**INTRODUCTION**

Human Immunodeficiency Virus (HIV) is an aggressive and deceptive disease. In the U.S. alone, more than 1.2 million individuals are currently living with HIV [1]. Furthermore, the onset of HIV is subtle, and oftentimes symptoms don’t appear until later in life [1]. As a result, about one in eight individuals are currently living with HIV unknowingly [1]. Furthermore, HIV is an opportunistic infection, meaning it spreads easily—especially among young homosexual males [2].

At the onset of HIV, the virus attacks numerous cells of the central nervous system (CNS) [3]. The main affected cells within the brain are microglia, astrocytes, and macrophages [3]. Microglia and astrocytes are glial cells that have direct contact with the neuron, where macrophages are phagocytic cells found at the site of HIV infection [3]. All of these cells play a key role in the first line of defense, and are responsible for the primary immune response of the CNS [3]. If these cells are compromised, this can lead to behavioral, cognitive, and motor neurological dysfunction and functional neuronal connectivity degradation [3,4]. Functional neuronal connectivity (or functional connectivity (FC)) is a measure of dependence between signals from two separate regions within the brain [8].

Previous research has utilized non-invasive magnetoencephalography (MEG) to investigate HIV-related cognitive disorders, and effectively observe neuronal connectivity via deduced neuromagnetic fields [5,7]. In addition, a significant brain network pattern has been confirmed that relates to HIV serostatus [6]. However, no definitive biomarkers that are linked to observable cognitive impairment have been identified [6]. Thus, a functional connectivity analysis of MEG data could possibly be used to distinguish HIV-infected and uninfected individuals.

**OBJECTIVE**

This experiment aimed to effectively analyze neuronal connectivity amongst HIV patients and controls utilizing resting state MEG data. All patients were subject to “resting state” MEG data acquisition, and HERMES software was used to compare the number and strength of functional neuronal connections amongst all brain regions.

**SUCCESS CRITERIA / HYPOTHESIS**

Success was determined by any qualitative and/or significant difference in connectivity between seropositive and seronegative individuals. It was hypothesized that less neuronal connectivity would be present amongst seropositive individuals when compared to seronegative individuals.

**METHODS**

54 individuals (31 HIV+), all 37-64 years old, 28 with higher education (≥14 years), and none with any histories of mental or neurological conditions or drug abuse participated in this study. An Elekta NeuroMag scanner at UPMC Presbyterian was used for all MEG recording collection [9]. The scanner has 306 sensors arranged in triplets (102 magnetometers, 204 gradiometers) in a helmet-shaped array covering the entire scalp [9]. The scanner was used to collect five minutes of “eyes open” “resting state” MEG data.

These electrical data signals were sent to surrounding head position indicator (HPI) coils to localize them with respect to the MEG sensor array [9]. All data was then de-identified and preprocessed using “MaxFilter” to increase the signal-to-noise ratio. The resting state data was then divided into consecutive 3-second epochs, and uploaded into the computer program HERMES.

HERMES was used to run a functional neuronal connectivity analysis, and the phase-locking value (PLV) data was collected from MATLAB. PLV measures the synchronization of signals between one sensor and another and can range from a value of zero to one. Several MATLAB codes were written to calculate the number of connections throughout the brain, and quantify the strength of each connection using the PLV data. Certain thresholds were set to compare the location of connections with varying strengths throughout the brain.

The strength and location of connections were qualitatively compared against various frequency bands and the patients age, education, and serostatus.

**RESULTS**

When compared to the serostatus of all patients, the physical number of connections showed no significant difference between seropositive and seronegative individuals. Likewise, when compared to the serostatus of all patients, the average PLV across the entire brain showed no significant difference between seropositive and seronegative individuals when calculated at all thresholds.

The average PLV within both the left and right temporal lobes for patients with low education was higher when compared to the left and right temporal lobes of patients with high education, regardless of serostatus and threshold. This difference proved to be non-significant.

When the PLV data was visualized at delta (1 – 3 Hz) and theta (4 – 6 Hz) frequency bands, at a threshold of 0.5, there was a higher number of connections amongst...
seronegative individuals within the frontal lobe [Figure 1].

This difference in connectivity proved to be non-significant.

Figure 1. Connectivity plots comparing connectivity between seropositive and seronegative patients, showing connections solely amongst seronegative patients (green), at delta (A) and theta (B) frequencies (threshold = 0.5).

DISCUSSION

The higher the average PLV within any region of the brain, the stronger the average strength of connections within that region. Since the average PLV amongst the left and right temporal lobes of patients with low education is higher when compared to patients with higher education, this suggests stronger connections in the temporal lobes of these patients. Though it is unclear what the significance of this is, it should not be ignored.

Furthermore, an increase in connections within the frontal lobe of seronegative patients, supports the initial hypothesis that seropositive individuals would have a lower number of connections when compared to seronegative patients, regardless of brain region.

Though these results are intriguing, none were found to be statistically significant. This indicates that further connectivity analyses are required to either support or refute the visual differences observed thus far. The phase lag index (PLI) incorporates time delay with any signal synchronization, and may be of future interest to analyze the strength of connections, especially within the temporal lobes. In addition, a volume analysis of brain region may lend insight into whether size may affect the detected signals and hence inferred strength of connections within any brain region.

HIV is a threatening disease and the need for a definitive biomarker is still in high demand. Although the MEG machine utilized in this study was tedious, and communication was time consuming, the results of this study are striking. Moreover, although HERMES was newly introduced and its results at times complex, its capabilities of analyzing functional neuronal connectivity should be more deeply sought after.

After thorough analysis, MEG is concluded to be a positive frontier when combined with HERMES, to serve as a definitive biomarker for HIV disease.

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