Brain structural and functional recovery following initiation of combination antiretroviral therapy

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Abstract NeuroAIDS persists in the era of combination antiretroviral therapies. We describe here the recovery of brain structure and function following 6 months of therapy in a treatment-naive patient presenting with HIV-associated dementia. The patient's neuropsychological test performance improved and his total brain volume increased by more than 5 %. Neuronal functional connectivity measured by magnetoencephalography changed from a pattern identical to that observed in other HIV-infected individuals to one that was indistinguishable from that of uninfected control subjects. These data suggest that at least some of the effects of HIV on the brain can be fully reversed with treatment.

Keywords HIV disease · NeuroAIDS · Magnetoencephalography · Functional connectivity

Introduction

In spite of changes in the treated history of HIV disease following the introduction of combination therapies (cART), there have been few detailed descriptions of the recovery of brain structure and function that occur following treatment initiation. We describe here a 54-year-old man who first presented for treatment with HIV-associated dementia (HAD), neuropathy, and myelopathy who had significant

recovery documented with neurobehavioral exams, brain structural data from magnetic resonance imaging (MRI), and functional connectivity of neuronal networks using magnetoencephalography (MEG).

Methods

Case summary

PG is a 54-year-old, high school-educated, right-handed African American man who was admitted to a local hospital and diagnosed with *Pneumocystis jirovecii* pneumonia and found to be HIV-infected. His family learned that he was unable to live independently, that he had been fired from his job, and that he had been evicted from his apartment due to memory loss, confusion, and the inability to care for himself. PG moved to live with his extended family and to establish care with an HIV specialty clinic (March 2010). At that time, they reported that he was confused, having problems with both short- and long-term memory, and was unsteady on his feet, resulting in several falls. He had lost 40 lb over 5 months.

His $CD4^+$ count in March 2010 was 12 cells/mm^3 (1 %), with an HIV-1 RNA level of 638,000 copies per milliliter ($\log_{10}$=5.80); therapy was started using the daily fixed-dose combination of efavirenz–emtricitabine–tenofovir. He returned to the clinic 1 month later, at which time both he and his family reported that he was functioning more independently. His $CD4^+$ count was 236 cells/mm^3 (8 %), and the HIV-1 RNA level was 7,510 copies per milliliter ($\log_{10}$=3.88). In May 2010, his viral load was 412 ($\log_{10}$=2.61), he was more independent, and he was intermittently using a cane to ambulate.

A clinical neuropsychological assessment was completed in May 2010 that revealed evidence of HAD, including moderate to severe deficits in cognitive functions. He was approached by his treating physician about his willingness to participate in a study of the utility of MEG as a biomarker in HIV disease. He consented to enroll and his data were compared with that of nine HIV-infected individuals and seven uninfected control subjects. With the exception of the Executive Domain Rating score from the neuropsychology test battery, there were no significant differences between the two comparison groups (HIV-positive vs. HIV-negative), so the data from all 16 participants were combined. The mean age (50.2±5.0) and education level (14.7±1.9) compared well with PG.

Procedures

Cognitive/Behavioral Evaluation

A neuropsychological examination was completed in May 2010, and again 6 months later, and included measures from multiple cognitive domains including memory, language, visual construction, psychomotor speed, motor and executive functions. PG underwent a semi-structured diagnostic interview and completed questionnaires concerning psychiatric symptomatology (see Becker et al. 2012a for details).

MRI study

PG had an MRI exam of the brain on a Siemens 3T TIM Trio using a protocol that was modified from that of the Alzheimer's Disease Neuroimaging Initiative (Mueller et al. 2005). The parameters of the sagittal magnetization prepared rapid acquisition gradient echo sequence were: FOV=256 mm; slices=160; TR=2,300 ms; TE=2.91 ms; TI=900 ms; flip angle=9°; slice thickness=1.2 mm. The MRI data were processed using SIENA, a fully automated method to measure the change between two MR images taken at different time points (Smith et al. 2002). The output from SIENA is the mean perpendicular edge motion across the entire brain surface converted into a percentage brain volume change estimate.

Magnetoencephalography

Elekta Neuromag© Vectorview (Elekta Oy, Helsinki, Finland) uses 306 MEG channels for registering the neuromagnetic signatures of the intracranial neural currents. The MEG acquisition included 5 min of "eyes open" and 5 min of "eyes closed" resting state; for this report, we analyzed only the eyes closed data as there were fewer artifacts (e.g., eye blinks) compared to the eyes open data. The MEG procedures and data preprocessing are detailed elsewhere (Becker et al. 2012a).

The MEG data were filtered on-line to 0.1–330 Hz and sampled at 1 kHz. For analysis, we filtered the data to 0.1–60 Hz and calculated the mutual information (MI) (Hlaváčková-Schindler et al. 2007) between the 102 sensor units (magnetometers and gradiometers), which gave us a symmetric and weighted correlation matrix of 102×102 elements for each analysis. We computed an "MI score" by taking the mean MI between the two groups of sensors where we have previously found significant statistical differences in the gradiometers (see Fig. 1b; Becker et al. 2012b).

Results

The change in PG's test scores over the 6-month interval was compared with the change observed in the comparison group (see Table 1). Significant improvements were observed on tasks of cognitive and motor speed; there were no significant changes in his performance on measures of either learning or memory.

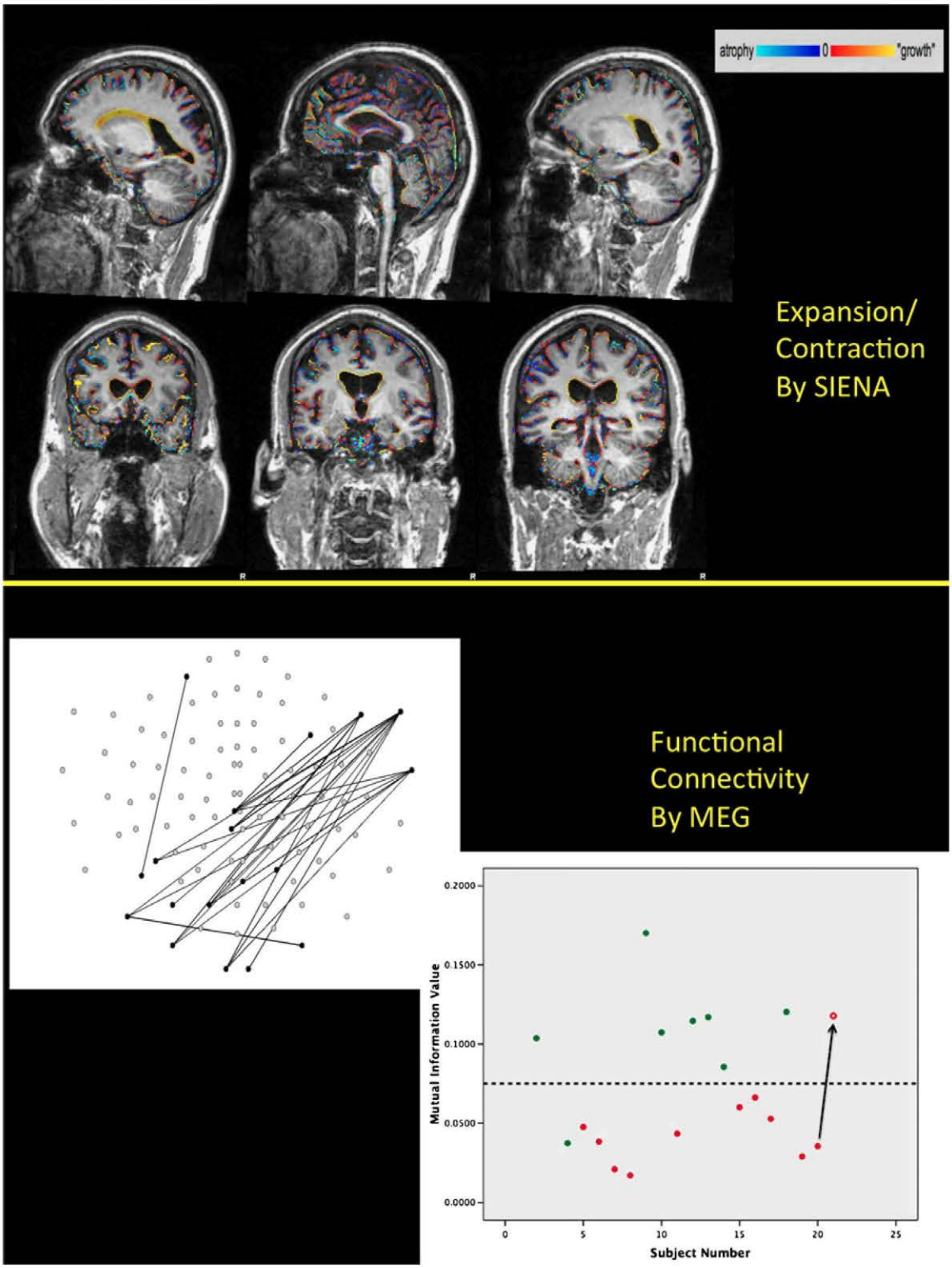

Fig. 1 **a** Results of the SIENA analysis (*upper panel*). The images show the changes in brain surface over the course of 6 months (*top row*, sagittal plane; *bottom row*, coronal row). Expansion of the brain (indicated in *yellow* and *red*) indicates a narrowing of the sulci (i.e., widening of the gyri) as well as shrinkage of the ventricles. **b** The results of the analysis of the MEG data are shown in the *lower panel*. On the *left* is a graph of the functional network that maximally differentiated HIV-infected from HIV-uninfected individuals. On the *right* is a graph of the MI score for each individual subject. The *green circles* indicate uninfected participants in the comparison group; the *red circles* indicate HIV-infected participants. The MI score for PG is shown as *two points connected by a line*

Table 1 Change in neuropsychological test performance in PG

Domain/measure	Comparison group[a]		Patient PG[b]		Statistics[c]	
	Baseline	Follow-up	Baseline	Follow-up	*Z* score	*p*
Fluency						
Letters	54.4 (8.4)	54.1 (8.9)	36	54	2.29	.02
Animals	57.5 (9.4)	57.1 (8.9)	43	58	1.90	.04
Domain score	2 (1–4)[d]	2 (1–4)[d]	5	2		
Executive						
Trail making B	67.3 (11.2)	64.4 (13.4)	31	43	1.29	.07
Domain score	2 (1–4)	1 (1–5)	6	4		
Speed of processing						
Digit symbol substitution	53.5 (9.3)	54.2 (9.0)	31	39	−0.25	.12
Trail making A	73.2 (11.4)	70.1 (11.7)	21	42	1.46	.02
Domain score	1 (1–3)	2 (1–4)	8	4		
Spatial skills						
Block design	59.8 (9.2)	61.6 (12.7)	25	33	2.67	.03
Domain score	1 (1–5)	1 (1–3)	7	6		
Learning						
HVLT-TR	49.3 (12.8)	51.3 (8.8)	20	32	0.85	.46
Domain score	2 (1–9)	2 (1–7)	8	6		
Memory						
HVLT delay	46.5 (13.3)	51.6 (8.5)	20	23	−0.22	.07
Domain score	2 (1–9)	2 (1–7)	8	8		
Motor						
Grooved pegboard	56.2 (8.7)	54.6 (8.0)	29	46	2.61	.02
Domain score	1 (1–5)	2 (1–2)	7	2		
Global impairment rating	4 (1–9)	4 (1–7)	9	8		

[a]Means and standard deviations of age, education, sex- and race-adjusted *T* scores (Heaton and Taylor 2004)

[b]Individual *T* scores for each performance measure

[c]Z-scores and *p* values of difference between predicted change (from comparison group) and that of PG (Crawford et al. 2010)

[d]Median and range of domain scores; n.b., higher scores (i.e., 5–9) indicate impaired performance

The neuropsychological test data were reduced to domain and global ratings of performance based on standardized and normative procedures (Woods et al. 2004). The scores have a range from 1 (superior) to 9 (severely impaired); 1–3 is considered normal, 4 is considered borderline, and scores of 5 and greater are considered abnormal. With the exception of the memory and learning ratings, his test performance improved from impaired to borderline and normal after 6 months of cART (see Table 1).

The mean change in whole brain volume in the comparison group was −0.29 % (SD=0.97). The percent change in brain volume in PG was 5.87 % (i.e., an increase in volume), which is significantly greater than that expected based on the comparison group (Z=6.36; see Fig. 1a). There is evidence of both expansion of gray matter (indicated in yellow and red in Fig. 1), reduction of ventricular volume, and widening of the gyri.

Figure 1b presents the results of the analysis of the MEG data. The left-hand graphs show the functional connectivity "map" between the MEG sensors; the right-hand graphic shows the MI score for each subject—PG and the comparison group. The MI score for PG is shown as two points connected by a line. As can be seen from this figure, his MI score at baseline was near the mean for the infected participants, while at the end of 6 months, his score had changed to a value close to the mean of the uninfected individuals.

Discussion

In spite of the declining incidence of HAD (Sacktor et al. 2001), cognitive dysfunction persists even with the use of cART (Sacktor et al. 2002). Severe immunosuppression is not a requirement for HAD (Dore et al. 1999). Undetectable CSF HIV does not prevent the progression of disease (Cysique et al. 2005), and even with effective viral suppression, there is a high rate of the milder forms of HIV-associated neurocognitive disorders (Simioni et al. 2010). These studies report group-level data; ours is one of the few reports of recovery of function among individuals diagnosed with HAD who had detailed cognitive testing, MR imaging, as well as an analysis of neuronal functional connectivity using MEG.

PG had virtual elimination of viral replication in the periphery (<50 copies at second visit) as well as a significant improvement in his $CD4^+$ cell counts. His performance on

the neuropsychological tests improved, and his overall brain volume increased more than 5 % with gyral widening and a reduction in the size of the lateral ventricles. What was most striking, however, was the "normalization" of his neuromagnetic signature. The MI score derived from the functional connectivity analysis of the MEG data reflects the extent to which the neuronal populations near the sensor nodes were functionally connected and differentiated infected from uninfected individuals. Over the course of treatment, his MI score changed from one that was virtually identical to that of other infected subjects to one that was indistinguishable from the uninfected controls, suggesting that CNS function was returning to normal.

With one exception, the HIV-infected individuals included in the comparison group had been infected for at least 10 years, had endured periods of uncontrolled viral replication, and had survived long enough to enjoy the benefits of cART. We speculate that the long-term uncontrolled or poorly controlled viral replication in the brain may have resulted in a permanent alteration in the functional networks, which is reflected in the MEG signature. PG's data suggest the possibility that all of the HIV-infected individuals in the comparison group at one time had the potential to have their functional connectivity return to normal, if effective therapy had been available to them.

In summary, we report the changes in CNS structure and function that occurred in a patient whose initial presentation and AIDS-defining illnesses included HAD following effective viral suppression. The recovery included a normalization of a functional brain network identified with MEG imaging, suggesting that MEG may be a useful tool in monitoring response to HIV therapeutics (Price et al. 2007).

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