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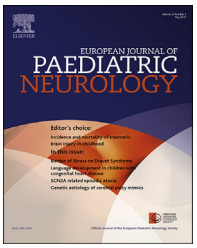

Original article

Is diffuse axonal injury on susceptibility weighted imaging a biomarker for executive functioning in adolescents with traumatic brain injury?

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ABSTRACT

Traumatic brain injury (TBI) is a heterogeneous disorder in which diffuse axonal injury (DAI) is an important component contributing to executive dysfunction. During adolescence, developing brain networks are especially vulnerable to acceleration-deceleration forces. We aimed to examine the correlation between DAI (number and localization) and executive functioning in adolescents with TBI.

We recruited 18 adolescents with a mean age of 15y8m (SD = 1y7m), averaging 2.5 years after sustaining a moderate-to-severe TBI with documented DAI. Susceptibility Weighted Imaging sequence was administered to localize the DAI lesions. The adolescents performed a neurocognitive test-battery, addressing different aspects of executive functioning (working memory, attention, processing speed, planning ability) and their parents completed the Behavior Rating Inventory of Executive Function (BRIEF) – questionnaire. Executive performance of the TBI-group was compared with an age and gender matched control group of typically developing peers. Based on these results we focused on the Stockings of Cambridge test and the BRIEF to correlate with the total number and location of DAI. Results revealed that the anatomical distribution of DAI, especially in the corpus callosum and the deep brain nuclei, may have more implications for executive functioning than the total amount of DAI in adolescents. Results of this study may help guide targeted rehabilitation to redirect the disturbed development of executive function in adolescents with TBI.

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1. Introduction

Pediatric traumatic brain injury (TBI) is the leading cause of non-congenital neurocognitive morbidity in childhood and adolescence.[1] Because the injury disrupts structural brain development and damages vulnerable immature brain connectivity, the development of neurocognitive skills is hampered.[2] Previous papers described that the long term consequence of a pediatric brain injury remains significant in adulthood, with a delayed achievement -or even failure to reach-important milestones such as employment, independent living, and engagement in valuable relationships.[2,3] Therefore, it is crucial to pursue a better understanding of the impact of TBI on a developing brain, recognize children at risk for persisting neurocognitive impairment, and provide individualized rehabilitation targeting dysfunctional pathways.

A prominent component of TBI that contributes to clinical symptomatology is diffuse axonal injury (DAI). Rotational acceleration-deceleration forces associated with traffic or sports accidents, cause widespread axonal shearing and tearing.[4] Prior studies revealed two mechanisms of diffuse axonal degeneration. Primary axotomy is caused by the shearing and strain of axonal fibers as a result of direct mechanical forces at the moment of injury. Secondary axotomy is a delayed consequence of inflammatory changes after a focal perturbation in the axon that impede axoplasmic transport, leading to local swelling of the axon and detachment from its downstream segment.[4–8] This secondary neuroinflammatory degeneration may continue even years after a single TBI.[6,7,9–11] Both mechanisms result in a degree of deafferentation or de-efferentation of cortical-subcortical regions, which is clinically characterized by a spectrum of neurological deficits ranging from comatose state to minor neurocognitive impairment.[12–16]

Several studies have investigated correlations between the amount or location of DAI and clinical outcome.[17,18] Most papers are reported on adults with TBI, however the impact of DAI on the immature brain is still unclear. As emerging cognitive skills seem to be more vulnerable to injury than established skills,[19,20] we specifically focused on Executive Functioning (EF) in adolescents with TBI.[21–27]

Executive function is an umbrella term that encompasses core (working memory, inhibitory control, cognitive flexibility),[28] higher-level (reasoning, planning, problem solving) and emotional/motivational executive functions (social cognition, emotion regulation, decision making, motivation)[29–31] Executive functions – genetically determined in origin[30,32–34] – have a protracted developmental trajectory from childhood into early adulthood with increased sensitivity to environmental influences and experience. Emerging executive skills and improvement in 'speed of processing' throughout childhood promote greater autonomy and support increasingly goal-directed and adaptive behaviour, which is crucial in future academic achievement and social development.[35–38] During adolescence EF becomes more and more complex with increases in the strength of mental representation, improvements in goal identification and better coordination of control processes.[39,40] The unfolding of higher-level executive skills (such as planning and problem solving) during adolescence parallels with the maturation of a complex distributed cortical – subcortical brain network.[41–46] Previous literature indicated that emerging cognitive skills seem to be more vulnerable to injury than established skills,[44,45] which support the hypothesis that a traumatic insult on this developmental progression of executive functioning is particularly critical for long term neurocognitive dysfunction.

To quantify the impact of DAI on the adolescent brain, we used Susceptibility Weighted Imaging (SWI), a Magnetic Resonance Imaging (MRI) sequence susceptible to hemosiderin remnants. Diffuse axonal injuries are regularly associated with microbleeds, caused by the disruption of adjacent small blood vessels. Because SWI sequence has a high sensitivity for paramagnetic blood products, it is therefore used as an indirect approach to the detection of traumatic axonal injury.[47–50] Previous studies on pediatric TBI found significant associations between the number of DAI lesions as identified on SWI and acute or long term clinical outcome measures (such as Glasgow coma scale, duration coma or intubation, Pediatric Cerebral Performance Category),[47,51] intelligence quotient[47,52,53] and social cognition.[21,54–56] Major constraints in these previous studies are their heterogeneity in brain lesions, time since injury, and age of the children at injury.

Besides the potential repercussion of the total amount of DAI on long term neurocognitive outcome, there is to the best of our knowledge no previous literature regarding the impact of DAI-lesion localization in the developing adolescent's brain. In our study we applied the extended anatomical grading for diffuse axonal injury recently introduced by Abu Hamdeh et al., 2017 which is an extended version of the anatomical grading of Adams et al., in 1989: Grade I: hemispheric lesions, Grade II: hemispheric and additionally corpus callosum lesions, Grade III: brainstem lesions, Grade IV: lesions in substantia nigra or mesencephalic tegmentum.[57,58] Today it is still debated in the literature whether these sequential anatomical grades reflect the degree of severity of a traumatic impact, or are rather the result of distinct injury mechanisms.[59,60] Based on previous findings we hypothesize 1) a positive correlation between the total number of hemorrhagic DAI lesions and the anatomical grades for DAI. 2) Secondly, we hypothesize a negative correlation between the total number of hemorrhagic DAI lesions on SWI and higher executive

functioning in adolescents. 3) Finally, we expect a negative correlation between the anatomical grade for DAI and higher executive skills.

2. Materials and methods

2.1. Participants

Twenty-six adolescents who acquired a moderate-to severe TBI were selected between March 2015 and January 2017 from medical reports in the Child Rehabilitation Centre, Ghent University Hospital and the Rehabilitation Centre for children and adolescents Pulderbos. The inclusion criteria for participation in this study were *(1)* age of 11–17 years at start of the study, *(2)* moderate to severe traumatic brain injury according to the Mayo Classification System for TBI,[61] *(3)* a documented closed head injury with the presence of diffuse axonal injuries, as identified on Susceptibility Weighted Imaging scans, *(4)* no concomitant considerable brain lesions or hemorrhages (only limited cortical encephalomalacia was allowed) and *(5)* chronic stage of TBI with 1–5 years since injury, with a minimum age of 10 years at injury. Nineteen adolescents with TBI agreed for participation. We were not able to administer the SWI sequence in one adolescent with TBI due to technical problems and he was excluded from this study. The final dataset included 18 participants with TBI (11 male, 7 female) with a mean age = 15y8m SD = 1y7m at the moment of the study and a mean age of 13y3m SD = 1y5m at the time of injury. Causes of TBI were traffic accidents or sports injuries and the average time between the accident and testing was 2y4m (SD = 1y1w).

One adolescent (11_TBI) did not receive rehabilitation, all the other adolescents underwent multidisciplinary rehabilitation with a mean duration of 11m4w (SD = 6m4d). The adolescents recovered well, with independent walking and autonomy in learned activities of daily living. At the end of their rehabilitation period, they had a mean total IQ 96,11 (SD = 16.91), verbal IQ 98.94 (SD = 17.55), performance IQ 93.94 (SD = 15.07) measured by the Wechsler IQ Scale for Children III. The adolescent who did not receive rehabilitation was assessed in our polyclinics. After rehabilitation, all adolescents with TBI were referred to a regular school, 55% of the adolescents restarted in a lower level of education compared to the level before the injury and 77% received additional academic and/or psychosocial support (see Table 1). In conversations during follow-up appointments post-rehabilitation, the adolescents with TBI and their parents reported persistent impaired executive functioning (especially planning and problem solving) and reduced adaptive behavior in daily living.

We have no objective evaluation of pre-injury neurocognitive functioning of the participants with TBI, however from an informal interview with all the parents we have knowledge of two adolescents (4_TBI and 10_TBI, see Table 1) diagnosed with pre-existing Attention Deficit Hyperactivity Disorder (ADHD) who received methylphenidate. According to the parents these adolescents functioned well before the TBI in a regular school and made expected progress in their development, but this was not objectivized by any

Table 1 – Clinical characteristics of the adolescents with TBI included in the study. (tIQ = total IQ, vIQ = verbal IQ, pIQ = performance IQ, GCS = Glasgow Coma Scale available in medical reports).

	Gender	Birthday	Age injury	Injury mechanism	Initial GCS	Age at start study	Post TBI tIQ	Post TBI vIQ	Post TBI pIQ	Post-TBI academic or psychosocial support	Post-TBI level of education in regular school
01_TBI	M	12/11/1998	30/05/2011	Motor vehicle	8	16y4m	124	122	120	no support	lower level than before TBI
02_TBI	M	20/07/1998	3/02/2012	Motor vehicle	3	16y8m	90	92	91	academic support	identical level
03_TBI	M	6/12/1998	18/01/2011	Motor vehicle	–	16y7m	113	129	92	academic support	identical level
04_TBI	M	22/12/1997	5/04/2013	Motor vehicle	–	17y6m	117	117	113	academic support	lower level than before TBI
05_TBI	F	17/12/1999	15/05/2012	Motor vehicle	–	15y6m	104	94	115	academic support	lower level than before TBI
06_TBI	F	21/03/2001	22/05/2014	Motor vehicle	5	14y5m	98	99	98	no support	lower level than before TBI
07_TBI	M	8/02/2000	18/12/2013	Motor vehicle	–	15y6m	95	106	85	no support	lower level than before TBI
08_TBI	M	26/05/1998	18/04/2014	Ski	7	17y2m	122	128	109	academic support	identical level
09_TBI	M	15/11/1999	22/01/2013	Motor vehicle	7	15y11m	76	71	88	academic support	lower level than before TBI
10_TBI	F	29/03/2005	11/03/2015	Motor vehicle	–	11y1m	105	106	102	no support	identical level
11_TBI	M	5/01/2001	6/08/2014	Motor vehicle	3	15y5m	78	89	71	academic-psychosocial support	identical level
12_TBI	F	6/04/1999	6/09/2013	Motor vehicle	–	17y2m	85	85	89	psychosocial support	lower level than before TBI
13_TBI	F	23/07/2003	30/11/2014	Motor vehicle	3	12y11m	91	93	91	academic support	identical level
14_TBI	F	31/12/2000	6/10/2015	Horse	–	16y0m	99	107	91	academic support	identical level
15_TBI	M	15/04/2003	25/08/2015	Motor vehicle	3	13y8m	64	70	63	academic-psychosocial support	lower level than before TBI
16_TBI	F	28/07/1999	7/02/2015	Horse	5	17y5m	76	83	77	academic support	identical level
17_TBI	M	3/05/2000	15/03/2014	Motor vehicle	–	15y10m	87	86	91	academic support	lower level than before TBI
18_TBI	M	4/07/1999	27/04/2012	Motor vehicle	–	16y10m	106	104	105	academic support	lower level than before TBI

neurocognitive assessment or questionnaire. There were no adolescents in our study population with other premorbid learning disabilities.

For every adolescent with TBI, we performed a diligently search for a non-clinical matched control via the social network of the researches. Healthy adolescents could only volunteer when they met our criteria of age, gender and typical development. This way we had 18 volunteers with a very close match in age (mean age TBI = 15y8m, SD = 1y7m and mean age controls = 15y7m, SD = 1y8m) and a perfect match in gender. According to the parents, these typically developing healthy adolescents had no neurologic or psychiatric history, no learning disabilities, they went to a regular school and did not receive any academic of psychosocial support.

As the long-term neurocognitive outcome of a child with TBI is mediated by familial inheritance and education,[62–67] we determined the educational level of the biological parents of the participants by the number of years of formal education. The average of the sum of years education of mother and father was 26y3m (SD = 5y3m) for the children with TBI, and 32y3m (SD = 1y11m) for typically developing controls.

Written informed consent was obtained from all children and their parents. The study was approved by the Ethics Committee of the Ghent University Hospital, Belgium. (EC 2014/0540)

2.2. MRI acquisition and analysis

All participants were scanned at Ghent University Hospital, Belgium, using the 3T-Siemens Tim TRIO scanner equipped with a 32-channel head coil. Following MRI sequences were applied: 3D-Fluid Attenuation Inversion Recovery (FLAIR: TR/TE = 6000/420 ms; TA = 7min14s; FOV = 250 mm; voxel size = 1,0 × 1.0 × 0,9 mm^3; slab thickness = 172.8 mm; BW = 781 Hz/pixel), Susceptibility Weighted Imaging (SWI: TR/TE = 28/20 ms; TA = 4min56s; flip angle = 15°; FOV = 230 mm; voxel size = 1,0 × 0.9 × 1,5 mm^3; slab thickness = 132 mm; BW = 20 Hz/pixel) and 3D-T1-weighted Magnetization Prepared Rapid Gradient Echo (3DMPRAGE: TR/TE = 2250/4.18 ms; TA = 5min14s; flip angle = 9°; FOV = 256 mm; voxel size = 1,0 × 1.0 x 1,0 mm^3; slab thickness = 176 mm; BW = 150 Hz/pixel). Two board-certified neuroradiologists (GE and DK) evaluated the SWI-sequences, and characterized the TBI lesions by describing the presence and location of hemorrhagic DAI. DAI lesions were defined as hypointense round or ovoid lesions with a dipole effect on SWI, single or clustered, with a maximal diameter up to 10 mm, clear margins, and not connected to the brain surface or the ventricular system.[59,68] In case of any uncertainty, the neuroradiologists inspected the FLAIR sequences to distinguish a DAI-microbleed from potential mimics (vessel flow voids, and calcium or iron deposits). In the present study we did not calculate the individual lesion volumes because due to an iron-induced magnetic field distortion, the signal loss caused by these hemorrhages is essentially larger than the true anatomic size of the lesion.[69] Furthermore we classified the hemorrhagic DAI lesions using the extended anatomical grading for diffuse axonal injury by Abu Hamdeh et al., 2017: Grade I: hemispheric lesions, Grade II: hemispheric and additionally corpus callosum lesions, Grade III: brainstem lesions, Grade IV: lesions in substantia nigra or mesencephalic tegmentum.[57] In addition we determined the presence of deep supratentorial lesions in basal ganglia, capsula interna and thalamus. After obtaining the DAI lesions in the different anatomical locations of the brain, a consensus reading was conducted by the two neuroradiologists, which was used for data analysis. Although the raters did not have any information about the identity of the children, the presence of diffuse and cortical brain lesions was obviously suggestive for TBI. No SWI microbleeds were detected in the control group.

2.3. Neurocognitive assessment

All participants underwent a neurocognitive test battery including Digit Span Forwards and backwards, Spatial Span Forwards and Backwards, Digit Symbol Substitution Test and the Stockings of Cambridge. The assessments were administered by neuropsychologists at the Child Rehabilitation Center, Ghent University Hospital, Belgium. The parents of the participants completed the Behavior Rating Inventory of Executive Function (BRIEF).

Digit Span Forwards and *Digit Span Backwards* are subtests from the Wechsler Intelligence Scale for Children IV and measures for working memory.[70] The examiner reads a digit string that increases from 2 to 8 digits, which the adolescent has to repeat in the same order (Digit Span Forwards) or in reverse order (Digit Span Backwards).[71] The total number of digits is the outcome measure of both verbal working memory tests.

Spatial Span Forwards and Backwards are subtests of the Cambridge Neuropsychological Testing Automated Battery (CANTAB)[72] and are visuospatial analogues of the Digit Span tasks.[71] This test assesses spatial working memory by showing an increasing number of squares. The outcome measure of both tests is the total number of squares in the correct order.

The *Digit Symbol Substitution Test* is a pen and paper task, and a subtests from the Wechsler Intelligence Scale for Children IV, which assesses information processing speed. The adolescent is given nine digit-symbol pairs that remain visible throughout the test. A matrix of digits is presented and the adolescent has to write down - as fast as possible - the corresponding symbol under each digit.[73] The total number of correct symbols within 120 s is the outcome measure.

The *Stockings of Cambridge* (SOC) is a touchscreen spatial planning test and is the CANTAB computerized version of the Tower of London Test.[72,74–76] The adolescent has to copy a pattern of colored balls, by moving one ball at a time to a certain position, in a minimum of moves to solution. The number of moves are a measure of the adolescent's planning ability.

Behavior Rating Inventory of Executive Function (BRIEF) parent-report is an ecologically valid evaluation of executive function, which gives information of possible difficulties in the adolescent's everyday adaptive functioning, reported by the parent. The BRIEF comprises 8 facet scales that combine to form two index scales, the Behavioral Regulation Index (BRI = sum of Inhibit, Shift and Emotional Control scale scores) and the Metacognition Index (MCI = sum of Initiate,

Working Memory, Plan/Organize, Organization of Materials and Monitor scale scores). The Global Executive Composite (GEC) is the sum of the BRI and MCI.[77–79] A higher score on the BRIEF indicates more executive dysfunctioning in daily life.

2.4. Statistical analysis

All analyses were performed in IBM SPSS Statistics (version 25). The mean parental education for the adolescents with TBI was significantly ($p < 0.001$) lower compared to the typically developing children (-6y0m 95% CI [-8y10m; 3y2m]). Therefore, we have included parental education as covariate in further statistical analyses.

The results of the neurocognitive assessments of the 18 adolescents with TBI were compared with the typically developing control group, by using linear regression analysis, adjusted for sex, age and parental education. Standardized effect sizes (Glass's delta) were calculated as the ratio of the adjusted mean difference in neurocognitive assessment and the raw SD of the control group. In addition we performed Spearman correlations between the standardized neuropsychological tests and the BRIEF-questionnaire in the group of adolescents with TBI.

As the total number of hemorrhagic DAI lesions was skewly distributed, observed median and Q1, Q3 were reported. The distribution of the total number of hemorrhagic DAI lesions was compared between the 4 anatomical grades of DAI using a Kruskall Wallis test, and between the subgroups of presence/absence of deep subcortical lesions using a Mann-Whitney *U* test. Furthermore, associations between executive performance measures (SOC and BRIEF-GEC) and the number of hemorrhagic DAI lesions were investigated by means of a rank-based measure of association, the Spearman correlation coefficient and 95% bias-corrected accelerated bootstrapped confidence interval. Finally, linear regression models were used to compare mean SOC and BRIEF-GEC scores, between the 4 anatomical grades of DAI, and the subgroup of presence/absence of deep subcortical lesions. Therefore, univariate linear models were fitted with the neurocognitive measures (SOC and BRIEF-GEC) as dependent variables. Independent variables were the 4 anatomical grades of DAI, and the subgroup of presence/absence of deep subcortical lesions, age, sex and parental education.

False discovery rate (FDR) correction was applied in order to protect against type I errors in group comparisons and correlation analyses. Corrected *p*-values lower than 0.05 were considered significant.

3. Results

3.1. Neurocognitive performance

Based on linear regression analysis in adolescents with DAI and typically developing peers (adjusted for total years of parental education, gender, and age), we found no statistical significant differences after FDR correction in the mean scores of the Digit span forwards ($p = 0.94$), Digit span backwards ($p = 0.91$), Spatial span forwards ($p = 0.62$), Spatial span backwards ($p = 0.03$), Digit symbol substitution ($p = 0.80$) and Stockings of Cambridge ($p = 0.17$). However, adolescents with TBI had significantly poorer executive functioning in daily life, as reported by their parents on the BRIEF compared to healthy controls ($p = 0.007$). The estimated mean BRIEF-GEC score for adolescents with TBI was 23.42 units higher (indicating more executive dysfunction) compared to healthy controls (Table 2). Spearman correlations between the standardized neuropsychological tests and the BRIEF-questionnaire in the group of adolescents with TBI, revealed a weak, not significant correlation between the BRIEF and the SOC (correlation coefficient = 0.312, $p = 0.068$). No other correlations were found between the BRIEF and neurocognitive measures.

3.2. Location of DAI on Susceptibility Weighted Imaging

All the adolescents with TBI had widely distributed hemorrhagic DAI lesions in their cerebrum on SWI, most frequently located in the grey-white matter junctions. The total number of hemorrhagic DAI in a single adolescent with TBI ranged from 1 to 814 (n = 18, mean = 52, Q1; Q3 = 21; 199). In 88.8% of the adolescents lesions were found in the temporal lobe ranging from 1 to 299 lesions, 83.3% of the adolescents had 3 to 218 lesions in the frontal lobe, 61,1% had 2 to 111 lesions in the parietal lobe, 55.5% had 1 to 139 lesions in the occipital lobe, and 27.7% of the adolescents had 1 to 10 lesions in the cerebellum. In 61.1% of the adolescents hemorrhagic DAI lesions were counted in the corpus callosum, with a range from 1 to 22 lesions, one adolescent (5%) had 3 lesions in the brainstem, and 16.6% of the adolescents had 1 to 8 lesions in the substantia nigra or mesencephalic tegmentum.

Table 2 – Mean differences in neurocognitive performance between adolescents with DAI and typically developing peers, based on linear model analysis adjusted for total years of parental education, gender, and age. Glass d: adjusted mean difference/raw SD in control group. (Please note FDR significant p-value > 0.007).

	TBI n = 18 mean (SD)		Controls n = 18 mean (SD)		Estimated mean score	FDR adjusted 95% Confidence Interval	Glass d Effect size	P-value
Digit span forward *(total digits)*	8.94	(1.98)	9.33	(1.88)	−0.06	[-2.71; 2.58]	−0.035	0.94
Digit span backward *(total digits)*	5.77	(1.80)	6.22	(1.59)	0.09	[-2,15; 2.33]	0.057	0.91
Spatial span forward *(total squares)*	7.17	(1,20)	7.00	(1.37)	0.29	[-1.43; 2.01]	0.211	0.62
Spatial span backw. *(total squares)*	6.94	(1.47)	6.39	(1.54)	1,464	[-0.40; 3.33]	0.951	0.03
Digit symbol subst. *(total symbols)*	64.89	(11.78)	69.89	(12.75)	−1,216	[-15.36; 12.93]	−0.095	0.80
Stock. of Cambridge *(total moves)*	17.49	(1.71)	16.10	(1.67)	1,014	[-1.09; 3.11]	0.607	0.17
BRIEF-parent GEC *(raw scores)*	138.67	(25.08)	95.53 (n = 17)	(12.04)	23,421	[-0.49; 47.33]	1.944	**0.007**

Furthermore, 33,3% of the adolescents had deep subcortical hemorrhagic lesions (lesions in thalamus, basal ganglia or capsula interna).

Using the extended anatomical grading for diffuse axonal injury: 38.9% of the adolescents had DAI grade I (hemispheric lesions in grey/white matter only), 44.4% of the adolescents DAI grade II (hemispheric and corpus callosum lesions), none of the adolescents had DAI grade III (the adolescent with 3 brainstem lesions had also lesions in the substantia nigra or mesencephalic tegmentum), and 16.7% of the adolescents had DAI grade IV (lesions in the substantia nigra or mesencephalic tegmentum). Descriptive statistics of the hemorrhagic DAI can be found in Table 3.

3.3. *The amount of DAI across DAI grades*

The observed median total number of DAI together with the first and third sample quartiles, are reported in Table 4 for the four grades of DAI and deep subcortical lesions. Based on the Kruskall–Wallis test ($p = 0.493$) for grades of DAI and based on the Mann-Whitney *U* test ($p = 0.395$) for deep subcortical lesions, no evidence of different distributions in the amount of DAI across DAI grades and deep subcortical lesion groups could be observed, although the observed median total number of DAI increases along more severe subgroups of both variables.

3.4. *Correlation between the amount of DAI and executive functioning*

Considering the fact that higher executive skills such as "planning and problem solving" progress distinctly throughout adolescence, they might be specifically vulnerable to injury in this developmental stage.[44,45] Therefore we focused on the BRIEF-parent Global Executive Composite and the Stockings of Cambridge (SOC). As such, the statistical analyses were limited in our small sample size.

We investigated the rank-based correlation between the total number of DAI and the BRIEF-parent (total score) and the SOC (total number of moves). Please note that higher scores on the BRIEF and SOC, reflect worse executive functioning. Non-significant negative correlation coefficients are observed between the total amount of DAI and performance on the Stockings of Cambridge ($r = -0.28$ (95% CI (−0.68; 0.20), $n = 18$) and the BRIEF-parent GEC ($r = -0.13$ (95% CI (−0.53; 0.36), $n = 18$)).

3.5. *Subgroup analyses in executive function for DAI-grades and deep subcortical lesions*

Higher executive functioning (SOC and BRIEF-GEC) was compared between the grades of DAI and the control group, and between the presence/absence of deep brain lesions and the control group. For the BRIEF-GEC, a significant lower mean BRIEF-GEC score was found for control adolescents compared to adolescents having DAI grade II (−36.1 units (95% Bonferroni corrected CI [-60.7,-11.4]). Pairwise comparisons between the different DAI-grades indicated no important differences in the estimated mean score of the SOC and the BRIEF, although the sample size of adolescents within the different DAI-grades was very small (Table 5).

For the deep subcortical lesions subgroups, the mean BRIEF-GEC score for adolescents with deep subcortical lesions is significantly higher (worse executive functioning) compared to the control group (29.4 units (95% Bonferroni corrected CI [7.6; 51.3])) (Table 5).

Table 3 – The amount of hemorrhagic DAI (with the observed median and Q1, Q3) and distribution according to the extended anatomical grading for diffuse axonal injury. Additionally the presence and localization of cortical encephalomalacia is indicated. Abbreviations: corp cal = corpus callosum; sub.ni = substantia nigra; m.t. = mesencephalic tegmentum; thalam. = thalamus; basal gang = basal ganglia; cap int = capsula interna.

	Grade I					Grade II	Grade III	Grade IV	Deep subcortical lesions			Total
	frontal	temporal	parietal	occipital	cerebellum	corp cal	brainstem	sub.ni/m.t.	thalam.	basal gang	cap int	DAI
TBI_01	34	150	26	64	1	0	0	0	0	0	0	275
TBI_02	7	12	0	2	1	2	0	0	0	2	0	26
TBI_03	0	0	0	0	0	1	0	0	0	0	0	1
TBI_04	50	42	9	3	0	1	0	0	0	0	0	105
TBI_05	3	0	0	0	0	0	0	0	0	0	0	3
TBI_06	9	1	2	1	10	0	0	0	0	0	0	23
TBI_07	108	39	111	106	0	1	0	0	0	0	0	365
TBI_08	11	32	4	3	2	0	0	0	0	0	0	52
TBI_09	13	5	2	0	0	1	0	0	0	2	1	24
TBI_10	0	3	5	0	0	0	0	0	0	0	0	8
TBI_11	215	46	57	90	0	0	0	0	0	2	0	410
TBI_12	9	6	0	0	0	0	0	0	0	0	0	15
TBI_13	33	18	0	0	0	20	0	5	5	0	0	81
TBI_14	43	25	7	0	0	7	0	2	0	0	0	84
TBI_15	0	6	0	0	4	22	0	0	1	7	0	40
TBI_16	84	63	4	9	0	3	3	8	0	0	0	174
TBI_17	218	299	110	139	0	20	0	0	10	17	1	814
TBI_18	7	30	0	12	0	2	0	0	0	0	0	51
	12	22	3	2	0	1	0	0	0	0	0	52
Q1;Q3	6;59	5;43	0;13	0;25	0;1	0;4	0;0	0;0	0;0	0;2	0;0	21;199

Table 4 – Median total number of DAI between the grades of DAI (by Abu Hamdeh et al., 2017) and the p-value of the Kruskall Wallis test for grades of DAI and Mann-Whitney U test for Deep subcortical lesions.

	adolescent n	%	Median total number of DAI [Q1; Q3]	p-value
DAI Grade I	7	38.9%	23 [8; 275]	0.493
DAI Grade II	8	44.4%	46 [25; 300]	
DAI Grade III	0	0%		
DAI Grade IV	3	16.7%	84 [81; 174]	
Deep subcortical lesions: *No*	12	66.7%	52 [10; 157]	0.395
Deep subcortical lesions: *Yes*	6	33.3%	61 [26; 511]	

4. Discussion

To quantify the impact of widespread hemorrhagic DAI on a developing brain network, we used Susceptibility Weighted Imaging (SWI). In accordance with previous publications,[51,80–83] the distribution of hemorrhagic DAI was diffuse all over the brain, but primarily located at the cortex-white matter boundary in the temporal, frontal, parietal and occipital lobe. Furthermore, in more than half of the adolescents DAI was found in the corpus callosum, whereas damage to the cerebellum, brainstem, basal ganglia and thalamus was observed in only a few adolescents.[84] We applied the extended anatomical grading for diffuse axonal injury and diagnosed most adolescents with DAI grade I (only hemispheric lesions) and DAI grade II (hemispheric and additionally corpus callosum lesions). Because it is still debated in the literature whether the severity of the impact of a TBI determine the anatomical grades, we investigated if there is a correlation between the amount of DAI (assuming that the amount of DAI reflects the severity of the traumatic impact) and the extended anatomical grading for DAI. Statistical analysis showed no evidence of a correlation between the amount of DAI and the DAI grades, although the observed median total number of DAI increased along higher anatomical grades. This result indicates that the grading for DAI quantifies the anatomical distribution of the lesions with corresponding severity in clinical outcome, but is not a measure reflecting the lesion load of a traumatic brain injury. We therefore could presume that the anatomical grades for DAI may rather be the result of distinct injury mechanisms (for instance a different angle of rotational forces) than reflecting the degree of severity of a traumatic impact. Future experimental investigations are needed to affirm this interpretation.

Our second hypothesis was that there would be a negative correlation between the total number of hemorrhagic DAI lesions on SWI and higher executive functioning in adolescents, approximately 2,5 years after sustaining a moderate-to-severe TBI. Higher executive skills such as planning and problem solving, progress distinctly throughout adolescence and might be specifically vulnerable to injury in this developmental stage.[44,45] In contrast to our expectations we observed no significant correlations between the amount of DAI and higher executive functioning (SOC or BRIEF-GEC parent), a finding similar to what has been reported in adult TBI.[85,86] This may seem remarkable as one would expect that the more DAI, the more potential risk there is that developing neural networks in the adolescent with TBI could be affected, with a devastating effect on neurocognitive maturation. Izzy et al., 2017 suggested in adults with TBI that the presence of DAI lesions in the dorsal brainstem on SWI has more prognostic value than the total number of lesions in the brain.[59] So, if the amount of DAI is not the determining factor in long term neurocognitive outcome in adolescents with TBI, could it be indeed then the location of DAI? This brings us to our final question: is there a correlation between the anatomical grades for DAI and executive functioning? The mean score of the SOC and BRIEF-GEC was compared between the grades of DAI and the control group. A statistically significant lower mean BRIEF-GEC score was found for typically developing adolescents compared to adolescents having DAI grade II. This result is in accordance with previous reports in adults with TBI, in which the presence of hemorrhagic DAI lesions on SWI in the corpus callosum also significantly correlated with outcome.[18,60,87] Furthermore, several authors associated a higher DAI grade with worse neurocognitive outcome in adults with TBI. Especially DAI lesions in the brain stem and substantia nigra or mesencephalic tegmentum have been shown to be a negative prognostic factor.[18,57,59,87] We were not able to ratify this

Table 5 – The adjusted estimated mean score of SOC and BRIEF-GEC in different grades of DAI and deep subcortical lesions, for children of average age, with average total years of parental education and for a gender distribution based on the available sample.

	n child	Estimated			p-value	n child	Estimated			p-value
		mean	95%CI				mean	95%CI		
		SOC	LL	UL			BRIEF-GEC	LL	UL	
Control	18	16.5	15.5	17.4	0.529	17	108.0	98.0	118.0	0.003
DAI Grade I	7	17.1	15.7	18.6		7	120.4	106.2	134.5	
DAI Grade II	8	17.6	16.1	19.0		8	144.1	130.0	158.2	
DAI Grade III	0					0				
DAI Grade IV	3	17.7	15.7	19.7		3	114.6	94.3	135.0	
Deep subcort lesions: *Yes*	6	18.5	17.1	19.9	0.074	6	134.4	123.0	145.9	0.007
Deep subcort lesions: *No*	12	17.0	15.9	18.0		12	118.5	102.5	134.4	
Control	18	16.5	15.6	17.4		18	105.0	94.5	115.5	

Abbreviations: CI=Confidence Interval, LL = Lower Limit, UL=Upper Limit.

theorem, as the subgroup of children with DAI grade IV was very small. However, no important differences in the estimated mean score of the SOC and BRIEF-GEC were observed between the different subgroups of grade of DAI, so we could not confirm that children diagnosed with DAI grade IV do perform worse than children diagnosed with DAI grade I.

The significance of DAI lesions in the deep subcortical brain structures on neurocognitive outcome has not been investigated much in earlier TBI-studies.[52] A few reports in adults with TBI indicated that deep midbrain damage may be particularly important in executive performance because of its dopaminergic projections to other regions of the brain, including the prefrontal cortex.[88,89] The results of our statistical analyses correspond with these few reports in adult TBI, indicating that the mean BRIEF-GEC score in adolescents with deep subcortical hemorrhagic lesions was significantly higher (implying worse executive functioning) compared to the typically developing control group. Adolescence is known to be a unique life phase in which structural developmental changes in striatal and thalamic brain regions alongside prefrontal lobe changes, parallel developmental functional modifications in fronto-striato-thalamic neural networks that mediate executive performance.[90–93] Damage in the striato-thalamic region by means of diffuse axonal injury, interrupts progressive maturation and may result in long-term executive impairment in daily living, as we observed in our study population.

In contrast to the BRIEF-GEC score, measuring real-world executive outcomes, we could not capture significant associations between the Stockings of Cambridge test (SOC) and the anatomical grades for DAI, nor with the presence of deep subcortical lesions. This contrariety might be due to problems with ecological validity of neuropsychological tests. Previous literature indicated the relationship between performance-based neuropsychological measures and behavioural ratings of the same domain to be weak.[79,94–98] We were able to confirm this assumption in our analyses, with no significant correlations between the standardized neuropsychological tests and the BRIEF-questionnaire in the group of adolescents with TBI. Performance based neuropsychological measures were administered in a structured and controlled environment, while the BRIEF-questionnaire measured executive functioning in daily life. It appears that adolescents with TBI have good executive abilities on performance measures, but may be unable to broaden the appropriate skills in their daily lives. This explains also the absence of significant difference in the mean outcomes of the standardized neurocognitive performance assessments in our test battery between adolescents with TBI and typically developing peers.

There are some limitations in this present study, which may have affected our capability to observe certain effects. First, due to the very strict inclusion criteria, our sample size of adolescents with DAI was small, which makes it difficult to draw firm conclusions. Secondly, two participants with TBI were known with pre-morbid ADHD. Although they received methylphenidate and the parents reported expected progress in their development before TBI, the neurocognitive results might have been influenced by this pre-morbid condition. Thirdly, we excluded adolescents with major additional brain lesions, but allowed some limited cortical encephalopathy. We did not measure the limited cortical encephalopathy, and therefore did not include this as a variable. Finally, we defined DAI as hypointense (hemorrhagic) foci on SWI, whereas in the pathology literature, DAI lesions are also reported non-hemorrhagic.[17,99–101] As a result, we could have underestimated the total amount of DAI. Moreover, although it has been argued that hemorrhagic DAI lesions may persist for many years,[102,103] reports of Moen et al., 2012 and Messori et al., 2003 demonstrated that hemorrhagic DAI lesions could diminish over time on T2* sequences.[17,104] SWI has been shown to be more sensitive in detecting cerebral microbleeds than conventional T2* sequences,[105,106] however unfortunately - to the best of our knowledge - we could not find a study with SWI, investigating the permanent presence of cerebral microbleeds. The development of computational methods to fuse several MRI imaging data and provide a more integrated analysis of the extent of DAI, should be subject of further investigations.[107–110]

5. Conclusion

Diffuse axonal injury has an important repercussion on the adolescent's brain, not only by its direct impact, but also by its interference in the vulnerable developmental organization of brain networks mediating executive cognitive skills. Persisting daily executive impairment in the chronic stage of TBI in adolescents, was not correlated with the total number of hemorrhagic DAI on SWI, but was instead associated with the anatomical location of the DAI. We found statistical evidence for impaired higher executive function in adolescents with hemorrhagic DAI lesions in the corpus callosum and deep subcortical brain regions. Future studies with larger sample sizes are needed to bolster these findings. The combination of advanced imaging data with epidemiological and clinical information of the adolescent will improve characterization of pediatric traumatic brain injury, which may help guide individual rehabilitation targeting the disturbed development of higher neurocognitive function.

Author declaration

All the authors listed (Vander Linden Catharine, Verhelst Helena, Genbrugge Eva, Ellen Deschepper, Caeyenberghs Karen, Vingerhoets Guy, Deblaere Karel) have read the manuscript and agree to its being submitted for publication. They all had complete access to the study data that support the publication. I declare that the submitted article and its essential substance is an original work, which has not previously been published and is not being considered for publication elsewhere. I have not submitted this manuscript to another journal simultaneously.

Conflict of interest

There were no contributors with funding sources for this study. The authors (Vander Linden Catharine, Verhelst Helena, Genbrugge Eva, Ellen Deschepper, Caeyenberghs Karen,

Vingerhoets Guy, Deblaere Karel) have stated that they had no interests which might be perceived as posing a conflict or bias.

Author disclosure statement

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