in multiple neurologic and psychiatric disorders. The impairments are similar to those observed after pediatric TBI; however, specific studies of catecholamine genes in pediatric TBI are lacking. Thus, the role these genes play in recovery after pediatric TBI needs to be further elucidated.

V. Historical perspectives on the topic of this report

TBI is the most common cause of morbidity and mortality in children. It is estimated that approximately 4 million TBIs occur in each year in the United States. In children aged 0-19 years, there are approximately 600,000 emergency department visits, 40,000 hospitalizations, and 3,000 deaths annually in the United States related to TBI (M Faul, Xu, Wald, & VG, 2010). The rate of TBI is highest in children aged 0-4 years (1,256 per 100,000) and older adolescents aged 15-19 years (757 per 100,000).(M Faul et al., 2010) Over 50% of TBIs in children are due to falls, about 25% are due to being struck by/against an object (e.g., colliding with a moving or stationary object), and approximately 7% are due to motor vehicle accidents. The rate of fall related TBI is highest among children aged 0-4 years (839 per 100,000) and the rate of motor vehicle crash- related TBI is highest among children aged 15-19 years (195 per 100,000). Boys are more likely to sustain a TBI than girls. Boys aged 0-4 years have the highest injury rate (1357 per 100,000); however, girls aged 0-4 years have the second highest injury rate (1150 per 100,000).

TBI in children is also associated with a large economic and societal cost. Pediatric TBI-associated hospital charges are over $2.56 billion annually in the United States (Shi et al., 2009). Additionally, it has been estimated that pediatric TBIs results in $60 billion direct and indirect medical costs in the United States (Finkelstein, Corso, & Miller, 2006). These economic and societal costs are likely continuing to grow.

VI. A brief review of the current status of the topic in Ohio, the surrounding states, and nationally

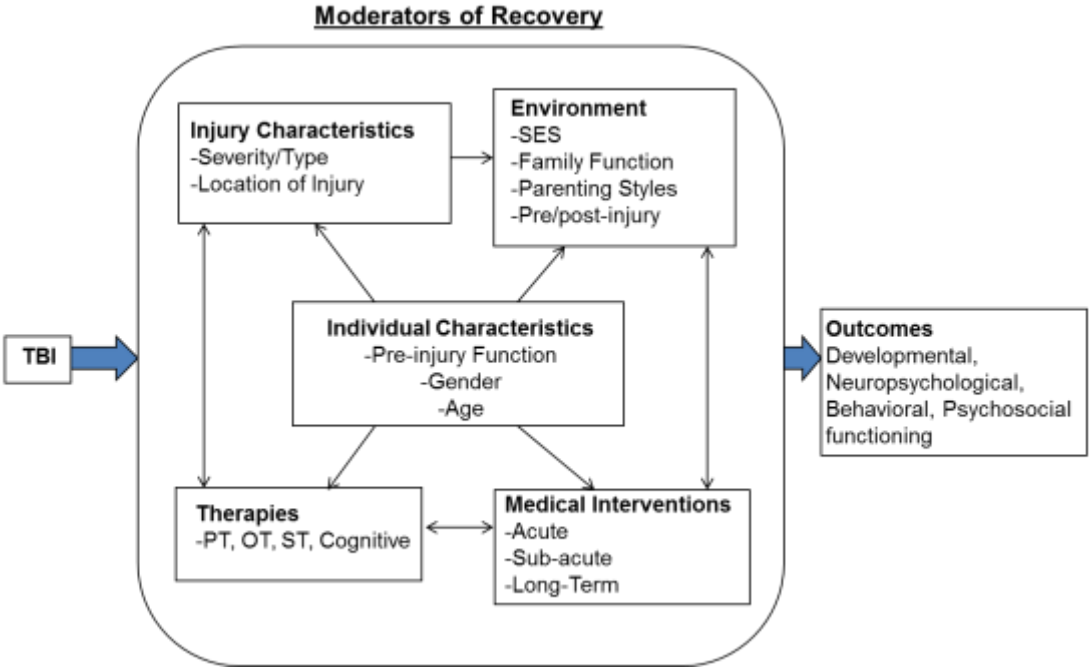
Similar to national trends as mentioned above, pediatric TBI is also the leading cause of morbidity and mortality in Ohio. Recent media attention highlighting the potentially long-term cognitive and behavioral problems of concussion or mild TBI has also generated awareness of the potential long-term consequences of TBI more broadly. With this increased awareness of the potential long-term impairments in cognitive, behavioral, and psychosocial functioning that may occur after TBI, families and practitioners are seeking ways to not only predict recovery trajectories, but also optimize outcomes. To date, there is a paucity of information available to accurately predict outcomes. Likely, injury, environmental, and individual factors interact with each other to ultimately determine outcomes (See Figure 1). Additionally, there is currently a paucity of studies evaluating the benefits of cognitive, behavioral, or medication interventions for the sequelae of pediatric TBI.

VII. Future trends, both regionally and nationally

There is a need to develop better ways to predict outcomes after TBI in children and manage their injury. Future research will continue to look for markers of injury acutely that may predict longer term recovery. Injury-related factors, including mechanisms of injury and severity of injury are being explored as ways to predict long-term outcomes. The association of individual factors, including age, gender, genetics, and pre-injury functioning with long-term

outcomes also needs to be better elucidated. Biomarkers, including blood biomarkers, brain imaging, and measures of cognitive and behavioral function will also be explored to evaluate their association with outcomes after injury. Furthermore, a better description of environmental factors that promote recovery is needed and better evidence-based cognitive, behavioral, and medication interventions need to be developed. Currently, there is a paucity of strong evidence-based interventions available for management of children after TBI.

Figure 1. Conceptual model of factors related to recovery after TBI



VIII. Financial issues and considerations

Not applicable for this research

IX. Education and training issues and considerations

Not applicable for this research

X. Legislative and regulatory issues and considerations

Not applicable for this research

XI. Data and information issues and considerations

To build on the original study, we collected information related to current executive, behavioral and psychosocial functioning to allow us to further characterize the longitudinal recovery after adolescent TBI in this cohort. To specifically address psychosocial functioning during the transitional age period, we administered several assessment tools to better characterize the degree of disability, community reintegration, and independent functioning.

Adaptability: The Mayo-Portland Adaptability Inventory (MPAI-4) was used to measure problems encountered after TBI across multiple domains: physical, cognitive, emotional, behavioral, and social (J. Malec, 2005; J. F. Malec & Lezak, 2008). The MPAI-4 provides an overall score and 3 subscale scores (Ability index, Adjustment index, and Participation index). The measure was primarily designed to assist with the clinical evaluation and the evaluation of rehabilitation programs used after TBI. T scores on the MPAI-4 represent a comparison of function in individuals with acquired brain injury. T scores between 40 and 60 are considered average or typical functioning in individuals after brain injury. T-scores below 30 represent relatively good outcomes, between 30 and 40 suggest mild limitations, between 40 and 50 represent mild to moderate limitations, 50 and 60 represent moderate to severe limitations, and above 60 suggest severe limitations.

Behavior: The Child Behavior Checklist (CBCL) was used to provide a parent-report of behavior problems for children in this study (Achenbach, 1991a; Achenbach & Rescorla, 2001). The CBCL has been used previously to characterize behavior problems after pediatric TBI (McCauley et al., 2011). Eight subscales within the CBCL assess various behavioral characteristics: “Anxious Depressed”, “Withdrawn Depressed”, “Somatic Complaints”, “Social Problems”, “Thought Problems”, “Attention Problems”, “Rule Breaking Behavior”, and

"Aggressive Behavior". The subscales are used to derive a Total Problems Score and an Internalizing and Externalizing Problems Score. T-scores between 60 - 63 correspond to the 10^{th} – 16^{th} percentile of a normative sample and are indicative of clinical concern (Achenbach & Rescorla, 2001). Scores above 63 correspond to scores obtained by less than 10 percent of a normative sample and are indicative of deviant behavior (Achenbach & Rescorla, 2001). The CBCL also generates competence scores in Activities, Social, and School domains. A total competence score is the sum of each of the three competence domain scores. T-scores of 31-35 correspond to the 10^{th} – 16^{th} percentile of a normative sample and are indicative of clinical concern and T-scores <31 correspond to scores obtained by less than 10 percent of a normative sample and are indicative of deviant behavior on the Activities, Social, and School domain scores (Achenbach & Rescorla, 2001). On the total competence scale, T-scores of 37-40 correspond to the 10^{th} – 16^{th} percentile of a normative sample and are indicative of clinical concern and a T-scores <37 correspond to scores obtained by less than 10 percent of a normative sample and are indicative of deviant behavior (Achenbach & Rescorla, 2001). The Youth Self-Report (YSR) was used to provided self-report perspectives on the child's behavior problems.(Achenbach, 1991b; Achenbach & Rescorla, 2001)

Executive function: The Behavior Rating Inventory of Executive Function (BRIEF) was completed by the participant's family-identified primary caregiver to assess executive function (Donders, DenBraber, & Vos, 2010; G. Gioia, Espy, & Isquith, 2003; G. Gioia, P. K. Isquith, S. C. Guy, & L. Kenworthy, 2000; G. A. Gioia & Isquith, 2004; G. A. Gioia, P. K. Isquith, S. C. Guy, & L. Kenworthy, 2000). The BRIEF has good internal consistency, inter-rater reliability, and test-retest reliability and has been validated in pediatric TBI.(Donders et al., 2010; G. A. Gioia & Isquith, 2004) The BRIEF provides an assessment of executive function in everyday settings and demonstrates good ecological validity (G. A. Gioia & Isquith, 2004). The Global Executive Composite (GEC) is a composite of the Behavioral Regulation Index (BRI) and the Metacognition Index (MI). The BRI provides ratings of a child's ability to appropriately stop

his/her own behavior; move freely from one situation to another; and modulate emotional responses appropriately (G. Gioia et al., 2000). The MI provides ratings of a child's ability to hold information in mind to complete a task; anticipate future events; carry out tasks in a systematic manner; keep workspace/play areas in an orderly manner; assess performance related to goal; and keep track of the effect of his/her behavior on others (G. Gioia et al., 2000). The BRI and MI are subdivided into specific subscales: BRI subscales are Inhibit, Shift, Emotional Control, and MI subscales are Initiate, Working Memory, Plan/Organization, Organization of Materials, and Monitor. Higher scores indicate more problems in executive function, with a score of 65 or greater indicating significant executive dysfunction (G. Gioia et al., 2003; G. Gioia et al., 2000).

Psychology functioning: The Brief Symptom Inventory (BSI) is a self-report symptom inventory that has been created to quantifiably observe psychological symptom patterns of individuals (Derogatis, 1993). This measure presents nine primary symptom dimensions: somatization, obsessive-compulsive, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism. The BSI also yields three global indices of distress: Global Severity Index, Positive Symptom Total, and Positive Distress Index. The BSI will benefit this study as it uses questions that relate to both adult populations as well as adolescent populations.

Community integration: The Community Integration Questionnaire (CIQ) was used to provide a measure of community integration after TBI (Dijkers, 2000; Willer, Ottenbacher, & Coad, 1994). It provides an assessment of overall community integration, but also measures integration in three specific domains: home integration, social integration and productive activities. Scores range from 0-29, with higher scores correlating with better community integration. A score of 29 indicates maximal community integration.

Quality of life: The Satisfaction with Life Scale (SWLS) was used to assess global life satisfaction (Corrigan, 2000; Diener, Emmons, Larsen, & Griffin, 1985). The SWLS has good

validity and reliability, and it has been used in the TBI Model Systems database since 1998 (Corrigan, 2000). Higher scores correlate with more satisfaction and are grouped into categories of very high satisfaction (30-35), high satisfaction (25-29), average satisfaction (20-24), mildly dissatisfied (15-19), moderately dissatisfied (10-14), and extremely dissatisfied (5-9).

Family Functioning: The family assessment device measure of global functioning (FAD-GF) has shown good reliability and validity (Byles, Byrne, Boyle, & Offord, 1988; Miller, Epstein, Bishop, & Keitner, 1985), and has been used previously in the evaluation of pediatric TBI to assess family functioning (S. L. Wade et al., 2003). Lower scores represent better family functioning. A score of 2.00 is considered average.

Education Status: We also obtained specific information through a questionnaire regarding the participants' current school status, including planned or completed high school graduation and planned or current enrollment in college, and we collected information about any specialized school-based services the adolescent may be receiving including school-based therapies, classroom accommodations, or Individualized Education Programs (IEP) or 504 plans. This allowed a qualitative assessment of services these individuals were receiving during this important transitional period after adolescent TBI.

Socioeconomic status (SES): An index of SES was constructed by averaging Z-scores for caregiver education and census tract income (Z-combined)

Table 3: Measures Administered - Organized by Domain/Construct, Measures, and Source

Domain/Construct	Measures	Source
Academic performance		
School functioning	Questionnaire*: School/Education status and need for specialized services	Parent/Adolescent
Neuropsychological and Executive Function Skills		
Executive Function	BRIEF*	Parent and Adolescent
Processing Speed	WISC-IV subtest	Adolescent
Memory	CVLT	Adolescent
Overall intelligence	WASI	Adolescent
Behavioral Function		
Social Competence/Behavior	HCSBS/CBCL*/YSR*	Parent and Adolescent
Global Behavioral functioning	CAFAS	Parent Interview

Social and Environmental Measures		
Chronic stresses and Resources	LESRI	Parent interview
Family Functioning	FAD*/IFIRS	Parent and adolescent interview/Observation
Socioeconomic status	Income, Education, Occupation	Parent interview
Adaptability	MPAI-4*	Parent and adolescent
Community Integration	CIQ*	Parent and adolescent
Quality of Life	SWLS*	Adolescent

* indicates measures collected with the long-term follow-up protocol.

BRIEF = Behavior Rating Inventory of Executive Function, WISC-IV = Wechsler Intelligence Scale for Children-Fourth Edition, WAIS-IV = Wechsler Adult Intelligence Scale, CVLT = California Verbal Learning Test, WASI = Wechsler Abbreviated Scale of Intelligence, HCSBS = Home and Community Social Behavior Scale, CBCL = Child Behavioral Check List, YSR = youth self-report, CAFAS = Child and Adolescent Functional Assessment Scale, , LESRI = Life Experiences and Social Resource Inventory, FAD = Family Adjustment Device, IFIRS = Iowa Family Interaction Rating Scale, MPAI-4 = Mayo-Portland Adaptability Inventory, CIQ = Community Integration Questionnaire, SWLS = Satisfaction With Life Scale.

XII. An analysis of the researcher findings

Description of participants: Thirty-seven participants completed the long-term outcome measures. The mean age at injury was 13.99 (stv: 1.66) years and follow-up assessment was 18.14 (stv: 1.93) years. Twenty-eight (75%) of the participants were male and 9 (24%) were non-white. Three (8%) were in 9^{th} grade, 6 (16%) were in 10^{th} grade, 7 (19%) were in 11^{th} grade, 5 (14%) were in 12^{th} grade, and 16 (43%) had completed high school. Six of the 16 that completed high school (38%) were attending college, and 18 of the 21 (86%) still in high school were planning on attending college.

Long-term follow-up outcome measures:

Adaptability: The average MPAI self-reported mean (stdv) T-score was 35.5 (11.3) and parent T-score ratings were 29.9 (18.1), indicating that individuals were self-reporting mild limitations and parents were reporting relatively good functioning overall in the cohort.

Behavior: The CBCL parent report indicated overall average functioning for the cohort with mean (stdv) T scores for internalizing behavior problems of 50.1 (10.4), externalizing behavior problems of 47.5 (9.8), and total behavioral problems of 48.7 (10.8). The youth self-report also indicated overall average functioning for the cohort with mean (stdv) T scores for internalizing

behavioral problem of 53.3 (11.8), externalizing behavioral problems of 50.9 (10.4), and total behavioral problems of 53.3 (11.3).

Executive function: Parent ratings of executive function indicating overall average functioning with mean (stdv) T scores of 52.6 (12.1) for the GEC, 53.3 (11.8) for the MI subscale, and 51 (12.5) for the BRI subscale. Self-report of executive function were also in the average range overall with mean (stdv) T scores of 52.0 (11.8) for the GEC, 53.2 (10.3) for the MI subscale, and 50.2 (13.6) for the BRI subscale.

Psychological functioning: Self-report BSI ratings indicated mild psychological dysfunction. The mean (stdv) T scores for the global severity index was 56.6 (14.4), positive symptom index was 55.6 (14.2), and positive distress index was 56.8 (10.4).

Community integration: Community integration total mean (stdv) self-rating was 22.0 (3.3) and parent-rating was 16.2 (4.2), indicating that individuals with TBI rated their community integration better than their parents.

Quality of life: The mean (stdv) of the SWL questionnaire was 25.3 (8.3), indicating in general above average satisfaction with life in the cohort.

Family Functioning: The mean (stdv) of child rated global family functioning (FAD-GF) was 1.9 (0.45) and parent rated global family functioning was 1.7 (0.36). Both of these ratings are below the cut-off for family dysfunction of 2.16.

Correlation of executive, behavioral, and psychological functioning with quality of life, adaptability, community integration, and family functioning.

Self-rated executive dysfunction (GEC) was associated with decreased satisfaction with life (SWL) ($R=-.52$, $p=.0016$), and poorer adaptability (MPAI parent ratings: $R=0.60$, $p=.0001$; MPAI self-ratings: $R=.70$, $p < .0001$) and poorer self-rated community integration ($R=-.44$, $p=.0097$). Parent rated executive dysfunction (GEC) was associated with decreased satisfaction with life (SWL) ($R=-.51$, $p=.0017$) and poorer adaptability (MPAI parent ratings: $R=.66$, $p<.0001$, MPAI self-ratings: $R=.45$, $p=.0082$), and poorer parent rated family functioning ($R=.34$, $p=.05$).

Higher scores for total behavior problems on both the youth self-report and parent versions of the CBCL were associated with decreased satisfaction with life (YSR: R=-.52, p=.002, CBCL parent ratings: R=-.64, p=<.0001). Higher levels of youth-reported total behavioral problems on the CBCL were associated with decreased parent- (R=.44, p = .009) and self-reported (R=.61, p=.0001) adaptability on the MPAI and self-reported (R=-.47, p=.0046) community integration. Similarly higher levels of parent-reported total behavioral problems on the CBCL were associated with decreased parent- (R=.68, p=<.0001) and self-reported (R=.46, p=.0054) adaptability on the MPAI. Increased psychological problems on the BSI global severity index was associated with decreased satisfaction with life (R=-.70, p<.0001), poorer adaptability (MPAI parent ratings: R=.51, p=.002, MPAI self-ratings: R=.68, p<.0001). More self-reported behavioral problems on the CBCL were associated with poorer parent-rated family functioning (R=.45, p=.0073) on the FAD-GF.

Genetic information: Forty-seven of 122 potential participants completed the genetics portion of the study. Individuals completing the genetics portion were younger at the time of injury (13.9 versus 14.8 years) and were more likely to have higher socioeconomic status as measured by a composite score of parental education and median household income for zip code (p=0.0032). There were no differences between gender, race, or injury severity between participants that completed the genetic portion of the study and those that did not.

Table 3 shows the allele frequency of genotype markers that were evaluated. All genotypes tested were within Hardy Weinberg equilibrium, except the APOE genotype; however, the major and minor allele frequencies in the sample are comparable to APOE frequencies in the general population (2 = 8.4%, 3= 77.9%, and 4 = 13.7%)(Farrer et al., 1997).

Table 3. Hardy Weinberg Equilibrium of participants with genetic information

Marker	Number Participants	Number Alleles	Major Allele	Minor Allele	Minor Allele Frequency (MAF)	Proportion Missing	p-value
rs4680	46	2	G	A	0.446	0.021	0.498
rs11604671	47	2	G	A	0.447	0	0.122
rs4938016	47	2	C	G	0.372	0	0.354

rs1800544	47	2	C	G	0.33	0	0.213
rs1800497	42	2	G	A	0.202	0.106	0.221
rs1800955	47	2	T	C	0.298	0	0.906
rs553668	47	2	G	A	0.149	0	0.23
Apolipo protein E(APOE)	**47**	**3**	**3**	**2,4**	**0.0851, 0.1277 (sum = 0.2128)**	**0**	0.0152
DAT	47	2	10 repeats	9 repeats	0.191	0	0.496
DRD4	46	5	4 Repeats		0.293	0.021	0.259

SNP in the row highlighted orange is out of HWE.
SNP in the row highlighted grey has 10.6% of subjects with missing genotypes.

Association of SNPs with executive, behavioral, and psychological functioning.

Univariate linear regression was used to evaluate the association of various SNPs with executive, behavioral, and psychological functioning. Only parent ratings of executive and behavioral functioning were utilized in the analysis. SNP rs1800544 demonstrates a trend of an association with parental ratings of global executive function (GEC) (R-Square = .15, p = .087). SNP rs 1800497 demonstrates an association with psychological functioning on the BSI global symptom inventory (R-square = .28, p=.02). There were no associations demonstrated between polymorphisms and behavioral functioning as measured by the parent ratings of total behavior problems on the CBCL. There were no significant interactions between genes and treatment effects.

XIII. Conclusions

In our cohort of adolescents with brain injury followed approximately 5 years after injury, we found that as a group they exhibited typical executive and behavioral function. Psychological functioning was mildly impaired. They also demonstrated overall above average satisfaction with life, mild problems with adaptability, and good community integration. However, we also found that poorer executive function, increased behavioral problems, and increased

psychological symptoms correlated with decreased satisfaction with life and poorer adaptability. Although the group showed overall average function across multiple areas of functioning, the findings indicate that individuals with executive dysfunction, more behavioral problems, and more psychological symptoms are at risk for poorer quality of life and adaptability. Monitoring executive function, behavioral, and psychological symptoms long-term after injury will be important, so early treatments can be provided to these individuals.

There were a few genetic polymorphisms associated with executive function and psychological functioning after injury. Our conclusions with regard to the genetic association with these longitudinal outcomes are limited by our sample size. Future studies will need to further evaluate potential genetic influences on neurocognitive and behavioral recovery. The influence of environmental and genetic factors on cognitive and behavioral recovery after pediatric TBI will need to be further explored in the future.

XIV. Recommendations

Individuals who sustained a TBI as an adolescent have good neurocognitive and behavioral recovery. Nonetheless, they should be monitored long-term for the emergence of problems that may affect their quality of life and community integration. Problems with executive function, behavior, and psychological functioning may lead to decreased satisfaction with life and community reintegration. Future work will need to better elucidate factors that place individuals at risk for long-term problems and better evidenced-based treatments need to be identified to maximize the quality of life of adolescents long-term after TBI. Future research also needs to be done to understand the influence of genetics in combination with environmental factors on neurobehavioral and cognitive recovery after injury.

XV.References

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