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Attention in HIV-infected children: Results from the Hemophilia Growth and Development Study

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Abstract

Attentional functioning was examined in three groups of 7- to 19-year-old male participants with hemophilia: (1) HIV seronegative controls (HIV−, $N = 66$), (2) HIV seropositive participants with CD4+ lymphocyte counts greater than or equal to 200 (HIV+ CD4+ ≥200, $N = 79$), and (3) severely immune suppressed HIV seropositive participants (HIV+ CD4+ <200, $N = 28$). Two measures sensitive to attention deficits were used: the Continuous Performance Test (CPT) and the Span of Apprehension (Span). On the CPT, there was a decrement in attention in both HIV+ groups, as indexed by an increase in false alarm rate from Block 1 to Block 3, that was not present in the HIV− group. The longer the HIV+ children were required to sustain attention to the CPT, the more they responded to the incorrect stimulus. This effect decreased as age increased. Span percent correct and latency to correct were associated with the presence of a premorbid history of intracerebral hemorrhage, but were not sensitive to HIV status or degree of immune suppression in the HIV+ children, suggesting morbidity related to hemophilia. The remaining CPT and Span variables—hit rate, sensitivity, latency, percent correct, and latency to correct—showed the expected associations with age, but none showed conclusive associations with HIV status or immune suppression in the HIV+ participants. (*JINS*, 2000, *6*, 443–454.)

Keywords: Hemophilia, HIV, Pediatric AIDS, Attention

INTRODUCTION

Reports of deficits in attentional processing appear prominently in the literature on the cognitive effects of human immunodeficiency virus (HIV) infection in both adults and children. Attention deficits are frequently recognized in children with symptomatic HIV infection and acquired immunodeficiency syndrome (AIDS)-HIV-1 encephalopathy (Brouwers et al., 1990; Fletcher et al., 1991; Watkins et al., 1992) and are among the hallmark characteristics of the HIV-associated cognitive–motor complex found in HIV-infected adults (American Academy of Neurology AIDS Task Force, 1991; Grant et al., 1992).

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Neuropsychological Effects of HIV Infection in Children

In childhood and adolescence, the neuropsychological effects of HIV infection vary widely in nature and severity, depending on a range of factors including mode of transmission of HIV, age of infection, time since seroconversion, age at testing, presence of cofactor illnesses, and factors unrelated directly to HIV such as perinatal drug exposure and illness of the parent. These factors are often confounded. Consistent with the pattern observed in other childhood brain diseases (Taylor & Alden, 1997), HIV infection appears to have the most pronounced and debilitating effect on development when infection and onset of encephalopathy occurs early. Studies of vertically infected children, those exposed at birth through the mother's HIV infection, report severe delays in cognitive and motor development in a large

subgroup of children (Belman, 1994; Brouwers et al., 1990). Several different developmental courses have been described, including a static encephalopathy and a progressive encephalopathy characterized by acquired microcephaly, motor dysfunction, and loss of previously acquired abilities (Belman, 1994; Brouwers et al., 1990; Fletcher et al., 1991). In contrast to the often severe outcome for younger children, those infected later by transfusion of whole blood (Cohen et al., 1991) or blood products used to treat hemophilia (Hooper et al., 1997; Loveland et al., 1994; Sirois & Hill, 1993; Whitt et al., 1993) may have long asymptomatic periods during which cognitive development is generally within normal limits.

The Hemophilia Growth and Development Study

The largest study of the latter group is the Hemophilia Growth and Development Study (HGDS). Children enrolled in the HGDS were exposed to HIV through contaminated clotting factor before universal screening was initiated and, as such, present a unique opportunity for the study of postnatally acquired HIV infection on developing children without many of the confounding psychosocial and medical risk factors found in vertically transmitted HIV infection. The HGDS neuropsychological findings paralleled those of earlier studies by Sirois and Hill (1993) and Whitt et al. (1993), showing that the largely asymptomatic cohort of HIV seropositive children and adolescents did not differ significantly from HIV seronegative hemophilic controls on a comprehensive battery of neuropsychological tests (Loveland et al., 1994) at baseline. However, follow-up of HGDS participants over a period of 5 years revealed significant declines in neuropsychological performance that directly related to declines in immune functioning (Loveland et al., in press). Although neuropsychological deficits were not associated with HIV infection or immune suppression at baseline, lowered neuropsychological performance was found in HGDS participants with a history of head trauma and coordination and/or gait abnormalities that probably reflect hemophilia-related morbidity (Sirois et al., 1998). The results of both the Loveland et al. (1994) and Sirois et al. (1998) studies were interpreted as showing that adaptive behavioral, academic, and cognitive difficulties in the baseline HGDS sample reflect the effects of hemophilia as a chronic illness rather than the effects of HIV infection.

Measures of Attentional Processes

Studies of HIV infected adults suggest that measures of attentional processing may be sensitive indexes of early effects of HIV infection on central nervous system (CNS) functioning (A. Martin et al., 1992; E. Martin, et al., 1995b; Mirsky, 1988). Eileen Martin and her colleagues reported slowing of decision-making time on choice reaction time tasks and mild deficits on tasks that are highly demanding of attentional resources in groups of nondemented HIV seropositive adults (E. Martin et al., 1992a, 1992b, 1995b; Sorensen et al., 1994). Eileen Martin's studies indicate that not all tests of attentional functioning are sensitive to HIV-related mental changes. Specifically, her studies implicate slowing of controlled attentional processes, which are voluntary and highly demanding of attentional capacity (E. Martin et al., 1993, 1995b; Sorensen et al., 1994). The above studies of attentional processing, all done with HIV-infected adults, raise the question of whether exposure to HIV in children results in specific impairments in attentional processing similar to those observed in adults.

The present study was designed to examine attentional processing in HIV seronegative and largely asymptomatic HIV seropositive children and adolescents drawn from the HGDS. We assessed attentional functioning in children using tasks that are sensitive to attention deficits in both adults and children: the Continuous Performance Test (CPT) and the Span of Apprehension (Span; Swanson et al., 1989). The CPT and Span provide a means of separating components of attentional processing, as well as measuring speed of motor response, and have the potential to define areas of deficit not measured by standard neuropsychological tests. We examined whether impairments in attentional processing precede or accompany severe immunosuppression in HIV-infected children.

We hypothesized that impairment in components of the CPT and Span most demanding of attentional resources would be found in severely immune suppressed HIV seropositive children, but not in HIV seronegative or HIV seropositive children with CD4+ lymphocyte counts of greater than or equal to 200. This was based on three converging lines of evidence. First, a number of studies report clinical impairment in attention and concentration in HIV infected children (Brouwers et al., 1990), although studies to date have not used laboratory or computerized measures of attention. Second, neuroradiological and neuropathological studies of pediatric AIDS reveal relative sparing of most of the cerebral cortex, with prominent pathology in subcortical white matter and basal ganglia (Epstein et al., 1988; Scarmato et al., 1996) and frontal lobes (da Cunha et al., 1997). We thus hypothesized that components of attentional processing mediated by subcortical and associated tertiary frontal systems would be selectively impaired in HIV-infected individuals. Third, there is increasing evidence that mental slowing and working memory impairments in symptomatic HIV seropositive adults results from impairment in controlled attentional processing associated with frontal–subcortical systems (E. Martin et al., 1995a). This report extends investigation of controlled attentional processing to children.

METHODS

The present study is part of a multicenter longitudinal evaluation of the effects of HIV infection in children and adolescents with hemophilia (the HGDS). The overall HGDS

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study methodology has been described by Hilgartner et al. (1993). Participants in the HGDS received annual evaluations of immune, growth–endocrine, neurologic, neuroradiologic, and neuropsychological functioning. In addition to the longitudinal evaluation, a thorough medical and developmental history of each participant was taken at baseline. The neuropsychological portion of the HGDS provided assessment of general intelligence, memory and learning, visual–spatial perception, expressive and receptive language, fine motor skills, executive function, adaptive behavior, academic achievement, and behavioral–emotional functioning (Stehbens et al., 1997).

Research Participants

Participants in the present study were drawn from a larger sample of 207 HIV seropositive and 126 HIV seronegative young males with hemophilia being treated at 14 Hemophilia Comprehensive Care Centers participating in the HGDS. Ten of the 14 HGDS Centers participated in the present study, yielding a total of 178 participants between the ages of 7 and 19 at study entry. Of the 178 participants, 5 were excluded from the analysis, 2 because of invalid neuropsychological data and 3 for whom no CD4+ lymphocyte counts were available, leaving a total of 173 participants. The CPT was valid for all 173 participants. The Span was invalid for 12 participants due to a mechanical malfunction in the controller (joystick). Retesting of these 12 participants was not feasible, so only their CPT scores were used in the present analyses.

Participants were stratified into three groups: HIV− controls ($N = 66$) and two HIV+ groups that were defined using CD4+ lymphocyte count at the time of testing for the present study. The HIV+ participants were divided into two groups in order to capture the degree of HIV related immune suppression, with HIV+ CD4+ <200 conforming to the *severe suppression* category in the *1994 Revised Classification System for HIV Infection in Children* (U.S. Department of Health and Human Services, 1994) and an indicator of AIDS in the *1993 Revised Classification System for HIV Infection and Expanded Surveillance Case Definition for AIDS Among Adolescents and Adults* (U.S. Department of Health and Human Services, 1992). Of the 107 HIV+ participants, 79 had CD4+ counts of greater than or equal to 200 and 28 participants had CD4+ lymphocyte counts of less than 200.

Physicians caring for HGDS eligible patients began treating many patients with CD4+ counts of less than 500 with AZT and other antiretroviral treatments following the August 1989 report by the National Institute of Allergy and Infectious Diseases indicating that asymptomatic persons with CD4+ counts remained healthier for longer than did those on a placebo (Protocol 019; NHGF, 1989). Of the 107 HIV+ participants, 46 were taking antiretroviral medications at the time of test administration, 56 were not taking antiretroviral medication, and 3 began antiretroviral therapy on the date of test administration. For 2 participants, antiretroviral use was not known. The type of treatment was primarily AZT (85%), with 11% taking DDI and 4% enrolled in randomized, treatment masked trials. This pattern of treatment was necessary for the medical care of the patients, but resulted in a design that did not provide an opportunity for a valid and controlled study of the effects of antiretroviral treatments within HGDS. Data on antiretroviral treatments are therefore reported only for the purpose of providing a full description of the sample. Tables 1 and 2

Table 1. Demographics for CPT sample

	HIV− ($N = 66$)		HIV+ CD4+ ≥200 ($N = 79$)		HIV+ CD4+ <200 ($N = 28$)	
Variable	*M*	*SD*	*M*	*SD*	*M*	*SD*
Age	11.7	3.1	13.3	3.3	14.3	2.7
Full Scale IQ	106.0	16.2	106.2	14.3	103.0	14.7
Verbal IQ	105.0	15.1	102.2	13.9	99.9	14.2
Performance IQ	106.2	16.1	109.5	15.1	106.3	15.9
Parent education	13.4	2.6	13.1	3.4	12.2	3.5
CD4+ lymphocytes	905.3	323.7	494.7	238.1	60.9	69.2
Factor level % < 1%		61.5		73.4		77.8
Ethnicity						
% White		77.3		74.7		67.9
% Hispanic		9.1		15.2		10.7
% African American		12.1		7.6		21.4
% Other		1.5		2.5		0
History of						
% Academic problems		32.3		35.9		22.2
% Head trauma		36.4		36.7		25.0
% Intracranial hemorrhage		19.7		10.1		3.6

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Table 2. Demographics for Span sample

	HIV− ($N = 62$)		HIV+ CD4+ ≥200 ($N = 73$)		HIV+ CD4+ <200 ($N = 26$)	
Variable	*M*	*SD*	*M*	*SD*	*M*	*SD*
Age	11.8	3.2	13.2	3.1	14.1	2.6
Full Scale IQ	106.1	16.5	106.7	14.6	102.2	14.4
Verbal IQ	105.2	15.5	102.6	14.2	99.4	14.3
Performance IQ	106.0	16.1	109.8	14.9	105.5	15.4
Parent education	13.4	2.7	13.0	3.3	12.1	3.6
CD4+ Lymphocytes	916.2	328.9	500.5	244.8	64.0	70.9
Factor level % <1%		60.7		72.6		76.0
Ethnicity						
% White	80.6	76.7	65.4			
% Hispanic	8.1	15.1	11.5			
% African American	9.7	5.5	23.1			
% Other	1.6	2.7	0			
History of						
% Academic problems		31.2		33.3		23.1
% Head trauma		35.5		35.6		23.1
% Intracranial hemorrhage		20.0		8.2		0

present demographic data for the CPT and Span separately for each of these three groups.

The three groups were compared using analysis of variance (ANOVA) for age at study entry, Verbal IQ, Performance IQ, Full Scale IQ, parent education, ethnicity, history of academic problems, history of head trauma, history of intracranial hemorrhage, factor level, and CD4+ count. Significant between-group differences were found only for age at study entry [$F(2,170) = 8.12$, $p < .001$] and, as expected, CD4+ count [$F(2,170) = 112.98$, $p < .0001$]. Pairwise comparisons showed age differences between HIV− *versus* HIV+ CD4+ <200 [$t(170) = -3.62$, $p < .001$] and age of HIV− *versus* HIV+ CD4+ ≥200 [$t(170) = -3.07$, $p < .01$]. The two HIV+ groups did not differ significantly on age. For the Span sample only, the HIV− children showed a significantly greater frequency of intracranial hemorrhage than either of the HIV+ CD4+ <200 or the HIV+ CD4+ ≥200 groups (Fishers Exact Test; $p < .05$ and .01, respectively).

Institutional Review Board approval for protection of human participants was obtained at each participating center. Written informed consent was obtained from each participant and/or his parent–guardian according to local IRB requirements.

Procedures

Experimental tasks

Continuous Performance Test (CPT). The CPT is the most widely used measure of sustained attention in clinical research and is sensitive to impairment in adults and children with a wide range of disorders, including attention deficit disorder (Nuechterlein, 1991). Broadly, the CPT measures skill in identifying a briefly presented visual target stimulus and the ability to sustain attention to a target stimulus over time.

A computerized version of the CPT was used that presents a series of one-digit numbers in random sequence at 1-s intervals. We employed a degraded stimulus version of the CPT that blurs the target number and thus requires more effort and concentration (Nuechterlein et al., 1983). Numbers appeared in the middle of the screen in 40 ms tachistoscopic exposures. The participant's task was to press a blue button on the joystick as quickly as possible with the index finger of the preferred hand every time a target digit, a zero, appeared. The target stimulus appeared randomly on 25% of the 480 trials. Practice and administration time was approximately 12 min for the CPT (2 min set-up and practice with nondegraded stimulus, 2 min practice with degraded stimulus, 8 min test). For purposes of analysis, the trials were divided into three consecutive blocks of 160 trials each. Correct responses (pressing the button following the target number), errors of omission (misses; not pressing the button when the target number appears), errors of commission (false alarms; pressing the button to a nontarget number), and latency to response were recorded. These variables were then used to derive an index of attention—A' (defined below).

Participants were read a script describing a game called "Space Watch" in which a spaceship is sending signals to try to find its home base. They were told that the correct signal from the ship was the zero and instructed thus: "Your job is to watch as carefully as you can and to press this button as fast as you can each time you see a zero. To locate the spaceship, you need to find as many zeros as you can."

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Span of Apprehension. The Span of Apprehension measures ability to direct attention to a visual target stimulus while screening out distractor stimuli. The term "span of apprehension" has been used to refer to the number of bits of information that can be attended to at one time. The version of the span used in the present study was the partial-report procedure first developed by Sperling (1960) and refined to a forced choice version by Estes and Taylor (1966). Participants were presented with a 4×4 matrix array containing an arrangement of varying numbers of letters. All letters were of the same size. Three array sizes were used: a 3-letter, a 5-letter, and a 10-letter array size. Each 4×4 matrix array contained one target stimulus, either a 'T' or an 'F' but never both on a single presentation. The 4×4 matrix arrays were organized into 16 trial blocks, with the target, either a 'T' or an 'F,' appearing once for each trial in each of the 16 positions within the 4×4 matrix. Two 3-letter array size blocks (32 trials), four 5-letter array size blocks (64 trials), and four 10-letter array size blocks (64 trials) were presented. Each trial was presented in 40-ms tachistoscopic flashes following visual fixation on a point at the center of the screen. Latency to response was recorded in ms for each trial. Measured variables include the number of correct detections, latency to correct responses, and latency to incorrect responses.

Participants were seated with eye level at midscreen, exactly 1 m from the monitor screen. Participants were instructed to identify whether a 'T' or an 'F' appeared on the screen by pressing one of two buttons labeled with a 'T' or an 'F' and to guess if they were not sure. They were further instructed: "Try to press the button as quickly and accurately as you can." Participants responded with the hand they use for writing and held the joystick with the other hand. Practice and administration time was approximately 12 min for the Span.

Equipment. Nine centers used one of two computers, a Compaq Deskpro 286 or a Compaq Portable II with an 80286 microprocessor. One center used an IBM-compatible computer with an 80286 microprocessor. All centers used a Taxon 720 monitor. Participants responded with a Gravis MK VI Analog Controller (joystick).

Order of administration. Because the primary objective of the study was prediction of external criteria (clinical course of HIV infection), the tasks were administered in a fixed order: (1) Span of Apprehension, and (2) CPT.

Relation to other HGDS procedures. The longitudinal design of the HGDS involved yearly comprehensive medical and neuropsychological evaluation and brief evaluations at 6-month intervals (Hilgartner et al., 1993; Stehbens et al., 1997). The CPT and Span in the current investigation were administered at the first 6-month follow-up (FU #1, $N = 130$) or the first 1-year follow-up (FU #2, $N = 43$). Comparison data from the HGDS Neuropsychological Battery used in the present study were obtained 6 months earlier for participants seen at FU #1 for the CPT and Span and at the same time as the CPT and Span for participants seen at FU #2.

Statistical methods

A repeated measures analysis of variance was performed using SAS PROC MIXED with an unstructured variance–covariance matrix (SAS Institute, 1992). Repeated measures were block for the CPT and number of letters for the Span; between-participant variables were age and HIV status. A step-down approach to model fitting was used and maximum likelihood estimates were obtained. Age was included in the model as a continuous independent variable. The initial model included all main effects of HIV status, age, and block (for the CPT) or number of letters (for the Span), the two-way interactions thereof, as well as Age^2. The quadratic term for age was included in the initial model because some of the dependent variables (percent correct, hit rate, false alarm rate, A') are bounded and the estimated lines are asymptotic to these boundaries. Preliminary analyses also examined the relation between age and IQ and showed no association between age and IQ for the entire sample or in models adjusting for HIV status.

Two models were fit for each dependent variable. One model used presence or absence of HIV infection to define two HIV status groups, HIV− and HIV+, and included actual CD4+ count of each participants as a continuous variable in the regression model. The second model used HIV status and CD4+ count as categorical variables to define three patient status groups: HIV−, HIV+ CD4+ ≥200, and HIV+ CD4+ <200. The CD4+ count was treated as a continuous variable in one model and categorical variable in the other in order to allow for both a linear association with the response variable and calculation of mean differences of response variable by different categories of CD4+ count. Results are reported for the model using the three patient status groups (categorical model), except where the two models produced different results.

Age at time of HIV seroconversion. Preliminary analyses investigated the possibility of including two additional covariates in the analyses: estimated time since HIV infection and chronological age at estimated time of HIV seroconversion. The mean age at infection for the HIV+ children was 6.1 years. At the time of test administration, the HIV+ cohort had been infected a mean of 7.5 years using the estimation method of Mahoney and Orav (1993). Methodological difficulties arise, however, if these estimates are included as covariates in the statistical models, because inclusion of age at infection and time since seroconversion pertain only to the HIV+ cohort, whereas inclusion of the HIV− participants was considered essential for this analysis. Exploratory analyses using the HIV+ HGDS cohort found that time since seroconversion was not significantly associated with neuropsychological functioning (Loveland et al., in press). This was not surprising, since a very large proportion of the HIV+ cohort was infected within roughly the same 18-month period, so that the restricted range in time

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since infection yielded little statistical power. Studies of adults have also reported that time since infection is not significantly related to outcome after results are adjusted for level of immune dysfunction, using measures such as CD4 cell count (Wilkie et al., 1992). Also because of the short time span within which HIV+ participants were infected, age at estimated time of seroconversion was highly correlated with age at testing in the HIV+ groups ($r = .96$). This multicollinearity made it impossible to separate the effects of age at testing and age at seroconversion. The only feasible way of capturing information regarding age at infection, therefore, was to include an interaction of HIV Status × Age at baseline, on the assumption that a differential effect of age at testing for HIV+ and HIV− groups would in part reflect an effect of age at seroconversion.

Transformations. For the CPT, an index of signal-noise discrimination, or sensitivity, A' [or P(A)], was computed for each of the three blocks of 160 trials using the following equation (Nuechterlein, 1991):

$$A' \text{ or } \mathrm{P}(A) = \frac{1}{2} + \frac{(\mathrm{HR} - \mathrm{FAR})(1 + \mathrm{HR} - \mathrm{FAR})}{4(\mathrm{HR})(\mathrm{I} - \mathrm{FAR})}$$

where HR = hit rate and FAR = false alarm rate. A' has an upper limit of 1.0, with a value of .50 representing a chance level of discrimination. Nonlinear transformations were used for all response variables in order to better comply with the normality and homoscedasticity assumptions of the data analysis method (see Table 3).

Transformations were chosen to linearize the relationships between variables, equalize the variances as much as possible, and reduce the skewness of distributions following previous research using these variables, as well as guidelines outlined by Cohen and Cohen (1975). Each variable presented different problems with nonlinearity and distribution, depending on whether the measurement involved time (as in latency), counts (as in hit rate and percent correct), or a linear combination of rates (as in A'). Square-root transformations were used for hit rate and percent correct, because that data, like many instances of counts on cognitive tasks, conformed with a Poisson distribution. A Poisson process is often obtained where a relatively infrequent event is counted within a restricted period of time, yielding a skewed, Poisson distribution of the data (Cohen & Cohen, 1975). An inverse transformation was used for both latency variables because the latency data were characterized by an asymptotic curve in relation to other variables in the models. An inverse log yielded the best empirical linearization for latency to correct. For the CPT A' variable, a 2 × arcsin transform was used based on previous studies using the same version of the CPT to correct for negative skewness that results from an upper limit of 1.0 for A' (Nuechterlein, 1991). Finally, a log transformation was used for false alarm rate to adjust for the change in FAR as a constant proportional relation to the other variables in the model. Transformations were chosen prior to the analyses of the experimental hypotheses and remained constant throughout data analysis.

Table 3. Transformations used to produce normality and homoscedasticity in test data

Variable	Transformation
Continuous Performance Test	
False alarm rate	Natural log
Hit rate	Square root
Sensitivity (A')	2 × Arcsin
Hit latency	Inverse
Span of Apprehension	
Percent correct	Square root
Latency to correct	Inverse Square root

RESULTS

Comparison With Larger HGDS Sample

A total of 178 of the 333 HGDS participants (53.7%) were enrolled in this substudy at baseline. To determine if the participants recruited into this substudy differed significantly from those in the overall HGDS study, comparisons of means (using ANOVA and Welch's t test) and proportions for baseline neuropsychological and background variables were performed. The two groups did not differ on any of the demographic variables, including age ($M = 12.2$, $SD = 3.2$ for in-CPT; $M = 12.5$, $SD = 3.2$ for not in-CPT) and absolute CD4+ count ($M = 647.8$, $SD = 423.8$ for in-CPT; $M = 598.0$, $SD = 440.3$ for not in-CPT). There were also no significant differences in ethnic distribution (White = 74.6%, Hispanic =12.1%, African American = 11.6%, other = 2% for in-CPT; White = 71.9%, Hispanic = 17.0%, African American = 9.1%, other = 2% for not in-CPT).

There was a significant difference between the in-CPT and not in-CPT groups on only one of the 32 neuropsychological test variables—the WISC–R Picture Completion subtest scaled score [$M = 11.5$, $SD = 2.6$ for in-CPT; $M = 10.6$, $SD = 2.6$ for not in-CPT, $t(324) = -3.22$, $p < .002$]. This small difference of less than 1 point is not clinically significant. These results suggest that the participants included in the present substudy are representative of the larger HGDS.

Effects of Intracranial Hemorrhage (ICH)

Because ICH was found more frequently in the HIV− group in the Span sample, analyses were conducted to examine the effect of ICH on our models. For each of the models tested, the effect of ICH was examined using a drop in deviance chi-squared test to determine if including three terms (ICH, ICH × HIV category, and ICH × Block for the CPT and ICH × Number of Letters for the Span) in the model accounted for a significant amount of variation in the data. For the CPT sample, the model including the ICH terms did not differ significantly from a model without the ICH terms, so ICH terms were not used for the analyses reported below. For the Span, ICH

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terms were significant when added to the models, so results for the Span report models adjusting for ICH.

Continuous Performance Test

All reported *p* values for both CPT and Span are those obtained using the transformed data, whereas graphs are back-transformed into the original units.

False alarm rate

Figure 1 presents CPT false alarm rate by block and age for each of the three HIV status groups. There were significant main effects for block [$F(2,169) = 3.98$, $p = .02$] and age [$F(1,169) = 70.77$, $p < .001$] and significant interactions of HIV Category × Block [$F(4,169) = 3.14$, $p < .015$] and Block × Age [$F(2,169) = 3.08$, $p < .05$].

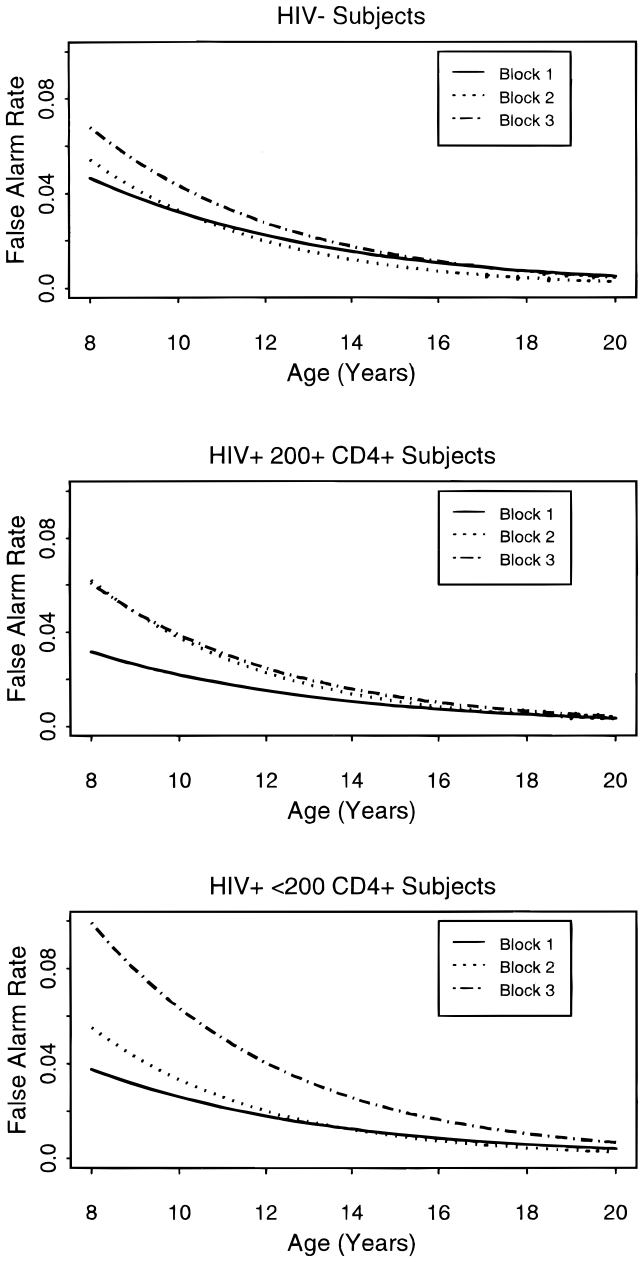

Fig. 1. CPT false alarm rate by block and age for each of the three groups: HIV−, HIV+ CD4+ ≥200, and HIV+ CD4+ <200.

At age 8, the HIV+ CD4+ <200 group showed more false alarms for Block 3 than for Blocks 1 ($p < .002$) and 2 ($p < .05$) (Figure 1, lower panel); the HIV+ CD4+ ≥200 group showed more false alarms for Blocks 2 and 3 than for Block 1 ($p < .001$ and $p = .003$, respectively)(Figure 1, middle panel); there were no significant differences between blocks for HIV− participants. The effect of block on the HIV+ groups decreased as age increased.

The slope of age was negative for all three blocks, showing that, as age increases, false alarm rate decreases. However, as reflected in the ordinal interaction of Block × Age, the slope of age for Block 2 was significantly steeper than the slope of age for Block 1 [$t(169) = 2.48$, $p < .02$]. Therefore, as age increased, the false alarm rate for Block 2 dropped faster than the false alarm rate for Block 1.

Hit rate

For CPT hit rate, there were significant main effects for block [$F(2,169) = 14.82$, $p < .001$], age [$F(1,169) = 28.88$, $p < .001$], and the interaction between Block × Age [$F(2,169) = 6.19$, $p < .002$]; there were no significant effects for HIV status. At age 8, there was greater difficulty (lower hit rate) with increasing time on task: Block 1 *versus* Block 2 [$t(169) = 5.91$, $p < .01$]; Block 1 *versus* 3 [$t(169) = 17.65$, $p < .01$]; and Block 2 *versus* 3 [$t(169) = 2.53$, $p < .01$]. As expected, children became more accurate (greater hit rate) with increasing age. Moreover, since the slope of age for Blocks 2 and 3 were significantly greater than Block 1 [$t(169) = -2.96$, $p = .003$] and [$t(169) = -3.13$, $p = .002$], respectively, the effect of block on hit rate decreased as age increased.

Sensitivity (A′)

For CPT sensitivity, there were significant main effects for block [$F(2,169) = 9.78$, $p < .001$], and age [$F(1,169) = 44.91$, $p < .001$], a borderline significant interaction between Block × Age [$F(2,169) = 2.76$, $p = .065$], and no significant association with HIV status. At age 8, A' decreased with increasing time on task: Block 1 to Block 2 to Block 3 ($p \leq .002$ for all three pairwise comparisons). Similar to hit rate, children's sensitivity (A') rose with increasing age. Furthermore, the slope of age for Blocks 2 and 3 was significantly greater than for Block 1 [$t(169) = 2.17$, $p = .03$; and $t(169) = 2.04$, $p = .04$], respectively. The younger the participant, the less able he was to sustain attention (as indexed by both A' and hit rate) over time.

Hit latency

For hit latency, there were significant main effects for HIV status [$F(2,166) = 3.24$, $p < .05$], block [$F(2,166) = 51.59$, $p < .001$], age [$F(1,166) = 13.77$, $p < .001$], and Age^2 [$F(1,166) = 6.94$, $p < .01$]. There was a significant HIV

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Status × Age interaction [$F(2,166) = 3.54$, $p < .05$]. Latencies increased from Block 1 to 2 to 3 [$t(166) = 7.13$, $p < .001$; $t(166) = 4.47$, $p < .001$, for Block 1 *vs.* 2 and Block 2 *vs.* 3, respectively]. Latencies decreased with age. Thus, there was a general trend for children to respond faster on hits with increasing age. However, this effect of age on response time became smaller as age increased (due to the significant Age^2 term).

The HIV Status × Age interaction indicated that at age 8 the HIV− participants had slower response times than HIV+ CD4+ ≥200 [$t(166) = 2.5$, $p < .05$], but HIV+ CD4+ <200 participants did not have significantly different response times than either HIV− or HIV+ CD4+ ≥200. However, the slope for age for HIV− participants was significantly steeper than the slope of age for HIV+ CD4+ ≥200 participants. Therefore, as age increased, the response times for HIV− participants dropped faster than the response times for HIV+ CD4+ ≥200 participants; consequently, the older HIV− participants responded faster than the older HIV+ CD4+ ≥200 participants.

To examine this effect more closely, estimates of mean hit latency were tested to determine between-groups differences for HIV status at each of seven age levels separated by 2-year increments. Pairwise comparisons of groups based on HIV status at each of these age levels revealed significant differences between HIV− and HIV+ CD4+ ≥200 groups at age 8 [$t(166) = -1.99$], age 16 [$t(166) = 2.17$], age 18 [$t(166) = 2.45$], and age 20 [$t(166) = 2.56$], $p < .05$ for all comparisons. The HIV+ CD4+ ≥200 group was significantly *faster* than the HIV− group at ages 8, but significantly *slower* at ages 16 to 20. Thus, there is an increasing efficiency of attentional processing as age increases in the HIV− group (decreasing hit latency), but less increase in efficiency as age increases in the HIV+ CD4+ ≥200 group. The lack of differences between the HIV+ CD4+ <200 group and the other two HIV status groups should be interpreted in light of the smaller number of participants in the HIV+ CD4+ <200 group, particularly in the groups less than 12 years of age (4 children).

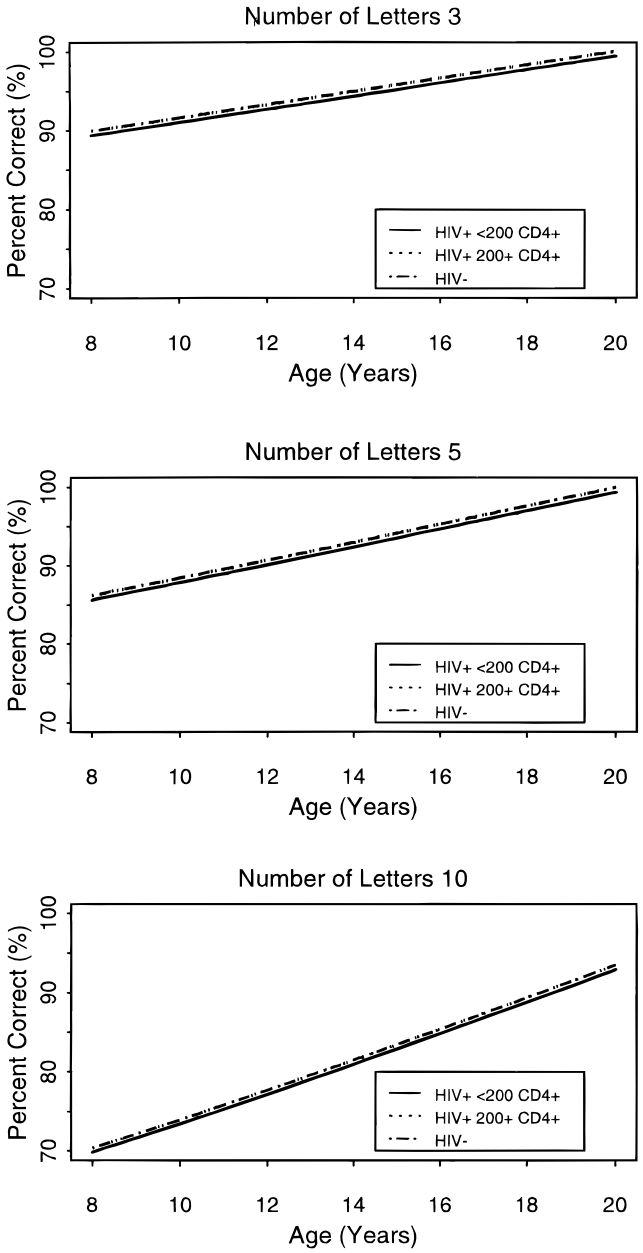

Fig. 2. Span of Apprehension percent correct as a function of age for the HIV−, HIV+ CD4+ ≥200, and HIV+ CD4+ <200 groups, shown separately for 3-, 5-, and 10-letter array sizes.

Span of Apprehension

Percent correct

Figure 2 presents Span percent correct for each of the three groups, with 3, 5, and 10 letters shown in separate panels. All models for the Span were adjusted for the effects of ICH. There were significant main effects for number of letters [$F(2,156) = 51.56$, $p < .001$] and age [$F(1,156) = 43.17$, $p < .001$] and a significant interaction between Number of Letters × Age [$F(2,156) = 13.60$, $p < .001$]. There were no significant differences between the HIV−, HIV+ CD4+ ≥200, and HIV+ CD4+ <200 groups.

Examination of the interaction between number of letters and age showed that, at age 8, there was greater difficulty (lower percent correct) with increasing array size [Size 3 *vs.* 5, $t(156) = 3.68$; Size 3 *vs.* 10, $t(156) = 15.46$; and Size 5 *vs.* 10, $t(156) = 13.76$; $p < .001$ for all comparisons]. The slopes of age for all three array sizes were positive, showing that the older the child, the better the performance (higher percent correct). Moreover, the slope of age for 10 letters was significantly higher than for 3 and 5 letters [Size 3 *vs.* 10, $t(156) = 5.14$; Size 5 *vs.* 10, $t(156) = 4.15$; $p < .001$ for both]. Thus, the effect of array size on percent correct decreased as age increased.

Latency to correct

For latency to correct, main effects of number of letters [$F(2,155) = 64.67$, $p < .001$], age [$F(1,155) = 16.78$, $p <$

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.001], and Age^2 [$F(1,155) = 8.54$, $p < .01$] were significant. Latency increased with an increase in the number of distractors: 3 to 5 to 10 letters [$t(155) = 13.01$, $p < .001$, $t(155) = 12.59$; $p < .001$] for 3- *versus* 5- and 5- *versus* 10-letter arrays, respectively. The estimated slope of age showed that the older the participant, the shorter the latency to correct. However, this effect of age on latency to correct became smaller as age increased. There were no significant differences between the HIV−, HIV+ CD4+ ≥200, and HIV+ CD4+ <200 groups.

DISCUSSION

Results of the present study revealed subtle, but significant differences between HIV seropositive and HIV seronegative children with hemophilia on the CPT. There were significant differences between the HIV− group and both HIV seropositive groups (HIV+ CD4+ ≥200 and HIV+ CD4+ <200) on one measure of sustained attention—CPT false alarm rate over time. For both groups of HIV+ children, there was a progressive increase in false alarms the longer the child performed the task (Blocks 3 had more false alarms than Block 1). This increase in false alarms was significant in the two HIV+ groups, but not in the HIV− group. False alarm rate measures the rate of errors of commission—pressing the button to a nontarget stimulus. The longer the HIV+ children were required to sustain attention to the CPT, the more they responded to the incorrect stimulus. This increase in false alarms over time was greater in the HIV+ groups and may reflect greater impulsivity in the HIV-infected groups when sustained attention over time is required. This effect appears to be related to HIV infection rather than to degree of immune suppression.

There was a complex interaction between HIV Status × Age for CPT hit latency. The HIV− participants were slower than HIV+ participants at age 8, but faster at older ages, suggesting an increasing efficiency of attentional processing at older ages in the HIV− group, but less increase in efficiency at older ages in the HIV+ group. This pattern may shed light on the nature of the cognitive differences that were also associated with a higher number of false alarms in the younger HIV+ children. In reviewing the literature on the relationship between response latency and errors of commission on cognitive tasks, Kagen (1966) and Kagen and Messer (1975) define impulsive children as individuals with faster response times and relatively more errors of commission on simple, highly speeded tasks that contain response uncertainty, in contrast to reflective children who have longer response times and fewer errors. For the CPT, more false alarms (errors of commission) and faster hit latency were found in the younger HIV+ children, whereas slower hit latency and fewer false alarms were found in the younger HIV− children, suggesting greater impulsivity in the HIV+ group and greater reflectivity in the HIV− group. As response uncertainty, and errors, decreased with age, hit latency also decreased and differences between the HIV+ and HIV− groups narrowed, consistent with Kagen and Messer's theory. This definition of impulsivity remains controversial, however, due in no small part to instability in the association of latency and errors across studies and comparison groups (Barkley, 1998; Sternberg & Grigorenko, 1997).

Of the six CPT and Span variables examined in this study, only decreases in false alarm rate across blocks on the CPT and hit latency were associated with HIV status. Span percent correct and latency to correct were associated with the presence of a premorbid history of intracerebral hemorrhage, but were not sensitive to HIV status. This result parallels Sirois et al. (1998), also reporting on the HGDS sample, who found that a documented history of head trauma was associated with lowered neuropsychological performance in both HIV+ and HIV− groups. History of head trauma was relatively common in both HIV+ and HIV− groups in both Sirois et al. (1998) and the present study. These findings suggest that lowered neuropsychological performance in Sirois et al. (1998) and differences on the Span percent correct and latency to correct in the present study are not related to HIV, but to hemophilia-related morbidity.

The CPT and Span appear to be tapping different aspects of attention. For the CPT, the increase in false alarm rate from Block 1 to Block 3 in the HIV seropositive groups provides evidence of an increase in errors of commission when sustained attention over time is required. The relatively greater increase in false alarm rate over time in the HIV seropositive groups suggests a greater impulsivity and a higher susceptibility of these HIV seropositive children to a type of vigilance decay. The Span, on the other hand, does not measure sustained attention, but instead measures ability to select or perceive a target letter ('T' or 'F') from an array of 3, 5, or 10 letters, tapping the child's ability to screen out irrelevant stimuli. Two additional factors differentiated the CPT and Span and may limit interpretation of differences between these two tasks. First, the space game presentation of the CPT may have been more engaging to the children than the Span, which was simply presented a a letter identification task. Second, the tasks were presented in fixed order, with the later CPT possibly being associated with greater fatigue and susceptibility to impairment in sustained attention.

Examination of trends across ages revealed the expected age-related changes in all CPT and Span variables. With increasing age, false alarm rate decreased, hit rate increased, sensitivity increased, and hit latency decreased. Thus, younger children were likely to detect the target less frequently and respond to the wrong stimuli more frequently than older children. For the Span, array size had a larger effect on younger children than on older children for the variable of percent correct. Latency to correct was faster in the older age groups. These effects indicate that the versions of the CPT and Span used in this study were sensitive to age-related changes in the 7- to 19-year age range.

Results from the CPT false alarm rate provide evidence of subtle difficulty with sustained attention in the HIV seropositive hemophilic boys in this study. These results are

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consistent with a growing literature indicating that impairment in attentional functioning may be present in nondemented HIV-infected adults (E. Martin et al., 1992a, 1992b). There is less data available to help with interpretation of CPT and Span performance in children, however. Most studies of children using these instruments have involved attention deficit hyperactivity disorder (ADHD) and schizophrenia. Studies of children with ADHD have used several versions of the CPT and have generally shown that false alarms (errors of commission) are more likely than errors of omission to discriminate ADHD from normal children and to show modest correlations with parent and teacher ratings of hyperactivity (Barkley, 1991). Using a version of the CPT like that used in the present study, Neuchterlein (1983) and O'Dougherty et al. (1984) found that elementary school-age ADHD children had more false alarms and lower sensitivity (*A′*) than normal comparison children, reflecting difficulty inhibiting impulsive responses in the ADHD children. In contrast, children of schizophrenic mothers showed lower scores on a larger number of CPT variables, as well as broader impairment in attention (Nuechterlein, 1983). Thus, HIV-infected children in the current study show a pattern of performance errors and impulsivity on the CPT that is similar to that reported for children with ADHD, in that both groups report more false alarms than comparison children. However, the HIV+ hemophilic children in the current study also showed a vigilance decay in the form of an increase in false alarms on the CPT over time—a finding that is not reliably reported in samples of ADHD children (Barkley, 1991).

Studies of children and adults with ADHD have reported that impairment in control of attention and motor activity are associated with metabolic abnormalities in subcortical and frontal systems (Barkley, 1991; Zametkin et al., 1990), and reviews of neuropsychological and neurological studies of ADHD consistently point to impairment in attention and executive functions associated with frontal–subcortical structures (Barkley, 1997, 1998; Benton, 1991; Tannock, 1998). In general, impairments in attentional processing and motor speed on the CPT correlate with lesions to basal ganglia and tertiary frontal systems in adults (Heilman et al., 1983; Mirsky, 1988). The finding vigilance decay and increased false alarms on the CPT in the current sample HIV+ boys thus accords well with studies showing pathology in subcortical white matter and basal ganglia (Epstein et al., 1988; Scarmato et al., 1996) and frontal lobes (da Cunha et al., 1997) in HIV-infected children. The absence of significant differences between HIV+ and HIV− participants in the HGDS baseline study (Loveland et al., 1994) may indicate that standard neuropsychological tests used in the HGDS are less sensitive to subcortical pathology.

Although the present study provides preliminary evidence that deficits in attentional processing may be early cognitive manifestations of HIV infection in hemophilic children, the underlying neuropathophysiological mechanism producing this effect is as yet unknown. Further studies relating performance on attentional processing measures to physiological parameters, MRI, and other neurological measures may help in this regard and are ongoing in the HGDS.

The HGDS is a natural history study of HIV infection in young men and, as such, presents some limitations to interpretation. First, 43% of the HIV+ participants were receiving antiretroviral medication at the time of test administration. Antiretroviral treatment was given at the discretion of the treating physician and treatment practices were likely influenced by disease progression and other clinical issues. Because the participants were not randomly assigned to these treatments and scheduling and dosing data were not collected, it is impossible to evaluate the effects of this medication on the development and health of the HGDS sample. Second, in addition to the effects of HIV disease, correlated and secondary factors such as illness-related fatigue, anxiety, and absences from school may contribute to the association between performance on these attentional measures and HIV status. However, the fact that the battery of neuropsychological tests given at the HGDS baseline (Loveland et al., 1994) did not produce similar results suggests that there is something specific in attentional functioning that is effected in these children.

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