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Executive dysfunction following traumatic brain injury: Neural substrates and treatment strategies

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Abstract. Executive dysfunction is among the most common and disabling aspects of cognitive impairment following traumatic brain injury (TBI), and may include deficits in reasoning, planning, concept formation, mental flexibility, aspects of attention and awareness, and purposeful behavior. These impairments are generally attributed to frontal systems dysfunction, due either to direct insult to the frontal lobes or to disruption of their connections to other brain regions. Evaluation of executive deficits typically includes neuropsychological assessment, though adjunctive interviews can be critical in detecting subtle dysexecutive symptoms that may not be apparent on standardized testing. Rehabilitation programs emphasizing cognitive-behavioral approaches to the retraining of planning and problem-solving skills can be effective in ameliorating identified executive deficits. In addition, pharmacological approaches may be useful in addressing aspects of executive dysfunction. This review summarizes the nature of executive deficits following TBI, their neuroanatomical substrates, selected assessment and treatment strategies, and recent research findings and trends.

Keywords: Executive functions, traumatic brain injury, TBI, assessment, treatment

1. Introduction

Executive dysfunction is an important component of neurobehavioral disruption following traumatic brain injury (TBI), often leading to significant functional impairment even in cases defined as "mild" TBI by commonly used medical criteria. Furthermore, the integrity of executive functions following TBI demonstrates significant associations with critical life outcomes such as vocational success and social autonomy, even when evaluated many years after injury [37,44]. The majority of cases of TBI involve some level of disruption in frontal-subcortical systems functioning, potentially resulting in impaired executive capacities. Such injuries include not only direct insult to the frontal lobes, such as through contusion resulting from coup or contrecoup injuries, but also indirect damage due to lesions in regions with afferent or efferent frontal connections, or disruption of these neuronal connections such as through white matter shearing. Cognitive and behavioral impairments resulting from executive dysfunction are often among the most persistent and prominent sequelae following TBI, despite otherwise good neurological recovery [6]. This article will outline those capabilities characterized as executive functions, their anatomic and neurochemical underpinnings, strategies for assessment of executive deficits, current remediation and treatment guidelines, and recent research developments.

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2. Definition of executive functions

Various authors have conceptualized executive functions in slightly different ways. Lezak [32] characterizes executive functions as consisting of four components: (1) volition; (2) planning; (3) purposive action; and (4) effective performance. Volition can be defined as the ability to conceptualize one's goals and form a plan to reach them, or the capacity for intentional, goal-directed behavior. The ability to exercise volition can be hampered by lack of insight into one's needs, lack of motivation to meet these needs, or difficulty initiating the behavior required to execute an action plan.

Planning includes the ability to organize the steps needed to complete an action, to prepare for various setbacks or difficulties in carrying out the plan, and to assemble the necessary materials and skills required to execute the plan. This requires the ability to exercise foresight, with reference both to oneself and to the environment, in order to prepare for various contingencies that may need to be addressed. Prerequisites for planning include adequate memory skills, sustained attentional capacity, motivation, volition, awareness, impulse control, the ability to consider and weigh options, and the ability to perform complex actions. The approach of an individual with TBI to novel situations will be illustrative with regard to his or her planning abilities. For example, persons with executive dysfunction may perseveratively follow familiar routines, even in situations where these routines are unproductive, rather than independently formulating new action plans. Individuals with TBI and their families also typically report difficulties in thinking ahead and anticipating possible problem situations that may arise.

Once a plan has been conceived, purposive action is required to implement it. This requires that the individual "initiate, maintain, switch, and stop sequences of complex behavior in an orderly and integrated manner" [32, p. 658]. The inability to carry out purposive actions can thwart a well-conceived plan, even if appropriate volition and planning skills are present. It is important to recognize that the ability to act is not synonymous with purposive behavior. It is also necessary to consider purposive behavior with relation to novel activities, rather than rote habits or behaviors, which may have become so familiar that they no longer require planning. Difficulties in discrete aspects of purposive behavior can have varying results. For example, individuals with TBI who have trouble initiating actions may repeatedly voice a plan yet never carry it out. Those with difficulty switching sequences may be unable to fine-tune or regulate action plans, or may perseverate and be unable to show mental flexibility.

Purposive or volitional behavior can also be negatively affected by impaired awareness, yet another aspect of executive dysfunction. This can include limited insight into emotional reactions or cognitive deficits, poor awareness of one's physical self, or limited recognition of appropriate cues in the external environment. Limited social awareness can be reflected by inappropriate interpersonal boundaries and interactions, or poor self-care, manners, and grooming skills. Each of these aspects is critical to successful completion of a task, and involves a distinct facet of activity-related behavior. However, these components are not mutually exclusive, and individuals with executive deficits are likely to demonstrate impairment in more than one of the above areas. For example, individuals with TBI who demonstrate impaired awareness may make inappropriate personal or sexual comments in social situations, or may fail to recognize verbal or nonverbal cues during interpersonal interactions.

Executive functions also include an individual's capacity for effective performance, which encompasses aspects of the execution of actions such as self-monitoring and self-correction. Here the quality of an individual's mistakes is important. Individuals with TBI experiencing executive dysfunction may make mistakes because they do not recognize that they have made an error, because they recognize the error but cannot shift cognitive set to fix it, or because they lack the motivation to correct the mistake. Luria noted that individuals with such deficits "lose not only control over their actions, but also the ability to check their results, although frequently they remember the task assigned to them perfectly well" [34, p. 210].

Other capacities often labeled as executive functions include attention and ideational fluency, defined as the ability to rapidly produce new or novel ideas [53]. Morse and Montgomery further define executive functions as "the processes and abilities involved in completing a goal or solving a problem" [42, p. 132]. These include recognizing the problem to be addressed, selecting a goal to be achieved and generating hypotheses to reach the goal, planning an approach to the task, initiating this plan, and self-monitoring the effectiveness of the plan in reaching the desired goal. This definition breaks planning down into several specific components in which impairment can lead to an inability to complete a given behavior.

Capabilities such as mental flexibility and avoidance of perseveration are integral to the functions described

above, and merit further elaboration. Individuals with executive deficits show an inability to respond to environmental feedback in such a way as to alter rigid thought and behavior patterns. Thus, perseveration reflects a lack of response inhibition. Those with impaired executive functions may also continually give the same response across a variety of situations, despite changes in environmental demands that make their response inappropriate or even dangerous. They are unable to shift response strategies in the face of new information or correction, at times even while verbalizing that they know their response to be in error.

Impairment in executive abilities has significant implications for the day-to-day life of those who have sustained TBI. When individuals are unable to respond adaptively to changes in the environment, their ability to function effectively is severely hampered, a pattern that may be reflected in "risk-taking" and "rule-breaking" behaviors, and which may result in failure to comply with guidelines, directions, or task instructions, and disregard for potential punitive consequences of following an incorrect plan. This type of perseverative set is also seen in the inability of those with impairments in executive functions to master associative learning. Such individuals are consistently unable to learn arbitrary associations, despite the intact ability to identify and distinguish various features of the associated items or concepts, as well as the ability to repeat the task instructions. Although not mutually exclusive with memory deficits, this specific problem cannot typically be attributed to memory impairment per se, but seems rather to result from the inability to internally regulate one's actions and responses [27]. Similarly, secondary impairment of other cognitive abilities may be seen as a result of executive dysfunction. For example, aspects of memory such as organization of information to facilitate encoding, discrimination of target from nontarget material, and working memory all have significant executive components. Deficits in these executive areas can therefore lead to pronounced memory impairment in individuals with TBI.

3. Neuroanatomy and neurochemistry of executive functions

Since the time of phrenologists such as Gall, it has been recognized that the frontal lobes of the cerebral cortex exhibit an organizing capacity for cognitive functions. In 1848, the famous case of Phineas Gage further provided a startling demonstration of the effects of massive frontal lobe damage on personality functioning [9]. More recently, it has been established that executive functions are sensitive primarily to damage of the frontal lobe, including dorsolateral, orbital, and medial structures of the prefrontal cortex. Impaired executive functions can also be seen with lesions to subcortical structures, including specific thalamic nuclei and areas of the limbic system, basal ganglia, and cerebellum, likely reflecting damage to the extensive connections between all of these areas and the frontal lobes. Of particular relevance to those studying the effects of frontal lobe systems impairment following TBI are important contributions by Stuss and Benson, Levin et al., and Fuster, which provide comprehensive discussions of research regarding frontal lobe structures and functional connectivity [15,29,54].

Luria [33] noted that the frontal lobes were the last of the cerebral structures to form evolutionarily, and that they have become progressively more prominent in "higher" animals. He conceptualized this region, particularly the prefrontal cortex, as tertiary association cortex, theoretically responsible for coordination of information from various associated areas. He stated that the relation of the frontal lobes to other brain regions enables us to understand "the important role of the frontal lobes in the regulation of vigilance and in the control of the most complex forms of man's goal-linked activity" [34, pp.187–188]. In accordance with Luria's theoretical framework, frontal structures demonstrate rich connections with many other brain regions, highlighting the importance of the frontal lobes in coordinating a variety of mental activities.

The frontal lobes include Brodmann's areas 4, 6, 8–14, 24–25, 32–33, and 44–47, encompassing the premotor, supplementary motor, primary motor, and prefrontal cortex. Medial aspects of these structures, including the precentral gyrus, supplementary motor cortex, superior frontal gyrus, anterior cingulate gyrus, and orbitofrontal cortex, are presented in Fig. 1. As noted above, frontal regions, and the prefrontal cortex in particular, also have connections to and from a range of cortical and subcortical structures. Insult to these structures or their frontal connections can likewise lead to deficits in executive functions. Brain regions with prominent neuronal connections to the dorsolateral prefrontal cortex include the posterior parietal cortex, superior temporal gyrus, cingulate cortex, basal ganglia, and superior colliculus. The inferior frontal area receives afferent connections from a variety of sites in the temporal lobe, amygdala, somatosensory, gustatory, and olfactory cortex, and has projections to

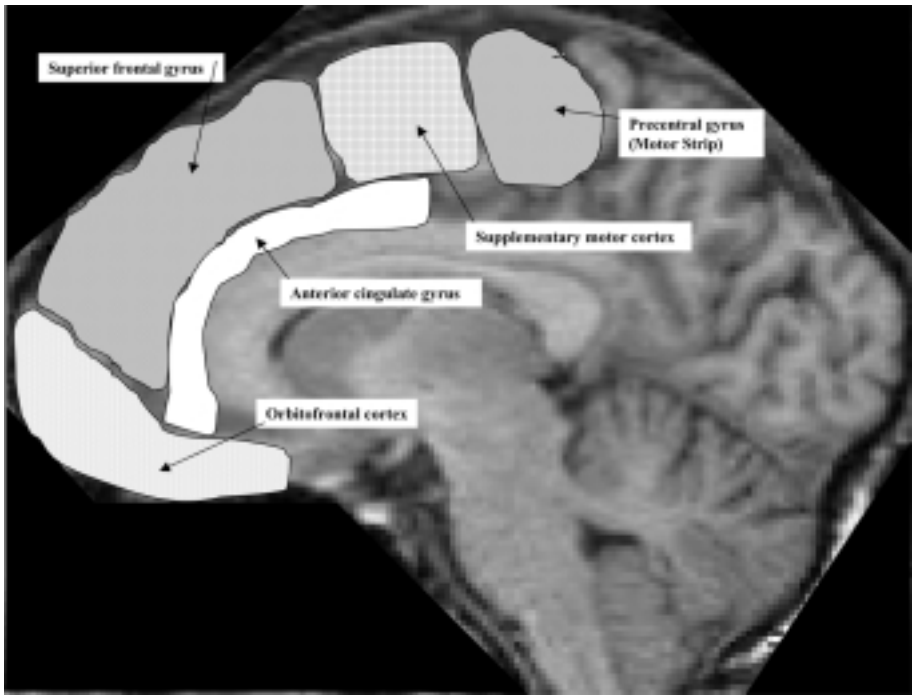

Fig. 1. Medial view of anatomic locations of selected frontal lobe subdivisions as displayed on a midsagittal T1-weighted MRI scan.

the amygdala and hypothalamus, thus influencing the autonomic nervous system.

In moderate to severe TBI, lesions affecting these regions will generally be readily apparent using neuroimaging techniques such as CT or MRI scans, at least in the acute stage, and executive deficits may be prominent in the neuropsychological test profile, as well as in behavior. Fontaine et al. [12] studied individuals with severe TBI at the subacute stage using PET, following resolution of CT or MRI abnormalities. These authors found that tests of executive functions, including measures of verbal fluency, divided attention, visual cancellation, and novel problem solving, correlated with regional metabolism in various frontal regions. This finding illustrates the expected structural substrate of several aspects of executive functioning, and highlights the susceptibility of individuals with TBI to impairment in these areas. The correlations observed by Fontaine et al. clustered in mesial and anterior areas, especially the left mesial prefrontal cortex (Brodmann's area 9) and middle and anterior cingulate gyri. Significant associations were also seen in the left frontobasal region and bilateral dorsolateral prefrontal regions (Brodmann's area 10), as well as in other prefrontal regions. While focal lesions may not necessarily correlate with neuropsychological impairment following TBI [30], global indicators of diffuse axonal injury or white matter atrophy have shown significant correlations with cognitive functioning [16].

Individuals who have experienced mild TBI may likewise report significant difficulties in executive capabilities and/or demonstrate notable impairment on cognitive testing, despite normal neuroimaging studies. Functional neuroimaging techniques such as PET, SPECT, and fMRI have been utilized to demonstrate differing activation patterns in individuals with TBI as compared to healthy controls, at times even in the presence of normal CT and MRI scans [21,36,43,45,52,57]. Studies have been able to demonstrate abnormalities in frontal systems activation even in individuals with mild TBI during completion of tasks with significant executive components, further highlighting the sensitivity of these functions to TBI [40,41].

Neurochemically, injury to frontal-subcortical regions disrupts several key brain neurotransmitter systems. Noradrenergic projections ascend bilaterally into the frontal poles from the pontine and medullary reticular formations and the locus ceruleus, and may contribute to the deficits in arousal, excitation, and attention seen in individuals with executive dysfunction, as do acetylcholine projections to the frontal lobes [14]. Cholinergic deficits resulting from TBI are also thought to contribute to various memory, behavioral, and motor deficits seen post-injury [10]. Dopaminergic neurons

are likewise clustered in frontal regions, including prefrontal cortex, and are thought to play a critical role in the initiation, planning, and organization of behavior deficits typically found in individuals with executive dysfunction [14]. DeKosky et al. [10] note that chronic catecholaminergic deficits following TBI are posited to contribute to aspects of cognitive impairment, including diminished attention, memory impairment, and slowed information processing.

4. Relationship of executive function deficits to injury profile in TBI

The typical profile of injury in TBI occurs when the moving head is stopped suddenly, with or without impact against another object. Such "acceleration-deceleration" injuries preferentially affect the frontal and temporal lobes, and can include contusions in the orbitofrontal and anterior and inferior temporal regions, and beneath or contralateral to the site of impact [17]. In addition, intracerebral hemorrhages can be seen in a variety of regions, and diffuse axonal injury may also occur, particularly in moderate to severe TBI. The latter is often most commonly apparent in the corpus callosum, the superior cerebellar peduncle, the basal ganglia, and the periventricular white matter. Furthermore, not all injury resulting from TBI occurs at the time of impact [10]. "Secondary injury" may be set in motion by the primary impact, but can evolve over subsequent minutes, hours, or even days. Sequelae due to secondary injury can therefore result in significant and far-reaching effects removed in location and time from the primary insult.

There is a direct relationship between increased degree of diffuse axonal injury resulting from TBI and injury severity. The frontal lobes, both the dorsolateral and orbitofrontal areas, and related circuitry (subcortical white matter, basal ganglia, thalamus, etc.) are vulnerable to TBI. As frontal regions are generally thought to be the anatomic "site" of executive functions, executive deficits can reasonably be expected to be prominent among cognitive sequelae of TBI, particularly given the predominance of frontal regions as a site of injury through the above-mentioned mechanisms [42]. Given the role these regions play in regulating and organizing behavior, impulse control, self-monitoring, planning, and reasoning skills, it is not surprising that individuals with TBI demonstrate such a strong tendency to evidence executive dysfunction, even in the case of "mild" TBI, or in the absence of other cognitive impairment.

5. Assessment of deficits in executive functions in individuals with TBI

Deficits in executive functioning can be evaluated to some extent by standardized assessment procedures such as neuropsychological evaluation. Unfortunately, however, the nature of the highly structured testing environment may minimize the effects of some types of executive deficits, particularly in individuals who sustain relatively "mild" impairments, which may nonetheless greatly impair their ability to function on a daily basis. For example, as pointed out by Cimino, "A patient may evidence gross deficits in everyday instances of judgment, planning, and decision making that render that patient virtually incapable of functioning effectively or independently in their environment. Nevertheless, that patient may score average or even well above average on measures of intellectual functioning such as the WAIS-R" [8, p.107].

Despite this difficulty, some standardized neuropsychological tests are sensitive to executive deficits. Brooks et al. [3] evaluated the sensitivity of various neuropsychological measures of executive functions to identify deficits in individuals with mild TBI. They found that, while many measures did not demonstrate significant differences between TBI subjects and controls, tasks tapping aspects of executive functions such as mental flexibility, ability to maintain cognitive set, and divided attention were sensitive to deficits in individuals with TBI. In particular, TBI subjects performed significantly worse than controls on Trail Making Tests A and B, the Controlled Oral Word Association Test, and several trials of the Paced Auditory Serial Addition Test (PASAT). Gronwall [e.g., 24] has likewise demonstrated the utility of the PASAT in discriminating between subjects with mild TBI and non-head-injured controls, and in assessing recovery of function following TBI. Research by Gentilini et al. [18] showed that individuals with mild TBI showed a trend toward poorer performance than controls on measures of executive aspects of attention, including selective, sustained, and divided attention, though only a measure of selective attention demonstrated a statistically significance difference between study groups. Raskin et al. [49] demonstrated that individuals with mild TBI were more likely to demonstrate impairment relative to normative data on executive tasks such as timed measures of complex attention, working memory, and mental flexibility, as well as on verbal memory tasks, rather than on tests of overall intellectual ability.

Table 1
Selective review of studies demonstrating executive deficits in TBI populations on standardized neuropsychological instruments

Author	Sample characteristics	Neuropsychological assessment techniques	Results
Bayless, Varney and Roberts [2]	25 vocationally-disabled adults with TBI; 25 employed adults with TBI; 25 healthy adult controls	Tinker Toy Test (TTT); Wechsler Adult Intelligence Scale (WAIS): Block Design subtest; test of Three-Dimensional Constructional Praxis	Impairment in TBI patients who were vocationally disabled on the Tinker Toy Test relative to TBI patients who had returned to work and controls
Brooks et al. [3]	11 adults with mild TBI; 13 demographically-matched healthy adult controls	Wechsler Intelligence Scale for Children, Revised: Mazes subtest; Trail Making Tests A and B (TMT); Boston Naming Test; Multilingual Aphasia Examination; Controlled Oral Word Association Test (COWAT); Paced Auditory Serial Addition Test (PASAT)	Impairment in TBI group relative to controls on Trails A and B, COWAT, and PASAT trials 2–4
Gutentag, Naglieri and Yeates [25]	22 children with moderate to severe TBI; 22 demographically-matched healthy child controls	Cognitive Assessment System (CAS)	Impairment in TBI group relative to controls on CAS Planning and Attention domains; Impairment in TBI group relative to controls on the CAS Matching Numbers, Planned Codes, Planned Connections, Number Detection, and Sentence Repetition subtests
Gentilini et al. [18]	50 adolescents and adults with mild TBI; 50 demographically-matched healthy controls	Selective Attention Test; Digits Forward Test; Word Recognition Test; Buschke's Selective Reminding Test; Working Memory Test; Raven Progressive Matrices	Impairment in TBI group relative to controls on the Selective Attention Test
Leon-Carrion et al. [28]	35 adults with moderate to severe TBI, 13 who required neurosurgical treatment and 22 who did not	Wisconsin Card Sorting Test (WCST); Tower of Hanoi/Sevilla (TOH)	Impairment in TBI surgical group relative to nonsurgical patients on WCST response time and TOH total moves required
Martzke, Swan and Varney [35]	20 adults with mild TBI who suffered post-traumatic anosmia	WAIS; Wechsler Memory Scale (WMS): Paired Associates subtest; Benton Visual Retention Test, Revised; Benton Facial Recognition Test; COWAT; WCST; Porteus Mazes; TTT	Scores below the 5th percentile for normals for 25–40% of subjects on COWAT, Porteus Mazes, and WCST; Scores below the 5th percentile for normals for 60% of subjects on TTT
Raskin, Mateer and Tweeten [49]	148 adults with mild TBI	WAIS-R; Symbol Digit Modalities Test; TMT; Attention Process Test; Visual Speed and Accuracy; WMS-R; California Verbal Learning Test (CVLT); Rey-Osterrieth Complex Figure; WCST; Stroop Color Word Interference Test; COWAT; Test of Reading Speed; Picture Rapid Naming; Wide Range Achievement Test, Revised, Level 2: Arithmetic subtest; Minnesota Multiphasic Personality Inventory	Greater impairment for TBI patients relative to normative data on measures of complex attention, working memory, and verbal learning, particularly on time-dependent tasks
Raskin and Rearick [50]	19 adults with mild TBI; 22 demographically-matched healthy controls	Animal Naming Test; COWAT (both groups); CVLT; WCST; PASAT (TBI only)	Impairment in TBI group relative to controls on Animal Naming and COWAT

Other researchers have shown that individuals with mild TBI also demonstrate impairments on phonemic and semantic verbal fluency tasks when compared to controls [50], as well as on the Wisconsin Card Sorting Test, a commonly used measure of novel problem-solving, conceptualization, and mental flexibility [55]. The Tinkertoy Test, another measure of purposeful, planned behavior, has also been shown to be sensitive to executive functioning deficits in individuals with mild to moderate TBI, as well as to correlate with the capac-

ity to return to work following injury [2,35]. Likewise, Gutentag et al. [25] demonstrated that children who have experienced TBI score significantly lower on measures of the Cognitive Assessment System which tap planning and attentional skills than neurologically normal children. Leon-Carrion et al. [28] also concluded that TBI subjects show executive deficits on the Tower of Hanoi/Sevilla task, a measure of planning and problem solving. These findings, which are summarized in Table 1, suggest that standardized tests can often be useful in detecting the executive deficits seen in individuals with TBI, and in tracking recovery of these functions over time. Furthermore, such research demonstrates that neuropsychological testing can be a valuable tool in assessing the presence of deficits even in individuals with mild TBI, who may not appear cognitively impaired to the typical observer, as opposed to those with moderate to severe TBI, whose neuropsychological impairments are more likely to be readily apparent both interpersonally and on formal assessment. Neuropsychological measures commonly used to evaluate executive functions and the specific cognitive functions they assess are listed in Table 2.

Additionally, impairments in executive functions may be assessed through interviews with individuals with TBI and their family members, as well as through self-report measures designed to assess deficits in executive capabilities as seen through difficulties in completing everyday activities. For example, individuals who have experienced TBI commonly report problems in organizing activities, remaining on task, regulating their emotional and/or behavioral response to a situation, and other symptoms which are typically reflective of executive deficits. Examples of structured interview tools which may be used to assess executive impairments include the Frontal Lobe Personality Scale [23] (now renamed the Frontal Systems Behavior Scale, or FrSBe), the Iowa Collateral Head Injury Interview [59], and the Behavior Rating Inventory of Executive Function (BRIEF) [19]. The FrSBe, for example, obtains self and/or informant ratings for adults both pre- and post-injury/illness, providing a measure of behavioral change which can be particularly useful for individuals with TBI. Test items tap such aspects of executive functioning as initiation of tasks or interactions, socially inappropriate behavior, organizational skills, mental flexibility, cognitive strategy use, and learning from mistakes. The BRIEF assesses similar capacities for children and adolescents through parent and teacher ratings, and includes items evaluating both behavioral and cognitive aspects of executive dysfunction, including response inhibition, mental flexibility, behavioral initiation, working memory, planning and organizational skills, self-monitoring, and emotional control.

6. Treatment of executive deficits post-TBI

Remediation of cognitive deficits following TBI typically includes cognitive rehabilitation strategies designed to target an individual's areas of deficit. Adjunctive pharmacological treatment may also be helpful in addressing the challenging emotional and behavioral difficulties often associated with executive dysfunction.

6.1. Cognitive rehabilitation

Interventions designed to remediate cognitive deficits resulting from TBI are a standard component of most rehabilitation programs. Indeed, Mazmanian et al. [38] found that 95% of rehabilitation facilities serving individuals with TBI provide cognitive rehabilitation services. Treatment is primarily provided in a one-on-one therapeutic relationship, though group, home-based, and self-directed treatment formats were also reported. Cicerone et al. define cognitive rehabilitation as a "systematic, functionally oriented service of therapeutic activities that is based on assessment and understanding of the patient's brain-behavioral deficits" [6, pp.1596–1597]. Such rehabilitation techniques typically aim either to ameliorate cognitive deficits by restoring skills as much as possible to their previous levels, or to help the person with TBI develop compensatory strategies for minimizing the effects of his or her deficits on daily life. These authors reviewed studies utilizing cognitive remediation techniques, with the aim of providing useful treatment parameters based on empirical evidence [6]. They found that treatments targeting executive deficits primarily utilized cognitive, behavioral, or combined cognitive-behavioral strategies, designed to promote skill acquisition, internal initiation, and self-monitoring of performance of these skills.

In one such program, von Cramon et al. [60] compared problem-solving training with memory training in 37 brain-injured subjects. This training program helped subjects develop skills in analyzing complex problems, breaking these problems into manageable components, forming viable alternative solutions, and choosing among these solutions. Results of comparisons of pre- and post-training neuropsychological assessment demonstrated significant improvement for the problem-solving training group on three of five

Table 2
Neuropsychological tests commonly used to assess executive functions

Test measure	Functions assessed
Wisconsin Card Sorting Test	Reasoning, concept formation, mental flexibility, learning from errors
Booklet Category Test	Reasoning, concept formation, mental flexibility, learning from errors
Trail Making Tests	Mental flexibility, visual scanning and sequencing, psychomotor speed
Paced Auditory Serial Addition Test	Divided attention, working memory
Tinker Toy Test	Initiation, concept formation, planning
Porteus Maze Test	Planning, generation of problem-solving alternatives, learning from errors
Tower Tests (London, Hanoi, Toronto)	Planning, problem solving
Figural Fluency Tests	Mental flexibility, susceptibility to interference, response generation
Phonemic and Semantic Fluency Tests	Mental flexibility, response generation, initiation
Stroop Color Word Test	Mental flexibility, selective attention, response inhibition
Continuous Performance Tests	Response inhibition, vigilance/sustained attention, distractibility

subtests of an intelligence measure, and on two tests of planning ability. Likewise, behavioral ratings by treatment providers showed significant improvements in the problem-solving training group as compared to the memory-training group on measures of day-to-day problem-solving behaviors, including awareness of deficits, goal-directed ideas, problem-solving skills, and premature actions. These findings were interpreted as demonstrating that the treatment promoted generalization of learned problem-solving skills to functional activities, rather than just improvement on isolated neuropsychological tests. While some subjects who received memory training also demonstrated improvement, these authors concluded that specially designed problem-solving training was more effective in remediating executive deficits than less targeted memory-training techniques.

Fox et al. [13] likewise employed a cognitive rehabilitation program which focused on problem-solving strategies relevant to everyday life. These authors reported on treatment techniques designed to promote skills in the areas of generating and selecting appropriate problem-solving plans in three individuals with TBI compared to three untreated controls. Subjects were taught to generate and select appropriate solutions to typical problem situations in four areas: community awareness and transportation; medication, alcohol, and drugs; stating one's rights; and emergencies, injuries, and safety, using a variety of behavioral techniques, including modeling, feedback, reinforcement, and self-monitoring strategies. Over the treatment period, subjects provided with training in problem-solving strategies demonstrated improvement in utilization of these strategies as measured by their responses to questions related to problem scenarios, and by ratings of interactions with facility staff in simulated problem situations. In contrast, the untreated controls demonstrated no significant improvement in problem-solving behavior. The gains made by the treatment group were maintained at 6-month follow-up, again demonstrating the utility of training in problem-solving techniques for individuals with TBI.

In a study designed to directly target deficits in executive functions, Cicerone and Giacino [7] utilized an individual treatment protocol to address impairments in planning and self-monitoring in five individuals with TBI. Over a five- to nine-week course of treatment, subjects received training utilizing self-instructional strategies with the Tower of London task. Analysis of results demonstrated significant improvement for most subjects with regard to task-specific errors. Pre- and post-treatment neuropsychological testing also demonstrated improvements on other measures of novel problem solving and response inhibition, showing improvement in executive functions which generalized beyond the training task. These authors also reported a reduction in off-task disinhibited behaviors both during treatment and at follow-up assessment, which they interpreted to indicate a generalization of treatment gains to everyday behaviors.

More recently, Levine et al. [31] utilized Goal Management Training (GMT) to remediate executive deficits in individuals with TBI. GMT targets the disorganization of behavior which is commonly seen following TBI, and aims to improve goal-directed behavior through training in discrete stages of goal completion, including assessing a situation and directing attention toward relevant goals, selecting appropriate goals and partitioning these into subgoals, encoding and retaining these goals and subgoals, and monitoring the outcome of an action with respect to the desired goal. In a randomized group trial, these authors found that, compared to a group that received only motor skills training, TBI subjects who received a one-hour GMT session improved their performance significantly on paper-and-pencil tasks that correspond to common everyday prob-

lem situations. The authors conclude that their results offer empirical validation for intervention strategies designed to target executive deficits commonly seen post-TBI, and indicate that such treatment can be beneficial even when administered in a time-limited fashion.

Based on their review of empirical treatment studies of cognitive rehabilitation programs, Cicerone et al. [6] conclude that training in formal problem-solving strategies and the application of such techniques to adaptive behavior and everyday problem situations is a recommended practice for post-acute treatment of TBI. Other authors [48] have also outlined specific treatment techniques for executive deficits, including compensation strategies, retraining of neuropsychological systems and underlying cognitive processes, and methods to enable generalization of rehabilitated skills across settings. In addition to being components of formal cognitive rehabilitation programs, such techniques can also be incorporated into individual, family, and group psychotherapeutic treatments. Research has suggested that the most effective cognitive rehabilitation programs are tailored to the personal profile of strengths and weaknesses of an individual with TBI, and set in a context of comprehensive rehabilitation services (e.g., cognitive rehabilitation, individual and/or group psychotherapy, speech and occupational therapies, vocational rehabilitation, etc.). Such an individualized program is more likely to be successful than a broad-based attempt to improve global cognitive functioning which does not focus on the specific deficits evidenced by a given individual, and does not first establish a foundation of basic skills upon which to retrain higher cognitive processes such as executive functions [22]. While Cicerone et al.'s [6] review of current cognitive rehabilitation studies offers a useful step towards empirical validation of the effectiveness of various approaches to remediating cognitive deficits following TBI, further research regarding effective behavioral treatment of executive impairment in this and other populations continues to be necessary.

6.2. *Pharmacological treatment of executive dysfunction and emotional/behavioral sequelae*

In addition to cognitive rehabilitation of neuropsychological functions, pharmacological treatment strategies may also be helpful in addressing the behavioral correlates of executive dysfunction following TBI. Individuals whose cognition and behavior become increasingly disorganized under stress may benefit from treatment with neuroleptic medications, though the potential cognitive and other side effects of these drugs may outweigh their benefits in terms of reduced agitation [4]. Those with amotivational symptoms typical of executive dysfunction may benefit from the activating effects of treatment with dopaminergic agents [58], while motor restlessness has been reported to improve with medications acting on both dopaminergic and noradrenergic pathways [56]. Tricyclic antidepressants have also been noted to improve arousal and initiation in some cases of severe TBI [51]. Other medications have been reported to be helpful in addressing the impairments in impulse control and regulation of aggression seen in individuals with TBI, including anticonvulsants, beta-adrenergic receptor blockers, serotonin reuptake inhibitors and other antidepressants, and mood stabilizers (e.g., lithium and valproic acid) [1,20, 39]. Research on the effectiveness of stimulants in improving memory, attention, and neurobehavioral disturbance following TBI has suggested that these medications have maximal utility in the early stages of recovery [5]. Other authors suggest that treatment of cognitive deficits with cholinesterase inhibitors may be a useful adjunct to pharmacological treatment of psychiatric disturbance in individuals with TBI [61].

6.3. *Novel physiological and pharmacological treatment strategies post-TBI*

Of great interest with regard to the potential for recovery of function following frontal systems disruption is recent research regarding the potential for neurogenesis in adult humans. It was previously thought that growth of new neurons in human brain ceased in adolescence. Recent research [11,26,46], however, has documented ongoing neurogenesis in adults, particularly in the hippocampus. Such findings offer exciting promise for novel treatment interventions for cognitive deficits resulting from TBI, among other conditions. Potential therapeutic strategies stemming from this research may foreseeably include gene therapies and pharmacological interventions designed to prevent cell death and promote neurogenesis in both the acute and longer-term stages following TBI, offering the potential to minimize or even prevent cognitive deficits, including executive dysfunction. Furthermore, research demonstrating the neurotrophic effects of mood-stabilizing medications such as lithium and valproic acid [62] may demonstrate another potential mechanism of action for these medications in the treatment of cognitive and mood sequelae of TBI.

In addition, research regarding the time course of neuronal damage following TBI offers insight into potential pharmacological strategies designed to target secondary neuronal damage occurring in the hours to days following injury. In a review of studies regarding pathobiological changes following TBI, Povlishock and Jenkins [47] note that not all neuronal changes following TBI occur immediately. For example, they posit that traumatic axonal damage is the delayed consequence of cytoskeletal changes initiated by the traumatic event, rather than the immediate result of tissue tearing in the course of TBI. These authors further note the sensitivity of the traumatized brain to later ischemic injury resulting from abnormal neurochemical activity (the "neurotransmitter storm") induced by the initial insult. Further research regarding the potential protective effects of pharmacological agents in preventing such secondary injury is yet another novel avenue in the treatment of individuals with TBI.

Ongoing research in our laboratory aims to assess the effectiveness of pharmacological challenges on remediating particular aspects of executive dysfunction following mild to moderate TBI. In a current study, McAllister et al., are investigating the effects of treatment with medications affecting the noradrenerginic and dopaminergic neurotransmitter systems on improving working memory deficits following TBI. Through examination of differential effects of these agents on performance of working memory tasks and brain activation during task completion, it is hoped that the neuronal mechanisms of executive dysfunction following TBI will be more clearly illustrated. Furthermore, the potential effectiveness of medication in ameliorating working memory deficits resulting from TBI will be examined.

7. Conclusion

Executive dysfunction is among the most common and troubling sequelae of TBI, even in instances classified as mild TBI using common medical criteria. This prevalence is largely due to the high incidence of damage to frontal systems in most cases of TBI, whether through coup or contrecoup injury to the frontal lobes themselves, or by disruption of frontal afferent or efferent connections to other brain regions. Impairment in executive abilities can have wide-ranging effects on an individual's ability to function effectively in his or her daily life, and can impair job performance, activities of daily living, and interpersonal relationships. Executive functions such as reasoning, concept formation, mental flexibility, planning skills, and self-monitoring are critical to execution of tasks ranging from correctly preparing a meal, to driving a car, to maintaining effective vocational functioning. For those with dysexecutive syndromes, evaluation of areas of cognitive deficit may include neuropsychological assessment utilizing test measures designed to target executive functions. More subtle deficits may not be evident on these tools, however, and patient and/or informant rating scales can also be invaluable for assessment of the presence of acquired executive deficits. Remediation of executive dysfunction most typically includes cognitive and behavioral rehabilitation strategies which focus on planning, problem-solving, and self-monitoring skills. Several such programs have demonstrated improvement in executive skills in comparison to untreated controls, or through pre- and post-testing using neuropsychological test results as dependent measures. Pharmacological treatment of some aspects of executive dysfunction can also be a useful adjunct to cognitive rehabilitation, particularly for those with prominent affective sequelae of TBI. Recent research regarding neurogenesis, secondary injury following TBI, and activation of various neurotransmitter systms during executive tasks also offers exciting potential for the future in terms of pharmacological interventions designed to minimize or prevent cognitive impairment following TBI. Given the prominence of executive impairment in individuals with TBI, and the pervasive influence of such impairment across activities of daily living, vocational functioning, and interpersonal relationships, it remains critically important to continue to empirically validate these and other effective treatment approaches to remediate these deficits.

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