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Executive Functioning Profiles from the BRIEF across Pediatric Medical Disorders: Age and Diagnosis Factors

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Abstract

Objective—To compare Executive Functioning (EF) profiles across several pediatric medical conditions and explored the influence of age of diagnosis and evaluation.

Methods—This was a retrospective, cross sectional study of 734 children ages 5-18 across five medical groups [brain tumor, leukemia (ALL), epilepsy (EPI), Neurofibromatosis Type 1 (NF1), and Ornithine Transcarbamylase Deficiency (OTC-D)], ADHD controls, and matched healthy controls. We compared groups across the subscales of a parent completed Behavior Rating Inventory of Executive Functioning (BRIEF) using MANOVA. Separate MANOVAs were conducted to look at age factors.

Results—The ADHD group differed from all other groups and had the highest level of reported EF problems. The NF1 and OTC-D groups differed significantly from the healthy comparison group for overall EF problems, while the EPI and cancer groups did not. Working Memory was the most elevated subscale across medical groups, followed by Plan/Organize. Children with medical disorders were two to four times as likely as healthy controls to have clinically significant problems in several EF domains. There was a main effect for age at diagnosis and age at evaluation..

Conclusions—A subset of children with medical disorders were found to have parent reported EF difficulties, with particular vulnerability noted in working memory and organizational/planning skills. This has relevance for the development of interventions that may be helpful across disorders. Children with particular diagnoses and earlier age of diagnosis and evaluation had greater reported EF problems.

Keywords

Executive Functions; Pediatric; Working Memory; Age at Diagnosis; Medical disorders

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Background

Executive functioning (EF) encompasses several component cognitive skills important for the regulation of behavior and emotions and the orchestration of other cognitive abilities toward an organized and efficient attainment of goals. Difficulties with EF skills are noted in many pediatric medical and developmental disorders. This is not surprising, as EF skills have a prolonged developmental trajectory compared to other skills, making them vulnerable to any disruption to brain development. EF skills are also at risk because their neurological underpinnings are complex and involve a widespread network including cortical (frontal, anterior cingulate, parietal) and subcortical (striate, cerebellum) neural structures (Makris et al., 2007; Miller & Cummings, 2007; Swanson & Xavier, 2002).

This study seeks to characterize and compare the real world EF profiles across diverse groups of neurologically compromised children in order to better understand the cognitive phenotype of children whose brain development is disrupted early in life, or even in utero. We chose five diverse pediatric medical conditions that are known to impact Central Nervous System (CNS) functioning including children with epilepsy (EPI), Ornithine Transcarbamylase Deficiency (OTC-D), Neurofibromatosis Type 1 (NF1), brain tumors, and acute lymphocytic leukemia (ALL). Each of these childhood medical conditions has evidence of associated cognitive deficits including executive dysfunction. EF skills in these populations have been examined with both paper-pencil measures of EF and parent/teacher report questionnaires. We focus on parent-reported outcomes as assessed by the Behavior Rating Inventory of Executive Functioning (BRIEF) because while both types of assessment are correlated, there are also distinct contributions of each method in identifying EF impairments (Parrish et al., 2007; MacAllister et al., 2012). In addition, parent report measures of EF (in particular working memory) have shown a relationship to underlying brain structure. Mahone, Martin, Kates, Hay, and Horska (2009) found that parent report of working memory from the BRIEF was significantly correlated with frontal gray matter volume (but not to gray volumes in other areas of the brain) in a group of healthy children. Faridi et al. (2009) demonstrated a significant correlation between the working memory and emotional control scales on the BRIEF and cortical thickness in the posterior parahippocampal gyrus.

Epilepsy

Several studies of children with epilepsy have identified greater EF difficulties than controls on parent reported and direct measures of executive dysfunction. In a sample of children with new-onset, well-controlled epilepsy and generally average IQ, children with localization-related or idiopathic generalized seizures had greater amounts of executive dysfunction than controls (Parrish et al., 2007). Forty-eight percent of these children with epilepsy had elevations on either of the composite scores (BRI or MCI), but the study did not examine subscale differences. Another study using the BRIEF in children with intractable epilepsy (focal and generalized) found greater dysfunction both in IQ—that was on average in the Borderline range—and on the BRIEF (Slick, Lautzenhiser, Sherman, & Eyrl, 2006). An examination of subscales noted that the most frequently elevated scales were Working Memory (53%) and Plan/Organize (49%). Sixty-eight percent of the sample had at

least one elevated score and 36% had four or more elevated scales. A recent study with both focal and general seizure types and mixed presentation with respect to seizure frequency, number of medications, and etiology also found increased parent-reported problems on the BRIEF. The average IQ of this sample was age-appropriate but ranged from intellectually disabled to well above average. They also found that the most frequent elevations were within the Metacognitive Index subscales including Working Memory (46.0%), Plan/Organize (41.4%), and Initiate (37.9%).

OTC-Deficiency

Prior research in children with Urea Cycle Disorders (including OTC-D) has generally found higher rates of ADHD diagnoses and mild elevations on parent reported measures of EF (BRIEF; Krivitzky et al., 2009; Diaz et al., 2013). In the largest study to date of children with Urea Cycle Disorders, Krivitzky et al. (2009) reported that 15% of the study group reported a diagnosis of ADHD at the time of enrollment and that mean BRIEF scores in several metacognitive domains were elevated (1 to 1.5 SD elevations) relative to the normative sample. Diaz et al. (2013) studied 22 subjects with Urea Cycle Disorders at baseline and following 12 months of treatment with glycerol phenyl butyrate. Results found that most BRIEF subscales at baseline were clinically elevated (i.e., close to a T score of 65), with significant improvement in reported symptoms noted over a 12 month period across index scores (Behavior Regulation Index-BRI- improved from T=60.4 to 53.7, Metacognitive Index-MCI-improved from T=67.5 to 57.5).

Neurofibromatosis Type 1

Studies on executive function development in children with NF1 have shown significant disruptions in the majority of functions within this domain. Multiple researchers have demonstrated significant impairments on performance-based assessments as well as behavior rating scales (BRIEF). Payne, Hyman, Shores, and North (2011) reported that children with NF1 were reported to have significant EF difficulties in comparison to typically developing same-aged peers in all areas assessed on the BRIEF. Areas that have been shown to be the most significantly affected in children with NF1 include working memory (Rowbotham, Pit-ten, Sonuga-Barke, & Huijbregts, 2009), strategic planning (Hyman, Shores, & North, 2005; Pride et al., 2010), self-monitoring, and inhibitory control (Huijbregts, Swaab, de Sonnevill, 2010; Rowbotham et al., 2009).

Brain Tumor

Problems with EF have also been reported in pediatric brain tumor survivors. Working memory deficits have been repeatedly documented in the pediatric brain tumor population (c.f., Wolfe et al., 2012), and have been associated with differences in brain activation (Robinson et al., 2014). Differing patterns have been discussed with regard to developmental trajectory and disruption associated with age and treatment factors, with children younger at diagnosis and those receiving whole brain radiation being the most susceptible (Spiegler et al., 2004; Briere et al., 2008; Scott et al., 2001; Waber et al., 2006). Other areas of executive function are also susceptible to disruptions and impairments following treatment for brain tumors, including strategic planning functions and cognitive flexibility (Maddrey et al., 2005; Spiegler et al., 2004). Tumor size has been documented to be associated with greater

cognitive impairments, including global executive dysfunction in pediatric brain tumor survivors (Tonning Olsson et al., 2014). Compared to survivors of pediatric leukemia, brain tumor survivors show more global and higher level executive function problems (Winter et al., 2014). Studies focusing on everyday functional disruptions in executive function in brain tumor survivors have not completely aligned with the rate and severity of executive dysfunction observed on performance-based tests. Wochos, Semerjian and Walsh (2012) have reported a notable lack of endorsement of executive function difficulties on the BRIEF reported by parents of pediatric brain tumor survivors. While group means were within the normal range, a proportion of survivors showed clinical impairments in working memory (teacher rating - 34%, parent rating - 24%), self-starting or initiation (teacher - 34%), planning and organizational skills (teacher - 31%) and cognitive flexibility (teacher - 26%, parent - 16%).

Leukemia

Executive dysfunction has been one of several neuropsychological late effects associated with treatment in children with leukemia, even in those without direct central nervous system involvement and chemotherapy only (c.f., Buizer et al., 2009). Winter et al. (2014) reported that survivors of pediatric ALL demonstrated executive functions that were significantly discrepant from intellectual functioning, but unlike brain tumor survivors, these discrepancies were limited to “lower level” executive functions – particularly processing speed. Research into the everyday disruptions in executive function in leukemia survivors (via parent report on the BRIEF) indicated age appropriate functions in the group as a whole (Walsh et al., 2014). However, a subgroup of survivors was identified as having clinically significant impairments by parent report. These elevations were significantly greater than what is observed in the general population in the areas of working memory (18% of ALL sample impaired), initiation (16% impaired), emotional regulation (14% impaired), and flexibility or shifting (13% impaired). While treatment factors were not associated with risk of impairments, an older age at the time of assessment was, specifically with regard to working memory and self-regulation (Walsh et al., 2014).

Present Study

The present study included these five medical groups for several reasons. First, these groups are all disorders that impact CNS functions, are seen in our diverse clinical/research programs, and in which executive difficulties have been previously reported. Second, we wanted a diverse group of medical disorders, thus we chose disorders with different etiologies, prevalence rates (from the more common to more rare conditions), and range of typical age of diagnosis/onset. We felt it was important to include disorders that disrupt development from birth (or even in utero) and disorders that may not impact development until later in childhood. In addition, only one other study that we know of has compared EF profiles across disorders (Gioia, Isquith, Kenworthy, & Barton, 2002) but none has examined pediatric medical disorders specifically. Pediatric medical disorders may share or differ on the neural underpinnings that lead to cognitive dysfunction. Thus, understanding the similarities and differences across pediatric medical populations may inform mechanisms of dysfunction, assessment practices, and development of early interventions that attempt to counteract the effects of disease states on EF development.

While cognitive dysfunction is evident, an observation common to all these disorders is the heterogeneity of cognitive outcomes, ranging from near typical neurodevelopment to severe cognitive impairment. Maureen Dennis' Developmental Stage Model provides a framework for understanding contributing factors to the “cognitive phenotype” seen in pediatric medical conditions (Dennis, 2000). A cognitive phenotype is the set of mental and behavioral deficits that are characteristic of a particular disorder and include concepts such as the modal profile, variability, core deficits, and how a child copes with various levels of challenge. Factors that contribute to a phenotype include disease and treatment (biology), reserve (family and environmental factors) and age/time factors. Age of onset of disease has been shown to be an important factor in predicting neurocognitive outcomes, with those with early disruption often demonstrating worse cognitive outcomes. This has been particularly true for disorders that have a more diffuse impact on the brain, such as pediatric TBI, bacterial meningitis, and children who have undergone cranial radiation (Duffner, 2004; Ewing-Cobbs et al., 2006; Mulhern et al., 2004; Taylor, Schatschneider, & Minich, 2000). Consideration of the child's age at the time of evaluation is also important, particularly in studying EF disruption given the protracted nature of EF development and the cortical changes occurring throughout childhood (Giedd & Rapoport, 2010). These correspond to changes in developmental expectations through childhood associated with EF, with increasing expectations for independent work, organization, and self-regulation as children get older. Thus, children may present with more difficulties as they get older, often referred to as “growing into their deficits.”

In order to better understand the “cognitive phenotype” of EF in children with complex medical disorders, we chose to look at the spectrum of component skills that make up this umbrella term. This is particularly important, as it may help to identify particular skill areas that could be targets for intervention. Working memory—the ability to keep information in mind while problem solving—is a particularly important aspect of EF, as it has a strong relationship with a child's learning and educational attainment (Gathercole & Alloway, 2008; Gathercole, Brown, & Pickering, 2003). Difficulties with working memory are often described in developmental disorders including ADHD, learning disabilities, and language disorders (Alloway & Gathercole, 2006). Prior research utilizing parent report measures in a profile analysis (i.e., the BRIEF) found that working memory was the highest or second highest rated EF problem in children with reading disabilities, moderate and severe traumatic brain injuries, ADHD-Inattentive subtype, and ADHD-Combined subtype (Gioia, Isquith, Kenworthy & Barton, 2002). Although there are certainly limitations to using only parent report data, the BRIEF has been shown to be a powerful tool in assessment of EF unique from traditional paper-pencil measures (Toplak, West, & Stanovich, 2013) including accounting for variance in neuroimaging findings of typically developing and patient populations (Wang et al., 2012; Warren et al., 2013; Ziegler, Dahnke, Winkler, & Gaser, 2013)

In order to characterize and compare the EF profiles across conditions, we utilized profile analysis to evaluate severity of executive dysfunction among disorders, whether a certain aspect of EF is particularly vulnerable regardless of disorder, and if the EF profile varies by disorder. In addition to including a comparison group of typically developing children, we also included an ADHD comparison group given the increased prevalence of ADHD in these

medical disorders compared to the general population. Further, problems with EF are hallmark characteristics of ADHD. We hypothesize that: 1) children with pediatric CNS disorders will have greater levels of dysfunction in EF skills than typically-developing peers, but lower levels of dysfunction than children with ADHD; 2) working memory will be the most impaired aspect of EF regardless of disorder and 3) the EF profile will differ among medical disorders. Mean score differences do not always capture the scope of the impairment, thus we calculated odds ratios to demonstrate how likely a clinical elevation occurs in each of the medical groups relative to the typical control group (Chelune, 2010). We hypothesized that the likelihood of having a clinically significant elevation in EF skills will be higher in each of the medical groups compared to typical controls. Lastly, we hypothesize that younger age at diagnosis and older age at testing will be associated with greater reported problems in EF in the medical groups.

Methods

Subjects

This is a retrospective, cross sectional study of five pediatric medical groups, one ADHD comparison group, and one age/sex matched healthy comparison group (n=734, age range 5-18). Inclusion criteria for all groups included the absence of significant medical or mental health co-morbidities. Co-morbidities were identified through various means including parent interview, physician report, and medical record review. Children in the medical groups were not excluded if they had co-morbid ADHD, learning disabilities, or mild mood/anxiety issues, as these types of problems are not uncommon in these disorders and are a part of the clinical picture. An IQ cut-off of 70 was used for inclusion, as we were interested in understanding EF profiles in children without intellectual disabilities.

Participants were evaluated through a clinical research protocol or standard clinic referral. Patients seen through standard clinical referral were all seen at a single institution while those seen through clinical research were seen through several different centers. Demographics are provided (Table 1) and are generally representative of the heterogeneity that is evident across all of these disorders. Brief descriptions of the groups' relevant characteristics (i.e., clinical features, prevalence rates) are provided in Table 2. The ADHD control group were from a group of clinically referred children with documented ADHD diagnoses based on DSM-IV criteria. The healthy comparison group was randomly selected age/sex matched cases from the original BRIEF normative sample from the published test.

Procedures

The primary measure used in this study is the Behavior Rating Inventory of Executive Functioning (BRIEF). The BRIEF is a questionnaire measure that was developed to assess a broad array of executive skills both related to behavioral regulation and regulation of cognitive skills. It consists of 86 questions that contribute to eight EF domains that compose a Behavioral Regulation Index and a Metacognition Index. Higher T-scores (> 65) indicate the presence of clinically significant symptomatology. Children included in this study had a parent report BRIEF available as part of their neuropsychological testing data from a larger battery of tests. Although there is high intercorrelation among the different subscales, we

chose to include the eight subscales for the primary analysis, as we were interested in studying the subcomponents of EF and not just the summary domains. All BRIEF scores included in the analysis were considered to be in the acceptable range on the Negativity and Inconsistency validity indices.

Institutional review board approval was obtained for all study procedures and informed consent and assent were obtained from all participants when appropriate.

Statistical Analysis

A repeated measures ANOVA was utilized with clinical group as the between-subjects predictor variable, and BRIEF subscale as the within-subjects variable. Post-hoc analyses were conducted and effect sizes are reported as Eta squared. For Eta squared, 0.02 is considered a small effect size, 0.13 a medium effect size, and 0.26 a large effect size. Alpha was set at .05 for this model.

While it is useful to know whether two groups differ on clinically significant scale elevations, it is also important to know the likelihood that a child with a condition of interest is likely to have difficulties compared to a typical child in a particular area such as EF (Chelune, 2010). To address this question, participants were classified as having clinically elevated symptom levels ($T \geq 65$) based on the BRIEF published cutoffs for each subscale. Chi-square analyses were conducted to examine differences in frequency of clinical elevation among the groups. Odds ratios reflect the odds of a clinical elevation occurring in a group relative to a typical comparison group.

Age at Diagnosis was divided into 3 categories to represent children with onset of disease in infancy (Dx Group 1: ages 0-2 years), early childhood (Dx Group 2: ages 3-7 years) and middle childhood to adolescence (Dx Group 3: ages 8 years and up). The analysis for *Age at Diagnosis* was run twice, with and without the NF-1 group, as this group's age at diagnosis is almost entirely skewed to the first year of life. *Age at Evaluation* was also divided into 3 categories to represent children tested in early school age (Evaluation Group 1: ages 5-7 years), middle childhood (Evaluation Group 2: ages 8-11 years) and adolescence (Evaluation Group 3: ages 12 years and up). The age groups for both *Age at Diagnosis* and *Age at Evaluation* were formed based on theoretical developmental stages, followed by data inspection to ensure that these divisions allowed for adequate sample sizes in each group. A repeated measures ANOVA was applied with age group (both *Age at Diagnosis* and *Age at Evaluation*) as the between-subjects variable. For these analyses, the two Composite scores, Behavioral Regulation (BRI) and Metacognitive Index (MCI), were included as the within-subjects, outcome variable. Post-hoc analyses were conducted and effect sizes are reported as Eta squared. Analyses for *Age at Diagnosis* and *Age at Evaluation* were run for only subjects in the five medical groups.

Results

Demographics

IQ data was not available for the typical control group. The ADHD group, and all of the clinical medical groups, had mean Full Scale IQ (FSIQ) scores within the average range,

although there was a significant difference for FSIQ between groups, $F(5,391)=9.24$, $p<.001$. Post-hoc analysis revealed that the ADHD group had significantly higher FSIQ scores than all of the other groups except the EPI group. The NF1 group also had significantly lower FSIQ than the EPI group (FSIQ, NF1=93, EPI=102). There was also a significant difference for gender, $\chi^2(6)=19.13$, $p=.004$, which is to be expected as some of these disorders have different gender prevalence rates (OTC-D is an X-linked disorder that is more prevalent in males). The ALL group also had a lower than expected percentage of males, which is not consistent with overall prevalence rates. However, this finding may reflect a referral bias, in that girls treated for leukemia tend to have greater cognitive disruption than boys (von der Weid et al., 2003). Also as expected, age at diagnosis differed by medical group, $F(4,286)=35.14$, $p<.001$, which is consistent with the typical age of onset/presentation for the various disorders (i.e., NF1 and OTC-D are both genetic disorders and thus typically diagnosed early in life). Age at evaluation also significantly differed by group, $F(6,733)=3.98$, $p=.001$, with the brain tumor group being older than the EPI, ADHD, and typical controls.

Diagnostic Group Profile Analysis

A main effect of clinical group was found with a medium to large effect size, $F(6, 707)=31.73$, $p<.001$, $\eta^2=.212$. Post-hoc analyses revealed that the ADHD group had the highest level of overall reported EF problems and significantly differed from all of the other groups. The NF1 and OTC-D groups had the next highest level of reported overall EF problems and significantly differed from the healthy comparison and brain tumor groups. In contrast, the EPI, ALL, and brain tumor groups did not differ from the healthy comparison group in terms of overall EF problems.

Results of Mauchly's Test of Sphericity indicated that assumption of sphericity assumption was violated, $\chi^2(27)=674.84$, $p<.01$. Therefore, the Greenhouse-Geiser correction was applied to all within subjects analyses. Results indicated a main effect for the BRIEF subscales with a small effect size, $F(5.37, 3793.93)=38.15$, $p<.01$, $\eta^2=.049$. Examination of the subscale means revealed that two particular aspects of metacognition, Working Memory and Plan/Organize, were typically the most elevated subscales, regardless of group membership (both scales in top 3 most elevated in all groups).

There was also clinical group by BRIEF subscales interaction, $F(32.19, 3793.93)=4.63$, $p<.01$, $\eta^2=.036$, indicating differences in EF patterns among the groups. Post-hoc examination revealed that the interaction was largely related to the brain tumor and ALL groups being particularly low on Inhibit; in fact, the brain tumor and ALL groups were reported to have significantly fewer problems than typical controls. Otherwise, the main effects of group were fairly consistent—the ADHD group was the most impaired, followed by the NF1 and OTC-D groups—with the degree of differences varying slightly across subscales as reflected by odds ratios described below.

Despite mean BRIEF scores that were below the clinical range, all medical groups had a subset of children that had clinically elevated scores across subscales, reaching as high as 43% in some domains (Table 3). Chi-square analyses revealed significant differences in the prevalence of clinically elevated scores among clinical groups. Elevations on the Working

Memory and Shift scales were at least threefold as likely to be elevated for all the medical groups (Working Memory OR 3.03 to 4.17; Shift OR 3.55 to 5.74), with the exception of the children with brain tumors who were two times as likely to have a clinical elevation on Working Memory and Shift (Working Memory OR=2.04; Shift OR=2.72). Consistent with the greater overall EF difficulty in the NF1 and OTC groups, these groups had a three to fivefold greater likelihood for clinically significant problems within Monitor (NF1), Plan/Organize (OTC-D) and Initiate (OTC-D). Similarly, the low reporting of problems in the brain tumor and ALL groups resulted in a lower likelihood than healthy controls to have clinically elevated problems with Inhibit (ALL and brain tumor) and Monitor (brain tumor only).

We also examined the distribution of patients in each group who present with no clinical elevations, a few specific EF deficits (e.g., elevations on only 1 or 2 BRIEF subscales) and those who show more broad impairments (e.g., elevations on at least 4 BRIEF subscales). With the exception of the brain tumor group, 20-25% of the individuals in each of the other medical groups showed clinically significant elevations on 4 or more subscales of the BRIEF. In comparison, 55% of the individuals in the ADHD control group and 12% of the typical controls have 4 or more clinically elevated scales on the BRIEF.

Age at Diagnosis

There was a main effect for age at diagnosis with a small effect size, $F(2, 268) = 5.49$, $p = .005$, $\eta^2 = .0399$. Post-hoc comparisons revealed that Group 1 (diagnosed 0-2 yrs) had significantly greater EF problems than Group 3 (diagnosed 8 yrs and older). Group 2 did not significantly differ from either of the other groups. This analysis was run again without the NF1 group, as this groups' age at diagnosis was almost entirely skewed to the first year of life. When the NF1 group was not included, there was still a main effect for age at diagnosis, $F(2, 219) = 3.036$, $p = .050$, with a slightly smaller effect size $\eta^2 = .0269$.

Consistent with our primary analysis, there was also a main effect for EF, $F(1, 268) = 48.64$, $p < .001$, $\eta^2 = .153$. The MCI was higher in all age groups (i.e., more reported problems) in comparison to the BRI. There was no interaction between age at diagnosis group and EF composite, $F(2, 268) = 0.66$, $p = .520$, $\eta^2 = .004$.

Age at Evaluation

There was a main effect for a relationship between age at evaluation and greater EF problems in the clinical medical groups again with a small effect size, $F(2, 269) = 3.034$, $p = .050$, $\eta^2 = .022$, and no interaction between age at evaluation group and EF composite, $F(2, 269) = .087$, $p = .917$, $\eta^2 = .001$. Post-hoc comparisons revealed that Group 1 (evaluated at 5 and 7 yrs of age) had significantly greater EF problems than Group 2 (evaluated at 8 to 11 yrs and older). Group 3 (evaluated between 12 and 18 years of age) did not significantly differ from either of the other groups. This is in contrast to what is seen in the healthy comparison group, in which the same analysis reveals a significant interaction effect, $F(2, 325) = 5.15$, $p = .006$, $\eta_p^2 = .030$ in which Metacognitive problems are significantly higher in the older age at evaluation groups (ages 8-11 and 12-18 years) and BRI problems are significantly higher in the younger group (ages 5-7 years).

Discussion

Differences in EF Between Pediatric Medical Disorders

Although many commonalities emerged in the profiles of EF skills across disorders, there were differences in EF dysfunction among disorders. The two medical groups with the greatest reported EF problems in this study were those with identified genetic disorders that are typically diagnosed early in life and likely alter cortical development even prior to birth (e.g., NF1, OTC-D). Children with epilepsy did not differ from typical controls on the profile analysis, although 24% of the children with epilepsy had 4 or more clinical elevations on the BRIEF subscales, while only 12% of typical controls show 4 or more elevations. Thus there is clearly a subset of children with focal epilepsy who are susceptible to multiple significant EF deficits. Perhaps, this variability among and within diagnostic groups is related to the effect of medication regimens that may have separate effects on cognitive functioning apart from the various medical etiologies.

Children with cancers (ALL and brain tumors) were not rated by their parents as having higher levels of EF problems in comparison to typical peers. In fact, our cancer survivors were found to be less likely than healthy peers to demonstrate clinically significant problems with inhibition. The findings in the cancer groups are consistent with prior research that has found a general lack of parent-reported EF deficits in cancer survivors (Howarth et al., 2013; Walsh et al., 2015; Wochos et al., 2014), although research using performance-based assessment has consistently demonstrated significant executive dysfunction in pediatric brain tumor and leukemia survivors (c.f., Wolfe, Madan-Swain, & Kana, 2012; Buzier, de Sonnevile, & Veerman, 2009). Further, we have shown that teachers are more likely than parents to report EF problems in pediatric brain tumor survivors, which may be associated with a response shift or rater bias in parents when reporting on their medically fragile child. Alternatively, these differences may highlight variances in EF demand across the home and academic environments, resulting in greater functional disruption in the school setting (Wochos et al., 2014). The low prevalence of inhibitory control deficits in the cancer survivor group is likely explained by the well-documented impairments in processing speed and the description of these survivors demonstrating characteristics of a “sluggish cognitive tempo,” which is defined by lethargy, diminished focus, and disorganization (Willard et al., 2014; Kahalley et al., 2013; Reeves et al., 2007).

Differences in EF between Pediatric CNS Disorders and ADHD Comparison Group

Although several of the medical groups demonstrated evidence of weaknesses in EF in comparison to typically developing peers, the overall level of executive dysfunction was lower in all medical groups in comparison to a group of ADHD controls. This finding is not surprising, as EF deficits are a core feature of ADHD and clinically significant difficulties in EF are expected to occur at high rates within this population.

Evidence for the Impact on Specific EF Functions across all Disorders

Our study results suggest that specific EF domains appear to be more sensitive than other EF domains to disruption across childhood medical disorders. As hypothesized, working memory showed the greatest level of disruption across all medical disorders (ranging from

27% to 45% of individuals falling into the clinically significant range vs. 15% in the matched typically developing controls and 69% of the ADHD group), supporting the idea that there is a specific vulnerability in the development of working memory regardless of the medical condition. This has particularly important implications for learning, as it has been suggested that deficits in working memory may be the “cognitive phenotype” for children who make slow progress in school but don't have specific learning disabilities (Holmes, Gathercole, & Dunning, 2010). Impairment in strategic planning and organization of thoughts and behaviors towards a goal was the next most common EF problem across medical disorders (ranging from 20% to 41% in the clinically significant range vs. 16% in the matched controls and 62% of the ADHD group).

These results may have implications for developing treatment interventions for children with EF difficulties. For example, studies have found that interventions aimed to help children with disrupted working memory improved not only working memory skills, but also had a positive impact on academic skills including reading and mathematical abilities (Dahlin, 2013; Holmes & Gathercole, 2013). Interventions aimed at improving strategic planning during problem solving have also been recognized in the treatment of other neurological disorders, particularly traumatic brain injury (Catroppa & Anderson, 2006; Kennedy et al., 2008). Thus, working memory and planning skills are important functional domains that should be considered as potential targets of intervention in these groups.

While the mean ratings from parents across all groups on all BRIEF domains were below the cutoff of what is considered “clinically significant” the odds of having a clinically significant EF impairment was notably greater in the medical groups than in typically developing children. The mean ratings reflect the fact that the majority of children in our sample of both clinically referred and study eligible children may not be demonstrating clinically significant problems, which is hopeful for the families that experience receiving a diagnosis for their child. The rates of impairment in our samples are similar to that documented in previous studies. Nonetheless, risk was at least 2 times as likely in most medical disorders compared to typically developing peers for significant disruptions in skills associated with adjusting to changes in routine (Shift), working memory, self-starting and initiating thoughts and behaviors (Initiate), as well as devising and implementing strategic problem-solving skills in an organized and goal-directed manner (Plan/Organize).

Age Factors

As has been described in the literature, our findings suggest that age factors are important in the presence or absence of EF deficits. We found significantly more EF difficulties in children diagnosed from birth through 2 years of age versus those diagnosed at ages 8 and up. There were no differences in EF profiles however in children diagnosed in infancy (0-2 years) versus preschool/early childhood (3-7 years). Our results show particular sensitivity to disrupted EF development in children with disorders that are inborn (NF1, OTC-D) and therefore diagnosed at very young ages. The age factor is confounded by the fact that the genetic alterations in these children likely impact cortical development in various ways.

We did not, however, find support for our hypothesis that children who were older at the time of assessment demonstrated greater problems based on the concept of “growing into

one's deficits" such that executive vulnerabilities become noticeable only when the increase in demands exceeds the child's ability to independently manage them in light of EF weaknesses. In fact, it was the youngest group (those evaluated from ages 5-7) that demonstrated greater EF problems. There may be several explanations for this finding. Children referred at a younger age for neuropsychological evaluations may represent a more impaired group, as they may be already showing difficulties at a young age. In contrast, many of the children in this study were diagnosed with their particular condition early in life and may have received intervention services from a young age, negating the hypothesized increasing difficulty with age and demand in our samples. These children and families may have learned coping techniques to deal with these issues or simply better understand/anticipate the problems. Thus, while some of these individuals may not show many deficits early on and instead "grow into" their deficits, others may show problems earlier and learn to accommodate.

This finding may also represent one of the limitations of this study. Samples from both clinical referrals and research groups were used, which may have led to some age and referral biases in the samples. For example, children in some of the studies were evaluated only at circumscribed age time points in accordance with study protocol. Although this may not have impacted the overall mean ages, the children in these particular groups may be clustered around particular age points. In addition, there were clinically significant differences in the age at testing among diagnostic group, which may have confounded these results. Specifically, the brain tumor group was the oldest group (mean age of 12 years), yet was also the group with the least reported problems (even sometimes less than the healthy controls). Finally, these groups may differ due to a referral bias; in that the groups that were from a clinical sample may represent a subset of patients with that disorder that are referred because of a particular concern/problem (at that time of evaluation) and not representative of the group as a whole. However, within our institution, neuropsychological evaluation is the standard of care for many of these populations, and they are referred because of risk for difficulties, and not only when they have exhibited functional problems.

Another limitation of the study is the use of only parent report, which may make it more challenging to generalize our findings. Given the possibility of different environmental demands and potential rater bias by parents, including data from teachers would provide a more complete picture and allow for greater generalizability. For example, prior studies have documented greater reported problems with attention and behavioral regulation on teacher report versus parent report in studies of children with a history of extremely low birth weight (Scott, Taylor, Fristad, Klein, & Espy, 2012) and ADHD (Mares, McLuckie, Schwartz, & Saini, 2007). Other studies have suggested that parents and teachers report different types of concerns on the BRIEF. For example, McCann, Rider, Weiss, Litman, and Baron (2013) utilized parent and teacher BRIEF in 124 children with ELBW. The authors found that the parents of ELBW children reported greater concerns with emotional regulation while teachers reported greater difficulties with behavioral regulation. Differences in parent and teacher report may be secondary to several factors, including reporting bias in parents and/or real differences in EF demands and supports between school and home, as we have suggested in our pediatric cancer work (Walsh et al., 2015; Wochos et al., 2014). Nonetheless, it could be argued that parents observe their children in multiple settings

(home, social) and likely receive information regarding their child's functioning in the classroom, and their ratings might reflect concerns that school personnel have described. In addition, performance-based measures of EF would allow for a more comprehensive evaluation of these skills in both the lab setting and the “real world.”

In summary, these findings highlight the importance of thorough neuropsychological evaluation to delineate the specific EF strengths and weaknesses in these susceptible pediatric populations, as it is clear that there are subsets of children with various CNS disorders that are more (or less) vulnerable to alterations in the typical development of EF. Longitudinal research will be crucial for an enhanced understanding of the risks and protective factors for the development of appropriate executive control in pediatric patients with CNS disorders. Moreover, this would inform models of intervention for EF impairments in these populations of children.

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Figure 1. BRIEF Score Profiles by Diagnosis

Figure 2. Percentage of Group Members With Clinical Scale Elevations (T ≥ 65) on BRIEF

Table 1

Demographic Data

Diagnostic Group	N	Gender %Male [†]	Mean Age at Testing [†]	Mean IQ [†]	Mean Age at Diagnosis [†]
Epilepsy	76	47.4	9.7 (3.0) Range 5 to 17	102 (16) Range 73 to 139	6.4 (3.1) Range 1 to 15
OTC-D	42	71.4	11.0 (4.3) Range 5 to 18	96 (14) Range 72 to 136	3.7 (3.9) Range 0 to 14
Brain Tumor	69	55.1	12.0 (3.7) Range 5-18	97 (16) Range 70-133	6.0 (4.2) Range 0 to 16
NF-1	53	58.5	10.2 (3.4) Range 5-17	93 (13) Range 72-126	*
ALL	51	33.3	10.9 (3.0) Range 5-17	99 (14) Range 72-124	4.7 (3.0) Range 0 to 14
ADHD Controls	115	61.7	10.0 (3.3) Range 6-18	107 (16) Range 74-156	Not available
Typical Control	328	51.5	10.2 (3.5) Range 5-18	Not available	N/A

* NF patients were generally diagnosed before the age of 1, with the exception of one patient diagnosed at age 5.

[†] Variables that had significant differences at p<.05. Further discussion provided in results section.

Table 2

Clinical Group Descriptive Features

GROUP	% from a Research Sample	Recruitment Strategy for research cases	Typical age of onset/diagnosis	Prevalence of the Disorder	Relevant Clinical Characteristics in this sample
Epilepsy	75.3%	Focal epilepsy- recruited all comers with normal MRI.	Childhood with modal onset <2 years	48:100,000+	Focal epilepsy (71% left hemisphere); range of seizure frequency (none to daily); majority on monotherapy; 68% normal MRI
OTC-D	100%	Natural history/ Longitudinal study- recruited all comers	Neonatal onset: first month of life Late onset (partial): more variable	1:56,500*	All OTC subjects were symptomatic and included both neonatal and late onset presentations
NF1	0%	n/a	Varies, but typically within first couple years of life	1:2700 [§]	All diagnosed per NIH diagnostic criteria for NF1 [±]
Brain Tumor	0%	n/a	Varies	4.5: 100,000 [^]	Location: 39% Infratentorial Treatment: 73% surgical resection, 65% chemotherapy, 70% radiation. All off treatment and medically stable.
ALL	0%	n/a	Varies	11,000 new dx/year (birth to 14 years)	All subjects were off therapies and medically stable.
ADHD	0%	n/a	Varies		DSM-IV Classification 28% Inattentive Type 65% Combined Type 7% ADHD-NOS

Table 3
Odds Ratios and Percentages by Diagnosis- Likelihood of and Percentages of Group with Clinical T score Elevations (T 65) in comparison to Typical Control Group

	Inhibit	Shift	Emotional Control	Initiate	Working Memory	Plan/Organize	Org. of Materials	Monitor
<i>Chi Square Analysis</i>	$\chi^2(5)=9.2$ p=.101	$\chi^2(5)=33.4$ p<.001	$\chi^2(5)=6.3$ p=.274	$\chi^2(5)=29.1$ p<.001	$\chi^2(5)=33.2$ p<.001	$\chi^2(5)=22.1$ p<.001	$\chi^2(5)=4.1$ p=.531	$\chi^2(6)=27.9$ p<.001
Epilepsy	1.19 (21%)	3.55 (17%)	1.57 (16%)	2.48 (24%)	3.73 (33%)	2.44 (32%)	1.35 (19%)	1.33 (22%)
OTC-D	1.40 (24%)	4.70 (21%)	1.97 (19%)	5.24 (40%)	4.17 (43%)	3.53 (41%)	0.81 (13%)	2.47 (34%)
Brain Tumor	0.28 (6%)	2.72 (14%)	0.84 (9%)	1.12 (13%)	2.04 (27%)	1.30 (20%)	0.92 (14%)	0.57 (11%)
ALL	0.60 (12%)	5.23 (24%)	1.56 (16%)	2.22 (22%)	3.03 (35%)	2.37 (31%)	1.25 (18%)	1.19 (20%)
NF1	0.91 (17%)	5.74 (25%)	1.95 (19%)	2.55 (25%)	3.11 (36%)	1.73 (25%)	1.85 (25%)	3.87 (45%)
ADHD	- 58%	- 37%	- 37%	- 44%	- 69%	- 62%	- 46%	- 53%
Typical Controls	- 18%	- 6%	- 11%	- 11%	- 15%	- 16%	- 15%	- 17%