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Interventions for attention problems after pediatric traumatic brain injury: what is the evidence?

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Abstract

Objective—To gain an understanding of the current state of the evidence for management of attention problems after traumatic brain injury (TBI) in children, determine gaps in the literature, and make recommendations for future research.

Type—Focused Systematic review

Literature Survey—PubMed/Medline and PsychINFO databases were searched for relevant articles published in English over the last 20 years. Keywords included “attention” “attention deficit and disruptive behavior disorders”, and “brain injuries”. Studies were limited to children.

Methodology—Titles were examined first and eliminated based on lack of relevancy to attention problems after brain injury in children. This was followed by an abstract and full text review. Article quality was determined based on the United States Preventative Services Task Force recommendations for evidence grading.

Synthesis—Four pharmacological and ten cognitive therapy intervention studies were identified. These studies varied in level of evidence quality but were primarily non-randomized or cohort studies.

Conclusions—There are studies that demonstrate benefits of varying pharmacological and cognitive therapies for the management of attention problems after TBI. However, there is a paucity of evidence available to definitively guide management of attention problems after pediatric TBI. Larger randomized controlled trials and multicenter studies are needed to elucidate optimal treatment strategies in this population.

Keywords

Brain Injury; Child; Attention; Intervention; Review

Introduction

Traumatic Brain Injury (TBI) is a leading cause of morbidity and mortality in children, leading to almost half a million emergency department visits, 35,000 hospitalizations, and over 2,000 deaths per year in the United States [1]. TBI results in numerous physical and cognitive sequelae. Cognitive deficits following TBI in children involve problems with attention, behavioral regulation, and executive function that worsen with increasing TBI severity [2–7]. Attention deficit hyperactivity disorder (ADHD) that develops post-injury without evidence of pre-injury ADHD is often referred to as secondary ADHD (S-ADHD). The prevalence of S-ADHD after TBI is estimated to be 14.5–19% [8, 9]. Developmental or primary ADHD (P-ADHD) has a higher prevalence in the TBI population at approximately 20% versus 4.5% in the general population [8]. S-ADHD is strongly associated with severity of TBI and children with severe TBI have a higher risk for developing post-injury attention problems than those with mild or moderate TBI [10]. When combining these percentages, almost half of children who sustain a TBI will have persisting, worsening, or new attention problems after injury. The consequences of attention problems extend beyond school and learning, and can have negative impacts on a child's social relationships, emotional well-being, and quality of life [11].

Because of the high prevalence of attention deficits in children after a TBI and their far-reaching negative effects, there is a critical need to optimize treatments to maximize recovery and function. To date, the majority of intervention studies that have evaluated attention problems after TBI are adult-focused [12–26]. While the results of these studies are starting points for identifying therapies for children, adult and pediatric brains are very different. Children's brains rapidly develop throughout childhood and adolescence, and have high degrees of plasticity compared to adults [27]. Differences between pediatric and adult brains are likely associated with differential recovery and beneficial treatments may vary between the two groups.

The objective of this review is to describe the current literature specific to interventions, both pharmacologic- and behavioral-based, for attention problems in children after TBI. Previous review articles have primarily described studies in adults and have focused on pharmacologic interventions [13, 14, 17–22, 25, 26]. This article fills a critical gap by describing the state of the science of the current treatment options for attention problems after pediatric TBI. Due to the high prevalence of TBI in children and risk of developing new or worsening attention problems, it is imperative that evidence-based treatments are implemented to allow optimal management of attention problems in children after TBI. A discussion of the findings includes recommendations for current treatment based on the evidence and suggestions for future research.

Methods

A literature search was conducted using PubMed/MEDLINE and PsychINFO databases. MeSH search terms were used in PubMed and altered for use in PsychINFO. The MeSH search terms used were “attention” or “attention deficit and disruptive behavior disorders” combined with “brain injuries”. “Brain injuries” was designated as the major topic in the

search. In the PsychINFO search “attention deficit and disruptive behavior disorders” was changed to “attention deficit” and “brain injuries was changed to “brain injury”. The search was limited in both databases to articles published in the last 20 years (January 1993 – July 2013), human studies, articles published in English, and the age range was defined as childhood (0–18 years).

The initial search returned 651 results. Results were not considered if they were a book, dissertation, or review article. After reviewing titles, 604 articles were excluded because the titles were not related to attention problems after brain injury. Review of the 47 abstracts eliminated 19 articles. After review of the remaining 28 full articles, a further 14 articles were excluded, leaving the 14 articles that are included in this review (Figure 1). Articles were excluded during the abstract or full text review if a primary or secondary outcome measure specific to attention was not used, the article was a case study, the study population was composed entirely or primarily of adults (e.g., average age of study population was over 18 years), the study was not an intervention study, the article was a review that had not been previously identified, or the study did not measure attention before the intervention was administered. Because of the specificity of this review and the small number of studies identified, articles with mixed study populations of children with TBI and other acquired brain injuries (ABI) were also included. The results also contain studies that include young adults provided that children under 18 comprised the majority of the study population.

The studies were rated for quality of evidence as per the guidelines provided by the US Preventative Services Task Force (USPSTF) as follows: Level I: Evidence obtained from at least one properly designed randomized controlled trial, Level II-1: Evidence obtained from well-designed controlled trials without randomization, Level II-2: Evidence obtained from well-designed cohort-or case control analytic studies, preferable from more than one center or research group, Level II-3: Evidence obtained from multiple time series with or without the intervention, Level III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees [28].

Results

The identified studies were grouped into three categories: pharmacologic intervention (Table 1), cognitive therapy/attentional training studies (Table 2), and mixed injury studies (Table 3). The mixed (TBI and ABI) brain injury studies were all in the cognitive therapy/attentional training category, but are discussed separately given the wider variety of etiologies. In the second group, two of the identified studies used the same treatment cohort, but one of the papers reported outcomes immediately after treatment while the other reported six-month follow-up data, so they will be discussed as one study. Several studies in both groups had other cognitive outcome measures in addition to attention, but the focus in this article is placed on the results of attention-specific testing.

Medication Therapy

Four of the studies examined pharmacologic interventions. Three of the studies looked at methylphenidate, a drug primarily used for treatment of P-ADHD [17]. Two of the studies were composed of double-blind, placebo controlled, crossover designs. In a level I study

Williams, et al. studied 10 children with mild to severe head trauma [29]. Outcome measures specific to attention were the Symbol Digit Modalities Test (SDMT), Continuous Performance Test (CPT), and the Sentence Repetition Task (SRT). No significant differences were detected between placebo and methylphenidate conditions for attention or any of the domains measured in the study [29]. In the other level I methylphenidate study Mahalick, et al. studied 14 children with TBIs of varying severity [30]. The Gordon Diagnostic System, Woodcock-Johnson Psychoeducational Test Battery Revised, and the Ruff 2 and 7 cancellation test were used as attention-specific outcomes. The methylphenidate treatment resulted in significantly higher scores on all tests when compared to placebo. Despite similar methodologies, several differences between the studies could have led to the dissimilar results. In the Williams study, subjects were given methylphenidate based on weight (e.g. subjects weighing < 20 kg received 5 mg methylphenidate twice a day, 7.5 mg if 21–29 kg, 10 mg if >30 kg). In the Mahalick study, all subjects received a dose of 0.3 mg/kg. Specific information on injury severity was not provided with the Williams paper, so it is unknown if the two study populations have comparable injury severity. In the Williams study, subjects received methylphenidate for 4 days while in the Mahalick study methylphenidate was administered for 2 weeks. It could be that the longer treatment course and more specific dosing regimen contributed to the presence of significant differences between the groups in the Mahalick study.

Hornyak, et al. performed a level II-3 study with a retrospective chart review [31]. They found qualitative improvements in attention and behavior as reported by those involved in the subjects' care when subjects were on methylphenidate, and worsening in these areas if the methylphenidate was weaned or stopped [31]. Despite retrospective reviews being subject to numerous biases, the results indicate that methylphenidate has the potential to improve post-TBI attention deficits.

The final drug intervention study is a level II-2 study by Zavadenko and Guzilova on the effects of piracetam on cognitive functioning. Children with TBI received piracetam while a control group of children with TBI received no drug. Two or 3 patients in each group were also receiving acetazolamide as part of their treatment but this was not factored into analysis. Outcome measures specific to attention were the correction test (Bourdon-Vos) for directed attention and Stroop test for distributed attention. The authors found significant improvements for both measures of attention in both the number of errors and the time it took to take the test for the piracetam treatment group [32]. The study also found that the piracetam treatment group had significant improvements in motor function and coordination [32]. There were no other studies identified examining the effects of piracetam on attention after TBI in children or adults, so more investigation is required before piracetam could be integrated into treatment protocols for attention deficits. However, the study indicates that piracetam is potentially useful for treatment of attention and other executive function deficits after TBI, especially in the context of corresponding motor or coordination deficits.

Cognitive Therapy/Attentional Training

Galbiati, et al. performed a level II-1 controlled study of intensive attention specific training in 65 children post-severe TBI [33]. The training was composed of tasks that targeted

different areas of attention, and tasks that stimulated meta-attention. The Continuous Performance Test II (CPT II) was used to measure attention at baseline, upon completion of training, and one year after training. Subscores used for the CPT II were omission, commission, hit reaction time (RT), standard error of RT, hit RT across interstimulus intervals (ISI), hit RT×block (measuring change of RTs across cues), risk taking, and overall index (whether or not an attention deficit is present). There were significant improvements in attention measures within the control group from baseline, but scores remained in the pathological range so these improvements were attributed to natural recovery after TBI. The treatment group had significant in-group gains in attention as well as significantly higher scores than the control group. At follow-up testing, IQ and attention scores for the treatment group improved into the low-normal range. The experimental group maintained their gains at the one year follow up with between group analysis showing the experimental group scoring significantly higher than controls in all CPT II subtests except for Hit RT and Hit RT ISI [33].

Thomas-Stonell, et al. performed a level I study that used the TEACHware™ program to train various aspects of cognition. The TEACHware™ program was designed to train 5 different skill areas: attention, memory and word retrieval, comprehension of abstract language, organization and reasoning/problem solving [34]. Significant within and between group improvements were limited primarily to tests examining word retrieval and problem solving/reasoning and no significant improvements were seen on the attention test, the Paced Auditory Serial Addition Task (PASAT)[34].

In a level III case series Catroppa, et al. used an executive functioning training program in three individuals [35]. The training consisted of 6 sessions, with each session focusing on different areas of executive functioning, including an attention-specific session. Attention specific testing for this study was the Number-Letter Trails test which measures divided attention. There was no significant change for any of the individuals in the test of attention from pre- to post-intervention[35]. Similarly to the Thomas-Stonell, et al. study, these results suggest that attention needs to be trained separately rather than part of a broader executive function intervention. However, these studies were limited by their relatively small sample sizes.

The final two studies, while not intervention studies in the traditional sense, examined aspects of cognition that could be used to shape cognitive therapy for children with S-ADHD. Sinopoli, et al. and Konrad, et al. both examined the effects of reward on attention in children with TBI [36, 37]. Sinopoli, et al. compared Stop Signal Reaction Time (SSRT) and percent inhibition in children with P-ADHD, S-ADHD, children with TBI, but without S-ADHD, and healthy controls [36]. Children in the P-ADHD group showed the most impaired inhibitory control, while children with S-ADHD fell between the other groups. The S-ADHD group did not differ significantly from either the controls or the P-ADHD group, indicating some impairment, though not to the same degree as P-ADHD. Only one subject in the S-ADHD group had sustained a severe TBI; therefore, the S-ADHD group may not be representative [36]. Konrad et al. compared response to reward in healthy controls, children with P-ADHD, and children with TBI (with S-ADHD and without S-ADHD in the same group) [37]. They found that while the SSRT improved during the reward condition for all

groups, the TBI group did not improve to the same degree as the P-ADHD group. Similar to the Sinopoli, et al. study, this study indicates that treatments for P-ADHD may be translated to the TBI population to some extent, but will likely need modification [37]. Although more research is needed to determine the exact effects of reward in children with S-ADHD and how this can be translated to therapy, a well-defined reward/consequence system is already a part of treatment for children with P-ADHD [38, 39]. Because children with S-ADHD have similar defects in response inhibition and similar responses to reward as children with P-ADHD, integrating reward/consequence systems into the treatment of S-ADHD may be beneficial. However, confirmatory studies are needed.

Mixed Brain Injury

Ho, et al. performed a level II-2 study that used diaries and self-instructional training in 15 children with mild, moderate, or severe ABI (9/15 subjects had TBI). Although the training focus and primary outcome measure in this study was memory, significant secondary gains were made on the Test of Everyday Attention for Children (TEAch) compared to pre-treatment scores [40].

Two of the identified studies used the Amsterdam Memory and Attention Training for Children (AMAT-C) as their treatment intervention. This training program is given over several weeks. A different skill is worked on each week and tasks increase in difficulty over time. The program focuses primarily on attention and memory training, but also includes training for other skills (e.g. behavior modification). Sjö et al. performed a level II-2 prospective cohort study in 7 children (3/7 subjects had TBI) where they measured neuropsychological aspects before and after 18–20 weeks of AMAT-C intervention [41]. After training, scores for the Test of Everyday Attention in Children (TEAch) showed significant improvement in one of 11 subtests; however, the majority of improvements were on tests of learning and memory [41].

Van't Hooft, et al. used a level I randomized, controlled study with 17 weeks of AMAT-C intervention in 38 children (21/38 subjects had TBI). Attention tests used were the Visual and Auditory Reaction Time Test, Vigilance Test of the Gordon Diagnostic System, Stroop Test, Binary Choice test, Coding test, and Trail Making Test (TMT). Immediately following the treatment intervention there were significant increases for the treatment group compared to controls in sustained attention (Gordon Diagnostic System) and selective attention (TMT, Binary Choice Reaction Time Test, Stroop test 1, and coding test) [42]. At six-month follow-up the gains made by the treatment group remained intact, with the treatment group scoring significantly higher in sustained attention (Gordon Diagnostic Test) and selective attention (Binary Choice Reaction Time Test). Significant improvements were also noted 6 months after treatment completion within the intervention group in selective attention (Stroop 1 and Coding test) [43]. The results of these two studies are conflicting. The Sjö, et al. study indicates that AMAT-C training is more beneficial for learning and memory skills while the Van't Hooft, et al. studies show that AMAT-C improves attention skills as well as memory. These inconsistencies may be secondary to the differing methodologies, sample sizes, and heterogeneity of brain injury etiologies of the groups.

De Kloet, et al. performed a Level II-2 study that looked at the use of video games in recovery from ABI [44]. After 12 weeks of individualized therapy in 45 subjects (22/45 subjects had TBI) using the Nintendo Wii, subjects saw significant improvement in a number of areas, including attention as measured by Baseline Speed and the Shifting Attentional Set – Visual[44]. Although the lack of a control group makes it difficult to determine the effects of the training versus natural recovery after injury, this study shows that video game therapy has the potential to be a useful treatment for a variety of sequelae after ABI.

Discussion

Despite the high prevalence of attention problems in children after TBI, there is a paucity of studies evaluating treatments for attention problems in this population. The current literature demonstrates that both pharmacologic and attention specific therapy have promise for management of attention problems after TBI in children. The influence of injury severity, characteristics of attention problems after injury, pre-injury history of attention problems and individual factors like age, gender, and genetics on the efficacy of interventions is unclear. A lack of common outcome measures across studies and measures that evaluate daily function make it difficult to determine broader effectiveness. Larger, prospective studies are needed to develop individualized evidence-based recommendations.

Methylphenidate is used as a first-line treatment of P-ADHD. I and our review indicated that methylphenidate may be effective for attention problems in children after TBI.. The discrepancies between the two prospective methylphenidate studies described above could be due to different dosing and treatment times. More studies are needed to determine its effectiveness for management of attention problems after pediatric TBI. The potential benefit of other stimulant and non-stimulant medications used for management of P-ADHD should also be evaluated in children with attention problems after TBI. While it was an isolated study, the evidence in the piracetam trial indicates that other classes of medications may be beneficial.

In terms of cognitive training, it appears that a variety of methods have the potential to improve attention problems after TBI. The best regimen is intensive attentional training as demonstrated in the Galbiati study. When multiple cognitive domains are targeted at the same time, attention shows minimal to no improvement. However, memory appears to be closely linked to attention, and training programs designed to improve memory in this population have led to gains in attention scores as well. Once the training program extends beyond attention and/or memory, its efficacy appears to decrease.

Of the four studies that had ABI populations, three demonstrated improvement in attention scores with the various interventions. Since these studies showed similar benefits to the TBI studies, results may be generalized to both ABI and TBI. The ABI and TBI outcomes were not evaluated separately; therefore, we are unable to determine if there were differential effects.

There are a number of limitations common among the studies that prevent drawing definitive conclusions about optimal treatment methods. One of the primary limitations is small sample size. Larger, multi-center studies are needed to inform the development of evidence-based treatment protocols. Another limitation is the heterogeneity of subject populations in terms of injury type and severity. Children with non-traumatic acquired brain injury also suffer from attention problems; however, they have different mechanisms of injury that likely affect their outcome and response to treatments. Most studies also include children with TBI of varying severities. Increasing severity of TBI is correlated with higher incidence of attention problems post-injury, so children with severe TBI might need more intensive or long-term treatment than children with mild TBI. It was not possible to differentiate the effects of treatments in children with a severe versus mild injuries from these studies. Future studies need to analyze for differential effects by injury severity. Most of the studies have different treatment interventions and outcomes, making it difficult to compare efficacy among them. Collaborative multicenter studies are needed to further elucidate the optimal treatment of attention problems in children and adolescents after TBI. There is also a need for more randomized, controlled, trials for both pharmacological and attention training interventions. Though it is difficult to blind subjects to treatment in attentional training studies, Couillet, et al. avoided this issue by using a cognitive training that did not target attention as a control condition, and referred to it with the subjects as an old versus new treatment method [45]. Another factor that should be considered when designing treatment plans is ADHD subtype [46]. In P-ADHD, there is debate in the literature as to the effect subtype (inattentive versus combined or hyperactive) has on treatment response [47–52]. The subtype of attention problems that develop after pediatric TBI may also influence treatment response and needs to be evaluated in future studies. Additionally, pre-injury diagnosis of ADHD was not assessed in the studies reviewed and may influence treatment response. About half of the studies used P-ADHD or other psychiatric disorders as an exclusion criterion while the others did not mention it explicitly. It is critical that future studies evaluate the influence of subtype and pre-injury ADHD diagnosis in the context of S-ADHD on treatment response.

The extent to which cognitive outcomes used in these studies can be applied to real world functioning is unclear. While various neuropsychological tests make good, objective measurements for research, they may not be the best predictors of daily functioning. Future studies should include ratings of behavior, attention, and executive function in typical settings, including the school, home, and community to get a complete picture of the effects of an intervention on TBI rehabilitation [53].

Combined behavioral and medication treatment have been explored for management of P-ADHD and evidence suggests that combining behavioral and medication management may be more beneficial [54]. To date, studies evaluating combined pharmacologic and attention training interventions in children with attention problems after TBI have not been performed. Since the studies examined in this review provide some promising results for the efficacy of each kind of intervention individually, studies of combined behavioral and medication treatments should be considered in the future.

In the last decade, pharmacogenomics has been a growing field and is beginning to be applied to the treatment of P-ADHD [55–57]. Catecholaminergic-related genes are of particular interest because their end products are influenced by stimulant medications commonly used for management of P-ADHD and they are integral to the modulation of memory, attention, and executive function after TBI [58–60]. These systems are also susceptible to injury and altered regulation after TBI [59, 61, 62] and are associated with neural recovery [62, 63]. Investigation of the influence of these genes on treatment response for attention problems after TBI should be considered in the future.

Limitations

The review was restricted to the last 20 years, omitting relevant articles that were published before 1993. Limiting the search to articles in English also excludes potentially relevant articles that were published in other languages. Restricting the review to articles published in peer-reviewed journals may have subjected our findings to publication bias. Additionally, the heterogeneity of the study populations and wide variety of outcome measures used across studies, make it difficult to make definitive management recommendations.

Conclusion

Traumatic brain injury is among the most common causes of morbidity and mortality in children. Development or worsening of attention problems occurs in close to half of children after significant TBI; however, there is a paucity of studies evaluating the benefit of pharmacologic or cognitive/behavioral interventions for attention problems after TBI in children [8, 9]. Overall, the findings are mixed. Methylphenidate is recommended as a first-line treatment for P-ADHD and demonstrates benefits in S-ADHD. Cognitive training appears to be beneficial when targeting attention or attention and memory specifically rather than mixing with other behavioral or cognitive interventions. Larger multi-center studies are needed to determine which interventions or combinations of interventions are most likely to improve S-ADHD. Additionally, future research should evaluate factors that may influence treatment response, ultimately leading to targeted individualized management.

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Definitions of abbreviations (alphabetical)

ABI	Acquired Brain Injury
ADHD	Attention Deficit and Hyperactivity Disorder
AMAT-C	Amsterdam Memory and Attention Training for Children
BRIEF	Behavior Rating Inventory of Executive Function
CCT	Craniocerebral Trauma

CPT (II)	Continuous Performance Test (II)
P-ADHD	Primary ADHD (developmental ADHD)
PASAT	Paced Auditory Serial Addition Task
S-ADHD	Secondary ADHD (ADHD acquired after trauma)
SDMT	Symbol Digit Modalities Test
SRT	Sentence Repetition Task
SSRT	Stop Signal Reaction Time
TBI	Traumatic Brain Injury
TEAch	Test of Everyday Attention in Children
TMT	Trail Making Test
VABS	Vineland Adaptive Behavior Scale
WAIS-R	Weschler Adult Intelligence Scale Revised
WISC III or R	Weschler Intelligence Scale for Children III or Revised

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Figure 1.
Methods of manuscript selection for review

Table 1

Summary of pharmacologic interventions

First Author/Year	Study Design	Population	Intervention	Primary Outcomes	Study Conclusions	Study Limitations	Level of evidence
Williams et al., 1998	Double-blind placebo-controlled, crossover study	10 subjects aged 5–16 years, 2 months to 9 years post-injury with history of mild to severe TBI; USA	Weight based methylphenidate dosing (if <20 kg get 5 mg; if 21–29 kg get 7.5 mg; if >30 kg get 10 mg) b.i.d. or placebo for 4 days;	Attention outcomes following treatment: SDMT, CPT, SRT	No difference between placebo and treatment groups on any outcome measures used.	All measures were not completed by all participants; one dose of the medication was given, short duration of treatment, small sample size, a prior power analysis unclear	Level I
Mahalik, et al., 1998	Double blind, placebo controlled, crossover study	14 subjects aged 5–14 years, 1 month to 5 years post-injury with TBI of varying severity (GCS 3–15); USA	0.3 mg/kg b.i.d. methylphenidate or placebo for 2 weeks	Attention outcomes following treatment: Gordon diagnostic system, Woodcock-Johnson Psychoeducational Test Battery Revised, Ruff 2 and 7 cancellation test	Statistically significant improvement on all tasks during methylphenidate treatment; no difference between placebo and baseline	Small sample size, short treatment duration, variable demographics	Level I
Hornyak, et al., 1997	Retrospective chart review	10 subjects aged 3–16 years at time of injury, 3 months to 4 years post-injury, with moderate and severe TBI (GCS 5–9); USA	Methylphenidate prescribed to treat post-injury sequelae; no dosing information available	Parent and teacher reports documented in the medical chart	Methylphenidate improved cognitive function, behavior, and arousal after TBI in children	Heterogeneous population, recall biases, documentation biases; not all subjects were given methylphenidate to improve attention, some were receiving it to improve arousal and agitation	Level II-3
Zavadenko and Guzilova, 2009	Comparative, non-randomized	44 subjects (20 experimental, 22 control) aged 12–18 years with moderate to severe TBI, 1.5–5 years post-injury; Russia	40–50 mg/kg/day dose of piracetam b.i.d. for one month or no drug given	Scores on various tests of function after treatment; for attention – Bourdon-Vos test and Stroop test	Significant increase in quality and improvement in performance time for both measures of attention	Control group was not receiving placebo; 2–3 subjects in each group were receiving acetazolamide as part of their treatment which was not accounted for in the analysis	Level II-2

Acronyms for Table 1 (in alphabetical order): b.i.d. = twice daily, CCT = craniocerebral trauma, CPT = Continuous Performance Task, GCS = Glasgow Coma Scale, SDMT = Symbol Digit Modalities Test, SRT = Sentence Repetition Task, TBI = Traumatic Brain Injury

Table 2

Summary of cognitive and attention training interventions

First Author/Year	Study Design	Population	Intervention	Primary Outcomes	Study Conclusions	Study Limitations	Level of Evidence
Galbiati, et al., 2009	Open-label controlled trial, non-randomized	65 subjects (40 experimental, 25 control) aged 6–18 years, 6–10 months post-injury with severe TBI (GCS <8); Italy	Attention-specific training consisting of both tabletop and computer based tasks 4x/week for 6 months	Cognitive (WISC-R/WAIS-R), behavioral (VABS), and attention (CPT II) testing immediately after and one year after training	While attention deficits improved without intervention, subjects that received specific intervention showed significantly more improvement than the control group, with IQ and CPT II scores in the normal range.	No VABS information collected about pre-injury function	Level II-I
Thomas-Stonell, et al., 1994	Prospective, randomized, controlled, cohort study	12 subjects (6 experimental, 6 control) aged 12–21 years, 3 months to 4 years post-TBI; Canada	TEACHware training program for 8 weeks or normal therapy regime	Neuropsychological scores after attention training; PASAT for attention	Significant gains between and within groups for word retrieval, memory, and problem solving/reasoning; all other tests, including PASAT were not significant for either analysis	Small sample size, subjects in various stages of recovery	Level I
Catroppa, et al., 2009	Case series	3 subjects, aged 11, 9, 10 at time of injury, 11, 11, 3 years post-TBI, respectively; Australia	One 1-hour session weekly for 6 weeks of executive function skills training	Various executive functioning tests after training; for divided attention – Number-Letter Trails test	Individual gains were made on various other tests, but not on the Number-Letter Trails test	Small sample size, no group analysis	Level III
Sinopoli, et al., 2011	Comparative Study	112 subjects aged 7–17 years in 4 groups: children with TBI (n=40), children with TBI and S-ADHD (n=9), normal controls (n=44), and children with P-ADHD (n=19); TBI groups were 1–6 years post-injury; Canada	Reward conditions during tasks	SSRT and percent inhibition with and without reward	P-ADHD had greatest deficits, S-ADHD fell between P-ADHD and control; reward improved inhibitory control across all groups - children with S-ADHD would likely respond to reward treatments used for P-ADHD	Small S-ADHD group	
Konrad, et al., 2000	Comparative study	Three groups (n=94) ages 8–12 years (ADHD = 31, TBI = 37, normal controls = 26), TBI group 6 months to 6 years post-injury; Germany	Reward conditions during tasks	SSRT with and without reward	All groups (ADHD, TBI, and control) showed improvement in SSRT with reward – however the ADHD group came within range of the control group, while the TBI group did not. This could indicate different mechanisms and therefore different treatment for attention deficit following TBI.	Did not examine mechanisms; 15 of the TBI group qualified to have S-ADHD but they weren't separated from the TBI group	Level III

Acronyms for Table 2 (alphabetical order): ABI = Acquired Brain Injury, ADHD = Attention Deficit Hyperactivity Disorder, AMAT-C = Amsterdam Memory and Attention Training for Children, CPT II = Continuous Performance Test II, GCS = Glasgow Coma Scale, P-ADHD = Primary Attention Deficit Hyperactivity Syndrome, PASAT = Paced Auditory Serial Addition Task, S-ADHD = Secondary Attention Deficit Hyperactivity Syndrome, SSRT = Stop Signal Reaction Time, TBI = Traumatic Brain Injury, TEACh = Test of Everyday Attention in Children, TMT = Trail Making Test, VABS = Vineland Adaptive Behavior Scale, WAIS-R = Wechsler Adult Intelligence Scale – Revised, WISC-R = Wechsler Intelligence Scale for Children – Revised

Table 3

Summary of Mixed 484 TBI and ABI studies

First Author/Year	Study Design	Population	Intervention	Primary Outcomes	Study Conclusions	Study Limitations	Level of evidence
Ho, et al., 2011	Prospective Cohort Study	15 subjects aged 11–17 years with mild, moderate, or severe ABI (GCS 3–15), 1–12 years since injury; Australia: 9/15 (60%) subjects had TBI; 3 had strokes, 2 had near drowning accidents, and 1 had an infection	6 week treatment protocol using diaries and self-instruction training	Memory and attention scores after treatment; for attention – subtests of TEAch	Although memory was the primary outcome targeted by treatment, attention scores improved significantly after the training (selective/focused attention and attentional control)	Self-selected cohort; not randomized; small sample; limited cognitive testing	Level II-2
Sjö, et al., 2010	Prospective cohort pilot study	7 subjects aged 11–15 years, 10 months – 8 years post-ABI; Denmark: 3/7 subjects had TBI; 2 had strokes, and 2 had brain tumors	AMAT-C intervention for 18 or 20 weeks	Neuropsychological evaluation after training; for attention – TEAch	Significant improvement in attention on 1/11 subtests; most improvement was noticed on tests of learning and memory	Small sample size, no control group, variety of diagnoses for brain injury	Level II-2
De Kloet, et al., 2012	Prospective cohort study	45 subjects aged 8–30 years, majority >2 years post-injury with various ABI; the Netherlands: 22/45 subjects had TBI; ABI types not specified	12 weeks of at least 2 hours/week of individually assigned games on the Nintendo Wii	Various neuropsychological and quality of life tests after treatment; for attention – Baseline Speed and Shifting Attentional Set – Visual (subsets of the Amsterdam Neuropsychological Tasks)	Among other improvements, significant gains were seen in both tests of attention	No control group; heterogeneity of study cohort	Level II-2
Van't Hooff, et al., 2007	Randomized, controlled trial	38 subjects aged 9 to 17 years, 1–5 years post-ABI; Sweden: 21/38 subjects had BI; 2 subjects had encephalitis, 1 had anoxia, and 14 had brain malignancies	AMAT-C intervention for 17 weeks or interactive control activity	Attention and memory scores 6 months after AMAT-C intervention; for attention – Visual and Auditory Reaction Time Test, Vigilance Test of the Gordon Diagnostic System, Stroop Test, Binary Choice test, Coding Test, TMT	Significant increase in sustained attention (Vigilance test of the Gordon Diagnostic System), selective attention (Binary Choice Reaction Time Test, Stroop test 3) were present 6 months after cessation of treatment; increases maintained in some memory tests as well	Small sample sizes, variety of diagnoses for brain injury	Level I

First Author/Year	Study Design	Population	Intervention	Primary Outcomes	Study Conclusions	Study Limitations	Level of evidence
Van't Hoof, et al., 2005	Randomized, controlled trial	38 subjects aged 9 to 17 years, 1–5 years post-ABI; Sweden; 21/38 subjects had TBI; 2 subjects had encephalitis, 1 anoxia, and 14 had brain malignancies	AMAT-C intervention for 17 weeks or interactive control activity	Attention and memory scores after AMAT-C intervention; for attention - Visual and Auditory Reaction Time Test, Vigilance Test of the Gordon Diagnostic System, Stroop Test, Binary Choice Test, Coding Test, TMT	Significant increase in sustained attention (Gordon Diagnostic System), selective attention (TMT, Binary Choice Reaction Time Test, Stroop test 1, coding test); increases in some memory tests as well	Small sample sizes, variety of diagnoses for brain injury	Level I

Acronyms for Table 3 (alphabetical order): ABI = Acquired Brain Injury, AMAT-C = Amsterdam Memory and Attention Training for Children, CPT II = Continuous Performance Test II, GCS = Glasgow Coma Scale, P-ADHD = Primary Attention Deficit Hyperactivity Syndrome, PASAT = Paced Auditory Serial Addition Task, S-ADHD = Secondary Attention Deficit Hyperactivity Syndrome, SSRT = Stop Signal Reaction Time, TBI = Traumatic Brain Injury, TEAch = Test of Everyday Attention in Children, TMT = Trail Making Test, VABS = Vineland Adaptive Behavior Scale, WAIS-R = Wechsler Adult Intelligence Scale – Revised, WISC-R = Wechsler Intelligence Scale for Children – Revised