Oxidative Stress and Executive Function in Children Receiving Chemotherapy for Acute Lymphoblastic Leukemia

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Abstract

Background—Neurocognitive sequelae following treatment for pediatric acute lymphoblastic leukemia (ALL) has been reported in a significant proportion of survivors, including those treated only with chemotherapy. Early identification of children "at risk" for neurocognitive problems is not yet reliable. Biomarkers of oxidative stress (e.g., oxidated phosphatidylcholine) in cerebral spinal fluid (CSF) have been correlated with intensity of methotrexate (MTX) treatment, suggesting an association with acute central nervous system toxicity.

Procedure—This study examined the association between oxidized CSF phospholipids and executive functions throughout chemotherapy. Measures of oxidative stress and executive functions were examined in 88 children newly diagnosed with ALL. The children were followed over three years with neurocognitive testing and parent ratings of executive functions.

Results—Results demonstrated an association between increased oxidative stress following induction and consolidation and decreased executive function two years later. Younger age at diagnosis was associated with both an increase in oxidative stress and in executive dysfunction; younger age was associated with poorer ability to organize materials in one's environment ($r(48) = 0.28$, $p < 0.05$) and with greater oxidated phosphatidylcholine in CSF at the end of chemotherapy ($r(48) = -0.27$, $p < 0.05$). As such, younger age appears to be the most prominent moderator of neurocognitive decline.

Conclusions—These results link functional changes to CSF biomarkers and underscore the importance of monitoring cognitive development in young children treated for ALL. Children with less advanced central nervous system development may be particularly vulnerable to the effects of chemotherapy.

Keywords

oxidative stress; neurocognitive; leukemia

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Introduction

Advances in treatment for pediatric acute lymphoblastic leukemia (ALL) have led to increased survival rates that now exceed 80%.[1,2] Therapies responsible for the dramatic improvement initially consisted of prophylactic cranial-spinal (C-S) radiation to prevent CSN relapse, though this approach often lead to neurocognitive difficulties and other undesirable late-effects.[3,4] Successful efforts to reduce neurotoxicities resulted in replacing C-S radiation with intensified intrathecal and intravenous methotrexate (MTX). [5,6] Although removing radiation from frontline therapy has improved neurocognitive outcomes, high-dose MTX still poses substantial risk to neurocognitive functions. Risk factors for neurotoxicity associated with MTX include younger age at treatment and being female.[7,8]

MTX has been routinely associated with leukoencephalopathy.[9,10] With disproportionately greater amounts of white matter in the frontal lobes, connections involving these areas may be at particularly high risk for dysfunction and may account for much of the cognitive, intellectual, academic, and psychiatric sequelae associated CNS treatment. Reduced frontal lobe white matter volume has been reported in long-term survivors of pediatric leukemia.[11]

The frontal lobes are also widely associated with executive functions, which have been defined as the ability to coordinate other functional systems through attending, planning, and monitoring behavior.[12] Executive functions are one's ability to self-regulate behavior through cognitive flexibility and initiate or switch purposive behavior to appropriately function within a given situation.[13] Although there is clearly some overlap between intellectual/cognitive functions and executive functions, it is somewhat surprising that there are not more studies specifically examining executive functions associated with chemotherapy given the connection between executive functions and frontal lobe white matter.

It is unclear whether leukoencephalopathy associated with MTX is due to oxidative stress or other factors, but an association between MTX and markers of oxidative stress is emerging and demonstrates treatment-related cellular breakdown within the CNS. Elevated concentration of phosphatidylcholine (PC), the most abundant CSF phospholipid and a critical component of CNS cell membranes, has been used to identify acute CNS injury associated with ALL and its chemotherapy.[14] More recently, the oxidized fraction of PC has been used as a sensitive biological marker of oxidative stress.[15] Studies with rats and humans provide converging evidence that MTX treatment triggers a decrease in protective factors against free radical damage[16,17] making polyunsaturated fatty acid chains within cell membrane more susceptible to attack by reactive oxygen species.[18] Oxidant attacks cause further lipid peroxyl radicals to form and propagates a cascade of cell membrane damage.[15,19] As increased levels of oxidized PC following MTX therapy for ALL have been associated with unfavorable intellectual, academic, spatial-perceptual, and working memory abilities,[8,20] oxidative stress may be a mechanism through which declines in functioning occur.

Despite evidence of oxidative stress, leukoencephalopathy, and neuropsychological dysfunction, the relation between executive functions and oxidative injury in patients treated with MTX has not yet been established. The main aim of this study was to investigate the association between markers of oxidative stress (following induction and consolidation phases of chemotherapy) and difficulties with executive functions at post-consolidation and at the end of therapy. The effects of known covariates (e.g. higher dose of MTX, younger

age at treatment, female sex) in the association between markers of oxidative stress and executive functions were also investigated.

Methods

Subjects

The sample included 88 children newly-diagnosed with pediatric ALL, who were consecutively recruited from two major southwestern cancer centers. Parents or legal guardians completed the informed consent process, and assent was obtained from patients when appropriate. The study was approved by the necessary institutional review boards.

Participants were treated on Pediatric Oncology Group (POG) protocols 9201, 9406, 9605, 9806, 9904, 9905, or 9906. Most children were treated with 1 gram (gm) of MTX/m^2 over 24 hour infusion or 2 gm of MTX/m^2 over 4 hour infusion by IV. Additionally, 6 children were treated with 100 mg of MTX/m^2 over 24 hour infusion and 1 child was treated with 2.5 mg MTX/m^2 over 4 hour infusion. These seven participants were not included in evaluation related to dose of methotrexate, but were included in analyses of the overall treatment group. Intrathecal MTX was administered in age-titrated doses according to protocol, and the number of IT injections was equivalent across the various protocols. Patients were excluded if diagnosed with CNS involvement any time during the course of therapy, if relapsed during therapy, or if treated with cranial irradiation. All children were between the ages of 3 and 16 years, the appropriate age range for reliable administration of the standardized neurocognitive tests used in this study. The mean age at diagnosis for the clinical sample was 7.1 years (SD = 3.1), and mean parent education level was 13.3 years (SD = 2.7). Males comprised 41% the sample.

CSF Sample Phospholipids

CSF samples were harvested from patients at the diagnosis lumbar puncture (LP) and during subsequent induction and consolidation LPs required for IT MTX therapy. Induction and consolidation PC measurements represent mean levels over those treatment phases. Protocols used in the process leading to CSF PC component quantification have been described previously.[15] The concentration of unoxidized PC in CSF samples was converted to µg/mL. Oxidized PC was recorded as a fraction for each sample (i.e. peak area of oxidized PC: peak area of unoxidized PC) instead of a concentration. Results are expressed as changes in unoxidized PC concentration and oxidized PC fraction from diagnosis to induction and diagnosis to consolidation.

Executive Function Measures

The Behavior Rating Inventory of Executive Function (BRIEF)[21] is a parent-completed questionnaire used to evaluate executive functions within the domains of behavioral regulation and metacognitive abilities. Specifically, it assesses nine domains of executive functions, including: 1) *Inhibition*- the ability to resist impulses and stop behavior appropriately; 2) *Shifting*- the ability to transition, tolerate change, and shift attention; 3) *Emotional control*- the expression and regulation of emotion; 4) *Self-monitoring*- the awareness of self-behavior on others; 5) *Initiation*- the ability to get started on physical or mental activities; 6) *Working memory*- the capacity to hold information in one's mind in order to complete tasks; 7) *Planning and organization*- the ability to determine the best way to achieve a goal and bring organized structure to information; 8) *Organization of materials*- the ability to organize things in one's environment; and 9) *Task monitoring*- the ability to attend to one's success or failure and modify strategy appropriately. The BRIEF transforms raw scores for each domain into sex and age-adjusted T-scores (M=50, SD=10) based on a

nationally representative normative sample. BRIEF assessments were conducted at approximately one year **post-consolidation** and at the **end of therapy**.

The Behavior Assessment System for Children Parent Rating Scale (BASC-PRS) is a widely-used, clinical assessment tool that evaluates behaviors and adaptive skills.[22] One of the scales from the BASC is *Attention Problems*; attention is a core component of proper executive functions. The raw scores for Attention Problems were also converted to sex and age-adjusted T-scores (M=50, SD=10) based on a nationally representative normative sample. BASC-PRS assessments were conducted at the same time points as the BRIEF.

Verbal fluency was assessed as part of the neurocognitive evaluation associated with this study.[23] Verbal fluency is a performance-based measure of executive functions that combines aspects of initiation and working memory. Using standard rules for administration, children were asked to name as many animals as they could within the span of one minute. Raw scores were converted to age adjusted scaled scores (M=10, SD=3). Verbal fluency evaluations were conducted at the same time as the BRIEF and BASC questionnaires.

Data Analysis

All data was analyzed using SPSS 16. T-tests were conducted to examine the change in oxidized PC levels across treatment phases and the change associated with the 1 gm MTX/m^2 IV treatment regimen vs. the 2 gm MTX/m^2 IV treatment. Bivariate Pearson Product correlations were used to evaluate the association between oxidative stress (oxidative PC fraction reactivity) and executive functions (BRIEF, BASC-PRS Attention Problems, and Semantic Fluency). Bivariate Pearson Product correlations were also used to evaluate whether certain covariates (age at diagnosis or parent education) were associated with amount of oxidative reactivity post-consolidation and at the end of therapy. Chi Square (χ^2) was used to examine oxidative PC fraction differences related to dichotomous risk factors such as sex and treatment dose (1 g MTX/m^2 or 2 g MTX/m^2). To accomplish this, a median split was used to create low and high groups of oxidated PC fraction reactivity. A repeated measures analysis of variance was used to examine changes in executive function from post-consolidation to end of therapy time point points.

Measures from the BRIEF, BASC-PRS, and Verbal Fluency were also compared to normative data. Using participants' standard errors from each test/subtest, 95% confidence intervals were created for each measure to identify differences between patients and national norms. Normative means falling outside of a confidence interval were considered reflective of a group difference for that particular measure.

Results

Table I presents basic demographic and treatment data related to the risk factors of interest in this study. There were no significant differences between the 1 gm/m^2 and 2 gm/m^2 group for Age at Diagnosis, $F(1, 71) = 1.7$, $p > 0.05$ or Parent Education, $F(1,67) = 0.028$, $p > 0.05$. Although there were more females in the sample overall, the proportion of males to females did not differ by treatment group ($\chi^2(1, 77) = 0.24$, $p > 0.05$). In addition, the 1 gm/m^2 and 2 gm/m^2 did not differ in regard to risk stratification ($\chi^2(1, 81) = 2.42$, $p > 0.30$).

Oxidized PC levels significantly increased from diagnosis (M = 0.015, SD = 0.006) to post-induction (M = 0.026, SD = 0.010), t(46) = 6.49, p < 0.001), and from diagnosis to post-consolidation (M = 0.026, SD = 0.0090) for both groups combined, t(52) = 8.35, p < 0.001). Although the 1 gm/m^2 group demonstrated a larger change in oxidized PC from diagnosis to post-induction (M = 0.012, SD = 0.013) compared to the 2 gm/m^2 group [(M = −0.006, SD = 0.005), t (41) = 2.41, p < 0.02], this change occurred prior to administration of the various

IV MTX doses during consolidation therapy. The change in oxidized PC from post-induction to post-consolidation, reflecting the change associated with consolidation therapy, was larger for the 2 gm/m^2 group (M = 0.006, SD = 0.010) compared to the 1 gm/m^2 group [M = −0.002, SD = .010), t(43) = 2.10, p < 0.05].

The overall group performance on measures of executive functions were elevated, though the patients did not significantly differ from the normative sample. However, patients displayed distributions that were positively skewed with greater variability than standardized norms, suggesting the presence of a subset of patients that may have been more adversely affected than others. Table II shows the means and standard deviations for each measure, stratified by IV MTX dose group. The vast majority of scores fall in the average range, though mild elevations and significant variability exists within certain scales.

Increased oxidative stress was associated with measures of executive functions (poorer working memory, poorer ability to organize materials, and attention problems) collected at the end of therapy. Table II presents the significant correlations between these executive functions and oxidized PC reactivity at induction and consolidation. All correlations support the hypothesis that increased measures of oxidative stress were associated with greater executive dysfunction. No significant correlations were found between oxidized PC reactivity and executive functions at the post-consolidation assessment time.

The only patient factor associated with oxidative stress was age at diagnosis r (48) = 0.268, $p < 0.05$, suggesting younger age was associated with higher oxidized PC reactivity at consolidation. Although most risk factors were noted to affect executive functions, only age at diagnosis was associated with oxidative stress and executive functions. Executive abilities varying by age at diagnosis include Verbal Fluency at the post-consolidation time point, r (47) = −0.58, $p < 0.001$, Verbal Fluency at the end of therapy time point, r (51) = −0.63, $p < 0.001$, and Organization of Materials at the end of therapy time point, r (44) = 0.28, $p < 0.05$. These results suggest older age at diagnosis was associated with poorer verbal fluency performance and better organization of materials.

Although other factors were not associated with oxidative stress, many did affect executive functions. Females had poorer working memory than males at the end of therapy, (χ^2 (1, N = 46) = 5.4, $p > 0.05$). On measures of emotional regulation, males made significant improvements from post-consolidation to end of therapy, while females did not F (1,28) = 8.0, $p > 0.01$). This sex by time interaction can be seen in Figure 1. Parent education level was not associated with executive functions after controlling for age of diagnosis (age at diagnosis and parent education were positively correlated r (71) = −0.277, $p = 0.01$). Controlling for parent education did not change the association between age of diagnosis and executive functions (Table III).

Discussion

Methotrexate (MTX) has been associated with cognitive and intellectual dysfunction,[24,25] leukoencephalopathy,[9,10] and oxidative stress.[15, 20] The present results further support the hypothesis that oxidative stress, as reflected through oxidized PC, increases with treatment intensity and, to some extent MTX dosage. Our study specifically examined the association between oxidative stress induced by MTX treatment and specific executive dysfunction. The hypothesis that poorer executive functioning would be associated with increased oxidative stress was supported. Significant correlations were found between greater oxidized PC reactivity (at induction and consolidation) and lower executive functioning at the end of chemotherapy treatment. Admittedly, the decline in executive functioning was small, with performances still falling in the average range, though the

decline was consistent and may reflect a beginning trend that results in clinically significant late-effects.

The specific functional areas associated with oxidative stress include working memory, organizational abilities, and verbal fluency. The delayed onset in problems with executive function (i.e. end of therapy but not one year post diagnosis) suggests that oxidative stress results in reduced development that may take time to manifest in observable behaviors. Oxidative stress may be an initial pathophysiological event that leads to apoptosis. Progressive degeneration of white matter and/or neurons may account for later manifestation of effects on executive functions. MTX has been associated with delayed onset and long-term cognitive effects in other studies, so this finding is not unique.[26,27] Furthermore, the pattern of problems in fluency and working memory is commonly reported in long-term survivor studies.[27,28]

The expectation that common factors associated with neurotoxicity (i.e., age at diagnosis, sex, treatment intensity, parent education) would be associated with more oxidative stress and poorer executive function outcome was partially supported. Younger age at diagnosis was associated with more oxidative stress after consolidation, but the other risk factors were not. As age and oxidative stress were related to similar executive functions, there does appear to be a connection between the vulnerability of younger children to oxidative stress and greater problems in organization and working memory. White matter also appears particularly vulnerable to oxidative stress because of its high lipid content.[29-31] As such, younger children may be more vulnerable to oxidative stress because of relatively more myelin development during this phase.[32]

Although literature suggests that younger age at diagnosis is largely associated with greater cognitive sequelae,[1,2,7] the present study's results appear contradictory. Children treated at a younger age were reported to have more problems with organization, though demonstrated fewer problems with verbal fluency. This pattern may not be completely inconsistent with the age sensitivity theory, as emerging research suggests that verbal fluency develops later than other executive functions, with full development not occurring until late adolescence or early adulthood.[33,34] Thus, verbal fluency problems may be more difficult to identify in younger children due to increased normal variability among the younger cohort. As children's verbal fluency skills develop, the variability in normal performance decreases making identification of problems in an older subset much easier. In addition, children treated at a younger age may complete therapy prior to the developmental window when verbal fluency matures, while children treated at an older age may have the development within this window disrupted by treatment agents.

No appreciable differences were found between the overall sample of participants diagnosed with ALL and the age-standardized norms on executive function measures (the BRIEF, BASC-PRS, and verbal fluency). This may be due to the fact that the children are still in the early stages of recovery and have not yet entered the long-term survival stage. The fact that the performance is correlated to biological markers of oxidative stress indicates that the outcomes are associated with physiological changes. These changes may reflect the onset of a neurological impact which may become more evident as the children age and reach long-term survivorship status. If this is the case, the biological markers of oxidative stress may be useful in the early identification of children at future risk for neurocognitive decline. With such an identifiable risk factor, preventative treatment strategies could be implemented.

There were limitations associated with this study. First, due to some missing data points within our data set, certain risk group comparisons were limited and reduced in power. With increased power, stronger associations between executive dysfunction and oxidative stress

could have emerged, though it is plausible that the missing data could have gone in a direct opposite of the currently apparent trend. Similarly, more associations between oxidative stress and known risk factors for toxicity and neurocognitive dysfunction might have been identified. Another limitation of this study was its prospective cohort design. While this design is ideal for establishing the relation between oxidative stress and executive functions for a specified period of time, longitudinal studies are still needed to better understand the course of executive dysfunction and the clinical impairment that may result if the current trend continues into the late-effect stage of cancer survivorship (i.e. 5 year post-diagnosis).

In summary, oxidative stress from MTX treatment appears to be associated with poorer executive functions in children at the end of chemotherapy. Longitudinal studies of ALL survivors are needed to determine whether these deficits develop into long-term effects or remit over time. The existing literature would suggest deficits are a byproduct of CNS integrity and cognitive problems may persist. This study adds converging evidence that age at diagnosis is a risk factor for poorer neuropsychological outcome. The emergence of certain deficits, however, may be associated with the developmental stage of the CNS at the time of evaluation. The results from this study suggest oxidative stress is one mechanism responsible for difficulties with executive functions and underscores the importance of taking special precautions when treating younger children with ALL.

Acknowledgments

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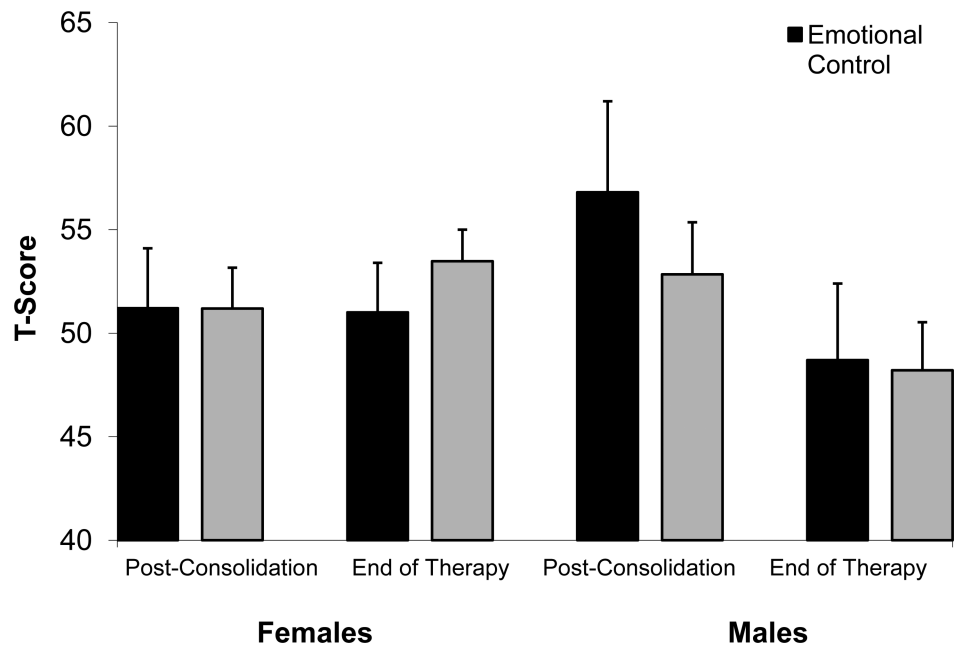
Figure 1.
Parent ratings on measures of Emotional Control and Working Memory functions from post-consolidation to end of therapy for females and males. Higher scores represent more problematic symptoms.

Table I

Demographics by Treatment Group

MTX	# Intrathecal MTX			Sex		Age at Diagnosis			Parent Education		
	M	SD	N	Male	Female	M	SD	N	M	SD	N
1gm/m²	16.68	1.28	28	21	34	6.5	2.8	52	13.3	2.9	47
2gm/m²	16.00	1.07	8	11	11	7.5	3.2	21	13.4	1.7	22
Total	16.53	1.25	36	32	45	6.8	2.9	73	13.3	2.7	69
	$F = 1.87, p > 0.05$			$X^2 = 0.24, p > 0.05.$		$F = 1.7, p > 0.05$			$F = 0.028, p > 0.05.$		

Note: Age and Parent Education expressed in years.

Table II

Executive Function Mean and SD by Oxidative Reactivity

| | Change in Oxidative Stress Marker | | | |
| | Diagnosis to Induction | | Diagnosis to Consolidation | |
Post-Consolidation	**High Reactors Mean (SD)**	**Low Reactors Mean (SD)**	**High Reactors Mean (SD)**	**Low Reactors Mean (SD)**
Inhibition	49.9 (9.96)	50.5 (10.89)	50.7 (11.11)	48.5 (7.95)
Shift	52.1 (11.33)	49.2 (8.09)	48.6 (9.14)	52.7 (11.08)
Emotional Control	51.9 (12.51)	54.7 (14.17)	49.8 (11.15)	54.3 (14.60)
Initiation	49.5 (9.69)	50.3 (10.49)	49.6 (10.78)	50.5 (9.36)
Working Memory	52.1 (10.27)	51.1 (9.37)	51.6 (10.16)	51.1 (8.96)
Plan / Organize	48.9 (8.33)	52.2 (10.04)	50.7 (10.20)	50.1 (7.92)
Organize Materials	52.2 (10.90)	50.5 (11.44)	49.7 (9.37)	52.8 (13.50)
Task Monitoring	48.4 (8.72)	49.5 (12.08)	49.0 (9.45)	48.5 (11.27)
Attention	50.8 (14.02)	49.4 (11.57)	50.7 (13.92)	49.3 (10.64)
Verbal Fluency	51.3 (25.70)	50.0 (17.3)	50.1 (22.07)	48.3 (19.47)
End of Treatment				
Inhibition	52.9 (8.43)	46.1 (6.49)	48.6 (6.70)	49.7 (8.48)
Shift	51.9 (8.97)	44.1 (5.19)	47.8 (8.27)	48.8 (8.32)
Emotional Control	52.6 (11.09)	49.2 (10.65)	48.0 (9.39)	51.2 (11.38)
Initiation	50.8 (10.52)	54.6 (7.35)	45.2 (7.55)	50.7 (9.48)
Working Memory	54.2 (9.54)	48.3 (7.10)	51.9 (9.21)	51.4 (8.51)
Plan / Organize	54.5 (9.06)	49.7 (9.47)	51.8 (9.04)	52.9 (8.91)
Organize Materials	55.6 (10.44)	48.1 (11.67)	52.3 (8.67)	51.9 (12.22)
Task Monitoring	50.7 (8.22)	46.6 (9.18)	47.7 (6.23)	48.8 (9.23)
Attention	54.6 (14.08)	49.3 (8.97)	58.5 (10.64)	50.5 (9.28)
Verbal Fluency	53.0 (20.58)	46.3 (11.55)	52.3 (16.06)	43.3 (15.09)

Note: All scores reported as T-Scores (Mean = 50 and Standard Deviation = 10), with higher scores reflecting more pathology.

Table III

End of Therapy Executive Functions and Oxidized Phosphatidylcholine Fraction (OP).

Executive Function	OP at Induction	OP at Consolidation
Working Memory	0.398[*]	0.346[*]
Organization of Materials	0.327[*]	0.335[*]
Attention Problems	0.437[*]	ns

[*] All correlations significant at the p< 0.05 level and suggest a significant increase in executive function problems with increasing oxidized PC fraction.

Table IV

Correlations between Executive Functions and Age Diagnosed and Parent Education

Executive Function	Age at Diagnosis (AD)		Parental Education (PE)	
	Original	PE Adjusted	Original	AD Adjusted
Verbal Fluency[1]	0.58**	0.52*	−0.30*	ns
Verbal Fluency[2]	0.63**	0.64**	−0.34**	ns
Organization of Materials[2]	0.28*	0.58**	−0.35**	ns

Note: Positive correlations suggest an increase in executive function problems associated with increasing age/parent education, while negative correlations suggest decreased executive dysfunction associated with these factors. PE Adjusted represents correlation between Age at Diagnosis and Executive Functions adjusting for Parent Education. AD Adjusted represents correlation between Parent Education and Executive Functions adjusting for Age at Diagnosis.

*
Correlation is significant at the 0.05 level.

**
Correlation is significant at the 0.01 level.