



Research article

Resting-state functional connectivity MRI analysis in Human Immunodeficiency Virus and Hepatitis C Virus co-infected subjects. A pilot study



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ABSTRACT

Background and purpose: Hepatitis C virus (HCV) co-infection's role on cognitive impairment of human immunodeficiency virus (HIV) positive patients is still debated and functional neuroimaging evaluation on this matter is lacking. To provide further insight about HCV's neuro-effects on HIV associated neurocognitive disorder (HAND), we performed a pilot resting state (RS) functional connectivity magnetic resonance imaging (fcMRI) study to find eventual functional connectivity alteration that could reflect HCV related cognitive performance degradation.

Methods: Eighteen patients (8 HIV, 10 HIV + HCV), either impaired or not impaired, were assessed with RS fcMRI. A statistic model including cognitive testing results was elaborated during data processing to evaluate brain networks alteration related to actual cognitive status in patients.

Results: Statistically significant different patterns of connectivity were found: HCV co-infection modified 17 ROIs' connectivity with 45 supra-threshold connections (p-FDR min 0.0022, max 0.0497). ROIs most involved were right pallidum, brainstem, vermal lobules 1–2 and right cerebellar lobule 10. Graph theory analysis did not demonstrate significant difference between networks, but HCV related modifications at ROI's local level were found, with particular involvement of ROIs of frontal lobe, basal ganglia and cerebellum. Increased fronto-striatal dysfunctions have been already reported as consequences of HCV infection and could reflect an additive effect. Cerebellar alterations are associated with HIV and HAND, but not with HCV infection, suggesting a synergic effect of HCV.

Conclusion: Our study demonstrates RS fcMRI can help to understand the interactions between HIV and HCV co-infection, and our preliminary results suggest synergic effects of HCV in HIV-related brain functional modification.

1. Introduction

HIV-associated neurocognitive disorder (HAND) is a frequent comorbidity of HIV infection, and its prevalence is still high, affecting about 50% of HIV infected patients despite combination antiretroviral therapy (cART) [1]. HIV associated neurocognitive disorder (HAND) includes variable degrees of impairment, from a sub-clinical stage defined asymptomatic neurocognitive impairment (ANI), to mild neurocognitive disorder (MND) and a last stage called HIV-associated

dementia (HAD) [2,3,4].

Several social, physiologic and pathologic factors can affect diagnosis and managing of HAND, i.e., education, poverty, substance abuse, age, neurologic, psychiatric and cardiovascular disease. [4]. An important co-morbidity is the hepatitis C virus (HCV) co-infection which is likely due to shared primary modes of transmission via intravenous drug use and sexual contact. Depending on the HIV population, co-infection with HCV can be found in up to 75–85% in high-risk groups, such as intravenous drug users, and up to 25% on overall HIV

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population [5].

HCV co-infection implies some specific issues in HIV positive patient: it influences the course and management of HAND, i.e. increasing the risk of antiretroviral drug-induced hepatotoxicity and with potential synergic cognitive effects even if there is no agreement for considering HCV status which is an independent risk factor for cognitive abnormalities in HIV positive patients. Several studies reported that both HCV and HIV are independently associated with cognitive impairment [6,7].

In addition, co-infected patients showed attention and concentration difficulties and greater global impairment [7,8]. Recent studies instead reported no significant cognitive differences between HIV infected and HIV + HCV co-infected patients after careful control of confounding variables such as drug use and hepatopathy, or when HCV viral load is undetectable. Functional imaging was not included in any of these studies [9,10].

RS-fcMRI has proved to be a sensitive tool to detect early and asymptomatic cognitive changes in HAND and demonstrated that HIV positive patients hyper-activate brain regions involved in attention, memory, and executive functioning, support brain reserve theory, with particular evidence of fronto-striatal dysfunction [11].

Analogously, to provide insight into the aetiology of HIV + HCV associated brain dysfunction, aiming to identify potential brain functional differences related to HCV co-infection, in a cohort of individuals with chronic HIV infection, having a sub-group of HCV co-infected patients. We examined RS-fcMRI connectivity measures and we correlated those with cognitive abilities evaluated by the Repeatable Battery for the Assessment of Neuropsychological Status [12]. To our knowledge, our paper is the first work that analyses this matter from a perspective of functional connectivity and graph theory.

2. Materials and methods

2.1. Sample

Our sample included 18 HIV positive patients, 10 with HCV co-infection. In cART treatment, it is important to note that all patients were treated with cART because it is related to different expression of impairment [13].

Inclusion criteria were being at least 18 years of age, with normal neurological exam. Exclusion criteria included history of seizure disorder, previous cerebrovascular events, demyelinating disease or any other non-HIV neurological disease. Demographic and clinical factors of the two populations were compared with Student's *t*-test to evaluate statistically significant differences.

2.2. Neuropsychological evaluation

All patients were assessed for cognitive impairment, using the RBANS and Frascati criteria. In particular, examination included immediate and delayed memory, visuoconstruction skills and visuo-perception ability, attention, and language functioning. All scores were normalized by age [2,12].

2.3. MR exam protocol

All RS fcMRI were performed in our radiology department with a Philips MR scanner Ingenia dStream 1.5T (Philips Healthcare, Eindhoven, NL). All participants received instructions for the exam (not to think of something in particular and not to fall asleep). After the localizing sequences structural T1 3D TFE and T2 TSE were performed to exclude significant brain pathology. The FE-EPI sequence had the following parameters: 2D acquisition with slice thickness of 5 mm, RT 3000 ms, ET 50 ms, FA 90°, EPI factor 37. All the scans have been considered negative for the presence of intracranial significant pathology. DICOM data were converted in NII format with dcm2niiGUI

(software created by Chris Rorden) and then loaded in the MATLAB® suite CONN: functional connectivity toolbox (MathWorks, INC. <https://it.mathworks.com/products/matlab.html>) (Neuroimaging Informatics Tools and Resources Clearinghouse (NITRC) <http://www.nitrc.org/projects/conn>) for pre-processing and processing [14]. CONN software implements a strategy for noise source reduction that does not rely on global signal regression allowing for interpretation of anticorrelations as there is no regression of the global signal; denoising of fMRI signal can be also performed by means of removal of movement artefacts, characterization and removing of temporal covariates, and temporal filtering of the residual blood oxygen level-dependent (BOLD) contrast signal. Then, first-level estimation of multiple standard functional connectivity magnetic resonance imaging (fcMRI) measures, and second-level random-effect analysis for resting state as well as task-related data can be performed with CONN tools. We set a band-pass filter of 0.0001–0.1 Hz, since low-frequency and extremely low frequency resting state networks (< 0.1 Hz) reveal coherent, spontaneous fluctuations characterising the functional architecture of the human brain [15].

Then, we used CONN default pre-processing pipeline for volume-based analyses (direct normalization to MNI-space), with smoothing FWHM of 8 mm and intermediate settings (97th percentile in normative sample in functional outlier detection sample). First level analysis (single subject) and second level analysis (group analysis) were performed according to the CONN software pipeline; data processing at second level has been performed by means of the ROI-to-ROI functional correlation approach to obtain connectivity maps of interest. Finally, graph theory measurements were performed in order to evaluate from the metric and topological point of view brain network alteration induced by HCV co-morbidity.

2.4. Statistical analysis

Using the statistical tools included in the CONN software ANCOVA-based models, aimed to underline connectivity effects of HCV on HIV positive patients, were developed and tested; RBANS total score values were included into the models to evaluate the influence of actual cognitive impairment as possible covariate. Results were corrected with FDR threshold ($P = 0.05$), which calculates the number of potential false positives related to the multiple comparisons performed. Finally, graph theory parameters were calculated for the networks exhibited in our data in order to evaluate nodes and vertex alteration of interest, according to the CONN analysis procedures.

3. Results

3.1. Sample analysis

Demographic and clinical factors are summarized in Table 1.

Considering the two population of our sample we can see that sex, age, education and cognitive test score are well-matched, while HAND diagnosis are balanced (3 ANI, 1 MND per group) but with different prevalence (50% impaired in HIV infection vs 40% in HIV + HCV.) Using Student's *T*-Test we found significant difference about years of HIV infection, nadir and actual CD4 count.

An overall prevalence of cognitive impairment of 45% (50% in HIV group and 40% in HIV + HCV group) with 33% of ANI (37% and 30%), 11% of MND (12,5% and 10%) and 0% of HAD was found.

3.2. Functional connectivity results

We found that HCV co-infection is associated to a statistically significant modification of connectivity in 17 interconnected brain regions in HIV positive patients. These 17 regions are organized in a network characterized by 45 supra-threshold connections (size) with an intensity of 208,47 (intensity is defined as sum of absolute *T*-values over

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