Plasticity of executive functions after traumatic brain injury in adolescents

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Abstract

Children with a moderate to severe traumatic brain injury do recover quite well when it comes to talking and walking. They frequently may appear to make a full physical recovery and at the end of the rehabilitation period do often perform within the average range in various physical and standardized neuropsychological assessments. However, regardless of their performance on standardized tests, everyday functioning at home or in school remains generally poor. 'The hidden disability' such as difficulties in executive function and sometimes an 'unusual' behavior jeopardizes future socio-economic integration and can be deeply distressing for parents and siblings. Rehabilitation is essential to foster reorganization and further maturation of the child's brain, not only immediately post-injury but alongside the ongoing acquisition of higher cognitive skills. A computerized training program can provide a therapeutic manipulation of functional and structural neuroplasticity in the traumatized developing brain to enhance recovery and continuing maturation of executive function.

Introduction

Pediatric traumatic brain injury (TBI) is one of the most common causes of acquired cognitive and behavior disabilities in childhood (1). The worldwide annual incidence of pediatric TBI varies greatly by country, with most reporting a range between 47 and 280 per 100.000 children (1). A bimodal age distribution is described, with young children (<5 years) and adolescents (11-17 years) more commonly injured (1). In the last decades more children survive traumatic brain injury due to the emerging subspecialty of pediatric neurocritical care and the use of advanced neuromonitoring approaches in the acute phase of pediatric TBI. However, many of these young survivors experience lifelong neurobehavioral impairments and face deficits in day-to-day function at home and in school (2). Adults with a history of pediatric TBI are generally confronted with a delayed achievement - or even failure to reach - important milestones such as employment, independent living and engagement in valuable relationships. In addition, some papers showed evidence that a history of TBI during childhood or adolescence increases the risk of hazardous alcohol or substance use and criminality in adulthood (3).

Each child is unique in the way it responds to a brain injury and the substantial difference with adults is that the injury happens when "the brain has unfinished business". In a setting of developmental physical, cognitive and social growth, the level of function continuously changes over time. Some post-injury clinical effects may be initially subtle and often do not become apparent until the impaired area of the brain fully matures (4). Moreover, as children with TBI grow older, higher cognitive challenges (e.g. executive functions) and social expectations for behavior regulation are requested. Giza et al 2009 entitled the emerging deficits with age as: "children with TBI grow into their lesion" (5).

Fortunately, besides being specifically vulnerable, a developing brain may have advantages in reorganization or compensation after injury compared to the adult counterpart. Increased neurogenesis, myelination and synaptogenesis, particularly during time frames of brain-developmental "growth spurt", may offer augmented opportunities to interfere with rehabilitation programs. The rate of functional recovery across development and the presence of sensitive windows (growth spurts) during development, are important determinants in the as-close-as-possible age-matched outcome of a pediatric TBI.

The importance of "Executive Function"

TBI is clinically correlated with a spectrum of neurological deficits, however one of the main causes of poor socio-academic outcome from a pediatric TBI is sustained executive dysfunctioning (6). Executive function is an umbrella term that encompasses a set of core cognitive skills (attention, response inhibition, working memory and cognitive flexibility) and higher executive functions (such as strategy development, planning and problem solving) (7). Executive function is genetically determined in origin and has a protracted developmental trajectory from childhood into early adulthood with increased sensitivity to environmental influences and experience (8). Furthermore, this developmental course is characterized by "growth spurts in executive function" which occur from birth to 2 years, 7 to 9 years and again in adolescence from 12 to 16 years (9). These time frames involve peak periods of structural changes in cortical – subcortical grey matter and white matter brain networks, particularly vulnerable for a traumatic impact or adverse socio-economic circumstances however specifically sensitive for environmental influences with enhanced opportunities for rehabilitation intervention (10). Emerging executive skills throughout childhood is crucial to achieve greater autonomy and increasingly flexible and adaptive behavior, which is essential in scholastic achievement and social development (11).

Pathophysiology of traumatic brain injury

Cortical injury

Traumatic brain injury causes both focal and diffuse damage of the brain. Given the shape of the skull and how the brain is held in situ, focal lesions are most frequently seen in the frontal and temporal cortex (12). Focal contusion of the cortex may directly injure neurons, initiating an adverse metabolic cascade that ultimately leads to apoptotic cell death, which from a magnetic resonance imaging perspective may be expressed as cortical gray matter loss (13). This pathophysiologic process has an important impact on the maturation of the cortex during childhood into adulthood. As we know from previous literature, typical maturation of the brain is characterized by a well described prepubertal expansion of the cortical grey matter (based on neurogenesis, glial cell proliferation, dendritic spine motility and synaptogenesis) followed by postpubertal sustained loss, reflecting pruning and dendritic abbreviation to generate more adequate specific synaptic transmission (14). Since cortical maturation of the prefrontal and temporal cortex is correlated with the development of higher executive function and since these cortices are most frequently injured due to the morphology of the skull, the expectation for higher neurocognitive problems (e.g. executive function) following traumatic brain injury is high (15).

White matter injury

While grey matter volumes of the prefrontal cortex are significantly correlated with cognitive measures of executive function, they do not independently predict executive intelligence. In contrast, prefrontal cortical activation is supported by a large distributed network of cortical-subcortical structures and white matter circuits (16). Many neuroimaging studies have highlighted the additional but important role of the parietal, temporal, occipital, cerebellar cortex, and also the basal ganglia and thalamus have been increasingly recognized as essential nodes in higher executive circuits (17). There is a strong cohesion between these cortical-subcortical brain regions underlying executive function, moving and changing together in a flexible broad executive network (18). Unfortunately, this vulnerable dynamic organization can be seriously disturbed by a TBI. Rotational acceleration-deceleration forces at the time of injury, often seen in traffic or sports accidents, cause widespread axonal shearing and tearing, called diffuse axonal injury (DAI) (19). Axonal injury results in a degree of de-afferentation or de-efferentation of diverse brain regions, which is clinically correlated with a spectrum of neurological deficits ranging from comatose state to minor neurocognitive impairment (20). Recent research indicated that the anatomical distribution of DAI may have more implications for executive functioning than the total amount of DAI (21). When DAI is found in the corpus callosum and the deep brain nuclei, the neurocognitive impairment is significantly more prominent (21).

Rehabilitation of “the hidden disability” in pediatric traumatic brain injury

In every day clinical practice, it is fascinating to watch a child with an acute traumatic brain injury, progress from coma through low-level states to a functional condition. This recovery process likely follows a rather characteristic sequence and there is a temptation to imagine an intrinsic program of functional recovery (from basic behaviors -partly reflexive in origin- to obeying a command, learning new information and social interaction). The brain is malleable, but adaptive plasticity (based on genetic and environmental factors) is not enough to ensure recovery. An interesting prospective, longitudinal study of Abdullah et al. (2005) showed poor spontaneously improvement in cognitive functions during the first year following mild to severe traumatic brain injury in children, who were deprived from professional rehabilitation due to a lack of facilities in a rural area of Malaysia (22). Brain-plasticity in children with traumatic brain injury requires guidance and encouragement, and rehabilitation is an important driving force in this process. Many previous papers advocate that during the multidisciplinary rehabilitation process, children with TBI make most progress in the physical areas of functioning and the least process in cognitive-social skills (23). As a consequence, clinicians or pediatricians may fall into the trap of a good looking child with traumatic brain injury and don’t recognize the serious “hidden disability” of executive dysfunctioning.

Cognitive training in pediatric TBI

Many pages have been written about the efficacy of cognitive interventions in acute pediatric TBI and after several months of intensive cognitive training, children with TBI often perform within the low average range of standardized neuropsychological assessments. However, months and years post-rehabilitation, as requirements for new skills increase with age and executive development is jeopardized due to TBI, usually these children gradually fall behind in cognitive/executive skills compared to their peers (24). Therefore, cognitive rehabilitation is needed alongside the ongoing acquisition of higher cognitive skills (23). It is clear that recovery from pediatric TBI may go on for many years and it is impossible to state whether a child or adolescent with TBI has been “fully recovered” until the impact on final adult daily function is clarified.

A major limitation of cognitive remediation in the chronic stage of pediatric TBI is the intensity and duration of intervention programs, which is rather unrealistic in a clinical setting where services need to be economical and efficient. Furthermore, as children go to school and their parents go to work, only a home-based cognitive training program seems feasible and cost-effective. Increasing sophistication of computer technology provides new opportunities in home-based individualized tailored brain training to improve cognitive functions.

Our research group developed a novel homebased iPad application “BrainGames” which contains in total 8 different games to train multiple executive components including verbal- and visuospatial working memory, attention, cognitive flexibility, response inhibition, planning, updating, and processing speed (25). (Figure 1 and see appendix for more details regarding the content of the games.)

The games are adaptive with tasks increasing in difficulty and complexity as the child’s performance improves. The ultimate purpose of this computerized cognitive training is trying to attain generalization of gains into every day “real world” activities.

In a recent controlled study, 16 adolescents (mean age 15y8m SD 1y7m) in the chronic stage of TBI (mean time post injury 2y4m SD 1y2w) with impaired executive function were enrolled in an intensive 8-week (5 days per week, 40 min per session) cognitive training program with Braingames (26). Within a week and 6 months after the cognitive training, the adolescents underwent the same neurocognitive test battery as pre-intervention. Analyses indicated this cognitive training program was successful, in that it showed immediately post-intervention significant improvements in executive performance, which remained after 6 months. Moreover, a generalization of gains to untrained executive tasks in daily living was observed, reflecting in less executive dysfunction measured by the BRIEF (Behavior Rating Inventory of Executive Function). After a period of 6 months post-intervention, daily executive function of the participants with TBI did not differ significantly anymore with the healthy control group (in contrast to pre-intervention). With this long-term benefit (> 6 months) we may suggest that a boost of executive training in the chronic stage of TBI during adolescence, could perhaps redirect the disturbed developmental trajectory of executive function.

Mechanisms underlying training effects for cognitive skills are largely unknown, but cortical-subcortical communication between prefrontal cortex and deep brain nuclei (striatum and thalamus), and interhemispheric transfer of information through the corpus callosum are critical to achieve higher levels of cognitive functioning (27). In this study we observed that adolescents with DAI in the deep brain nuclei showed indeed significant lower benefit from the cognitive training on daily executive function (BRIEF) compared to TBI-adolescents without DAI in the deep brain nuclei. Furthermore, we noticed that adolescents with DAI in the corpus callosum showed no significant improvement in the BRIEF in contrast to TBI-adolescents without DAI in corpus callosum. Unexpectedly, we could not find a significant difference in training benefit in the presence or absence of prefrontal cortical encephalomalacia. This finding was surprising given the prominent role of the prefrontal cortex in executive functioning (16).

Grey matter correlates of cognitive training.

The integrity of grey matter in the prefrontal cortex and deep brain nuclei plays a crucial role in the level of executive functioning of the child with TBI (15). An important question is, are we able to “reconstruct” these injured brain-regions by cognitive training, and to what extent could training related (sub)cortical plasticity contribute to improvement of executive function? Several neuroimaging studies in healthy adults associated improvements in cognitive skills with measurable plastic alterations in brain grey matter after cognitive intervention. In these papers, a training induced expansion–renormalization model is described, including an expansion of grey matter in regions related to the trained function during and shortly after training, followed by a renormalization within a couple of weeks. Renormalization of grey matter indicates a remodeling of activity in efficient neuronal circuits with pruning and dendritic abbreviation, contributing to improved functional performance (28). This reported experience-dependent brain plasticity provides belief to the notion that cognitive training in children or adolescents with TBI targeting executive impairments, may also lead to adaptive changes in brain architecture. In our recent study with 16 adolescents in the chronic stage of TBI, we tried to find correlations between training related cognitive improvements and longitudinal structural grey matter changes in regions of interest (29).

Nine bilateral cortical/subcortical grey matter regions of interest (ROI) from the Desikan-Killiany parcellation atlas were selected (superior frontal, caudal middle frontal, rostral middle frontal, superior parietal, inferior parietal, anterior cingulate, caudate nucleus, putamen and thalamus) and 3 control regions (primary visual, primary auditory and primary somatosensory cortex) in which no cognitive training related changes were expected. After 8 weeks of intensive cognitive training with BrainGames, we could not observe statistical significant expansions in the mean grey matter volume of the 9 ROI's in our study population with TBI between onset and post-intervention, however comparing with the 3 control regions we did find a significant difference in change of grey matter volume over time post-intervention (29) Unfortunately, we were not able to identify significant correlations between structural and functional post-intervention variations.

Conclusion

Pediatric traumatic brain injury (TBI) is widespread and leads to important disability in thousands of children around the world each year. Overall, the incidence of pediatric TBI is likely to increase in absolute terms in the future because of the advances in pediatric neurocritical care. Children recovering from traumatic brain injury often have an 'invisibly injured' profile of a young person who talks, walks and has independence in learned activities of daily living, but who remains very incapacitated by new executive skill weaknesses. This persisting deficit impacts on the child's capacity to interact with the environment effectively and to harness experience in an adaptive fashion, resulting in problems in academic and social skill acquisition with increasing gaps between injured children and their peers as they move through adolescence into adulthood.

Figure 1. Screenshot of BrainGames on the iPad.

Appendix: "BrainGames"

Copy from our pilot-study: ***How to Train an Injured Brain? A Pilot Feasibility Study of Home-Based Computerized Cognitive Training.*** *Helena Verhelst, Catharine Vander Linden, Guy Vingerhoets, Karen Caeyenberghs. Games Health Journal 2017, 6, 28-38.*

Eight games of "Braingames"*:*

1. ***The vault***: verbal working memory.

   The player is a thief about to heist the contents of a vault. The player's accomplice communicates the digit combination verbally over the phone.

   The player is asked to remember auditory presented sequences of numbers. The response sequences of the player must be an exact match to the sequences as they were presented.
2. ***Stingrays***: inhibitory control and selective attention

   Stingrays swim in schools, but some stingrays will not swim in the same direction. The player is a deep sea diver, who keeps a close eye on them.

   Five stingrays are shown with the four outer stingrays pointing in the same direction and the central stingray either in the same (congruent) or in a different (incongruent) direction. The player has to indicate the direction of the middle stingray as fast as possible.
3. ***Moles in the garden***: visuospatial working memory

   There is a serious mole plague in the garden. The player is a gardener asked to catch the moles using traps.

   The player is asked to remember visuospatial presented sequences of moles in a 4 · 4 grid. The response sequences of the player must be an exact match to the sequences as they were presented.
4. ***Fishing***: vigilance and alertness

   The player is enjoying a lovely day while fishing on the lake.

   Whenever the fishing float moves (which occurs infrequently), the player has to collect the fish quickly.
5. ***Pictures***: monitoring, updating, working memory

   The player is reorganizing his photo albums and some of the pictures have to be removed.

   Pictures are shown one by one and the player has to remove the picture if the picture is the same picture as n trials before (n = 1, 2, or 3).
6. ***Shooting monsters***: selective attention, inhibitory control, cognitive flexibility

   The player is a space explorer, who just landed on a planet. He has to be careful; some of the inhabitants are not that friendly.

   Monsters are shown successively on the screen at different locations and the player has to shoot down target monsters and ignore distractor monsters.
7. ***Caterpillars***: visuospatial monitoring, updating, working memory

   It is caterpillar season and the player, who is a biologist, has to observe the caterpillars in a certain manner.

   Caterpillars crawl across the screen one by one. After this presentation, the player has to indicate which two/three/four caterpillar(s) crawled last (instructions vary according to the level)
8. ***Ice cream parlor***: divided attention and multitasking

   As a staff member of the ice cream parlor, the player is working hard on this busy day to keep the customers happy.

   The player has to prepare ice cream cones according to the orders he receives (comprising a cone type, flavor, and topping). He has to keep track of multiple ice cream stations at the same time and needs to react quickly so the ice cream does not melt.

Our research indicated that adolescents in the chronic phase of TBI improved in daily executive functioning after an 8-week home-based computerized cognitive intervention, with a long-term (6 months) effect and approximation to the executive skills of typically developing peers. Simultaneously, we observed alterations in grey matter volumes of regions of interest, acting over time significantly different from control regions.

Based on the long-term improvement of executive function, we could assume this persisting training-benefit is established by a positive redirection of the disturbed ongoing executive development in the chronic stage of TBI. Therefore we advocate post-rehabilitation repeating cognitive training programs alongside the neurocognitive development in children and adolescents, in order to keep them on track with their peers and provide them the optimal chances in academic, social and economic objectives. The frequency of these "cognitive boosts" has to be subject of further research, but starting with the key transition stages such as moving to the first, second or third grade at school could be an interesting idea. Obviously, studies measuring the effect of repeating cognitive training will need a very long term follow up to confirm whether these survivors of pediatric TBI "catch up" with their peers in terms of developmental gains and academic outcome.

Interestingly, in our cognitive-executive training study we were able to identify a subgroup of adolescents with TBI, who didn't perform so well pre- and post-intervention. Although previous literature reported that the success of executive function training has been most pronounced in children with the poorest executive performance, we suggest the opposite in adolescents with TBI (7). We indicated that adolescents with DAI in the deep brain nuclei and/or corpus callosum not only have the poorest outcomes in executive functioning, but also have the poorest training benefit from a computerized cognitive training program. In this particular group of adolescents with DAI, we have to take into account that executive benefit from repeating training programs as suggested above, might be insufficient.

We believe that the field of pediatric rehabilitation by neuro-modulation can be propelled by being mindful of the mounting knowledge of critical and sensitive periods in brain maturation. These promising windows with enhanced plasticity are unique and may offer a tremendous opportunity to intervene in the disrupted development. The assumption that adolescence is such a remarkable period of enhanced susceptibility for training effects, has already been demonstrated in prior research, and indeed in our study we measured convincing positive long-term effects of a cognitive intervention targeting executive function. However, more research in TBI-children of different developmental ages is needed to strengthen this belief of advantage. It is foreseeable in the near future that we can identify *when and which* traumatic lesions in the developing brain are more or less sensitive to therapeutic interventions. A deeper understanding of developmental neuroplasticity will change our rehabilitation approach for pediatric TBI into time-sensitive and lesion-specific based interventions covering the concept of "precision" pediatric neuro-modulation.

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Conflict of interest

There are no conflicts of interest in this study

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