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

Manuela Martín Bejarano-García, Beatriz Ruiz-Sáez, Berta Zamora, Ana Martínez de Aragón, Cristina García-Navarro, Santiago Jiménez de Ory, Carlos Velo, José T. Ramos, Talía Sainz, Luis Escosa, Noemí Núñez-Enamorado, Christian Stephan-Otto, M. Luisa Navarro, M. Isabel González-Tomé

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 theirpeers.

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-

Paediatric Neuropsychology Department (M. Martín Bejarano-García, B. Zamora); Radiology Department (A. Martínez de Aragón); Paediatric Infectious Diseases Department (C. García-Navarro, C. Velo, M.I. González-Tomé); Paediatric Neurology Department (N. Núñez-Enamorado). Hospital Universitario 12 de Octubre. Foundation for Biomedical Research of the Hospital Universitario 12 de Octubre (FIBH12O) (M. Martín Bejarano-García, C. Velo). Molecular Immunobiology Laboratory; HIV Spanish BioBank (B. Ruiz-Sáez, S. Jiménez de Ory); Instituto de Investigación Sanitaria Gregorio Marañón (IiSGM) (S. Jiménez de Ory); Research Group CoRISpe. Paediatric Infectious Diseases Department (M.L. Navarro, M.I. González-Tomé). Hospital Universitario Gregorio Marañón. Paediatric Department; Hospital Universitario Clínico San Carlos (J.T. Ramos). Paediatric Infectious Diseases Department; Hospital Universitario La Paz (T. Sainz, L. Escosa). Hospital La Paz Institute for Health Research (IdiPAZ) (T. Sainz). Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM) (C. Stephan-Otto); Madrid. Parc Sanitari Sant Joan De Déu; Sant Boi de Llobregat, Barcelona, Spain (C. Stephan-Otto).

Corresponding author:
Dr. Beatriz Ruiz Sáez. Molecular Immunobiology Laboratory; HIV Spanish BioBank. Hospital Gregorio Marañón. c/ Dr. Esquerdo, 46. E-28007 Madrid.

E-mail:
bruizsaez@gmail.com

Funding:
This work was supported by Instituto de Salud Carlos III [FIS 15/00694] which is co-funded by Fondo Europeo de Desarrollo Regional (FEDER): Una manera de →

hacer Europa; BRS received a Río Hortega grant (health care post-training contract [CM 16/0022]).

Accepted:
06.04.21.

How to cite this article:
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. doi: 10.33588/rn.7210.2020536.

Versión en español disponible en neurología.com

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.

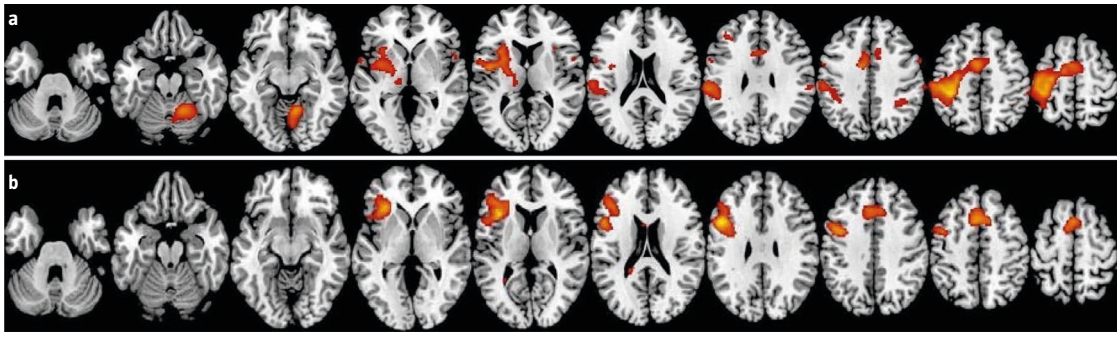
In our study, the absence of differences between groups might be due to the careful selection of patients with good immunovirological control. Those patients who are young adults, have been on cART for more than half their life (median of 13.7 years) and with persistent undetectable viral load (median 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.

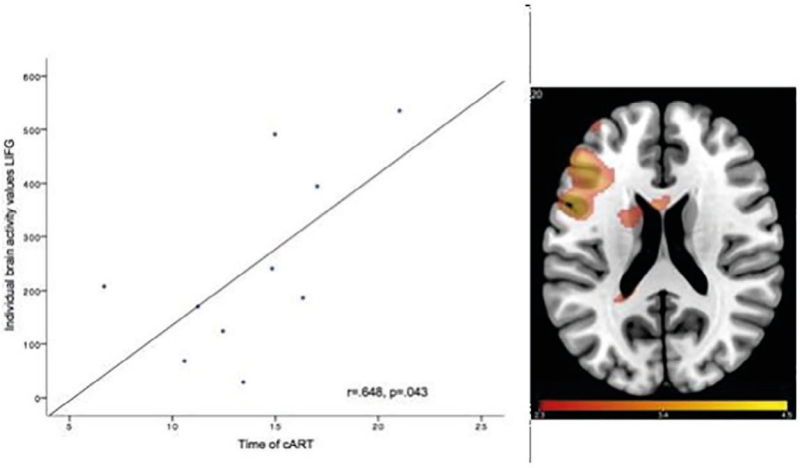
Conclusions

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.