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Callosal degradation in HIV-1 infection predicts hierarchical perception: A DTI study

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ABSTRACT

HIV-1 infection affects white matter circuits linking frontal, parietal, and subcortical regions that subserve visuospatial attention processes. Normal perception requires the integration of details, preferentially processed in the left hemisphere, and the global composition of an object or scene, preferentially processed in the right hemisphere. We tested whether HIV-related callosal white matter degradation contributes to disruption of selective lateralized visuospatial and attention processes. A hierarchical letter target detection paradigm was devised, where large (global) letters were composed of small (local) letters. Participants were required to identify target letters among distractors presented at global, local, both or neither level. Attention was directed to one (global or local) or both levels. Participants were 21 HIV-1 infected and 19 healthy control men and women who also underwent Diffusion Tensor Imaging (DTI). HIV-1 participants showed impaired hierarchical perception owing to abnormally enhanced global facilitation effects but no impairment in attentional control on local–global feature selection. DTI metrics revealed poorer fiber integrity of the corpus callosum in HIV-1 than controls that was more pronounced in posterior than anterior regions. Analysis revealed a double dissociation of anterior and posterior callosal compromise in HIV-1 infection: compromise in anterior but not posterior callosal fiber integrity predicted response conflict elicited by global targets, whereas compromise in posterior but not anterior callosal fiber integrity predicted response facilitation elicited by global targets. We conclude that component processes of visuospatial perception are compromised in HIV-1 infection attributable, at least in part, to degraded callosal microstructural integrity relevant for local–global feature integration.

1. Introduction

Human immunodeficiency virus (HIV-1) enters the brain soon after initial infection and remains there throughout the course of HIV-1 disease (Gartner, 2000; Major, Rausch, Marra, & Clifford, 2000). The virus infection induces oxidative stress by enhancing the production of cytotoxic markers associated with synaptic changes and neuronal cell death in the central nervous system (Acheampong et al., 2007; Hauser et al., 2007; Moroni & Antinori, 2003). HIV-1 also affects white matter circuits linking frontal, parietal and specific subcortical regions (Chang, Wong, et al., 2008; Meyerhoff et al., 1999; Pfefferbaum et al., 2006, 2009) that subserve visuospatial and attention processes (Devinsky & D'Esposito, 2003). Despite evidence of cognitive impairment in HIV-1 infection in motor speed, memory, and visuoconstruction, which have been related to cerebral white matter damage (Chen et al., 2009; Cloak, Chang, & Ernst, 2004; Paul et al., 2007; Ragin, Storey, Cohen, Epstein, & Edelman, 2004, Ragin et al., 2005; Wu et al., 2006), little is known about the neural substrates affected by HIV-1 infection and contributing to impairment of visuospatial perception and attention.

A paradigm widely used to study visuospatial functions is a target detection task that uses a hierarchical letter scheme involving large (global) letters that are made of smaller (local) letters, modeling the hierarchical structure of visual world scenes (Fink et al., 1997; Navon, 1977). These multilevel scenes can be decomposed into component features and then integrated into more complex stimuli, objects and scenes—a concept originated from investigations of the visual cortex (Felleman, Burkhalter, & Van Essen, 1997; Pandya & Sanides, 1973). Global–local processing starts on a perceptual level (Fink, Marshall, Halligan, & Dolan, 1999; Mevorach, Humphreys, & Shalev, 2006; Mevorach, Shalev, Allen, & Humphreys, 2009) that can be facilitated by redundant target information (Müller-Oehring, Schulte, Raassi, Pfefferbaum, & Sullivan

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2007, Müller-Oehring, Schulte, Fama, Pfefferbaum, & Sullivan 2009; Schulte, Mueller-Oehring, Rosenbloom, Pfefferbaum, & Sullivan, 2005). Depending on task requirements, processing of local features (details or parts), the global composition, or both levels is modulated by attentional allocation, interference processing, and response control (Han & He, 2003; Han & Jiang, 2006; Müller-Oehring et al., 2007; Qin & Han, 2007; Yoshida, Yoshino, Takahashi, & Nomura, 2007).

Asymmetries between right and left parietal lobe function have been described for global and local processing, with preferentially right parietal activation for global visuospatial attention (Corbetta, Miezin, Shulman, & Petersen, 1993), arousal, and vigilance (Paus et al., 1997), and left parietal lobe activation for local visuospatial attention and feature processing (Kimchi & Merhav, 1991; Sergent, 1982; van Kleeck, 1989; for a review). Lesion studies of lateralized temporo-parietal cortical damage (Delis, Robertson, & Efron, 1986; Robertson & Lamb, 1991) and electrophysiological studies (e.g., Yamaguchi, Yamagata, & Kobayashi, 2000; Yoshida et al., 2007) have confirmed this right-global and left-local hemispheric specialization. Normal perception requires the integration of these two stimulus features, achieved through transfer of information between the hemispheres via the corpus callosum (Barnett, Kirk, & Corballis, 2007; Corballis, Barnett, Fabri, Paggi, & Corballis, 2004; Engel, König, Kreiter, & Singer, 1991; Gazzaniga, 1987, 2000; Gazzaniga, Bogen, & Sperry, 1965; Stephan, Marshall, Penny, Friston, & Fink, 2007).

Local–global visuospatial processing in HIV-1 has been investigated using a hierarchical letter task in which attention was implicitly manipulated by varying target probabilities to favor local, global, or neither level (Martin et al., 1995; Olesen, Schendan, Amick, & Cronin-Golomb, 2007). HIV-1 infected individuals exhibited greater cost effects than controls for global and local targets (Martin et al., 1995) or for local targets only (Olesen et al., 2007) when attention was implicitly biased away from the target level, but performed similarly to controls in the unbiased condition. Local–global processing deficits in HIV-1 were restricted to controlled (biased) attentional processes but did not affect automatic (non-biased) attentional processes (Martin et al., 1995), possibly reflecting HIV-1-related functional compromise in parietal visuospatial attention systems (Olesen et al., 2007). Consistent with this interpretation, functional neuroimaging studies have indicated reduced efficiency in fronto-parietal attention networks as evidenced by less activation in fronto-parietal regions but greater activation in adjacent or contralateral brain regions in HIV-1 patients than controls during an attentionally challenging task (Chang et al., 2004; Chang, Yakupov, Nakama, Stokes, & Ernst, 2008; Ernst, Chang, Jovicich, Ames, & Arnold 2002).

In addition to HIV-1-related impairment of lateralized local–global functions, white matter microstructure compromise observed with diffusion tensor imaging (DTI) occurs in HIV-1 involving callosal fiber tracts connecting bilateral frontal (Filippi, Ulug, Ryan, Ferrando, & van Gorp 2001; Thurnher et al., 2005), temporal and parietal (Pfefferbaum, Rosenbloom, Adalsteinsson, & Sullivan, 2007; Wu et al., 2006) and occipital cortical regions (Filippi et al., 2001; Pfefferbaum et al., 2009; Wu et al., 2006), despite the effectiveness of antiretroviral treatment (Gongvatana et al., 2009).

To examine the functional implications and neural substrates of HIV-1 infection-related compromise on component local–global processes, we devised a hierarchical letter task that permitted examination of attention, interference, and response control based on global versus local information. We then related behavioral measures from this task to DTI measures of the integrity of tissue microstructure of the corpus callosum. We assumed that HIV-1-related impairment in attentional control would be related to compromised integrity in anterior and middle callosal fibers connecting frontal and parietal cortices. Attentional control is required when local and global information is incongruent (i.e., a global E made up from local Ts) (Hibi, Takeda, & Yagi, 2002; Müller-Oehring et al., 2007; Navon, 1977; Proverbio, Minniti, & Zani, 1998) and is associated with conflicting responses (Müller-Oehring et al., 2007; Volberg & Hübner, 2006). Because we had observed earlier (Müller-Oehring et al., 2007, 2009) that redundant target information at both local and global processing levels results in response facilitation, an effect attributable to perceptual preattentive processing (Martin, Sorensen, Robertson, Edelstein, & Chirurgi, 1992; Martin et al., 1995; Sorensen, Martin, & Robertson, 1994; Tzelgov, Henik, & Berger, 1992), we assumed that HIV-1-related impairment in local–global facilitation would be related to compromise in posterior callosal microstructural integrity connecting occipito-temporal visual processing areas.

Table 1
Subject table.

	HIV (16m, 5w)	CTL (11m, 8w)	ANOVA	
			F	*P*
Age	42.7 (10.3)	41.5 (8.8)	0.17	0.69
Body mass index	25.5 (5.7)	25.7 (3.9)	0.04	0.85
Handedness[a]	26.5 (11.8)	22.7 (12.2)	0.99	0.32
Education (years)	14.4 (3.0)	15.5 (2.1)	1.78	0.19
Socioeconomic status (SES)	32.6 (14.5)	29.9 (15.3)	0.29	0.59
Verbal intelligence NART IQ	110.7 (8.3)	114.2 (5.5)	2.06	0.16
Global functioning (GAF)	69.6 (11.6)	77.2 (10.1)	3.34	0.078
Depressive symptoms (BDI)	12.1 (9.3)	2.4 (2.2)	15. 4	0.0001
CD4+ count	519 (169.8)	–	–	–
Viral load	13,096 (26,516)	–	–	–

Right handedness = 14–32; left handedness = 50–70.
[a] Crovitz and Zener (1962).

2. Methods

2.1. Participants

The study sample comprised 19 normal healthy controls (CTL) (8 women, 11 men) and 21 HIV-1 positive patients (HIV-1) (5 women, 16 men) (Table 1). Participants in both groups had normal or corrected to normal visual acuity. Study groups did not significantly differ in sex distribution (*Chi-square* = 1.52, *ns*). All subjects underwent a panel of blood tests to determine HIV-1 status. HIV-1 infected participants had average CD4 T-cell counts of 519 ± 170 (range = 279–920), and viral loads of 13,096 ± 23,516 (range = 49–100,001 units). Six HIV-1 infected men had had an acquired immunodeficiency syndrome (AIDS)-defining event or low CD4 T-cell counts (<200) in the course of their illness; one was also infected with hepatitis C. Of the 21 HIV-1 participants, 15 received HAART medication, 3 received other HIV-1 medication, and 3 were without pharmacological treatment at the time of testing.

Participants received a Structural Clinical Interview for DSM-IV diagnosis (American-Psychiatric-Association, 1994) by trained clinicians to rule out nontarget psychiatric and neurological disease. Additional interviews and questionnaires assessed global functioning (GAF; First, Spitzer, Gibbon, & Williams 1998), depression (BDI; a quantitative measure of depressive symptoms; Beck, Steer, & Brown, 1998); socioeconomic status (SES; a two-factor scale based on education and occupation; Hollingshead & Redlich, 1958); handedness (Crovitz & Zener, 1962); and body mass index (height/weight in cm/kg^2; an index of nutritional status). General cognitive status was assessed with the National Adult Reading Test (NART, Nelson, 1982), a retrospective estimator of premorbid verbal intelligence. Means, SD, and statistical significance of these and other demographic values are presented in Table 1. No group differences were found for age, body mass index (BMI), handedness (Crovitz score), verbal intelligence (NART IQ), education, and socioeconomic status (SES). On average both groups had an education beyond high school. HIV-1 infected participants showed a trend for lower global functioning (GAF) and expressed more depressive symptoms (BDI) than healthy controls. HIV-1 infected individuals with lower CD4+ counts reported lower socioeconomic status ($r = .52$, $p = 0.019$). Furthermore, lower global functioning scores in HIV-1 infected individuals were associated with higher depression scores ($r = -.56$, $p = 0.010$). No patient was clinically demented. Written informed consent was obtained from all participants and the Institutional Review Boards of Stanford University and SRI Inter-