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Full-length Article

Lower total and regional grey matter brain volumes in youth with perinatally-acquired HIV infection: Associations with HIV disease severity, substance use, and cognition

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ABSTRACT

Despite improved survival due to combination antiretroviral therapy (cART), youth with perinatally-acquired HIV (PHIV) show cognitive deficits and developmental delay at increased rates. HIV affects the brain during critical periods of development, and the brain may be a persistent reservoir for HIV due to suboptimal blood brain barrier penetration of cART. We conducted structural magnetic resonance imaging (sMRI) and cognitive testing in 40 PHIV youth (mean age = 16.7 years) recruited from the NIH Pediatric HIV/AIDS Cohort Study (PHACS) who are part of the first generation of PHIV youth surviving into adulthood. Historical and current HIV disease severity and substance use measures were also collected. Total and regional cortical grey matter brain volumes were compared to a group of 334 typically-developing, HIV-unexposed and uninfected youth (frequency-matched for age and sex) from the Pediatric Imaging, Neurocognition, and Genetics (PING) study (mean age = 16.1 years). PHIV youth had smaller (2.8–5.1%) total and regional grey matter volumes than HIV-unexposed and uninfected youth, with smallest volumes seen among PHIV youth with higher past peak viral load (VL) and recent unsuppressed VL. In PHIV youth, worse cognitive performance correlated with smaller volumes. This pattern of smaller grey matter volumes suggests that PHIV infection may influence brain development and underlie cognitive dysfunction seen in this population. Among PHIV youth, smaller volumes were also linked to substance use (alcohol use: 9.0–13.4%; marijuana use: 10.1–16.0%). In this study, collection of substance use information was limited to the PHIV cohort; future studies should also collect substance use information in controls to further address interactions between HIV and substance use on brain volume.

1. Introduction

Worldwide, it is estimated that there are over three million youth living with HIV globally, with the majority of youth acquiring HIV perinatally (Sohn and Hazra, 2013; UNAIDS, 2014). Youth with perinatally-acquired HIV (PHIV) may show cognitive deficits as well as developmental delay even among those with reconstituted immunologic and virologic status, (Cohen et al., 2014;

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Crowell et al., 2014; Ene et al., 2014; Koekkoek et al., 2008; Linn et al., 2015; Malee et al., 2016; Martin et al., 2006; Nichols et al., 2016; Nozyce et al., 2006; Redmond et al., 2016; Sherr et al., 2014; Sirois et al., 2016; Smith et al., 2012; Smith and Wilkins, 2015) making PHIV a common infectious cause of perinatally-acquired developmental disability globally (Armstrong et al., 1993; Institute of Medicine, 2001; UNAIDS, 2015). Combination antiretroviral therapy (cART) for children with PHIV has resulted in substantial improvements in health with survival beyond childhood and reductions in morbidity and mortality (Brady et al., 2010; Gona et al., 2006; Hazra et al., 2010).

Early HIV infection, immune activation, and viral persistence (due to suboptimal blood brain barrier penetrance of cART regimen) during a critical period of development may be especially detrimental to developing brains in youth with PHIV (Annunziata, 2003; Churchill et al., 2015; Cohen et al., 2015; Ene et al., 2011; González-Scarano and Martín-García, 2005; Kramer-Hammerle et al., 2005; Linn et al., 2015; Martin et al., 2006; Nesbit and Schwartz, 2002; Sarma et al., 2014; Thompson et al., 2011). Brain development is an extended process that begins prenatally and continues throughout the first two decades of life, with increased sensitivity to experience during the first year of life in pathways responsible for sensory, language and higher order cognitive development (Fox et al., 2010; Tierney and Nelson, 2009). Adolescence is also a crucial developmental window marked by a period of rapid brain maturation via synaptic pruning and myelination. White matter volume increases while grey matter volume decreases (Ernst and Mueller, 2008), with parietal grey matter reduction prominent before adolescence, followed by dorsal, mesial, and orbital frontal grey matter reduction during and after adolescence (Sowell et al., 2004).

Studies including neuroimaging combined with cognitive evaluation allow for an *in vivo* characterization of how HIV and cART may mediate brain development (Thompson and Jahanshad, 2015). In adults, studies of post-mortem tissue and *in vivo* neuroimaging combined with cognitive testing have revealed atrophy in cortical and subcortical structures that is related to HIV severity and cognitive performance (Ances et al., 2012; Archibald et al., 2004; Becker et al., 2012, 2011; Cohen et al., 2010a; Heindel et al., 1994; Jernigan et al., 1993; Kallianpur et al., 2013; Stout, 1998; Thompson et al., 2005; Thompson and Jahanshad, 2015). Still, the effects of early HIV infection on the underlying brain in adolescents with PHIV have not been well-characterized (Cohen et al., 2015; Hoare et al., 2014; Musielak and Fine, 2015).

Adolescent brains are also subject to environmental influences, including substance use. Neuroimaging and neuropsychological studies in youth who use substances have found structural brain abnormalities, including grey matter volume reductions, as well as cognitive dysfunction (Battistella et al., 2014; Churchwell et al., 2010; Jacobus and Tapert, 2014; Peng et al., 2015; Squeglia et al., 2009; Substance Abuse and Mental Health Services Administration, 2011; Williams et al., 2010; Yakolev and Lecours, 1967). Youth with worse HIV disease severity are more likely to engage in substance use (Williams et al., 2010). Thus, to carefully study effects of PHIV on youth treated with cART, it is important to account for substance use.

We present one of the first studies to investigate the impact of HIV severity and coincident substance use on regional and total brain volumes and their association with cognition in PHIV youth. Other studies on grey matter volumes in PHIV do not focus on regional grey matter or substance use or are in PHIV populations with varying clinical characteristics from our cohort (Cohen et al., 2015; Sarma et al., 2014). Since PHIV youth often exhibit global cognitive functioning, working memory, and processing speed deficits (Crowell et al., 2014; Hazra et al., 2010; Koekkoek et al., 2008; Linn et al., 2015; Raskino et al., 1999), we hypothesized that frontal and parietal regions, regions important for higher-order cognitive functioning, would show volume reduction as compared to typically-developing, HIV-unexposed and uninfected youth and smaller volumes would be associated with worse cognitive performance. We also hypothesized that HIV disease severity and substance use would be associated with reduced cortical grey matter volumes among adolescents with PHIV.

2. Materials and methods

2.1. Study population

40 PHIV youth from a single site (Ann & Robert H. Lurie Children's Hospital of Chicago) participating in the Adolescent Master Protocol (AMP) study of the NIH Pediatric HIV/AIDS Cohort Study (PHACS) network were recruited. Institutional review board approvals were obtained. Parents, legal guardians, or youth aged 18 years or older provided written informed consent; minors provided written assent. A control group of 334 typically developing, HIV-unexposed and uninfected youth was generated using frequency-matching for sex and age from the Pediatric Imaging, Neurocognition, and Genetics (PING) study (http://pingstudy.ucsd.edu/welcome.html). Magnetic Resonance Imaging (MRI) database from five sites (Massachusetts General Hospital; Sackler Institute; University of Hawaii; Yale; University of California-Los Angeles). Of note, information regarding alcohol and drug use was not collected in the PING cohort.

2.2. HIV disease markers, substance use, and cognitive functioning in PHIV youth

Visits occurred semi-annually (2007 through 2010), then annually, as described previously (Lewis-de los Angeles et al., 2016; Smith et al., 2012). Lifetime laboratory results including CD4 T-lymphocyte percentages (CD4%), plasma HIV RNA concentration (viral load (VL)), and CDC HIV classification (World Health Organization, 2007) were obtained from medical charts. Past HIV disease severity measures were determined by collecting the lowest known lifetime CD4% ("nadir CD4%") and highest known lifetime HIV VL ("peak VL") prior to entry. A measure of ongoing viremia was calculated as percentage of measures exceeding 1000 copies/mL in the five years prior to neuroimaging. Recent VL was defined as VL closest to neuroimaging.

Substance use (alcohol, tobacco, marijuana, and other illicit drugs) was collected starting at 10 years of age by Audio Computer-Assisted Self-Interview (ACASI), which was used to decrease under-reporting as a result of social stigma (Alperen et al., 2014; Mellins et al., 2011). A binary variable for lifetime prevalence of alcohol, marijuana and tobacco use was created for any self-reported use on ACASI performed within one year preceding neuroimaging.

Standardized neuropsychological examinations (Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV) (6–16 years), and Wechsler Adult Intelligence Scale, Fourth Edition (WAIS-IV) (17 years and older)) were performed. Working memory and processing speed indices, standardized to have mean = 100 and standard deviation (SD) = 15 in the general population, were used to calculate cognitive proficiency index (CPI), an estimate of the information processing efficiency for learning, problem solving, and higher-order reasoning (Weiss et al., 2006).

2.3. Image acquisition and processing

MRI scans were performed using standardized PING acquisition protocols (Jernigan et al., 2015; Lewis-de los Angeles et al., 2016;