

Executive Functioning in Children and Adolescents with Perinatal HIV Infection

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List of Abbreviations:

AIDS – Acquired Immunodeficiency Syndrome

AMP – Adolescent Master Protocol

BASC-2 – Behavioral Assessment System for Children, Second Edition

BRIEF – Behavior Rating Inventory of Executive Function

CCTT- Children’s Color Trails Test

CDC – Centers for Disease Control

CELF-4 – Clinical Evaluation of Language Fundamentals, Fourth Edition

EF – Executive Function

FSIQ – Full Scale IQ

HIV – Human Immunodeficiency Virus

IQ – Intelligence Quotient

M – Mean

PHACS – Pediatric HIV/AIDS Cohort Study

PHEU – HIV-exposed, uninfected

PHIV – Perinatally acquired Human Immunodeficiency Virus

PR – Parent Report

SD – Standard deviation

SR – Self-report

VL – Viral load

WIAT-II-A – Wechsler Individualized Achievement Test, 2nd Edition,

Abbreviated

WISC-IV – Wechsler Intelligence Scale for Children, 4th Edition

Abstract

Background: Perinatal HIV infection (PHIV) may place youth at risk for impairments in executive functioning (EF). We examined associations of EF with HIV infection, disease severity and other factors among youth with PHIV and perinatally exposed, uninfected youth (PHEU).

Methods: Within the U.S.-based Pediatric HIV/AIDS Cohort Study, 354 PHIV and 200 PHEU youth completed a standardized EF measure (Children's Color Trails Test, CCTT) and youth and/or caregivers completed a questionnaire measuring everyday EF (Behavior Rating Inventory of Executive Function, BRIEF). Covariates included HIV status, current and historical disease severity, demographic and caregiver variables, and other cognitive measures. Analyses utilized linear and logistic regression and proportional odds models.

Results: No significant HIV status group differences were found on CCTT scores. Caregiver BRIEF ratings indicated significantly fewer problems for PHIV than PHEU youth. However, PHIV youth with past encephalopathy self-endorsed significantly greater metacognitive (i.e., cognitive regulation) problems on the BRIEF and performed more slowly on the CCTT than PHEU youth. CCTT and caregiver BRIEF scores had significant associations with indicators of past and present disease severity. Both PHIV and PHEU had significantly worse scores than population means on CCTT and BRIEF; scores had significant associations with demographic covariates.

Conclusions: Youth with PHIV show EF problems likely associated with risk factors other than HIV. However, cognitive slowing and self-reported metacognitive problems were evident in PHIV youth with a history of encephalopathy. Assessment and treatment of EF impairment may be important to identifying PHIV youth at particular risk for poor health and behavioral outcomes

INTRODUCTION

The impact of perinatally acquired human immunodeficiency virus (PHIV) on cognitive and behavioral development is an ongoing concern. Children with PHIV are generally comparable in global intellectual functioning to perinatally HIV-exposed but uninfected (PHEU) children, who are similar in other risks to development (e.g., poverty, familial psychiatric and cognitive history, disrupted caregiving) and in prenatal exposure to maternal HIV and antiretroviral agents, which may impact growth and development¹⁻³. However, a subset of children with PHIV who experienced significant immunocompromise and acquired immunodeficiency syndrome (AIDS)-defining illnesses, particularly encephalopathy, exhibit significantly increased risk for cognitive impairment⁴⁻⁶.

Concerns persist regarding subtle impairments in specific cognitive domains and their functional impact. A domain particularly at risk for HIV-related impairment in adults⁷ is executive functioning (EF), which includes skills involved in performing goal-directed behaviors⁸ (e.g., problem solving, inhibition, monitoring of self and environment, and flexibly shifting behavior or mental focus). EF has been linked to functional outcomes relevant to HIV treatment and prevention, such as medication management⁹, sexual risk behaviors¹⁰, and to life skills, including occupational functioning^{9,11}, driving¹², and educational outcomes¹³. The impact of EF impairments for youth may be magnified by affecting acquisition of skills necessary for successful transition to adulthood; further, they may increase the likelihood of sexual and substance-related risk behaviors¹⁴. EF impairments may present in adolescence, the

developmental period during which EF skills are consolidated, playing an increasingly important role in day-to-day functioning¹⁵. Identification of such impairments could inform appropriate treatment and preventive interventions.

Few existing studies of children with PHIV have addressed EF, the majority with small samples¹⁶, and results thus far are equivocal¹⁷⁻²⁰. Nagarajan and colleagues found lower processing speed but not EF functioning in PHIV compared with PHEU youth¹⁷. Other studies have found differences between PHIV and PHEU children on EF measures that were not explained solely by processing speed¹⁸⁻²⁰. Recently, Llorente and colleagues²¹ reported results from a prospective, longitudinal study of EF in PHIV and PHEU children, aged 8-12 years, including a subgroup of PHIV youth with Centers for Disease Control (CDC) Class C, or AIDS-defining, diagnoses. Although unadjusted analyses suggested an impact of HIV infection on EF, the effects of HIV were not significant when analyses accounted for treatment and psychosocial risk factors (e.g. maternal education), suggesting that, while EF deficits may occur in children with PHIV, their origin may lie in risk factors other than HIV.

In this investigation, we examined EF in a large cohort of children and adolescents aged 7-16 years with perinatal HIV exposure, including both PHIV and PHEU youth. Our goal was to examine whether PHIV confers risk for EF impairment, using both an EF task and report of day-to-day EF by caregivers and youth, and to elucidate other factors associated with EF. Exploratory analyses accounted for the influence of other cognitive domains such as language that may underlie performance of EF tasks²². We hypothesized that youth with PHIV would demonstrate greater EF

problems than PHEU and that poorer EF performance would be associated with greater current and past HIV disease severity.

METHODS

Participants

Participants were enrolled in the Adolescent Master Protocol (AMP) of the Pediatric HIV/AIDS Cohort Study (PHACS), a prospective cohort study of the long-term effects of perinatal HIV infection and its treatments on biomedical and neurobehavioral outcomes (see <https://phacsstudy.org/>). Participants were enrolled at one of 15 urban AMP sites throughout the United States, including Puerto Rico, between March 2007 and October 2009. Eligibility criteria included perinatal HIV infection or exposure, age 7 to <16 years, and previous medical care with accessible HIV treatment history. Youth included in these analyses had valid data for the Children's Color Trails Test (CCTT)²³ and either the caregiver-report or youth self-report versions of the Behavior Rating Inventory of Executive Functioning (BRIEF)^{24 25}. Because the BRIEF was not available in Spanish during data collection, it was not administered to children and caregivers without proficient English fluency.

Procedure

Institutional Review Boards at the Harvard School of Public Health and each PHACS site approved the AMP study. Informed consent and age-appropriate assent were obtained for all youth participants according to local IRB guidelines.

Measures

Primary Outcomes

The *CCTT* is a standardized paper-and-pencil assessment of alternating and sustained visual attention, sequencing, psychomotor speed, cognitive flexibility, planning and inhibition-disinhibition. Age-norm-referenced scores include standard scores for each trial completion time (mean (M)=100; standard deviation (SD)=15; higher scores indicate faster performance), and percentile ranges for the Interference Index ($[(CCTT-2 \text{ Time raw score} - CCTT-1 \text{ Time raw score}) / CCTT-1 \text{ Time raw score}]$), a measure of cognitive flexibility and interference susceptibility (higher percentiles indicate less interference).

The *Behavior Rating Inventory of Executive Functioning, Parent-Report Form (BRIEF-PR)*²⁴ and the *BRIEF-Self-Report (BRIEF-SR)*²⁵ are norm-referenced rating inventories that assess EF in the performance of everyday tasks, across multiple domains. Included are: Behavioral Regulation Index (combines Inhibit, Shift, and Emotional Control scales); Metacognition Index (combines Initiate, Working Memory, Plan/Organize, Organization of Materials, and Monitor scales); and General Executive Composite computed by combining scores from the Behavioral Regulation Index and Metacognitive Index. Age-norm-referenced T-scores (i.e., $M=50$, $SD=10$) are computed, whereby higher T-scores indicate more difficulties and T-score ≥ 65 indicates clinical significance. Caregivers completed the BRIEF-PR regardless of participant age. Per BRIEF-SR guidelines, children and adolescents age 11 and older completed the BRIEF-SR.

Demographic, Caregiver and Health Information

Demographic information collected via structured interview with the primary caregiver included age, sex, race/ethnicity, and primary language of child, household income, and caregiver relationship to child and education. For PHIV youth, chart abstraction provided current (at study entry) and peak HIV-1 RNA viral load (VL) and age at peak VL; current, nadir and age at nadir CD4+ T-lymphocyte count and percent; CDC classification of HIV disease and age at classification; diagnosis of encephalopathy and age at diagnosis; and current antiretroviral treatment. Encephalopathy diagnosis was based on medical record review.

Other Measures of Child Functioning

Other measures of cognitive and behavioral functioning (Table 1) were used as covariates in exploratory analyses of the contribution to EF group differences of internalizing problems (anxiety, depression and somatization) and non-EF-specific functioning (i.e., Full Scale IQ, reading and language).

Data Collection

Administration of measures was staggered across study visits to minimize participant burden. Biannual visits included physical exam, medical chart review of health and medication status, structured demographic interviews, and neurodevelopmental evaluations as follows: At study entry, youth were administered the Wechsler Intelligence Scale for Children-IV²⁶ (WISC-IV) and Behavior Assessment System for Children-2²⁷ (BASC-2) Self-Report of Personality; caregivers completed the BASC-2 Parent Report and youth medical and developmental history were assessed. At

the 6-month visit, youth were administered the Clinical Evaluation of Language Fundamentals-4²⁸ (CELF-4). At the 1-year visit, youth completed the CCTT, Wechsler Individual Achievement Test-II²⁹ (WIAT-II), and BRIEF-SR (for those 11 years and older); caregivers completed the BRIEF-PR.

Statistical Methods

Demographic characteristics were compared using analysis of variance and chi-square tests, as appropriate. Generalized estimating equations for binary, continuous, and ordinal outcomes were used to estimate associations while adjusting for potential confounders. Potential confounders were chosen *a priori* based on associations within the literature and previous PHACS analyses; these included age, gender, race, Hispanic ethnicity, caregiver relationship to the youth, caregiver education, English use in the home, caregiver reported internalizing problems in the child, and site region. Exploratory analyses examined whether associations with EF measures remained after inclusion of measures of other cognitive and behavioral domains that have potential non-EF-specific impact on task performance (i.e., WISC-IV Full Scale IQ, WIAT-II Word Reading, CELF-4 Composite score).

For the CCTT interference index outcome, ordinal logistic regression was used by grouping the index into three percentile categories: <5, 5-16, and >16. The summaries for the odds ratio (OR) in the ordinal logistic models are relative to lower percentile categories (the odds of: <5 and 5-6, and <5). The assumption of proportional odds was assessed using a score test and by inspection of separate logistic regression models.

Analyses with p-values <0.05 were considered to be statistically significant, and 95% confidence intervals (CI) are reported. SAS 9.2 was used for all analyses.

RESULTS

Group Characteristics

Table 1 presents means or proportions of demographic and other potential confounding variables. Data are shown separately for PHIV groups without and with a past diagnosis of encephalopathy (PHIV/No Enceph and PHIV/Enceph) for clarity in interpreting analyses shown below. Mean (standard deviation) age was 10.3 (2.4), 12.0 (2.6) and 12.4 (2.3) years for PHEU, PHIV/No Enceph and PHIV/Enceph groups, respectively; the PHIV groups were on average older. PHIV participants were significantly more likely to be Black and non-Hispanic and speak English at home. Primary caregivers of PHIV participants were less likely to be a biological parent or to have an annual income $\leq \$20,000$. The PHIV/Enceph group had significantly lower Full Scale IQ and WIAT-II Word Reading scores than other groups. Group by study-site geographical distribution differed significantly; however, all sites recruited both PHIV and PHEU participants. Youth included in analyses, versus those excluded due to incomplete data, were less likely to be of Hispanic ethnicity ($p=0.017$), more likely to be from Western sites, and less likely to be from South or Northeast/Midwest sites ($p=0.039$).

Table 2 presents HIV disease severity and treatment information for the PHIV/No Enceph and PHIV/Enceph groups. Youth were generally healthy at study entry, with mean CD4%=32. Mean log VL at study entry was 2.5 and 2.4 (copies/mL) for PHIV/No Enceph and PHIV/Enceph participants, respectively. Mean nadir CD4%, peak log VL (copies/mL), and age at nadir CD4%, peak log RNA, and initiation of antiretroviral treatment did not differ between groups. About 16% of PHIV/No Enceph participants and 95% of PHIV/Enceph had received a CDC Class C diagnosis at or prior to study entry; 11.3% of all PHIV youth had a diagnosis of encephalopathy. About 93% of both PHIV groups was currently on ART; the small number not on treatment precluded analysis of treatment effects.

Measures of Executive Functioning

Comparisons with standardization samples. Table 3 presents mean scores for the CCTT and percent of BRIEF scores in the clinically elevated range ($T \geq 65$) for PHEU, PHIV/No Enceph and PHIV/Enceph participants. Time T-scores on both CCTT-1 and CCTT-2 were significantly below standardization means for all three groups; however, only the PHIV/No Enceph group had a significantly higher than expected proportion with an Interference Index $\leq 16^{\text{th}}$ percentile. The PHEU and PHIV/No Enceph groups made significantly fewer CCTT-1 number sequence errors than expected based on norms; the PHEU group also made significantly fewer CCTT-2 number sequence errors than expected. The PHEU and both PHIV groups had a significantly higher proportion of scores equal to or exceeding the T-score cutoff indicating clinical significance than

would be predicted based on norms for the General Executive Composite, Behavioral Regulation Index and Metacognitive index for both BRIEF-PR and BRIEF-SR.

Comparisons of EF between PHIV and PHEU. We did not observe statistically significant associations between HIV status and any components of the CCTT or BRIEF-SR. For the BRIEF-PR, we observed statistically significant differences between PHEU and PHIV for the General Executive Composite; this difference was largely influenced by lower Behavioral Regulation Index for the PHIV groups (slope = -4.95, CI (-7.16, -2.74), p-value <0.001).

HIV Disease Severity

Historical Disease Severity Associations. Table 4 displays unadjusted and adjusted estimates of associations when comparing PHIV/No Enceph and PHIV/Enceph to PHEU for CCTT, BRIEF-SR, and BRIEF-PR. In adjusted analyses, PHIV/Enceph compared to PHEU youth had significantly lower CCTT-1 Time T-scores (slope=-10.36, CI (-15.07, -5.65), p-value<0.001), lower CCTT-2 Time T-scores (slope=-9.06, CI (-13.70, -4.42), p-value<0.001), lower BRIEF-PR Behavioral Regulation Index (slope=-3.66, CI (-6.74, -0.57), p-value=0.02), and higher BRIEF-SR Metacognitive Index (slope=7.06, CI (0.98, 13.14), p-value=0.023).

Table 5 shows adjusted effect estimates, CI and p-values for associations of historical and current HIV disease severity markers with CCTT and BRIEF scores among PHIV youth. PHIV/Enceph youth, compared to PHIV/No Enceph, had on average lower CCTT-1 time T-scores (slope=-9.65, CI (-15.06, -4.25), p-value<0.001);

lower CCTT-2 time T-scores (slope=-8.22, 95% CI (-13.13, -3.31), p-value=0.001); and higher BRIEF-SR General Executive Composite, largely influenced by the Metacognitive Index (slope=7.35, CI (2.77, 11.93), p-value=0.002).

Older age at peak VL was associated with increased odds of a lower CCTT interference index percentile category (OR=1.14, CI (1.04, 1.25), p-value=0.008), and an increase in the BRIEF-SR Behavioral Regulation Index (slope=0.40, CI (0.04, 0.77), p-value=0.031). A one year increase in age at nadir CD4 count was associated with an increase in the CCTT-1 Time T-score (slope=0.87, CI (0.50, 1.25), p-value<0.001) and CCTT-2 Time T-score (slope=0.51, CI (0.07, 0.95), p-value=0.022), and a decrease in the BRIEF-SR Metacognitive Index (slope=-0.41, CI (-0.77, -0.05), p-value=0.026). Higher nadir CD4% was associated with increased odds of a lower CCTT interference index category (OR=1.06, CI (1.01, 1.10), p-value=0.010), and an increase in the BRIEF-SR Behavioral Regulation Index (slope=0.15, CI (0.00, 0.29), p-value=0.049). For every one million copies/ml increase in peak VL we observed an associated decrease in the CCTT-1 time T-score (slope=-0.45, CI (-0.67, -0.23), p-value<0.001), increase in the BRIEF-SR Metacognitive Index (slope=0.22, CI (0.04, 0.39), p-value<0.015); and increase in the BRIEF-PR General Executive Composite, mostly attributable to the Metacognitive Index (slope=0.44, CI (0.11, 0.78), p-value=0.010). There were no significant associations with age at ARV initiation.

Current Disease Severity. Higher log VL measured at study entry was associated with increased odds of a lower interference index percentile category (OR=1.44, CI (1.01, 2.06), p-value=0.046), decreased odds of a lower color sequence percentile score

(OR=0.59, CI (0.37, 0.94), p-value=0.028); and a decrease in the BRIEF-PR General Executive Composite, mostly attributable to the Metacognitive Index (slope=-2.01, CI (-3.14, -0.87), p-value=0.001).

Adjustment for Associations with Other Cognitive and Behavioral Measures.

Inclusion of other cognitive and behavioral measures in the models did not affect direction or significance of the results reported above; however, the association between BRIEF-SR Metacognitive Index and diagnosis of encephalopathy was diminished slightly by inclusion of child Full Scale IQ in the model (data not shown).

DISCUSSION

The results of this study demonstrate that children and adolescents perinatally exposed to HIV exhibit greater problems on EF measures than would be expected compared with normative samples. This finding was observed using both direct (paper-and-pencil performance test) and indirect (questionnaire) measures of EF. However, the hypothesis that EF would be impaired in PHIV compared to PHEU children was only partially supported. Similar to Llorente and colleagues²¹, we found PHIV and PHEU participants performed similarly when demographic and other influences were taken into account. In fact, caregiver reports indicated fewer everyday EF problems among PHIV youth. These results are consistent with other cognitive and behavioral findings from PHACS^{4,30,31} and others²¹ in suggesting that differences from the normative population may be related to risk factors other than HIV infection, although the effect of prenatal HIV or antiretroviral exposure cannot be ruled out by our study. Other risk factors may

include stressful life events, poverty and resulting lower environmental or educational enrichment, parental illness and functional impairment, and family history of psychiatric disorders³⁰. Assessment of these factors is critical in studies of cognitive functioning with PHIV.

Although the PHIV group as a whole did not differ from the PHEU group, youth with past encephalopathy had slower CCTT performance despite immune recovery; slowing also was associated with higher peak VL and with nadir CD4 occurring at younger age. Thus, indicators of greater or earlier disease severity are associated with psychomotor slowing. Our results are in agreement with previous literature indicating that psychomotor speed is vulnerable to the impact of HIV^{19,20,32,33}. However, our results did not demonstrate problems with EF-specific aspects of the CCTT in addition to slowing. Caregivers and providers of youth with a history of encephalopathy should be alert to cognitive slowing and consider supportive or compensatory interventions, such as cognitive rehabilitation, particularly if difficulties in academic, social or occupational functioning are observed.

The association of more self-reported problems in metacognitive functioning, particularly working memory, with past disease severity (encephalopathy, higher peak VL, and earlier nadir CD4) suggests youth with greater and earlier past disease severity are aware of cognitive difficulties. Although including IQ as a covariate attenuated the finding for nadir CD4, the findings for encephalopathy and peak VL remained significant. These findings support the sensitivity of self-report measures to problems in everyday EF and their use in clinical and research assessments of youth with PHIV. In contrast, lower interference index and more self-reported problems with behavioral regulation

were seen in youth who had higher nadir CD4% and were older at the time of their peak VL, i.e. had HIV disease that was less severe or manifested later. It is possible that slowing and other changes associated with greater disease severity, such as internalizing distress, are associated with lower likelihood of acting out; that children with greater HIV disease severity experience closer clinical monitoring and consequently earlier identification of behavioral issues or greater caregiver supervision; or that differences in developmental trajectories of metacognition and behavioral regulation result in different relationships with timing of severe disease. Regardless, the differences in findings for metacognitive and behavioral regulation measures highlight the importance of assessing multiple aspects of everyday EF rather than relying on global scores.

Caregiver BRIEF ratings indicated fewer concerns about behavioral regulation in youth with PHIV than those with PHEU even after accounting for caregiver factors and other differences between the groups. This is consistent with previous findings from PHACS showing higher ratings for behavioral problems in PHEU than PHIV youth³⁰. Proposed explanations have included greater likelihood of interventions or support for PHIV children as a result of their frequent contact with providers. In addition, differing caregiver involvement and greater latitude regarding behavioral and functional expectations for children with PHIV may result in ratings bias. One also could speculate that cognitive changes or slowing associated with HIV decrease the likelihood of acting-out behavior, supported by the finding that youth who were younger at the time of their peak VL or had lower nadir CD4 self-reported fewer problems with behavioral regulation and had less likelihood of a low CCTT interference index percentile.

There were few and inconsistent associations of current disease severity with EF in PHIV. Possible reasons for this are that the majority of PHIV youth in our sample had good viral control, diminishing the range and possibility of seeing associations, or that EF is impacted by chronic disease burden rather than ongoing fluctuations.

Longitudinal studies in youth with greater VL range, or incorporating measures of long-term disease burden such as VL area under the curve, may provide clarification.

This study has several limitations. Few measures of EF were included in the battery due to the need to provide a broad assessment of cognitive, psychosocial and biomedical outcomes while limiting burden. We did not have access to youth who were not perinatally exposed to HIV, an exposure that may affect development. Caregivers may have enrolled PHEU youth in AMP due to ongoing concerns about their cognitive or behavioral functioning, which could bias results. Conversely, youth with severe cognitive limitations may have been unable to complete the BRIEF self-report. Study participants committed to an intensive longitudinal study and may not reflect youth with perinatal HIV exposure as a whole. Caregiver and environmental differences for the PHEU and PHIV groups could affect outcomes and use and sensitivity of the BRIEF, although caregiver identity and some environmental variables were included as confounders. Antiretroviral treatment history for PHIV participants varied and may affect EF; we were unable to examine this complex issue in the present analysis. Finally, these analyses are cross-sectional, limiting conclusions about directionality of observed associations, and include a relatively wide age range over a period that normally is characterized by significant EF development.

In summary, this study represents the largest investigation to date of EF in PHIV youth to include a comparison group and both caregiver- and self-report measures of everyday EF. The availability of a broad range of demographic, disease-related, and cognitive data allowed for statistical modeling to account for their unique or combined influence on EF outcomes. The results demonstrate difficulties on both direct paper-and-pencil and indirect questionnaire measures of EF in both PHIV and PHEU youth, compared to population norms, that were not accounted for by other cognitive or language abilities. Youth with histories of more severe or early HIV disease performed more slowly and self-reported more problems in metacognition, primarily working memory. Observed EF difficulties may place youth at risk for poor health and behavioral outcomes as they become more responsible for their own well-being. For PHIV youth, especially those with histories of encephalopathy, providers, caregivers and schools might consider evaluation for impairment in processing speed and other cognitive functions that could indicate the need for supportive accommodations. Future longitudinal analyses and neuroimaging studies may clarify developmental trajectories of EF and the impact of age, ongoing viral suppression and treatment; association of EF with brain function; and long-term behavioral and functional outcomes in PHIV. Key findings from this study are that both PHIV and PHEU youth are at risk for problems with EF and may benefit from services to prevent and treat EF dysfunction.

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