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SHORT COMMUNICATION

Altered prefronto-striato-parietal network response to mental rotation in HIV

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Abstract The present study used functional magnetic resonance imaging to examine the neural substrates of mental rotation in 11 individuals with HIV infection and 13 demographically similar HIV seronegative volunteers. Individuals with HIV showed increased brain response to mental rotation in prefrontal and posterior parietal cortices, striatum, and thalamus, with significant HIV by angle interactions emerging in the prefrontal cortex and caudate. Results indicate that HIV infection is associated with altered brain response to mental rotation in fronto-striato-parietal pathways, which may reflect compensatory strategies, recruitment of additional brain regions, and/or increased neuroenergetic demands during mental rotation needed to offset underlying HIV-associated neural injury.

Keywords Human immunodeficiency virus · Mental rotation · Spatial cognition · Functional magnetic resonance imaging

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Introduction

It is widely held that spatial cognition is not impaired in HIV disease, which is more commonly linked to deficits in psychomotor skills, episodic memory, and executive functions (Heaton et al. 2010). However, there is emerging evidence that HIV infection may have detrimental effects on mental rotation—one of the most widely studied aspects of spatial cognition (Olesen et al. 2007; Weber et al. 2010). Mental rotation refers to the cognitive manipulation of visual images in space and requires the coordination of a number of cognitive processes, including not only visuospatial perception and mental imagery but also motor processes (i.e., projected action). As such, mental rotation is subserved by a distributed neural network and is associated with the integrity of the posterior parietal cortex and parieto-striato-prefrontal neural networks (Shepard and Metzler 1971). This is a relevant and novel area of investigation because the neuropathophysiological substrates of HIV infection impact the structure and function of the parieto-striato-frontal networks (Fischer et al. 1999), which are critical to normal mental rotation abilities. Therefore, the aim of the present study was to examine the neural substrates of mental rotation in persons with HIV infection using functional magnetic resonance imaging (FMRI).

Methods

Participants

The study was approved by the University of California Human Research Protections Program, and all participants provided written, informed consent. Participants included 11 individuals with HIV infection (HIV+) as determined by enzyme linked immunosorbent assays and a Western Blot confirmatory test, as well as 13 HIV seronegative control volunteers (CON). Individuals with histories of psychiatric (e.g., mental retardation, psychotic disorders, or recent substance use disorders) or neurological (e.g., seizure disorders, traumatic brain injury, or cerebrovascular disease) conditions known to adversely affect cognition were excluded. The groups did not differ statistically in age (HIV+ = 41.8± 6.1 years; CON=42.5±14.5 years), education (HIV+ = 13.9± 2.4 years; CON=14.9±2.1 years), sex (HIV+ = 82% male; CON=77% male), handedness (HIV+ = 82% right; CON= 85% right), or ethnicity (HIV+ = 93% Caucasian; CON=92% Caucasian). Sixty-four percent of the HIV+ group met criteria for AIDS, with a median nadir CD4 lymphocyte count of 140 (interquartile range=29, 300). Ten HIV-infected individuals were prescribed highly active anti-retroviral therapies (HAART) at the time of evaluation.

Materials and procedure

All participants completed a mental rotation task during FMRI. Each participant indicated whether a pair of three-dimensional figures was identical using a fiber-optic button box. The task consisted of four series of randomized, alternating blocks of Shepard and Metzler (1971) figures rotated in the *X*, *Y*, or *Z* plane to 0°, 45°, 105°, or 165° (Cohen et al. 1996). After a 9000-ms fixation period, each series began with an active baseline block of 0° rotation items (three trials at 3000 ms per trial) and was followed by a randomly selected active rotation (either 45°, 105°, or 165°) block consisting of six trials at 6000 ms per trial. Blocks of 0° rotation trials were subsequently presented after every active rotation block. Total task time was 10 min and 21 s. Response time and accuracy were recorded for all trials, with the exception of series 3, which was not available for analysis. In order to familiarize volunteers with the task, each participant received training on an abbreviated version of the task prior to scanning.

Imaging parameters and processing

Scanning consisted of T1-weighted spoiled GRASS images collected in the sagittal plane (echo time = 6 ms, repetition time = 20 ms, flip angle = 30°, matrix = 256×256, field of view = 240 mm, one hundred twenty-four 1.3-mm slices) and spiral gradient recall echo imaging for FMRI (single shot, echo time = 40 ms, repetition time = 3000 ms, flip angle = 90°, field of view = 240 mm, reconstructed matrix size = 128×128, ≈ 30 five-millimeter axial slices, 207 repetitions). Data were processed and analyzed using the Analysis of Functional NeuroImages software package (AFNI) (Cox 1996). An automated motion correction algorithm was applied to the time series data (Cox and Jesmanowicz 1999). The volume registration aligned the time series to a base volume using a six-parameter affine transformation. Data from individual voxels were converted to percent signal change by dividing voxel intensity by the time series mean. Non-brain data were excluded from analyses by applying an intracranial mask. A multiple regression approach estimated voxel-wise fits with 11 regressors. There were four rotation regressors, three motion regressors (pitch, roll, and yaw), four baseline regressors (fourth order Legendre polynomials), and a constant. The task-related time series was convolved with an idealized gamma variate function for each of the following trial conditions: 0°, 45°, 105°, or 165°. Motion regressors adjusted for motion-related activation, and the polynomial baseline adequately modeled the time series baseline without over-fitting. Deconvolution analysis estimated the voxel-by-voxel amplitudes. A 3.5 full-width at half-maximum Gaussian filter blurred voxel data in order to account for individual differences in brain anatomy and improve signal to noise. Finally, a 12 subvolume, piecewise affine transformation aligned the functional map to Talairach and Tournoux coordinate space, and functional data were re-sliced to 4 mm^3. Manual selection of the anterior and posterior commissure, mid-sagittal points, and brain extrema from the cardinal directions produced the necessary transformation matrix from the T1-weighted structural image.

Data analyses

A mixed effects model that examined differences in percent signal change across trials that required participants to rotate figures was used for analysis of the FMRI data. There were two fixed factors (HIV serostatus: HIV + and CON; rotation angle: 45°, 105°, or 165°) and one random factor (subjects). Simple effects analyses were conducted for statistically significant interaction clusters. In order to minimize type I error, a combination of cluster size and individual voxel thresholding was used. Cluster size and threshold value were calculated separately for subcortical structures and cortical structures. Given the small volume of individual subcortical structures of particular interest in this study (e.g., caudate nucleus), these clusters would not be expected to survive conservative cluster size and threshold-based type I protection typically used to identify significant cortical activation. In order to accomplish this two-tiered

clustering approach, a binary mask was created for the following bilateral structures: caudate nucleus, putamen, globus pallidus, nucleus accumbens, and thalamus. The mask was created using AFNI-based pre-labeled structures from the Talairach and Tournoux atlas. The subcortical mask was subtracted from a whole brain mask yielding a brain mask without the subcortical structures. Monte Carlo simulation determined that the individual voxel probability of 0.025 for the subcortical search region provides protection against false positive error when the cluster size was at least 270 μLand the cluster connection distance was 4.0 mm. The simulation specified that the individual voxel probability of 0.05 provided protection against false positive error when the cortical cluster size was at least 640 μL with a cluster connection distance of 4.0 mm.

AFNI and Matlab 7.1 (Mathworks Inc., Natick, MA) were used for statistical analysis of functional imaging data. Simple effects analyses and behavioral data were analyzed with JMP 5.1.1 (SAS Institute, Cary, NC) by averaging individuals' signal within each significant cluster.

Results

The primary study findings are reported in Table 1. In brief, main effects were found for serostatus, with HIV + participants displaying significantly increased brain response to mental rotation in prefrontal (e.g., BA 13 and 47) and posterior parietal (e.g., BA 7) cortices, lenticular nuclei, and thalamus. Table 2 shows that significant serostatus-by-rotation-angle interactions were evident in the insula (BA 13), right inferior occipital gyrus (BA 17, 18), and left caudate ($ps<0.05$). Independent samples *t*-test revealed that HIV + and CON had comparable accuracy and reaction times on task trials requiring mental rotation ($ps>0.10$). Figure 1 provides a graphical representation highlighting notable results.

Discussion

Although it is widely held that HIV infection does not affect spatial abilities, HIV-associated neuropathology is evident

Table 1 Group main effects for mental rotation

Anatomic region	Broadmann's area	Volume (μL)	Talairach coordinate (max intensity)			Cohen's *d*[a]
			X	*Y*	*Z*	
Group main effects						
HIV+ > CON						
L posterior cingulate, L precuneus, R posterior cingulate, R precuneus	7, 23, 31	7168	2	53	24	2.88[b]
R transverse temporal gyrus, R precentral gyrus, R insula	41	3392	−50	17	12	2.19[c]
R lingual gyrus, R inferior occipital gyrus, R fusiform	17, 18	1408	−10	93	−4	1.39
R precuneus	7	1152	−10	57	40	2.25[c]
L middle occipital gyrus, L precuneus	31	896	22	81	16	3.26
R inferior frontal gyrus	47	832	−34	−15	−8	1.33
L inferior frontal gyrus, L insula	47	832	38	−15	−8	1.56[c]
L precentral gyrus	44	832	54	1	8	1.66[c]
R superior temporal gyrus	41	832	−46	33	16	1.83[c]
L inferior parietal lobule, L insula	13	832	34	29	24	1.50[b]
R middle/inferior temporal gyrus	20, 21	704	−62	9	−12	1.54[c]
L insula	13	704	42	17	16	2.60[c]
R thalamus, lentiform nucleus	–	704	−18	9	16	1.89[c]
R cuneus	19	640	−2	77	32	2.28[b]
R thalamus	–	384	−10	9	16	1.77
CON > HIV+						
L middle temporal gyrus	21, 22	704	58	25	−8	−1.4[d]

L left, *R* right

[a] Positive Cohen's *d* indicates HIV+ > CON, and negative Cohen's *d* indicates CON > HIV+

[b] One sample *t*-test follow-up showed CON < 0 ($p<0.05$)

[c] One sample *t*-test follow-up showed HIV+ > 0 ($p<0.05$) and CON < 0 ($p<0.05$)

[d] One sample *t*-test follow-up showed HIV+ < 0 ($p<0.05$)

Table 2 Group (HIV+, CON) by angle (45°, 105°, 165°) interaction for mental rotation

Anatomic region	Broadmann's area	Volume (μL)	Talairach coordinate (max intensity)			Simple effects
			X	*Y*	*Z*	
Interaction effects						
L insula	13	3136	34	–15	16	[a, c]
L anterior cingulate	32	896	18	–35	–4	[d]
R inferior occipital gyrus	17, 18	768	–26	93	–8	[a, b, c]
L caudate head	–	320	6	–3	0	[b]
L caudate body	–	320	14	–19	20	[d]

L left, *R* right
[a]45°, HIV+ > CON
[b]105°, HIV+ > CON
[c]165°, HIV+ > CON
[d]105°, CON > HIV+

in posterior parietal (PPC)-striato-frontal networks, which are essential to normal spatial cognitive functions, including mental rotation. To this end, Olesen et al. (2007) recently reported increased errors and response latencies to object rotation in a small sample of HIV-infected persons, which were interpreted as likely reflective of HIV-associated parietal injury. In a subsequent study, Weber et al. (2010) observed elevated hand rotation errors in an HIV sample, which were correlated with measures of executive functions and working memory. In contrast to the conclusions drawn by Olesen and colleagues, these mental rotation findings were interpreted to implicate a broader dysregulation in PPC-striato-frontal networks. However, both of these prior studies were limited by inferential neural interpretations derived from behavioral evidence. As such, the present study extends this literature by directly evaluating the altered neural substrates of mental rotation (i.e., the mental manipulation of visual images in space) in HIV.

Consistent with our a priori hypotheses, HIV-infected individuals demonstrated increased activation to mental rotation in widespread areas of the PPC-striato-frontal pathway. Further, significant interactions were found such that individuals with HIV-1 infection showed overactive left insular cortex and right occipital cortex but diminished brain response in the anterior cingulate during mental rotation. Considered in the context of previous neuropsychological research showing clear deficits in mental rotation in HIV disease (Olesen et al. 2007; Weber et al. 2010), our findings may suggest a brain compensatory strategy to perform mental rotation in HIV-1 infection. Indeed, Olesen et al. (2007) reported HIV-associated object rotation impairments, particularly at higher degrees of rotation. Accordingly, one possible explanation for our observed interaction effects may be increased orientation to spatial attention and visual memory at the expense of diminished conflict monitoring (i.e., reduced brain response) in the anterior cingulate gyrus.

While these findings are preliminary and await confirmation from future research, they are consistent with the notion of increased brain response to perform attention tasks in HIV infection (Chang et al. 2001). For example, Ernst and colleagues (2009) reported that HIV-1-infected individuals displayed increased brain response to a spatial attention test not only as task difficulty increased but also after 1 year elapsed in a longitudinal study, while seronegative participants showed decreased activation after the 1-year interval. These results may be interpreted as increased compensatory brain response to perform spatial attention in HIV-1 as a function of disease and also time. Our results, however, extend prior findings by showing widespread changes in the PPC-striato-frontal pathways implicated in performing mental rotation in individuals with HIV. Moreover, our

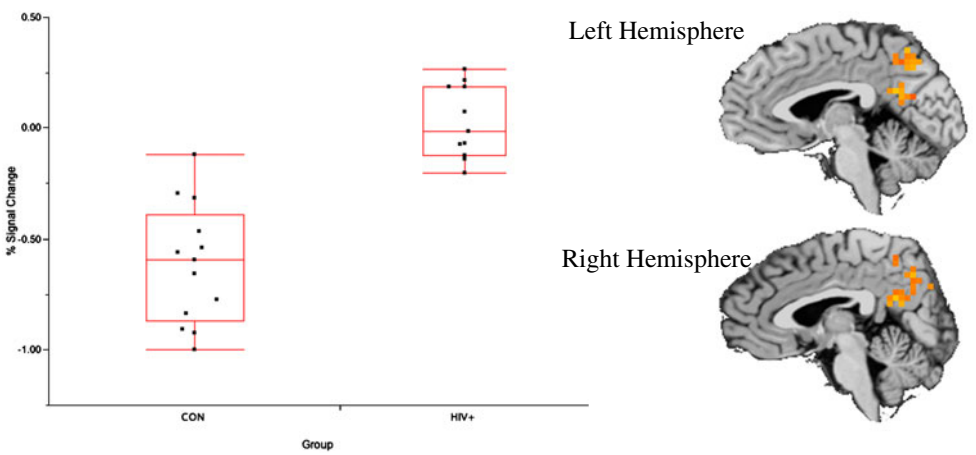

Fig. 1 Main effect of mental rotation percent signal change for HIV-infected (HIV+) and HIV seronegative controls (CON). *Orange*, *red*, and *yellow* clusters indicate brain regions displaying significantly greater brain response to mental rotation in HIV+ relative to CON. Box and whisker plots display each individual's average percent signal change for the cluster (7168 μL) displayed on the brain images. Cohen's *d* effect size = 2.88

observations in this study are suggestive of increased brain resource demands independent of task difficulty, which is consistent with previous HIV-1 studies (Ernst et al. 2002).

One intriguing possibility is that the observed compensatory increases in activation are related to HIV-associated inflammation, as BOLD signal increases to attention tasks have been positively associated with a magnetic resonance spectroscopy marker consistent with glial activation (i.e., a process common in inflammatory states) (Ernst et al. 2003). Another possibility is that the HIV-1-infected brain experiences increased generalized energetic demands that result in the observed increased brain response to FMRI tasks. To this end, Ances and colleagues (2011) showed significant cerebral blood flow increases to a simple motor task paradigm in HIV, which may be related to increased metabolic and neuronal activity. Interestingly, increased metabolic activity such as rapid glutamate–glutamine neurotransmitter cycling (see Shulman and Rothman 1998) may be strongly related to and partly underlie the observed BOLD signal in functional magnetic resonance imaging. HIV is often associated with glutamate excitotoxicity as a "final common pathway" of injury (Lipton 1994). Thus, enhanced or abnormal glutamate function may be one neurobiological reason for the observation of increased BOLD signal in HIV studies.

The regional vulnerability of the HIV-infected brain is often described as fronto-striatal. However, there is a great deal of research showing HIV-related brain abnormalities in numerous regions. The present work supports the notion that fronto-striatal systems are implicated in HIV-related neuropathology and extends this notion to related circuits (i.e., fronto-striato-thalamo-cortical involvement), as well as additional regions not commonly discussed in HIV brain pathology such as cuneus (i.e., occipital lobe). The challenge of studies such as this is to interpret the work in the context of networks, and this highlights the magnitude of effects across various regions. It is not entirely clear if the effect size difference across various brain regions reflects proportional metabolic or neuronal defects. At this time, it appears that the most accurate interpretation may be that the magnitude of effects in one region compared to another represent a larger percent increase in blood oxygen level dependent (BOLD) signal relative to task baseline across groups with the possibility of differential impact of task demands due to disease state. Further, selective brain changes in the HIV group could account for this observation, and the authors recommend the pursuit of combined or multi-modal neuroimaging for further explanation. One example would be to evaluate diffusion tensor imaging fiber pathway integrity between regions with BOLD differences or an examination of the cortical thickness from BOLD activation-derived cortical regions of interest.

Future research on the cognitive and neural mechanisms of HIV-associated deficits in spatial cognition is clearly indicated, particularly given the potential relevance of this construct to important aspects of everyday functioning (e.g., automobile driving) (Marcotte et al. 2006). In addition, functional magnetic resonance imaging may be a good outcome measurement in studies examining the impact of antiretroviral treatment given the repeatable nature of these studies and the relatively large observed effect sizes. This may be particularly valuable in the early stages of HIV infection as functional brain change could precede gross structural change, thus providing an early indicator of HIV brain involvement.

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