

Intra-hemispheric alpha coherence decreases with increasing cognitive impairment in HIV patients

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Abstract

Inter-hemispheric and intra-hemispheric canonical coherences in the alpha range between EEG signals collected from frontal and posterior groups of electrodes were estimated for 38 HIV positive subjects and 23 uninfected controls. Neuropsychological testing was used to categorize the degree of cognitive impairment evident in each of the subjects. A linear regression analysis provided evidence that intra-hemispheric coherence decreased with increasing cognitive impairment in impaired HIV⁺ subjects, as measured by a Global Impairment Score (GIS). There was no evidence that cognitively unimpaired HIV⁺ subjects differed in coherence when compared to uninfected control subjects. Severely impaired HIV⁺ subjects showed significantly decreased coherence compared to uninfected controls. These data contradict previous work demonstrating increased intra-hemispheric and inter-hemispheric alpha coherence in impaired HIV subjects. In addition, they provide evidence that intra-hemispheric (and possibly inter-hemispheric) disconnection is associated with cognitive impairment in HIV. © 1997 Elsevier Science Ireland Ltd.

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1. Introduction

Infection with human immunodeficiency virus (HIV) often results in progressive central nervous system (CNS) degeneration. CNS symptoms occur in as many as 60% of AIDS patients, with neuropsychological testing and autopsy indicating CNS morbidity in up to 90% of AIDS cases (Portegies, 1994). CNS pathology most often includes abnormalities in the white matter and sub-cortical gray matter, with cortical involvement occurring relatively late in the disease (Ho et al., 1985). In the CNS, the HIV virus itself is localized mainly in microglia and macrophages (Pajeau and Roman, 1992). Magnetic Resonance Imaging (MRI) studies of AIDS patients often reveal white matter signal hyperintensities in the corpus callosum, indicating white matter disease affecting inter-hemispheric connections (Georgy et al., 1993). The CNS

effects of HIV can result in HIV-Associated Dementia Complex (HADDC), which is characterized by impairments in cognition, behavior, and motor coordination, as well as mood (Fernandes do Prado et al., 1994). The cognitive impairments observed in HIV disease suggest that the earliest and some of the most severe dysfunctions occur in frontal regions of the brain (Bornstein et al., 1993).

EEG coherence is a measure of the degree to which the signals (in a given frequency band) measured at two distinct scalp locations are linearly related to one another, where one signal may be lagged in relation to the other. A high coherence (near 1) indicates that the two regions are linearly associated through either direct or indirect anatomical connections, while a low coherence (near 0) indicates that the two regions are not linearly related. Thatcher has demonstrated a relatively high EEG coherence between scalp regions connected by known white matter tracts (Thatcher et al., 1986).

Coherence is independent of the power of the EEG signals in the frequency bands under examination (Diggle,

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1990). Coherence therefore yields information about connectivity rather than variables affecting EEG power, such as alertness. However, there are a number of potential factors underlying the EEG coherence phenomena and a simple interpretation of coherence as reflecting direct white matter connectivity between regions is unwarranted. If, for example, a subject exhibits decreased coherence between two scalp regions, the underlying cause could be either damage to white matter tracts connecting the two regions leaving the gray matter intact, or damage to one of the neuronal populations responsible for the signals measured at the two scalp regions leaving the white matter tracts intact. In addition, a decrease in coherence may be caused by damage to a tract which indirectly connects two regions through a third region, or by damage to a region of the brain simultaneously driving both. Regardless of the mechanism, the decrease in EEG coherence reflects a functional disconnection between the two regions.

EEG coherence has been most commonly estimated using common-referenced potential data; however, we have previously shown that the use of such data can lead to errors in coherence estimates because such estimates depend upon the power and phase of the signals measured at the reference and recording electrodes as well as coherence between the signals at the recording electrodes (Fein et al., 1988). This problem can be avoided by using a local measure of scalp electrical activity which removes the effect of a common reference, such as the current source density (CSD). For the purpose of coherence estimation, we have also shown that global CSD estimation techniques, such as the spherical spline method (Perrin, 1989), can result in inaccuracies (mostly inflation) in coherence estimates (Biggins et al., 1991), although global methods which weight information from distant electrodes less strongly than the spherical spline method are less prone to this problem. Local CSD estimation methods, such as that by Le et al. (1994), do not suffer from this problem. However, they tend to be more susceptible to the effects of noise with high spatial frequencies.

There has been an extensive discussion in the literature debating the relative merits of alternative scalp-derived measures of brain electrical activity, with conflicting theories and results. We have demonstrated artifactually high coherence estimates resulting from the use of common-reference recordings when the reference is electrically active (Fein et al., 1988) and suggested the use of CSDs, which are free of the effect of a *common* reference potential which is identical across recording channels. Rappelsberger, in a simulation study, showed that the use of an electrically silent common reference or a common reference with low signal power was superior to his estimates of CSDs or common average reference recordings (Rappelsberger, 1989).

In Rappelsberger's paper, he criticized the definition of CSD estimates as 'reference-free' measures because they are obtained by subtracting a weighted average of the

common-referenced potential measured at each of the surrounding electrodes from the common-referenced potential measured at the electrode of interest. Therefore, the CSD estimate can be considered to be referenced to this unknown, weighted average potential and, by Rappelsberger's definition, not reference-free. However, the weights in the weighted average are chosen such that the effect of the *common* reference is removed, and so the CSD is always a measure based only upon local activity. It is in this sense that we call the CSD reference-free. Because the data from each recording channel is only dependent on local activity, it is free of the coherence estimate inflation which can occur when activity in the vicinity of a single, common reference electrode is incorporated into the potential differences measured across all of the recording channels in a common-reference data set.

Rappelsberger simulated the EEG with random processes with specified coherences among the electrode locations. He estimated CSDs, common-average-referenced and common-referenced (to a reference with a specified signal strength) data from the simulated series and found that the common-referenced data with low reference power performed better than common-average-referenced data and CSD estimates. However, CSD estimation is based upon a physical model of EEG signals in the brain in which a finite number of sources generate the potentials on the scalp surface, with these potentials propagated from the sources to the scalp surface through volume conduction. Because Rappelsberger's simulations did not utilize such a model, the basic assumptions underlying CSD estimation were not met and the resulting CSD estimates could not be expected to preserve the coherences of the simulated signals. While Rappelsberger's conclusion about the validity of using common-referenced EEG recordings with electrically silent or almost silent references is accurate, we believe that the use of a locally estimated CSD is preferable because a truly silent reference is impossible to attain.

Another advantage of the use of the CSD for coherence estimation is its spatial filtering property. Because the CSD is the second spatial derivative of the scalp potential distribution, it acts as a high-pass spatial filter which depends much less on the activity of distant generators than does the surface potential itself. For this study, the goal was to investigate the connectivity between cortical regions. This goal is more easily met using CSDs than surface potentials because CSDs more strongly reflect the activity of cerebral cortex located closest to the recording electrode and tend to filter out the effects of subcortical structures or more distant cortical regions.

Several studies have examined EEG coherence in HIV, and have found conflicting results. Newton et al. (1994) found increased coherence between left and right posterior regions (presumably connected via the corpus callosum) and in temporo-frontal, temporo-parietal, and fronto-occipital connections in mildly impaired AIDS patients. They

Table 1
Summary of the subject groups

Group	N	Race				CDC			NP %ile	GIS	Age	Education
		AA	C	H	P	A	B	C				
HIV-SI	9	1	8	0	0	0	3	6	17.0 ± 9.8	7.3 ± 1.7	40.9 ± 5.3	15.3 ± 1.7
HIV-MI	17	2	14	1	0	0	10	7	36.1 ± 9.9	3.1 ± 0.93	39.8 ± 7.4	15.0 ± 2.2
HIV-U	12	1	11	0	0	1	10	2	55.1 ± 12.8	0.33 ± 0.49	38.0 ± 6.6	15.0 ± 1.8
Control	23	1	21	0	0	–	–	–	56.0 ± 11.2	0.35 ± 0.49	37.8 ± 7.1	15.9 ± 2.4

Table shows number of subjects (N), number of subjects in each race category (AA, African American; C, Caucasian; H, Hispanic; P, Polynesian), number of subjects at each CDC clinical stage, average neuropsychological testing percentile scores (NP %ile), global impairment scores (GIS), age, and education statistics. HIV-SI, HIV⁺ subjects with severe cognitive impairment (GIS ≥ 6), HIV-MI = HIV⁺ subjects with mild to moderate cognitive impairment (2 ≤ GIS ≤ 5), HIV-U = cognitively unimpaired HIV⁺ subjects (GIS ≤ 1). There were no significant differences in age or education between the groups. The race of one of the control subjects is unknown.

hypothesized that this increase in coherence can be attributed to increased subcortical metabolic activity, which can synchronously drive multiple regions of the brain. Using PET techniques, they found increased subcortical metabolic activity early in the course of HIV infection.

In a study examining sleep EEG in AIDS patients, Terstege et al. found decreased coherence in delta, theta and alpha bands between left and right frontal regions in REM and NREM sleep, as well as decreased inter-occipital coherence in the theta range in REM sleep (Terstege et al., 1993). Because previous studies had shown a decrease in sleep spindle density in AIDS patients, the authors hypothesized that these changes in spindle activity might also have an influence on inter-occipital coherence. Their finding of significantly decreased inter-frontal coherences in AIDS patients is consistent with the observed later stage neuropathology and neuropsychological disturbances associated with HADC. Because the authors only performed sleep EEG recordings, it is difficult to directly compare their results with those of Newton et al. Most importantly, Terstege et al. used common reference recordings which could potentially suffer from the artifacts we described in our 1988 paper (depending upon the strength of the activity at the common reference), calling into question the interpretation of their results as clearly reflecting HIV/AIDS associated effects on inter-connection between brain regions.

In the present study, the hypothesis was tested that, as a consequence of damage to long-distance cortico-cortical connections, cognitively impaired HIV⁺ patients would exhibit decreased coherence between left and right brain regions and between frontal and posterior regions as compared to uninfected controls. Thirty-eight (38) HIV positive patients (26 cognitively impaired and 12 cognitively unimpaired) and 23 HIV negative controls were studied. Common reference EEG data were collected from each subject and reference-free CSDs were estimated. Inter-hemispheric and intra-hemispheric coherences were estimated from the CSDs calculated at sets of left and right frontal and left and right posterior electrodes.

2. Materials and methods

2.1. Subjects

A total of 61 male subjects were studied, 38 HIV positive subjects and 23 uninfected controls. Control subjects were of comparable age and education as the HIV⁺ subjects. Subjects who met DSM III-R criteria for a lifetime history of drug or alcohol dependence or with a history of psychiatric disorder (bipolar disorder, schizophrenia, or psychoses) were excluded from the study. All of the HIV⁺ subjects had CD4% below 27 (mean = 7.0 ± 6.3). The subject group information is summarized in Table 1.

All subjects received a comprehensive neuropsychological assessment which took place over two sessions. One assessment involved administration of the MicroCog Assessment of Cognitive Functioning, standard version (Powell et al., 1993), a computerized battery that takes 1 h to complete and includes 18 subtests. The other session involved administration of the following tests and assessments: Beck Depression Inventory (Beck et al., 1961), Rey-Osterreith Complex Figure (copy, immediate, and delay) (Osterreith and Rey, 1944), Shipley Institute of Living Scale (SILS) (Shipley, 1940), Trail Making Test A and B (Reitan and Wolfson, 1985), Controlled Oral Word Association Test (Benton and Hamsher, 1983), Symbol Digit Modalities Test (Smith, 1968), Grooved Pegboard (Klove, 1963), Short Category Test (Weitzel, 1982), Stroop Color Word Test (Golden, 1975), and a psychosocial interview which details education, job history, sexual orientation, living arrangements, social support, leisure time activities, therapy and psychiatric treatment experiences, and medical history.

Composite Z-scores and percentiles for nine domains were generated from age and education adjusted scores on all tests. Age and education adjusted scaled scores for each test (or MicroCog subtest, denoted by an asterisk) were first converted to Z-scores and the Z-scores were averaged for each domain. The domains and the tests that comprise them were as follows: Attention (numbers

forward*, numbers reversed*, alphabet*, wordlist 1*); Verbal (Controlled Oral Word Association, Shipley Institute of Living – vocabulary subtest); Abstraction (Shipley Institute of Living – abstraction subtest, short categories, Stroop Interference, Trails B, Analogies*, Object Match A and B*); Spatial Processing (Tic Tac*, Clocks*); Psychomotor (Trails A, Symbol Digit written and oral); Memory (Story 1, 2 and address delay*, Rey Complex figure delay); Learning (Story 1 and 2 immediate*, Rey complex figure immediate, word list 2*); Motor (Grooved pegboard); Reaction Time (simple auditory and visual timers*, cued audio/visual timers*).

A global clinical impairment score across domains was also generated as follows:

1. Each domain Z score will be converted into a percentile score,
2. The percentile scores received a clinical impairment rating of 0–2 as follows (0: %ile > 15; 1: 15 ≥ %ile > 5; 2: %ile ≤ 5), and
3. These clinical impairment ratings will be summed across domains to yield the global clinical impairment score.

Using the GIS, the HIV subjects were split into a severely impaired group (HIV-SI, GIS ≥ 6, $N = 9$), a mildly to moderately impaired group (HIV-MI, $2 \leq \text{GIS} \leq 5$, $N = 17$) and an unimpaired group (HIV-U, GIS = 0–1, $N = 12$).

Five additional subjects (1 HIV-U, 2 HIV-MI, 1 HIV-U, and 1 control) were excluded from this study due to large amounts of artifact in the EEG recordings. These subjects each had at least 4 electrodes at which every EEG trial had very large wandering baselines. The EEG recordings were done at the end of a 3 h electrophysiological recording session, and it is likely that these electrodes either became detached or the electrode paste had dried, resulting in very large impedances. Because these artifacts existed on every recorded trial in these subjects, they were excluded from the study.

2.2. EEG data

Twenty-nine (29) artifact-free epochs, each containing 1 s of resting EEG data, were collected from each subject at 30 scalp electrodes. In addition, 2 channels of EOG data measuring vertical and horizontal eye movements were collected from 4 electrodes placed around the left eye. The subjects were instructed to keep their eyes closed, relax, and try not to move their eyes during data acquisition. Data were collected using an Electro-Cap with tin electrodes placed at Fz, Cz, Pz, Oz, Fp1, Fp2, F7, F8, T3, T4, C3, C4, T5, T6, F3, F4, F5, F6, P3, P4, P5, P6, O1, O2, FC3, FC4, CP3, CP4, AF3, and AF4, with all recordings referenced to an electrode placed on the left ear lobe. The electrode array is diagrammed in Fig. 1. The EEG signals were amplified using Grass Instruments

preamplifiers with bandpass half-amplitude filter settings from 0.1 to 100 Hz. The signals were then digitized at 250 samples/second using a National Instruments A/D board in a Pentium-based PC. These signals were digitally band-pass filtered from 1 to 40 Hz and eye movement corrected using information obtained from the EOG data (Gasser et al., 1985).

2.3. Coherence estimation

As discussed above, it has been shown that estimates of coherence derived from common-referenced potential data sets can be artifactually inflated by the spectrum and phase of the activity at the reference and recording electrodes (Fein et al., 1988). The use of a reference-free measure of activity, such as the current source density (CSD) avoids this problem. The local CSD estimation technique developed by Le et al. (1994) was used for this study because it avoids the problems in coherence estimation associated with the use of global CSD estimates, such as the spherical spline (Biggins et al., 1991). In addition, the CSD filters out activity due to more distant generators, resulting in a measure of local brain activity. Common-referenced potentials incorporate information not only from local sources, but also from more distant sources through volume conduction. Because the reference electrode is electrically active (although the magnitude of the activity may be small), information from generators near the reference electrode will also be incorporated. In addition, since this study was concerned with measuring the effects of HIV on the connections between local generators rather than on global changes in the brain, CSDs were more

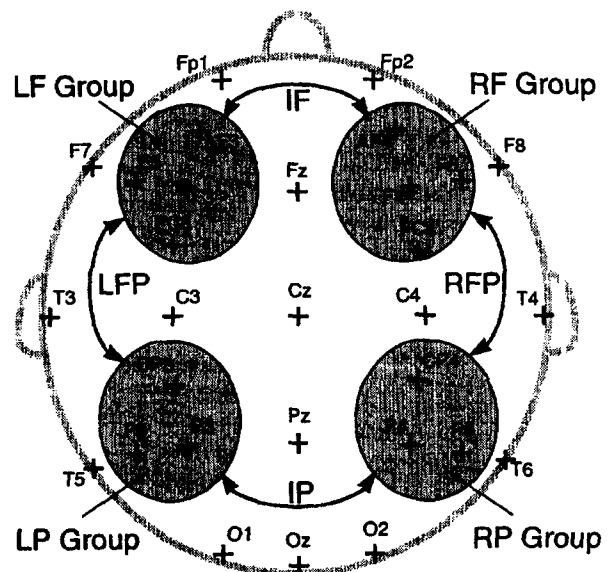


Fig. 1. Electrode locations and electrode groups used to compute canonical coherences. The curved lines indicate the canonical coherences examined.

appropriate measures for coherence estimation than common-referenced potentials.

CSDs were computed from the eye-movement corrected EEG data using the local CSD estimation method, and the resulting time series were prewhitened by filtering them with a third order autoregressive model fit to the 29 EEG sweeps recorded at each channel. This was necessary in order to reduce bias in the coherence estimates which might result from any sharp peaks in the spectra of the individual signals (Brillinger, 1981). Note that application of a linear filter to each time series has no effect on the coherence between the two series (Brillinger, 1981). The prewhitened CSD time series (each containing 250 points) were tapered and zero-padded to 500 points and transformed to the frequency domain using a Fast Fourier Transform.

Canonical coherences were estimated between groups of electrodes in 4 regions of the scalp. Canonical coherences are obtained by taking linear combinations of the Fourier coefficients of the individual time series in the

frequency range of interest which yield a maximum coherence between the two groups (Brillinger, 1981). It allows estimation of coherence between groups of electrodes, thus pooling the information available and reducing the effects of noise. It is a useful summary measure because it weights the contribution of each individual channel so as to maximize the estimated coherence. Canonical coherence is more parsimonious than taking all possible coherences between series from two different regions and is a method developed specifically to estimate an appropriate weighted average of the individual coherences. For a full description of the algorithm used to compute canonical coherences, see the Appendix.

The left-frontal (LF) group contained F3, F5, AF3 and FC3, the right-frontal (RF) group contained F4, F6, AF4 and FC4, the left-posterior (LP) group contained P3, P5 and CP3, and the right-posterior (RP) group contained P4, P6 and CP4. These groups are shown in Fig. 1. Because CSD estimation at a particular electrode requires information about the gradient of the potential in all directions

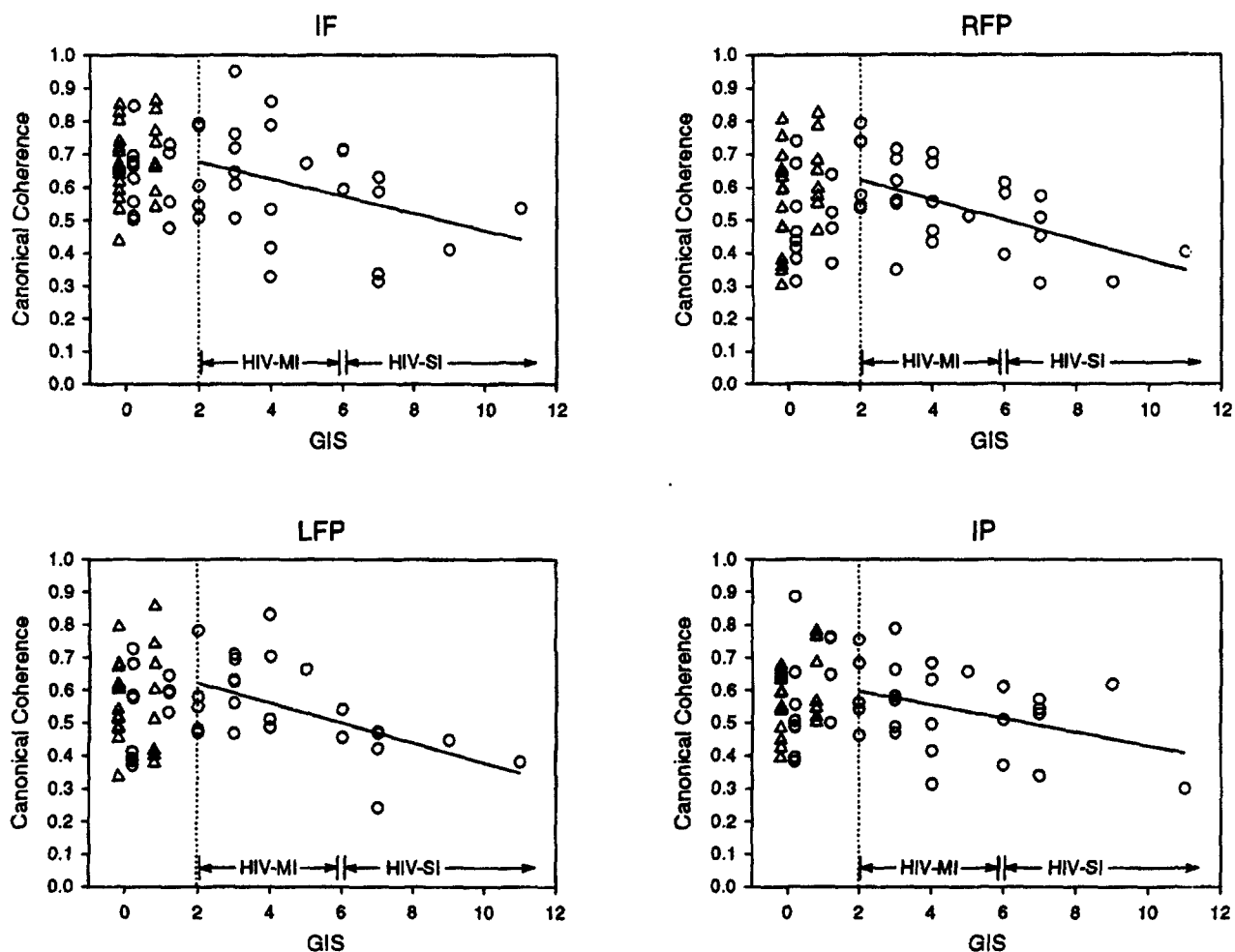


Fig. 2. Canonical coherence vs. GIS for all HIV-infected subjects (circles) and controls (triangles). Results are shown for inter-frontal (IF), right frontal-posterior (RFP), left frontal-posterior (LFP), and inter-posterior (IP) electrode groupings. (Note that for subjects with GIS = 0 or 1, placement on the X-axis is shifted to differentiate between controls and HIV⁺ subjects.)

Table 2

Comparison of canonical coherences between HIV negative controls (CONT) and HIV positive unimpaired subjects (HIV-U), as well as between controls and HIV positive severely impaired subjects (HIV-S)

Subject group	IF Coherence	RFP Coherence	LFP Coherence	IP Coherence
CONT (N = 23)	0.680 ± 0.112	0.581 ± 0.147	0.566 ± 0.133	0.587 ± 0.107
HIV-U (N = 12)	0.627 ± 0.110 (P = 0.190)	0.496 ± 0.130 (P = 0.102)	0.541 ± 0.123 (P = 0.599)	0.584 ± 0.157 (P = 0.945)
HIV-MI (N = 17)	0.647 ± 0.165 (P = 0.455)	0.588 ± 0.118 (P = 0.874)	0.601 ± 0.115 (P = 0.384)	0.573 ± 0.126 (P = 0.704)
HIV-SI (N = 9)	0.537 ± 0.150 (P < 0.006)	0.450 ± 0.115 (P < 0.04)	0.431 ± 0.0829 (P < 0.009)	0.488 ± 0.121 (P < 0.03)

Inter-frontal (IF), right frontal-posterior (RFP), left frontal-posterior (LFP) and inter-posterior (IP) coherences are shown.

around the electrode, it is not possible to obtain good estimates of the CSD at electrodes on the outer ring of the array. Therefore, it was not possible to examine coherences involving the most frontal electrodes (Fp1 and Fp2) or the occipital electrodes (O1 and O2). Canonical coherences were computed between LF-RF (inter-frontal, IF), between LP-RP (inter-posterior, IP), between LF-LP (left frontal-posterior, LFP), and between RF-RP (right frontal-posterior, RFP).

Coherence was examined in the alpha band (7–13 Hz), based upon the predominance of activity in this band in awake subjects with eyes closed and on the findings reported in previous work on coherence in AIDS patients (Newton et al., 1994). A relatively wide alpha band was examined because of previous findings indicating slowing of alpha activity in AIDS patients (Fernandes do Prado et al., 1994).

2.4. Hypotheses

Given the evidence that white matter tracts and deep gray matter structures are preferentially affected by HIV, the main hypothesis tested in this study was that cognitively impaired HIV⁺ subjects would demonstrate decreasing inter-hemispheric and intra-hemispheric canonical coherence with increasing cognitive impairment as measured by neuropsychological testing, while cognitively unimpaired HIV⁺ subjects would demonstrate comparable inter-hemispheric coherence to controls. In addition, because the cognitive impairments associated with HIV are frontal in nature, a secondary hypothesis was that coherences involving frontal regions would evidence the effects of HADC more strongly than would inter-posterior coherence.

3. Results

The IF, IP, LFP and RFP coherences for all of the subjects vs. GIS are shown in Fig. 2. *T* tests did not yield any evidence that there were differences in coherence between control subjects and the unimpaired HIV⁺ subjects (HIV-U) or the moderately impaired HIV⁺ subjects (HIV-MI).

However, when IF, IP, LFP, and RFP canonical coherences for uninfected controls were compared to severely impaired HIV⁺ subjects (HIV-SI), significant group differences were found for all coherences, with HIV-SI subjects exhibiting decreased coherence compared to controls. These results are summarized in Table 2.

The scatter plots in Fig. 2 suggest the possibility of linearly decreasing coherences with increasing GIS for impaired HIV⁺ subjects. A linear model was fit to the data by performing a linear regression of canonical coherence on GIS for all impaired HIV⁺ subjects. The results are summarized in Table 3. For the intra-hemispheric coherences (LFP and RFP), the linear regression results were significant (*P* < 0.01), and slopes of –0.0315 (for LFP) and –0.0304 (for RFP) were estimated. For the inter-hemispheric coherences, the linear regression results did not reach significance (IF: *P* = 0.061, IP: *P* = 0.051), but the results suggest a trend similar to that found for the intra-hemispheric coherences (estimated slopes for IF = –0.0261, IP = –0.0209) which should be examined either in a replication study or when data from additional subjects are available.

In order to compare the use of CSDs and canonical coherence with a more traditional analysis technique, coherences were estimated using bipolar derivations in left frontal (F3-Fp1), right frontal (F4-Fp2), left posterior (P3-O1) and right posterior (P4-O2) regions. The same linear regression analysis was then performed on these coherences, and the results are summarized in Table 4. Scatterplots of the coherence data overlaid with the linear

Table 3

Slopes, standard errors (SE), *F*- and *P*-values of the linear regression of canonical coherence estimated from CSDs on GIS

	Slope	SE	<i>F</i> -value	<i>P</i> -value
IF	–0.0261	0.0133	3.87	0.061
RFP	–0.0315	0.00919	11.7	0.0022
LFP	–0.0304	0.00953	10.2	0.0039
IP	–0.0209	0.0102	4.21	0.051

Inter-frontal (IF), right frontal-posterior (RFP), left frontal-posterior (LFP), and inter-posterior (IP) electrode groups for cognitively impaired HIV⁺ subjects are shown.

Table 4

Slopes, standard errors (SE), *F*- and *P*-values of the linear regression of coherence estimated from bipolar recordings on GIS

	Slope	SE	<i>F</i> -value	<i>P</i> -value
IF	-0.0028	0.0108	0.066	0.8001
RFP	-0.0191	0.0088	4.76	0.0392
LFP	-0.0204	0.0089	5.17	0.0323
IP	0.0084	0.0092	0.828	0.3719

Inter-frontal (IF), right frontal-posterior (RFP), left frontal-posterior (LFP), and inter-posterior (IP) electrode pairs for cognitively impaired HIV⁺ subjects are shown.

fits are shown in Fig. 3. While the bipolar data demonstrated the same linear trend of decreasing intra-hemispheric coherence with increasing GIS, these slopes were not significantly different from 0 when adjusted for 4 comparisons.

The number of trials of raw EEG data containing eye movement artifact above threshold (90 μ V) for each of the

subject groups were also examined in order to ascertain whether more impaired subjects were generating a greater number of eye movements. There were no differences between the groups in the number of trials containing eye movements above threshold.

Fisher *r* to *z* transforms were applied to the coherence data and histograms of the residuals from the linear fits were examined. The transformed data exhibited significantly greater skewness and kurtosis than the untransformed data. Therefore, the untransformed data were used. Note that, although this transform helps to normalize variations in coherence within an individual, it is not necessarily required for comparisons between individuals.

4. Discussion

This study provides additional evidence supporting the theory that HIV-related cognitive impairments reflect disconnection of distant cortical areas. Visual inspection of the data in Fig. 2 suggests that there may be a slight

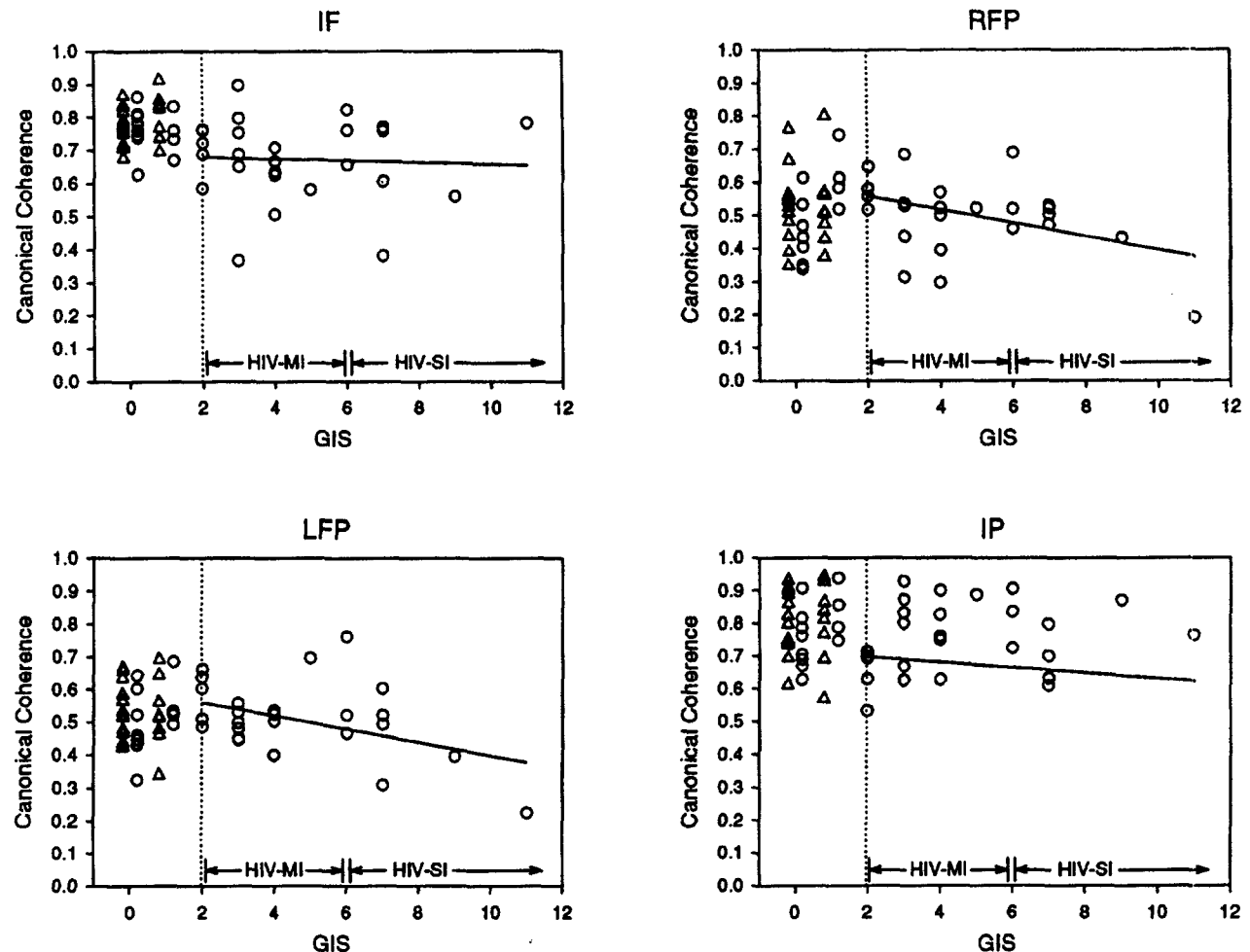


Fig. 3. Coherence derived from bipolar recordings vs. GIS for all HIV-infected subjects (circles) and controls (triangles). Results are shown for inter-frontal (IF), right frontal-posterior (RFP), left frontal-posterior (LFP), and inter-posterior (IP) electrode groupings. (Note that for subjects with GIS = 0 or 1, placement on the axis is shifted to differentiate between controls and HIV⁺ subjects.)

increase in coherence in very mildly impaired HIV⁺ subjects (GIS = 2–3) as compared to controls and unimpaired HIV⁺ subjects. However, a linear fit of the data from GIS = 0 to GIS = 2 yielded a slope significantly different from zero for only the RFP coherence (slope = 0.0674, $P = 0.017$). These data corroborate, to an extent, the results of Newton et al., who found increased fronto-occipital coherence in mildly impaired AIDS patients compared to controls, possibly due to increased subcortical metabolic activity observed early in the disease. However, these results suggest that inter-frontal and inter-posterior coherences may not be increased in mildly impaired HIV infected patients as reported by Newton et al. Clearly, the evidence provided by this study of increased coherence in mildly impaired HIV⁺ subjects is inconclusive.

The examination of coherence estimated from bipolar derivations in left and right frontal and left and right posterior groups suggests that the use of canonical coherence and CSD provides a more sensitive measure of coherence differences between groups. While similar linear trends were seen in intra-hemispheric coherences estimated using both methods, those obtained with canonical coherence and CSD estimates were statistically significant while those obtained from bipolar recordings did not reach statistical significance.

There are a number of possible explanations for the discrepancies between these results and those of Newton et al. The most likely explanation for the difference is that a more valid measure of coherence was obtained in the present study through the use of both the CSD and canonical coherence. Alternatively, it is possible that the results differ because a different alpha frequency range was used in the present study. Newton et al. labeled frequencies from 6–10 Hz alpha, rather than the more standard 8–12 Hz, because of the finding that the alpha rhythm is slowed in HIV infected patients (Leuchter et al., 1987). However, this choice of frequency range introduces the potential problem (if in fact HIV⁺ subjects have a slowed alpha rhythm) that coherence estimates in the control subjects may not be reflecting alpha activity while those in the HIV⁺ subjects are reflecting alpha activity. Because the data were collected in a resting, eyes-closed, alert condition, alpha will predominate, and the increased coherence reported may be due simply to the fact that alpha activity was missed in the controls. The frequency range used for this study (7–13 Hz) is wide enough to capture alpha which is slower than normal while still covering the normal alpha range. Plots of the frequency spectra of the common-referenced EEG at the occipital electrodes showed that the alpha peaks for all subjects in this study fell within the 7–13 Hz range.

Our finding that cognitively impaired HIV positive patients exhibit decreased intra-hemispheric coherence with increasing cognitive impairment is consistent with the known anatomical pathologies associated with HIV infection of the CNS, including disease of white matter

tracts and frontal subcortical gray matter. In addition, it agrees with the frontal nature of the cognitive impairments commonly found in HIV disease. The estimated slopes of the linear fits to the intra-hemispheric coherences seem to be steeper than those of the inter-hemispheric coherences, but these differences are not statistically significant. Replication studies or additional subjects may provide more insight into the relative sensitivities of intra-hemispheric and inter-hemispheric coherences to cognitive impairment, but the present data do not provide conclusive evidence that there are differences.

The ability of this study to examine inter-occipital and frontal-occipital coherences was limited by the placement of electrodes and the inability to estimate CSDs at the edge electrodes in the array. Clearly, alternative arrays containing more electrodes or grouping the available electrodes in regions of interest would allow better information to be obtained, especially in the more posterior regions. Neuroimaging studies have found damage to the splenium of the fornix, which forms inter-hemispheric connections between visual areas of occipital cortex, in AIDS patients (Georgy et al., 1993). This finding suggests that inter-occipital coherence could be examined for further evidence of this type of damage and the functional consequences of these anatomical lesions.

In conclusion, these findings suggest that subjects with greater cognitive impairment show a decrease in intra-hemispheric coherence when compared to less impaired subjects, which is proportional to the difference in their degrees of impairment as measured by neuropsychological testing. This may be a result of increasing damage to direct connections through white matter tracts, subcortical gray matter, or indirect connections via other cortical areas with the progression of the disease. However, EEG coherence differences can only provide evidence for changes in functional connectivity. They cannot provide information about the specific anatomical or physiological changes responsible for these functional connectivity effects. In addition, there is some evidence that inter-hemispheric coherence also decreases with increasing cognitive impairment, but replication studies or additional subjects will be needed to verify this finding. Finally, subjects early in the course of HIV infection may exhibit somewhat increased intra-hemispheric alpha coherence between frontal and posterior regions, possibly due to increased subcortical metabolic activity as reported by Newton et al. (1994), but the data from this study is inconclusive on this issue.

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Appendix A Computation of canonical coherence between two groups of time series

Canonical coherence is the frequency domain analogue of canonical correlation. It is a statistic describing the coherence between two groups of variables in a given frequency range, and can be thought of as the maximum coherence which can be obtained by taking linear combinations of the variables in each of the two groups. This appendix describes the algorithm used to compute the canonical coherences reported in this paper, which is based upon the time domain algorithm described by Gitins (1985).

Notation as follows: n is the number of EEG sweeps collected from each subject; f , the number of Fourier frequencies in the range of interest; p_1 , the number of electrodes in grouping 1; and p_2 , the number of electrodes in grouping 2 ($p_1 \geq p_2$).

The procedure utilized involved the following 5 steps.

1. Compute the complex Fourier coefficients of each of the prewhitened time series in each of the two groups using a Fast Fourier Transform (FFT). The Fourier coefficients in the frequency range of interest are assembled into two complex matrices \mathbf{X} ($N \times p_1$) and \mathbf{Y} ($N \times p_2$), where $N = n \times f$.

2. QR decompose the complex matrices \mathbf{X} and \mathbf{Y} .

$$\mathbf{X}_{N \times p_1} = \mathbf{Q}_{N \times p_1}^{(X)} \mathbf{R}_{p_1 \times p_1}^{(X)}$$

$$\mathbf{Y}_{N \times p_2} = \mathbf{Q}_{N \times p_2}^{(Y)} \mathbf{R}_{p_2 \times p_2}^{(Y)}$$

where $\mathbf{Q}^{*T} \mathbf{Q} = \mathbf{I}$, $*T$, denotes a conjugate-transpose of the matrix, and \mathbf{R} is an upper triangular matrix.

3. Form the complex matrix \mathbf{K} .

$$\mathbf{K}_{p_1 \times p_2} = [\mathbf{Q}^{(X)}]_{p_1 \times N}^{*T} \mathbf{Q}_{N \times p_2}^{(Y)}$$

4. Singular value decompose the complex matrix \mathbf{K} .

$$\mathbf{K}_{p_1 \times p_2} = \mathbf{W}_{p_1 \times p_2} \mathbf{D}_{p_2 \times p_2} \mathbf{Z}_{p_2 \times p_2}$$

where \mathbf{D} is a real-valued diagonal matrix.

5. Extract the largest singular value from the matrix \mathbf{D} . This is the first canonical coherence between the two sets of time series (analogous to the squared coherence).

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