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Abnormal cortical sources of resting state electroencephalographic rhythms in single treatment-naïve HIV individuals: A statistical *z*-score index

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HIGHLIGHTS

- This pilot study tested a statistical *z*-score procedure to identify single treatment-naïve HIV individuals having abnormal resting state electroencephalographic (EEG) sources.
- Compared to HIV individuals with normal EEG sources, those (47.6%) with abnormal *z*-score values showed worse cognitive and serological markers.
- This procedure is promising to assess effects of HIV on brain function in single treatment-naïve HIV individuals.

ABSTRACT

Objective: This study tested a simple statistical procedure to recognize single treatment-naïve HIV individuals having abnormal cortical sources of resting state delta (<4 Hz) and alpha (8–13 Hz) electroencephalographic (EEG) rhythms with reference to a control group of sex-, age-, and education-matched healthy individuals. Compared to the HIV individuals with a statistically normal EEG marker, those with abnormal values were expected to show worse cognitive status.
Methods: Resting state eyes-closed EEG data were recorded in 82 treatment-naïve HIV (39.8 ys. ± 1.2 standard error mean, SE) and 59 age-matched cognitively healthy subjects (39 ys. ± 2.2 SE). Low-resolution brain electromagnetic tomography (LORETA) estimated delta and alpha sources in frontal, central, temporal, parietal, and occipital cortical regions.
Results: Ratio of the activity of parietal delta and high-frequency alpha sources (EEG marker) showed the maximum difference between the healthy and the treatment-naïve HIV group. *Z*-score of the EEG marker was statistically abnormal in 47.6% of treatment-naïve HIV individuals with reference to the healthy group ($p < 0.05$). Compared to the HIV individuals with a statistically normal EEG marker, those with abnormal values exhibited lower mini mental state evaluation (MMSE) score, higher CD4 count, and lower viral load ($p < 0.05$).
Conclusions: This statistical procedure permitted for the first time to identify single treatment-naïve HIV individuals having abnormal EEG activity.

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Significance: This procedure might enrich the detection and monitoring of effects of HIV on brain function in single treatment-naïve HIV individuals.

1. Introduction

Human immunodeficiency virus (HIV) infection induces neuropathological changes in 80–90% of subjects, subclinical neuropathy in 10–40% of asymptomatic HIV and AIDS subjects and neurologic symptoms in 50–100% of subjects during the course of illness (McArthur, 1987; Chavanet et al., 1988; Gastaut et al., 1989; Chalmers et al., 1990; Fauci and Lane, 1998; Williams et al., 2002, 2012; Selnes, 2005; Anthony and Bell, 2008; Antinori et al., 2007; Roberts et al., 2010). Neurological and neuropsychological symptoms were found to be mitigated in HIV subjects receiving a combination of antiretroviral therapies or cART (Clifford, 2008), thanks to the reduction of viral load and to the maintenance of CD4 cell counts (Graham et al., 1992; Hammer et al., 1997; Hunt et al., 2003; Williams et al., 2012). However, the prevalence of HIV patients with neurological and neuropsychological symptoms is increasing more and more (Cysique et al., 2009; Sevigny et al., 2004). This motivates the quest of biomarkers indexing the HIV effects on brain function for clinical purposes and for drug discovery and monitoring.

Resting state EEG rhythms are an emerging functional feature of brain and probe general neurophysiologic mechanisms of cortical neural synchronization during the fluctuation of cortical arousal and attention alertness (Babiloni et al., 2011). Therefore, quantitative EEG biomarkers may potentially contribute not only to a preliminary instrumental assessment of HIV subjects but also to a better understanding of neurophysiologic mechanisms underlying the HIV effects on brain function. In this vein, previous studies have described spatial-frequency features of resting state eyes-closed EEG rhythms in HIV subjects at group level. Compared to healthy group (control), HIV group showed a decrement of posterior alpha (8–13 Hz) power density (Gruzelier et al., 1996; Baldeweg et al., 1997). Abnormalities of the alpha power density preceded cognitive and neurological impairment at the symptomatic stage of HIV infection, were associated with changes in psychiatric status, and were normalized by cART (Baldeweg et al., 1997). Furthermore, abnormalities of theta (4–7 Hz) and alpha power density were related to mood ratings and immune status (i.e. CD4 counts) in asymptomatic HIV group (Gruzelier et al., 1996).

A recent contribution to the study of resting state EEG rhythms in HIV subjects was the mathematical estimation of cortical sources of these rhythms by the popular freeware called low-resolution brain electromagnetic tomography (LORETA; Pascual-Marqui and Michel, 1994; Pascual-Marqui et al., 1999, 2002). Compared to a control group of age-matched healthy subjects, a group of treatment-naïve HIV subjects showed higher activity of central and parietal sources of delta rhythms (<4 Hz), as well as lower activity of topographically diffuse sources of low- and high-frequency alpha rhythms (Babiloni et al., 2012). Furthermore, the alteration of cortical sources of EEG rhythms was less marked in a group of HIV subjects experiencing a long chronic treatment of cART. Compared to a control group of age-matched healthy subjects, that group of HIV subjects pointed to a similar activity of delta sources. Furthermore, it pointed to a less intense reduction of activity of cortical sources of alpha rhythms with respect to the group of treatment-naïve HIV subjects (Babiloni et al., 2014). These findings suggest that a successful cART therapy partially restores cortical synchronization mechanisms generating the resting state EEG rhythms in experienced HIV subjects.

In the present pilot study, we tested for the first time a simple statistical procedure to identify single treatment-naïve HIV individuals having such abnormal EEG sources with reference to a control group of matched healthy individuals. Compared to the HIV individuals with a statistically normal EEG marker, those with abnormal values were expected to show worse cognitive status. The design of the present study included the recording of resting state eyes closed EEG data in treatment-naïve HIV subjects and matched healthy subjects. Delta and alpha (LORETA) sources were estimated in several cortical regions of interest. Afterward, *z*-score of these EEG sources was computed in single treatment-naïve HIV individuals with reference to the group of healthy subjects ($p < 0.05$). Results of the present study were discussed as ability of *z*-score values to identify single treatment-naïve HIV subjects with statistically abnormal EEG sources and cognitive deficits compared with the control healthy group.

2. Methods

2.1. Subjects

This study included EEG and clinical data of 82 treatment-naïve HIV male subjects (mean age 39.8 ys. ± 1.2 standard error, SE), recruited at University S. Andrea Hospital and Tor Vergata Hospital of Rome (Italy). It also included EEG and clinical data of an age-matched control group of 59 cognitively normal male subjects (healthy; mean age 39 ys. ± 2.2 SE) selected from an university archive to obtain the best matching of age and gender between the two groups.

All experiments were performed with the written informed consent of each participant and approval by the local ethical committee, in line with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and the standards established by the Author's Institutional Review Board.

2.2. Diagnostic criteria

All participants were asked to provide a blood sample for the confirmation of HIV serostatus. The clinical laboratory evaluation also included Complete Blood Count (CBC), HIV RNA viral load, CD4 lymphocyte count and percent, Treponema screening, HBV–HCV screening, toxoplasmosis and cytomegalovirus antibody titers, renal and liver function, serum protein, and albumin. Toxicological analyses for cocaine, opiates, amphetamine, and marijuana were performed on urine samples. It is noted that none of the treatment-naïve HIV subjects showed CD4 counts compatible with a diagnosis of full-blown AIDS. All treatment-naïve HIV subjects belonged to the sexual transmission risk group (about 50% homosexually active individuals).

A structured psychiatric interview (i.e. Computerized Diagnostic Interview Schedule Version IV, CDIS-IV) was used for detecting DSM-IV Axis I and II disorders. All participants completed questionnaires or brief interviews assessing medical history, medication use, parental psychopathology, demographics, psychiatric