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The Neuropsychology of Traumatic Brain Injury: Looking Back, Peering Ahead

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Abstract

The past 50 years have been a period of exciting progress in neuropsychological research on traumatic brain injury (TBI). Neuropsychologists and neuropsychological testing have played a critical role in these advances. This study looks back at three major scientific advances in research on TBI that have been critical in pushing the field forward over the past several decades: The advent of modern neuroimaging; the recognition of the importance of non-injury factors in determining recovery from TBI; and the growth of cognitive rehabilitation. Thanks to these advances, we now have a better understanding of the pathophysiology of TBI and how recovery from the injury is also shaped by pre-injury, comorbid, and contextual factors, and we also have increasing evidence that active interventions, including cognitive rehabilitation, can help to promote better outcomes. The study also peers ahead to discern two important directions that seem destined to influence research on TBI over the next 50 years: the development of large, multi-site observational studies and randomized controlled trials, bolstered by international research consortia and the adoption of common data elements; and attempts to translate research into health care and health policy by the application of rigorous methods drawn from implementation science. Future research shaped by these trends should provide critical evidence regarding the outcomes of TBI and its treatment, and should help to disseminate and implement the knowledge gained from research to the betterment of the quality of life of persons with TBI. (*JINS*, 2017, *23*, 806–817)

INTRODUCTION

The 50th anniversary of the International Neuropsychological Society provides a golden opportunity to take stock of research on the neuropsychology of traumatic brain injury (TBI). TBI is a major public health and socioeconomic burden worldwide (Humphrey et al., 2013; Roozenbeek, Mass, & Menon, 2013), as well as a primary focus for many neuropsychologists in their research and clinical practice (Podell et al., 2014). Entire volumes have been devoted to the role of neuropsychology in the assessment and management of TBI (Sherer & Sander, 2014).

Neuropsychologists and neuropsychological testing have played a critical role in research documenting the outcomes of TBI. The literature on the consequences of TBI is extensive, and a detailed review is beyond the scope of this study. In general, however, research indicates that TBI, especially when severe, can produce deficits in a variety of domains: alertness and orientation; language and communication skills; nonverbal skills; attention, memory, and executive functions; corticosensory and motor skills; academic achievement and work performance; social functioning; and adaptive functioning and emotional/behavioral adjustment (Roebuck-Spencer & Sherer, 2008; Yeates, 2010). Our goal in this study is look back at three major scientific advances in research on TBI that we believe have been critical in pushing neuropsychological research on TBI forward over the past several decades, and peer ahead to discern two important directions that seems destined to influence the field over the next 50 years.

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LOOKING BACK: ADVANCES IN NEUROPSYCHOLOGICAL RESEARCH ON TBI

Advance #1: Modern Neuroimaging

Structural imaging

One of the signature advances in neuropsychological research on TBI in the past 50 years was the advent of modern neuroimaging methods. Early neuroimaging techniques revolutionized our ability to visualize brain lesions, and have continued to advance our understanding of the pathophysiology associated with TBI.

Computed tomography. Introduced in the 1970s, computed tomography (CT) was the first imaging modality to characterize the heterogeneity in pathophysiology of acute TBI and elucidate its chronic neuropathology *in vivo*. Noninvasive and accessible to adults and children, CT enabled investigators in the National Institutes of Health (NIH) Trauma Coma Data Bank (TCDB) to classify severe TBI patients by specific types of pathology and improve prediction of global outcome (Eisenberg et al., 1990; Marshall et al., 1992). The TCDB also implemented central reading of the CT scans to ensure satisfactory reliability and developed a coding form that was a forerunner to the National Institutes of Health Common Data Elements for imaging.

Analysis of acute CT showed that focal left hemisphere lesions were associated with longer time until the patient began to obey commands (Levin, Gary, & Eisenberg, 1989), that is, the highest-level motor score on the Glasgow Coma Scale (GCS) (Teasdale & Jennett, 1974). Validated, predictive models for outcome of moderate to severe TBI have since included CT classification, combined with the total GCS score (or Motor score), age, and pupillary response (Roozenbeek et al., 2012). For mild TBI, acute CT showing contusions and other intracranial pathology ("complicated mild TBI") was found to predict worse neurobehavioral outcome than in patients with normal scans (Williams, Levin, & Eisenberg, 1990). In chronic TBI, the ventricle-to-brain ratio provided an index of brain atrophy that was related to cognitive and behavioral sequelae (Turkheimer et al., 1984).

Magnetic resonance imaging. The introduction of magnetic resonance imaging (MRI) in the 1980s greatly expanded investigation of brain–behavior relations in TBI because it offered improved spatial resolution without exposure to ionizing radiation and was better suited to longitudinal studies. Heterogeneity in TBI pathology characterized by MRI was reported even in patients with the same GCS total score of 8 (Saatman et al., 2008). MRI also better identified pathology associated with TBI, facilitating investigation of neural mechanisms mediating neurobehavioral phenotypes. For example, basal ganglia pathology was identified in children who had mutism early after TBI (Levin et al., 1983). Morphometric MRI enabled investigators to identify pathology in structures such as the corpus callosum, which atrophied in adults and lagged in development in children following moderate to severe TBI (Ewing-Cobbs et al., 2008; Levin et al., 2000).

Powerful software for imaging analysis of MRI became widely accessible during the past 20 years, enabling investigators to more efficiently measure brain region volumes and parcellate tissue into gray matter, white matter, and cerebrospinal fluid compartments. Researchers have reliably measured brain region volumes in children and adults with TBI, finding reductions in volumes of specific regions that are related to neurobehavioral outcomes of moderate to severe TBI. Improved efficiency of pipelines for analyzing imaging data has also facilitated measurement of cortical thickness; investigators have found cortical thinning during early and chronic phases of recovery in a wide spectrum of acute TBI severity, including mild TBI (Govindarajan et al., 2016). Neuropsychologists have also reported that reduced cortical thickness is related to the cognitive and behavioral effects of TBI, again including mild TBI (Mayer et al., 2015).

Diffusion tensor imaging. More recently, diffusion tensor imaging (DTI) has provided a method for assessing the organization and robustness of white matter tracts and other regions by noninvasively measuring the directional coherence of water diffusion in tissue. With myelination continuing through the third decade, DTI is sensitive to brain development and to the effects of TBI in children on subsequent white matter maturation (Ewings-Cobbs et al., 2008). Animal models and clinical studies have supported the sensitivity of DTI to diffuse axonal injury, and suggested that TBI is a disorder of disrupted brain connectivity (Hayes, Bigler, & Verfaellie, 2016). DTI has been especially informative in mild TBI, as compared with the limited findings reported for clinical MRI (Wilde et al., 2015). Major tracts that frequently have abnormal mean diffusivity (MD), suggesting axonal injury or demyelination, or altered fractional anisotropy (FA), indicative of reduced neuronal integrity after TBI, include the genu of the corpus callosum, the cingulum bundle, and the uncinate fasciculus (Hulkower, Poliak, Rosenbaum, Zimmerman, & Lipton, 2013).

Functional imaging

Functional imaging techniques, including task-related functional MRI (fMRI) and resting state fMRI (rs-fMRI), as well as positron emission tomography (PET), developed after structural techniques, and have been used to study patterns of neural activity underlying cognitive deficits and other neurobehavioral sequelae of TBI.

Task-related fMRI. Task-related fMRI, which became available to investigators earlier than rs-fMRI, has often shown increased brain activation associated with various cognitive, sensorimotor, emotional, and social cognitive functions following TBI, including both mild TBI (McAllister et al., 1999), and moderate to severe injuries (Scheibel et al., 2009). In contrast to task-related fMRI in uninjured persons, increments in activation may also be a nonlinear function of task difficulty following recent mTBI (McAllister et al., 1999). In tasks that assess functions such as working memory or cognitive control, brain injured participants may activate posterior cortical and subcortical regions that are not typically as active during performance by healthy subjects, who activate primarily lateral prefrontal cortex and inferior parietal cortex (Scheibel et al 2009). This aberrant pattern of activation after TBI has been interpreted as a compensatory mechanism, implicating reorganization of function (Newsome et al., 2010).

Resting state fMRI. When a person rests and is not engaged in a task, brain regions in the default mode network (DMN) are activated. The DMN consists of regions (e.g., posterior cingulate cortex, medial prefrontal cortex, lateral parietal cortex, temporal parietal junction) that exhibit synchronous activation at rest, that is, are functionally connected (Fox et al., 2005). In contrast, these regions normally deactivate during performance of an external task. DMN dysfunction, such as failure to deactivate when an unexpected external event demands cognitive control, may result from (1) altered within-network functional connectivity (FC), as in reduced connectivity between posterior cingulate cortex with ventromedial prefrontal cortex (Sharp, Scott, & Leech, 2014) or (2) alteration of between-network FC, such as increased connectivity between one or more DMN regions and ventrolateral prefrontal cortex, a task-related region (Figure 1; Newsome et al., 2016).

Emerging evidence indicates that failure of task-related regions to deactivate during rest or of DMN regions to deactivate during task performance are related to residual cognitive dysfunction (Sharp et al., 2014). TBI may also produce aberrant connectivity between the DMN and the

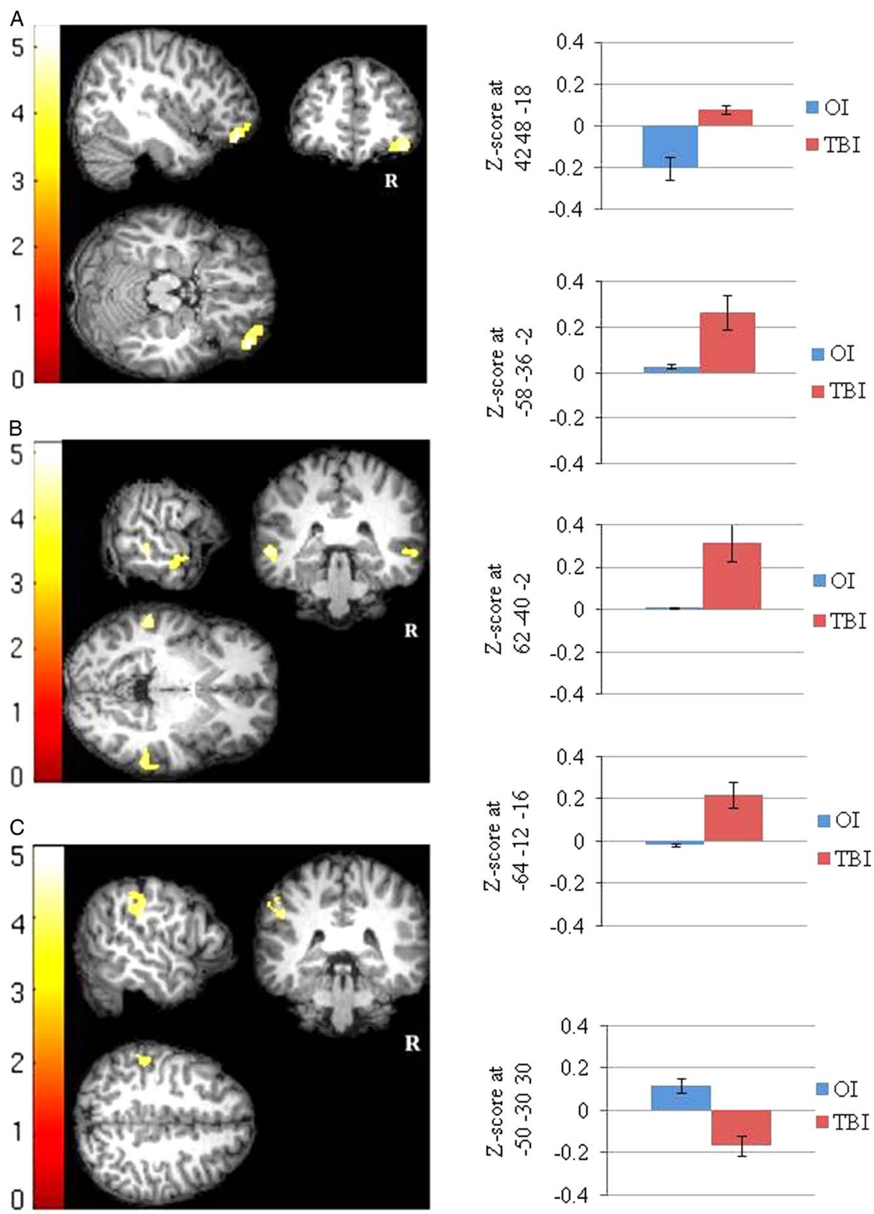

Fig 1. Thirty days after sports related concussion (SRC), high school athletes differed in FC of the DMN from a demographically similar group of athletes who had sustained an orthopedic injury (OI). (A) Using a posterior cingulate cortex seed, FC to ventrolateral prefrontal cortex was greater in the SRC than OI group; (B) With a right lateral parietal cortex seed, FC with right and left middle temporal cortex was also increased in the SRC group relative to OI athletes. (C) In contrast, a right lateral parietal cortex seed showed greater FC with the right supramarginal gyrus in the OI than SRC group, possibly related to residual pain or other sensation following orthopedic injury. From Newsome et al., 2016. Reproduced with permission by M. Newsome and *Frontiers of Neurology*.

salience network (i.e., anterior insula and dorsal anterior cingulate cortex), a network that underpins selective attention to relevant stimuli and switching between attention to internally generated mental activity and external events, However, the long range implications of aberrant FC following TBI remain to be elucidated. Longitudinal imaging is necessary to elucidate the long-term effects on connectivity, evaluate whether DMN status is a useful prognostic biomarker, and determine if measurement of FC is useful for evaluating interventions in TBI patients.

Positron emission tomography. Epidemiological and neuropathological studies of TBI have produced strong evidence that a single moderate to severe TBI is a risk factor for Alzheimer's disease (AD) and other dementias (Washington, Vilapol, & Burns, 2016). Moreover, mild TBI in persons older than 65 years has also been linked to dementia (Gardner et al., 2014). These reports have given impetus to research with PET, which can be used to measure the uptake of radioligands that selectively bind to beta-amyloid, providing an indirect index of amyloid plaques associated with dementia (Gatson et al., 2016). To prospectively evaluate *in vivo* p-tau deposits in former athletes, ongoing PET studies are using radioligands that selectively bind to p-tau (Dickstein et al., 2016). PET research also is underway to evaluate the chronic inflammation that is thought to result from TBI and contribute to neurodegenerative processes.

Network dysfunction and multimodality brain imaging

Although early imaging research on TBI focused on specific lesions or regional volumetric changes, current imaging research supports the view that studying network dysfunction can elucidate the neural mechanisms of acute neurobehavioral disturbance, such as posttraumatic amnesia, as well as chronic impairments, including attention and memory deficits (Sharp et al., 2014). Neural mechanisms of social cognitive and behavioral sequelae can also be understood by analysis of the relevant brain networks. Local and global connectivity and other metrics of network efficiency may prove to be useful as outcome measures for clinical trials in TBI (Bullmore & Sporns, 2012).

Usage of multimodality imaging also is a current trend in TBI research, facilitated by reduced acquisition times and motivated by discovering how different neural mechanisms interact in injury and repair processes and contribute to neurodegenerative conditions. For example, the interrelationship of structural to functional connectivity provides converging data that enhances the validity of each technique in isolation (Bullmore & Sporns, 2009). Multimodality imaging could potentially characterize the underpinnings of response to interventions, including pharmacologic and non-pharmacologic treatments.

Advance #2: Non-injury Influences on TBI Outcomes

At the same time that neuroimaging began to allow for much more precise characterization of the pathophysiology of TBI, researchers were becoming increasingly cognizant that injury severity accounted for only a small proportion of the variance in outcomes after TBI. A second critical advance in the field, therefore, was the recognition of the importance of non-injury related influences on recovery. For instance, research on childhood TBI was heavily influenced by the seminal studies of Rutter and colleagues showing that psychosocial adversity moderated the behavioral outcomes of childhood TBI (Brown, Chadwick, Shaffer, Rutter, & Traub, 1981).

Pre-injury factors

A variety of pre-injury factors have been identified over the years as important in predicting the outcomes of TBI. For instance, demographic factors such as age at injury are known to affect outcomes, with poorer outcomes demonstrated for both the youngest and oldest segments of the population (Anderson, Catroppa, Morse, Haritou, & Rosenfeld, 2000; Hukkelhoven et al., 2003). Pre-injury cognitive ability also has been shown to moderate the effect of TBI, with higher cognitive ability fostering better outcomes (Fay et al., 2010). Premorbid behavioral or psychiatric problems affect the outcomes of TBI as well. For instance, among adults with TBI, a prior history of depression predicts higher post-TBI rates of major depressive disorder (Alway, Gould, Johnston, McKenzie, & Ponsford, 2016; Bombardier et al., 2010).

Similarly, premorbid attention problems heighten the likelihood of an increase in post-injury attention problems among children with moderate to severe TBI (Yeates et al., 2005). Research indicating that pre-injury factors such as IQ or behavioral adjustment moderate the outcomes of TBI fueled theories of cognitive and brain reserve capacity, which suggest that vulnerability to neurological insults varies as a function of pre-injury functioning and brain integrity (Dennis, Yeates, Taylor, & Fletcher, 2007; Stern, 2000).

More recently, interest has turned to the potential role of genetics and epigenetics in modifying recovery from TBI (Kurowski, Martin, & Wade, 2012; McAllister, 2015). A variety of genes have been studied to date, with apolipoprotein E receiving the most attention. Associations with recovery have been inconsistent, but much additional research is needed, with sample sizes large enough to explore not only main effects, but also gene X environment interactions (Treble-Barna et al., 2016).

Comorbid conditions

TBI often occurs alongside other conditions that can hamper recovery. For instance, post-traumatic stress disorder (PTSD) can co-occur with TBI, although its estimated incidence varies widely (Bryant & Harvey, 1999), and PTSD is associated with poorer outcomes after TBI (Alway, McKay, Gould, Johnston, & Ponsford, 2016). The relationship between PTSD and TBI severity is uncertain, although the prevalence of PTSD is often higher in patients with mild TBI than moderate to severe TBI (Hoge et al., 2008; Zatzick et al., 2010). Sleep disturbance, cognitive problems, or emotional distress associated with PTSD may negatively influence recovery from TBI (Lew et al., 2009).

TBI is also frequently associated with comorbid pain, as a result of physical trauma, and possibly because of changes in brain functioning that affect sensory and motor functioning and, perhaps, perception of pain stimuli (Sherman, Goldberg, & Bell, 2006). A systematic review found a 75% prevalence of chronic pain among adults with mild TBI and 32% among those with moderate to severe TBI (Nampiaparampil, 2008). Among adolescents with TBI of all severities, 24% reported persistent pain 3 years after a TBI (Tham et al., 2013). Chronic pain is often associated with other problems, including functional disability, psychological distress, and vocational issues (Lew et al., 2009). In addition, pain and PTSD are often associated, as chronic pain can provoke PTSD-related thoughts and PTSD symptoms such as hyperarousal may increase pain intensity (Lew et al., 2009).

Compensation-seeking behavior or litigation is another common comorbidity with TBI that is associated with poorer outcomes. TBI survivors who are actively engaged in litigation generally report more and longer-lasting symptoms, which in turn are associated with longer delays in return to work and higher levels of psychological stress (Paniak et al., 2002).

Contextual factors

Contextual influences are another potential source of non-injury related variance in outcomes. For example, a substantial literature demonstrates that the home environment is an important predictor of the outcomes of childhood TBI. Measures of socioeconomic status are consistent predictors, as are more proximal measures of family status and the home environment (Taylor et al., 1999; Yeates et al., 1997). Notably, the home environment moderates the impact of childhood TBI, by buffering or exacerbating consequences (Taylor et al., 1999, 2002; Yeates et al., 1997). Specifically, the effects of severe TBI relative to orthopedic injuries are more pronounced for children from dysfunctional families than for children from more functional families.

The relative importance of injury severity and family environment varies according to the specific outcome, however, with injury severity playing a larger role for cognitive outcomes and the family environment assuming more importance for behavioral and functional outcomes (Yeates, Taylor, Walz, Stancin, & Wade, 2010). Among adults, better family functioning also has been associated with improved outcomes after TBI, including reductions in overall disability, improvements in adaptive functioning, and increased employability; in contrast, family stress and unhealthy family communication can hamper recovery (Sander et al., 2002).

Medical and non-medical intervention

The recognition that non-injury factors play a significant role in moderating the outcomes of TBI raised hopes that active interventions, ranging from acute medical care to education and workplace accommodations, could promote more rapid and complete recovery after TBI. However, the empirical evidence for most interventions remains limited. Guidelines exist for the acute medical management of TBI, but by and large are not based on rigorous evaluation through randomized controlled trials (RCT) (Jankowitz & Adelson, 2006), and many RCTs that have been attempted have failed (Adelson, 2010). As the next section shows, cognitive rehabilitation has been a focus of substantial research, although empirical evidence of its effectiveness remains limited, especially for children (Ylvisaker, Adelson, et al., 2005). The inclusion of family members in the rehabilitation of both children and adults with TBI has received some support (Braga, Da Paz Júnior, & Ylvisaker, 2005; Kreutzer et al., 2009). Family interventions may include educational, skill-building, and psychological support components. Much less is known regarding the effectiveness of educational or workplace interventions for persons with TBI (Mateer & Sira, 2006; Ylvisaker et al., 2001).

Advance #3: Non-physical Problems and Cognitive Rehabilitation

The heterogeneous nature of TBI results in considerable variability in the nature and severity of resultant impairments. Nevertheless, due to the high frequency of injury to fronto-temporal brain regions, as well as diffuse axonal injury, certain sequelae are particularly common. Over 50 years of research has shown that TBI often results in cognitive deficits in memory, attention, processing speed, word finding, and planning and problem-solving; behavioral difficulties such as lack of initiative, irritability, and poor temper control; somatic symptoms such as headaches, dizziness, fatigue, sleep disturbance, and poor balance and coordination; and psychological distress, including anxiety and depression (Dikmen, Machamer, Fann, & Temkin, 2010). Although these difficulties usually resolve to some degree, they persist in many cases even decades after injury (Himanen et al., 2006; Hoofien, Gilboa, Vakil, & Donovick, 2001; Ponsford, Downing, et al., 2014), and result in long-term difficulties with independence in daily activities and participation in work or study, leisure activities, and social and personal relationships (Ponsford, Downing, et al., 2014; Sherer et al., 2002).

In the 1980s, the growing realization that cognitive, emotional, and behavioral deficits had a greater impact on long-term functional outcomes than physical impairments led to the birth of the field of cognitive rehabilitation. The field has experienced tremendous growth since then. Early systematic reviews and guidelines initially identified only a handful of studies with rigorous methodology (Cicerone et al., 2000), but the number has grown steadily (Cicerone et al., 2005, 2011). Even so, few specific techniques are yet underpinned by strong evidence. Cognitive rehabilitation interventions can be broadly classified as either restorative, aiming to restore impaired functions, or compensatory, aiming to develop strategies or use residual strengths to minimize the functional impact of impairments.

Fatigue and sleep disturbance

Fatigue and sleep disturbance are debilitating and persistent problems for individuals with TBI of all severities (Ponsford et al., 2012). Until recently, these problems have not been the focus of treatment. Blue light therapy has been shown to reduce fatigue and daytime sleepiness in one pilot RCT (Sinclair, Ponsford, Taffe, Lockley, & Rajaratnam, 2014). Cognitive behavioral therapy has also shown some promise for addressing both sleep disturbance and fatigue (Nguyen et al., 2017).

Attentional problems

Both children and adults with TBI display a range of attention problems (Ponsford, Bayley, et al., 2014; Yeates et al., 2005). Substantial research has been devoted to evaluating methods of rehabilitating attention. Many studies in adults, and more recently in children, have focused on retraining attention using computer-mediated tasks. These reveal gains on the trained tasks, with generalization to similar cognitive measures but not to everyday attentional behavior (Laatsch et al., 2007; Ponsford, Bayley, et al., 2014). Stronger evidence suggests that metacognitive strategies can be applied to everyday tasks to compensate for everyday attention problems in adults, with evidence of potential for training in multi-tasking (Ponsford, Bayley, et al., 2014). Variability in nature and severity of cognitive impairments, self-awareness, and capacity to implement compensatory strategies are likely important determinants of success of any rehabilitative intervention for attention, although the influence of these factors has not been systematically studied. No studies have evaluated changes to the individual's environment to alleviate attention problems, although such interventions are frequently recommended for both adults and children (Savage, DePompei, Tyler, & Lash, 2005).

Memory problems

The use of restorative techniques such as computer-based training to enhance impaired memory processes after TBI has received little support (Velikonja et al., 2014). However, increasing evidence supports the use of compensatory strategies for memory problems. Studies have shown that internal memory strategies, such as mnemonics, visual imagery, and self-instructional methods, can enhance performance on neuropsychological tests (Velikonja et al., 2014). Self-instructional methods that also enhance the individual's understanding of manifestations of their memory problems have been successfully applied to prospective memory tasks in adults (Shum, Fleming, Gill, Gullo, & Strong, 2011; Velikonja et al., 2014) and children (Lawson & Rice, 1989).

Individuals with less severe cognitive deficits have shown more benefit from such memory strategies than those with more severe deficits, presumably reflecting the need for executive skills, including self-awareness, to implement strategies. Stronger evidence indicates that environmental supports, including diaries, notebooks, paging devices, mobile/smart phones, and Google calendar, are helpful to adults with memory impairments (Sohlberg et al., 2007). Use of picture prompts or the Neuropage has been effective in children (Lawson & Rice, 1989; Wilson, Emslie, Quirk, & Evans, 2001). An important determinant of successful use of such aids is the ability to manage the sophistication of the device, as influenced by age, executive skills, prior experience, access to supportive technology, and having a family member available to support and monitor use of the device (Velikonja et al., 2014). Errorless learning, spaced retrieval, and vanishing cues techniques also have all been shown to be effective methods of learning in individuals with TBI (Ehlhardt et al., 2008).

Disorders of communication and social cognition

Many communication disturbances associated with TBI involve changes in pragmatic skills that impair social competence for both children and adults with TBI (Togher et al., 2014). The recent development of theories of social communication after TBI has led to new approaches to assessment and treatment (Coelho, Ylvisaker, & Turkstra, 2005). Social communication training for adults with TBI, predominantly in group formats, has been shown to be effective for individuals 6–24 months post-injury (Togher et al., 2014). Training that incorporates everyday communication partners has been more successful, encouraging practice of skills beyond the period of the training (Ylvisaker, Turkstra, & Coehlo, 2005). RCTs focusing on emotion recognition and social inference have shown benefits (McDonald et al., 2013; Radice-Neumann, Zupan, Tomita, & Willer, 2009). Recognition is growing that interventions should be provided and evaluated in the natural environments of the person's everyday life, including with communication partners (Togher et al., 2014).

Executive dysfunction

Interventions for executive impairments have addressed self-awareness, planning, problem solving, self-monitoring, abstract reasoning, and cognitive flexibility. Metacognitive strategy training methods have some support, including goal-management training (Levine et al., 2011), multifaceted strategy training (Spikman, Boelen, Lamberts, Brouwer, & Fasotti, 2010), and training in problem orientation and problem solving in adults (Tate et al., 2014). As with other cognitive interventions, the likelihood of generalization is limited for individuals with severe executive and memory deficits, and is maximized by application in everyday contexts (Dawson et al., 2009; Grant, Ponsford, & Bennett, 2012). Several RCTs have successfully promoted reasoning abilities, including gist reasoning and categorization (Tate et al., 2014). Self-awareness deficits have been treated with involvement in contextualized activities, training to anticipate obstacles, feedback, self-monitoring, and self-evaluation techniques (Fleming & Ownsworth, 2006). Direct, within-task feedback also has been supported by RCTs (Tate et al., 2014).

Behavioral problems

Interventions for behavioral problems after TBI have received limited attention (Cattelani Zettin, & Zoccolotti, 2010; Ylvisaker et al., 2007). In the 1980s and 1990s, programs using structured contingency approaches to behavior modification were favored (Eames & Wood, 1985). In more recent years, advocates have promoted contextual approaches with Positive Behavior Support interventions, designed to teach or shape adaptive and cooperative social behaviors as well as to promote physical and functional independence (Ylvisaker, Jocobs, & Feeney, 2003). However, evidence for these interventions remains limited. Cognitive behavioral approaches to anger control were successful in one small RCT (Medd & Tate, 2000). In children with TBI, the focus has been on training social problem-solving, often in conjunction with parents, whose stress levels and parenting styles are strongly predictive of children's' behavior problems. Successful Interventions for behavioral problems have focused on families, delivered in person or online (Wade et al., 2011).

Anxiety and depression

The negative impact of psychological distress on functional outcome after TBI is increasingly recognized. Anxiety and depressive disorders occur in a significant proportion of adults with TBI (Alway, Gould, et al., 2016). In children, attention deficit hyperactivity disorder and depression predominate (Bloom et al., 2001). Although results have been mixed, recent evidence from RCTs suggests that cognitive behavioral therapy adapted to circumvent the effects of memory and executive impairments may reduce anxiety and depression symptoms after TBI (Ponsford et al., 2016). Adapted cognitive behavioral interventions for social anxiety are also being trialed in children.

PEERING AHEAD: THE FUTURE OF TBI RESEARCH

Although we do not claim to have a crystal ball, we agree that two important trends can be discerned in the field that are likely to shape neuropsychological research on TBI in the coming decades. One is the growing emphasis on "big data," as reflected in the development of large, multi-site research consortia and adoption of common data elements. The other trend is the increasing focus on knowledge translation, or how to translate research on TBI into clinical practice, especially in the domain of cognitive rehabilitation.

Big Data and Big Science: The Age of Consortiums and Common Data Elements

Early research on TBI often suffered from small, unrepresentative samples, disagreements about definitions of TBI severity and associated inclusion and exclusion criteria, and inconsistencies in predictor and outcome measurement. In recent years, the field has begun to overcome those problems by conducting large, multi-site studies with very large samples, in the context of both prospective observational research and RCTs, using common data elements that are collected consistently across all studies. Examples of individual studies that represent this movement include the TRACK-TBI study (Yue et al., 2013), the CARE consortium (Broglio, 2015), the 5P study (Zemek, Osmond, & Barrowman, 2013) and the ADAPT trial (Larsen et al., 2016). The selection and use of common data elements have been promoted by government funding agencies, such as NIH and Canadian Institutes of Health Research (e.g., Hicks et al., 2013; McCauley et al., 2012), as well as by large research consortia, such as the International Initiative for Traumatic Brain Injury Research (InTBIR) (Tosetti et al., 2013).

Recent multicenter studies of TBI also have implemented uniform imaging protocols and quality assurance procedures that have enhanced the feasibility of aggregating imaging data across different MRI platforms (Yuh et al., 2013). Central analysis of the data has also mitigated site differences in the review of pathology. Common data elements for reporting pathology based on MRI has enhanced harmonization of data across different centers (Duhaime et al., 2010). TRACK-TBI investigators have reported that punctate lesions seen with a gradient echo sequence are indicative of hemorrhagic axonal injury and, along with the presence of contusions, improve prediction of three month outcome of mild TBI even after taking into account CT results and other clinical data (Yuh et al., 2013). This finding suggests that imaging biomarkers may enrich studies of mild TBI patients (and other TBI groups). This strategy could facilitate clinical trials by selecting those patients who are at high risk for persistent problems and reducing heterogeneity in the samples.

Translating Research Into Clinical Practice

A second important trend in TBI research involves attempts to translate research into clinical practice. Although substantial gains have been made in understanding the impairments that impede adults and children who sustain TBI, and developing and evaluating interventions to overcome them, a significant gulf remains between research evidence and clinical practice. Almost all cognitive rehabilitation studies have been completed in experimental settings using artificial tasks, and have evaluated treatment efficacy using neuropsychological tests bearing little resemblance to the demands of everyday life.

Some recent studies suggest that a greater focus on making interventions relevant to the individual goals and needs of the adult or child with TBI and embedding them in everyday contexts will maximize the durability of gains (Togher et al., 2014). More studies in real world contexts are badly needed, especially studies that also examine what factors moderate response to intervention, including non-injury factors such as age, education, IQ, psychiatric status, family and social support, nature and severity of cognitive deficits, motivation, and environmental demands and supports.

Successful treatments need to be manualized, and methods of training clinicians and barriers to implementation evaluated. Over the last two decades, some clinical practice guidelines (CPG) have been developed in the domain of cognitive rehabilitation, guided by best available evidence (e.g., Cicerone et al, 2011; Bayley et al., 2014). Some evidence suggests that such guidelines can improve decision making and ultimately, clinical outcomes (Keris, Lavendelis, & Macane, 2007). However, a recent study auditing the use of the International Cognitive Rehabilitation working group guidelines by clinicians (Bayley et al., 2014) suggested a significant gap between the availability of CPGs and their use in clinical practice, even in specialized brain injury rehabilitation centers. An important next step is to evaluate the use of CPGs and associated clinical pathways using rigorous methods drawn from implementation science (Grimshaw, Eccles, Lavis, Hill, & Squires, 2012), with the goal of increasing evidence-based practice and improving patient outcomes.

CONCLUSION

The past 50 years have been a period of exciting progress in neuropsychological research on TBI. The advent of modern neuroimaging tools, the recognition of the importance of non-injury factors in determining recovery from TBI, and the explosion of research on cognitive rehabilitation, have all helped to push the field forward significantly. We now have a better understanding of the pathophysiology of TBI and how recovery from the injury is shaped by pre-injury, comorbid, and contextual factors, as well as a growing body of evidence suggesting that active interventions, including cognitive rehabilitation, may help to promote better outcomes. Future large-scale observational studies and RCTs using common data elements should capitalize on these past advances to provide critical evidence regarding the outcomes of TBI and its treatment; and formal knowledge translation efforts built on rigorous implementation science methods should help to disseminate and implement the knowledge gained from research into health care and health policy, to the eventual betterment of the quality of life of persons with TBI.

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