



Cortical sources of resting state electroencephalographic rhythms probe brain function in naïve HIV individuals



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HIGHLIGHTS

- Resting EEG rhythms slightly correlate with neuropsychological scores in HIV subjects.
- These rhythms also show moderate discrimination between HIV and control individuals.
- EEG markers unveil HIV neuroinvasion effects at the individual level.

ABSTRACT

Objective: Here we evaluated the hypothesis that resting state electroencephalographic (EEG) cortical sources correlated with cognitive functions and discriminated asymptomatic treatment-naïve HIV subjects (no AIDS).

Methods: EEG, clinical, and neuropsychological data were collected in 103 treatment-naïve HIV subjects (88 males; mean age 39.8 years \pm 1.1 standard error of the mean, SE). An age-matched group of 70 cognitively normal and HIV-negative (Healthy; 56 males; 39.0 years \pm 2.0 SE) subjects, selected from a local university archive, was used for control purposes. LORETA freeware was used for EEG source estimation in fronto-central, temporal, and parieto-occipital regions of interest.

Results: Widespread sources of delta (<4 Hz) and alpha (8–12 Hz) rhythms were abnormal in the treatment-naïve HIV group. Fronto-central delta source activity showed a slight but significant ($p < 0.05$, corrected) negative correlation with verbal and semantic test scores. So did parieto-occipital delta/alpha source ratio with memory and composite cognitive scores. These sources allowed a moderate classification accuracy between HIV and control individuals (area under the ROC curves of 70–75%).

Conclusions: Regional EEG abnormalities in quiet wakefulness characterized treatment-naïve HIV subjects at the individual level.

Significance: This EEG approach may contribute to the management of treatment-naïve HIV subjects at risk of cognitive deficits.

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1. Introduction

Human immunodeficiency virus (HIV) causes neurological, cognitive, and behavioral symptoms during the progression of the infection (Reger et al., 2002; Anthony and Bell, 2008; Antinori et al., 2007a, 2007b). From an epidemiological point of view, subclinical neuropathy was reported in 10–40% of asymptomatic subjects with HIV and 53–100% in those with the AIDS (Chavanet et al., 1988; Gastaut et al., 1989). Also, 50–70% of subjects with HIV suffer from neurologic and the so-called HIV-associated neurocognitive disorders (HANDs) including deficits of episodic memory, attention, cognitive-motor, and executive functions such as planning and problem solving (Selnes, 2005).

Neuropsychological assessment is crucial for the diagnosis of cognitive deficits in HIV subjects. According to the “Frascati criteria” (Antinori et al., 2007a, 2007b), seven cognitive domains should be tested in HIV subjects, namely verbal/language, attention/working memory, abstraction/executive, episodic memory, the speed of information processing, sensory-perceptual, and motor skills. Deficits in these cognitive domains determine the diagnosis as the asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND), and HIV-associated dementia (HAD). ANI includes cognitive deficits at least in 2 cognitive functions and proper daily functionality; MND is characterized by cognitive deficits and some functionality impairment; HAD presents moderate to severe cognitive deficits and functionality impairment. Furthermore, Robertson et al. (2009) extended these cognitive domains to premorbid Intelligence, constructional abilities, and visuoperception. Of note, neuropsychological tests to diagnose these cognitive deficits vary from study to study (Antinori et al., 2007a, 2007b; Robertson et al., 2009; Gandhi et al., 2010). HANDs have an adverse impact on survival (Sevigny et al., 2007), self-care ability and quality of life (Heaton et al., 2004), work performance (Heaton et al., 1994), drug adherence (Woods et al., 2008; Hinkin et al., 2002), and driving (Marcotte et al., 2006).

Unfortunately, cognitive deficits are often diagnosed even in some HIV subjects treated with an effective combination antiretroviral therapy (cART), possibly due to the escape of the virus in the brain reservoir (Graham et al., 1992; Hammer et al., 1997; Hunt et al., 2003; Sevigny et al., 2004; Clifford, 2008; Williams et al., 2012; Cysique et al., 2009). In the cART era, mild HAND persists at all infection stages, even in long-standing aviremic HIV-positive patients (Heaton et al., 1995, 2010). HAND was evidenced in 82% of the HIV patients complaining cognitive deficits and in 64% of those not complaining cognitive deficits. ANI symptoms are the most frequent manifestation of HAND (Simioni et al., 2010). Only HAD cases are strongly reduced (Grant et al., 1987). In the pre-cART era, cognitive impairment in treatment-naïve HIV subjects regarded principally speed of information processing, motor skills, and verbal fluency while this impairment regarded more executive and memory function in the cART era (Heaton et al., 2011).

Previously advanced immunosuppression with low CD4 cell count is one of the factors predicting subsequent cognitive impairment over time, even in HIV subjects under cART (Robertson et al., 2007; Heaton et al., 2010). Other factors may depend on their lifestyle (e.g. nutrition and healthy physical activity), general medical condition (e.g. central obesity, diabetes), premorbid Intelligence, education, and socio-economic factors (Robertson et al., 2009; McCutchan et al., 2012; Wright et al., 2015). As a logical consequence, it can be theoretically stated that being the serological biomarkers of HIV and global cognitive status equal in two example subjects, the level of brain dysfunction due to the infection can be entirely different. Such dysfunction would be greater in the HIV individual showing the best lifestyle, general psychophysical, premorbid Intelligence, education, and socio-economic factors. An HIV

subject with ideal premorbid intelligence, lifestyle, socio-economic, and education factors could have “normal” scores to neuropsychological tests for several years meanwhile escape of the virus in the brain induces “silent” neuroinflammation and white and gray matter lesions.

The above data and considerations motivate the research of biomarkers indexing cerebral dysfunction due to HIV for the use in clinical applications (i.e. prevention and monitoring of abnormal brain functions in HIV subjects) as well as the discovery of pharmacological and nonpharmacological interventions with particular beneficial effects on HIV localized in the brain. A cost-effective and non-invasive technique for the measurement of brain function is the recording of electroencephalographic rhythms at electrodes placed on the scalp while subjects with HIV stay in quiet wakefulness, namely eyes-closed resting state condition (rsEEG). These rsEEG rhythms probe neurophysiological mechanisms regulating time-by-time brain arousal and the level of vigilance (Pfurtscheller and Lopes da Silva, 1999).

Previous rsEEG studies in HIV subjects have shown a general decrease of alpha (8–12 Hz) rhythms when compared to healthy (HIV-negative) subjects with some exceptions (Gruzelier et al., 1996; Baldeweg et al., 1997; Polich et al., 2000). In 20–30% of HIV subjects, there is a paradoxical and poorly understood increase in the alpha rhythms (Gabuzda et al., 1988; Nuwer et al., 1992; Baldeweg and Gruzelier, 1997), which might be related to the evolution of the infection or some mental symptoms (Koralnik et al., 1990; Baldeweg et al., 1997).

The abnormalities of rsEEG rhythms can be also observed at other frequencies. In HIV subjects with subclinical symptoms (no AIDS), delta (2–4 Hz) and theta (4–7 Hz) rhythms are abnormally high in amplitude, similarly to a classical observation reported in seniors with cognitive symptoms (Itil et al., 1990). This observation was even much more evident in HIV subjects when they suffer from AIDS (Itil et al., 1990). Furthermore, delta or theta rhythms with abnormally increased amplitude in fronto-temporal and frontal areas were reported in 25% of HIV subjects with no AIDS and 30% of those with lymphadenopathy (Parisi et al., 1989). Some of them were characterized by abnormal scores of neuropsychological tests (30%) and the mild cerebral atrophy (20%). Moreover, delta and theta rhythms were found to be abnormally high in amplitude at 28-month follow-up while they were stable in the HIV subjects under ART (Baldeweg et al., 1995). These findings globally confirm preceding results based on visual analysis of the rsEEG traces in HIV individuals without and with AIDS (Enzensberger et al., 1985; Gabuzda et al., 1988; Prado et al., 1993; Sinha and Satishchandra, 2003).

The above-mentioned rsEEG results derive from the spectral analysis of EEG activity at scalp electrodes. Recently, we have contributed to this field using a popular procedure for the estimation of the cortical generators of rsEEG rhythms in HIV individuals, namely the open software named low-resolution brain electromagnetic tomography (LORETA), developed by Dr. Pascual-Marqui (Pascual-Marqui and Michel, 1994; Pascual-Marqui et al., 1999, 2002). We used the same procedure successfully applied for the study of abnormal EEG sources in elderly subjects with cognitive symptoms induced by Alzheimer’s disease or other brain diseases (see Babiloni et al., 2015a for a review). In brief, compared to a group of healthy subjects, a group of treatment-naïve subjects with HIV showed higher activity in the parietal and central delta sources and lower activity in widespread alpha sources (Babiloni et al., 2012). These abnormalities were less prominent in a group of HIV subjects under a chronic treatment with the cART than a group of naïve treatment HIV individuals was (Babiloni et al., 2014). Furthermore, this cART effect on the delta and alpha rsEEG sources was also found in a group of naïve HIV subjects after

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