Programa de Doctorado en Ciencias de la Salud

Evaluación neurocognitiva, pruebas de neuroimagen y biomarcadores de daño neuronal en pacientes con infección perinatal por VIH

Tesis Doctoral presentada por:

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“Nada en la vida es para ser temido, es sólo para ser comprendido. Ahora es el momento de entender más, de modo que podamos temer menos”

Marie Curie.

A mi madre y a mi padre.

A Raúl, Elsa y Leire.

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ABREVIATURAS

ABREVIATURAS EN ESPAÑOL

ARV Antirretroviral (es)

BHE Barrera hematoencefálica

Cels células

CoRISpe Cohorte de la Red en Investigación de SIDA pediátrico

CV Carga viral

DE Desviación estándar

FE Funciones ejecutivas

FV Fluidez verbal

FI Factor de impacto

GFII Giro Frontal Inferior Izquierdo

IF Inteligencia fluida

IL-1 Interleucina 1

IL-6 Interleucina 6

L litro

LCR Líquido cefalorraquídeo

Log logaritmo

MM3 milímetros cúbicos

Ml mililitro

Ng nanogramo

NS Estadísticamente no significativo

Pg picogramo

PreTAR previa al tratamiento antirretroviral combinado

RIQ Rango intercuartílico

RM Resonancia magnética

RMf Resonancia magnética funcional

SNC Sistema nervioso central

TAR Tratamiento antirretroviral combinado

T Teslas

TNC Tests neurocognitivos

VIH- Virus de la Inmunodeficiencia Humana

VIH-TV Transmisión vertical del virus de la inmunodeficiencia humana

ABREVIATURAS EN INGLÉS

AD Axial diffusivity

ART Antiretroviral treatment

BOLD Blood Oxigenation Level-Dependent

CT Cortical Thickness

CDC *Center for Disease Control and Prevention*

DBM Deformations based morphometry

DTI Diffusion tensor imaging

FA Fractional anisotropy

fMRI functional magnetic resonance image

GM Gray matter

HAD HIV associated dementia

HAND HIV associated neurocognitive disorders

IQ Coeficiente intelectual

LIFG Left Inferior Frontal Girus

MD Mean diffusivity

NFL Neurofilament Light Chain Protein

PHIV Perinatal HIV

pNfL Neurofilament Light Chain Protein measured in plasma

RD Radial diffusivity

ROI Regions of interest

VBM Voxel based morphometry

WM Whitte matter

SBM Surface based morphometry

TNFα Tumor necrosis factor

La presente tesis doctoral, de acuerdo con el informe correspondiente autorizado por la directora de la tesis, y en cumplimiento con la normativa aprobada por el Órgano Responsable del Programa de Doctorado, se presenta como un compendio de cuatro publicaciones. Tres ya publicadas y la cuarta en revisión en el momento de redacción de esta memoria. Las referencias completas de los artículos que constituyen el cuerpo de la tesis son los siguientes:

1. Ruiz-Saez B, García MM, Aragon AM, Gil-Correa M, Melero H, Malpica NA, Ory SJ, Zamora B, Guillen S, Rojo P, Falcon-Neyra L, Alvarez A, Fernandez P, Lorente-Jareño ML, Ramos JT, Sainz T, Velo C, Navarro ML, Gonzalez-Tomé MI. **Effects of perinatal HIV-infection on the cortical thickness and subcortical gray matter volumes in young adulthood**. Medicine 2021;100:15(e25403). FI 1.55 (Segundo cuartil, Medicina).

2. Martín-Bejarano M, Ruiz-Saez B, Martinez-de-Aragón A, Melero H, Zamora B, Malpica NA, Ramos JT, Gonzalez-Tomé MI. **A Systematic Review of Magnetic Resonance Imaging Studies in Perinatally HIV-Infected Individuals**. AIDS Rev. 2021 Mar 18. doi: 10.24875/AIDSRev.20000088. FI 2.28 (Segundo cuartil, Medicina)

3. Martín Bejarano-García M, Ruiz-Sáez B*, Zamora B, Martínez de Aragón A, García-Navarro C, Jiménez de Ory S, Velo C, Ramos JT, Sainz T, Escosa L, Núñez-Enamorado N, Stephan-Otto C, Navarro ML, González-Tomé MI. **Brain activity in well-controlled perinatally human immunodeficiency virus-**

infected young adults: a functional magnetic resonance imaging pilot study. Rev Neurol. 2021 May 16;72(10):343-351. doi: 10.33588/rn.7210.2020536. FI 0.87 (Tercer cuartil, Medicina)

4. Ruiz-Saez B, Martín-Bejarano M, Martínez de Aragon A, Gisslen M, Zetterberg H, Blennow K, Jimenez de Ory S, Alvarez-Losada S, Muñoz-Fernández, Ramos JT, Melero H, Navarro ML, González-Tomé MI. **Plasma neurofilament light as a biomarker of neuronal injury in adolescents cwith perinatal HIV infection.** Enviado a *BMC Infect Dis.* Agosto 2021. FI 2.86 (Primer cuartil, Enfermedades Infecciosas)

Los resultados expuestos han sido presentados en los siguientes foros científicos internacionales:

1. Martín-Bejarano M, Ruiz-Saez B, García-Navarro C, Zamora B, Martínez de Aragón A, Velo C, Jiménez de Ory S, Stephan-Otto C, González Tomé MI. **Compensatory brain activity in well controlled vertical HIV young adults**. 11th International Symposium on Neuropsychiatry & HIV. Barcelona, 18-19 mayo 2018.
2. García-Navarro C, Martín-Bejarano M, Jiménez de Ory S, Cuéllar-Flores I, Zamora B, Ruiz-Séz B, Velo C, Martínez de Aragón A, González-Tomé MI. **Impact of HIV severity on neurocognitive profile in perinatally HIV-infected young adults.** 11th International Symposium on Neuropsychiatry & HIV. Barcelona, 18-19 mayo 2018.

3. Ruiz-Saez B, Martin-Bejarano M, Martinez de Aragon A, Rojo Conejo P, Sainz T, Alvarez A, Ramos JT, Guillen S, Falcon L, Gil-Correa M, Fernandez P, Jimenez de Ory S, Navarro ML, Gonzalez-Tome MI, or the NeuroCoRISpe. **Lower frontal grey-matter brain volumes and basal ganglia enlargement in perinatal HIV**. Abstract 458. 27th CROI, Seattle, 4-7 marzo 2019.
4. Martin-Bejarano M, Ruiz-Saez B, Martinez De Aragon A, Velo C, Gil-Correa M, Guillen S, Lorente ML, Rojo Conejo P, Zamora B, Sainz T, Ramos JT, Guzman J, Navarro ML, González-Tomé MI, for the NeuroCoRISpe. **Effects of perinatal HIV infection on the cortical thickness in young adulthood.** Abstract 394. 28th CROI, Virtual Meeting, 8-11 marzo 2020.
5. Ruiz-Saez B, Martín-Bejarano M, Gisslen M, Zetterberg H, Blennow K, Jiménez de Ory S, Alvarez-Losada S, Muñoz M.A., Ramos-Amador JT, Navarro ML, González-Tomé MI. **Plasma Neurofilament Light Chain protein as biomarker of neuronal injury in perinatally HIV adolescents.** 38th ESPID, Virtual Meeting, 26-29 de octubre de 2020.
6. Martín-Bejarano M, Ruiz-Saez B, Martinez-de-Aragón A, Melero H, Zamora B, Malpica NA, Ramos JT, Gonzalez-Tomé MI. **A Systematic Review of Magnetic Resonance Imaging Studies in Perinatally HIV-Infected Individuals**. 39th ESPID, Virtual Meeting, 24-29 de mayo de 2021.

Así mismo, se ha considerado oportuno mencionar que parte del trabajo de investigación que ha resultado en esta Memoria ha sido reconocido con los siguientes premios/proyectos investigación:

1. Proyecto FIS 2015, denominado “Impacto del tratamiento antirretroviral en el SNC del paciente pediátrico con infeccion VIH. Correlación con neuroimagen y perfil neurocognitivo” FIS PI15/00694, cuya investigadora Principal es la directora de esta tesis doctoral, la Dra María Isabel González-Tomé, 2015.
2. Tercer premio a la mejor comunicación oral IX congreso de SEIP, 2018: Estudio neurocognitivo de casos-controles en jóvenes infectados por el VIH. Neurocorispe
3. CROI New Investigator Scholarship 2019 a la Investigadora Beatriz Ruiz Sáez. Hospital Universitario Gregorio Marañon.

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RESUMEN

INTRODUCCIÓN

Una de las consecuencias más importantes de la infección por el Virus de la Inmunodeficiencia Humana (VIH), es su impacto sobre el sistema nervioso central (SNC). Tras la introducción del tratamiento antirretroviral combinado (TAR) las complicaciones neurológicas severas, incluida la encefalopatía, se han reducido de forma considerable, pero todavía hay pacientes que experimentan alteraciones neurocognitivas relevantes asociadas al VIH.

Por otro lado, se ha descrito una penetrancia limitada de los antirretrovirales a través de la barrera hematoencefálica, lo que permitiría al SNC actuar como reservorio. Por ello, es esencial entender como el VIH puede mediar en el desarrollo cerebral, y asegurar la detección temprana de posibles alteraciones neurocognitivas. Y para ello, en los últimos años se han desarrollado una variedad de novedosas técnicas de neuroimagen en las que apoyarse. De la misma forma, múltiples biomarcadores de SNC han sido analizados.

OBJETIVOS Y METODOLOGÍA

En relación a todo ello, el objetivo principal de este trabajo de investigación fue analizar posibles alteraciones a nivel de SNC en un grupo de pacientes adolescentes y adultos jóvenes con VIH, infectados por transmisión vertical, pertenecientes a la Cohorte Nacional Pediátrica de VIH (CoRISpe), a través de la realización de un estudio multicéntrico transversal mediante: 1) la evaluación de pruebas neurocognitivas; 2) realización de técnicas de neuroimagen; 3) medición en plasma de un fiable biomarcador de lesión neuronal, conocido como neurofilamento de cadena ligera (NfL).

De forma específica, realizamos un estudio de evaluación neurocognitiva y pruebas de neuroimagen mediante técnicas de RM estructural con la finalidad de evaluar el grosor de la corteza cerebral y volúmenes subcorticales de sustancia gris en pacientes de 5 hospitales de Madrid, y los comparamos con un grupo control sin VIH pareados por edad, sexo, nivel educativo y socioeconómico. A su vez, estudiamos el efecto del VIH sobre los volúmenes regionales a nivel de los ganglios basales, siendo la principal hipótesis que el grupo VIH de transmisión vertical (VIH-TV) mostraría menor desarrollo de los volúmenes cerebrales y un mayor adelgazamiento cortical, y por otro lado que un peor control inmunovirológico, se asociaría a un menor volumen de los ganglios basales en los pacientes con VIH-TV.

Con el fin de unificar la información sobre los estudios de neuroimagen realizados en pacientes VIH-TV y así evaluar que regiones cerebrales parecen estar más afectadas en este grupo de población, realizamos una revisión sistemática de los estudios que habían utilizado las principales técnicas de neuroimagen: la RM estructural (que engloba la RM volumétrica y la RM por tractografía o imagen por tensor de difusión) y la RM funcional. A su vez, recogimos las variables clínicas y sociodemográficas que se habían tenido en cuenta a la hora de realizar dichos estudios.

Por otro lado, evaluamos los patrones de actividad neuronal usando la resonancia magnética funcional (RMf) a través de la realización de tareas motora y de fluidez verbal, en un grupo de adolescentes VIH-TV con buen control inmunovirológico, y adecuadas funciones cognitivas y funcionales, comparándolo con un grupo control no VIH de características similares. Se evalúo también la posible existencia de alteraciones psicológicas en estos sujetos.

Por último, en un grupo de pacientes pertenecientes a CoRISpe, analizamos las concentraciones plasmáticas del neurofilamento de cadena ligera y las comparamos con un grupo sin VIH. Para su realización se almacenaron las muestras en el Biobanco de VIH perteneciente al Hospital Gregorio Marañon, y posteriormente enviadas al laboratorio de Neuroquímica de la Universidad de Gothemburg (Suecia) para la determinación de los niveles de NfL mediante la realización de un inmunoensayo con la técnica Simoa HD-1 Analyzer (Quanterix, Billerica, MA). De forma secundaria, en un subgrupo de participantes con VIH-TV, se llevó a cabo un sub-estudio en el que se exploraron posibles correlaciones entre las concentraciones de NfL y los volúmenes de sustancia blanca y pruebas neurocognitivas. Es el primer estudio que analiza dicho biomarcador en población VIH-TV, pues no existe hasta la fecha ningún estudio publicado en población pediátrica o adolescente, únicamente algún estudio realizado en población adulta con infección por VIH.

RESULTADOS

Efectos de la infección perinatal por VIH sobre el grosor cortical y volúmenes subcorticales de sustancia gris en adultos jóvenes.

Se incluyeron 50 participantes en el estudio de neuroimagen y evaluación neurocognitiva (25 pacientes con VIH-TV y 25 controles sin VIH) con una mediana de edad de 20 años (RIQ 19-23). No se encontraron diferencias en los tests neuropsicológicos, ni en los tests neurocognitivos (TNC). Sin embargo, el estudio de neuroimagen mostró que el grupo con VIH-TV presentaba un adelgazamiento cortical en diferentes regiones: giro fusiforme izquierdo ($p = 0.000$) y derecho ($p=0.009$); giro lateral-orbitofrontal izquierdo ($p= 0.006$) y derecho ($p= 0.024$); y en el giro parsorbitalis

derecho (p=0.047). Respecto a los volúmenes subcorticales de sustancia gris, los pacientes con VIH-TV mostraron un menor volumen a nivel de amígdala derecha (p=0.014) y putamen izquierdo (p=0.016) al compararlos con el grupo control VIH-. Dentro del grupo VIH-TV un mayor recuento de CD4 fue asociado con un mayor volumen a nivel del putamen derecho (p=0.047). Paradójicamente un inicio tardío de del TAR y un nadir de CD4 más bajo fueron asociados a un mayor volumen a nivel del núcleo accumbens izquierdo (p = 0.033, p = 0.0045). No se encontraron diferencias en volúmenes cerebrales subcorticales o grosor cortical a nivel total.

Revisión sistemática de estudios de resonancia magnética en pacientes VIH infectados por transmisión vertical.

La Revisión Sistemática de los estudios de neuroimagen realizados en población VIH-TV mostró que en el momento del análisis habían sido publicados 26 estudios (23 de RM estructural y 3 de RM funcional) que incluyeron un total de 1182 participantes con VIH-TV. Esta revisión encuentra de forma consistente una amplia evidencia de que los pacientes con VIH-TV presentan un menor volumen en regiones de sustancia gris, un menor grosor cortical, menor desarrollo de los giros o circunvoluciones y en la tractografía se observa una disminución del índice FA (anisotropía fraccional) con un aumento de MD (difusividad media) indicando alteración en la integridad de la sustancia blanca. Por otro lado, los datos preliminares sugieren que la RM funcional en reposo es lo suficientemente sensible para detectar alteraciones funcionales en este grupo de población. Sin embargo, la mayoría de los estudios no recogen datos básicos que tienen gran importancia en el desarrollo cerebral, como son el nivel socioeconómico y educativo, el uso de drogas, y las

características de los pacientes VIH incluyendo edad al diagnóstico, edad al inicio del TAR, clasificación CDC, y la asociación o no de encefalopatía u otras comorbilidades.

Medición de la actividad cerebral a través de la RM funcional en jóvenes VIH infectados por transmisión vertical.

En el estudio de activación neuronal mediante la realización de RMf, 20 sujetos fueron evaluados, 10 pacientes VIH-TV y 10 controles VIH negativos (60% mujeres, 75% caucásicos) con una mediana de edad de 19 años (RIQ 17-21.7) y una mediana de número de años de educación de 11.5 años (RIQ 10-12). Los dos grupos no mostraron diferencias significativas en las características sociodemográficas ($p > 0.05$ para todas las variables). Pudo realizarse análisis de fluidez verbal a todos los sujetos, y análisis de tarea motora a 18 participantes. Para la comparación entre grupos no se observó activación de clusters para ninguno de los contrastes considerados. Para el análisis completo, el movimiento de dedos mostró la activación de los clusters localizados en en Cortex Motor Izquierdo (LMC; MNI coordinadas: - 36, -34, 50), Cerebelo Derecho (RC; 8, -54, -10), Sulcus Intraparietal (IS; 34, -44, 40) y Cortex Premotor Ventral (VPC; 60, 6, 38). Durante la realización de la tarea de fluidez verbal ("generación de palabras versus repetición de palabras") se observó la activación de los clusters localizados en el Giro Frontal Inferior Izquierdo (GFII; -50, 12, 30). Los sujetos con VIH-TV mostraron que con más tiempo de TAR presentaban mayor activación de GFII durante la tarea de fluidez verbal ($r=.648$, $p=0,043$).

Evaluación del neurofilamento de cadena ligera como biomarcador de lesión neuronal en pacientes VIH de transmisión vertical.

Finalmente, al analizar las concentraciones plasmáticas del Neurofilamento de cadena ligera, como biomarcador de daño neuronal, no se encontraron diferencias estadísticamente significativas entre pacientes y controles, pero se observó que aquellos pacientes con mala adherencia al TAR y carga viral detectable presentaban niveles más elevados de NfL (pNfL 9.19, DE 5.18) al compararlos con pacientes indetectables (pNfL 6.6 pg/ml, DE 4.15) o con el grupo control (pNfL 5.29 pg/ml, DE 1.75) con un valor de p cercano a la significación (p = 0.059). Respecto a la correlación de NfL con tests neurocognitivos y volúmenes cerebrales en el grupo VIH, se observó una correlación negativa, al encontrar que los pacientes con menor volumen de sustancia blanca en ciertas regiones cerebrales y un score más bajo en los tests neurocognitivos (Digit Symbol-Coding subtest), fueron asociados con una mayor concentración de NfL en plasma. Con respecto a los volúmenes cerebrales, el grupo con VIH-TV presentó menores volúmenes de sustancia blanca de forma ES a nivel de cerebelo izquierdo y derecho (p = 0.030, p = 0.028), núcleo accumbens izquierdo y derecho (p = 0.010, p <0.001), lóbulo occipital izquierdo y derecho (p = 0.020, p = 0.042) y la circunvolución poscentral izquierda (p = 0.022). No se encontraron diferencias ES en los volúmenes totales de sustancia blanca.

CONCLUSIONES

A pesar del buen control de la infección por VIH en pacientes infectados por transmisión vertical se observa un mayor adelgazamiento cortical a nivel temporal, orbitofrontal y en lóbulos occipitales, así con un menor volumen regional de sustancia gris a nivel subcortical, no estando clara la posible traducción clínica de estos resultados. Sin embargo, estos hallazgos apoyan que los estudios de neuroimagen podrían ayudar a detectar alteraciones neurológicas de forma más precoz, aun cuando

las evaluaciones psicométricas sean normales. Además, se requiere la realización de estudios longitudinales que permitan determinar las implicaciones futuras de dichas alteraciones cerebrales observadas a edades más tempranas de la vida.

Los estudios de neuroimagen evidencian una clara alteración en el desarrollo cerebral de la población con VIH-TV, pero no hay consenso sobre que estructuras cerebrales estarían más afectadas, y la inclusión de datos relacionados con el VIH (incluidas las características clínicas, inmunovirológicas y la información detallada del TAR) puede ser de vital importancia para entender mejor el impacto de la enfermedad en el SNC.

El estudio de RMf no encuentra diferencias en los patrones de activación neuronal en un grupo de pacientes VIH-TV con buen control inmunovirológico, y un grupo control sin VIH, sugiriendo que una supresión de la replicación del VIH en el SNC mediante el uso temprano y duradero de TAR, podría reducir la demanda metabólica cerebral.

Por último, el primer estudio que ha medido las concentraciones plasmáticas de NfL en pacientes con VIH-TV, muestra valores más elevados en pacientes con mal control virológico, pudiendo indicar un mayor daño neuronal en este grupo de pacientes y concluye que, este método ultrasensible, es un biomarcador fiable y accesible, evitando la realización de una punción lumbar para su medición.

SUMMARY

BACKGROUND

One of the most important consequences of HIV infection is its impact on the CNS. Fortunately, cases of HIV encephalopathy and severe neurological complications have been reduced considerably after the introduction of combined antiretroviral treatment (cART). However, many patients continue to experience different degrees of HIV-associated neurocognitive disorders (HAND). Additionally, some authors have described limited penetration of cART in the CNS allowing the brain to act as a viral reservoir and making the infection of CNS a generalized condition of HIV patients. It is therefore essential to understand how HIV and cART might mediate in brain development, and to ensure an early detection of HAND. For these purposes, a variety of novel, non-invasive, neuroimaging techniques and CNS biomarkers have been developed to support the quantitative characterization of the brain structure.

AIM AND METHODS

Taking in account all these factors and the previous results the present study attempts to determine CNS alterations in a group of adolescents and young adults with perinatal HIV infection addressed to CoRISpe (Spanish National Cohort of Pediatric HIV) group trough a multicentric transversal study that included: 1) neurocognitive evaluations; 2) functional and structural MRI study 3) plasma measure of a reliable CNS biomarker known as Neurofilament Light Chain Protein.

Specifically, we performed a cross-sectional study that included a neurocognitive evaluation and structural MRI techniques to evaluate cortical thickness and gray matter subcortical volumes, in PHIV patients from 5 pediatric research centers in Madrid. Those PHIV patients were compared with a control group without

HIV, matched by age, sex, educational level, and socioeconomic status. Moreover, we analyzed the effect of HIV on regional grey volumes at basal ganglia. The main hypothesis would be that the PHIV group would show lower brain volumes and greater cortical thinning, and on the other hand that those PHIV patients with worse immunovirological control, would associate lower volumes of the basal ganglia.

Secondly, to unify the information of the neuroimaging studies performed in PHIV patients and evaluate which brain regions seem to be more affected in this population group, we carried out a systematic review of the studies that had used the main neuroimaging techniques: structural MRI (which includes volumetric MRI and diffusion tensor imaging [DTI]) and functional MRI. We also collected which clinical and sociodemographic variables had been included and evaluated in these studies.

Moreover, we studied described impaired cognitive processes using fMRI on a group of PHIV adolescents with good immunovirological indications and healthy matched controls. Psychological status and neurocognitive functions were also assessed.

Finally, in a group of PHIV participants belonging to CoRISpe and a matched HIV negative control group, pNfL concentrations were compared. To carry it out, the samples were stored in the HIV Biobank belonging to the Gregorio Marañon Hospital, and later were sent to the Neurochemistry laboratory of the University of Gothemburg (Sweden) for the determination of pNfL levels by performing an immunoassay with the technique Simoa HD-1 Analyzer (Quanterix, Billerica, MA). Secondarily, in a subgroup of participants, a sub-study was carried out in which correlations between pNfL concentrations and regional whitte matter brain volumes, and neurocognitive tests were explored. This is the first study to analyze this biomarker in PHIV population.

RESULTS

Effects of perinatal HIV-infection on the cortical thickness and subcortical gray matter volumes in young adulthood.

Fifty participants were included in the neuroimaging and neurocognitive study (25 PHIV patients and 25 participants without HIV) with a median age of 20 years (IQR 19-23). No differences regarding neuropsychological and neurocognitive tests were found between groups. Nevertheless, the PHIV-infected patients showed thinner cortices compared with their peers in different regions: fusiform gyrus left (p =0.000) and right (p=0.009); lateral-orbitofrontal gyrus left (p= 0.006) and right (p= 0.024); and right parsorbitalis gyrus (p=0.047). Regarding subcortical GM volumes, PHIV patients showed lower right amygdala (p=0.014) and left putamen (p=0.016) volumes when compared with HIV- controls. Within the PHIV group, higher CD4 count was associated with higher volumes in right putamen (p=0.047). Moreover, increased age at cART initiation and lower nadir CD4 count was associated with larger volumes in left accumbens (p = 0.033, p = 0.0045). No significant differences were observed between groups for total cortical or subcortical brain volumes.

A Systematic Review of Magnetic Resonance Imaging Studies in Perinatally HIV-Infected Individuals.

The systematic review of the neuroimaging studies in PHIV patients included 26 studies (23 using structural MRI and 3 using fMRI) involving 1182 PHIV-infected participants. Ample evidence has been provided of reduce grey matter volumes, and cortical surface area, decreased gyrification, reduction on FA, and increase in MD in the PHIV-infected group. Furthermore, preliminary data suggest resting state fMRI is

sensitive to detect functional alterations in this population. However, some of the parameters that would be determinant in neuroimaging studies are missing, such as socioeconomic and health conditions, drug use and HIV characteristics including age at PHIV diagnosis, age at treatment onset, CDC classification, association of encephalopathy and other medical comorbidities.

Brain activity measured trough fMRI, in well-controlled perinatally human immunodeficiency virus-infected young adults.

Twenty subjects were assessed (60% females, 75% Caucasians, 80% were born in Spain) with a median age of 19 years old (IQR 17- 21.7) and median number of years of education 11.5 (IQR 10-12). No significant differences were found between groups for sociodemographic characteristics (all $p > 0.05$). Functional series from 20 participants were available for fluency task analysis and 18 participants were available for motor task. For the between group comparisons no activation clusters were observed for any of the contrasts considered. From the whole sample analysis, the 'finger motion + touching tips versus rest' contrast resulted in activation clusters located at the left motor cortex (LMC; MNI coordinates: –36, –34, 50), right cerebellum (RC; 8, –54, –10), intraparietal sulcus (IS; 34, –44, 40) and ventral premotor cortex (VPC; 60, 6, 38) (For the phonological fluency task, the 'word generation versus word repetition' contrast lead to a significant activation cluster in the left inferior frontal gyrus (IFG; –50, 12, 30 (Figure 1b). In the verbal fluency task, within the PHIV group prolonged time on cART was observed to be positively associated with greater activity at the LIFG activation peak ($r = 0.648$, $p = 0{,}043$)

Assessment of plasma neurofilament light as a biomarker of neuronal injury in young adults with perinatal HIV infection.

Finally, when pNfL concentrations were analyzed as biomarker of neuronal injury, no statistically significant differences were found between patients and controls, but higher levels of pNfL were found in patients with increased viral load compared with undetectable patients and controls with a media pNfL of 9.19 pg/ml (SD 5.18) in patients with detectable viral load vs 6.6 pg/ml (SD 4.15) in undetectable patients and 5.29 pg/ml (SD 1.75) in the control group ($p = 0.059$).

With regard to brain volumes and NT, in the PHIV group, lower regional white matter volumes and lower score in the coding subtest were associated with higher pNfL values. Regarding brain volumes, the HIV infected group had significantly lower regional white matter volumes in left and right cerebellum ($p = 0.030$, $p = 0.028$), left and right nucleus accumbens ($p =0.010$, $p < 0.001$), left and right occipital lobe ($p=0.020$, $p= 0.042$) and left postcentral gyrus ($p =0.022$), but no significant differences were found in total white matter volumes when compared with the HIV- group.

CONCLUSIONS

Despite good control of HIV infection and no differences in neurocognitive evaluation, HIV vertically infected patients showed thinner cortices of the temporal, orbitofrontal, and occipital lobes and lower subcortical GM volumes, although the clinical significance/translation of these findings is still unclear. These results support the need to perform complementary neuroimaging studies that could help to detect more subtle neuroalterations not observed by psychometric evaluations. Moreover, longitudinal studies are required to determine the clinical impact these alterations on brain structure.

The neuroimaging studies provide ample evidence of HIV effects on underlying brain structure. However, information recorded in the studies is commonly incomplete and results sometimes contradictory. In addition to future improvements and dissemination of tools for the developing brain MRI processing and analysis, the inclusion of data related to HIV infection itself (including clinical and immunovirological characteristics as well as detailed information about antiretroviral treatment such as age at ART initiation) may be of vital importance to the better understanding of the impact of the disease on CNS.

Our results showed that there were no significant differences between HIV+ and HIV– groups in fMRI activity for verbal phonological fluency and motor tasks suggesting that more efficient suppression of CNS HIV replication by using effective cART in PHIV patients could most likely reduce the metabolic demand in the brain.

Finally, the first study measuring pNfL concentrations in PHIV patients, demonstrated higher levels in patients with detectable viral load, showing that persistent viral replication may contribute to neuronal damage and concludes that this ultrasensitive method to measure pNfL provides an easily accessible biomarker in perinatally HIV infected patients avoiding lumbar puncture.

INTRODUCCIÓN

EPIDEMIOLOGÍA DEL VIH E IMPACTO EN EL SNC

Se estima que, aproximadamente, 1.7 millones de niños están infectados por el VIH. Gracias a los avances e implementación de los programas de prevención de la transmisión vertical de VIH, la tasa de transmisión materno-infantil se ha reducido un 54% de 2010 a 2020.[1]

Sin embargo, la cobertura de los servicios para la prevención de la transmisión vertical se produce de forma desigual y se calcula que siguen infectándose alrededor de 160.000 niños/año. [2]

Mientras tanto, en nuestro medio, la población con infección por VIH-TV, son en su gran mayoría adolescentes y adultos jóvenes, supervivientes, que se infectaron antes de la instauración de dichos programas preventivos, en la era previa al desarrollo del TAR, habiendo recibido en su gran mayoría, tratamientos subterapéuticos. Sin embargo, con la llegada del TAR, la esperanza y calidad de vida en los pacientes con VIH se ha incrementado de forma muy considerable. [3]

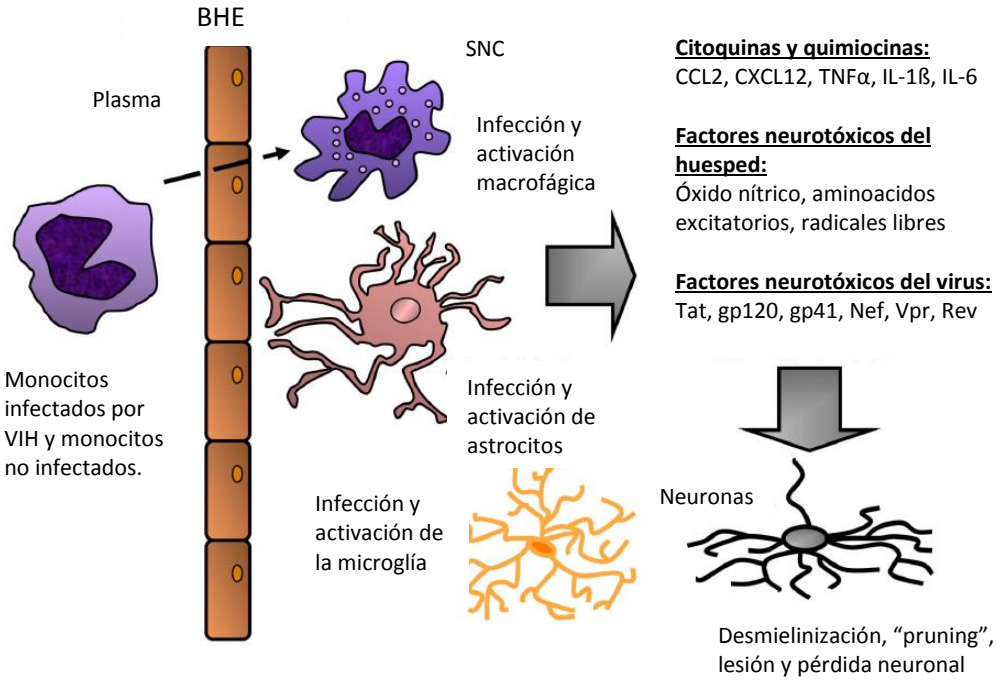
No obstante, el impacto de la infección sobre el SNC y lo síndromes neurológicos, continúan siendo un desafío en la práctica clínica habitual. Aunque afortunadamente, los casos de encefalopatía y las complicaciones neurológicas severas se han visto reducidas gracias al inicio del TAR, [4] todavía muchos pacientes continúan experimentando diferentes grados de alteraciones neurocognitivas asociadas al VIH.[5] A este respecto, los pacientes infectados por transmisión vertical son mucho más vulnerables a la hora de presentar alteraciones neurológicas y neurocognitivas, debido a que la invasión del virus a sistema nervioso central se produce en las primeras semanas de vida.[6]

FISIOPATOLOGÍA DEL VIH EN SNC

La fisiopatología de la infección por el VIH en el SNC aboga por que el virus penetra en SNC en las semanas posteriores a la primoinfección, lo que conlleva a una neuroinflamación e inmunoactivación. [7-8] A través de la infección de monocitos por el VIH, éstos atravesarían la barrera hematoencefálica (BHE), produciendo, de forma indirecta un daño neuronal mediante la activación de macrófagos y de la microglía y un pequeño porcentaje de astrocitos, que favorecerían la liberación de citoquinas y otros factores de activación inmune como el factor de necrosis tumoral o la interleukina-1 y 6 y quimiocinas como CCL2, CXCL12, radicales libres, óxido nitroso, etc. generando más neurotoxinas. A su vez, las células infectadas liberarían proteínas virales como Tat y gp120 que activarían más células del SNC. Todo ello favorecería la generación del daño y pérdida neuronal (**Figura 1**).[9-10]

La elaboración de factores quimiotácticos, inflamatorios y de neurotoxicidad perpetuarían el ciclo de la inflamación crónica a nivel de SNC lo que resultaría en el daño neuronal asociado con las alteraciones neurocognitivas asociadas al VIH (HAND).[10]

Figura 1. Esquema de los mecanismos fisiopatológicos por los que el VIH produce la activación y el daño a nivel de SNC



Adaptado de Williams DC et al. Monocytes mediate HIV neuropathogenesis: mechanisms that contribute to HIV associated neurocognitive disorders. *Curr HIV Res*. 2014;12:85-96

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Sin embargo, no está claro que estas alteraciones inflamatorias y de activación inmune, así como la presencia del virus en el SNC, pueda provocar lesiones cerebrales desde el inicio de la infección. [11]

Durante los siguientes meses, en la mayoría de los casos, el sistema inmune es capaz de controlar la infección a nivel de SNC, pero en caso de no iniciar TAR en estadíos iniciales, se pueden producir alteraciones neurológicas muy significativas como la encefalopatía o la demencia asociadas al VIH.[12] De forma adicional, algunos

autores han descrito una limitación a la penetración del TAR en el SNC, permitiendo al cerebro actuar como un reservorio del virus y haciendo por tanto de la infección del SNC una condición generalizada para los pacientes VIH.[13] En otros casos, diversos autores han mostrado que ciertos antirretrovirales, como el efavirenz, pueden tener efectos adversos neuropsiquiátricos. [14-15]

Por tanto, es esencial entender como el VIH y el TAR pueden mediar en el desarrollo cerebral y asegurar una detección temprana de posibles alteraciones neurocognitivas asociadas al VIH (HAND). Para ello, se han desarrollado en los últimos años, diferentes estudios que combinan la evaluación neurocognitiva con técnicas de neuroimagen, además de estudios de biomarcadores en líquido cefalorraquídeo, con la finalidad de entender mejor las alteraciones que se producen a nivel de SNC y detectarlas en sus fases más tempranas.

EVALUACIÓN NEUROCOGNITIVA EN POBLACIÓN VIH-TV

Las alteraciones neurocognitivas han sido ampliamente evaluadas en población VIH durante las dos últimas décadas. Varios estudios han demostrado deterioros cognitivos globales y específicos en pacientes infectados por VIH-TV, incluso tras la introducción del TAR.[16-17] Sin embargo, otros estudios han mostrado que el rendimiento cognitivo de grupos de pacientes con infección por VIH-TV se mantenía dentro de la media poblacional. [18-19]

Los efectos de la infección por VIH-TV pueden ser difíciles de evaluar, ya que las poblaciones incluidas en estos estudios presentan características sociodemográficas, culturales e inmunovirológicas muy heterogéneas. Esta evaluación, se complica aún más por la falta de consenso entre los investigadores

sobre que herramientas utilizar para la evaluación neuropsicológica, y la ausencia, en ocasiones, de grupo control bien pareado.

Las alteraciones neurocognitivas más frecuentemente encontradas en población VIH son aquellas que afectan a la atención, a las funciones ejecutivas (FE) y a la fluidez verbal (FV), incluso en pacientes clínicamente estables.[20-23] Por otro lado, la literatura muestra como el rendimiento cognitivo parece estar influenciado de forma positiva por el inicio del TAR, tras conseguir la inmunosupresión.[22,24-26] Además, se ha mostrado un menor rendimiento cognitivo en la población VIH estadío C al compararlos con población VIH estadío no C. [20,22]

TÉCNICAS DE NEUROIMAGEN.

Se han desarrollado diferentes estudios de neuroimagen en los últimos años para intentar identificar el impacto de la gravedad del VIH en SNC, contribuyendo a un diagnóstico precoz de las manifestaciones neurológicas y alteraciones neurocognitivas en pacientes con VIH de transmisión vertical. [27]

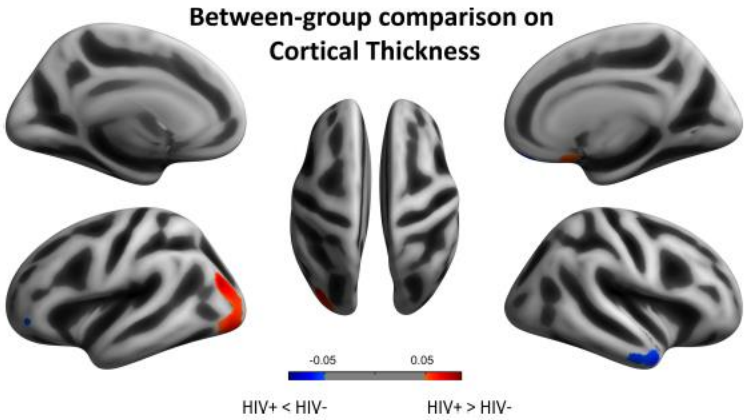
La adquisición de imágenes por resonancia magnética (RM), es una técnica no invasiva que permite, por un lado, a través de la RM estructural obtener imágenes anatómicas cerebrales de alta resolución, proporcionando información estática detectando posibles alteraciones en los tejidos, y por otro lado, mediante la RM funcional (fMRI), medir la actividad cerebral proveyendo información fisiológica dinámica.[28] Se han utilizado para los estudios de neuroimagen, RM de campo magnético de 1.5 T (teslas) en los estudios más iniciales, y en los últimos años, la mayoría han sido realizados en RM de 3 T para obtener una mejor calidad de la imagen en un menor tiempo de exploración.

RM ESTRUCTURAL.

El análisis de neuroimagen estructural permite diferenciar el tejido neuronal en mediciones de sustancia gris, sustancia blanca y líquido cefalorraquídeo (LCR) y compararlos entre diferentes sujetos. Estos métodos de morfometría cerebral dependen del contraste entre los diferentes tejidos para definir la densidad y volumen de la sustancia gris, sustancia blanca y de la superficie cortical. El desarrollo de los diferentes enfoques de procesamiento automático para el análisis de morfometría cerebral incluye morfometría basada en Voxel (Voxel Based Morphometry, VBM),[29] morfometría basada en deformaciones (Deformations Based Morphometry, DBM), [30] y morfometría basada en superficies (SBM). [31]

VBM es una técnica automatizada cuyo objetivo es estimar las diferencias en la composición del tejido cerebral completo o por regiones de interés (ROI) y compararla entre sujetos.[29] Mientras que VBM se centra en la imagen residual, DBM analiza cuanto cambian los volúmenes de los vóxeles durante el registro de la imagen. Por otro lado, con SBM se pueden analizar diferentes características sustancia gris, como el área de superficie, el grosor cortical, la curvatura y el volumen y permite establecer mayor precisión con valores de espesor asignados a vértices individuales en lugar de vóxeles. [32-34] Ejemplo de RM estructural con medición de grosor cortical (**Figura 2**).

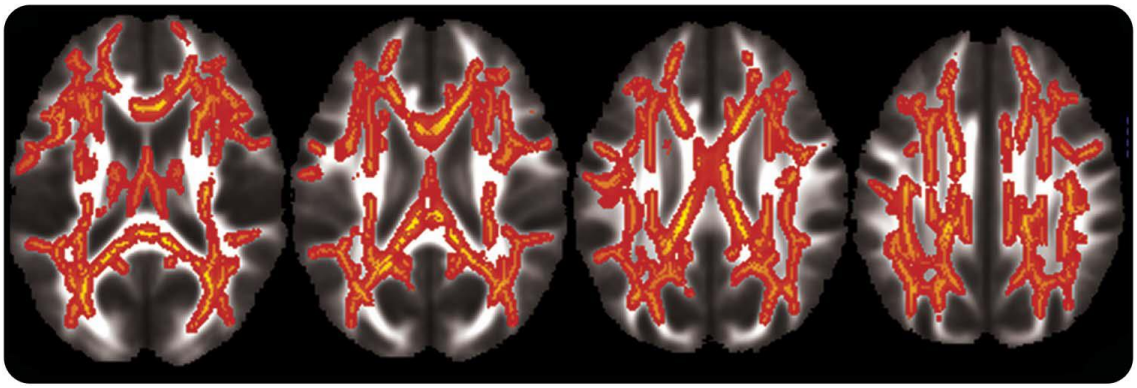
Figura 2. Imagen de RM estructural que compara el grosor cortical entre pacientes VIH-TV y un grupo control sin VIH



El grupo de niños con VIH-TV muestra mayor CT (en rojo) y menor CT (en azul) en comparación con el grupo control sin VIH. Adaptado de Yu X et al. Neuroanatomical Changes Underlying Vertical HIV Infection in Adolescents. *Front Immunol*. 2019;10:814

Por otro lado, existe otra técnica conocida como DTI (Imagen por tensor de difusión) también conocido como tractografía, que es un método de RM no invasivo que utiliza las propiedades de difusión del agua en el cerebro para estimar la integridad de los tractos neurales de sustancia blanca utilizando diferentes variables.[34] La FA (Anisotropía fraccional) representa el índice de la coherencia de la difusión, indicando el grado de mielinización axonal. [35] Este es el índice que se utiliza con mayor frecuencia al realizar estudios con DTI. De igual manera, existente otros índices que aportan información relevante con respecto a la integridad de la sustancia blanca como son la MD (difusividad media), RD (difusividad radial) y AD (difusividad axial). MD es una medida global del desplazamiento de las moléculas de agua y proporciona información sobre la magnitud de la difusión. Una disminución de la FA combinada con un aumento de MD es un indicador de alteración de la sustancia blanca.[36] Por otro lado, la AD y RD son indicadores de integridad del axón y de las vainas de mielina respectivamente. [37] Ejemplo de DTI (**Figura 3**)

Figura 3. RM estructural mediante técnica DTI que compara los tractos neurales en un grupo de pacientes con VIH-TV y un grupo sin VIH



DTI: Patrón difuso que muestra un aumento de MD en niños con VIH-TV comparado con un grupo control de niños sin VIH. Adaptado de Cohen et al. Cerebral injury in perinatally HIV-infected children compared to matched healthy controls. *Neurology* 2016;86:19–27

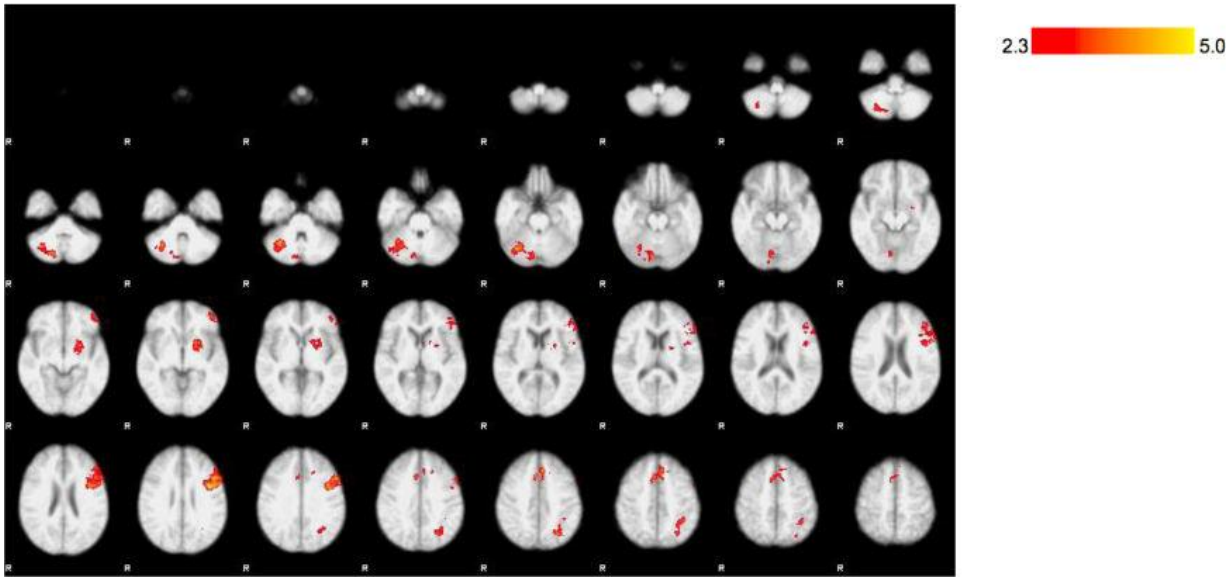
RESONANCIA MAGNÉTICA FUNCIONAL (RMf)

La RMf (fMRI por sus siglas en inglés) es una técnica de neuroimagen que mide en tiempo real la actividad cerebral a través de la medición del flujo sanguíneo en el cerebro. Cuando se realiza una determinada tarea, el aumento de la actividad neuronal se asocia a un aumento en las demandas metabólicas que se compensa con el suministro y consumo de glucosa y oxígeno. Esto se basa en el efecto BOLD (Blood Oxigenation Level-Dependent), que refleja la compleja combinación de cambios en el flujo sanguíneo cerebral, la tasa metabólica cerebral de consumo de oxígeno y el volumen sanguíneo cerebral.[38] Esta técnica permite una visión directa de los sistemas neuronales que pueden alterarse durante la cognición.[39] Existen dos formas de medir la actividad neuronal mediante el efecto BOLD. La RMf mediante la realización de tareas y la RMf en reposo. La RMf que se lleva a cabo por realización de tareas se efectúa durante la realización de una actividad que consta de una parte denominada “tarea” en la que se produce activación y otra de reposo. El flujo sanguíneo cerebral

varía dependiendo de la energía requerida por las neuronas durante una tarea, y por lo tanto, de la respuesta hemodinámica BOLD, que de forma indirecta representa una medida de actividad neuronal. A continuación, se comparan las imágenes obtenidas durante las dos partes de la actividad y se mide la señal de cada voxel o cluster, para determinar si ha existido una variación de activación en el área a analizar, generando un mapa de la actividad cerebral. Ejemplo de RMf (**Figura 4**).

Por otro lado, la RMf en reposo revela la conectividad funcional entre redes neuronales distribuidas al identificar regiones en las que la señal BOLD muestra coherencia temporal. Este método ofrece información de la actividad cerebral mientras la mente está “en reposo” y no participa en la realización de ninguna tarea. [41]

Figura 4. RM funcional que muestra patrones de actividad cerebral en un grupo VIH durante la realización de una tarea de fluidez verbal.



RMf que muestra regiones cerebrales activadas durante la realización de una tarea de fluidez verbal (contar palabras seguidas de un periodo de descanso). Adaptado de Thames et al. Increased subcortical neural activity among HIV individuals during a lexical retrieval task. Neurobiol Dis *2015;10:*175-182

ESTUDIOS DE NEUROIMAGEN EN POBLACIÓN VIH-TV

En la última década se han desarrollado una variedad de técnicas de neuroimagen no invasivas, arriba explicadas, con la finalidad de realizar un detallado análisis de regiones cerebrales, o áreas cerebrales específicas. Pero hasta la fecha, los estudios de neuroimagen realizados en niños y adolescentes con VIH-TV son escasos. Los hallazgos preliminares de estos, muestran que incluso en la era del TAR, los pacientes con VIH-TV presentan alteraciones en las regiones microestructurales del cerebro. [42]

Respecto a la morfometría cerebral, la mayoría de los estudios realizados señala un menor volumen de sustancia gris (GM, *gray matter*) total [43-45] o regional, especialmente a nivel de ganglios basales,[44,46,47] y un menor volumen de sustancia blanca (WM, *whitte matter*) global o regional. [43,48]

Sin embargo, otros estudios que han reportado un mayor volumen de GM a nivel regional[48-50] y el estudio publicado por Paul et al. describe un mayor volumen global de GM en los pacientes VIH-TV menores de 12 años. [50]

Los estudios de grosor cortical (CT) refieren, en líneas generales, adelgazamiento de ciertas regiones de la corteza cerebral en el grupo VIH-TV al compararlo con población sin infección por VIH. [46,50]

En cuanto a los estudios realizados con DTI para valorar la integridad de la sustancia blanca, los cuatro índices más populares (FA, AD, MD, RD) se exploraron en prácticamente todos los estudios realizados. Los principales hallazgos parecen coincidir en una reducción de FA y un aumento de MD en el grupo VIH-TV,[42,52-54] pero la localización de los tractos afectados varía según el estudio realizado. Por ejemplo, algunos autores describen una reducción significativa de FA en el fascículo

frontooccipital y fascículo longitudinal inferiores [52], mientras que otros describen esta reducción de FA en el fascículo longitudinal superior,[53] en el tracto corticoespinal,[54] o a nivel del cuerpo calloso[42,53] en el grupo VIH-TV.

Dentro de la población VIH-TV, las alteraciones estructurales cerebrales se han relacionado con un peor estado inmunovirológico,[43,49,50,55] en su mayoría definidos por una carga viral no controlada, un recuento bajo de CD4, y un inicio de TAR tardío. Y es que, el inicio temprano del TAR, parece preservar mejor el grosor cortical y los volúmenes de ciertas regiones cerebrales como son los ganglios basales.[43,45,50] Algunos autores describen correlaciones positivas entre en recuento actual de CD4 y los volúmenes cerebrales,[53,55] pero la mayoría no encuentra dicha asociación. Sin embargo, se observa que la mayoría de los estudios realizados hasta el momento no incluyen apenas datos completos sobre la enfermedad y tratamiento antirretroviral.

A su vez, hay estudios que sugieren que las estructuras corticales y subcorticales alteradas, y la alteración en los tractos neurales en pacientes pediátricos y adolescentes con VIH-TV puede verse asociados con un mayor déficit cognitivo. Por ejemplo, son varios los autores que han correlacionado menores volúmenes regionales con un peor rendimiento cognitivo, sin un claro consenso sobre las regiones cerebrales afectadas.[42-44,47,51] Respecto a los estudios de DTI, se postula que los tests neurocognitivos no son lo suficientemente sensibles para detectar alteraciones en la integridad de la WM causadas por el VIH.[56] Sin embargo, esta misma autora señala en un estudio, una posible correlación entre el bajo rendimiento en un test que mide funciones ejecutivas (EF) con una disminución de FA a nivel del tracto longitudinal superior.[57] De forma similar, Uban et al encontraron que una mayor CV se correlacionaba con un peor rendimiento en tests de memorización y una disminución de FA a nivel de tractos fronto-occipitales inferiores derechos. [58]

Respecto a los estudios de RM funcional, únicamente se han realizado 4 estudios en población VIH-TV, tres de ellos en reposo [59-61] y el último, publicado por NeuroCoRISpe y que se integra en esta memoria, de RMf mediante la realización de tareas.[62] Los estudios realizados en reposo (resting-state) muestran en líneas generales que aquellos pacientes con peor control inmunovirológico presentan una conexión entre redes neuronales más pobre. Por el lado contrario, el estudio llevado a cabo por nuestro grupo, se realizó en sujetos con buen control inmunovirológico, no encontrando diferencias con el grupo control, pero si observando que los pacientes que llevaban más años con TAR presentaban una mayor actividad cerebral en determinadas regiones cerebrales (giro frontal inferior izquierdo) durante la realización de una tarea que valoraba la fluidez verbal. Hallazgos similares han sido presentados en población adulta con infección por VIH. [63]

Por tanto, podemos resumir, que la mayoría de los estudios de neuroimagen en población VIH-TV con TAR, postulan que sigue habiendo alteraciones estructurales en regiones cerebrales. Sin embargo, la mayoría de los estudios realizados hasta el momento son transversales, empleando tamaños muestrales reducidos y difieren en la metodología empleada.

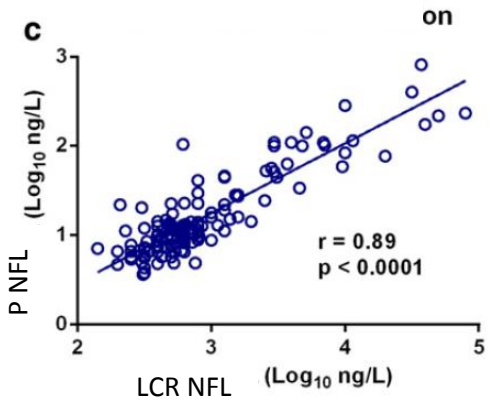
PROTEÍNA DE CADENA LIGERA DEL NEUROFILAMENTO (NFL), COMO BIOMARCADOR DE DAÑO NEURONAL Y ESTUDIOS EN POBLACIÓN VIH

Para comprender mejor cómo se produce el desarrollo del daño neuronal, la activación inmune y la inflamación intratecal, diferentes biomarcadores han sido investigados en LCR, siendo la proteína de cadena ligera del neurofilamento (NfL) el biomarcador más útil para el estudio de la lesión axonal inducida por el VIH.[64] Esta

proteína es uno de los componentes estructurales de las vainas de mielina y es esencial para mantener el calibre axonal, facilitando de esta forma, la conducción nerviosa de forma eficaz. [65]

Sin embargo, la medición de NfL en LCR requiere un procedimiento invasivo, que es la realización de una punción lumbar, por lo que su uso es limitado. Por ello, en los últimos años, se ha desarrollado una nueva técnica mediante inmunoensayo ultrasensible (Simoa) para cuantificar NfL en sangre. Los resultados obtenidos con este nuevo método muestran que la NfL plasmática (pNfL) se correlaciona perfectamente con las concentraciones de NfL en el LCR en todos los estadíos de la infección por VIH. [66] **(Figura 5)**

Figura 5. Correlación entre concentración de NfL plasmático y NfL en LCR



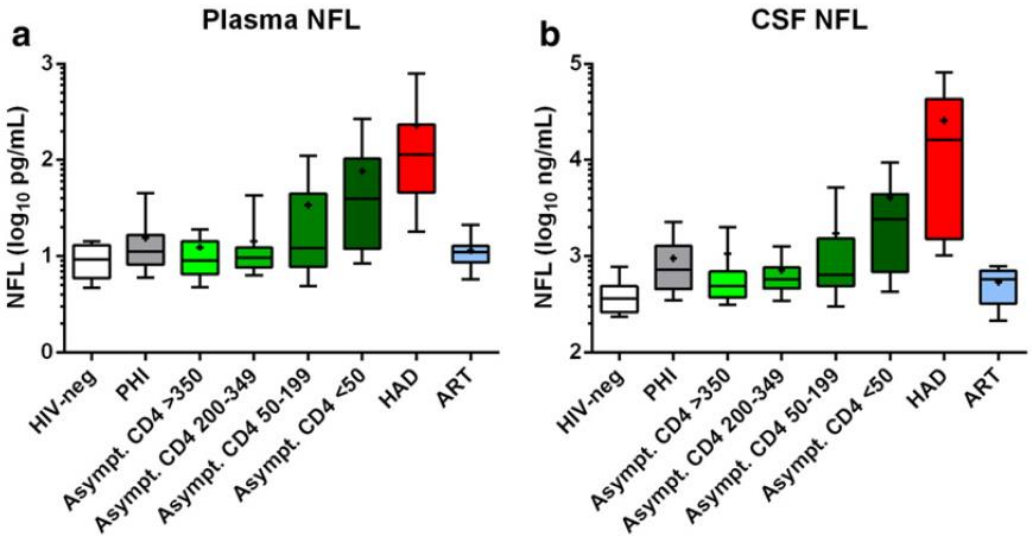
Adaptado de Gisslen et al. Plasma concentration of the neurofilament light protein (NFL) is a biomarker of CNS injury in HIV infection: a cross-sectional study. EBioMedicine. 2016;3:135–140

Es un biomarcador sensible pero no específico, de degeneración neuronal o daño neuronal agudo, y se utiliza como biomarcador en enfermedades neurodegenerativas como el Parkinson, la Esclerosis Múltiple, o el Alzheimer. [67]

Respecto al VIH, varios estudios realizados en adultos infectados por VIH han mostrado un aumento de niveles de NfL en el LCR, en pacientes con demencia asociada al VIH, pero también en pacientes neuroasintomáticos, con recuentos bajos de linfocitos T CD4.[63-67]

Sin embargo, las personas tratadas y virológicamente suprimidas que viven con el VIH tienen niveles más bajos de NfL en LCR, aunque siguen siendo ligeramente más elevados que las personas sin VIH.

Figura: 6. Concentraciones de NFL en plasma (a) y LCR (b) en 7 grupos de sujetos VIH y en un grupo control VIH negativo



Gisslen et al. Plasma concentration of the neurofilament light protein (NFL) is a biomarker of CNS injury in HIV

Hasta el momento no se han desarrollado estudios de NfL en población con VIH de TV.

OBJETIVOS

El objetivo general de esta memoria ha sido:

Estudiar el desarrollo neurológico y el perfil estructural del cerebro en una cohorte de pacientes con infección por VIH de transmisión vertical nacidos en la era preTAR y pertenecientes a CoRISpe (Cohorte Española de VIH pediátrico), y compararlo con una población de características similares sin VIH ni otras comorbilidades neurológicas.

Los objetivos específicos han sido:

1. Determinar el perfil estructural cerebral en un grupo de adolescentes y adultos jóvenes con VIH-TV mediante la medición de grosor cortical y volúmenes de sustancia gris y sustancia blanca subcortical.
2. Comparar dicho perfil con un grupo control sin VIH de características similares pareándolo por sexo, edad, nivel educativo y socioeconómico.
3. Estudiar el efecto del VIH sobre el desarrollo de los ganglios basales, determinando si hay diferencias en función de las variables dependientes del virus y del tratamiento antirretroviral.
4. Analizar y comparar el perfil neurocognitivo evaluando funciones ejecutivas e inteligencia fluida en los dos grupos de estudio.
5. Analizar y comparar posibles alteraciones psicopatológicas en los dos grupos de estudio.
6. Evaluar los patrones de activación neuronal mediante RMf, a través de la realización de tareas motora, y de fluidez verbal en un subgrupo de pacientes VIH-TV con buen control inmunovirológico, adecuadas funciones ejecutivas y funcionales y compararlo con un grupo control de similares características.

7. Analizar las concentraciones plasmáticas de un sensible biomarcador de daño neuronal (neurofilamento de cadena ligera en plasma), en un grupo de pacientes con VIH-TV y compararla con un grupo sin VIH de similares características.
8. Explorar posibles correlaciones entre las concentraciones del neurofilamento de cadena ligera y los volúmenes de sustancia blanca y pruebas neurocognitivas en el grupo con VIH-TV.
9. Describir las características de los estudios de neuroimagen basados en RM estructural y funcional, realizados en población VIH y evaluar que parámetros relacionados con la infección por VIH y características sociodemográficas incluyen dichos estudios.

PUBLICACIONES

CAPÍTULO 1

Efectos de la infección perinatal por VIH sobre el grosor cortical y volumen de sustancia gris subcortical en adultos jóvenes.

JUSTIFICACIÓN Y OBJETIVOS

La esperanza y calidad de vida de los niños y adolescentes con VIH infectados durante el periodo perinatal ha mejorado de forma muy significativa gracias al tratamiento antirretroviral combinado. De la misma forma, la encefalopatía en estos pacientes ha pasado de un 76% a un 1.6%. Sin embargo, el impacto del VIH sobre el desarrollo cerebral en población con VIH-TV sigue siendo una incógnita. Pocos estudios han evaluado las alteraciones en el perfil de neuroimagen en este grupo poblacional, y la mayoría de ellos, se han llevado a cabo en pacientes que viven en países con recursos limitados cuyas características sociodemográficas son muy diferentes.

En la mayoría de ellos se ha observado que los pacientes con VIH-TV presentan atrofia cortical y menor volumen regional o total de sustancia gris y sustancia blanca.

Los objetivos de este capítulo son:

1) Evaluar el desarrollo neurocognitivo mediante una batería de 10 tests neuropsicológicos que miden FE e IF en una cohorte de adolescentes y adultos jóvenes con VIH-TV y compararlo con un grupo control sin VIH de características similares pareándolo por sexo, edad, nivel educativo y socioeconómico.
2) Evaluar posibles alteraciones psicopatológicas a través de escalas estandarizadas de ansiedad (STAI: State-Trait Anxiety Questionnaire) y depresión (BDI: Beck Depression Inventory) en este grupo de estudio, que puedan influir en el desarrollo neurológico.

3) Analizar y comparar el perfil estructural cerebral en el grupo VIH y grupo control, mediante la medición de grosor cortical y volúmenes de sustancia gris subcortical.
4) Estudiar el efecto del VIH sobre el desarrollo de los ganglios basales, determinando si hay diferencias en función de las variables dependientes del virus y del tratamiento antirretroviral.

RESULTADOS

- Veinticinco jóvenes con VIH-TV y 25 controles sin VIH se incluyeron en el estudio.
- Las características sociodemográficas fueron muy similares en ambos grupos: 60% mujeres con una mediana de edad de 20 años en ambos grupos, el 62% presentaba un nivel educativo bajo y el 76% era de etnia caucásica.
- No se encontraron diferencias estadísticamente significativas en los tests neurocognitivos que medían FE e IF ni en las evaluaciones de sintomatología psicopatológica, detectando en ambos grupos que alrededor de un tercio de los participantes presentaban síntomas depresivos leves-moderados, un 6% severo y una prevalencia clínica de ansiedad rasgo 14% y ansiedad estado 10%.
- Dentro del grupo VIH el 40% se encontraba en un estadío C del CDC, y el 12% tenía datos de encefalopatía por VIH previa. La mediana de CD4 nadir fue de 11.4% (RIQ 5-17), y sin embargo la mediana de CD4 actual era superior a 500 cels/mm3 (687 cels/mm3 [RIQ 497–830]). El 100% de los pacientes estaba recibiendo TAR y un 84% mantenían una carga viral por debajo de 50 copias/ml. De los pacientes con carga viral detectable (n = 4), todos tenían <

1000 copias/ml (RIQ 185-530). La mayoría de los pacientes recibía TAR desde hace años: mediana de 17.1 años (RIQ 14.8-18.5 años)

- En el análisis de neuroimagen de grosor cortical definido por el Atlas DK40 mediante SBM, se encontraron diferencias estadísticamente significativas entre el grupo VIH-TV y el grupo control sin VIH. Los pacientes VIH presentaron adelgazamiento cortical en las siguientes áreas: giro fusiforme izquierdo (p =0.000, valor t = 4.766, valor z =4.274) y derecho (p=0.009, valor t = 4.766, valor z = 3.639); giro lateral-orbitofrontal izquierdo (p= 0.006, valor t =3.942, valor z= 3.383) y derecho (p= 0.024, valor t = 3.627, valor z 3.383); y en el giro parsorbitalis derecho (p=0.047, valor t = 3.402, valor z = 3.196). El grupo control sin VIH no presentó adelgazamiento cortical en ninguna región en comparación con el grupo VIH-TV.
- El análisis de volúmenes de sustancia gris subcortical, acorde con el Atlas *Neuromorphometrics* los pacientes con VIH-TV mostraron un menor volumen a nivel de amígdala derecha (p=0.014) y putamen izquierdo (p=0.016) al compararlos con el grupo control VIH negativo.
- Dentro del grupo VIH-TV un mayor recuento de CD4 fue asociado con un mayor volumen a nivel del putamen derecho (b = 0.00000038, p=0.045). Paradójicamente un inicio tardío de del TAR y un nadir de CD4 más bajo fueron asociados a un mayor volumen a nivel del núcleo accumbens izquierdo (b= 0.0000046, p = 0.033; b = -0.00000008, p = 0.0045).
- No se encontraron diferencias en volumen subcortical de sustancia gris total ni en grosor cortical total.

Observational Study

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Effects of perinatal HIV-infection on the cortical thickness and subcortical gray matter volumes in young adulthood

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Abstract

Brain atrophy has been observed in perinatally HIV-infected patients (PHIV) despite initiation on combined antiretroviral treatment (cART), but neuroimaging studies are limited. We aimed to evaluate cortical thickness (CT) and subcortical gray matter (GM) volumes of PHIV youths with stable immunovirological situation and with a normal daily performance.

A prospective cross-sectional study was conducted. A total of 25 PHIV patients on cART and 25 HIV-negative (HIV-) controls matched by age, sex, level of education, and socioeconomic status underwent a magnetic resonance imaging scan. CAT12 toolbox was used to extract CT values from T1w images using parcellations from Desikan–Killiany atlas (DK40). To measure regional brain volumes, native segmented images were parceled in regions of interest according to the Neuromorphometrics Atlas. Neuropsychological assessment and psychopathological symptoms were documented.

Fifty participants were included (60% females, median age 20 years [interquartile range, IQR 19–23], 64% Whites). No differences regarding neuropsychological tests or psychopathological symptoms were found between groups (all $P > .05$). All participants

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The authors report no conflicts of interest.

All data generated or analyzed during this study are included in this published article (and its supplementary information files).

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presented an average performance in the Fluid Intelligence (FI) test (PHIV mean: −0.12, HIV- mean: 0.24), When comparing CT, PHIV-infected patients showed thinner cortices compared with their peers in fusiform gyrus ($P = .000$, $P = .009$), lateral-orbitofrontal gyrus ($P = .006$, $P = .0024$), and right parsobitalis gyrus ($P = .047$). Regarding subcortical GM volumes, PHIV patients showed lower right amygdala ($P = .014$) and left putamen ($P = .016$) volumes when compared with HIV- controls. Within the PHIV group, higher CD4 count was associated with higher volumes in right putamen ($B = 0.00000038$, $P = .045$). Moreover, increased age at cART initiation and lower nadir CD4 count was associated with larger volumes in left accumbens ($B = 0.0000046$, $P = .033$; $B = -0.00000008$, $P = .045$, respectively).

PHIV patients showed thinner cortices of areas in temporal, orbito-frontal and occipital lobes and lower volumes of subcortical GM volumes when compared with the HIV- control group, suggesting cortical and subcortical brain alterations in otherwise neuroasymptomatic patients. Nevertheless, larger and longitudinal studies are required to determine the impact of HIV on brain structure in PHIV patients and to further identify risk and protective factors that could be implicated.

Abbreviations: BDI = Depression Inventory of Beck, BG = basal ganglia, cART = combined antiretroviral treatment, CNS = central nervous system, CT = cortical thickness, DK40 = Desikan–Killiany atlas, DK40 = Desikan–Killiany atlas, EF = Executive Functions, FI = fluid intelligence, GM = gray matter, HAND = HIV-associated neurocognitive disorders, HIV− = HIV negative, IQR = interquartile ranges, K-BIT = Kaufman Brief Intelligence Test, PHIV = perinatally HIV-infected, ROI = regions of interest, SD = standard deviation, SES = socioeconomic status, STAI = measures, State-Trait Anxiety Questionnaire, uVL = undetectable viral load.

Keywords: basal ganglia, cortical thickness, HIV, neuroimaging, perinatal, volume

1. Introduction

One of the most important consequences of the human immunodeficiency virus (HIV) infection is its impact on the central nervous system (CNS).[1] Fortunately, the cases of HIV encephalopathy and severe neurological complications have declined due to the introduction of combined antiretroviral therapy (cART). However, many patients continue to experience milder degrees of HIV-associated neurocognitive disorders (HAND).[2] In this regard, perinatally HIV (PHIV)-infected patients are more vulnerable than adults to displaying CNS alterations as the viral invasion occurs earlier in life.[3]

Additionally, some authors have described limited penetration of cART in the CNS[4] allowing the brain to act as a viral reservoir[5] and making the infection of CNS a generalized condition of HIV patients. It has also been shown that some antiretroviral drugs can sometimes cause neuropsychiatric adverse effects.[6,7] For the aforementioned reasons, finding a balance between the CNS penetration of antiretroviral treatment and possible neurotoxic effects is decisive for the well-being of HIV patients.

It is therefore essential to understand how HIV and cART might mediate in brain development, and to ensure an early detection of HAND. For these purposes, a variety of novel, noninvasive, neuroimaging techniques have been developed to support the quantitative characterization of the brain structure. Preliminary findings of this research in PHIV children and young adults has demonstrated that even in the cART era, there are alterations in microstructural brain regions.[1] However, the outcomes are not consistent,[9] being very difficult to isolate the effect caused by the different psychosocial backgrounds of the selected participants.

The most frequently reported findings have included lower total[3,8,10] or regional cortical and subcortical[8,11,12] gray matter (GM) volumes. Nevertheless, it is interesting that different results have been presented by other authors in recent years, showing increased regional or total GM volumes.[9,13,14] Moreover, although some authors did not find significant differences in cortical thickness (CT) between PHIV patients and HIV- control group,[1] other studies found thinning of certain cortical areas in PHIV patients.[12,15]

Commonly, within the PHIV population the alterations found in brain structure have been usually related to a poor immunovirological status and to the lack of an effective antiretroviral treatment.[9,14,17,18]

Taking into account all these factors and the previous results, the present study attempts to determine the characteristic pattern of cortical thinning and subcortical (total and regional) in a predominant viral suppressed perinatal HIV population with an average cognitive functioning and compare it with an HIV- control group strictly matched by age, sex, level of education, and socioeconomic status. Mindful of the need to restrict the number of statistical comparisons, we also studied the effect of HIV status on all main subregions of the basal ganglia (BG) volumes. In consonance with existing literature, we first hypothesize that the PHIV-infected group will show greater atrophy and thinner cortices in brain structure related to the HIV- controls. Secondly, we tested the hypothesis that a worse immunovirological status will be associated with smaller volumes of the BG since it has been reported to be particularly impacted.[11,12,14,16–18]

2. Materials and methods

2.1. Study design and participants

A cross-sectional study was performed between January 2017 and December 2017.

Initial sample participant number was 30 PHIV patients and 33 HIV-, but 13 participants were excluded (5 PHIV and 8 HIV- controls) due to outlier MRI image quality markers when compared with the sample average quality-assurance measurements.

Twenty-five PHIV patients and 25 HIV- peers, matched by age, sex, educational level, and socioeconomic status participated in a cross-sectional study. Data were collected at 5 pediatric research centers that belong to the CoRISpe (Spanish National Cohort of Pediatric HIV) group.[19]

Patients with current brain infection, neurological or psychiatric disorder, or any congenital abnormality were not included in the sample. Nonetheless, 3 patients with history of encephalopathy were included since they all had normal neuropsychological performances at assessment.

Table 1

Neuropsychological assessment battery.

Cognitive Domains	Subcomponents	Tool	Test
Intelligence	Fluid intelligence	Kaufman Brief Intelligence test[51]	Nonverbal (fluid)
Composite *z* score for executive function (EF10Z)	Processing speed	Stroop Test[52,53]	Stroop-Word
			Stroop-Color
		Wechsler Adult Intelligence Scale-4th edition (WAIS-IV)[54]	Coding subtest
		Trail Making Test[55]	TMT-Part A
	Decision-making, cognitive flexibility, verbal fluency, working memory, planning, inhibition	Trail Making Test[55]	TMT-Part B
		Semantical verbal fluency test[56]	Animals
		Phonological verbal fluency test[56]	*P*
		BADS[57]	Zoo Map
		Stroop Test[52,53]	Stroop-Word-Color
		Wechsler Adult Intelligence Scale-4th edition (WAIS-IV)[54]	Digits-Backward

The HIV- peers were selected from voluntary recruitment through the advertising of the study.

The Institutional Review Boards of each research center approved the study, and a written, informed consent was obtained from all participants in accordance with the Helsinki Declaration. When participants were underage, an assent form was signed by themselves, and their legal guardians provided the informed consent.

2.2. Disease markers in PHIV youth

In relation to the control of the infection, the following parameters were collected: CDC classification, encephalopathy, undetectable viral load (defined as viral load <50 copies/mL), time of undetectable viral load, viral load in detectable patients, total numbers and percentages of CD4 nadir and current CD4 viral load, CD4/CD8 ratio, cART history, and adherence to treatment. This information was obtained from the CoRISpe database.

2.3. Measures

A sociodemographic self-report semistructured questionnaire was created for this project. International Standard Classification of Education (ISCED) criteria were used to categorize the level of education attained by the participants.

Neuropsychological assessment assessed fluid intelligence (FI) through Kaufman Brief Intelligence Test (K-BIT) and Executive Functions (EF) measures by 10 neuropsychological tests (Table 1).

To assess *psychopathological symptoms*, 2 standardized evaluation tools were used State-Trait Anxiety Questionnaire, STAI[20] (Beck, Steer & Carbin, 1988) and Depression Inventory of Beck, BDI.[21]

2.4. Imaging acquisition protocol

Different MRI scanner systems were used at each hospital study site. For specific details of the acquisition parameters, see Supplementary material.

Image quality was assessed in 2 independent processes. Radiologist checked for the presence of any brain pathology, such as tumor, cyst, or any other lesion.

Additionally, image quality and processing experts checked for motion artifacts, low contrasts, incomplete whole brain coverage, low signal-to-noise ratio, and low resolution, excluding 5 PHIV patients and 8 HIV- controls as mentioned above. In a further analysis, all the acquisitions were correlated to determine the homogeneity of the image sample.

2.5. Image processing

2.5.1. Image analysis. The Computational Anatomy Toolbox (CAT12, http://dbm.neuro.uni-jena.de/cat/ version 1492), as an extension of SPM (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/ version 7487), provides a standard processing pipeline for surface and volume-based morphometry. These pipelines allow the extraction of several morphometric parameters including CT and tissue volumes.

For surface data, the processing includes local adaptive segmentation of the T1-weighted images, topological correction,[22] spherical mapping,[23] spherical registration, CT, and central surface estimation.[24]

Mean CT values were calculated inside regions of interest (ROIs) defined by the Desikan-Killiany Atlas (DK40),[25] which is the most extensive in SBM studies and following the standard software procedure.

To measure brain volumes, native segmented images were parceled in ROIs according to the Neuromorphometrics atlas and tissue volumes (cubic millimeters) were estimated for each ROI and normalized by the total intracranial volume for each subject.

2.6. Statistical analysis

2.6.1. Sociodemographic, clinical, cognitive and Psychological assessment. Results were expressed as mean and standard deviation (SD), except for sociodemographical and immunological results which were expressed as median and interquartile ranges (IQRs) for quantitative variables or as frequencies and percentages for qualitative variables. To compare categorical variables Pearson χ^2 or Fisher exact tests were used, whereas quantitative variables were compared using the Mann–Whitney *U* test. All tests with a *P* value <.05 were considered statistically significant. Raw scores on cognitive tests were transformed into a standard form (*z* scores), where the transformation was based on knowledge about the standardization sample mean and SD by each test. SPSS v. 24 was used for data analysis.

Table 2

Means (standard deviation) of demographic, psychosocial, neurocognitive, and psychopathological characteristics.

	PHIV (n=25)	HIV- (n=25)	*P*
Sex (female), % (n)	60% (15)	60% (15)	1.000
Age at assessment, % (n)	20.60 (3.16)	20.40 (2.84)	.815
Level of education, % (n)			
Low	70.8% (17)	63.6% (14)	.294
Medium	16.7% (4)	4.5% (1)	
High	12.5% (3)	31.8% (7)	
Annual income, % (n)			
<12.000 €	21.7% (5)	26.1% (6)	.175
12.000–16.000 €	26.1% (6)	34.8% (8)	
16.001–20.000 €	13% (3)	17.4% (4)	
20.001–26.000 €	13% (3)	13% (3)	
26.001–30.000 €	17.4% (4)	8.7% (2)	
>30.000 €	8.7% (2)	0% (0)	
White, % (n)	76% (19)	52% (13)	.080
STAI-STATE	21.22 (12.99)	15.45 (11.45)	.246
STAI-TRAIT	23.70 (12.40)	21.45 (11.41)	.657
BDI	10.17 (9.60)	10.05 (9.67)	.918
Fluid intelligence*	-0.12 (0.73)	0.24 (0.66)	.059
Composite *z* score for executive function (EF10Z)*	0.26 (0.44)	0.17 (0.51)	.515

* *z* scores <1.0 SD indicate "borderline" cognitive impairment; 1.5 SD indicates minor cognitive impairment and 2.0 SD indicates major cognitive impairment.

Table 3

Clinical measures in PHIV patients (n [%] or median [IQR]).

Age at HIV diagnosis, y	0.50 (0.24–3.44)
CDC Stage C3	10 (40%)
Encephalopathy	3 (12%)
NADIR CD4, cells/mm^3	249 (84–343)
NADIR CD4 (%)	11.9 (5–17)
CD4 count, cells/mm^3	687 (497–830)
CD4 count (%)	32.7 (30–39)
CD4/CD8	0.99 (0.69–1.42)
Age at treatment onset, y	1.4 (0.3–4.2)
Age at onset on cART, y	2.3 (1.4–5.4)
Total time of treatment with cART	17.1 (14.8–18.5)
Number of cART regimens	7 (5–9)
Patients with uVL	21 (84%)
Time with uVL, y	10.8 (6.8–13.1)
VL in detectable patients, copies/mL	416 (185–530)
Type of CART	
2 NRTIs + 1 NNRTI	3 (12%)
2 NRTIs + 1 PI	3 (12%)
2 NRTIs + 1 II	9 (36%)
1 PI + 1 II	3 (12%)
Other combinations	7 (28%)

CART = combination antiretroviral therapy, CDC = Centers for disease Control and Prevention, II = integrase inhibitor, NNRTI = non-nucleotide reverse transcriptase inhibitor, NRTIs = nucleotide reverse transcriptase inhibitors, PI = protease inhibitor, uVL = undetectable viral load, VL = viral load.

2.6.2. Neuroimaging analysis. Mean thickness values for all ROIs were compared between PHIV and HIV- to observe the intergroup differences. A 2-sample *t* test analysis was performed through CAT12 statistical models adjusting for age and sex as nuisance variables.[26] Results were subjected to a multiple comparison Holm-Bonferroni correction and a *P* value <.05 was considered statistically significant.

2.6.3. HIV status and volumes for subcortical GM regions. These procedures resulted in the extraction of volumes for seven bilateral subcortical GM ROIs: the thalamus, putamen, pallidum, amygdala, accumbens, caudate, and hippocampus. Mean volumes inside ROIs were extracted and a linear regression analysis using the forward method was performed to study the effect of HIV-related clinical variables on BG volumes, covarying for age, and sex.

3. Results

3.1. Characteristics of study population

Twenty-five PHIV patients and 25 HIV- controls were enrolled. Sociodemographic characteristics were very similar between cases and controls: 60% were females with a median age of 20 years in both groups, 62% of the participants had low level of education, and 76% of the PHIV patients were Whites. No differences regarding FI, EF10Z, or psychopathological symptoms were found between groups (all $P > .05$, Table 2).

Regarding the PHIV group: 40% showed a previous event that led them to a CDC stage C3, among them 12% (N=3) had encephalopathy. Median CD4 nadir was 11.9% (IQR 5–17); however, at baseline median CD4 was >500 cells/mm^3 (687 cells/mm3 [IQR 497–830]). At the time of the assessment, 100% were under cART, 84% had viral load <50 copies/mL. Among patients with viral load above 50 copies/mL (N=4), all had <1000 copies/mL being the median viral load in detectable patients of 416 copiesp/mL (IQR 185–530). Most of the patients have been receiving cART for long (median time on cART 17.1 years [IQR 14.8–18.5]), being the median time with undetectable viral load (uVL) of 10.8 years (IQR 6.8–13.1) (Table 3).

3.2. CT

Between-group statistical differences in thickness were observed in several areas defined by the DK40 atlas. Specifically, VIH patients present thinner cortex in the left ($P=.000$, t value=4.766, z value=4.274) and right ($P=.009$, t value=3.942, z value=3.639) fusiform gyri, the left ($P=.006$, t value=4.068, z value=3.740) and right ($P=.024$, t value=3.627, z value=3.383) lateral-orbitofrontal gyri, and the right pars orbitalis ($P=.047$, t value=3.402, z value=3.196) (Fig. 1). The opposite contrast (PHIV > HIV-) did not show any significant difference.

3.3. Volumes for subcortical GM regions

Regarding subcortical GM volumes, according to the Neuromorphometrics Atlas PHIV patients showed lower right amygdala ($P=.014$) and left putamen ($P=.016$) volumes when compared with HIV-. No differences were observed between groups for total GM, total white matter, total intracranial volume, or cerebrospinal fluid.

Within the PHIV group, higher CD4 count was associated with higher volumes in right putamen (B=0.00000038, $P=.045$) (Fig. 2). Moreover, increased age of cART initiation and lower nadir CD4 count was associated with larger volumes in left accumbens (B=0.0000046, $P=0.033$; B=−0.00000008, $P=0.045$, respectively).

4. Discussion

In this research, we used surface-based analysis to study CT and BG volumes in PHIV youths compared to a well-matched healthy

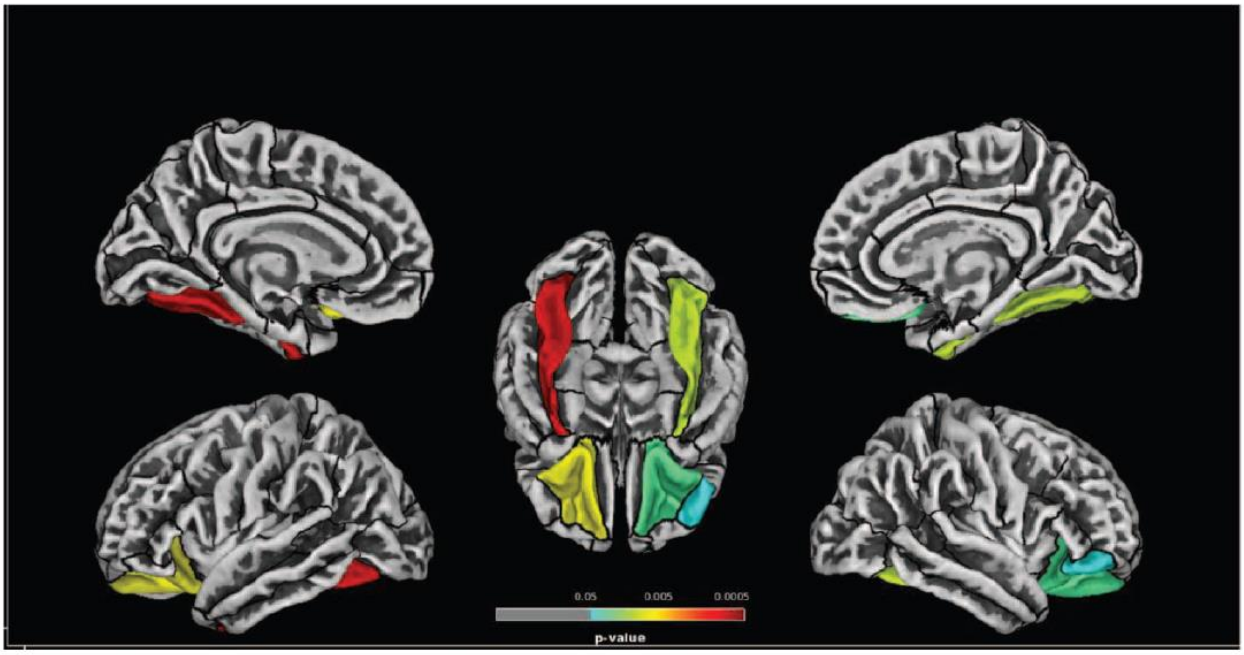

Figure 1. Significant differences in cortical thickness between healthy controls (HIV-) and pediatric HIV patients (PHIV) according to the DK40 atlas parcellation. As shown in the figure, patients present thinner cortex in the bilateral fusiform gyrus, the bilateral orbitofrontal gyrus and the right pars orbitalis (HIV- >PHIV; $P < .05$, Holm-Bonferroni corrected).

control group using two popular atlases. The study detected differences in CT with thinning of different functional areas of the temporal, orbitofrontal, and occipital lobes and lower volumes of right amygdala and left putamen in otherwise well-controlled perinatally HIV-infected youths.

Cortical thinning is a biomarker of neurodegeneration. Recent studies have identified specific atrophy patterns in the most common neurodegenerative diseases. In Alzheimer disease (AD), prominent mesiotemporal and hippocampal atrophy is typically present.[27] Most consistent findings in Parkinson disease studies

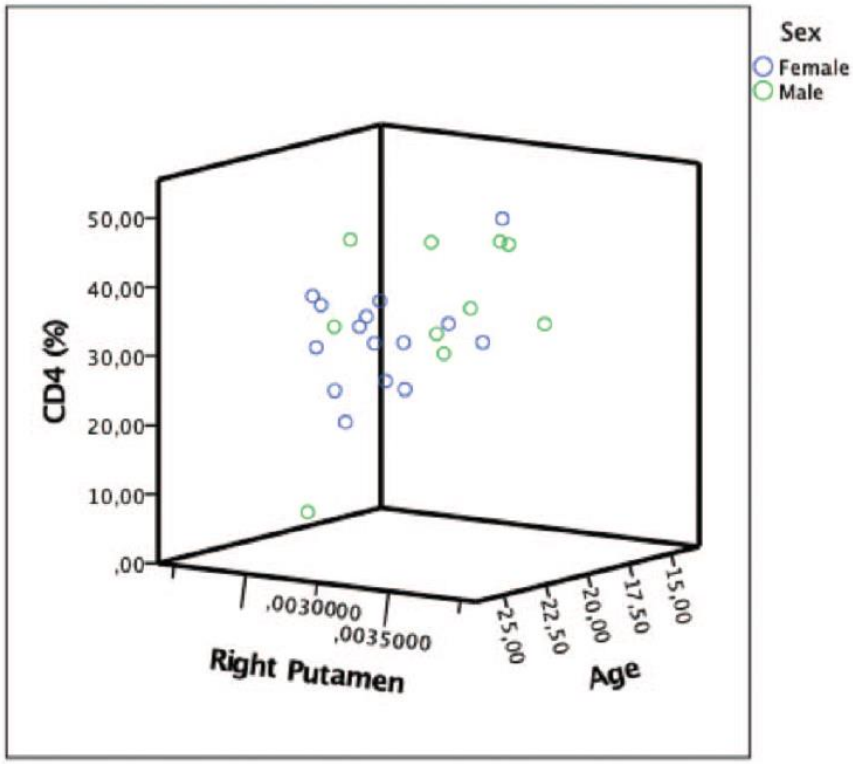

Figure 2. Positive association between CD4 and right putamen volumes (B = 0.00000038, $P = .045$).

show atrophy mainly in the frontal regions.[27] In this regard, increased apparent brain aging, predicted using neuroimaging, has been observed in HIV-positive adults, despite undetectable viral load.[28]

Pathophysiologic mechanisms to explain these alterations in PHIV population could be an early HIV-related CNS damage, as well as ongoing low-grade viral replication and immune activation.[3]

The alterations of neuronal microstructure in the PHIV population found in the present study are supported by previous neuroimaging results. For example, in 2019 Yu et al[15] observed significantly thinner cortices in the temporal and orbitofrontal regions and thicker cortices in left occipital and right olfactory sulcus in HIV patients perinatally infected. Nevertheless, research regarding CT had shown conflicting outcomes in regard to the differences observed between PHIV-infected children and healthy control groups. Nwosu et al[10] found thicker cortex in patients compared to uninfected controls in a small left inferior lateral occipital region. Yadav et al[12] found regional CT decreases in bilateral postcentral and right superior temporal regions, although increases in bilateral medial frontal regions in 10 to 11-year-old PHIV children on cART. It should be noted that some studies did not show any differences in thickness between groups.[1,29]

The difference in thickness between PHIV patients and HIV- orbitofrontal regions could explain the alterations that are frequently shown in those patients whose executive functions are predominantly affected.[30–32] For example, diminished CT in the orbitofrontal area in adolescence correlates to impulsive behavior,[33] and an executive function known as inhibition, deficit of which has been widely described in PHIV patients.[34–36]

We also reported a significant thinning in the fusiform gyrus in PHIV patients compared to healthy controls. This area has been associated with: early atrophy in AD,[37] impact on executive function domains such as working memory[38] and impulsivity,[39] depression,[40] and drug use.[41–43]

With regard to subcortical GM volumes, PHIV patients in our study showed lower right amygdala and left putamen volumes when compared with HIV-. Reductions of amygdala and caudate have been previously reported in the HIV adult population,.[16,44] Similar findings have been described by Li et al[11] in PHIV adolescents, where loss of volume of right pallidum was described.

Within the PHIV group, we found higher volumes of right putamen in patients with higher CD4 count. The association between a low CD4 T-cell count and reduced subcortical regional volumes may indicate that prolonged immunosuppression could play and additional role in CNS damage, explaining the better brain development of well controlled patients. In line with this, Wade et al[18] described increased rates of volume growth in determined subcortical areas in children with higher CD4 counts and similarly, Cohen et al[3] published that longer time with low CD4 T-cell counts was associated with a lower total GM volume.

Furthermore, we found that a delay of cART initiation and lower nadir CD4 count was associated with larger volumes in left accumbens. According to our findings, different studies in the PHIV population showed an enlargement of caudate,[9] nucleus accumbens,[9,12] and putamen[14,45] when compared to a healthy control group. The authors postulated 2 principal hypotheses. First, although the exact pathophysiology for hypertrophy is not well understood, they suggest it could be related to stress-induced hypertrophy of medium spiny neurons resulting in an imperfect pruning. Secondly, BG hypertrophy may be also a result of neuroinflammation, since it is known to be an ongoing detectable process even after cART introduction.[46] Putamen hypertrophy in HIV+ adults has also been attributed to possible inflammation and dopaminergic system dysfunction.[47]

All these results, including the differences in CT between PHIV and negative controls, imply that an earlier and adequate continuous cART is probably the most important key for protection of the CNS.

Nevertheless, it is also important to highlight that although the PHIV showed lower subcortical GM volumes and thinner cortices, no significant differences were found in neurocognitive and neuropsychiatric evaluations, signposting the importance of performing complementary neuroimaging studies that could help detect more subtle neuroalterations not observed by psychometric evaluations.

These neuroimaging findings provide important data, constituting the first neuroimaging study measuring CT and subcortical GM volumes in the White-European PHIV population. Correlations with neuropsychological, psychological, and multiple HIV parameters in PHIV patients have been described. Moreover, it benefits from a meticulous selection of a healthy control group with very similar sociodemographic characteristics similar to the PHIV patients.

Although several studies reflect different results in brain volumes and CT when comparing by age, sex, socioeconomic status, and educational level,[48–50] most of the studies have been performed in African or Asian population where the background can be very different, being most patients CDC stage C, with significant differences in nutritional status and different sociodemographic characteristics. All that may justify the inconsistency of results in the PHIV neuroimaging studies.

This study is no exception in having its limitations, including the cross-sectional design of the study and the reduced number of participants. However, although our sample size is small, it can be considered as representative of younger perinatally HIV-infected adults receiving care in a developed setting, where all the patients are receiving cART and most of them show stable and good immunovirological situation for a long period of time.[51] Cohort studies are usually potentially limited by unmeasured differences, confounding but in our case this was controlled by recruiting a comparable healthy control population with a very similar socioeconomic status. Another limitation is the confounding effects derived from the differences in scanner and head coil parameters between sites. This limitation was minimized by strictly appraising the image quality, assessing the similarity between images from different scanners, thus controlling the comparability. The broad spectrum of findings can be explained since there are no studies using the same neuroimaging analysis tools and atlases, which makes it difficult to generalize and compare results. It is possible that the lack of consensus in terms of MRI analysis techniques and matching processes used are the reasons for the inconsistency of results in the neuroimaging field.

Finally, it is important to take into account that this cohort of young patients with PHIV infection comes from the pre-cART era, which implies that most of these patients received suboptimal treatments during the first years of their lives. There is a chance that the virus could have caused neurological damage during the crucial early years of brain development, highlighting the importance of an earlier and continuous treatment, but there is no way of knowing how or what damage has occurred nor whether it is reversible. Nevertheless, most of these young

patients have been well controlled under cART for >10 years, rendering undetectable or very low detectable viral loads, and all of them exhibit a good daily performance and therefore they constitute a unique group. It could be also very interesting to compare this population with a group of early treated young PHIV adults matched by age, to determine the differences and therefore to try to further clarify the origin of this alterations and if they could be prevented.

5. Conclusion

Despite good control of HIV infection and no differences in neurocognitive evaluation, HIV vertically infected patients showed thinner cortices of the temporal, orbitofrontal, and occipital lobes and lower subcortical GM volumes, although the clinical significance/translation of these findings is still unclear. These results support the need to perform complementary neuroimaging studies that could help to detect more subtle neuroalterations not observed by psychometric evaluations. Moreover, longitudinal follow-up would be important to determine the HIV impact on brain structure in PHIV patients and whether these findings will have a clinical expression in the future.

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References

[1] Hoare J, Fouche J-P, Phillips N, et al. Structural brain changes in perinatally HIV infected young adolescents in South Africa. AIDS 2018;1.

[2] Heaton RK, Franklin DR, Ellis RJ, et al. HIV-associated neurocognitive disorders before and during the era of combination antiretroviral therapy: differences in rates, nature, and predictors. J Neurovirol 2011; 17:3–16.

[3] Cohen S, Caan MWA, Mutsaerts H-J, et al. Cerebral injury in perinatally HIV-infected children compared to matched healthy controls. Neurology 2016;86:19–27.

[4] Letendre S, Marquie-Beck J, Capparelli E, et al. Validation of the CNS Penetration-Effectiveness rank for quantifying antiretroviral penetration into the central nervous system. Arch Neurol 2008;65:65–70.

[5] Van Rie A, Harrington PR, Dow A, et al. Neurologic and neurodevelopmental manifestations of pediatric HIV/AIDS: a global perspective. Eur J Paediatric Neurol 2007;11:1–9.

[6] González-Tomé MI, García-Navarro C, Ruiz-Saez B, et al. Sleep profile and self-reported neuropsychiatric symptoms in vertically HIV-infected adolescents on cART. J Pediatr Infect Dis 2018;13:300–7.

[7] Du Plessis S, Perez A, Fouche J, et al. Efavirenz is associated with altered fronto-striatal function in HIV+ adolescents. J Neurovirol 2019;25:783–91.

[8] Lewis-de Los Angeles CP, Williams PL, Huo Y, et al. Lower total and regional grey matter brain volumes in youth with perinatally-acquired HIV infection: associations with HIV disease severity, substance use, and cognition. Brain Behav Immun 2017;62:100–9.

[9] Paul R, Prasitsuebsai W, Jahanashad N, et al. Structural neuroimaging and neuropsychologic signatures of vertically acquired HIV. Pediatr Infect Dis J 2017;1.

[10] Nwosu EC, Robertson FC, Holmes MJ, et al. Altered brain morphometry in 7-year old HIV-infected children on early ART. Metab Brain Dis 2018;33:523–35.

[11] Li J, Gao L, Wen Z, et al. Structural covariance of gray matter volume in HIV vertically infected adolescents. Sci Rep 2018;8:1182Published 2018 Jan 19.

[12] Yadav SK, Gupta RK, Garg RK, et al. Altered structural brain changes and neurocognitive performance in pediatric HIV. NeuroImage Clin 2017;14:316–22.

[13] Sarma MK, Nagarajan R, Keller MA, et al. Regional brain gray and white matter changes in perinatally HIV-infected adolescents. NeuroImage Clin 2014;4:29–34.

[14] Randall SR, Warton CMR, Holmes MJ, et al. Larger subcortical gray matter structures and smaller corpora callosa at age 5 years in HIV infected children on early ART. Front Neuroanat 2017;11.

[15] Yu X, Gao L, Wang H, et al. Neuroanatomical changes underlying vertical HIV infection in adolescents. Front Immunol 2019;10:814Published 2019 Apr 17.

[16] Ances BM, Ortega M, Vaida F, et al. Independent effects of HIV, aging, and HAART on brain volumetric measures. J Acquir Immune Defic Syndr 2012;59:469–77.

[17] Wade BS, Valcour VG, Wendelken-Riegelhaupt L, et al. Mapping abnormal subcortical brain morphometry in an elderly HIV+ cohort. Neuroimage Clin 2015;9:564–73. Published 2015 Oct 8.
[18] Wade BSC, Valcour VG, Puthanakit T, et al. Mapping abnormal subcortical neurodevelopment in a cohort of Thai children with HIV. NeuroImage Clin 2019;23:101810.
[19] de Jose MI, Jiménez de Ory S, Espiau M, et al. Working groups of CoRISpe and HIV HGM BioBankA new tool for the paediatric HIV research: general data from the Cohort of the Spanish Paediatric HIV Network (CoRISpe). BMC Infect Dis 2013;13:2.
[20] Beck AT, Steer RA, Garbin MC. Psychometric properties of the Beck Depression Inventory: twenty-five years of evaluation. Clin Psychol Rev 1988;8:77–100.
[21] Guillén-Riquelme A, Buela-Casal G. Actualización psicométrica y funcionamiento diferencial del ítem en el State Trait Anxiety Inventory (STAI). Psicothema 2011;23:510–5.
[22] Yotter RA, Nenadic I, Ziegler G, et al. Local cortical surface complexity maps from spherical harmonic reconstructions. Neuroimage 2011;56: 961–73.
[23] Yotter RA, Thompson PM, Gaser C. Algorithms to improve the reparameterization of spherical mappings of brain surface meshes. J Neuroimaging 2011;21:e134–47.
[24] Dahnke R, Yotter RA, Gaser C. Cortical thickness and central surface estimation. Neuroimage 2013;65:336–48.
[25] Desikan RS, Ségonne F, Fischl B, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. NeuroImage 2006;31:968–80.
[26] Barnes J, Ridgway GR, Bartlett J, et al. Head size, age and gender adjustment in MRI studies: a necessary nuisance? NeuroImage 2010;53:1244–55.
[27] Krajcovicova L, Klobusiakova P, Rektorova I. Gray matter changes in Parkinson's and Alzheimer's disease and relation to cognition. Curr Neurol Neurosci Rep 2019;19:85.
[28] Cole JH, Underwood J, Caan MW, et al. Increased brain-predicted aging in treated HIV disease. Neurology 2017;88:1349–57.
[29] Andronikou S, Ackermann C, Laughton B, et al. Corpus callosum thickness on mid-sagittal MRI as a marker of brain volume: a pilot study in children with HIV-related brain disease and controls. Pediatr Radiol 2015;45:1016–25.
[30] Elliott R, Friston KJ, Dolan RJ. Dissociable neural responses in human reward systems. J Neurosci 2000;20:6159–65.
[31] Rich EL, Stoll FM, Rudebeck PH. Linking dynamic patterns of neural activity in orbitofrontal cortex with decision making. Curr Opin Neurobiol 2018;49:24–32.
[32] Huber B, Yeates M, Meyer D, et al. The effects of screen media content on young children's executive functioning. J Exp Child Psychol 2018;170:72–85.
[33] Pehlivanova M, Wolf DH, Sotiras A, et al. Diminished cortical thickness is associated with impulsive choice in adolescence. J Neurosci 2018; 38:2471–81.
[34] Malee KM, Chernoff MC, Sirois PA, et al. Impact of perinatally acquired HIV disease upon longitudinal changes in memory and executive functioning. J Acquir Immune Defic Syndr 2017;75:455–64.
[35] Nichols SL, Chernoff MC, Malee KM, et al. Executive functioning in children and adolescents with perinatal HIV infection and perinatal HIV exposure. J Pediatric Infect Dis Soc 2016;5(suppl 1):S15–23.
[36] Kerr SJ, Puthanakit T, Malee KM, et al. Increased risk of executive function and emotional behavioral problems among virologically well-controlled perinatally HIV-infected adolescents in Thailand and Cambodia. J Acquir Immune Defic Syndr 2019;82:297–304.
[37] Parker TD, Slattery CF, Zhang J, et al. Cortical microstructure in young onset Alzheimer's disease using neurite orientation dispersion and density imaging. Hum Brain Mapp 2018;39:3005–17.
[38] Owens MM, Duda B, Sweet LH, et al. Distinct functional and structural neural underpinnings of working memory. Neuroimage 2018;174: 463–71.
[39] McLaughlin KA, Sheridan MA, Lambert HK. Childhood adversity and neural development: deprivation and threat as distinct dimensions of early experience. Neurosci Biobehav Rev 2014;47:578–91.
[40] Couvy-Duchesne B, Strike LT, de Zubicaray GI, et al. Lingual gyrus surface area is associated with anxiety-depression severity in young adults: a genetic clustering approach. eNeuro 2018;5: ENEURO.0153-17.2017. Published 2018 Jan 19.
[41] Mashhoon Y, Sava S, Sneider JT, et al. Cortical thinness and volume differences associated with marijuana abuse in emerging adults. Drug Alcohol Depend 2015;155:275–83.
[42] Thames AD, Kuhn TP, Williamson TJ, et al. Marijuana effects on changes in brain structure and cognitive function among HIV+ and HIV- adults. Drug Alcohol Depend 2017;170:120–7.
[43] Wang L. Lower total and regional grey matter brain volumes in youth with perinatally-acquired HIV infection: associations with HIV disease severity, substance use, and cognition. Brain Behav Immun 2017;62: 100–9.
[44] Thames AD, Foley JM, Wright MJ, et al. Basal ganglia structures differentially contribute to verbal fluency: evidence from Human Immunodeficiency Virus (HIV)-infected adults. Neuropsychologia 2012;50:390–5.
[45] Blokhuis C, Mutsaerts HJ, Cohen S, et al. Higher subcortical and white matter cerebral blood flow in perinatally HIV-infected children. Medicine (Baltimore) 2017;96:e5891.
[46] Anthony IC, Ramage SN, Carnie FW, et al. Influence of HAART on HIV-related CNS disease and neuroinflammation. J Neuropathol Exp Neurol 2005;64:529–36.
[47] Castelo JMB, Courtney MG, Melrose RJ, et al. Putamen hypertrophy in nondemented patients with human immunodeficiency virus infection and cognitive compromise. Arch Neurol 2007;64:1275–80.
[48] Hair NL, Hanson JL, Wolfe BL, et al. Association of child poverty, brain development, and academic achievement. JAMA Pediatr 2015;169: 822–9.
[49] Noble KG, Houston SM, Brito NH, et al. Family income, parental education and brain structure in children and adolescents. Nat Neurosci 2015;18:773–8.
[50] Piccolo LR, Merz EC, He X, et al. Pediatric imaging, neurocognition, genetics study. age-related differences in cortical thickness vary by socioeconomic status. PLoS One 2016;11:e0162511Published 2016 Sep 19.
[51] UNAIDS data 2018. Global and regional data.
[52] Kaufman AS, Kaufman NL. Manual del Test breve de inteligencia de Kaufman (K-BIT). [Manual for the Kaufman Brief Intelligence Test]. Madrid, Spain: TEA Ediciones; 2000.
[53] Stroop JR. Studies of interference in serial verbal reactions. J Exp Psychol 1935;18:643–62.
[54] Peña-Casanova J, Qui-ones-Ubeda S, Gramunt-Fombuena N, et al. Spanish multicenter normative studies (NEURONORMA Project): norms for the Stroop color-word interference test and the Tower of London-Drexel. Arch Clin Neuropsychol 2009;24:413–29.
[55] Wechsler D. WAIS-IV. Escala de inteligencia de Wechsler para adultos-IV. Manual de aplicación y corrección. Madrid: NCS Pearson, Inc. Edición original; 2012. 2008.
[56] Tamayo F, Casals-Coll M, Sanchez-Benavides G, et al. Spanish normative studies in a young adult population (NEURONORMA young adults Project): norms for the verbal span, visuospatial span, Letter-Number Sequencing, Trail Making Test and Symbol Digit Modalities Test. Neurologia 2012;27:319–29.
[57] Peña-Casanova J, Quiñones-Ubeda S, Gramunt-Fombuena N, et al. Spanish Multicenter Normative Studies (NEURONORMA Project): norms for verbal fluency tests. Arch Clin Neuropsychol 2009;24:395–411.
[58] Wilson BA, Alderman N, Burguess PW, Emslie H, Evans JJ. In: Behavioural Assessment of the Dysexecutive Syndrome (BADS) Souza Ricardo O., Schmidt Sergio L., translators. Bury St Edmunds, U.K.: Thames Valley Test Company; Rio de Janeiro: Cognição; 1996.

CAPÍTULO 2

Revisión sistemática de estudios de resonancia magnética en pacientes VIH de transmisión vertical.

JUSTIFICACIÓN Y OBJETIVOS

En nuestra cohorte de adolescentes y adultos jóvenes con VIH-TV se ha observado un menor volumen regional en áreas de sustancia gris a nivel de putamen y amígdala; menor volumen de sustancia blanca en regiones occipitales y parietales y una mayor atrofia cortical en determinadas regiones de áreas orbitofrontales, temporales y occipitales. Sin embargo, los estudios de neuroimagen realizados en población VIH-TV muestran hallazgos muy diversos, o incluso en ocasiones, contradictorios.

Por otro lado, la mayoría de los estudios no parecen tener en cuenta parámetros determinantes en estudios de neuroimagen, referentes a variables sociodemográficas, clínicas o terapéuticas.

Los objetivos de este capítulo son:

1) Unificar la información sobre los estudios de neuroimagen, que utilizan RM funcional y estructural, realizados en pacientes VIH-TV, con la finalidad de evaluar que regiones cerebrales parecen estar más afectadas en este grupo de población, en función de la técnica empleada.
2) Recoger que variables sociodemográficas, clínicas y terapéuticas son tenidas en cuenta a la hora de realizar estos estudios en población VIH-TV.

RESULTADOS

- En el momento del análisis habían sido publicados 26 estudios (23 de RM estructural y 3 de RM funcional).
- De los 23 estudios de RM estructural, 12 analizaron morfometría cerebral, 9 emplearon DTI, y dos estudios evaluaron ambas técnicas.

- La mayoría de los estudios de morfometría cerebral evidenciaron que los pacientes con VIH-TV presentar un menor volumen en regiones de sustancia gris, un menor grosor cortical y menor desarrollo de las circunvoluciones cerebrales, excepto tres estudios que describen mayor volumen o grosor cortical, y un estudio no encontró ninguna diferencia entre pacientes y grupo control.
- No se puede establecer un consenso sobre, que áreas cerebrales parecen estar más afectadas, aunque en los ganglios basales se encuentran cambios con mayor frecuencia.
- Los estudios de DTI, muestran en líneas generales, una disminución del índice FA (anisotropía fraccional) con un aumento de MD (difusividad media) indicando alteración en la integridad de la sustancia blanca.
- No hay consenso sobre la localización de los tractos neurales más afectados en los estudios de DTI.
- Las alteraciones estructurales en la población VIH, fueron atribuidas con mayor frecuencia a un mal control inmunovirológico.
- Un inicio temprano del TAR parece preservar el grosor cortical y los volúmenes regionales según varios estudios. Dos estudios de volumetría refieren encontrar una correlación entre CD4 actual y volúmenes regionales y un estudio los correlaciona con la integridad de los tractos neurales.
- Los únicos 3 estudios publicados de RM funcional en el momento de realizar la revisión sistemática, muestran que los estudios se realizaron en reposo, y que son lo suficientemente sensibles para detectar alteraciones funcionales en la población VIH.

- La mayoría de los estudios no recogen datos básicos, como son el nivel socioeconómico y educativo, calidad de vida, u otras comorbilidades médicas relacionadas con un peor desarrollo cognitivo, incluido el consumo de drogas, trastornos psiquiátricos, o el estado nutricional en poblaciones con escasos recursos.
- La gran mayoría de estudios recoge muy pocas variables relacionadas con el VIH-TV, obviando la edad al diagnóstico, edad al inicio del TAR, tipo de TAR, clasificación CDC, y la asociación o no de encefalopatía.
- De los 26, únicamente un estudio recoge múltiples datos sociodemográficos y relacionados con la enfermedad por VIH.

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AIDS Rev. (ahead of print)

A Systematic Review of Magnetic Resonance Imaging Studies in Perinatally HIV-Infected Individuals

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Abstract

Over the past few years, neuroimaging studies have been performed in young adults with perinatally acquired HIV (PHIV) to study the impact of HIV infection on the central nervous system (CNS), but no recent reviews have been published. This review aims to identify brain areas where PHIV seems to have greater impact taking into account demographic, behavioral, and clinical characteristics in PHIV infected patients. For this purpose, PubMed and Medline searches were carried out which included studies from 2010 to April 2020. We performed a systematic review and included 26 articles using structural (brain morphometry and diffusion tensor imaging) and functional magnetic resonance imaging methods involving 1182 PHIV-infected participants. Ample evidence has been provided of HIV effects on underlying brain structure. However, information recorded in the studies is commonly incomplete and results sometimes contradictory. In addition to future improvements and dissemination of tools for the developing brain MRI processing and analysis, the inclusion of data related to HIV infection itself (including clinical and immunovirological characteristics importance to the better understanding of the impact of the disease on CNS. (AIDS Rev. 2021;23:1-19)

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Key words

HIV/AIDS. Perinatal. Young adults. Magnetic resonance imaging. Neuroimaging.

Introduction

Despite continuing progress in stopping new HIV infections among children, there are 1.8 million children living with HIV, and approximately 160,000 children became infected in 2018[1]. Neurological complications such as encephalopathy associated with HIV (HIVE) in patients perinatally infected (PHIV) were very common in the pre-antiretroviral therapy (ART) era. The incidence of such complications has been significantly reduced in children with the introduction of combined ART (cART); frequent subtle cognitive or behavioral deficits continue to be present[2].

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Individuals who have been diagnosed with PHIV infection may suffer lifelong difficulties, mostly due to neuropsychiatric or cognitive disorders, including deficits in executive functioning (EF), attention, and processing speed (PS)[3-6].

The mechanisms are still unclear, although different non-exclusive factors that could be implicated in persistent central nervous system (CNS) damage have been proposed: presence of HIV-1 RNA in the CNS compartment, toxicities of the cART and/or persistent low-level inflammation in the CNS[7]. This takes on special importance in PHIV infected patients, since the viral CNS invasion occurs within the 1st weeks of life[8].

On the other hand, cART has completely modified the course of HIV infection to a chronic disease in which life expectancy is similar to the HIV negative population[9]. The initiation of cART in infancy and early childhood probably has a direct effect on the child's maturing CNS.

For this reason, several studies have been performed over the past few years to attempt to identify the impact of HIV severity in the CNS on this population group. For instance, neuroimaging studies have contributed to the diagnosis of CNS disorders in PHIV patients, and advances have significantly helped to define the neurological manifestations of HIV infection since the onset of the AIDS pandemic. One of the most relevant tools is magnetic resonance imaging (MRI), a non-invasive neuroimaging technique that allows high-resolution anatomical images of the brain *in vivo* (structural MRI) to be obtained and the observation of brain activity (functional MRI). The quantification of T1-weighted structural data provides relevant measures of brain volume (grey matter, white matter, and cerebrospinal fluid [CSF]; regional volume estimation; and voxel-based morphometry [VBM]) and cortical thickness, whereas Diffusion-Weighted Imaging (DWI) provides measures of fractional anisotropy (FA) and mean diffusivity (MD). The combination of these varied structural measures allows for estimation of the impact of the disorder on the integrity of brain tissue. In addition, functional MRI (fMRI) characterizes brain activity based on the changes that occur in blood flow, volume, and oxygenation (Blood-Oxygen-Level Dependent signal or BOLD signal)[10]. This enables the observation of the functional networks involved in various cognitive tasks (task-based fMRI[11], as well as networks that remain active at rest resting-state fMRI or rs-fMRI[12]). This functional information is essential to understand the cognitive impact of PHIV infection even in the absence of detectable structural alterations.

The first goal of this article is to review recent neuroimaging research findings in patients with PHIV. Specifically, we aim to identify brain areas where PHIV seems to have greater impact taking into account demographic, behavioral, and clinical characteristics in PHIV infected patients. Two MRI techniques have been used in this study: structural (MRI volumetrics and diffusion tensor imaging [DTI]) and functional (fMRI). Other neuroimaging modalities such as magnetic resonance spectroscopy or positron emission tomography have also been used to study this population but have not been evaluated in this systematic review. Single photon emission computed tomography studies do not appear to have been carried out in the PHIV population.

Method

Literature search

The databases searched were PubMed and Medline revealing articles that describe studies from 2010 to April 2020 that have used structural and fMRI measures to build our knowledge of PHIV-associated CNS alterations. Please see Supplemental Material (S1) for an in-depth description of the keywords searched in each neuroimaging technique described.

Study selection criteria

Three qualified researchers systematically evaluated the keywords, titles, and abstracts associated with each individual article to determine those papers that may have met the inclusion and exclusion criteria. If there was confusion or ambiguity regarding an article, it was reviewed independently by the other coauthors and rejected or retained based on the consensus of the research team. Please see figure 1 for an overview of the study selection.

Results

The results of the current review are presented in sections, with two sections accounting for structural (DTI, volume, and cortical thickness) and functional neuroimaging methods (fMRI). For all studies a descriptive table with socio-demographic, cognitive and psychiatric data (see Supplementary Material S2) and medical features of the clinical sample (Table 1) were devised. For each part, two tables (Table 2 for structural neuroimaging and Table 3 for functional neuroimaging) are presented to include information regarding the methods used in each study and the major findings.

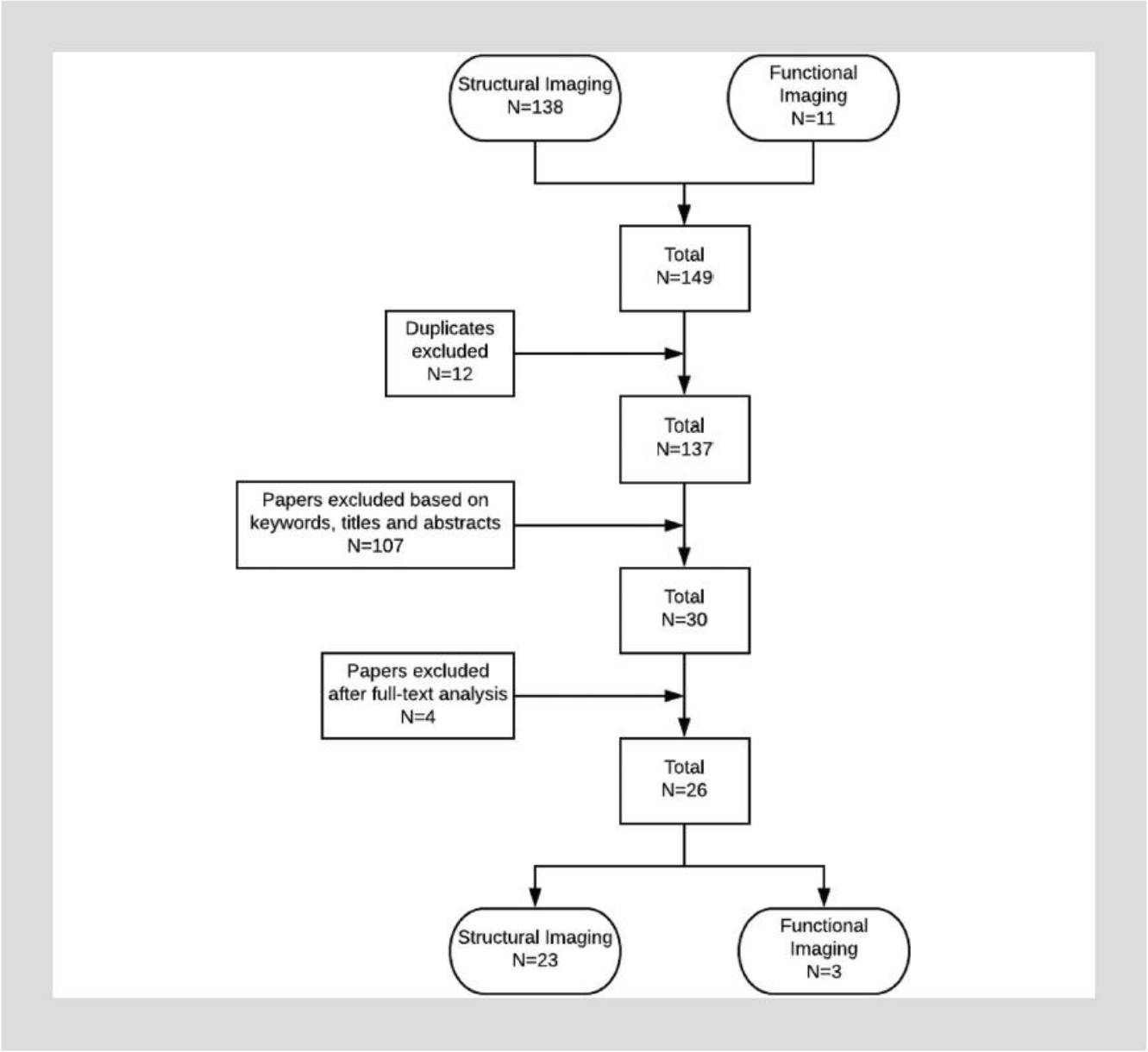

Figure 1. *Literature search flow chart.*

Demographic and behavioral characteristics of the studies selected population

The selected types of neuroimaging studies done on PHIV patients have included 1182 participants[2,13-36]. They have been performed predominantly on sub-Saharan African patients, with seven patients from the Asian population and four Americans. All except four studies have included an HIV negative control group, 50% matched by age (n = 13), 38% by sex (n = 10), and 11% by ethnicity (n = 3). Only two studies matched by years of education and one by socioeconomic status. Fifty percent (n = 13) of the studies have described the education level. Regarding the neuropsychological evaluation, seven papers did not consider cognitive status, and three describe it using screening tools. Among those that used neuropsychological instruments, the main focus with regard to cognitive domains were IQ, PS and EF, with a significant presence of working memory measures included in this last domain.

Only one of the studies included a psychiatric evaluation of the participants, although 27% (n = 7) of the studies referenced psychiatric disorders as exclusion criteria (please see S2).

Clinical measures

The PHIV clinical characteristics that have been recorded and associated with the neuroimaging

Table 1: HIV disease and treatment characteristic

Study	Age at HIV diagnosis (y)	CDC, n (%)	Encephalopathy, n (%)	CD4 Nadir (cells/mm^3, %)	Most recent CD4 at MRI (cells/mm^3, %)	Undetectable viral load, n (%)	HIV on cART, n (%)	Age at cART initiation (years)	Time on cART (years)
Ackermann et al., 2016[13]	NA	NA	NA	NA	cells/mm^3: 1128 (471)	34 (87)	36 (92)	Early cART 0.15 (0.03) Late cART 0.7 (0.3)	NA
Andronikou et al., 2014[15]	NA	NA	0 (0)	cells/mm: 1099 (823-1639) %: 21.4 (16.6-25.6)	cells/mm: 1403 (1026-1766) %: 33.9 (23.9-40.2)	NA	33 (100)	NA	0.29 (0.12)
Andronikou et al., 2015[14]	NA	NA	NA	NA	NA	NA	33 (100)	NA	NA
Cohen et al., 2016[8]	1.2 (0.6-4.9)	N: 4 (13) A: 5 (16) B: 13 (42) C: 9 (29)	2 (8)	Z-score: −0.7 (−1.5-0.4)	cells/mm^3: 800 (590-1.030)	27 (87)	28 (90)	2.2 (0.9-5.2)	11.8 (7.7-14.5)
Herting et al., 2015[16]	NA	NA	2 (6.4)	%: 17 +− 9.5	NA	NA	NA	NA	NA
Hoare et al., 2012[17]	NA	C: 0 (0)	0 (0)	NA	cells/mm^3: 585	11 (91)	0 (0)	-	-
Hoare et al., 2015[18]	NA	NA	NA	NA	NA	NA	NA	NA	NA
Hoare et al., 2015[2]	NA	NA	14 (18.7%)	NA	cells/mm^3: Encephalopathy 1061 ± 464.72 HIV on cART: 1013 ± 552.84 HIV ART naive 615 ± 210	NA	55 (73)	NA	NA
Hoare et al., 2018[19]	NA	NA	NA	NA	cells/mm: 955.12 (587.75)	174 (85)	204 (100%)	3.41	7.18 (2.46)
Hoare et al., 2019[20]	NA	NA	NA	NA	Age of initiation ART < 2 years cells/mm 872.3 (414.54) Age of initiation ART > 2 years cells/mm 989.7 (457.75)	NA	100%	Age of initiation ART < 2 years 1.05 (0.54) Age of initiation ART > 2 years 4.98 (2.41)	Age of initiation ART < 2 years 9.44 (0.73) Age of initiation ART > 2 years 5.75 (2.38)

Table 1: HIV disease and treatment characteristic *(Continued)*

Study	Age at HIV diagnosis (y)	CDC, n (%)	Encephalopathy, n (%)	CD4 Nadir (cells/mm^3, %)	Most recent CD4 at MRI (cells/mm^3, %)	Undetectable viral load, n (%)	HIV on cART, n (%)	Age at cART initiation (years)	Time on cART (years)
Jankiewicz et al., 2017[21]	NA	A: 6 (9) B: 10 (16) C: 49 (75)	8 (12)	cells/mm: 1750 (927) %: 32 (10)	cells/mm^3: 1124 (464) %: 37 (6)	62 (95)	65 (100)	Early cART 0.16 (0.03) Late cART 0.66 (0.34)	Late cART 6.57 (0.37)
Los Angeles et al., 2016[22]	NA	NA	NA	%: 16.5 (8.0-23.8)	%: 35.9 (27.6-2.9)	34 (85)	37 (92)	3.5 (1.4-6.3)	NA
Los Angeles et al., 2017[23]	5.7 (2.2, 10.9)	NA	NA	%: 16.5 (8.0-23.8)	%: 35.9 (27.6-42.9)	34 (85)	37 (92)	NA	NA
Li et al., 2015[24]	NA	NA	0 (0)	NA	cells/mm^3: 605.8 (345.0)	15 (100)	15 (100)	9.5 (3.4)	NA
Li et al., 2018[25]	NA	NA	0 (0)	NA	cells/mm^3: 597 (257)	18 (72)	25 (100)	8.5 (3.3)	6.3 (2.9)
Nwosu et al., 2018[26]	NA	A: 9 (15) B: 19 (32) C: 32 (53)	9 (15)	cells/mm^3: 1899 (914) %: 33 (9.4)	cells/mm^3: 1240 (460) %: cART 36 (6.5)	56 (93)	60 (100)	Early cART 0.16 (0.03) Late cART 0.65 (0.32)	Late cART 6.5 (0.36)
Paul et al., 2018[27]	NA	NA	NA	cells/mm^3: 578 (290-946)	NA	34 (67)	36 (71)	NA	34 (33-42)
Randall et al., 2017[28]	NA	NA	NA	NA	cells/mm^3: 1.029 (677) %: 37 (8)	38 (89)	43 (100)	0.35 (0.31)	Late cART 4.6 (0.46)
Sarma et al., 2013[29]	NA	NA	NA	NA	cells/mm^3: 536 (340)	9 (56)	16 (100)	4.6 (4.8)	NA
Sarma et al., 2019[30]	4.3	NA	NA	NA	cells/mm^3: 630.2 ± 307.5	Log viral load < 1.68: 10	14 (100)	4.9 (4.7)	12.9 (5.3)
Toich et al., 2018[31]	NA	NA	NA	NA	cells/mm^3: 1222 ± 400 %: 36 ± 6	27 (100%)	15 (55) 12 (45) on interrupted cART	10 (8-23)	335 ± 40
Uban et al., 2015[32]	NA	C: 9 (25)	NA	%: 16 (9.5)	%: 33.5 (11.5)	34 (85)	NA	NA	NA
Wade et al., 2019[33]	NA	NA		NA	728 (323)	32 (75)	32 (75)	9.39 (3.23)	NA

(Continues)

Table 1: HIV disease and treatment characteristic *(Continued)*

Study	Age at HIV diagnosis (y)	CDC, n (%)	Encephalopathy, n (%)	CD4 Nadir (cells/mm^3, %)	Most recent CD4 at MRI (cells/mm^3, %)	Undetectable viral load, n (%)	HIV on cART, n (%)	Age at cART initiation (years)	Time on cART (years)
Wang et al., 2018[34]	NA	NA	NA	641.75 ± 291.67	NA	NA	13 (100)	NA	6.50 ± 2.89
Yadav et al., 2017[35]	NA	NA	NA	NA	cells/mm^3: 483 (240)	NA	34 (100)	NA	NA
Yu et al., 2019[36]	NA	NA	0 (0)	NA	558.87 (199.89)	16 (100)	16 (100)	NA	NA

*Data are displayed as mean and SD or median and IQR. NA: not available; SD: standard deviation; IQR: interquartile range; ART: antiretroviral therapy; cART: combined ART, CDC: Centers for Disease Control.

Table 2: Summary information of structural neuroimaging data in each study included

Study	Scanner strength, MRI sequence and acquisition parameters	Analysis software	Measures	Statistical analysis/threshold	Major findings
Ackerman et al., 2016[13]	3T DWI: 30 directions, b factor = NA, TR/TE = 9500/86 ms, FOV = NA, slice thickness = NA, number of slices = NA, gap = NA, acquisition matrix = NA, voxel size = 2 × 2 × 2 mm^3 Sagittal MPRAGE: TR/TE = 2530/1.53/3.19/4.86/6.53 ms, TI = 1160 ms, FOV = 224 × 224 mm^2, flip angle = 7°, number of slices = 144, gap = NA, slice thickness = NA, acquisition matrix = NA, voxel size = 1.3 × 1.0 × 1.0 mm^3	FSL	FA, MD, AD, RD	ANOVA and Chi-square tests $p < 0.05$ (NA)	Two clusters were identified in the right CST, where FA was lower in HIV children than in controls, predominantly due to increased RD. CST rather than the CC were predominantly involved. Children on early-interrupted ART had lower FA compared with those receiving continuous treatment
Andronikou et al., 2014[15]	1.5 T Axial T2 weighted: TR/TE = 5460/103 ms, FOV = NA, acquisition matrix = NA, slice thickness = 5 mm, gap = 1.5 mm, number slices = NA Sagittal T1 weighted: TR/TE = 531/14, FOV = NA, acquisition matrix = NA, slice thickness = 5 mm, gap = 1.5 mm, number of slices = NA	SPM	GM WM, TBV (VBM) y CC thickness and length	Pearson and Spearman $p < 0.05$ (NA)	Premotor segment of the CC mean thickness correlated with age. Motor CC maximum thickness correlated significantly with general developmental quotient; CC length correlated with a diagnosis of acquired microcephaly and to CD4 level closest to date of the MRI scan

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Table 2: Summary information of structural neuroimaging data in each study included *(Continued)*

Study	Scanner strength, MRI sequence and acquisition parameters	Analysis software	Measures	Statistical analysis/threshold	Major findings
Andronikou et al., 2015[14]	1.5 T Axial T2 weighted: TR/TE = 5460/103 ms, FOV = NA, acquisition matrix = NA, slice thickness = 5 mm, gap = 1.5 mm, number slices = NA Sagittal T1 weighted: TR/TE 531/14, FOV = NA, acquisition matrix = NA, slice thickness = 5 mm, gap 1.5mm, N° slices = NA	SPM	GM WM, TBV (VBM) y CC thickness and length	t or Mann–Whitney tests Pearson correlation and Spearman $p < 0.05$ (NA)	There were no significant differences between HIV infected patients and uninfected controls. Significant correlations included overall CC (mean) and total brain volume; prefrontal CC maximum with WM volume; premotor CC mean with TBV and WM volume, premotor CC maximum with WM volume and sensory CC mean with TBV
Cohen et al., 2016[8]	3.0 T DWI (DTI): 64 directions, b factor = 1000 s/mm^2, TR/TE = 9476/92 ms, FOV = 224 × 224 mm^2, slice thickness = NA, number of slices = NA, acquisition matrix = NA, voxel size = 2 × 2 × 2 mm^3 Sagittal MPRAGE: TR/TE = 7.0/3.18 ms; TI = 900 ms; FOV = 256 × 256 mm^2, flip angle = 9°, number of slices = 180, slice thickness = NA, gap = NA, acquisition matrix = NA, voxel size = NA	FSL	tWM, CGM, tGM FA, MD, RD, AD	t or Mann–Whitney U-test, Chi-square test Multivariable linear regression $p < 0.05$ (NA)	A lower GM and WM volume, more WMH, and a higher WM diffusivity were observed in the cases. Within the HIV-infected children, a poorer clinical, immunologic, and virologic state were negatively associated with volumetric, WMH, and diffusivity markers
Hoare et al., 2012[17]	3T MRI DWI: 30 directions, b factor = 1000 s/mm^2, TR/TE = 8800/88 ms, FOV = NA, slice thickness = NA, number slices = NA, gap = NA, acquisition matrix = NA, voxel size = 1.8 × 1.8 × 2 mm^3	FSL	FA, MD, RD	t-test and Pearson $p < 0.05$, corrected	"Slow progressors" had lower FA, higher MD and RD in the CC, and increased MD in the SLF, compared to controls. A correlation was found between poor performance on a test of EF and a test of attention with CC FA, and a test of EF with lowered FA in the SLF
Hoare et al., 2015[18]	3T DWI (DTI): 30 directions, b factor = 1000 s/mm^2, TR/TE = 8800/88 ms, FOV = 220, slice thickness = NA, number of slices = NA, gap = 0, acquisition matrix = NA, voxel size = 1.8 × 1.8 × 2 mm^3	FSL	FA, MD, RD, AD	Multiple regression model $p < 0.05$ (NA)	Decreased FA was associated with being on second-line cART, low hemoglobin, and younger age. Children with increased MD, were younger, had reduced albumin and hemoglobin, and increased VL. Decreased AD was associated with increased VL and total protein, decreased albumin and hemoglobin, younger age, poorer fronto-striatal cognition, and being on second-line cART. Increased RD was associated with younger age, low current CD4 count, low albumin and hemoglobin, and higher VL and total protein

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Table 2: Summary information of structural neuroimaging data in each study included *(Continued)*

Study	Scanner strength, MRI sequence and acquisition parameters	Analysis software	Measures	Statistical analysis/threshold	Major findings
Hoare et al., 2015[2]	3T DWI (DTI): 30 directions, b factor = 1000 s/mm^2, TR/TE = 8800/88 ms, FOV = 220 mm, acquisition matrix = NA, slice thickness = NA, number of slices = NA, gap = 0, acquisition matrix = NA, voxel size = 1.8 × 1.8 × 2 mm^3	FSL (TBSS) pipeline	FA, MD, RD, AD	ANCOVA $p < 0.05$ corrected	Results of the ANCOVA examining DTI indices between healthy control and HIV-infected group revealed decreased FA, indicating damaged neuronal microstructure, in the left cerebral peduncle and fornix of the HIV-infected group Within the HIV-infected group, children with HIV encephalopathy had poor WM integrity when compared to ART-treated children without encephalopathy, and there was significant myelin loss in ART-naive children, compared with ART treated children. ART-treated children had significant axonal damage in the CC
Hoare et al., 2018[19]	3T DWI (DTI): 30 directions, b factor = 1000 s/mm^2, TR/TE = 8800/88 ms, FOV = 220, slice thickness = NA, number of slices = 65, NA, gap = 0, acquisition matrix = NA, voxel size = 1.8 × 1.8 × 2 mm^3 MPRAGE: TR/TE = 2530/1.53/3.21/ 4.89/6.57 ms, TI = 1100 ms, FOV = 256 × 256 mm^2, flip angle = 7°, number of slices = 144, slice thickness = 1 mm, acquisition matrix = NA, voxel size = 1.3 × 1.0 × 1 mm^3	FSL (TBSS) pipeline Freesurfer	FA MD tWM, tGM, CT and cortical surface area	GLM Pearson and Spearman $p < 0.05$ corrected	HIV infected adolescents had significant FA decreases, MD increases, and decreases in cerebral GM volumes, cortical surface area and decreased gyrification. WB mean FA was significantly reduced in the HIV-infected group. There were significant correlation coefficients between greater total GM and WM volume with the WASI and the Becks self-concept subscale. Lower WB FA was associated with higher scores on the Becks anger and disruptive behavior subscales. Higher WB MD was associated with apathy
Hoare et al., 2019[20]	3T DWI: 30 directions, b factor = 1000 s/mm^2, TR/TE = 8800/88 ms, FOV = 220 mm, slice thickness = NA, number of slices = 65, gap = 0, acquisition matrix = NA, voxel size = 1.8 × 1.8 × 2 mm^3 MPRAGE: TR/TE = 2530/1.53/3.21/ 4.86/6.57 ms, TI = 1100 ms, FOV = 256 × 256 mm, flip angle = 7°, number of slices = 144, gap = NA, slice thickness = 1 mm, acquisition matrix = NA, voxel size = 1.3 × 1.0 mm^3	FSL (TBSS) pipeline	FA, MD, RD, AD	ANOVA t-test $p < 0.05$ (NA)	There was a trend towards attention and WM being poorer in the group who initiated ART > 2 years. FA was lower in the > 2-year group in the superior CR, and the external capsule. MD was higher in the > 2-year group in the cerebral peduncle, the superior CR, and the SFOF. RD was higher in the > 2-year group in the superior CR, the cerebral peduncle, and the SFOF. However, the higher AD in the > 2-year group in the superior CR was not in the expected direction

(Continues)

Table 2: Summary information of structural neuroimaging data in each study included *(Continued)*

Study	Scanner strength, MRI sequence and acquisition parameters	Analysis software	Measures	Statistical analysis/threshold	Major findings
Jankiewicz et al., 2017[21]	3T DWI: 30 directions, b factor = 1000 s/mm^2, TR/TE = 10000/86 ms, FOV = 224 × 224 × 144 mm^3, slice thickness = NA, number of slices = NA, gap = NA, acquisition matrix = 112 × 112 × 72, voxel size = 2 × 2 × 2 mm^3. MPRAGE: TR/TE = 2530/1.53/3.19/4.86/6.53 ms, TI = 1160 ms, FOV = 224 × 224 x 144 mm, flip angle = 7°, number of slices = NA, gap = 0, slice thickness = NA, acquisition matrix = NA, voxel size = 1.3 × 1.0 × 1.0 mm^3	TORTOISE FSL general linear model	FA, MD, RD, AD	General linear model (GLM) $p < 0.05$ (NA)	At 7 years, we found two regions in the left IFOF and left ILF with lower FA in HIV+ children compared to controls. Higher MD was observed in a similar region in the IFOF, albeit bilaterally, as well as multiple clusters bilaterally in the superior CR, the anterior thalamic radiation and the right forceps minor. Unlike at 5 years, we found no impact on WM of ART initiation. In HEU children, we found a cluster in the right posterior CR with higher FA compared to HU children, while bilateral regions in the CST demonstrated reduced MD
Los Angeles et al., 2016[22]	3T Sagittal MPRAGE: TR/TE = 2170/4.37 ms, TI = 1100 ms, FOV = 256 × 256 mm, flip angle = 7°, number of slices = 144, gap: NA, slice thickness = NA, acquisition matrix = 256 × 256 × 160, voxel size = 1 × 1 × 1.2 mm^3	Freesurfer	Surface-based shape	Pearson GLM $p < 0.05$ corrected	Negative correlations between shape deformation and peak HIV VL were found in clusters in the caudate tail, globus pallidus, lateral putamen, and anterior and medial thalamus. Positive correlations between shape deformation and nadir CD4% were found in clusters in the medial and posterior thalamus. Inward deformation in caudate and thalamic clusters correlated with worse cognition
Los Angeles et al., 2017[23]	3T Sagittal MPRAGE: TR/TE = 2170/4.37 ms, TI = 1100 ms; FOV = 256 × 256 mm, flip angle = 7°, number of slices = NA, gap = NA, slice thickness = NA, acquisition matrix = NA, voxel size = 1 × 1 × 1.2 mm^3	Freesurfer	Total and regional GM brain volumes	Spearman, t-test, Pearson linear regression models, GLM $p < 0.05$ (NA)	PHIV youth had smaller total and regional GM volumes than HUE and uninfected youth, with smallest volumes seen among PHIV youth with higher past peak VL and recent unsuppressed VL. In PHIV youth, worse cognitive performance correlated with smaller volumes. Among PHIV youth, smaller volumes were also linked to substance use
Li et al., 2015[24]	3T DWI: 20 directions, b factor = 1000 s/mm^2, TR/TE = 6000/87 ms, FOV = 240 × 240 mm, slice thickness = 3 mm, number of slices = NA, gap = NA, acquisition matrix = 128 × 128 zero filed to 256 × 256, voxel size = NA	FSL	FA, MD, RD, AD	Multiple linear regression analysis 1-way analysis of covariance $p < 0.05$, uncorrected	Relative to HIV-negative controls, HIV-positive adolescents demonstrated significantly reduced FA in the CC, superior and posterior CR, frontal and parietal WM, pre-/post-central gyrus, and SLF. In the affected regions, FA reductions were caused by an increase in RD, and no changes were observed in AD. Moreover, FA values in the bilateral frontal WM were negatively correlated with the duration of HAART and were positively associated with the age at onset of HAART

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Table 2: Summary information of structural neuroimaging data in each study included *(Continued)*

Study	Scanner strength, MRI sequence and acquisition parameters	Analysis software	Measures	Statistical analysis/threshold	Major findings
Li et al., 2018[25]	3T Axial MPRAGE: TR/TE = 1900/2.1 ms, TI = 900 ms, FOV = NA, flip angle = 9°; number of slices = 160, gap = NA, slice thickness = 1 mm; acquisition matrix = 320 × 320, voxel size = 1 × 1 mm	SPM12	VBM and structural network analysis (global and regional properties)	t-test, Chi-square test $p < 0.05$, corrected	GM losses were pronounced in ACC, right pallidum, right occipital lobe, inferior parietal lobe, and bilateral cerebellum crus. The global brain network measures were not significantly different between groups; however, the nodal alterations were most pronounced in frontal, temporal, basal ganglia, cerebellum, and temporal lobes. Brain hubs in the HIV-infected subjects increased in number and tended to shift to sensorimotor and temporal areas. In the HIV-infected subjects, decreased GMVs in ACC and bilateral cerebellum were related to lower MMSE scores; the CD4 counts were positively related to the GMVs in ACC and sensorimotor areas
Nwosu et al., 2018[26]	3T MPRAGE: TR/TE = 2530/1.53/3.19/4.86/6.53 ms, TI = 1160 ms, FOV = NA, flip angle = NA, number of slices = 144, gap = NA, slice thickness = NA, acquisition matrix = NA, voxel size = 1.3 × 1.0 × 1.0 mm^3.	Freesurfer	gyrification, regional and total brain volumes	t-test, Chi-square test Linear regression $p < 0.05$	HIV+ children showed reduced gyrification compared to controls in bilateral medial parietal regions, as well as reduced volumes of the right Pu, left hippocampus, and global WM and GM and thicker cortex in small lateral occipital region. Earlier ART initiation was associated with lower gyrification and thicker cortex in medial frontal regions. Early ART appears to preserve CT and volumes of certain brain structures, HIV infection is associated with reduced gyrification in the parietal cortex, and lower Pu and hippocampus volumes
Paul et al., 2018[27]	1.5T MRI Axial 3D SPGR: TR/TE = 11.2/minimum ms, TI = NA, FOV = mm, flip angle = 7°, number of slices = , gap = NA, slice thickness = 1.0mm, acquisition matrix = 256 × 256, voxel size = NA	FSL Freesurfer	caudate, Pu, GP, amygdala, NA, hippocampus, total WM, GM, cortical GM	Chi-square test or Fisher's exact tests and independent t-tests, Linear regression Factor analysis $p < 0.05$ (NA)	HIV- infected children exhibited larger volumes of the caudate, NA, total GM, and cortical GM when compared to the controls. Volumetric differences were predominately evident in children under 12 years of age. Neither cognitive performances nor laboratory markers corresponded to brain volumes in the HIV-infected children

Table 2: Summary information of structural neuroimaging data in each study included *(Continued)*

Study	Scanner strength, MRI sequence and acquisition parameters	Analysis software	Measures	Statistical analysis/threshold	Major findings
Randall et al., 2017[28]	3T MRI Sagittal MPRAGE: TR/TE = 2530/1.53/3.19/4.86/6.53/ms, TI = 1160 ms, FOV = NA, flip angle = 7°, number of slices = 144, gap = NA, slice thickness = NA, acquisition matrix = NA, voxel size = 1.3 × 1.0 × 1.0 mm^3	MultiTracer+ Freesurfer	Basal ganglia and CC	ANOVA Linear regression Multiple regression $p < 0.05$ (NA)	HIV+ children had significantly larger NA and Pu volumes bilaterally and left GP volumes than controls, whilst CC was smaller. Bilateral Pu was larger in both treatment groups compared to controls, while left GP and bilateral NA were enlarged only in ART-After 12 weeks children. CC was smaller in both treatment groups compared to controls, and smaller in ART-After 12 weeks compared to ART-Before 12 Wks. Within infected children, delayed ART initiation was associated with larger Pu volumes, effects that remained significant when controlling for sex and duration of treatment interruption, and lower CD4/CD8 with larger caudates controlling for sex. Volumetric differences were greater in children who initiated ART after 12 weeks
Sarma et al., 2013[29]	3T MPRAGE: TR/TE = 2200/2.34 ms, TI = 900 ms, FOV = 230 × 230 mm, flip angle = 9°, number of slices = 192, gap = NA, slice thickness: 0.9 mm, acquisition matrix = 320 × 320, voxel size = NA	SPM	global and regional GM, WM, and CSF volumes	ANCOVA; uncorrected threshold, $p = 0.001$, uncorrected	WM atrophy appeared in perinatally HIV-infected youths in brain areas including the bilateral posterior CC, bilateral external capsule, bilateral ventral temporal WM, mid cerebral peduncles, and basal pons over controls. GM volume increase was observed in HIV-infected youths including the left superior frontal gyrus, inferior occipital gyrus, gyrus rectus, right mid cingulum, parahippocampal gyrus, bilateral inferior temporal gyrus, and middle temporal gyrus compared with controls. Global WM and GM volumes did not differ significantly between groups
Sarma et al., 2019[30]	3T Axial DWI: 64 directions, b factor = 700 s/mm^2, TR/TE = 10000/90 ms, FOV = 256 × 256 mm, slice thickness = 2 mm, number of slices = 75, gap = 0, acquisition matrix = 130 × 130, voxel size = NA MPRAGE: TR/TE = 2200/2.2 ms, TI = 900 ms, FOV = 240 × 240 mm, flip angle = 9°, number of slices = 176, gap = NA, slice thickness: 1 mm, acquisition matrix = 256 × 256, voxel size = mm^3	SPM	FA, MD, RD, AD	ANCOVA; uncorrected threshold, $p = 0.001$, uncorrected	Regional increases in FA in the PHIV youths were found in left middle frontal gyrus, right precuneus, right lingual gyrus, and left supramarginal gyrus. Increased MD was found in the right precentral gyrus while decreased MD was found in the WM of the right superior parietal lobule and right inferior temporal gyrus/fusiform gyrus. Regions of increased/decreased RD overlapped with regions of increased/decreased MD. Both increased and decreased AD were found in three to four regions respectively

(Continues)

Table 2: Summary information of structural neuroimaging data in each study included *(Continued)*

Study	Scanner strength, MRI sequence and acquisition parameters	Analysis software	Measures	Statistical analysis/threshold	Major findings
Uban et al., 2015[32]	3 T DWI: 30 directions, b factor = 1000 s/mm2, TR/TE = 172,000/86,000 ms, FOV = NA, slice thickness = 2.5 mm, number of slices = NA, gap = NA, acquisition matrix = 96 × 96, voxel size = NA	FSL	FA, MD, RD, AD	ANOVA Pearson Statistical trends were reported (corrected $p < 0.10$)	WB FA was reduced, but RD and MD were increased in PHIV compared with control youth. Within PHIV youth, more severe past HIV disease was associated with reduced FA of the right IFO and left uncinate tracts; elevated MD of the F minor; and increased streamlines comprising the left ILF. Associations of higher peak VL with lower working memory performance were partly mediated by reductions in right IFO FA levels
Wade et al., 2019[33]	1.5 T Axial 3DSPGR: TR/TE = 11.2/minimum ms, FOV = NA, flip angle = , number of slices = NA, gap = NA, slice thickness: 1 mm, acquisition matrix = 256 × 256, voxel size = isotropic	SPM	Thalamus, Pu, pallidum, amygdala, NA, caudate, hippocampus, subcortical shape	Fixed effects multivariate linear regression analyses Longitudinal models $p < 0.05$ (NA)	The PHIV sample were randomized to initiate cART when CD4 counts were 15–24% or when CD4 < 15%. A pallidal subregion was significantly thinner in children with PHIV. Regional thickness, surface area, and volume of the pallidum were associated with CD4 count in children with PHIV. Longitudinal morphometry was not associated with HIV or cART status or timing, however, the trajectory of the left pallidum volume was positively associated with baseline CD4 count
Yadav et al., 2017[35]	3 T Fast spoiled gradient echo FSPGR: TR/TE = 8.4/3.32 ms, TI = 400, FOV = 240 × 240 mm^2, flip angle = 13°, number of slices = NA, gap = NA, slice thickness = 1 mm, acquisition matrix = 512 × 512, voxel size = NA.	Freesurfer	CT and subcortical volumes	t-test, Chi-square test Pearson $p < 0.05$, corrected	Altered CT, subcortical volumes, and abnormal neuropsychological test scores were observed in pediatric HIV patients. The structural network connectivity analysis depicted lower connection strengths, lower clustering coefficients, and higher path length in pediatric HIV patients than HC. The network between ness and network hubs in corticolimbic regions were distorted in pediatric HIV patients

(Continues)

Table 2: Summary information of structural neuroimaging data in each study included *(Continued)*

Study	Scanner strength, MRI sequence and acquisition parameters	Analysis software	Measures	Statistical analysis/threshold	Major findings
Yu et al., 2019[36]	3T Axial MPRAGE: TR/TE = 5000/2.88 ms, TI = 700 ms, FOV = NA, flip angle = 4°, number of slices = 176, gap = NA, slice thickness = 1 mm, acquisition matrix = 256 × 256, voxel size = 1 × 1 mm^2	SPM	VBM (volume change and GMV) and CT	t-test, ANOVA $p < 0.05$, corrected	Cross-sectional studies showed that the GM volume of HIV-infected children was widely reduced in the bilateral frontal, temporal, and insular regions, and cerebellum. Longitudinal studies showed that the GM volume reduction of HIV+ children after 1 year occurs in the advanced functional area of the right prefrontal, parietal lobe and the motor area, cortical thinning of brain regions were sensorimotor cortex and the limbic system. The GM volume of the bilateral cerebellum was positively correlated with the WCST, while the CT of the right dorsolateral prefrontal cortex was negatively correlated with WCST

L: left; R: right; S: superior; i: inferior; a: anterior; p: posterior; FA: fractional anisotropy; RD: radial diffusivity; ART: antiretroviral therapy; HC: healthy controls; CC: *corpus callosum*; GMDS: Griffiths Mental Development Scores; HAART: highly active ART; CD4: CD4 lymphocyte; HIV-: HIV-exposed uninfected; HIV+: HIV-infected; BVT: brain volume Total; CT: cortical thickness; GM: gray matter; WM: white matter; WMH: white matter hyperintensity; WB: whole brain; CDC: Centers for Disease Control; MD: mean diffusivity; SLF: superior longitudinal fasciculus; HEU: HIV exposed uninfected; HU: HIV unexposed uninfected; IFOF: inferior fronto-occipital fasciculus; CST: corticospinal tract; CR: *corona radiata*; ATR: anterior thalamic radiation; WMI: Working Memory Index; PSI: Processing Speed Index; CPI: Cognitive Proficiency Index; GP: *globus pallidus*; VL: viral load; LH: left hemisphere; NA: nucleus accumbens; IC Interior capsule; FLAIR: fluid-attenuated inversion recovery; ACC: anterior cingulate cortex; GMV: GM volume; MMSE: Mini-Mental State Examination; SWI: susceptibility-weighted imaging; IFO: inferior fronto-occipital; ILF: left inferior longitudinal fasciculus; HC: healthy control; FWE: Family Wise Error; TFCE: threshold-free cluster enhancement; WCST: Wisconsin Card Sorting Test; GLM: general linear model, MRI: magnetic resonance imaging; AD, axial diffusivity; NA: not available; CST: corticospinal tract; VBM: voxel-based morphometry; TGM: total GM; TWM: total WM; CGM: cortical GM; EF: executive functioning.

parameters are quite variable, finding predominantly registration of number of patients on cART (23/26), actual CD4 count (21/26), and percentage of patients with undetectable viral load (18/26). Only ten of the 26 studies (38%) have recorded the number of patients with PHIV encephalopathy, and five of those cited this as an exclusion criterion. Five studies (24%) have taken into account the clinical CDC classification of the participants. Moreover, with relation to early initiation of cART, only five studies included this information, and just three of the 26 studies have recorded age at diagnosis (please see Table 1).

Structural neuroimaging

Description of the methods

Structural imaging analysis can currently differentiate neuronal tissue into grey matter, white matter, and CSF measurements in single subjects and across large populations. These *brain morphometry methods* depend on an excellent contrast between different tissues to define grey matter density, grey matter volume, and the inner and outer surface of the cortex. The development of different automatic processing approaches to brain morphometry analysis includes *VBM, deformation-based morphometry (DBM),* and *surface-based morphometry (SBM).*

VBM is a fully automated technique that aims to estimate local differences in tissue composition, after minimizing gross anatomical differences between individuals[37]. The entire brain or specific regions of interest both in healthy subjects and patient groups can be analyzed using VBM[38,39].

While VBM focuses on the residual image variability after subject image transformation, DBM analyses how much the voxel volumes change during subject image registration to the reference template. Using SBM separate features of grey matter anatomy such as surface area, cortical thickness, curvature and volume can be analyzed. SBM differs from VBM and DBM approaches which ultimately analyze image properties at the level of voxels. Surface based cortical thickness measures have the advantage that they allow for subvoxel precision with thickness values being assigned to individual vertices rather than voxels.

DTI is a non-invasive MRI method. The diffusion properties of water in the brain[40] can be used to estimate the integrity of WM tracts using different variables. FA represents an index of the coherence of the diffusion, the degree of myelination of the fibers and

Table 3: Summary information of functional neuroimaging data in each study included

Study	Scanner strength, MRI sequence and acquisition parameters	Analysis software	Modality	Statistical analysis/threshold	Major findings
Herting et al., 2015[16]	3T RS-fMRI: TR/TE = 2000/30 ms, FOV = 64×64 mm^2, flip angle = 75°, Number slices = 33, gap: 4.99, slice thickness: 4 mm, acquisition matrix = NA, voxel size = NA, volumes = 180. MPRAGE: TR/TE = 2170/4.33 ms, TI = 1100 ms, FOV = NA, flip angle = 7°, Number slices = 192, gap: NA, slice thickness: 1.1 mm, acquisition matrix = 256×256, voxel size = NA.	FSL	rs	t-test, Chi-square tests multiple regressions $p < 0.05$, corrected	Global alterations in DMN within- and between-network connectivity, with significant associations between disease severity and DMN BOLD correlations. Furthermore, patterns of connectivity with the posterior cingulate cortex (PCC, p 0,011) and medial prefrontal cortex (mPFC, p 0.006) that varied as a function of peak HIV RNA were found to predict processing speed ability
Toich et al., 2018[31]	3T RS-fMRI: TR/TE = 2000/30 ms, FOV = 220×220×164 mm^3, flip angle = 77°, number of slices = 33, gap = 1mm, slice thickness: 4 mm, acquisition matrix = NA, voxel size = 3.44×3.44×5 mm^3, volumes = 180 Sagital MPRAGE: TR/TE = 2530/1.53/3.19/4.86/6.53 ms, TI = 1160 ms, FOV = 224×224×144 mm^2, flip angle = 7°, number of slices = NA, gap = NA, slice thickness = NA, acquisition matrix = NA, voxel size = 1.3×1 × 1.3 mm^3.	FSL	rs	Regressions $p < 0.05$, NA	No differences within any ICA-generated RSNs between HIV+ and uninfected children, whole brain connectivity to seeds located at RSN connectivity peaks revealed several loci of FC differences, predominantly from seeds in midline regions (posterior cingulate cortex, paracentral lobule, cuneus, and anterior cingulate). Reduced long-range connectivity and increased short-range connectivity suggest developmental delay. Within the HIV+ children, clinical measures at age 7 years was not associated with FC values in any of the RSNs; however, poor immune health during infancy was associated with localized FC increases in the somatosensory, salience and basal ganglia networks
Wang et al., 2018[34]	3T RS-fMRI: TR/TE = 2000/30 ms, FOV = NA, flip angle = 90°, number of slices = 30, gap = 0; slice thickness = 4.5 mm, acquisition matrix = 64×64, voxel size = mm^3, volumes = 210. MPRAGE: TR/TE = 1900/2.1 ms, TI = 900 ms, FOV = NA, flip angle = 9°, number of slices = 176, gap = NA, slice thickness = 1 mm, acquisition matrix = 256×256, voxel size = NA	SPM	rs	t-test, pearson correlation $p < 0.05$, corrected	Significant differences of ReHo values in PHIV+ adolescents compared to PHIV- controls, the areas with ↑ ReHo values include bilateral precentral/post-central gyrus and right middle temporal pole. And the areas with ↓ ReHo values locate in right putamen/pallidum/insula; left caudate/putamen/insula, right superior temporal pole/insula, right caudate/putamen, bilateral anterior cingulate cortex and left inferior temporal pole. Furthermore, age, cognitive scores and nadir CD4+ T-cell counts did not show any significant correlation with altered ReHo values of brain regions neither in PHIV+ groups nor in PHIV- control groups

DMN: default mode network; BOLD: blood-oxygen-level dependent; PCC: posterior cingulate cortex; mPFC: medial prefrontal cortex; RNA: ribonucleic acid; ICA: independent component analysis; RSNS: resting state networks; WB: whole brain; cART: combination antiretroviral therapy; CD4%: CD4 lymphocyte percentage; RS- MRI: magnetic resonance imaging; fMRI: resting state functional MRI; PHACS: Pediatric HIV/AIDS Cohort Study; PHIV: perinatally acquired HIV; FC: functional connectivity; NA: not available, RSNs: resting state networks; ReHo: regional homogeneity.

the degree of axonal damage[41]. This index is the most commonly reported of DTI measures, however, other indices also offer relevant information regarding WM integrity, such as MD, radial diffusivity (RD), and axial diffusivity (AD). MD is an overall measure of displacement of the water molecules and provides information regarding the magnitude of diffusion. A decrease in FA combined with an increase in MD has been suggested to be an indicator of an alteration of WM[42]. AD and RD are indicators of the integrity of the axon and the integrity of the myelin, respectively[43].

Structural neuroimaging in the PHIV population

A summary of structural neuroimaging studies performed in the PHIV+ population are presented in table 2. Initially, 1.5 T field MRI was used to acquire high resolution T1-weighted images, but 3T has been more commonly used in recent studies. SPM, Freesurfer, and FSL are the most widely used analysis software.

Twelve studies used brain morphometry methods (most of them through VBM approach), nine used DTI and two used both methods. With regard to brain morphometry studies comparing PHIV to healthy controls, most of them show reduced GM volumes, cortical surface area and decreased gyrification in the PHIV group except three[27,28,30] which found larger volumes in the same brain areas. One study did not find differences among groups[14]. There is no consensus as to which brain areas seem to be more affected although basal ganglia were often impacted.

In terms of DTI studies, the four most popular indexes were explored in all of them with one exception which only reported FA and MD. Findings seem to agree on FA reduction in the PHIV group and increase in MD within white matter integrity, but no consensus was found regarding the location of these changes depending on the study. For instance, a significant FA reduction was found by some authors in inferior fronto-occipital fasciculus, inferior longitudinal fasciculus[21], whereas this reduction was found by others in superior longitudinal fasciculus (SLF)[24], corticospinal tract[13], or corpus callosum (CC)[17,24] relative to HIV-negative controls.

The alterations in brain structure within the PHIV+ population was related to a poor immunovirological status, in most of the cases defined by high viral load, delayed ART initiation, and lower CD4 count but results are quite variable across the different studies. In general, early ART appears to partially preserve cortical thickness and volumes of certain brain structures[8,26,28], although some abnormalities in white matter are also present in well controlled patients when compared with HIV negative controls[13]. Some authors found associations between actual CD4 count and regional brain volumes[25,33] or brain connectivity[18] but most of them did not. Nevertheless, only one study[8] included complete data about PHIV disease and treatment as recorded in table 1. In this last case, a poorer clinical, immunologic and virologic state were negatively associated with volumetric, WMH, and diffusivity markers.

Several findings suggest that altered cortical and subcortical structures and regional brain connectivity in pediatric HIV patients may contribute to deficits in their cognitive functions[35]. For example, smaller volumes were associated with worse cognitive performance[8,19,23,35,36] with no consensus in the brain structures that experience these changes. However, Paul et al., 2018[27], found that cognitive performances did not correspond to brain volume changes in PHIV-infected children. Where DTI is concerned, some authors posit that similar performance in neurocognitive domains suggests that neurocognitive tests may not be as sensitive as DTI in detecting brain alterations caused by PHIV infection[20]. It is worth noting that some studies have shown some FA changes are sensitive to cognitive performance. Hoare et al.[17] found a correlation between poor performance on a test of EF and a test of attention with CC FA, and a test of EF with lowered FA in the SLF. Similarly, Uban et al.[32] found associations of higher peak viral load with lower working memory performance were partly mediated by reductions in right IFO FA levels. For MD, a negative association with cognition has been described[8,18]. Only one study reported a decrease in AD related to poorer fronto-striatal cognition (PS, EF, and attention)[2].

In overall terms, these studies suggest structural alterations in the PHIV receiving cART. Most studies have been performed cross sectionally, in small samples and differ in terms of neuroimaging methods. International protocols are needed to assess the impact of PHIV-infection on the brain.

fMRI

Description of the method

fMRI is a neuroimaging method that measures brain activity by detecting changes associated with cerebral

blood flow. The neural activity of the brain is indirectly determined by the BOLD response, which is influenced by different factors including cerebral blood flow, blood volume, and the ratio of deoxyhemoglobin to oxyhemoglobin[44].

Two main designs use the BOLD signal to determine the energy used by brain cells: task-related fMRI and resting-state fMRI. Task-related fMRI measures brain activity while someone performs a task while in the scanner. Cerebral blood flow varies depending on the energy required by neurons during a task, and hence the BOLD hemodynamic response, which indirectly represents a measure of neuronal activity[45].

On the other hand, resting-state fMRI reveals the functional connectivity (FC) between distributed neural networks by identifying regions at which the BOLD signal shows temporal coherence. This design offers information about the activity of the brain while the mind is "at rest" and not engaged in tasks.

Several methods to process resting-state fMRI data have been proposed. These can be placed into two groups: model-dependent and model-free methods.

Model-dependent methods ("seed method") are a way of examining the FC of a particular brain region. It is a method that allows for the correlation of the resting-state time-series of the represented brain region against the time-series of all other regions, resulting in a FC map (fcMap) defining the FC of the predefined brain region[46-48]. This region of interest is typically called *seed*.

In contrast to seed-based methods, model-free methods search general patterns of (unique) connectivity across brain structures. Several model-free methods have been suggested and efficiently applied to resting-state time-series, including principal component analysis (PCA)[49], independent component analysis (ICA)[50-52] and hierarchical[53,54], Laplacian[55], and normalized cut clustering[56]. ICA-based methods are the most frequently used and search for a variety of underlying sources that can explain the resting-state patterns, looking for the presence of spatial sources of resting-state signals that are maximally independent from each other. ICA methods can be applied to whole-brain voxel-wise data and as the temporal signals of the independent resting-state components can be easily chosen for further examination of possible group differences between healthy controls and patients. A potential disadvantage of ICA methods might be that the independent components are usually considered more challenging to understand than seed-dependent fcMaps. This could be because they contain a more complex representation of the data, which could confuse the translation of between-group results to clinical relevance[57].

fMRI in the PHIV population

Table 3 summarizes the only three studies that have used resting-state fMRI in PHIV+. 3 T field MRI was used in all studies. SPM and FSL were the software used for analysis.

Evidence of PHIV-related developmental delay has been provided through resting-state FC[16,31,34], showing that young adults with more advanced PHIV disease severity had a "less mature" default mode network. The same regions seem to be at particular risk of alteration in the PHIV population, specifically the medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC), R lateral parietal and occipital cortices, R middle frontal gyrus, L superior frontal gyrus, as well as inferior frontal gyri, although in different hemispheres[16,31].

Wang et al.[34] evaluate regional homogeneity (ReHo) finding differences in several brain areas when compared to a control group. Toich et al.[31], however, found no group differences when using ICA but did find FC differences in whole brain connectivity to seeds located at resting-state networks connectivity peaks revealed several loci, predominantly in the PCC, paracentral lobule, cuneus, and anterior cingulate).

In terms of immunovirological variables, FC was related to viral load and nadir CD4[16] and actual CD4[31]. Wang et al.[34] found no correlation between ReHo and nadir CD4.

In respect of neuropsychological testing only one study[16] evaluated different cognitive domains. Patterns of connectivity with the PCC and mPFC that varied as a function of peak HIV RNA were found to predict PS ability.

Overall, there is preliminary evidence to suggest alterations in FC at rest[16,31,34] finding the method sufficiently sensitive to detect functional alterations in the PHIV population. Further studies are needed with larger sample sizes, better defined control groups, and longitudinal designs.

Conclusions and future directions

All the reviews of neuroimaging research have provided ample evidence that PHIV also has effects on underlying brain structure. Research into the

mechanisms that cause long-term brain disorders is a promising strategy to prevent them. However, there are still limitations, not least of which neuroimaging research is cost- and labor-intensive, and typical studies of only 20-40 patients may be underpowered. The situation is exacerbated in PHIV studies, where recruitment is often more challenging with large variability in multiple variables that often are not recruited. Some of the parameters that would be determinant in neuroimaging studies are missing, such as socioeconomic and health conditions, quality of life, medial characteristics including cART and age at treatment onset, and age at PHIV diagnosis, CDC classification including encephalopathy, other medical comorbidities, including psychiatric disorders or drug use. Furthermore, important factors such as nutrition are not well controlled in African population studies.

High-quality research can be supported by the funding of larger studies, involving collaboration across multiple research groups. However, in spite of the lack of substantial grant funding, researchers can find innovative ways to maximize research resources and boost power through collaboration[58].

Another limitation is that neuroimaging in general, and PHIV brain imaging in particular, contains incomplete, inconsistent, and sometimes contradictory results. This lack of consistency and the differences in techniques account for the variations in research findings[59]. The neuroimaging community has responded to these challenges by synchronizing protocols and data sharing data. Although limited in number, large scale (> 1000 subjects) MRI datasets of healthy infants are available to the scientific community these have not been used in any of the studies reviewed, despite most of the recruited patients being of brain development age. Future PHIV studies ought to employ matching hardware and scan sequences, allowing for comparisons to normative data. While new PHIV imaging studies may want to focus on more specific hypotheses or on more refined imaging technologies, the PHIV community would benefit considerably by also adopting an open-data approach and harmonizing data collection methods and analytical approaches with these larger neuroimaging efforts.

Although remarkable progress has been made, conducting more accurate research has implications studies require more resources, take longer to run / than longitudinal studies, and often yield more conservative results. Solutions including pre-registration of study protocols[60]; transparent reporting of methods and results to limit false interpretations of chance findings[61,62] together with designing studies with sufficient statistical power[58] could have a beneficial impact. On the other hand, transparency can be facilitated by public registration of study protocols and analysis plans before data are collected. This creates an audit trail and clearly delineates confirmatory tests of a priori hypotheses and *post hoc* explorations of data. Statistics should also be openly reported so that others can use the data for power calculations or meta-analysis. Brain volumes means and standard deviations, as well as effect sizes and confidence intervals, should be routinely reported in addition to test statistics and p values. Some of the studies reviewed here did not report actual p values rather than p </> 0.05 which guards against the temptation for rounding errors[63] and did not specify whether results are expressed at an uncorrected or corrected p value threshold.

In summary, this review still found consistent statistical evidence of reduce grey matter volumes, and cortical surface area, decreased gyrification, reduction on FA, and increase in MD in the PHIV-infected group. Furthermore, preliminary data suggest resting-state fMRI is sensitive to detect functional alterations in this population. We believe that future improvements and dissemination of tools for the developing brain MRI processing and analysis will allow us to better chart and understand the dynamic brain developmental trajectories in infants with PHIV-infection, thus informing early diagnosis and intervention.

The inclusion in these studies of data related to PHIV infection itself including clinical and immunovirological characteristics as well as detailed information about antiretroviral treatment such as age at ART initiation may be of vital importance to better understand the impact of the disease on CNS.

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Supplementary data

Supplementary data are available at AIDS Reviews online (http://www.aidsreviews.com/). These data are

provided by the corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole responsibility of the authors.

References

1. UNAIDS. UNAIDS Data 2019 Available from: https://www.unaids.org/en/resources/documents/2019/2019-UNAIDS-data.
2. Hoare J, Fouche JP, Phillips N, Joska JA, Donald KA, Thomas K, et al. Clinical associations of white matter damage in cART-treated HIV-positive children in South Africa. J Neurovirol. 2015;21:120-8.
3. Koekkoek S, de Sonneville LM, Wolfs TF, Licht R, Geelen SP et al. Neurocognitive function profile in HIV-infected school-age children. Eur J Paediatr Neurol. 2008;12:290-7.
4. Judd A, Le Prevost M, Melvin D, Arenas-Pinto A, Parrott F, Winston A, et al. Cognitive function in young persons with and without perinatal HIV in the AALPHI cohort in England: role of non-HIV-related factors. Clin Infect Dis. 2016;63:1380-87.
5. Nachman S, Chernoff M, Williams P, Hodge J, Heston J, Gadow KD. Human immunodeficiency virus disease severity, psychiatric symptoms, and functional outcomes in perinatally infected youth. Arch Pediatr Adolesc Med. 2012;166:528-35.
6. Smith R, Chernoff M, Williams PL, Malee KM, Sirois PA, Kammerer B, et al. Impact of HIV severity on cognitive and adaptive functioning during childhood and adolescence. Pediatr Infect Dis J. 2012;31:592-8.
7. Masters M, Ances, B. Role of neuroimaging in HIV-associated neurocognitive disorders. Semin Neurol. 2014;34:89-102.
8. Cohen S, Caan MW, Mutsaerts HJ, Scherpbier HJ, Kuijpers TW, Reiss P, et al. Cerebral injury in perinatally HIV-infected children compared to matched healthy controls. Neurology. 2016;86:19-27.
9. Justice AC, Modur SP, Tate JP, Althoff KN, Jacobson LP, Gebo KA, et al. Predictive accuracy of the veterans aging cohort study index for mortality with HIV infection: a North American cross cohort analysis. J Acquir Immune Defic Syndr. 2013;62:149-63.
10. Kwong KK, Belliveau JW, Chesler DA, Goldberg IE, Weisskoff RM, Poncelet BP, et al. Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. Proc Natl Acad Sci U S A. 1992;89:5675-9.
11. DeYoe EA, Bandettini P, Neitz J, Miller D, Winans P. Functional magnetic resonance imaging (FMRI) of the human brain. J Neurosci Methods. 1994;54:171-87.
12. Biswal B, Yetkin FZ, Haughton VM, Hyde JS. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. Magn Reson Med. 1995;34:537-41.
13. Ackermann C, Andronikou S, Saleh MG, Laughton B, Alhamud AA, van der Kouwe A, et al. Early antiretroviral therapy in HIV-infected children is associated with diffuse white matter structural abnormality and corpus callosum sparing. AJNR Am J Neuroradiol. 2016;37:2363-9.
14. Andronikou S, Ackermann C, Laughton B, Cotton M, Tomazos N, Spottiswoode B, et al. Corpus callosum thickness on mid-sagittal MRI as a marker of brain volume: a pilot study in children with HIV-related brain disease and controls. Pediatr Radiol. 2015;45:1016-25.
15. Andronikou S, Ackermann C, Laughton B, Cotton M, Tomazos N, Spottiswoode B, et al. Correlating brain volume and callosal thickness with clinical and laboratory indicators of disease severity in children with HIV-related brain disease. Childs Nerv Syst 2014;30:1549-57.
16. Herting MM, Uban KA, Williams PL, Gautam P, Huo Y, Malee K, et al. Default mode connectivity in youth with perinatally acquired HIV. Medicine (Baltimore). 2015;94:1417.
17. Hoare J, Fouche JP, Spottiswoode B, Donald K, Philipps N, Bezuidenhout H, et al. A diffusion tensor imaging and neurocognitive study of HIV-positive children who are HAART-naïve "slow progressors". J Neurovirol. 2012;18:205-12.
18. Hoare J, Fouche JP, Phillips N, Joska JA, Paul R, Donald KA, et al. White matter micro-structural changes in ART-naive and ART-treated children and adolescents infected with HIV in South Africa. AIDS. 2015;29:1793-801.
19. Hoare J, Fouche JP, Phillips N, Joska JA, Myer L, Zar HJ, et al. Structural brain changes in perinatally HIV-infected young adolescents in South Africa. AIDS. 2018;32:2707-18.
20. Hoare J, Heany SJ, Fouche JP, Phillips N, Joska JA, Myer L, et al. Initiation of antiretroviral therapy after the critical neuronal developmental period of the second postnatal year affects white matter microstructure in adolescents living with HIV. J Neurovirol. 2019;25:254-62.
21. Jankiewicz M, Holmes MJ, Taylor PA, Cotton MF, Laughton B, van der Kouwe AJW, et al. White matter abnormalities in children with HIV infection and exposure. Front Neuroanat. 2017;11:88.
22. Los Angeles CP, Alpert KI, Williams PL, Malee K, Huo Y, Csernansky JG, et al. Deformed subcortical structures are related to past HIV disease severity in youth with perinatally acquired HIV infection. J Pediatric Infect Dis Soc. 2016;5:6-14.
23. Los Angeles CP, Williams PL, Huo Y, Wang SD, Uban KA, Herting MM, et al. Lower total and regional grey matter brain volumes in youth with perinatally-acquired HIV infection: associations with HIV disease severity, substance use, and cognition. Brain Behav Immun. 2017;62:100-9.
24. Li J, Wu G, Wen Z, Zhang J, Lei H, Gui X, et al. White matter development is potentially influenced in adolescents with vertically transmitted HIV infections: a tract-based spatial statistics study. AJNR Am J Neuroradiol. 2015;36:2163-9.
25. Li J, Gao L, Wen Z, Zhang J, Wang P, Tu N. Structural covariance of gray matter volume in HIV vertically infected adolescents. Sci Rep. 2018;8:1182.
26. Nwosu EC, Robertson FC, Holmes MJ, Cotton MF, Dobbels E, Little F, et al. Altered brain morphometry in 7-year-old HIV-infected children on early ART. Metab Brain Dis. 2018;33:523-35.
27. Paul R, Prasitsuebsai W, Jahanshad N, Puthanakit T, Thompson P, Aurpibul L, et al. Structural neuroimaging and neuropsychologic signatures in children with vertically acquired HIV. Pediatr Infect Dis J. 2018;37:662-8.
28. Randall SR, Warton CM, Holmes MJ, Cotton MF, Laughton B, van der Kouwe AJW, et al. Larger subcortical gray matter structures and smaller corpora callosa at age 5 years in HIV infected children on early ART. Front Neuroanat. 2017;11:95.
29. Sarma MK, Keller MA, Macey PM, Michalik DE, Hayes J, Nielsen-Saines K, et al. White matter microstructure among perinatally HIV-infected youth: a diffusion tensor imaging study. J Neurovirol. 2019; 25:313-23.
30. Sarma MK, Nagarajan R, Keller MA, Kumar R, Nielsen-Saines K, Michalik DE, et al. Regional brain gray and white matter changes in perinatally HIV-infected adolescents. Neuroimage Clin. 2013;4:29-34.
31. Toich JT, Taylor PA, Holmes MJ, Gohel S, Cotton MF, Dobbels E, et al. Functional connectivity alterations between networks and associations with infant immune health within networks in HIV infected children on early treatment: a study at 7 years. Front Hum Neurosci. 2018;11:635.
32. Uban KA, Herting MM, Williams PL, Ajmera T, Gautam P, Huo Y, et al. White matter microstructure among youth with perinatally acquired HIV is associated with disease severity. AIDS. 2015;29:1035-44.
33. Wade BS, Valcour VG, Puthanakit T, Saremi A, Gutman BA, Nir TM, et al. Mapping abnormal subcortical neurodevelopment in a cohort of Thai children with HIV. Neuroimage Clin. 2019;23:101810.
34. Wang P, Li J, Wang X, Thapa D, Wu GY. Asymptomatic human immunodeficiency virus vertical transmitted adolescents' brain functional changes: based on resting-state functional magnetic resonance imaging. AIDS Res Hum Retroviruses. 2018;34:699-704.
35. Yadav SK, Gupta RK, Garg RK, Venkatesh V, Gupta PK, Singh AK, et al. Altered structural brain changes and neurocognitive performance in pediatric HIV. Neuroimage Clin. 2017;14:316-22.
36. Yu X, Gao L, Wang H, Yin Z, Fang J, Chen J, et al. Neuroanatomical changes underlying vertical HIV infection in adolescents. Front Immunol. 2019;10:814.
37. Ashburner J, Friston KJ. Voxel-based morphometry--the methods. Neuroimage. 2000;11:805-21.
38. Geva S, Baron JC, Jones PS, Price CJ, Warburton EA. A comparison of VLSM and VBM in a cohort of patients with post-stroke aphasia. Neuroimage Clin. 2012;1:37-47.
39. Rowan A, Vargha-Khadem F, Calamante F, Tournier JD, Kirkham FJ, Chong WK, et al. Cortical abnormalities and language function in young patients with basal ganglia stroke. Neuroimage. 2007;36:431-40.
40. Johnson VE, Stewart W, Smith DH. Axonal pathology in traumatic brain injury. Exp Neurol. 2013;246:35-43.
41. Yang E, Nucifora PG, Melhem ER. Diffusion MR imaging: basic principles. Neuroimaging Clin North Am. 2011;21:1-25.
42. Sundman M, Doraiswamy PM, Morey RA. Neuroimaging assessment of early and late neurobiological sequelae of traumatic brain injury: implications for CTE. Front Neurosci. 2015;9:334.
43. Wheeler-Kingshott CA, Cercignani M. About "axial" and "radial" diffusivities. Magn Reson Med. 2009;61:1255-60.
44. Schleim S, Roiser JP. FMRI in translation: the challenges facing real-word application. Front Hum Neurosci. 2009;3:63.
45. Dickerson BC. Advances in functional magnetic resonance imaging: technology and clinical applications. Neurotherapeutics. 2007;4:360-70.
46. Biswal BB, Van Kylen J, Hyde JS. Simultaneous assessment of flow and BOLD signals in resting-state functional connectivity maps. NMR Biomed. 1997;10:165-70.
47. Cordes D, Haughton VM, Arfanakis K, Wendt GJ, Turski PA, Moritz CH, et al. Mapping functionally related regions of brain with functional connectivity MR imaging. AJNR Am J Neuroradiol. 2000;21:1636-44.
48. Jiang T, He Y, Zang Y, Weng X. Modulation of functional connectivity during the resting state and the motor task. Hum Brain Mapp. 2004;22:63-71.
49. Friston KJ. The disconnection hypothesis. Schizophr Res. 1998;30:115-25.

50. Beckmann CF, DeLuca M, Devlin JT, Smith SM. Investigations into resting-state connectivity using independent component analysis. Philos Trans R Soc Lond B Biol Sci. 2005;360:1001-13.
51. Calhoun VD, Adali T, Pearlson GD, Pekar JJ. A method for making group inferences from functional MRI data using independent component analysis. Hum Brain Mapp. 2001;14:140-51.
52. De Luca M, Beckmann CF, De Stefano N, Matthews PM, Smith SM. FMRI resting state networks define distinct modes of long-distance interactions in the human brain. Neuroimage. 2006;29:1359-67.
53. Cordes D, Haughton V, Carew JD, Arfanakis K, Maravilla K. Hierarchical clustering to measure connectivity in fMRI resting-state data. Magn Reson Imaging. 2002;20:305-17.
54. Salvador R, Suckling J, Coleman MR, Pickard JD, Menon D, Bullmore E. Neurophysiological architecture of functional magnetic resonance images of human brain. Cereb Cortex. 2005;15:1332-42.
55. Thirion B, Dodel S, Poline JB. Detection of signal synchronizations in resting-state fMRI datasets. Neuroimage. 2006;29:321-7.
56. van den Heuvel M, Mandl R, Hulshoff Pol H. Normalized cut group clustering of resting-state FMRI data. PLoS One. 2008;3:2001.
57. Fox MD, Raichle ME. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat Rev Neurosci. 2007;8:700-11.
58. Button KS, Ioannidis JP, Mokrysz C, Nosek BA, Flint J, Robinson ES, et al. Power failure: why small sample size undermines the reliability of neuroscience. Nat Rev Neurosci. 2013;14:365-76.
59. Jovicich J, Marizzoni M, Sala-Llonch R, Bosch B, Bartrés-Faz D, Arnold J, et al. Brain morphometry reproducibility in multi-center 3T MRI studies: a comparison of cross-sectional and longitudinal segmentations. Neuroimage. 2013;83:472-84.
60. Dickersin K, Rennie D. The evolution of trial registries and their use to assess the clinical trial enterprise. JAMA. 2012;307:1861-4.
61. Rennie D. CONSORT revised--improving the reporting of randomized trials. JAMA. 2001;285:2006-7.
62. Simera I, Moher D, Hirst A, Hoey J, Schulz KF, Altman DG. Transparent and accurate reporting increases reliability, utility, and impact of your research: reporting guidelines and the EQUATOR Network. BMC Med. 2010;8:24.
63. John LK, Loewenstein G, Prelec D. Measuring the prevalence of questionable research practices with incentives for truth telling. Psychol Sci. 2012;23:524-32.

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PERMANYER

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A Systematic Review of Magnetic Resonance Imaging Studies in Perinatally HIV-Infected Individuals

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Table S1: Database keyword search

Neuroimaging studies	Searched keywords	Total results (*n*)
Structural neuroimaging (including surface-based and diffusion tensor imaging measures)	"HIV"[Title/Abstract] AND "children" [Title/Abstract] AND "white matter"[Title/Abstract]	57
	"HIV"[Title/Abstract] AND "children" [Title/Abstract] AND "surface-based"[Title/Abstract]	0
	"HIV"[Title/Abstract] AND "children" [Title/Abstract] AND "grey matter"[Title/Abstract]	1
	"HIV"[Title/Abstract] AND "perinatal" [Title/Abstract] AND "white matter"[Title/Abstract]	3
	"HIV"[Title/Abstract] AND "perinatal" [Title/Abstract] OR "vertical" [Title/Abstract] AND "grey matter"[Title/Abstract]	1
	"HIV"[All Fields] AND "children" [All Fields] AND "diffusion tensor imaging" [All Fields]	9
	"vertically HIV"[All Fields] AND "diffusion tensor imaging" [All Fields]	4
	"perinatal HIV"[All Fields] AND "diffusion tensor imaging" [All Fields]	3
	"HIV"[Title/Abstract] AND "DWI"[Title/Abstract] AND "perinatal" OR "vertical" [Title/Abstract]	0
	"HIV"[Title/Abstract] AND "VBM"[Title/Abstract] AND "perinatal" OR "vertical" [Title/Abstract]	0
	"HIV"[Title/Abstract] AND "thickness"[Title/Abstract] AND "perinatal" OR "vertical" [Title/Abstract]	4
	"PHIV"[All Fields] AND "diffusion tensor imaging"[All Fields]	1
	"HIV"[All Fields] AND "children" [All Fields] AND "volumetric" [All Fields]	19
	"vertically HIV" [All Fields] AND "volume" [All Fields]	16
	"perinatally HIV" [All Fields] AND "volume" [All Fields]	15
	"HIV"[All Fields] AND "children" [All Fields] AND "morphometric" [All Fields]	4
Functional Neuroimaging (including resting-state and task-based fMRI)	"perinatal HIV"[All Fields] AND "fMRI" [All Fields]	7
	"HIV children" [Title/Abstract] AND "fMRI" [Title/Abstract]	4

DWI: diffusion-weighted imaging; VBM: voxel-based morphometry; PHIV: perinatal HIV; fMRI: functional magnetic resonance imaging.

Table S2. Demographic and behavioral characteristics

Study	Study	No.	Sex* (%males)	Age (years)**	Matched by	Ethnicity	Education (years)***	Neuropsychological tests	Psychiatric Evaluation
Ackerman *et al.*, 2016[13]	*Ackerman *et al.*, 2016	39 HIV+ 13 HIV–	HIV+ 38% HIV– 38%	HIV– 5.7 ± 0.5 HIV+ 5.4 ± 0.3	Age	South Africans	NA	NA	NA
Andronikou *et al.*, 2014[15]	Andronikou *et al.*, 2014†	HIV+ 33	48%	2.5 (0.6-4)	NA	African and mixed-race	NA	GMDS	NA
Andronikou *et al.*, 2015[14]	Andronikou *et al.*, 2015†	HIV+ 33 HIV– 11	HIV– 48% HIV+ 54%	HIV+ 2.5 (0.6-4) HIV– 2.6 (1-4)	NA	African and mixed-race	NA	GMDS	NA
Cohen *et al.*, 2016[8]	*Cohen *et al.*, 2016†	31 HIV+ 37 HIV–	HIV+ 52% HIV– 49%	HIV+ 13.4 (11.4-15.9) HIV– 12.1 (11.5-15.9)	Age, sex, ethnicity, and socioeconomic status.	(Black) HIV+ 81% HIV– 76%	(HIV+ , HIV–) Primary 9,19 High 13,14 Special 7,1 Other 5,3	Verbal IQ, performance IQ, Total IQ, processing speed index, TMT A speed score, digit span, forward and backward, RAVLT immediate and delayed recall, TMT B speed score, and Beery VMI.	exclusion criteria
Herting *et al.*, 2015[16]	Herting *et al.*, 2015‡	HIV+ 31	HIV+ 61%	16.5 ± 2.49	NA	70%African- American 12.5% Hispanic	NA	IQ, Working Memory Index, Processing Speed Index.	NA
Hoare *et al.*, 2012[17]	*Hoare *et al.*, 2012	HIV+ 12 HIV– 12	No=s	HIV+ 10.40 ± 1.45; HIV– 9.83 ± 1.16	Age, sex and ethnicity	Xhosa except one female colored	HIV+ : 3.00 (1.00); HIV– : 2.43 (1.27)	WASI; GPT; Lafayette Instrument Company; Symbol Search, Subtests from the WISC-IV; CTT; RCFT; category fluency test and NEPSY-II Inhibition subtest	NA
Hoare *et al.*, 2015[18]	*Hoare *et al.*, 2015B	HIV+ 75 HIV– 3	HIV+ 59% HIV– 50%	HIV+ 10.03 ± 2.41 HIV– 9.76 ± 2.31	Age, sex and ethnicity	(Black African/mixed) HIV+ 69/4 HIV– 28/2	HIV+ 3.14 (1.86) HIV– 3.07 (1.94)	Subtests from the WISC-IV; CTT; category fluency test and NEuroPSYchological Assessment-II Inhibition subtest.	NA
Hoare *et al.*, 2015[2]	*Hoare *et al.*, 2015A	50 HIV+	46%	9.58 ± 2.08	age and years of education	South African 94% black	2.76	Subtest from WISC-IV, Color Trails 1, Category, Phonetic fluency, Color Trails 2, NEPSY inhibition and switching.	NA
Hoare *et al.*, 2018[19]	Hoare *et al.*, 2018	HIV+ 204 HIV – 44	HIV+ 49% HIV– 45%	HIV+ 10.38 (0.88) HIV– 10.38 (1.09)	Age and sex	(Black African) HIV+ 91% HIV– 100%	HIV+ 3.20 (1.13) HIV– 3.39 (1.35)	WASI	Beck Youth Inventories Children=s Motivation Scale Child Behaviour Checklist
Hoare *et al.*, 2019[20]	Hoare *et al.* 2019	Age of initiation (AoI) ART < 2 years N 46 AoI ART > 2 year N 79	AoI ART < 2 years 63% AoI ART>2 year 47%	Age of initiation ART < 2 years 10.43 (0.83) Age of initiation ART > 2 year 10.49 (0.82)	age, sex, SES, and years of education for neurocognitive testing	South Africa AoI ART < 2 years is0Xhosa=93% AoI ART > 2 year is0Xhosa=90%	Current school grade AoI ART < 2 years 4.09 (1.11) AoI ART > 2 years 4.32 (1.05)	WASI, subtest from the NEPSY-II, Grooved Pegboard Test, Subtests from WISC-IV, The Rey Complex Figure Test, the Boston Naming Test-Short Form-South Africa, verbal fluency, recall trials of the RCFT and the Hopkins Verbal Learning Test-Revised, the Color Trails Test 2.	NA
Jankiewicz *et al.*, 2017[21]	*Jankiewicz *et al.*, 2017	65 HIV+ 46 HIV–	HIV+ 46% HIV– 54%	HIV+ 7.2 ± 0.1 HIV– 7.3 ± 0.1	Age	South Africa HIV+ 56:9 HIV– 37:9	NA	NA	NA
Lewis de los Angeles *et al.*, 2016[22]	Lewis de los Angeles *et al.*, 2016†	40 HIV+	47%	16.7 ± 2.4	NA	Black 73%	NA	WISC-IV and WAIS-IV indices	NA
Lewis de los Angeles *et al.*, 2017[23]	Lewis de los Angeles *et al.*, 2017†	HIV+ 40 HIV– 334	HIV+ 47% HIV– 52%	HIV+ 16.7 ± 2.4 HIV– 16.1 ± 2.7	Age and sex	(Black) HIV+ 73% HIV– 19%	NA	WISC-IV and WAIS-IV. Working memory and processing speed indices to calculate cognitive proficiency index (CPI)	NA
Li *et al.*, 2015[24]	*Li *et al.*, 2015	HIV+ 15 HIV– 26	HIV+ 53% HIV– 50%	HIV+ 15.3 ± 1.3 HIV– 15 ± 1.6	NA	China	HIV+ 7.5 ± 1.2 HIV– 8.7 ± 1.9	MoCA, MMSE	exclusion criteria
Li *et al.*, 2018[25]	Li *et al.*, 2018†	HIV+ 25 HIV– 33	HIV+ 56% HIV– 48%	HIV+ 15.0 ± 1.7 HIV– 14.8 ± 1.6	Age and sex	China	HIV+ 8.0 ± 1.6 HIV– 8.1 ± 1.9	MMSE	exclusion criteria
Nwosu *et al.*, 2018[26]	Nwosu *et al.*, 2018†	HIV+ 60 HIV– 42	HIV+ 47% HIV– 58%	HIV+ 7.20 ± 0.13 HIV– 7.23 ± 0.16	NA	South Africa	NA	KABC	NA
Paul *et al.*, 2018[27]	Paul *et al.*, 2018†	HIV+ 51 HIV– 50 (exposed and unexposed)	HIV+ 33% HIV– 40%	HIV+ 11.4 ± 2.5 HIV– 10.6 ± 2.6	NA	Thai	Kindergarten (2% in both) Elementary (–66, + 73) High school (32%, 25%)	Subtest from the WISC-III, Memory for Beads/Sentences and Memory for Digits/Objects (Stanford Binet). Child Color Trails Test. Beery VMI and Purdue Pegboard.	exclusion criteria
Randall *et al.*, 2017[28]	Randall *et al.*, 2017†	HIV+ 43 HIV– 18	HIV+ 40% HIV– 44%	HIV+ 5.4 ± 0.25 HIV– 5.6 ± 0.50	NA	Black African	NA	NA	NA
Sarma *et al.*, 2014[29]	Sarma *et al.*, 2014†	HIV+ 16 HIV– 14	HIV+ 50% HIV– 64%	HIV+ 17.0 ± 2.9 HIV– 16.3 ± 2.3	Age	Americans	NA	NA	exclusion criteria
Sarma *et al.*, 2019[30]	Sarma *et al.*, 2019	HIV+ 14 HIV– 17	HIV+ 35% HIV– 41%	HIV+ 17.9 ± 2.5 HIV– 18.0 ± 3.0	Age and sex	Americans	NA	NA	NA
Toich *et al.*, 2018[31]	Toich *et al.*, 2018‡	HIV+ 27 HIV– 18	HIV+ 33% HIV– 39%	HIV+ 7.2 ± 0.1 HIV– 7.2 ± 0.2	NA	South Africans	NA	NA	NA
Uban *et al.*, 2015[32]	*Uban *et al.*, 2015	HIV+ 40 HIV– 314	HIV+ 48% HIV– 50%	HIV+ 16.7 ± 2.4 HIV– 16.1 ± 2.7	Age, sex and scanner type	Americans	NA	WISC-IV and WAIS-IV indices	NA
Wade *et al.*, 2019[33]	Wade *et al.*, 2019	HIV+ 43 HIV– 50	HIV+ 46% HIV– 58%	HIV+ 11.09 ± 2.36 HIV– 11.26 ± 2.80	Age	Thailand	high school or greater/up to elementary school HIV+ 18/25 HIV– 23/26	NA	exclusion criteria
Wang *et al.*, 2018[34]	Wang *et al.*, 2018‡	HIV+ 20 HIV– 28	HIV+ 40% HIV– 36%	HIV+ 15.06 ± 1.61 HIV– 15.41 ± 1.5	NA	China	HIV+ 8.1 ± 1.59 HIV– 8.66 ± 1.84	MoCA	NA
Yadav *et al.*, 2017[35]	Yadav *et al.*, 2017†	HIV+ 34 HIV– 32	HIV+ 62% HIV– 53%	HIV+ 10.2 ± 1.7 HIV– 11.2 ± 2.9	NA	Indian	HIV+ 3.93 ± 2.7 HIV– 3.42 ± 2.19	RAKIT	NA
Yu *et al.*, 2019[36]	Yu *et al.*, 2019	HIV+ 16 HIV– exposed uninfected 25	HIV+ 50% HUE 48%	HIV+ 13.63 ± 1.83 HEU 11.2 ± 2.9	Age and sex	China	HIV+ 7.31 ± 2.20 HUE 7.16 ± 1.51	Word Semantics Tets, Verbal Working Memory Test, Wisconsin Card Sorting Test, Picture Memory Test. Indicate the Midpoint Test of the Line Segments.	Exclusion criteria

*Data are displayed as male percentage (%).
†Data are displayed as mean and standard deviation (SD) or median and ranges.
‡Data are displayed as mean and standard deviation (SD) or just mean.
NA: not applicable or available; GMDS: Griffiths Mental Development Scores; IQ: Intelligence quotient; TMT: Trail Making Test; CTT: Color Trails Test NT: neuropsychological testing; WASI: Wechsler Abbreviated Scale of Intelligence; CPI: Cognitive Proficiency Index; WAIS-IV: Wechsler Adult Intelligence Scale, Fourth Edition; RAKIT: Revised Amsterdamse Kinder Intelligence Test; RAVLT: Rey Auditory-Verbal Learning Test; Beery VMI: Beery Development of Visomotor Integration; WASI: Wechsler Abbreviated Scale of Intelligence; GPT: Grooved Pegboard Test; WISC-IV: Wechsler Intelligence Scale for Children—Fourth Edition; CTT: Color Trails Test; RCFT: Rey Complex Figure Test; MoCa: Montreal Cognitive Assessment; MMSE: Mini-Mental State; VIQ: Verbal Intelligence Quotient; PIQ: Performance Intelligence Quotient; KABC: Kaufman Assessment Battery for Children; WISC-III: Wechsler Intelligence Scale for Children-third edition.

CAPÍTULO 3

Medición de la actividad cerebral a través de la RM funcional en jóvenes VIH infectados por transmisión vertical

JUSTIFICACIÓN Y OBJETIVOS

En los últimos años múltiples estudios han combinado los tests neurocognitivos con la RM funcional, una herramienta que mide en tiempo real la actividad cerebral permitiendo una visión directa de los sistemas neuronales. De esta forma, la RMf puede ayudar a dilucidar como las distintas regiones cerebrales se orquestan para ejecutar tareas complejas como leer, memorizar o percibir el espacio.

En población adulta VIH + sin alteraciones cognitivas, se ha demostrado una mayor magnitud de la activación neuronal en determinadas regiones cerebrales que en población sin VIH, sugiriendo un daño incipiente de los sustratos neurales que podría requerir un mayor uso de la reserva neurológica para mantener una adecuada función cognitiva. Sin embargo, hasta ahora, apenas hay datos acerca del uso de la RMf en niños y adolescentes con infección por VIH, y hasta donde sabemos no se han realizado estudios de RMf con realización de tareas en población VIH-TV.

Los objetivos de este capítulo son:

1) Evaluar los patrones de actividad neuronal usando la RMf mediante realización de tareas que miden fluidez verbal y tarea motora en un grupo de adolescentes VIH-TV en estadío no C3 del CDC, con buen control inmunovirológico (CV < 50 copias/ml durante más de 5 años, CD4 > 25%), adecuadas funciones cognitivas y funcionales, comparándolo con un grupo control no VIH de características similares
2) Analizar posibles alteraciones psicopatológicas a través de escalas estandarizadas de ansiedad (STAI: State-Trait Anxiety Questionnaire), y depresión (BDI: Beck Depression Inventory); calidad de vida a través del

cuestionario de salud SF-36; y alteraciones del sueño (PSQI: Pittsburgh Sleep Questionnaire Inventory) que podrían tener relación en la actividad neuronal.

3) Evaluación y comparación de las funciones cognitivas de los participantes en el estudio a través de una batería de tests neurocognitivos que miden inteligencia fluida, atención y velocidad de procesamiento, funciones ejecutivas y habilidades motoras.

RESULTADOS

- Diez pacientes VIH-TV y 10 controles sin VIH participaron en el estudio.
- Las características sociodemográficas fueron muy similares en ambos grupos (60% mujeres, 75% caucásicos, 80% nacidos en España), con una mediana de edad de 19 años (RIQ 17-21.7) y una mediana de número de años de educación de 11.5 años (RIQ 10-12).
- En el cuestionario de salud SF-36, no se encontraron diferencias significativas salvo para la sub-escala de dolor físico (p= 0.042). Respecto al cuestionario sobre calidad del sueño, la mayoría de nuestros pacientes fueron considerados como “buenos dormidores” (70%), sin encontrar diferencias entre pacientes y controles y tampoco se observaron diferencias ES en las escalas de evaluación psicopatológica.
- Basado en los criterios Frascati, confirmamos que el 100% de los pacientes VIH-TV tenían un resultado promedio en los tests neurocognitivos (ninguno de los pacientes presentó más de 1 Z score entre - 1 y -1.99)

- En relación con a las características de los pacientes VIH, la mediana de CD4 fue 780 cels/mm3 (RIQ 580-1056) y la mediana de CD4 nadir fue 14.5% (RIQ 13.2-18). La mediana del cociente CD4/CD8 fue 1.0 (RIQ 0.78-1.20). La mediana de número de años con TAR fue 13.7 años (RIQ 9.6-15.8). La mediana de número de años con CV indetectable fue de 9.5 años (RIQ 5.9-11.7). El 90% (n = 9) pertenecían al estadío B del CDC y 1 paciente pertenecía a estadío A.
- Para la comparación entre los dos grupos, no se observó activación de clusters para ninguno de los contrastes considerados.
- Para el análisis completo de todos los participantes, el movimiento de dedos dio como resultado la activación de los clusters localizados en: Cortex Motor Izquierdo (LMC; MNI coordinadas: - 36, -34, 50), Cerebelo Derecho (RC; 8, -54, -10), Sulcus Intraparietal (IS; 34, -44, 40) y Cortex Premotor Ventral (VPC; 60, 6, 38)
- Para la tarea de fluidez verbal, la “generación de palabras versus repetición de palabras” resultó en una activación de los clusters que engloban al Giro Frontal Inferior Izquierdo (LIFG; -50, 12, 30). En la tarea de fluidez verbal, dentro del grupo VIH a mayor tiempo con TAR se observó una mayor activación de LIFG (r=.648, p=0,043).
- No se observaron asociaciones entre el nadir de CD4 o el valor actual de CD4 y la activación de los clusters durante la realización de tareas de fluidez verbal ni motora

Brain activity in well-controlled perinatally human immunodeficiency virus-infected young adults: a functional magnetic resonance imaging pilot study

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Introduction and aim. Perinatal transmission of human immunodeficiency virus (PHIV) is considered a chronic disease that has highlighted several cognitive deficits. From birth to early adulthood, cognition is known to play a fundamental role. However, although neurocognitive processes associated with PHIV have been extensively described by psychometric testing, data is scarce on neural activity from functional magnetic resonance imaging (fMRI) which provides in vivo physiological information.

Subjects and methods. We studied described impaired cognitive processes using fMRI on a group of PHIV adolescents with good immunovirological indications and healthy matched controls. Psychological status and neurocognitive functions were also assessed.

Results. There were no significant differences between HIV+ and HIV– groups, either on neurocognitive testing nor in fMRI activity for phonological fluency tasks. Prolonged duration of cART was positively associated with greater brain activity in left inferior frontal gyrus (LIFG) which could indicate functional compensation.

Conclusions. These results suggest that neural activity through fMRI in PHIV adolescents with good daily functioning and good immunovirological control may be similar to their peers.

Key words. Adolescents. cART. Fluency. fMRI. Neuroimaging. Perinatal HIV.

Introduction

Perinatally acquired Human Immunodeficiency Virus (PHIV) remains a challenge worldwide. It is well known that HIV is a neurotropic virus that can severely affect the central nervous system (CNS) [1].

In light of new advances in antiretroviral therapy (ART), some manifestations like encephalopathy have decreased dramatically and although the expectation and quality of life (QoL) of patients with HIV infection has improved, new challenges and uncertainties remain.

The presence of neurocognitive deficits has been described in adult and pediatric patients [2,3]. Where infection of the CNS occurs in children the effect on the developing brain could have a greater impact. In this respect, problems in school performance and adaptive functioning have been described in PHIV patients [4,5]. Cognitive deficits most frequently affect executive functions and attention [6].

However, since the real etiology of these findings remains challenging, many factors could be implicated, making it difficult to establish the impact of each one on global development. Malnutrition, prematurity and being exposed to drugs during pregnancy should also be taken into account as their negative impact on neurodevelopment is well known [7]. In addition, neurocognitive deficits have been linked to an impairment in the quality of life and treatment adherence [8].

This explains why in recent years, multiple studies in HIV patients have combined Neurocognitive Testing (NT) with functional Magnetic Resonance Imaging (fMRI) [9], a technique that involves measuring real-time activation of brain systems. For instance, when a task is performed, increased neural activity is associated with metabolic demands that are coupled with a compensatory delivery and consumption of glucose and oxygen. The Blood Oxygen Level Dependent (BOLD) fMRI signal reflects this complex combination of changes in cerebral blood flow, cerebral metabolic rate of oxygen con-

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sumption, and cerebral blood volume [10]. This technique allows for direct insight into the neural systems that can be disrupted during cognition [11].

Nevertheless, data in children and adolescents with PHIV are very scarce and to our knowledge there are no studies available on performing task-related fMRI in PHIV adolescents who were born in the pre-cART era.

Our aim was to study neural activity patterns using fMRI on a group of PHIV adolescents with good cognitive and daily functioning and good immunovirological control compared with a strictly matched group.

Subjects and methods

Study population (inclusion criteria, exclusion criteria)

Twenty right-handed adolescents and young adults from 16 to 25 years of age were included in the study (10 with HIV infection and 10 HIV negative peers). All were matched by age and educational level (±1 years of school). HIV patients were recruited from those who have good current immunovirological control defined as CD4 > 25% plus undetectable viral load (VL) for at least the last 5 years with good adherence to treatment and stable cART for more than one year. Participants were excluded if they presented: a) encephalopathy or AIDS category C3; b) history of active illegal drug consumption during pregnancy; c) coinfection with hepatitis C virus (HCV); d) psychiatric disease, drug or alcohol abuse; e) prematurity, and f) poor performance with daily living activities. Clinical status was confirmed by medical records. Cognitive, psychological and QoL data were only included when administered within six months of fMRI scanning.

Following the recruitment of participants and written informed consent obtained from participants (or from a parent or guardian if the participant was a minor) standard protocol approvals and registrations were obtained. ethical approval was obtained from the ethics committee of every participating hospital. This study was conducted from January 2015 to April 2017. The study is adhered to the Helsinki Declaration.

Disease markers in PHIV youth

In relation to the control of the infection different variables were obtained from CoRISpe database (Cohort of the Spanish Pediatric HIV Network). This network has collected epidemiological, clinical, immunovirological and antiretroviral from HIV-infected children and adolescents, with follow-up in Spanish pediatric units since 2008, as well as retrospective data from children since 1995. Noteworthy among the variables included were: time of undetectability (defined as number of years with a maintained HIV viral load < 50 cop/mL), CDC classification, total numbers and percentages of CD4 nadir and current CD4 viral load, CD4 / CD8 ratio, ART history and adherence to treatment.

MRI acquisitions

Images were acquired with a Philips Achieva 1.5T with a 8Ch SENSE head coil. Echo-planar imaging (TR/TE/flip angle = 3000 ms/50 ms/90 degrees, matrix size = 64 × 64, field of view = 230 × 230) of the brain was performed. A spatial resolution of 3,59 × 3,59 × 4 mm was obtained by acquiring 28 AC–PC aligned axial slices, 4 mm thickness, with no slice gap.

For the study of brain morphology, a T1-weighted structural scan was acquired (sagittal slices to cover the entire brain, FOV 250 × 250, TR = shortest, TE = shortest, flip angle = 8 deg, 1.1 × 1.1 x 1.2 mm voxel size).

fMRI task

On the day of the scanning, subjects performed a brief training session of a shortened version of the paradigm outside of the scanner to ensure complete understanding. All participants indicated that they understood the task requirements.

A verbal fluency task containing a letter-word was used to measure prefrontal brain activation associated with executive function. We used a block design involving presentation of an activation (phonological fluency task) condition for 30 s and a control condition (repetition) for 30 s. This cycle was repeated five times over the course of 5 min and 18 s during which 100 EPI volumes were obtained. Participants were cued by auditory presentation of a letter (i.e., 'A', 'S', 'C') to generate as many different words as possible beginning with that letter. Both groups were instructed to 'think' rather than vocalize the generated words for each trial, so the participants remained in silence during the task and control condition. For the control condition, participants were instructed to repeat constantly the word '*cosa*', ('thing').

Participants from both groups reported that they were able to perform both tasks in the scanner

without difficulty. In addition, six dummy scans were acquired at the beginning of each task to allow for T_1 equilibrium processes.

Cognitive functioning

All participants underwent NT, evaluating intelligence Kaufman Brief Intelligence Test Spanish version (K-BIT [12]), attention and processing speed (WAIS-IV-Digit Span-Forward [13], Trail Making Test A [14], WAIS-IV-Coding [13]), executive function (Trail Making Test B [14], Phonological and Semantic Verbal Fluency [15], Luria-DNA Battery-Attention Control subtest [16], WAIS-IV-Digit Span- Backward-Sequencing [13]) and motor skills (Finger Tapping Test [17]).

Psychological symptoms, sleep quality and quality of life assessment

All patients were evaluated by a clinical psychologist with experience in the diagnosis of psychological disorders. The questionnaires used were:

- State-Trait Anxiety Questionnaire, STAI [18]. Evaluates the current level of anxiety and the predisposition of the person to respond to stress.
- Depression Inventory of Beck, BDI [19]. 21-item self-report instrument designed to assess the severity of depressive symptomatology.
- SF-36 Health Questionnaire [20]. Self-report questionnaire to evaluate health-related CV. It values 8 dimensions: Physical Function, Social Function, Physical Role, Emotional Role, Mental Health, Vitality, Corporal Pain, General Health.
- The Pittsburgh Sleep Quality Index, PSQI [21]. Self-administered questionnaire that evaluates the quality of sleep and alterations in a time interval of 1 month.

Data analysis

Demographic, clinical, cognitive and psychological assessment

Results were expressed as mean and standard deviation (SD) for quantitative variables, except demographical and immunological results. These were expressed as median and interquartile ranges (IQR). Qualitative variables were expressed as frequencies and percentages. To compare categorical variables Pearson χ^2 or Fisher exact tests were used, whereas quantitative variables were compared using the Mann-Whitney U test. All tests with a p value less than 0.05 were considered statistically significant. Raw scores on NT and psychological assessment were transformed into Z-scores, using the test normative data provided by the manufacturers [12-21] adjusted for age (all tests), years of education (*Finger Tapping Test* and Luria) and race (*Finger Tapping Test*), by subtracting the mean and dividing by the SD of test scores based on a national reference population.

Statistical analysis was performed using IBM Statistical Package for the Social Sciences (IBM SPSS Statistics, v.24) (SPSS, Chicago, IL, USA).

fMRI

Functional acquisitions were preprocessed using FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl) version 5.0. The analysis protocol consisted in the following: Structural T_1-weighted volumes were skull-stripped with FSL's bet function. Functional images were processed with FSL's FEAT feature, with the following options: 100 s high-pass filter cutoff, motion correction with MCFLIRT (using the Standard Motion Parameters option), spatial smoothing with a Full Width at Half Maximum value of 8 mm. Brain extraction of functional images with bet. Functional series were linearly registered to each subject's T_1 image using the BBR algorithm, then, individual structural images were linearly registered to MNI standardized space using 12 degrees of freedom.

A general linear model was constructed in which experimental conditions were modeled with blocks. A gamma function convolution of the haemodynamic response function was employed, adding its temporal derivative to the statistical model. Two contrasts were constructed: 'finger motion + touching tips versus rest', for the finger motion task; and 'word generation versus word repetition' for the phonological fluency task.

Group differences in brain activity were assessed by means of a two sample t-test. Then the control and patient groups were entered together in a one sample t-test to elucidate common brain activity. A $Z > 2.3$ voxel-level threshold followed by a family-wise error corrected cluster significance threshold $p < 0.05$ were applied to all tests [22]. The correlation between clinical measures and brain activity scores extracted from activation peaks was then assessed by means of Spearman tests.

Results

Demographic, cognitive, psychological and clinical measures

Twenty subjects were assessed (60% females, 75%

Table I. Demographic and behavioral characteristics of participants.

	Patients	Controls	*p* value
Demographic Characteristics	*n* (%)	*n* (%)	
Caucasian	8 (80%)	7 (70%)	0.356
Born in Spain	8 (80%)	8 (80%)	1
Age at assessment in years (median, IQR)	19 (17-22)	20 (17-21)	0.854
Female gender	7 (70%)	5 (50%)	0.361
Currently working	3 (30%)	0 (0%)	0.211
Exercise regularly	6 (60%)	8 (80%)	0.403
Good sleeper	7 (70%)	4 (40%)	0.178
Single	6 (60%)	4 (40%)	0.398
Years of education (median, IQR)	11 (10-12)	12 (10-12)	0.371
Cognitive measures	Mean (SD)	Mean (SD)	
IQ	−0.017 (0.54152)	−0.069 (0.53276)	0.97
Processing speed and attention	−0.226 (0.75948)	−0.172 (0.68855)	0.85
Executive function	−0.033 (0.52493)	−0.094 (0.48356)	0.821
Phonological verbal fluency	−0.167 (0.7589)	−0.535 (0.50112)	0.309
Fine motor skills	1.8 (0.57246)	1.961 (0.31519)	0.405
Finger tapping test (dominant hand)	2.088 (0.59503)	0.595 (0.2203)	0.307
Psychological testing	Mean (SD)	Mean (SD)	
STAI- Trait	0.021 (1.46827)	−0.246 (0.91895)	0.405
STAI- State	−0.544 (0.88425)	−0.787 (0.84363)	0.762
SF-Physical functioning	1.034 (0.07589)	0.979 (0.23154)	0.914
SF- Role functioning-physical	0.905 (0.77476)	1.089 (0.1929)	0.942
SF-Role functioning-emotional	0.43 (0.7969)	0.594 (0.77792)	0.33
SF-Energy fatigue	0.416 (0.78155)	0.885 (0.7585)	0.159
SF-Emotional well being	−0.291 (0.98293)	0.219 (0.74314)	0.222
SF-Social functioning	0.389 (0.63048)	0.585 (0.77476)	0.102
SF-Pain	0.531 (0.68125)	0.944 (0.5288)	0.042
SF-General health	0.783 (1.08395)	0.995 (1.0368)	0.732
SF-Health change	0.143 (0.9224)	0.361 (0.89386)	0.491
BDI (% normal)	6 (60%)	8 (80%)	0.232

BDI: Depression inventory of Beck; IQR: interquartilic range; SD: standard deviation; SF: *Short Form-36;* STAI: *State Trait Anxiety Inventory.*

Caucasians, 80% were born in Spain) with a median age of 19 years old (IQR 17- 21.7) and median number of years of education 11.5 (IQR 10-12). No significant differences were found between groups for sociodemographic characteristics (all $p > 0.05$).

Except for the Pain subscale in SF-36 ($p = 0.042$), no differences attained significance in SF-36 Health Questionnaire. The majority of our patient group were considered 'good sleeper' (70%) and the 60% presented BDI results within the average range, without finding significant differences among groups. With regard to STAI, patients and healthy controls presented similar results in both, Trait and State subscales ($p = 0.405$, $p = 0.762$, respectively). Based on the Frascati criteria, we confirm that 100% of the PHIV subjects had average NT results (none of the patients presented more than 1 Z score between −1 and −1.99) (Table I).

Regarding HIV patients, their median CD4 numbers were 780 cel/mm^3 (IQR 580-1056) and the median percentage of CD4 nadir was 14.5% (IQR: 13.2-18). Median CD4/CD8 ratio was 1.0 (IQR: 0.78-1.20). The median number of years on cART was 13.7 years (IQR: 9.6-15.8). Regarding type of cART, three patients were on non-nucleoside reverse transcriptase inhibitors (NNRTIs), five patients on protease inhibitor (PI) and two patients were receiving PI + integrase inhibitor (II), all in combination with two nucleoside reverse transcriptase inhibitors (NRTIs). Equally median number of years with undetectable VL was 9.5 years (IQR: 5.9 -11.7) (Table II).

fMRI findings

A total of 20 subjects underwent fMRI. Functional series from 20 participants were available for fluency task analysis.

For the between group comparisons no activation clusters were observed for any of the contrasts considered. From the whole sample analysis, the 'finger motion + touching tips versus rest' contrast resulted in activation clusters located at the left motor cortex (LMC; MNI coordinates: −36, −34, 50), right cerebellum (RC; 8, −54, −10), intraparietal sulcus (IS; 34, −44, 40) and ventral premotor cortex (VPC; 60, 6, 38) (Figure 1a). For the phonological fluency task, the 'word generation versus word repetition' contrast lead to a significant activation cluster in the left inferior frontal gyrus (IFG; −50, 12, 30 (Figure 1b). In the verbal fluency task, within the PHIV group prolonged time on cART was observed to be positively associated with greater activity at the LIFG activation peak (r =

0.648, p = 0,043) (Figure 2). There were no significant associations between recent or nadir CD4 count and activity at the cluster peaks in this task.

Discussion

Currently the primary method to evaluate neurocognitive disorders is NT. However, to better understand the effects of HIV infection on the CNS, it is necessary to know which brain structures are mainly involved, justifying the importance of neuroimaging.

In our study we evaluated neural activity through BOLD fMRI in a group of adolescents with good daily functioning and good immunovirological control although there were not treated with effective antiretroviral treatment early in life.

Our results showed that there were no significant differences between HIV+ and HIV– groups either on NT nor in fMRI activity for verbal phonological fluency tasks. In addition, psychological variables taken in account, finding no differences between groups. This is significant, as previous studies have shown that psychological disorders are often associated with HIV infection, which could affect their quality of life [23-26].

Our methodology included a phonological fluency task in which the region primarily involved was the left IFG as it has been previously described as one of the most prominent functional nodes for phonemic verbal fluency [27-30]. Interestingly, neither have we found differences of activation between groups, highlighting the importance of good immunovirological control in PHIV patients despite the widely described literature about executive deficits [31-34]. Furthermore, our findings of PHIV+ individuals with more years on cART presenting greater left IFG activation during this task is consistent with our knowledge of functional compensation, suggesting that this structure may be important for successful phonemic fluency performance. Similarly, it has been reported by Thames et al [11], that recent CD4 + count was positively associated with greater percent signal change in the left IFG and left basal ganglia during the phonemic fluency task.

In contrast, other studies of neural activation during verbal fluency tasks and in HIV infected adults have reported differences between HIV patients and seronegative controls, finding greater activation on the HIV group [11], but most of these studies have not taken in account the immunovirological status, since not all patients were not on cART. In addition, comparative data on fMRI while engaged tasks in our study's population is absent, making the interpretation of results difficult.

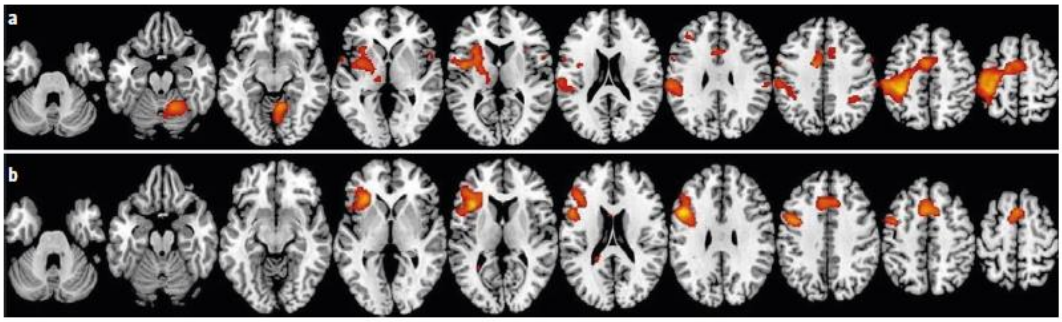
In our study, the absence of differences between groups might be due to the careful selection of patients with good immunovirological control. Those patients who are young adults, have been on cART for more than half their life (median of 13.7 years) and with persistent undetectable viral load (median of 9.5 years). Moreover, although in our cohort, patients were not commonly treated in the first year of life with cART, which seems an important protector of the CNS as some studies have shown [35] the absence of differences could be due to the fact that these patients have shown a good immunovirological control which could also protect the CNS. Therefore, two issues have been described in many articles as relevant factors to prevent neurocognitive impairment due to HIV infection. The first one seems to be the early initiation of antiretroviral treatment, however, not all studies have shown the same results. In this line, Crowell et al

Table II. Clinical features of PHIV participants.

STAGE B (*n*, %)		9 (90%)
CD4 Median and IQR (cls/mm^3)		781 (588-781)
CD4 Median and IQR (%)		38 (33-40)
NADIR CD4 cells/mm^3 (median, IQR)		222 (123-388)
NADIR CD4 % (median, IQR)		14.5 (13.2-18)
Antiretroviral therapy	Median age at HIV diagnoses	2.7 (0.3-6.3)
	Median age at start ART	5.2 (1.4-6.9)
	Median age at the start of cART	7.2 (4.3-11.1)
	Time of treatment with ART	14.1 (11.1-16.5)
	Time of treatment with cART	13.7 (9.6-15.8)
	Median number of ART regimens	6 (5-8)
	Median number of cART regimens in years (median, IQR)	6 (4-8)
	Time of viral load <50 cop/mL (years)	9.5 (6-11.8)
Current treatment situation	*Good adherence to treatment (n, %)*	10 (100)

cART: combined antiretroviral therapy; IQR: interquartilic range.

Figure 1. Patterns of brain activation (all participants) during 'finger motion + touching tips vs rest (a) and during letter retrieval (b, 'words from letter vs word repetition'). Images are presented using the neurological convention (the right side of the depicted brain is the right side of the reader).



[36] have reported that virologic suppression during infancy or early childhood is associated with improved neurocognitive outcomes in school-aged PHIV+ children and similar results were found by Judd et al in their study [37]. Furthermore, with regard to the influence of antiretroviral therapy as a measure to control the HIV infection, and according to our results, a recent study showed better neurocognitive performance among those HIV children who initiated soon and showed longer duration of ART [38]. In other studies, no differences have been seen in children's cognition in relation to age of antiretroviral treatment (ART) initiation [4]. The second factor described in many studies, is the positive influence of the immunovirological control on CNS [39].

The principal strength of our study is that it is the first one measuring neural activity in well- controlled PHIV patients, through phonological verbal fluency tasks. In addition, not only cognitive and neuroimaging has been done but also neuropsychiatric sleep disorders and quality of life variables have been recorded.

However, this conclusion needs to be taken with caution as this study has several limitations. As a pilot study our goal was hypothesis generating not hypothesis testing; our very limited sample size decreases the statistical power. Nevertheless this point has been partially compensated in someway by the selection of a strictly matched peer group with a very complete evaluation that includes HIV data and neurocognitive plus psychological evaluation as it was already referred Moreover, the study includes patients that belong to the preHAART era who have had a good immunovirological control for long. Luckily, thanks to the great improvements in the diagnose and treatment of HIV infection, currently, this population is uncommon and therefore this makes this group unique. Although we have measured emotion alterations such as depression or anxiety, other factors could influence the results since it is known that chronic illness and a parent´s psychological status can alter adolescence [40,41]. Moreover, the images of our study were acquired in a 1.5T which could limit the results by no detecting more subtle alterations than for example a 3T could detect.

Finally, another important limitation would be that only verbal fluency has been evaluated, while other cognitive deficits that typically affect to PHIV population, such attention or memory defects have not been explored in our study.

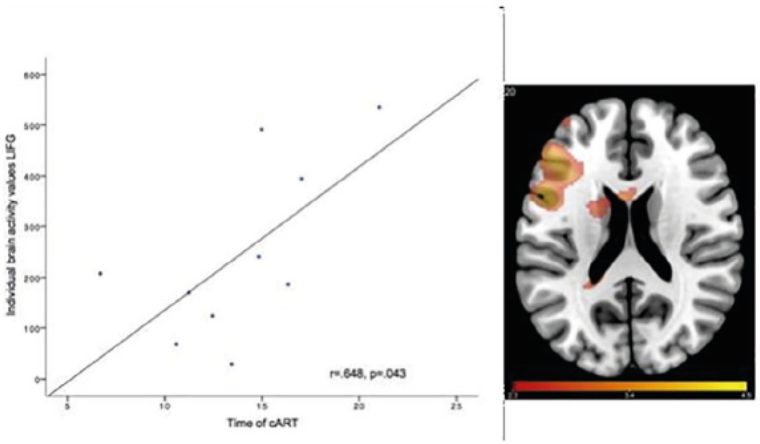
Conclusions

Although future research is needed to explore the generalisationality of these findings, our study may demonstrate that more efficient suppression of CNS HIV replication by using effective cART in PHIV patients could most likely reduce the metabolic demand in the brain where HIV is replicating. This means that an average neurocognitive profile could be related to good immunovirological control in PHIV patients, knowing that other non-studied factors could be also implicated.

Even though the exact mechanism governing brain recovery remains unknown, our findings

seem to suggest the implementation of compensatory mechanisms, indicating the potential benefit of early achievement of good immunovirological control and avoiding neurocompromise.

Figure 2. Effects of time of cART (years) on individual brain activity in LIFG. Plots show positive correlations of time of cART and individual brain activity in LIFG of PHIV+ subjects during verbal fluency task (Spearman correlation; $p = 0.043$). Images are presented using the neurological convention (the right side of the depicted brain is the right side of the reader).



References

1. Arnhem LA, Bunders MJ, Scherpbier HJ, Majoie CB, Reneman L, Frinking O, et al. Neurologic abnormalities in HIV-1 infected children in the era of combination antiretroviral therapy. PLoS One 2013; 8: e64398.
2. Doare KL, Bland R, Newell M. Neurodevelopment in children born to HIV-infected mothers by infection and treatment status. Pediatrics 2012; 130: e1326-44.
3. Crowell CS, Malee KM, Yogev R, Muller WJ. Neurologic disease in HIV-infected children and the impact of combination antiretroviral therapy. Rev Med Virol 2014; 24: 316-31.
4. Puthanakit T, Ananworanich J, Vonthanak S, Kosalaraksa P, Hansudewechakul R, Lugt JV, et al. Cognitive function and neurodevelopmental outcomes in HIV-infected children older than 1 year of age randomized to early versus deferred antiretroviral therapy. Pediatric Infect Dis J 2013; 32: 501-8.
5. Medin G, García-Navarro C, Gómez MN, Amador JT, Mellado MJ, Jiménez S, et al. Disease disclosure, treatment adherence, and behavioural profile in a cohort of vertically acquired HIV-infected adolescents. NeuroCoRISpeS study. AIDS Care 2015; 28: 124-30.
6. Woods SP, Moore DJ, Weber E, Grant I. Cognitive neuropsychology of HIV-associated neurocognitive disorders. Neuropsychol Rev 2009; 19: 152-68.
7. García-Navarro C, García, I, Medín G, Ramos-Amador JT, Navarro-Gómez M, Mellado-Peña MJ, et al. Aspectos psicosociales en una cohorte de adolescentes con infección por el virus de la inmunodeficiencia humana por transmisión vertical. NeuroCoRISpeS. Enfermedades Infecciosas y Microbiología Clínica 2014; 32: 631-7.
8. Mannheimer SB, Matts J, Telzak E, Chesney M Child C, Wu AW, et al. For the Terry Beirn Community Progr. Quality of life in HIV-infected individuals receiving antiretroviral therapy is related to adherence. AIDS Care 2005; 17: 10-22.
9. Hakkers CS, Arends JE, Barth RE, Plessis SD, Hoepelman AI, Vink M. Review of functional MRI in HIV: effects of aging and medication. J Neurovirol 2016; 23: 20-32.
10. Buxton RB. Introduction to functional magnetic resonance imaging. Cambridge: Cambridge University Press; 2002. p. 85-100.
11. Thames AD, Sayegh P, Terashima K, Foley JM, Cho A, Arentoft A, et al. Increased subcortical neural activity among HIV individuals during a lexical retrieval task. Neurobiol Dis 2016; 92: 175-82.
12. Kaufman AS, Kaufman NL. K-BIT Manual: Test Breve de inteligencia de Kaufman. Madrid: TEA; 1997.
13. Wechsler D. WAIS-IV: escala de inteligencia de Wechsler para adultos-IV. Madrid: Pearson; 2012.
14. Tamayo F, Casals-Coll M, Sánchez-Benavides G, Quintana M, Manero R, Rognoni T, et al. Spanish normative studies in a young adult population (NEURONORMA young adults project): guidelines for the span verbal, span visuo-spatial, Letter-Number Sequencing, Trail Making Test and Symbol Digit Modalities Test. Neurologia 2012; 27: 319-29.
15. Casals-Coll M, Sánchez-Benavides G, Quintana M, Manero R, Rognoni T, Calvo T, et al. Spanish normative studies in young adults (NEURONORMA young adults project): norms for verbal fluency tests. Neurologia 2013; 28: 33-40.
16. Manga D, Campos FR. Batería Luria-DNA: diagnóstico neuropsicológico de adultos: manual. Madrid: TEA; 2000.
17. Heaton RK, Heaton RK. Revised comprehensive norms for an expanded halstead-reitan battery: demographically adjusted neuropsychological norms for African American and Caucasian adults, professional manual. Lutz, FL, EE. UU: Psychological Assessment Resources; 2004.
18. Guillén-Riquelme A, Buela-Casal G. Actualización psicométrica y funcionamiento diferencial del ítem en el State Trait Anxiety Inventory (STAI). Psicothema 2011; 23: 510-5.
19. Sanz J, Vásquez C. Fiabilidad, validez y datos normativos del inventario para la depresión de Beck. Psicothema 1998; 10: 303-18.
20. Alonso J, Prieto L, Anto JM. The Spanish version of the SF-36 health survey: an instrument for measuring clinical results. Med Clin 1995; 104: 771-6.
21. Macías Fernández JA, Royuela Rico A. La versión española del índice de calidad de sueño de Pittsburgh. Informaciones Psiquiátricas 1996; 146: 465-72.
22. Worsley KJ. Statistical analysis of activation. In Jezzard P, Matthews PM, Smith SM, eds. Functional MRI: an introduction to methods. Oxford: Oxford University Press; 2001, p. 251-70.
23. Howland LC, Storm DS, Crawford SL, Ma Y, Gortmaker SL, Oleske JM. Negative life events: risk to health-related quality of life in children and youth with HIV infection. J Assoc Nurses AIDS Care 2007; 18: 3-11.
24. Ciesla JA, Roberts JE. Meta-analysis of the relationship between HIV infection and risk for depressive disorders. Am J Psychiatry 2001; 158: 725-30.
25. Elliott-Desorbo DK, Martin S, Wolters PL. Stressful life events and their relationship to psychological and medical functioning in children and adolescents with HIV infection. J Acquir Immune Defic Syndr 2009; 52: 364-70.
26. Ances BM, Roc AC, Korczykowski M, Wolf RL, Kolson DL. Combination antiretroviral therapy modulates the blood oxygen level-dependent amplitude in human immunodeficiency virus-seropositive patients. J Neurovirol 2008; 14: 418-24.
27. Wagner S, Sebastian A, Lieb, K, Tüscher O, Tadić A. A coordinate-based ALE functional MRI meta-analysis of

brain activation during verbal fluency tasks in healthy control subjects. BMC Neurosci 2014; 15: 19.
28. Tecelão D, Mendes A, Martins D, Bramon E, Toulopoulou T, Kravariti E, et al. The impact of psychosis genome-wide associated ZNF804A variation on verbal fluency connectivity. J Psychiatr Res 2018; 98: 17-21.
29. Herrmann MJ, Horst AK, Löble S, Möll MT, Katzorke A, Polak T. Relevance of dorsolateral and frontotemporal cortex on the phonemic verbal fluency – a fNIRS-study. Neuroscience 2017; 367: 169-77.
30. Miró-Padilla A, Bueichekú E, Ventura-Campos, N, Palomar-García M, Ávila C. Functional connectivity in resting state as a phonemic fluency ability measure. Neuropsychologia 2017; 97: 98-103.
31. Martínez-Banfi M, Vélez JI, Perea MV, García R, Puentes-Rozo PJ, Chams MM, et al. Neuropsychological performance in patients with asymptomatic HIV-1 infection. AIDS Care 2018; 30: 623-33.
32. Sheppard DP, Woods SP, Doyle KL, Verduzco M. Random number generation in HIV disease: associations with neuropsychological functions and activities of daily living. Arch Clin Neuropsychol 2016; 32: 53-62.
33. Cohen RA, Siegel S, Gullett JM, Porges E, Woods AJ, Huang H, et al. Neural response to working memory demand predicts neurocognitive deficits in HIV. J Neurovirol 2017; 24: 291-304.
34. Nichols SL, Montepiedra G, Farley JJ, Sirois PA, Malee K, Kammerer B, et al. Cognitive, academic, and behavioral correlates of medication adherence in children and adolescents with perinatally acquired HIV infection. J Dev Behav Pediatr 2012; 33: 298-308.
35. Heany SJ, Phillips N, Brooks S, Fouche J, Myer T, Zar H, et al. Neural correlates of maintenance working memory, as well as relevant structural qualities, are associated with earlier antiretroviral treatment initiation in vertically transmitted HIV. J Neurovirol 2019; 26: 60-9.
36. Crowell CS, Huo Y, Tassiopoulos K, Malee KM, Yogev R, Hazra R, et al. Early viral suppression improves neurocognitive outcomes in HIV-infected children. AIDS 2015; 29: 295-304.
37. Judd A, Prevost ML, Melvin D, Arenas-Pinto A, Parrott F, Winston A, et al. Cognitive function in young persons with and without perinatal HIV in the AALPHI cohort in England: role of non-HIV-related factors. Clin Infect Dis 2016; 63: 1380-7.
38. Brahmbhatt H, Boivin M, Ssempijja V, Kagaayi J, Kigozi G, Serwadda D, et al. Impact of HIV and antiretroviral therapy on neurocognitive outcomes among school-aged children. J Acquir Immune Defic Syndr 2017; 75: 1-8.
39. Wade BS, Valcour VG, Puthanakit T, Saremi A, Gutman BA, Nir TM, et al. Mapping abnormal subcortical neurodevelopment in a cohort of Thai children with HIV. Neuroimage Clin 2019; 23: 101810.
40. Taylor RM, Gibson F, Franck LS. The experience of living with a chronic illness during adolescence: A critical review of the literature. J Clin Nurs 2008; 17: 3083-91.
41. Nöthling J, Martin CL, Laughton B, Cotton MF, Seedat S. Maternal post-traumatic stress disorder, depression and alcohol dependence and child behaviour outcomes in mother–child dyads infected with HIV: a longitudinal study. BMJ Open 2013; 3: e003638.

Actividad cerebral en jóvenes infectados por el virus de la inmunodeficiencia humana por transmisión vertical: estudio piloto de resonancia magnética funcional

Introducción y objetivos. La infección por el virus de la inmunodeficiencia humana de transmisión vertical (VIH-TV) constituye una enfermedad crónica que puede asociar múltiples alteraciones cognitivas que pueden influenciar el desarrollo de estos pacientes desde la infancia a la vida adulta. Sin embargo, aunque las alteraciones neurocognitivas vinculadas al VIH-TV están ampliamente descritas y valoradas mediante pruebas psicométricas, no existen apenas estudios de actividad neuronal medida a través de la resonancia magnética funcional (RMf).

Sujetos y métodos. Analizar la utilidad de la RMf a través de la realización de tareas motoras y de fluidez verbal en un grupo de adolescentes y jóvenes con VIH-TV con buen control inmunovirológico y compararlo con un grupo control negativo de características similares. Se evaluaron también alteraciones psicológicas y funciones neurocognitivas.

Resultados. No se encontraron diferencias significativas entre el grupo VIH+ y el grupo control para las tareas ejecutadas durante la RMf ni en la evaluación neurocognitiva. Un mayor tiempo de terapia combinada antirretroviral se asoció de forma directa con una mayor actividad en el giro frontal inferior izquierdo, lo cual podría indicar una posible compensación funcional.

Conclusiones. Estos resultados sugieren que la actividad neuronal medida a través de la RMf en adolescentes con VIH-TV y buen control inmunovirológico es similar a la de sus pares.

Palabras clave. Adolescentes. cART. Fluidez. Neuroimagen. RMf. VIH perinatal.

CAPÍTULO 4

Evaluación del neurofilamento de cadena ligera como biomarcador de lesión neuronal en pacientes con infección por VIH de transmisión vertical.

JUSTIFICACIÓN Y OBJETIVOS

Con la finalidad de entender mejor el daño neuronal que se produce en diferentes enfermedades neurológicas y neurodegenerativas se han investigado en los últimos años, diferentes biomarcadores de SNC, siendo el biomarcador del Neurofilamento de Cadena Ligera (NfL) uno de los más sensibles a la hora de estudiar lesión neuroaxonal inducida por el VIH. Esta proteína es componente fundamental de las vainas de mielina, permitiendo la conducción nerviosa.

Diferentes estudios realizados en población VIH han mostrado un aumento de los niveles de NfL a nivel de LCR. Es más elevado en pacientes con demencia asociada al VIH y también en pacientes neuroasintomáticos con cifras bajas de CD4. Sin embargo, la población VIH con buen control inmunovirológico presenta niveles más bajos de NfL, aunque las concentraciones siguen siendo ligeramente más elevadas que en población sin VIH. Para evitar la obtención de LCR, que requiere un método invasivo, como es la punción lumbar, se ha desarrollado una técnica similar mediante realización de inmunoensayo ultrasensible (Simoa®- Quanterix digitial biomarker biomarker detection technology) que ha demostrado una fuerte correlación para medir concentraciones de NfL en sangre.

No se han realizado, hasta la fecha estudios de NfL en población VIH de transmisión vertical.

Apenas hay estudios en población VIH que hayan explorado correlaciones entre morfometría cerebral y los tests neurocognitivos con niveles de NfL.

Los objetivos de este capítulo son:

1) Analizar las concentraciones plasmáticas de NfL en un grupo de pacientes con VIH-TV y compararla con un grupo sin VIH de similares características.

2) Evaluar si las concentraciones plasmáticas de NfL son más elevadas en pacientes con mal control virológico.
3) Analizar y comparar la morfometría cerebral de sustancia blanca en un subgrupo de pacientes con VIH-TV y un grupo de características muy similares sin VIH
4) Explorar posibles correlaciones entre las concentraciones de NfL en plasma y los volúmenes de sustancia blanca y pruebas neurocognitivas en el grupo con VIH-TV.

RESULTADOS

- Se incluyen en el estudio 33 jóvenes con infección perinatal por VIH y 25 controles sin VIH
- En el grupo VIH-TV el 54% eran mujeres y el 73% era de etnia caucásica. La mediana de edad fue de 20.7 años (RIQ 17.8-23.4). En el grupo sin VIH la mediana de edad fue de 21.3 años (RIQ 19.7-23.1) siendo el 60% mujeres. No había diferencias estadísticamente significativas entre ambos grupos.
- Dentro del grupo VIH, el 42% se encontraba en un estadío C del CDC, y el 21% tenía datos de encefalopatía por VIH previa. La mediana de CD4 nadir fue de 274 cels/mm3 (RIQ 104- 382 cels/mm3). La mediana de CD4 actual fue de 738 cels/mm3 [RIQ 578-978]). El 100% de los pacientes estaba recibiendo TAR con una mediana de 16.42 años (RIQ 12.99-18.70 años), y un 85% mantenían una carga viral por debajo de 50 copias/ml. De los 5 pacientes con carga viral detectable la mediana de CV era de 69900 copias/ml (36774-267541 copias/ml). Estos pacientes tenían CV detectable con una mediana de tiempo de 5.75 años (RIQ 5.03-16.75).

- Al analizar las concentraciones plasmáticas de NfL, no se encontraron diferencias estadísticamente significativas entre pacientes y controles.
- Aquellos pacientes con mala adherencia al TAR y carga viral detectable presentaban niveles más elevados de NfL plasmático (NfL 9.19, DE 5.18) al compararlos con pacientes indetectables (NfL 6.6 pg/ml, DE 4.15) o con el grupo control (NfL 5.29 pg/ml, DE 1.75) con un valor de p cercano a la significación (p = 0.059).
- No se encontraron correlaciones ni diferencias entre los valores de NfL en plasma y el tiempo al diagnóstico de la infección VIH, el tiempo con TAR, valores de CD4 actual, CD4 nadir, el estadío CDC o la presencia de encefalopatía.
- En el subestudio exploratorio de correlación de NfL con volúmenes de sustancia blanca y tests neurocognitivos participaron 25 pacientes VIH y 23 controles sin VIH sin diferencias en las características sociodemográficas.
- El grupo VIH-TV presentó menor puntuación en el test que mide Inteligencia fluida, pero ambos grupos obtuvieron resultados dentro de la media poblacional. El resultado global de los tests neurocognitivos, obtenido mediante el PS composite z-score, fue más baja en el grupo VIH-TV: mediana Z-score -0.68 (DE 0.98) vs mediana Z-score en el grupo VIH negativo de 0.00 (DE 1.00) ($p< 0.05$)
- La comparación de morfometría cerebral a nivel de sustancia blanca objetivó menores volúmenes de sustancia blanca a nivel regional en el grupo VIH con respecto al grupo sin VIH en las siguientes regiones: cerebelo (p = 0.030, p = 0.028), lóbulo occipital lateral (p = 0.020), núcleo accumbens (p =0.010, p <

0.001), lóbulo occipital (p=0.020, p= 0.042) y giro postcentral izquierdo (p =0.022).

- En el grupo VIH-TV, la correlación de Spearman mostró una asociación negativa entre las concentraciones de NfL plasmáticas y Tests neurocognitivos que evalúan velocidad de procesamiento (Digit Symbol-Coding subtest) (r -,425 p= 0.039).
- En el grupo VIH-TV, se observó una correlación negativa entre determinados volúmenes regionales de sustancia blanca y las concentraciones plasmáticas de NfL a nivel de cerebelo izquierdo y derecho (r -,440 p = 0.028; r -,0386, p= 0.056) tronco de encéfalo izquierdo y derecho (r -,440 p = 0.028; r -,417 p = 0.038) y núcleo accumbens derecho (r-,403, p = 0.046).

ASSESSMENT OF PLASMA NEUROFILAMENT LIGHT AS A BIOMARKER OF NEURONAL INJURY IN YOUNG ADULTS WITH PERINATAL HIV INFECTION

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ABSTRACT:

Background: Higher plasma concentration of neurofilament light (pNfL) is associated with neurodegeneration. However, to our knowledge, up to now, there are no data in HIV patients with infection due to vertical transmission. This is the first study to report pNfL in a cohort of HIV perinatally infected (PHIV) young adults compared with non-HIV (HIV-) controls.

Methods: Thirty-three PHIV patients and 25 age-matched HIV- were recruited to this cross-sectional study. Plasma NfL concentrations were compared between both groups. In a subgroup of 48 participants (25 PHIV patients and 23 HIV-), brain volumes through magnetic resonance imaging (MRI) and neuropsychological testing (NT), were also conducted and compared with pNfL values.

Plasma NfL concentration was measured using Single Molecule Array (Simoa) immunoassay.

NT included fluid intelligence and processing speed through the WAIS-IV Coding subtest, and the Stroop Test.

Results

Fifty-eight participants were included, median age 20.7 years [IQR 17.8-23.4]. 100% of the patients were under antiretroviral treatment (cART) and 85% had viral load <50 copies/ml.

Although no statistically significant differences were found between patients and controls regarding pNfL concentration, there was a trend towards higher levels in patients with viral load >50 copies/ml.

With regard to brain volumes and NT, in the PHIV group, lower white matter volumes and lower score in the coding subtest were associated with higher pNfL values.

Conclusions

Most PHIV adolescents under cART have similar levels of pNfL than HIV-. As reported in adults, those with HIV-RNA >50 copies/ml showed higher values and lower white matter volumes that may imply an ongoing CNS injury. Plasma NfL could be a feasible biomarker of CNS injury in PHIV patients with unsuppressed viral load.

Key words

Plasma NfL, perinatal HIV, neuroimaging, neurocognitive, cART

ASSESSMENT OF PLASMA NEUROFILAMENT LIGHT AS A BIOMARKER OF NEURONAL INJURY IN YOUNG ADULTS WITH PERINATAL HIV INFECTION

BACKGROUND

The incidence of HIV encephalopathy and severe neurological complications has been significantly reduced in perinatally HIV-infected patient since the introduction of combined antiretroviral therapy[1]. Nevertheless, in the PHIV population, CNS invasion of HIV occurs within the first 3 weeks of life, with a subsequent immune activation throughout the primary infection. This is among the most important reasons why research concerning the detection of persistent neurologic problems is essential[2]. This research could explain why less severe cognitive impairment often could persists in this population, especially in children who did not start treatment in early life[3].

To better understand how the development of brain injury and intrathecal immune activation and inflammation occur, several CSF biomarkers have been investigated, with CSF neurofilament light (NfL) being the most useful biomarker for the study of HIV-induced neuroaxonal injury[4]. This major structural component of myelinated axons is essential to maintain axonal calibre and to facilitate effective nerve conduction[5]. It is a sensitive, but disease-unspecific, biomarker for neuronal degeneration or acute neuronal damage[6].

Several studies performed in HIV-infected adults have shown increased CSF NfL levels in patients with HIV associated dementia but also in neuroasymptomatic subjects with low CD4+ T-cell counts[5-7]. Meanwhile, treated and virologically suppressed people living with HIV have lower CSF NfL levels, but this is still slightly higher than HIV-negative individuals [5].

Measuring CSF NfL uses the invasive procedure of lumbar puncture, so its use is limited. Therefore, a new technique has been developed using ultrasensitive (Simoa) immunoassay for measuring NfL in blood samples[8]. Results derived using this new method show that plasma NfL correlates strongly with CSF NfL levels at all stages of HIV infection[8].

To our knowledge, no study of plasma or CSF NfL has been performed in the perinatally HIV-infected population.

It is worth stating, that in recent years, several neuroimaging studies have been performed in PHIV children and young adults demonstrating that, even in the cART era, there are alterations and lower volumes in brain structure[9]. As NfL CSF levels reflect leakage from injured or degenerating neurons, it correlates with white matter lesions and other injuries to subcortical brain regions[10]. To date, there are no studies correlating white matter brain volumes and pNfL values in perinatally HIV-infected patients.

Therefore, the current study aimed to investigate, firstly, the pNfL levels in a group of PHIV population and compared them with a group of HIV-negative controls participating in the NeuroCoRISpe study. Secondly, a sub-study was performed to explore possible correlations between pNfL concentration and white matter volumes and processing speed performance in a group of participants.

METHODS

Population and Study Design

A multicentre cross-sectional study was carried out from 2016 to 2018 in a cohort of vertically HIV-infected adolescents and young adults followed at five public hospitals participating in the Madrid Cohort of HIV-Infected Children and Adolescents and in the Cohort of Spanish Pediatric HIV Network (CoRISpe) [11].

The HIV- were selected from voluntary recruitment through advertising.

Thirty-three PHIV patients and 25 HIV- controls matched by age were recruited.

For the study, all participants met the following inclusion criteria: (1) age 15 to 25 years old, (2) absence of neurological or psychiatric disorder other than history of older HIV encephalopathy, (3) HIV participants should be under cART treatment.

Participants with current brain infection, neurological or psychiatric disorder, those who referred history of drug or alcohol abuse, or had any congenital abnormality, were excluded.

The Institutional Review Boards (IRBs) of each research centre approved the study and written informed consent was obtained from all participants. Where participants were underage, an assent form was signed by themselves, with legal guardians providing the informed consent in accordance with the Helsinki Declaration.

HIV-related measures

In relation to the control of the infection the next parameters were collected: CDC classification, encephalopathy, suppressed viral load (defined as plasma HIV-RNA <50 copies/ml), time of suppressed viral load, viral load in detectable patients, total numbers, and percentages of CD4 nadir, and current CD4, CD4 / CD8 ratio, cART

history and adherence to treatment. These data were collected from clinical charts and the CoRISpe database.

Plasma NfL measurements

Whole blood was collected in EDTA tubes which were sent to the Spanish HIV HGM BioBank for centrifugation (2000 g) and aliquoted into cryo tubes in 1 mL portions and stored at −80° for subsequent analysis[12]. Plasma NfL concentration was measured using a sensitive in-house sandwich immunoassay on the (Simoa) HD-1 Analyzer (Quanterix, Billerica, MA), as previously described in detail[8].

Neuropsychological and neuroimaging sub-study

A subgroup of 48 participants (25 PHIV +, 23 HIV-) with no differences in sex, age, level of education and socioeconomic status between groups, underwent NT testing and MRI scan. These subjects participated previously in a neurocognitive and neuroimaging study (Ruiz-Saez et al, 2021) [13] and whole blood was collected at the same time and stored at the HIV HGM Biobank for subsequent pNfL analysis.

The NT included fluid intelligence (FI) by the Kaufman Brief Intelligence Test [14] (K-BIT; Kaufman & Kaufman, 2000), and processing speed measured through two tests, the Digit Symbol-Coding subtest of the Wechsler Adult Intelligence Scale- 4th edition[15] (WAIS-IV, Weschler, 2012), and the first trial of the Stroop Test[16] (Golden, 2001).

In this study, we focused on fluid intelligence to make sure abstract reasoning and problem solving in novel situations independently of experience was average in both

groups. Processing speed was also evaluated, because is one of the main cognitive deficits in HIV patients[17]. Scores on all neuropsychological tests were converted into a Z-score relative to HCs. Scores on the Digit Symbol- Coding and Stroop-Card 1 were averaged into one PS composite Z-score.

MRI data acquisition

Different MRI scanner systems were used at each hospital study site. For specific details of the acquisition parameters see Supplementary material.

Image quality was assessed in two independent processes. Radiologist checked for the presence of any brain pathology, such as tumour, cyst, or any other lesion.

In addition, image quality and processing experts checked for motion artefacts, low contrasts, incomplete whole brain coverage, low SNR and low resolution. In a further analysis, all the acquisitions were correlated to determine the homogeneity of the image sample.

Image processing

The standard processing pipeline for volume based morphometry provided by The Computational Anatomy Toolbox (CAT12, http://dbm.neuro.uni-jena.de/cat/ version 1492), as an extension of SPM (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/ version 7487), was used for tissue segmentation and the extraction of tissue volumes. To measure regional brain volumes, native segmented images were parceled in regions of interest (ROI) according to the Hammers atlas [18-19](Hammers et al. 2003;

Gousias et al. 2008) and tissue volumes (mm^3) were estimated for each ROI and normalized by the total intracranial volume for each subject.

Statistical analysis

Categorical variables were summarized by using counts and proportions and continuous variables employing medians and interquartile ranges (IQR) or means and standard deviations (SD). Comparisons between patients and controls (NfL, age, Fluid Intelligence, Stroop, Coding and Composite z-score) were performed with the Student t test or the Mann–Whitney *U* test, if the variables did not follow a normal distribution. Comparisons between categorical variables were assessed using the Chi-square or the Fisher test. In the case of patients with and without undetectable viral load and controls, variables were analyzed with the Kruskal-Wallis test. Regarding the PHIV group, univariate analysis was performed to study associations between HIV variables and NfL. Spearman's correlation test was used to assess association pNfL concentrations and white matter volumes. P values less than 0.05 were considered statistically significant. All analyses were performed using SPSS software ver. 22.0 (IBM, Armonk, NY, USA). Figure 2 was made using Stata Version 12 (STATA Corp, Texas, USA).

RESULTS

Thirty-three young adults with perinatal HIV infection and 25 HIV-negative individuals were included.

In the PHIV group, 54% were women and 73% were Caucasians. Median age was 20.7 years (IQR 17.8-23.4). In the HIV-negative group, median age was 21.3 years (IQR 19.7-23.1) and 60% were women. There were no significant differences between the two groups regarding these characteristics ($p>0.05$).

Regarding the PHIV group, 42% had a history of previous AIDS-defining diagnoses (21% with old and stable encephalopathy). At assessment, 100% were under cART for a median time of 16.42 years (IQR 12.99-18.70), and 85% had suppressed viral load (HIV RNA < 50 copies/ml); Only five patients had HIV-RNA > 50 copies/ml with a median of 69900 copies/ml (IQR 36774-267541). Those five patients had detectable viral load for a median of 5.75 years (IQR 5.03-16.75). Median CD4 was 738 cells/mm^3 (IQR 578-978) and median CD4 nadir 274 (IQR 104- 382). (Table 1).

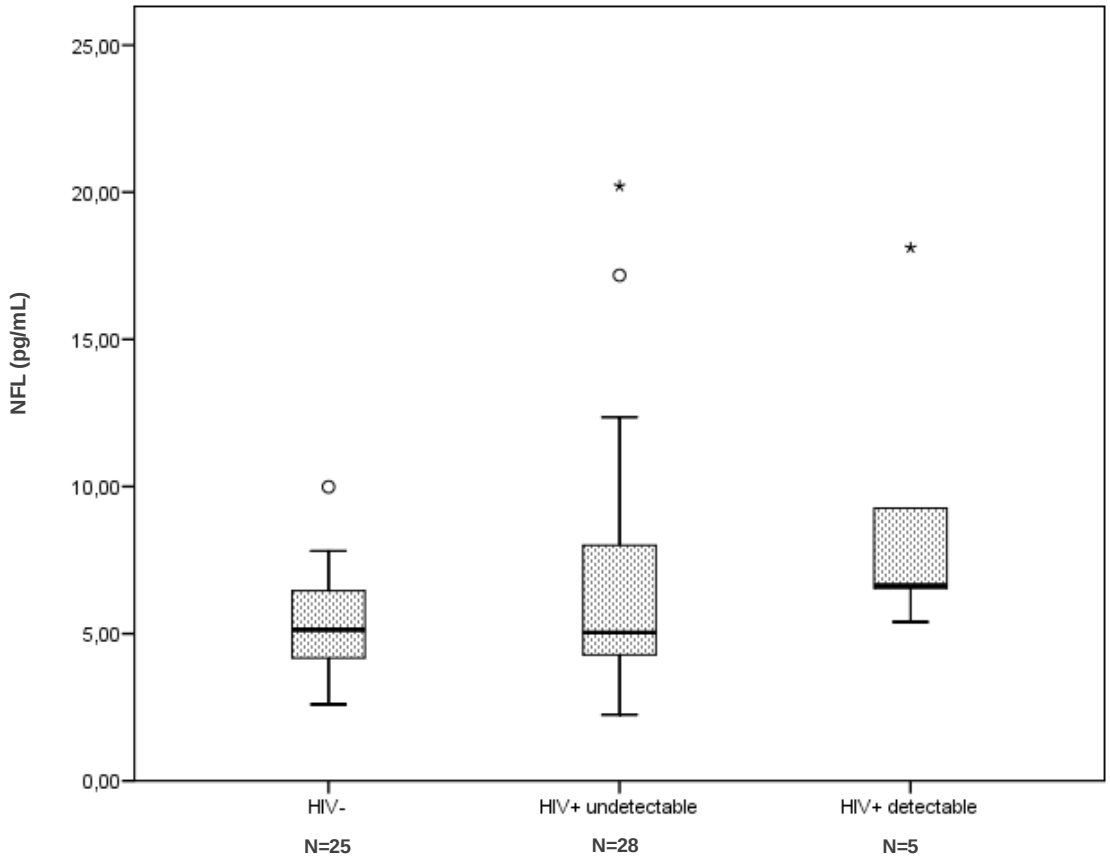
Table 1. Clinical measures in 33 PHIV patients (n (%) or median

Age at HIV diagnosis (years)	0.50 [0.24-4.08]
CDC Stage C3	14 (42.4%)
Encephalopathy	7 (21.2%)
NADIR CD4 (cells/mm3)	274 [124-376]
NADIR CD4 (%)	12 [6-17]
CD4 count (cells/mm3)	718 [490-771]
CD4 count (%)	36 [32-39]
CD4/CD8	1.03 [0.80-1.31]
Age at treatment onset (years)	1.33 [0.44-4.56]
Age at onset on cART (years)	4.28 [1.03-6.66]
Total time of treatment with cART (years)	16.42 [12.99-18.70]
Patients with uVL	28 (85%)
Time with uVL (years)	9.97 [6.92-13,48]
VL in detectable patients (cop/ml) (N = 5)	69900 [36774-267541]

No statistically significant differences were found between patients and controls regarding pNfL concentrations, but higher levels of pNfL were found in patients with increased viral load compared compared with undetectable patients and controls with a media pNfL of 9.19 pg/ml (SD 5.18) in patients with detectable viral load vs 6.6 pg/ml

(SD 4.15) in undetectable patients and 5.29 pg/ml (SD 1.75) in the control group (p = 0.059) (Fig 1).

Figure 1. Plasma NfL concentrations in 3 different groups: HIV-negative control group, PHIV patients with detectable VL, and PHIV patients with undetectable viral load.



Furthermore, no correlations were found between pNfL levels and viral load, time to diagnosis, time on cART, CDC stage or presence of encephalopathy (p > 0.05 for all comparisons).

In the correlation sub-study of pNfL with neuroimaging and neuropsychological evaluations, 25 PHIV+ and 23 HIV-negative controls were evaluated.

Sociodemographic characteristics are described in Table 2. In relation to NT, we found that PHIV had significantly lower FI, but both groups had average results. Differences between groups in Stroop test performance were observed, but not in Coding. The mean PS composite z-score was lower in the PHIV group (Mean Z-score -0.68 (SD 0.98)) compared to the HIV-negative group (Mean Z-score 0.00 (SD 1.00)) ($p < 0.05$)

Table 2. Means (standard deviations) of demographic, psychosocial, neurocognitive and psychopathological characteristics.

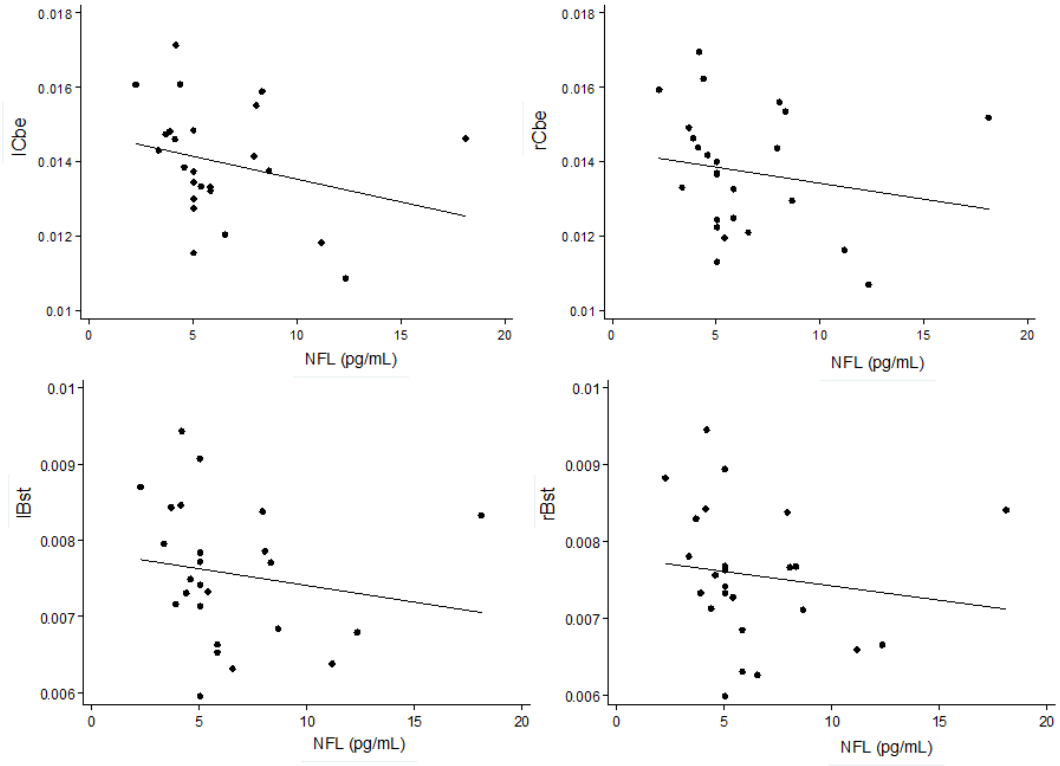
	PHIV (n= 25)	HIV- (n= 23)	P value
Sex (female) (%, n)	64 (16)	56,5 (13)	0.597
Age at assessment	21.0 (3.03)	20.9 (2.66)	0.522
Level of education (%, n) **Low** **Medium** **High**	N=24 62.5 (15) 16.7 (4) 20.8 (5)	N=21 76.2 (16) 0 (0) 23.8 (5)	0.146
Annual Income (%, n) **Low** **Medium** **High**	N=23 43.5 (10) 30.4 (7) 26.1 (6)	N=22 59.1 (13) 36.4 (8) 4.5 (1)	0.135
Caucasian (%, n)	72 (18)	56,5 (13)	0.263
Fluid Intelligence *	-0.72 (1.13)	0.01 (0.98)	**0.021**
Stroop	-0.84 (1.09)	0.00 (0.99)	**0.009**
Coding	-0.31 (0.86)	-0.12 (1.14)	0.512
Composite Processing Speed	-0.68 (0.98)	-0.00 (1.00)	**0.025**

Z-score			

Regarding brain volumes, the HIV infected group had significantly lower regional white matter volumes in left and right cerebellum (p = 0.030, p = 0.028), lateral occipital lobe (p= 0.020), left and right nucleus accumbens (p =0.010, p < 0.001), left and right occipital lobe (p=0.020, p= 0.042) and left postcentral gyrus (p =0.022), but no significant differences were found in total white matter volumes.

In the HIV group, Spearman's correlation test revealed negative association between pNfL concentrations and different regional white matter volumes of left and right cerebellum (r -,440 p = 0.028; r -,0386, p= 0.056), left and right brainstem (r -,440 p = 0.028; r -,417 p = 0.038) and right nucleus accumbens (r-,403, p = 0.046) (Fig 2), and also a negative correlation was found between pNfL concentration and Coding score (r -,425 p= 0.039). This association between NfL and brain volumes and coding score persisted when controlling for undetectable viral load.

Figure 2. Spearman correlations for cerebellum and brainstem volumetric measures and pNfL concentrations in HIV-infected patients.



*lCbe: left cerebellum; rCbe: right cerebellum; lBst: left brainstem; rBst: right Brainstem

DISCUSSION

NfL is a neurofilament subunit particularly abundant in axons[20]. Plasma NfL concentration was recently reported as a potential prognostic biomarker of disease onset and progression in neurodegenerative diseases including HIV[4-8].

In this study, we have shown that treated and virologically suppressed PHIV people, presented pNfL concentrations similar of those found in HIV-negative individuals. In addition, even considering the limitation of the small sample, patients with detectable

viral load had higher pNfL levels, showing that persistent viral replication may contribute to neuronal damage.

This has been demonstrated similarly in the HIV adult population, in which the HIV-driven axonal degeneration can be halted by cART, which correlates to reduced CSF and pNfL concentrations over time after cART initiation[5,21-22]. These results emphasize the importance of an early and continuous antiretroviral therapy to avoid neuronal damage in children.

In this exploratory study of PHIV adolescents and young adults, we found that higher pNfL concentration was significantly associated with lower regional brain volume and lower coding score. Similarly, Anderson *et al*. published that a higher pNfL was significantly associated with worse neuropsychological performance in the HIV adult population[23].

High concentration of NfL has been shown in multiple neurological diseases where processing speed is also one of the most affected cognitive processes, such as amyotrophic lateral sclerosis (ALS) [24,25] (Menke et al., 2015; Lu et al., 2015), Alzheimer's disease[26] (Mattsson et al., 2017) and frontotemporal dementia[27] (Rohrer et al., 2016). Processing speed performance is considered to depend to a large extent on the properties of the white matter[28-30](Posthuma et al, 2003; Borghesani et al., 2013; Jacobs et al., 2013). White matter includes myelinated axons in the brain, and the thickness of the myelin sheath is associated with nerve conduction velocity; therefore, its relation to processing speed and NfL seems consistent. Hence plasma NfL could be a feasible biomarker of milder neurocognitive alterations in the PHIV population.

Likewise, increased NfL levels and reduced brain volume in cortical and subcortical grey matter and within the white matter has been found in patients with different

neurodegenerative conditions[31-32]. However, research performed in the HIV adult population found that CSF neuronal damage biomarkers, including NfL, were not associated with imaging measures of brain structures[33].

It should be noted that NfL has the limitation that it is not a disease-specific biomarker. As we have mentioned, elevated NfL is observed in many other neurological disorders, including neurodegenerative diseases, peripheral neuropathy, and traumatic brain injuries[6,34].

Regarding brain volumes we found that the HIV group showed WM atrophy in selected brain regions despite being on cART for years. Some studies performed in adolescents living with PHIV has reported similar results showing lower white matter volumes when compared with HIV negative controls[35,36].

Limitations of this study include the small sample size and lack of longitudinal biomarker data. The small sample size has been partially compensated for by strict selection criteria for the control group. Moreover, other limitations of the study are that this age group is potentially more likely to be involved in sports with head trauma, and this group of population may have different stressors, that have not been measured. Number of adverse childhood events (ACEs) would be a useful marker but has not been used. These are potentially important considerations in the adolescent age group during a time of dynamic myelination.

Finally, this current work was exploratory and therefore multiple statistical tests were performed, which might have resulted in type I errors.

Strengths of our study are, the inclusion of young adults living with PHIV, who have not previously been examined regarding plasma NfL levels, and that we were able to correlate brain volumes and processing speed in this population.

This research is representative of most young adults living with HIV vertically infected in developed healthcare systems. Moreover, thanks to the current great improvements in the diagnosis and treatment of HIV infection, this population that were born in the preTAR era making the study unique.

CONCLUSIONS

We can conclude that the ultrasensitive method to measure pNfL concentration provides an easily accessible biomarker in perinatally HIV infected patients avoiding lumbar puncture. Nevertheless, it remains unclear how pNfL varies in the PHIV population with virologic suppression or how its levels could be influenced in this population by the earlier initiation of effective antiretroviral therapy. Therefore, larger longitudinal studies are required in this group to further evaluate pNfL as a clinically useful biomarker of neurological deterioration.

Abbreviated title

Plasma NfL in adolescents with perinatal HIV infection

Running head title

pNfL in perinatally HIV infected adolescents

DECLARATIONS SECTION:

Ethics approval and consent to participate:

The Institutional Review Boards (IRBs) of each research centre approved the study and written informed consent was obtained from all participants. Where participants were underage, an assent form was signed by themselves, with legal guardians providing the informed consent in accordance with the Helsinki Declaration.

Consent for publication: We hereby verify that the manuscript has not been submitted or accepted elsewhere. All authors have given consent for its publication.

Availability of data and material:

The authors confirm that all data underlying the findings are fully available without restriction. All relevant data are within the paper and its Supporting Information files.

Competing interests:

a) NeuroCoRISpe group declare no competing financial interest.

b) The Sahlgrenska Academy at the University of Gothenburg group have no competing interests that could be construed as influencing the contents of this paper. However, the authors list the following general potential conflicts of interest:

HZ has served on scientific advisory boards for Denali, Roche Diagnostics, Wave, Samumed, Siemens Healthineers, Pinteon Therapeutics and CogRx, has given lectures in symposia sponsored by Fujirebio, Alzecure and Biogen, and is a co-founder

of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program (outside submitted work).

KB has served as a consultant, at advisory boards, or at data monitoring committees for Abcam, Axon, Biogen, JOMDD/Shimadzu. Julius Clinical, Lilly, MagQu, Novartis, Roche Diagnostics, and Siemens Healthineers, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program.

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Authors' contributions:

BRS, MMB, MGT, MM conceptualized and designed the study, participated in analysis and interpretation of the data, drafted the initial manuscript and contributed and approved the final manuscript as submitted. BRS, MMB, MG, HZ, KB, AMA, SOJ, SAL, MAM, HM, JTR, MLN, MIGT were involved in the provision of study subjects, reviewed the manuscript drafts, and approved the final manuscript as submitted. All authors read and approved the final manuscript

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REFERENCES

1. Patel K, Ming X, Williams PL, Oleske JM, Seage GR 3rd; International Maternal Pediatric Adolescent AIDS Clinical Trials 219/219C Study Team. Impact of HAART and CNS-penetrating antiretroviral regimens on HIV encephalopathy among perinatally infected children and adolescents. AIDS. 2009;23:1893–1901.
2. Cohen S, Caan MWA, Mutsaerts H-J, Scherpbier HJ, Kuijpers TW, Reiss P, *et al.* Cerebral injury in perinatally HIV-infected children compared to matched healthy controls. *Neurology* 2016; 86:19–27.
3. Judd A, Le Prevost M, Melvin D, Arenas-Pinto A, Parrott F, Winston A, et al. Cognitive function in young persons with and without perinatal HIV in the AALPHI cohort in England: role of non-HIV-related factors. Clin Infect Dis.2016;63:1380–7.
4. Yilmaz A, Blennow K, Hagberg L, Nilsson S, Price RW, Schouten J, et al. Neurofilament light chain protein as a marker of neuronal injury: review of its use in HIV-1 infection and reference values for HIV negative controls. Expert Rev Mol Diagn 2017; 17:761–70
5. Jessen Krut J, Mellberg T, Price RW, et al. Biomarker evidence of axonal injury in neuroasymptomatic HIV-1 patients. Plos One. 2014;9:e88591.
6. Ashton NJ, Hye A, Rajkumar AP, Leuzy A, Snowden S, Suárez-Calvet M, et al. An update on blood-based biomarkers for non-Alzheimer neurodegenerative disorders. Nat Rev Neurol 2020;16(5):265-284.
7. Peterson J, Gisslen M, Zetterberg H, Fuchs D, Shacklett BL, Hagberg L et al. Cerebrospinal fluid (CSF) neuronal biomarkers across the spectrum of HIV infection: hierarchy of injury and detection. Plos One. 2014;9:e116081.
8. Gisslen M, Price RW, Andreasson U, Norgren N, Nilsson S, Hagberg L, et al. Plasma concentration of the neurofilament light protein (NFL) is a biomarker of CNS injury in HIV infection: a cross-sectional study. EBioMedicine. 2016;3:135–140.
9. Hoare J, Fouche JP, Phillips N, Joska JA, Myer L, Zar H, et al. Structural Brain Changes in Perinatally HIV Infected Young Adolescents in South Africa. AIDS. 2018;32:2707-18

10. Jonsson M, Zetterberg H, van Straaten E, Lind K, Syversen S, Edman et al. Cerebrospinal fluid biomarkers of white matter lesions - cross-sectional results from the LADIS study. Eur J Neurol. 2010 Mar;17(3):377-82
11. De Jose MI, Jiménez de Ory S, Espiau M, Fortuny C, Navarro ML, Soler-Palacín P, et al.. A new tool for the paediatric HIV research: general data from the Cohort of the Spanish Paediatric HIV Network (CoRISpe). BMC Infect Dis 2013 Jan 2;13:2. doi: 10.1186/1471-2334-13-2.
12. García-Merino I, de Las Cuevas N, Jiménez JL, García A, Gallego J, Gómez C et al. Pediatric HIV BioBank: a new role of the Spanish HIV BioBank in pediatric HIV research. AIDS Res Hum Retroviruses. 2010;26:241–244.
13. Ruiz-Saez B, Martín-Bejarano M, de Aragon AM, Gil-Correa M, Melero H, Malpica NA et al. . Effects of perinatal HIV-infection on the cortical thickness and subcortical gray matter volumes in young adulthood. Medicine (Baltimore). 2021;16:100-115.
14. 14. Kaufman, A. S., Kaufman, N. L. (2000) Manual del Test breve de inteligencia de Kaufman (K-BIT) [Manual for the Kaufman Brief Intelligence Test]. Madrid, Spain: TEA Ediciones.
15. Wechsler, D. (2012). WAIS-IV. Escala de inteligencia de Wechsler para adultos-IV. Manual de aplicación y corrección. Madrid: NCS Pearson, Inc. Edición original, 2008.
16. Golden, C. J. (2020). STROOP. Test de Colores y Palabras – Edición Revisada (B. Ruiz-Fernández, T. Luque y F. Sánchez-Sánchez, adaptadores). Madrid: TEA Ediciones.
17. Phillips N, Amos T, Kuo C, Hoare J, Ipser J, Thomas KG, et al. HIV-Associated Cognitive Impairment in Perinatally Infected Children: A Meta-analysis. Pediatrics. 2016 Nov;138(5):e20160893
18. Hammers A, Allom R, Koepp MJ, Free SL, Myers R, Lemieux L, et al. Three-dimensional maximum probability atlas of the human brain, with particular reference to the temporal lobe. Hum Brain Mapp 2003, 19: 224-247.
19. Gousias IS, Rueckert D, Heckemann RA, Dyet LE, Boardman JP, Edwards AD, et al. Automatic segmentation of brain MRIs of 2-year-olds into 83 regions of interest. Neuroimage 2008 Apr 1;40(2):672-684.

20. Gaetani L, Blennow K, Calabresi P, Di Filippo M, Parnetti L, Zetterberg H et al. Neurofilament light chain as a biomarker in neurological disorders J Neurol Neurosurg Psychiatry 2019;90:870-8121.
21. Mellgren A, Price RW, Hagberg L, Rosengren L, Brew BJ, Gisslen M. Antiretroviral treatment reduces increased CSF neurofilament protein (NfL) in HIV-1 infection. Neurology 2007;69:1536–41.
22. Price RW, Peterson J, Fuchs D, Angel TE, Zetterberg H, Hagberg L, et al. Approach to cerebrospinal fluid (CSF) biomarker discovery and evaluation in HIV infection. J Neuroimmune Pharmacol 2013;8: 1147–58.
23. Anderson AM, Easley KA, Kasher N, Franklin D, Heaton RK, Zetterberg H Neurofilament light chain in blood is negatively associated with neuropsychological performance in HIV-infected adults and declines with initiation of antiretroviral therapy. Journal of NeuroVirology 2018;24:695–701
24. Menke RA, Gray E, Lu CH, Kuhle J, Talbot K, Malaspina A, et al. CSF neurofilament light chain reflects corticospinal tract degeneration in ALS. Ann Clin Transl Neurol. 2015;2:748-55
25. Lu CH, Macdonald-Wallis C, Gray E, Pearce N, Petzold A, Norgren N, et al. Neurofilament light chain: a prognostic biomarker in amyotrophic lateral sclerosis. Neurology 2015;84:2247-57.
26. Mattsson N, Andreasson U, Zetterberg H, Blennow K; Alzheimer's Disease Neuroimaging Initiative. Association of plasma neurofilament light with neurodegeneration in patients with alzheimer disease. JAMA Neurol 2017;74:557-66.
27. Rohrer JD, Woollacott IO, Dick KM, Brotherhood E, Gordon E, Fellows A, et al. Serum neurofilament light chain protein is a measure of disease intensity in frontotemporal dementia. Neurology. 2016;87:1329-36
28. 28. Posthuma D, Baaré WFC, Hulshoff Pol HE, Kahn RS, Boomsma DI, De Geus EJC. Genetic correlations between brain volumes and the WAIS-III dimensions of verbal comprehension, working memory, perceptual organization, and processing speed. Twin Research. 2003;6:131–9.
29. Borghesani PR, Madhyastha TM, Aylward EH, Reiter MA, Swarny BR, Schaie KW, et al. The association between higher order abilities, processing speed, and age are variably mediated by white matter integrity during typical aging. Neuropsychologia. 2013;51:1435–44.

30. Jacobs HIL, Leritz EC, Williams VJ, Van Boxtel MPJ, Elst Wvd, Jolles J, et al. Association between white matter microstructure, executive functions, and processing speed in older adults: the impact of vascular health. Human brain mapping. 2013;34(1):77–95. pmid:21954054
31. Johnson EB, Byrne LM, Gregory S, Rodrigues FB, Blennow K, Durr A, Leavitt BR, Roos RA, Zetterberg H, Tabrizi SJ, Scahill RI, Wild EJ; TRACK-HD Study Group. Neurofilament light protein in blood predicts regional atrophy in Huntington disease. Neurology. 2018 Feb 20;90:717-23
32. Li QF, Dong Y, Yang L, Xie JJ, Ma Y, Du YC.,et al. Neurofilament light chain is a promising serum biomarker in spinocerebellar ataxia type 3. Mol Neurodegener. 2019:4;14-39.
33. Van Zoest R , Underwood J, De Francesco D , Sabin CA, Cole JH , Wit FW, et al. Structural Brain Abnormalities in Successfully Treated HIV Infection: Associations With Disease and Cerebrospinal Fluid Biomarkers. J Infect Dis 2017: 27;217:69-81.
34. Bridel C, van Wieringen WN, Zetterberg H, Tijms BM, Teunissen CE, Alvarez-Cermeno JC, et al. Diagnostic value of cerebrospinal fluid Neurofilament light protein in neurology: a systematic review and meta-analysis. JAMA Neurol. 2019; Epub ahead of print.
35. Cohen S, Caan MWA, Mutsaerts H-J, Scherpbier HJ, Kuijpers TW, Reiss P, *et al.* Cerebral injury in perinatally HIV-infected children compared to matched healthy controls. *Neurology* 2016; 86:19–27
36. Sarma, M. K., Nagarajan, R., Keller, M. A., Kumar, R., Nielsen-Saines, K., Michalik, D. E., et al. Regional brain gray and white matter changes in perinatally HIV-infected adolescents. *NeuroImage: Clinical*, 2014:*4*;29–34.

DISCUSIÓN

Los resultados de este trabajo de investigación refuerzan la evidencia de que la infección por VIH en pacientes infectados durante el periodo perinatal produce una alteración de la estructura cerebral, a pesar de un buen control inmunovirológico.

Los participantes con VIH-TV pertenecen en su totalidad a CoRISpe, la Cohorte Nacional de Pacientes Pediátricos con Infección VIH. CoRISpe nace en el año 2008 y tiene como principal objetivo el contribuir a ampliar el conocimiento científico sobre la infección por el VIH en niños y adolescentes, proporcionando datos demográficos, sociopsicológicos, clínicos y de laboratorio de pacientes pediátricos VIH+. Todos los datos se recogen de forma retrospectiva desde el año 1995 y de forma prospectiva desde el año 2008.

En nuestro estudio el análisis de neuroimagen estructural muestra una disminución del grosor cortical y un menor volumen en ciertas regiones subcorticales en adolescentes y jóvenes VIH-TV. Sin embargo, el subestudio de neuroimagen funcional en el que únicamente participaron jóvenes con infección VIH-TV con un muy buen control inmunovirológico, en estadío no C del CDC, y con adecuadas funciones cognitivas, no se objetivaron diferencias en los patrones de activación neuronal durante la realización de tareas de fluidez verbal y motora. Por otro lado, la medición del biomarcador plasmático NfL, que mide daño axonal, ha evidenciado mayores niveles de pNfL en pacientes con mal control y CV detectable.

No obstante, estas alteraciones en las estructuras cerebrales y marcadores de lesión neuronal, habitualmente solo se han traducido en un peor desarrollo neurocognitivo en pacientes con mal control y pacientes con VIH-TV estadío C, lo que pone de manifiesto, una vez más, la importancia de un diagnóstico e inicio del tratamiento precoz.

EFECTOS DE LA INFECCIÓN PERINATAL POR VIH SOBRE EL GROSOR CORTICAL Y VOLÚMENES SUBCORTICALES DE SUSTANCIA GRIS EN ADULTOS JÓVENES.

Este estudio muestra una disminución del grosor cortical cerebral en diferentes áreas a nivel temporal, orbitofrontal y occipital y un menor volumen en ciertas regiones subcorticales (amígdala derecha y putamen izquierdo) en el grupo VIH-TV, al compararlo con un grupo control bien pareado y sin infección por VIH. Sin embargo, no se observan diferencias ES en las evaluaciones neurocognitivas que medían FE e IF, ni en las psicopatológicas mediante evaluación de escalas de ansiedad y depresión.

Las alteraciones del desarrollo de la estructura cerebral encontradas en este estudio han sido evidenciadas por resultados observados en otros estudios de neuroimagen en población VIH-TV. Por ejemplo, en 2019 Yu et al. publicaron resultados similares a los encontrados en nuestro estudio, al demostrar que los pacientes con VIH-TV presentaban de forma ES adelgazamiento cortical en regiones temporales y orbitofrontales, y curiosamente mayor grosor cortical a nivel occipital izquierdo y sulco olfatorio al compararlos con un grupo sin VIH de características similares. [51]

Sin embargo, otras investigaciones que evalúan grosor cortical en pacientes con VIH-TV y grupos control sin VIH han mostrado resultados muy variables. Nwosu et al. encuentra mayor grosor cortical en el grupo VIH-TV en la región latero-inferior occipital izquierda, [45] y el estudio de Yadav et al, muestra mayor adelgazamiento cortical en regiones post-centrales bilaterales y región temporal superior derecha, pero mayor grosor cortical en regiones frontales bilaterales.[47] Y finalmente, algunos estudios no han encontrado diferencias en el grosor cortical. [42,68]

Las diferencias en el grosor cortical a nivel de regiones orbitofrontales entre pacientes con VIH-TV y los controles sin VIH, justificarían por que los pacientes con VIH muestran una mayor afectación de las funciones ejecutivas. Hay estudios que han observado que una disminución del grosor cortical en el área orbitofrontal de adolescentes con VIH-TV se correlaciona con un comportamiento impulsivo y una mayor inhibición de las funciones ejecutivas,[69] uno de los déficits neurocognitivos que más ha sido descrito en la población VIH-TV.[70-72] De la misma forma, hemos observado un mayor adelgazamiento del giro fusiforme en los pacientes con VIH-TV comparado con el grupo control sin VIH. La atrofia de esta región se ha asociado con el desarrollo temprano de la enfermedad de Alzheimer,[73] mayor impacto en las funciones ejecutivas como la memoria de trabajo [74] e impulsividad, [75] y también mayor grado de depresión [76] y aubso de drogas. [77-79]

Respecto a los volúmenes subcorticales de sustancia gris, el grupo VIH-TV mostró menor volumen en amígdala derecha y putamen izquierdo. Disminuciones de volumen a nivel de amígdala y núcleo del caudado han sido reportadas previamente en estudios de adultos con infección por VIH. [80-81] De forma similar, otros autores han observado menor volumen a nivel de otros ganglios basales, como el globo pálido, en adolescentes con VIH-TV. [46,55]

Dentro del grupo VIH, nuestro estudio encontró que un mayor volumen del putamen derecho se correlacionaba con cifras más elevadas de CD4. En esta línea, Wade et al, describieron que un grupo de niños con VIH-TV con recuetos más altos de CD4 presentaban mayor volumen en determinadas áreas subcorticales.[55] De forma similar, Cohen et al. publicaron que un tiempo más prolongado con bajo recuento de CD4 se asociaba con menor volumen total de GM. [43]

Además, en nuestro estudio observamos que un retraso en el inicio del TAR y un nadir de CD4 más bajo, se asociaba con volúmenes más elevados a nivel del núcleo accumbens. Acorde con estos resultados, otros estudios han encontrado en población VIH-TV un aumento de los núcleos caudado, accumbens y putamen. [49-50] Aunque la fisiopatología de porque se puede producir un mayor volumen en ciertas regiones cerebrales no es bien conocida, se postulan dos principales hipótesis: la primera sugiere que puede estar relacionada con hipertrofia inducida por estrés secundario a una alteración en el "prunning" de las neuronas espinosas medianas que ocupan esta región. En segundo lugar, la hipertrofia puede ser el resultado de una neuroinflamación y neuroactivación mantenida. Todos estos resultados pueden ser traducidos en que un temprano, adecuado y mantenido TAR es probablemente la clave para una adecuada protección del SNC.

Sin embargo, también es importarte señalar que, aunque los pacientes con VIH-TV presentaron menores volúmenes de sustancia gris y adelgazamiento cortical, no se observaron diferencias ES en las evaluaciones neurocognitivas y neuropsiquiátricas, lo que hace plantear que los estudios de neuroimagen son capaces de detectar alteraciones del neurodesarrollo más sutiles. La traducción clínica de estos resultados no estaría clara todavía y precisa de estudios longitudinales para determinar su evolución y relevancia en el funcionamiento del paciente a largo plazo.

Finalmente, es importante tener en cuenta que esta cohorte de jóvenes con VIH-TV, en su mayoría forman parte de la era pre-TAR, lo que implicaría que muchos de ellos han recibido tratamientos subóptimos durante los primeros años de vida. Hay posibilidad de que el virus haya causado un cierto daño neurológico durante los primeros años de vida, que son cruciales en el desarrollo cerebral. A pesar de ello, la gran mayoría de estos pacientes mantienen un buen control inmunovirológico desde

el inicio del TAR hace más de 10 años, manteniendo cargas virales indetectables o con niveles muy bajos de detectabilidad, con un buen rendimiento en su vida diaria, constituyendo un grupo único e irrepetible que le dan un valor añadido al estudio. Sería muy interesante comparar este grupo poblacional con un grupo de pacientes tratados de forma precoz pareados por edad y nivel educativo y socioeconómico, con la finalidad de determinar el origen de estas alteraciones del desarrollo cerebral, y si estas podrían ser prevenidas con un diagnóstico y temprano inicio de TAR.

REVISIÓN SISTEMÁTICA DE ESTUDIOS DE RESONANCIA MAGNÉTICA EN PACIENTES VIH INFECTADOS POR TRANSMISIÓN VERTICAL

Los datos obtenidos mediante la revisión sistemática de todos los estudios de neuroimagen realizados hasta el momento en población VIH-TV evidencian clara afectación sobre el desarrollo de las estructuras cerebrales, especialmente: reducción de volúmenes regionales de sustancia gris, menor desarrollo de las circunvoluciones cerebrales, disminución del grosor cortical; en estudios de tractografía se ha observado una disminución de FA y aumento de MD; y los estudios preliminares de RMf en reposo evidencian alteraciones en la conectividad funcional. Sin embargo, no existe un claro consenso sobre que estructuras cerebrales parecen estar más afectadas.

La mayoría de los estudios de neuroimagen realizados en población VIH-TV tiene importantes limitaciones, especialmente el tamaño muestral, que suele ser inferior a 20-40 pacientes, lo que favorece que se traten, en su mayoría, de estudios con poca potencia estadística. Gracias a los avances en los programas de prevención de transmisión materno infantil del VIH, en los países con altos ingresos el número de

pacientes con VIH-TV es escaso, por lo que los estudios realizados en estos países, cuenta generalmente, con un muy limitado número de participantes.

Además, la mayoría de los estudios analizados no recogen apenas variables clínicas, sociodemográficas y psicológicas, como si recoge nuestro estudio. Algunos de los parámetros que son determinantes en estudios de neuroimagen, como las condiciones socioeconómicas y de salud, la calidad de vida, otras comorbilidades incluidos alteraciones psiquiátricas y abuso de drogas, no son tenidas en cuenta. Respecto a las variables relacionadas con la infección por VIH, incluida la edad al diagnóstico, clasificación CDC, asociación o no de encefalopatía por VIH, tipo de TAR o edad al inicio de TAR no son recogidas en la mayoría de los estudios realizados, ni existe un consenso sobre que variables deberían ser tenidas en cuenta a la hora de plantear realizar futuros estudios de neuroimagen en población VIH.

Investigaciones de mayor calidad pueden incluir estudios más amplios a través de colaboraciones con múltiples grupos de investigación. A pesar de la falta de subvenciones sustanciales, los investigadores pueden encontrar formas innovadoras de maximizar recursos en investigación y aumentar la potencia de los estudios a través de la colaboración. [82]

Otra limitación de los estudios de neuroimagen en general, y de los estudios de RM cerebral en población VIH-TV en particular, es que la metodología respecto a las técnicas empleadas es muy variable, lo que también podrían explicar las diferencias en los resultados.[83] La comunidad implicada en los estudios de neuroimagen ha respondido a estos retos con la sincronización de protocolos y compartiendo sus datos.

Los futuros estudios de VIH-TV deberían emplear las mismas secuencias y el mismo “hardware”, lo que permitiría realizar comparaciones y normalizar los datos.

Mientas que los estudios de neuroimagen en pacientes con VIH-TV se quieren focalizar en hipótesis muy específicas o tecnologías más refinadas, la población VIH-TV se beneficiaría al adoptar un enfoque de los datos más abierto, y realizar el esfuerzo de armonizar la metodología empleada y realizar análisis similares con la finalizad de homogeneizar los estudios de neuroimagen en este grupo poblacional.

La diseminación de herramientas para el procesamiento y análisis de las pruebas de neuroimagen nos permitirá trazar y comprender mejor las trayectorias dinámicas del desarrollo cerebral en niños con VIH-TV, apoyando que intervenciones pueden mejorar el pronóstico neurológico de estos pacientes. La inclusión en estos estudios, de datos relativos a la infección VIH, incluyendo características clínicas e inmunovirológicas, así como información detallada sobre la edad al inicio del TAR, es de vital importancia para entender mejor el impacto de la enfermedad sobre el SNC.

MEDICIÓN DE LA ACTIVIDAD CEREBRAL A TRAVÉS DE LA RM FUNCIONAL EN PACIENTES VIH DE TRANSMISIÓN VERTICAL

Los resultados obtenidos del estudio de neuroimagen funcional que compara la activación neuronal medida por RMf mediante realización de tareas, en un subgrupo de pacientes con buen control inmunovirológico, en estadío no C del CDC, y con adecuadas funciones cognitivas y en un grupo control sin VIH, no se encuentran diferencias significativas. Sin embargo, dentro del grupo VIH, mayor tiempo con TAR se asocia con mayor activación en el giro frontal inferior izquierdo, lo que podría indicar una posible compensación funcional

La metodología del estudio incluyó una tarea de fluidez fonológica en la que la región principalmente implicada fue el GFII, que se ha descrito previamente como uno de los nodos funcionales más destacados para la fluidez verbal fonológica. [84-86]

Además, nuestros hallazgos de que los individuos VIH-TV a más años de TAR presentan una mayor activación del GFII durante la realización de la tarea, es consistente con nuestro conocimiento de la compensación funcional, sugiriendo que esta estructura es importante para el desempeño exitoso de la fluidez fonológica. De forma similar, Thames et al. observaron que el recuento de CD4 se asoció de forma directa con un mayor porcentaje de cambio de señal en el GFII durante la tarea de fluidez verbal fonológica. [63]

Por el contrario, estudios sobre la activación neuronal durante la realización de tareas que implican atención, funciones ejecutivas y memoria, en adultos infectados por el VIH, han reportado diferencias entre los pacientes con VIH y los controles seronegativos, encontrando una mayor activación en el grupo VIH.[87] Sin embargo, la mayoría de estos estudios no han tenido en cuenta el estado inmunovirológico, ya que no todos los pacientes recibían TAR. Además, no existen datos comparativos sobre RMf durante la realización de tareas en población VIH-TV, lo que dificulta la interpretación de los resultados.

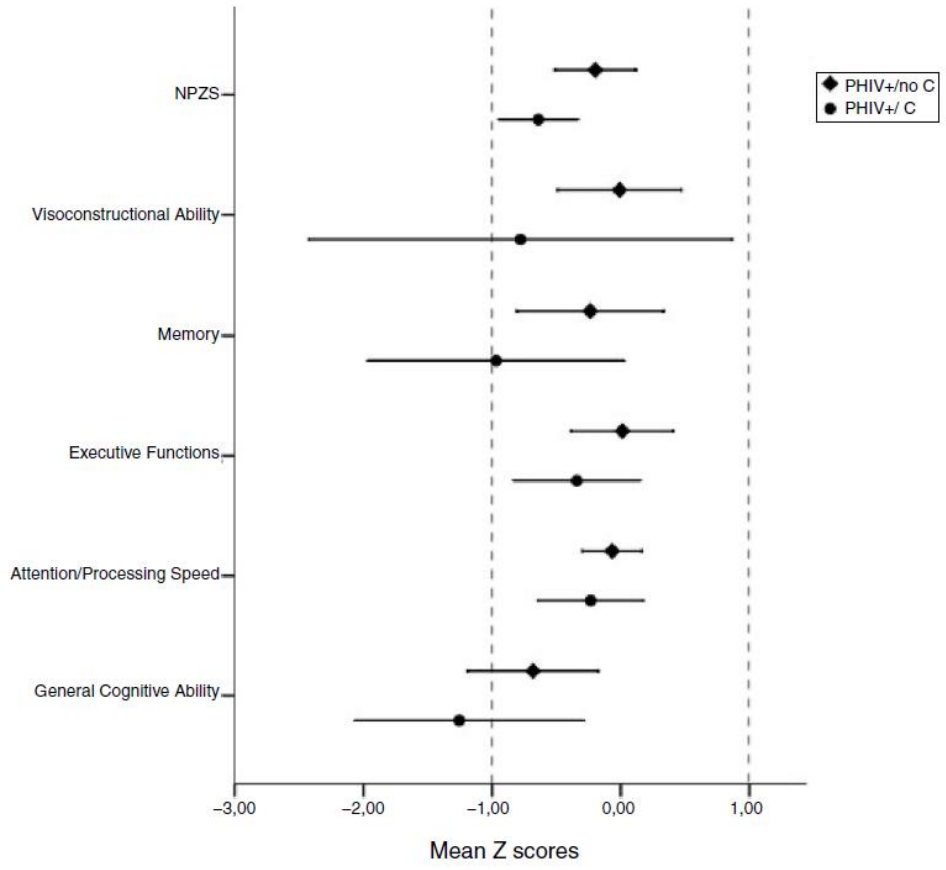
En nuestro estudio, la ausencia de diferencias entre grupos podría deberse a la cuidadosa selección de un grupo de pacientes con excelente control inmunovirológico. Se trata de 10 pacientes, adultos jóvenes, que llevan más de la mitad de su vida recibiendo TAR (mediana de 13,7 años), con una CV indetectable de forma mantenida (mediana de 9,5 años), y a su vez pertenecientes todos a estadío A o B del CDC, excluyendo aquellos pacientes en estadío C.

Varios estudios recientes, incluido un estudio realizado por NeuroCoRISpe, acerca del desarrollo neurocognitivo en pacientes con VIH-TV, indican que únicamente los pacientes en estadío C del CDC van a mostrar un peor rendimiento

cognitivo, sugiriendo que aquellos niños infectados por el VIH que no habían desarrollado enfermedad severa antes del inicio del TAR, presentaban un riesgo similar al resto de sus pares no infectados por el VIH, de manifestar dichas alteraciones cognitivas. [22,88] En el estudio de evaluación neurocognitiva en un grupo de adolescentes VIH-TV realizado por NeuroCoRISpe y que se incluye como anexo a esta memoria, se observó que los pacientes VIH estadío C presentaban un rendimiento más bajo en todos los dominios, incluido NPZ-5 que representa una puntuación global (media de Z-scores de todos los dominios), pero especialmente en inteligencia cristalizada (relacionada con el aprendizaje y nivel cultural), en el cociente de inteligencia, en habilidades cognitivas y en memoria. Sin embargo, el grupo VIH no estadío C, puntuó de forma muy similar al grupo no VIH (**Figuras 7 y 8**) [88]

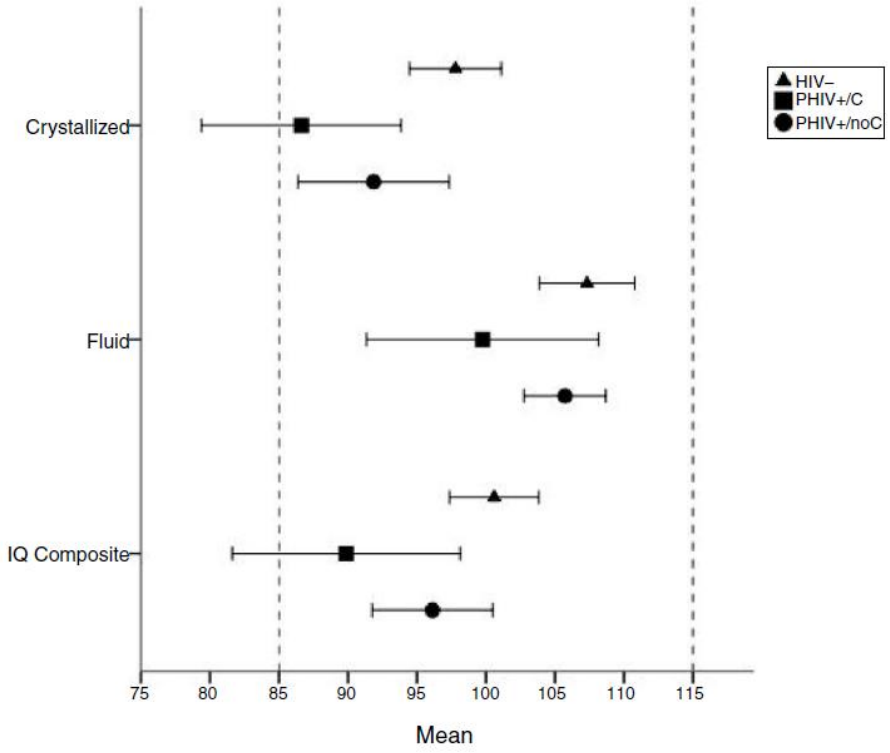
Por tanto, podemos afirmar que, aunque los mecanismos exactos que gobiernan la recuperación neuronal siguen siendo desconocidos, estos hallazgos apoyan la teoría de que una temprana y más duradera terapia antiretroviral, serían los mejores factores neuroprotectores para este grupo poblacional.

Figura 7. Media de Z-scores de la evaluación neurocognitiva en diferentes dominios entre pacientes VIH estadío C y pacientes VIH estadío no C.



La media Z-score indica dónde se compara la puntuación del paciente con la puntuación media del grupo sin VIH (cuántas desviaciones estándar por debajo o por encima de la media del grupo de referencia). Los resultados entre -1 DE y +1 DE se consideran normales. Se encontraron diferencias significativas entre PHIV + / C y PHIV + /noC: NPZ-5, Media Z-score [DE], −0,64 [0,34], −0,19 [0,64] respectivamente, p = 0,037; Memoria, media Z-score [DE], −0,97 [1,08], −0,21 [1,18], respectivamente; p = 0,067

Figura 8. Puntuaciones estándar de inteligencia fluida, inteligencia cristalizada y coeficiente intelectual en pacientes VIH agrupados por estadíos clínicos del CDC.



Todas las escalas representan puntuaciones estándar basadas en la edad (media = 100, DE = 15).
La inteligencia cristalizada se ve más afectada por la cultura, la educación y la experiencia, mientras que la inteligencia fluida está relacionada con la capacidad de pensar lógicamente y resolver problemas en situaciones novedosas y su base es genética. A partir de ambos, se calcula una puntuación compuesta global (puntuación compuesta de coeficiente intelectual- IQ Composite).
Se encontraron diferencias significativas entre PHIV+/C vs. VIH negativo: capacidad cristalizada (diferencia media: 11,175, p = 0,025); IQ Composite (diferencia media: 10,725, p = 0,016).

EVALUACIÓN DEL NEUROFILAMENTO DE CADENA LIGERA COMO BIOMARCADOR DE LESIÓN NEURONAL EN PACIENTES VIH DE TRANSMISIÓN VERTICAL

El Neurofilamento de Cadena Ligera, constituye una subunidad imprescindible como parte de los axones neuronales.[89] La medición de concentraciones plasmáticas de NfL se ha reportado recientemente, como un fiable biomarcador pronóstico al inicio y durante la progresión de enfermedades neurodegenerativas, incluido el VIH. [64-67,90]

En este estudio, hemos mostrado que pacientes con VIH-TV que reciben TAR y mantienen carga viral suprimida presentan concentraciones plasmáticas de NfL muy similares a aquellas encontradas en individuos VIH negativos. De forma adicional, incluso considerando la limitación de un reducido tamaño muestral, los únicos 5 pacientes que presentan carga viral detectable mantienen concentraciones de pNfL más elevadas, lo que indicaría que una persistente replicación viral puede contribuir a un daño neuronal mantenido.

Esto ha sido demostrado de forma similar en población adulta con VIH, indicando que la degeneración axonal inducida por el VIH puede ser suprimida gracias al TAR, y encontrando correlaciones en las concentraciones plasmáticas y LCR de NfL a lo largo del tiempo tras el inicio del TAR. [64,91,92]

Estos resultados enfatizan la importancia de un inicio temprano y mantenido del TAR con la finalidad de evitar un mayor daño neuronal en los niños.

Por otro lado, en este estudio exploratorio en adolescentes y adultos jóvenes con VIH-TV, hemos encontrado que concentraciones más elevadas de pNfL se asocian con menores volúmenes regionales y una peor puntuación en el test neurocognitivo que evalúa la velocidad de procesamiento (*Digit Symbol-Coding subtest*). La velocidad de procesamiento indica cuan rápida se capta una información,

se procesa y se responde a ella. Esta información puede ser visual o auditiva y es uno de los procesos más afectados en población VIH.

De forma similar, Anderson et al. publicaron que concentraciones más elevadas de pNfL se asociaban con peor rendimiento en las evaluaciones neurocognitivas en población adulta con VIH. [93]

Igualmente, otros estudios muestran que concentraciones más elevadas de NfL aparecen en múltiples enfermedades neurológicas en los que la velocidad de procesamiento es uno de los procesos cognitivos más afectados, como la esclerosis lateral amiotrófica, [94-95] la Enfermedad de Alzheimer, [96] o la demencia frontotemporal.[97] Se considera que la velocidad de procesamiento es dependiente de las propiedades de la sustancia blanca. [98-100] La sustancia blanca se compone de los axones mielinizados, y el grosor de las vainas de mielina está asociado con la velocidad de la conducción nerviosa; por ello, la relación entre la velocidad de procesamiento y las concentraciones de NfL parecen consistentes.

Por otro lado, diferentes estudios han mostrado que niveles elevados de pNfL se asocian con menor volumen cortical y subcortical de sustancia gris y sustancia blanca en pacientes con enfermedades neurodegenerativas.[101,102] Pero, sin embargo, el único estudio realizado en población adulta con VIH en el que se evaluaban biomarcadores de daño neuronal en LCR, incluido NfL, no se asociaban con las medidas de imagen de las estructuras cerebrales. [103]

Es importante reseñar, que el NfL tiene como limitación que no se trata de un biomarcador específico. Como ya hemos mencionado, niveles elevados de NfL se observan en múltiples enfermedades neurológicas, incluidas enfermedades neurodegenerativas, pero también en neuropatía periférica y traumatismos craneoencefálicos.[65,104] El NfL plasmático y en LCR también puede encontrarse

elevado en ciertas infecciones del SNC, [105] incluido la infección por SARS-CoV-2 en pacientes con sintomatología neurológica.[106] Sin embargo, y aunque no se trate de un marcador de daño neurológico específico, es un biomarcador útil, puesto que es sencillo de realizar aportando una medición aproximada de daño neuronal secundaria a una inflamación mantenida del SNC. Sería útil realizar estudios longitudinales y a largo plazo que valorase si estos pacientes con mayores concentraciones plasmáticas de NfL, van a desarrollar en el futuro más enfermedades neurodegenerativas como son el Parkinson y Alzheimer.

En referencia a los volúmenes cerebrales, en este estudio encontramos que el grupo VIH-TV presentaba menor volumen de sustancia blanca en determinadas regiones cerebrales como el cerebelo, lóbulos occipitales y núcleo accumbens. Como ya hemos visto previamente, diversos estudios realizados en adolescentes con VIH-TV han reportado similares resultados mostrando menor volumen de sustancia blanca regional o total al compararlo con un grupo control sin VIH. [43,48]

Finalmente, es importante reseñar, que pocos estudios realizados hasta la fecha en población VIH-TV, aportan tantos datos de evaluación del neurodesarrollo, incluyendo evaluaciones neurocognitivas y neuropsicológicas, pruebas de neuroimagen y medición de daño neuronal a través de la medición de NfL plasmático, contribuyendo a aportar valiosa información del impacto que tiene el VIH sobre el sistema nervioso central.

Los estudios realizados en este trabajo de investigación parecen indicar que un mejor control del virus, gracias al inicio temprano del TAR, manteniendo un buen control inmunovirológico, es el mejor factor neuroprotector.

CONCLUSIONES

CONCLUSIONES

1. La cohorte de adultos jóvenes con infección VIH de transmisión vertical (VIH-TV) con buen control inmunovirológico, no muestra diferencias en las evaluaciones neurocognitivas al compararlas con un grupo control pareado por sexo, edad y nivel socioeconómico.

2. Sin embargo, el estudio de morfometría cerebral muestra un mayor adelgazamiento del grosor cortical a nivel temporal, orbitofrontal y occipital, y un menor volumen regional de sustancia gris a nivel subcortical en el grupo VIH-TV, no estando clara la posible traducción clínica de estos resultados en la actualidad y a largo plazo.

3. Dentro del grupo VIH-TV, un mayor recuento de linfocitos T CD4, se asocia con un mayor volumen regional a nivel del putamen. De la misma forma un inicio tardío de del TAR y un nadir de linfocitos T CD4 más bajo, presentan correlación con un mayor volumen a nivel del núcleo accumbens.

4. Estos resultados sugieren que los estudios de neuroimagen estructural son capaces de detectar alteraciones del desarrollo cerebral en los pacientes con VIH infectados verticalmente, a pesar de que las evaluaciones psicométricas sean normales.

5. En un subgrupo de pacientes con VIH-TV con muy buen control inmunovirológico, sin antecedentes de enfermedad severa pertenecientes a

estadíos A o B del CDC, con TAR estable y un buen rendimiento en sus actividades diarias, no se encuentran diferencias en los patrones de actividad neuronal medida por RMf.

6. En el estudio de RMf, durante la realización de una tardea de fluidez verbal, los pacientes con mayor tiempo de TAR presentaban una mayor actividad neuronal en los clusters que engloban el giro frontal inferior izquierdo, que se traduce en un aumento de la demanda metabólica mediante consumo de glucosa y oxígeno para llevar a cabo dicha tarea.

7. Los estudios de neuroimagen que han sido publicados hasta la fecha evidencian, de igual forma, una clara alteración en el desarrollo cerebral de la población con VIH-TV, pero no existe un consenso sobre que estructuras cerebrales estarían más afectadas.

8. Es fundamental que se unifiquen los criterios necesarios que deben incluir los estudios de neuroimagen en población VIH, siendo de vital importancia la evaluación de datos relacionados con la infección por VIH (incluidas las características clínicas, inmunovirológicas e información detallada del tratamiento antirretroviral) y características socioeconómicas y demográficas, con la finalidad de entender mejor el impacto del virus en el SNC.

9. El Neurofilamento de cadena Ligera (NfL), es un biomarcador fiable y accesible de lesión neuronal, que evita la realización de una punción lumbar para su medición en líquido cefalorraquídeo.

10. No encontramos diferencias entre los niveles en plasma de NfL de pacientes con VIH-TV y un grupo control pareado por edad.

11. Las concentraciones plasmáticas de NfL en pacientes con VIH-TV, son más elevadas en pacientes con mal control virológico, lo que podría indicar mayor daño neuronal en este grupo de pacientes.

12. Los pacientes con VIH-TV muestran menor volumen regional de sustancia blanca en cerebelo, lóbulos occipitales y núcleo accumbens (región sustancia blanca).

13. Este estudio exploratorio muestra posible correlación entre ciertas regiones de sustancia blanca cerebral, evaluación neurocognitiva y la concentración plasmática de NfL en población VIH-TV.

14. En esta memoria se han evaluado, de forma detallada, las posibles alteraciones de desarrollo cerebral y daño neuronal que presentan adultos jóvenes con VIH de transmisión vertical en un país con un sistema de salud desarrollado.

15. Sería fundamental realizar un seguimiento longitudinal de estos pacientes para evaluar la traducción clínica de estos resultados a largo plazo.

16. Se trata de un estudio único e irrepetible, puesto que este grupo de participantes pertenece, en su mayoría, a la época previa al inicio del TAR,

habiendo recibido en los primeros años de vida tratamiento subóptimos y permitiendo que el virus se estableciese en el SNC como reservorio

17. Un inicio del TAR temprano y mantenido, evitando así progresión de la infección a estadíos más graves (estadío C del CDC), parece ser el principal factor neuroprotector.

ANEXO 1:

OTRAS PUBLICACIONES

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Neurocognitive and quality of life study in perinatally HIV-infected young people and their peers. NeuroCoRISpeS study

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ABSTRACT

Background: Assessing the role of HIV and non-HIV related factors is essential for a better understanding of the neurocognitive outcomes in perinatally HIV-infected (PHIV+) young people. The aim of our study was to assess cognition and quality of life (QoL) of a PHIV+ cohort of young people and to compare it with a control group.

Methods: Thirty PHIV+ and 30 HIV(−) healthy young adults matched by age, sex and socioeconomic status completed a protocol that included neurocognitive tests, a psychosocial semi-structured interview and a QoL questionnaire (PedsQL). Neurocognitive domain-specific and domain-general (NPZ-5) *Z*-scores were calculated. CDC AIDS-defining category C or not C (PHIV+/C, PHIV+/noC) was considered to evaluate differences within the PHIV+ group. Univariate and multivariate analysis were performed.

Results: Sixty patients were included; 67% were female; median age (IQR) 19 years (18–21). Regarding PHIV+ young people, 27% showed CDC C category (none encephalopathy), 93% were on ART and 77% had undetectable viral load. No differences regarding occupation were found, although the HIV(−) group repeated less grades ($p = 0.028$) and had a higher education level ($p = 0.021$).

No differences were found between PHIV+/noC and HIV(−) participants. However, the PHIV+/C group showed poorer performance than PHIV+/noC (NPZ-5, $p = 0.037$) and HIV(−) subjects (crystallised intelligence, $p = 0.025$; intelligence quotient, $p = 0.016$). Higher nadir CD4+ T-cell count was related to better *Z*-score in memory ($p = 0.007$) and NPZ-5 ($p = 0.025$). Earlier and longer exposure to ART resulted in better performance in memory ($p = 0.004$) and executive functions ($p = 0.015$), respectively.

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Sleep Profile and Self-Reported Neuropsychiatric Symptoms in Vertically HIV-Infected Adolescents on cART

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Abstract

Background Sleep quality (SQ) data in human immunodeficiency virus (HIV) pediatric population are scarce. Our main objective was to assess SQ in our cohort and to determine the impact of antiretroviral therapy (ART) on sleep in a cohort of HIV-infected adolescents on cART.

Materials and Methods The SQ was assessed through the Pittsburgh Sleep Quality Index (PSQI). Neuropsychiatric symptoms (NS) were recorded using an auto-administered questionnaire. To determine the antiretroviral (ARV) impact of efavirenz (EFV) on SQ, patients on EFV versus protease inhibitors-based regimens were compared.

Results Forty-six patients were evaluated (median age: 16 years, interquartile range [IQR]: 10.8, 17)). Age at the start of ART: 1.3 years (0.4, 5.2); 23.9% showed acquired immunodeficiency syndrome (AIDS) category. Median CD4 at baseline was 656 (550, 808) cells/mm^3; 91.3% had viral load <50 copies/mL. Median time on cART was 11.3 years (7.5, 15.2). Fifty-two percent of the patients were on EFV-based regimen. No differences were found in clinical and immunovirological variables although patients on EFV were older and were exposed for a longer time to ARV. Poor SQ was found in 26.1% of patients. Most frequent complaints were: sleep disturbances (76.1%), sleep latency (63%), and daytime dysfunction (54.3%). Similarly, there were no significant differences in NS between both treatment groups according to patients' reports but were significantly more common in bad sleepers. Patients on EFV-based regimen were

Keywords
- perinatal HIV infection
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- antiretrovirals
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ORIGINAL

Prevalencia y factores de riesgo de síntomas psicológicos en una muestra española de jóvenes con VIH en comparación con pares no infectados

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Jóvenes

Resumen
Introducción: Los objetivos principales del estudio fueron dos: a) identificar la prevalencia de síntomas depresivos y de ansiedad y trastornos del sueño en pacientes jóvenes con infección por VIH de transmisión vertical en comparación con un grupo de pares no infectados, y b) identificar factores sociodemográficos, psicosociales y relacionados con la medicación y otros factores de riesgo y protectores relacionados con los síntomas psicológicos.
Métodos: Estudio transversal en dos grupos con medidas independientes: 36 sujetos con VIH (transmisión vertical) y 39 sin VIH (no infectados). Se emplearon tres instrumentos de evaluación estandarizados y un cuestionario sociodemográfico/psicosocial (STAI, BDI, PSQI y test sociodemográfico adaptado). Se realizó análisis univariante y multivariante.

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BIBLIOGRAFÍA

1. UNAIDS. 2021 UNAIDS Global AIDS Update- Confronting inequalities –Lessons for pandemic responses from 40 years of AIDS. Disponible y consultada el 05 de agosto de 2021: https://www.unaids.org/en/resources/documents/2021/2021-global-aids-update.

2. UNAIDS. Start Free, Stay Free, AIDS Free- Final report on 2020 targets. Disponible y consultada el 05 de agosto de 2021. https://www.unaids.org/sites/default/files/media_asset/2021_start-free-stay-free-aids-free-final-report-on-2020-targets_en.pdf

3. Lohse N, Hansen AB, Pedersen G, Kronborg G, Gerstoft J, Sorensen HT, et al. Survival of persons with and without HIV infection in Denmark, 1995- 2005. *Annals of internal medicine* 2007; 146(2):87-95.

4. Patel K, Ming X, Williams PL, Robertson KR, Oleske JM, Seage GR III. Impact of HAART and CNS-penetrating antiretroviral regimens on HIV encephalopathy among perinatally infected children and adolescents. AIDS 2009; 23:1893–901.

5. Heaton RK, Franklin DR, Ellis RJ, et al. HIV-associated neurocognitive disorders before and during the era of combination antiretroviral therapy: differences in rates, nature, and predictors. J Neurovirol 2011;17:3–16.

6. González-Scarano F, Martín-García J. The neuropathogenesis of AIDS. Nat Rev Immunol 2005;5:69–81.

7. Spudich S, Gisslen M, Hagberg L, Lee E, Liegler T, Brew B, et al. Central nervous system immune activation characterizes primary human immunodeficiency virus 1 infection even in participants with minimal cerebrospinal fluid viral burden. *The Journal of infectious diseases* 2011; 204(5):753-760.

8. Valcour V, Chalermchai T, Sailasuta N, Marovich M, Lerdlum S, Suttichom D, et al. Central nervous system viral invasion and inflammation during acute HIV infection. *The Journal of infectious diseases* 2012; 206(2):275-282.

9. Spudich S, Gonzalez-Scarano F. HIV-1-related central nervous system disease: current issues in pathogenesis, diagnosis, and treatment. *Cold Spring Harbor perspectives in medicine* 2012; 2(6):a007120.

10. Williams DW, Veenstra M, Gaskill PJ, Morgello S, Calderon TM, Berman JW. Monocytes mediate HIV neuropathogenesis: mechanisms that contribute to HIV associated neurocognitive disorders. *Curr HIV Res*. 2014;12:85-96.

11. Spudich S. HIV and neurocognitive dysfunction. *Current HIV/AIDS reports* 2013; 10(3):235-243.

12. Langford TD, Letendre SL, Larrea GJ, Masliah E. Changing patterns in the neuropathogenesis of HIV during the HAART era. *Brain pathology* 2003; 13(2):195-210

13. Eden A, Price RW, Spudich S, Fuchs D, Hagberg L, Gisslen M. Immune activation of the central nervous system is still present after >4 years of effective highly active antiretroviral therapy. *The Journal of infectious diseases* 2007; 196(12):1779-1783

14. Underwood J, Robertson KR, Winston A. Could antiretroviral neurotoxicity play a role in the pathogenesis of cognitive impairment in treated HIV disease? *AIDS* 2015; 29(3):253-261.

15. Robertson K, Liner J, Meeker RB. Antiretroviral neurotoxicity. *Journal of neurovirology* 2012; 18(5):388-399.

16. Hoare J, Fouche JP, Spottiswoode B, Donald K, Philipps N, Bezuidenhout H, et al. A diffusion tensor imaging and neurocognitive study of HIV-positive childrenwho are HAART-naïve “slow progressors”. J Neurovirol. 2012;18:205–12

17. Ruel TD, Boivin MJ, Boal HE, Bangirana P, Charlebois E, Havlir DV, et al. Neurocognitive and motor deficits in HIV-infected Ugandan children with high CD4cell counts. Clin Infect Dis. 2012;54:1001–9

18. Bagenda D, Nassali A, Kalyesubula I, Sherman B, Drotar D, Boivin MJ, et al. Health, neurologic, and cognitive status of HIV-infected, long-surviving, and antiretroviral-naive Ugandan children. Pediatrics. 2006;117:729–40.

19. Koekkoek S, de Sonneville LM, Wolfs TF, Licht R, Geelen SP. Neurocognitivefunction profile in HIV-infected school-age children. Eur J Paediatr Neurol.2008;12:290–7

20. Smith R, Chernoff M, Williams PL, Malee KM, Sirois PA, Kammerer B, et al. Impact of HIV severity on cognitive and adaptive functioning during childhood and adolescence. Pediatr Infect Dis J. 2012;31:592–8.8.

21. Boyede GO, Lesi FE, Ezeaka VC, Umeh CS. Impact of sociodemographic factors on cognitive function in school-aged HIV-infected Nigerian children. HIV AIDS (Auckl). 2013;5:145–52.

22. Judd A, Le Prevost M, Melvin D, Arenas-Pinto A, Parrott F, Winston A, et al. Cognitive function in young persons with and without perinatal HIV in the AALPHI cohort in England: role of non-HIV-related factors. Clin Infect Dis.2016;63:1380–7.

23. Phillips N, Amos T, Kuo C, Hoare J, Ipser J, Thomas KG, et al. HIV-Associated cognitive impairment in perinatally infected children: a meta-analysis.

Pediatrics.2016;138:e20160893.

24. Brahmbhatt H, Boivin M, Ssempijja V, Kagaayi J, Kigozi G, Serwadda D, et al. Impact of HIV and antiretroviral therapy on neurocognitive outcomes among school-aged children. J Acquir Immune Defic Syndr. 2017;75:1–8.

25. Crowell CS, Huo Y, Tassiopoulos K, Malee KM, Yogev R, Hazra R, et al. Early viral suppression improves neurocognitive outcomes in HIV-infected children. AIDS.2015;29:295–304

26. Weber V, Radeloff D, Reimers B, Salzmann-Manrique E, Bader P, Schwabe D, et al. Neurocognitive development in HIV-positive children is correlated with plasma viral loads in early childhood. Medicine (Baltimore). 2017;96:e6867.

27. Masters M, Ances B. Role of neuroimaging in HIV-associated neurocognitive disorders. Semin Neurol. 2014;34:89-102.

28. Kwong KK, Belliveau JW, Chesler DA, Goldberg IE, Weisskoff RM, Poncelet BP, Kennedy DN, Hoppel BE, Cohen MS, Turner R, et al. Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. Proc Natl Acad Sci U S A. 1992;89:5675-9.

29. Ashburner J, Friston KJ. Voxel-based morphometry-the methods. Neuroimage. 2000;11:805-21.

30. Ashburner J, Hutton C, Frackowiak R, Johnsrude I, Price C, Friston K. Identifying global anatomical differences: deformation-based morphometry. Hum Brain Mapp. 1998;6:348-57.

31. Dale, A.M., Fischl, B., and Sereno, M.I. Cortical surface based analysis: I. segmentation and surface reconstruction. NeuroImage, 1999;9:179–194.

32. Geva S, Baron JC, Jones PS, Price CJ, Warburton EA. A comparison of VLSM and VBM in a cohort of patients with post-stroke aphasia. Neuro-image Clin. 2012;1:37-47

33. Rowan A, Vargha-Khadem F, Calamante F, Tournier JD, Kirkham FJ, Chong WK, Baldeweg T, Connelly A, Gadian DG. Cortical abnormalities and language function in young patients with basal ganglia stroke. Neuroimage. 2007;36:431-40

34. Johnson VE, Stewart W, Smith DH. Axonal pathology in traumatic brain injury. Exp Neurol 2013;246:35-43.

35. Yang E, Nuncifora PG, Melhem ER. Diffusion MR imaging: basic principles.

Neuroimaging Clin North Am 2011;21:1-25

36. Sundman M, Doraiswamy PM, Morey RA. Neuroimaging assessment of early and late neurobiological sequelae of traumatic brain injury: implications for CTE. Front Neurosci. 2015;9:334

37. Wheeler-Kingshott CA, Cercignani M. About "axial" and "radial" diffusivities. Magn Reason Med. 2009;61:1255-60.

38. Buxton RB. Introduction to Functional Magnetic Resonance Imaging. 2009. Cambridge International Press. https://doi.org/10.1017/CBO9780511605505

39. Thames, A. D., Sayegh, P., Terashima, K., Foley, J. M., Cho, A., Arentoft, A., et al. (2016). Increased subcortical neural activity among HIV individuals during a lexical retrieval task. *Neurobiology of Disease. 2015;10:*175-182.

40. Dickerson BC. Advances in functional magnetic resonance imaging: technology and clinical applications. Neurotherapeutics. 2007;4:360-70.

41. Biswal BB, Van Kylen J, Hyde JS. Simultaneous assessment of flow and BOLD signals in resting-state functional connectivity maps. NMR Biomed. 1997;10:165-70

42. Hoare, J., Fouche, J.-P., Phillips, N., Joska, J. A., Myer, L., Zar, H. J., et al. Structural brain changes in perinatally HIV infected young adolescents in South Africa. AIDS. 2018;32:2707-18

43. Cohen S, Caan MWA, Mutsaerts H-J, Scherpbier HJ, Kuijpers TW, Reiss P, *et al.* Cerebral injury in perinatally HIV-infected children compared to matched healthy controls. *Neurology* 2016; 86:19–27.

44. Lewis-de Los Angeles CP, Williams PL, Huo Y, Wang SD, Uban KA, Herting MM, *et al.* Lower total and regional grey matter brain volumes in youth with perinatally-acquired HIV infection: Associations with HIV disease severity, substance use, and cognition. *Brain Behav Immun* 2017; 62:100–109.

45. Nwosu, E. C., Robertson, F. C., Holmes, M. J., Cotton, M. F., Dobbels, E., Little, F., et al. Altered brain morphometry in 7-year old HIV-infected children on early ART. *Metabolic Brain Disease*, 2018;*33*:523–535

46. Li J, Gao L, Wen Z, et al. Structural Covariance of Gray Matter Volume in HIV Vertically Infected Adolescents. *Sci Rep*. 2018;8:1182..

47. Yadav, S. K., Gupta, R. K., Garg, R. K., Venkatesh, V., Gupta, P. K., Singh, A. K.,

et al. Altered structural brain changes and neurocognitive performance in pediatric HIV. *NeuroImage: Clinical*, 2017;*14*:316–322.

48. Sarma, M. K., Nagarajan, R., Keller, M. A., Kumar, R., Nielsen-Saines, K., Michalik, D. E., et al. Regional brain gray and white matter changes in perinatally HIV-infected adolescents. *NeuroImage: Clinical*, 2013;4:29-34

49. Paul, R., Prasitsuebsai, W., Jahanashad, N., Puthanakit, T., Thompson, P., Aurpibul, L., et al. Structural Neuroimaging and Neuropsychologic Signatures of Vertically Acquired HIV: *The Pediatric Infectious Disease Journal*, 2018;37:662-668

50. Randall, S. R., Warton, C. M. R., Holmes, M. J., Cotton, M. F., Laughton, B., van der Kouwe, et al. Larger Subcortical Gray Matter Structures and Smaller Corpora Callosa at Age 5 Years in HIV Infected Children on Early ART. *Frontiers in Neuroanatomy*, 2017;11:95

51. Yu X, Gao L, Wang H, et al. Neuroanatomical Changes Underlying Vertical HIV Infection in Adolescents. *Front Immunol*. 2019;10:814.

52. Jankiewicz M, Holmes MJ, Taylor PA, Cotton MF, Laughton B, van der Kouwe AJW, Meintjes EM. White Matter Abnormalities in Children with HIV Infection and Exposure. Front Neuroanat. 2017;29:11-88

53. Li J, Wu G, Wen Z, Zhang J, Lei H, Gui X, Lin F. White Matter Development is Potentially Influenced in Adolescents with Vertically Transmitted HIV Infections: A Tract-Based Spatial Statistics Study. AJNR Am J Neuroradiol. 2015;36:2163-9

54. Ackermann C, Andronikou S, Saleh MG, Laughton B, Alhamud AA, van der Kouwe A, Kidd M, Cotton MF, Meintjes EM. Early Antiretroviral Therapy in HIV-Infected Children Is Associated with Diffuse White Matter Structural Abnormality and Corpus Callosum Sparing. AJNR Am J Neuroradiol. 2016;37:2363-9

55. Wade BSC, Valcour VG, Puthanakit T, Saremi A, Gutman BA, Nir TM, Watson C, Aurpibul L, Kosalaraksa P, Ounchanum P, Kerr S, Dumrongpisutikul N, Visrutaratna P, Srinakarin J, Pothisri M, Narr KL, Thompson PM, Ananworanich J, Paul RH, Jahanshad N; PREDICT and Resilience Study Groups. Mapping abnormal subcortical neurodevelopment in a cohort of Thai children with HIV. Neuroimage Clin. 2019;23:101810

56. Hoare J, Heany SJ, Fouche JP, Phillips N, Joska JA, Myer L, Zar HJ, Stein DJ. Initiation of antiretroviral therapy after the critical neuronal developmental period of the second postnatal year affects white matter microstructure in adolescents living with HIV. J Neurovirol. 2019;25:254-62

57. Hoare J, Fouche JP, Spottiswoode B, Donald K, Philipps N, Bezuidenhout H, Mulligan C, Webster V, Oduro C, Schrieff L, Paul R, Zar H, Thomas K, Stein D. A diffusion tensor imaging and neurocognitive study of HIV-positive children who are HAART-naïve "slow progressors". J Neurovirol. 2012;18:205-12.

58. Uban KA, Herting MM, Williams PL, Ajmera T, Gautam P, Huo Y, Malee KM, Yogev R, Csernansky JG, Wang L, Nichols SL, Sowell ER; Pediatric HIVAIDS Cohort and the Pediatric Imaging, Neurocognition, and Genetics Studies. White matter microstructure among youth with perinatally acquired HIV is associated with disease severity. AIDS. 2015;29:1035-44

59. Herting MM, Uban KA, Williams PL, Gautam P, Huo Y, Malee K, Yogev R, Csernansky J, Wang L, Nichols S, Van Dyke R, Sowell ER. Default Mode Connectivity in Youth With Perinatally Acquired HIV. Medicine (Baltimore). 2015;94:e1417

60. Toich JTF, Taylor PA, Holmes MJ, Gohel S, Cotton MF, Dobbels E, Laughton B, Little F, van der Kouwe AJW, Biswal B, Meintjes EM. Functional Connectivity Alterations between Networks and Associations with Infant Immune Health within Networks in HIV Infected Children on Early Treatment: A Study at 7 Years. Front Hum Neurosci. 2018;11:635.

61. Wang P, Li J, Wang X, Thapa D, Wu GY. Asymptomatic Human Immunodeficiency Virus Vertical Transmitted Adolescents' Brain Functional Changes: Based on Resting-State Functional Magnetic Resonance Imaging. AIDS Res Hum Retroviruses. 2018;34:699-704.

62. Martín-Bejarano M, Ruiz-Sáez B, Zamora B, Martínez de Aragón-Calvo A, García-Navarro C, Jiménez-de Ory S, et al. Brain activity in well-controlled perinatally human immunodeficiency virus-infected young adults: a functional magnetic resonance imaging pilot study. Rev Neurol 2021; 72: 343-51.

63. Thames AD, Sayegh P, Terashima K, Foley JM, Cho A, Arentoft A, et al. Increased subcortical neural activity among HIV individuals during a lexical retrieval task. Neurobiol Dis 2016; 92: 175-82.

64. Jessen Krut J, Mellberg T, Price RW, Hachberg L, Fuchs D, Rosengren L, et al. Biomarker evidence of axonal injury in neuroasymptomatic HIV-1 patients. Plos One. 2014;9:e88591.

65. Ashton NJ, Hye A, Rajkumar AP, Leuzy A, Snowden S, Suárez-Calvet M, et al. An update on blood-based biomarkers for non-Alzheimer neurodegenerative disorders. Nat Rev Neurol 2020;16:265-84.

66. Peterson J, Gisslen M, Zetterberg H, Fuchs D, Shacklett BL, Hagberg L et al. Cerebrospinal fluid (CSF) neuronal biomarkers across the spectrum of HIV infection: hierarchy of injury and detection. Plos One. 2014;9:e116081.

67. Gisslen M, Price RW, Andreasson U, Norgren N, Nilsson S, Hagberg L et al. Plasma concentration of the neurofilament light protein (NFL) is a biomarker of CNS injury in HIV infection: a cross-sectional study. EBioMedicine. 2016;3:135–40

68. Andronikou S, Ackermann C, Laughton B, Cotton M, Tomazos N, Spottiswoode B et al. Corpus callosum thickness on mid-sagittal MRI as a marker of brain volume: a pilot study in children with HIV-related brain disease and controls. Pediatr Radiol. 2015;45:1016–25.

69. Pehlivanova M, Wolf DH, Sotiras A, Kaczkurkin AN, Moore TM, Ciric R, et al. Diminished cortical thickness is associated with impulsive choice in adolescence. J Neurosci 2018 ;38:2471–81.

70. Malee KM, Chernoff MC, Sirois PA, Williams PL, Garvie PA, Kammerer BL, et al. Impact of perinatally acquired HIV disease upon longitudinal changes in memory and executive functioning. J Acquir Immune Defic Syndr 2017;75:455–64.

71. Nichols SL, Chernoff MC, Malee KM, Sirois PA, Woods SP, Williams PL, et al. Executive functioning in children and adolescents with perinatal HIV infection and perinatal HIV exposure. J Pediatric Infect Dis Soc 2016;5(suppl 1):S15–23.

72. Kerr SJ, Puthanakit T, Malee KM, Thongpibul K, Ly PS, Sophonphan J, Suwanlerk T, et al. Increased risk of executive function and emotional behavioral problems among virologically well controlled perinatally HIV-infected adolescents in Thailand and Cambodia. J Acquir Immune Defic Syndr 2019;82:297–304.

73. Parker TD, Slattery CF, Zhang J, Nicholas JM, Paterson RW, Foulkes AJM, et al. Cortical microstructure in young onset Alzheimer's disease using neurite orientation dispersion and density imaging. Hum Brain Mapp 2018;39:3005–17.

74. Owens MM, Duda B, Sweet LH, MacKillop J. Distinct functional and structural neural underpinnings of working memory. Neuroimage 2018;174:463–71.

75. McLaughlin KA, Sheridan MA, Lambert HK. Childhood adversity and neural development: deprivation and threat as distinct dimensions of early experience. Neurosci Biobehav Rev 2014;47:578–91.

76. Couvy-Duchesne B, Strike LT, de Zubicaray GI, McMahon KL, Thompson PM, Hickie IB et al. Lingual gyrus surface area is associated with anxiety-depression

severity in young adults: a genetic clustering approach. eNeuro 2018;5:153-17

77. Mashhoon Y, Sava S, Sneider JT, et al. Cortical thinness and volume differences associated with marijuana abuse in emerging adults. Drug Alcohol Depend 2015;155:275–83.

78. Thames AD, Kuhn TP, Williamson TJ, Nickerson LD, Silveri MM. Marijuana effects on changes in brain structure and cognitive function among HIV+ and HIVadults. Drug Alcohol Depend 2017;170:120–7.

79. Wang L. Lower total and regional grey matter brain volumes in youth with perinatally-acquired HIV infection: associations with HIV disease severity, substance use, and cognition. Brain Behav Immun 2017;62:100–9.

80. Ances BM, Ortega M, Vaida F, Heaps J, Paul R. Independent effects of HIV, aging, and HAART on brain volumetric measures. J Acquir Immune Defic Syndr 2012;59:469–77.

81. Thames AD, Foley JM, Wright MJ, Panos SE, Ettenhofer M, Ramezani A, et al. Basal ganglia structures differentially contribute to verbal fluency: evidence from Human Immunodeficiency Virus (HIV)-infected adults. Neuropsychologia 2012;50:390–5.

82. Button KS, Ioannidis JP, Mokrysz C, Nosek BA, Flint J, Robinson ES, et al. Power failure: why small sample size undermines the reliability of neuroscience. Nat Rev Neurosci. 2013 May;14:365-76

83. Jovicich J, Marizzoni M, Sala-Llonch R, Bosch B, Bartrés-Faz D, Arnold J, et al. Brain morphometry reproducibility in multi-center 3T MRI studies: a comparison of cross-sectional and longitudinal segmentations. Neuroimage. 2013;83:472-84

84. Wagner S, Sebastian A, Lieb K, Tüscher O, Tadić A. A coordinate-based ALE functional MRI meta-analysis of brain activation during verbal fluency tasks in healthy control subjects. BMC Neurosci. 2014;24;15-9

85. Tecelão D, Mendes A, Martins D, Bramon E, Toulopoulou T, Kravariti E, et al. The impact of psychosis genome-wide associated ZNF804A variation on verbal fluency connectivity. J Psychiatr Res. 2018;98:17-21

86. Herrmann MJ, Horst AK, Löble S, Möll MT, Katzorke A, Polak T. Relevance of Dorsolateral and Frontotemporal Cortex on the Phonemic Verbal Fluency - A fNIRS-Study. Neuroscience. 2017;367:169-77

87. Hakkers CS, Arends JE, Barth RE, Du Plessis S, Hoepelman AI, Vink M. Review

of functional MRI in HIV: effects of aging and medication. J Neurovirol. 2017;23:20-32

88. García-Navarro C, Martín-Bejarano M, Jimenez de Ory S, Zamora B, Ruiz-Saez B, Velo C et al. Neurocognitive and quality of life study in perinatally HIV-infected young people and their peers. NeuroCoRISpeS study. Enferm Infecc Microbiol Clin. 2020;38:417-24

89. Gaetani L, Blennow K, Calabresi P, Di Filippo M, Parnetti L, Zetterberg H. Neurofilament light chain as a biomarker in neurological disorders. J Neurol Neurosurg Psychiatry. 2019;90:870-81.

90. Yilmaz A, Blennow K, Hagberg L, Nilsson S, Price RW, Schouten J, et al. Neurofilament light chain protein as a marker of neuronal injury: review of its use in HIV-1 infection and reference values for HIV negative controls. Expert Rev Mol Diagn 2017; 17:761–70

91. Mellgren A, Price RW, Hagberg L, Rosengren L, Brew BJ, Gisslen M. Antiretroviral treatment reduces increased CSF neurofilament protein (NfL) in HIV-1 infection. Neurology 69: 1536-41.

92. Price RW, Peterson J, Fuchs D, Angel TE, Zetterberg H, Hagberg L, et al. Approach to cerebrospinal fluid (CSF) biomarker discovery and evaluation in HIV infection. J Neuroimmune Pharmacol. 2013;8: 1147–58.

93. Anderson A, Easley KA, Kasher N. Neurofilament light chain in blood is negatively associated with neuropsychological performance in HIV-infected adults and declines with initiation of antiretroviral therapy. Journal of NeuroVirology. 2018;24:695–701.

94. Menke RA, Gray E, Lu CH, Kuhle J, Talbot K, Malaspina A, et al. CSF neurofilament light chain reflects corticospinal tract degeneration in ALS. Ann Clin Transl Neurol. 2015 Jul;2(7):748-55

95. Lu CH, Macdonald-Wallis C, Gray E, Pearce N, Petzold A, Norgren N, et al. Neurofilament light chain: a prognostic biomarker in amyotrophic lateral sclerosis. Neurology 2015;84:2247- 2257.

96. Mattsson N, Andreasson U, Zetterberg H, Blennow K; Alzheimer's Disease Neuroimaging Initiative. Association of plasma neurofilament light with neurodegeneration in patients with alzheimer disease. JAMA Neurol 2017;74:557-566.

97. Rohrer JD, Woollacott IO, Dick KM, Brotherhood E, Gordon E, Fellows A, et al. Serum neurofilament light chain protein is a measure of disease intensity in frontotemporal dementia. Neurology. 2016 Sep 27;87(13):1329-36

98. Posthuma D, Baaré WFC, Hulshoff Pol HE, Kahn RS, Boomsma DI, De Geus EJC. Genetic correlations between brain volumes and the WAIS-III dimensions of verbal comprehension, working memory, perceptual organization, and processing speed. Twin Research. 2003;6(02):131–9.

99. Borghesani PR, Madhyastha TM, Aylward EH, Reiter MA, Swarny BR, Schaie KW, et al. The association between higher order abilities, processing speed, and age are variably mediated by white matter integrity during typical aging. Neuropsychologia. 2013;51(8):1435–44. pmid:23507612.

100. Jacobs HIL, Leritz EC, Williams VJ, Van Boxtel MPJ, Elst Wvd, Jolles J, et al. Association between white matter microstructure, executive functions, and processing speed in older adults: the impact of vascular health. Human brain mapping. 2013;34(1):77–95. pmid:21954054

101. Johnson EB, Byrne LM, Gregory S, Rodrigues FB, Blennow K, Durr A, et al. TRACK-HD Study Group. Neurofilament light protein in blood predicts regional atrophy in Huntington disease. Neurology. 2018;90:717-23

102. Li QF, Dong Y, Yang L, Xie JJ, Ma Y, Du YC, et al. Neurofilament light chain is a promising serum biomarker in spinocerebellar ataxia type 3. Mol Neurodegener. 20194;14:39.

103. Van Zoest R , Underwood J, De Francesco D , Sabin CA, Cole JH , Wit FW, et al. Structural Brain Abnormalities in Successfully Treated HIV Infection: Associations With Disease and Cerebrospinal Fluid Biomarkers. J Infect Dis. 2017;217:69-81

104. Bridel C, van Wieringen WN, Zetterberg H, Tijms BM, Teunissen CE, Alvarez-Cermeno JC, et al. Diagnostic value of cerebrospinal fluid Neurofilament light protein in neurology: a systematic review and meta-analysis. JAMA Neurol. 2019;76:1035-48.

105. Tyrberg T, Nilsson S, Blennow K, Zetterberg H, Grahn A. Serum and cerebrospinal fluid neurofilament light chain in patients with central nervous system infections caused by varicella-zoster virus. J Neurovirol. 2020;26:719-26

106. Virhammar J, Nääs A, Fällmar D, Cunningham JL, Klang A, Ashton NJ. Biomarkers for central nervous system injury in cerebrospinal fluid are elevated in

COVID-19 and associated with neurological symptoms and disease severity. Eur JNeurol. 2020;28