

# HIV Infection Affects Parietal-Dependent Spatial Cognition: Evidence From Mental Rotation and Hierarchical Pattern Perception

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Human immunodeficiency virus (HIV) in the asymptomatic phase of the infection impairs some aspects of cognition, but little is known about how visuospatial functions are affected. In the present study, performance on tasks of mental rotation and hierarchical pattern perception was investigated in 14 HIV-positive men and 12 age- and education-matched HIV-negative men. Processes related to mental rotation of objects and hands were impaired in HIV-positive participants as compared to the HIV-negative group. The HIV-positive group was also impaired on hierarchical pattern perception of local targets under global biasing conditions. Consistent with these results, the HIV-positive participants showed impaired performance on standard clinical neuropsychological tests of visuospatial function. These findings indicate that the detrimental effects of HIV on cognition appear even in asymptomatic individuals and affect diverse visuospatial functions that depend upon the integrity of parietal brain regions.

*Keywords:* visuospatial, attention, cognition, basal ganglia, parietal cortex

Research on cognitive problems in asymptomatic patients infected with human immunodeficiency virus (HIV) is an important ongoing area that is relevant to characterizing cognitive impairments in these patients as well as to understanding how the virus attacks the central nervous system (CNS). It is also critical to identify how HIV affects the brain because cognitive impairment may negatively impact treatment adherence (Hinkin et al., 2004)

and the ability to complete daily activities and may be a behavioral risk factor for survival (Ellis et al., 1997).

Evidence for cognitive problems in patients at early stages of HIV infection has been mixed, with some studies not having found an effect of the virus in the asymptomatic stage of the infection (Damos, John, Parker, & Levine, 1997; Harrison et al., 1998; McAllister et al., 1992; Samuelsson et al., 2006). A number of other studies of asymptomatic individuals, however, have identified problems with multiple cognitive abilities (Heaton et al., 1995; Lunn et al., 1991; Sahakian et al., 1995; Villa et al., 1996) and changes in the brain (Heaton et al., 1995; Meyerhoff et al., 1999; Suwanwela et al., 2000). Moreover, altered brain activation in HIV-positive individuals has been documented even when performance on neuropsychological tests falls in the normal range (Castelo, Sherman, Courtney, Melrose, & Stern, 2006; Ernst, Chang, Jovicich, Ames, & Arnold, 2002).

The cognitive problems seen in individuals with HIV are consistent with neuroimaging evidence that the infection affects frontal and parietal cortex and specific subcortical structures. Working memory (Hinkin et al., 2002; Stout et al., 1995; York, Franks, Henry, & Hamilton, 2001) and attention (Heaton et al., 1995; Marcotte et al., 2006) have been shown to be impaired in HIV-positive individuals and are related cognitive abilities that recruit similar frontoparietal networks (Courtney, 2004; Postle, 2006). Neuroimaging findings show that HIV infection can be related to altered activation of frontal and parietal areas (Castelo et al., 2006; Chang et al., 2001; Ernst et al., 2002), and decreased brain activation in these attention-related networks has been observed in HIV-positive individuals (Chang et al., 2004). HIV infection has also been related to tissue loss in the frontal and parietal areas (Thompson et al., 2005) and in the caudate nucleus (Ances et al.,

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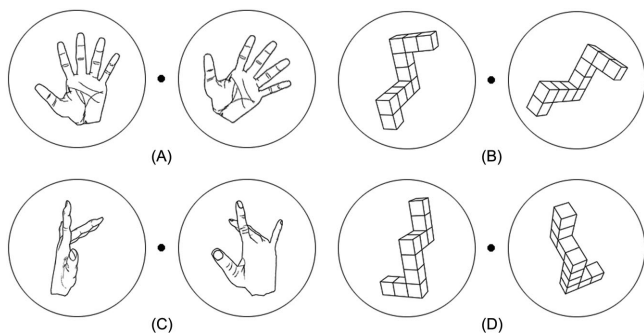
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2006; Hall et al., 1996; Heyes et al., 2001; Stout et al., 1998). Additional signs of CNS involvement include changes in white matter integrity (Tucker et al., 2004) in the frontal lobes (Pomara, Crandall, Choi, Johnson, & Lim, 2001), corpus callosum (Filippi, Ulug, Ryan, Ferrando, & van Gorp, 2001), and subcortical areas (Filippi et al., 2001). Neuropathological findings support the hypothesis that HIV infection is associated with neuronal changes in the parietal cortex (Everall, Luthert, & Lantos, 1993; Fischer, Jorgen, & Pakkenberg, 1999).

Few studies have investigated visuospatial abilities that recruit parietal cortex in asymptomatic HIV-positive individuals. Sahakian et al. (1995) used standard neuropsychological tests and found that HIV-positive individuals were unimpaired on certain tests of visual memory, whereas a preliminary study by our lab (Sharma, Amick, Schendan, & Cronin-Golomb, 2003) found subtle deficits on several standard visuospatial tasks. Experimental paradigms used in cognitive neuroscience are designed to engage specific parietal processes and so may be more sensitive for detecting subtle deficits.

The present study aimed to investigate how performance on two well-established visuospatial tasks drawn from cognitive neuroscience work is affected in asymptomatic individuals with HIV infection: mental rotation (MR; a visuospatial transformation task) and hierarchical pattern perception (HPP; a visuospatial perception and attention task). We chose these tasks on the basis of their dependence on brain regions that may be affected by HIV, specifically striatal structures and the parietal and frontal cortex. We have found that both tasks are sensitive to dysfunction associated with Parkinson's disease (PD), which, like HIV, is a disorder affecting the basal ganglia and frontoparietal networks (Amick, Schendan, & Cronin-Golomb, 2004; Amick, Schendan, Ganis, & Cronin-Golomb, 2006).

The MR task (see Figure 1) is a well-established test of spatial cognition in which two objects appear in different orientations and are either identical to each other (*same*) or left-right mirror images



**Figure 1.** Mental rotation task: Examples of stimuli. Pairs of hands and objects rotated in two-dimensional (2D) (Figures 1A and 1B) and three-dimensional (3D) (Figures 1C and 1D) space. Figures 1A and 1B show examples of trials where the correct response is *S* for “same” because the stimuli pairs show identical figures in the two circles. Figures 1C and 1D show examples of trials where the correct response is *D* for “different” because the stimulus pairs show mirror-imaged figures. Reprinted with permission from “Frontostriatal circuits are necessary for visuomotor transformation: Mental rotation in Parkinson’s disease,” by M. M. Amick, H. E. Schendan, G. Ganis, and A. Cronin-Golomb, 2006, *Neuropsychologia*, 44, p. 343. Copyright 2006 by Elsevier.

of each other (*different*). Response time (RT) and errors related to same or different judgments increase linearly as the difference in orientation between the two objects increases. This linear relation is interpreted as evidence that observers imagine one object rotating through space along a continuous trajectory as if they were physically rotating the object into the position of the other target object (Cooper & Shepard, 1975).

Neuroimaging studies with a parametric design reveal a linear increase in activation of the ventral caudal intraparietal sulcus and the adjacent transverse occipital sulcus region (Brodmann’s Area [BA] 19) as the degree of rotation is increased, implicating these dorsal stream regions specifically in the scaling of MR task performance with angular disparity (Carpenter, Just, Keller, Eddy, & Thulborn, 1999; Ecker, Brammer, David, & Williams, 2006; Harris & Miniussi, 2003; Podzbenko, Egan, & Watson, 2002). During MR, activation has also been found in the other areas of the intraparietal sulcus extending onto adjacent superior and inferior parietal gyri (BA 7, 39, 40; Alivisatos & Petrides, 1997; Cohen et al., 1996; Kosslyn, DiGirolamo, Thompson, & Alpert, 1998; Schendan & Stern, 2007), the frontal lobes (BA 6, 8, 12, 44, 47), anterior cingulate, and basal ganglia structures at the tail of the caudate and globus pallidus (Alivisatos & Petrides, 1997; Cohen et al., 1996; Hugdahl, Thomsen, & Erslund, 2006; Jordan, Heinze, Lutz, Kanowski, & Jancke, 2001; Kosslyn et al., 1998; Schendan & Stern, 2007). Parietal, frontal, and striatal brain structures are differentially involved in MR of hands versus objects. The area around the intraparietal sulcus and the posterior part of the ventrolateral prefrontal cortex (BA 44/6) is considered critical for mental transformations of objects (Corballis, 1997; Harris & Miniussi, 2003; Parsons, 2003; Richter et al., 2000; Vanrie, Beatse, Wagemans, Sunaert, & Van Hecke, 2002; Zacks, Gilliam, & Ojemann, 2003), whereas the primary motor cortex and frontostriatal circuits are additionally necessary for the MR of hands (Ganis, Keenan, Kosslyn, & Pascual-Leone, 2000).

The HPP task requires perceptual processing and controlled visuospatial attention processes with hierarchically structured visual images (Robertson, Lamb, & Knight, 1988). In a hierarchically organized visual pattern, stimuli appear at a local and a global level relative to each other. In the present task, target letters are detected at the local or the global level (see Figure 2), and attention is neutral or cued toward one level. Notably, although the intraparietal sulcus but not the lateral parietal cortex is necessary for MR, evidence suggests the opposite parietal anatomy for HPP. Performance on the HPP task depends upon processing in the superior temporal gyrus and in the adjacent lateral inferior and superior parietal cortex (Han, Jiang, & Gu, 2004; Robertson et al., 1988; Yamaguchi, Yamagata, & Kobayashi, 2000) and does not depend upon the integrity of the dorsolateral prefrontal cortex (Robertson, Lamb, & Knight, 1991).

On the basis of the similarity between the neuroanatomical correlates of MR and the brain regions that are affected by HIV (frontal–intraparietal sulcus–basal ganglia networks), we hypothesized that HIV-positive participants would be impaired on MR of both objects and hands. The HPP task was used to determine whether HIV infection can affect a spatial cognition task that has been found to depend primarily upon the lateral inferior parietal cortex with relatively less dependence upon the dorsolateral prefrontal cortex. Supportive results would suggest that HIV infection may affect circuits involving the parietal lobe and not just those

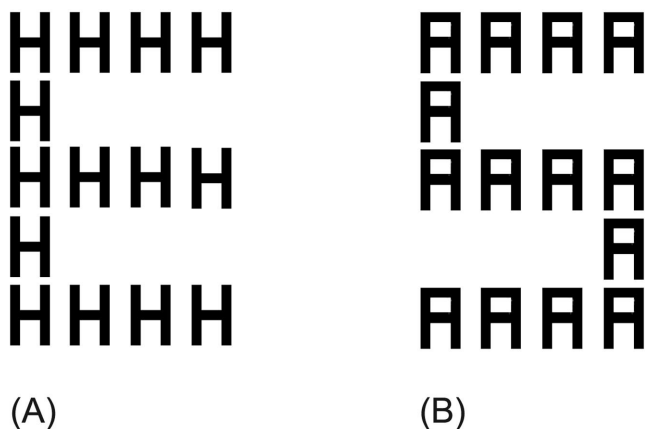


Figure 2. Hierarchical patterns. The target letters, *H* and *S*, could appear either at the local (Figure 2A) or the global (Figure 2B) level of the figures. The letters *A* and *E* were used as foil letters. For the trials presented above, the correct replies would be *H* (Figure 2A) and *S* (Figure 2B).

involving the frontal lobe. We hypothesized that any impairment in HIV-positive participants would be stronger on the MR task, especially with hand stimuli, compared to the HPP task, because of the additional frontal involvement on MR relative to HPP, and especially on MR of hands. Standardized neuropsychological tests of visuospatial performance were also given in order to relate the findings from the MR and HPP tasks to tests that are commonly used clinically.

Method

Participants

The study included 14 HIV-positive and 12 HIV-negative Caucasian men. The groups were matched for age and education (see Table 1). Volunteers were recruited from the local community and gave informed consent to participate in the study. Methods were approved by the Boston University Institutional Review Board.

Exclusion criteria for all participants included having neurological disorders besides HIV and having a history of stroke, seizures, electroconvulsive therapy, eye disease, and/or intravenous drug use. Volunteers were excluded if they were dependent on or had actively abused any drugs or alcohol in the last year, according to self-reports from interviews with the participants. Although originally we recruited both men and women for the study, all but 1 of the women with HIV in the recruitment pool who were otherwise eligible for the study had a history of intravenous drug use, and for this reason we limited the study to men. We included 4 individuals with a history of drug abuse, excluding intravenous drugs (3 HIV-positive and 1 HIV-negative participant), who had been abstinent from drugs for more than 2 years. All participants had normal or corrected-to-normal vision, and English was their first language.

The HIV-positive participants were asymptomatic for CNS effects at the time of testing, with 3 participants reporting current peripheral neuropathy. None reported any CNS effects, including a history of CNS-opportunistic infections. None had been diagnosed with AIDS, HIV-associated dementia, or hepatitis C. Measures of CD4 count and viral load were obtained from interviews with the participants. The participants were asked to report the most current information they had received from their doctors. The counts had been obtained no more than 5 months previous to participating in the study (range = 0.5–5 months; data not available for 1 participant). Mean CD4 count was 592/mm<sup>3</sup> (*SD* = 373, range = 34–1,270/mm<sup>3</sup>). Viral load was undetectable in 8 participants, and for the remaining participants, mean log viral load was 4.1 (*SD* = 1.2, range = 2.4–5.5). Participants with HIV had been diagnosed on average 11.1 years ago (*SD* = 5.0, range = 3–18 years). We classified the HIV-positive participants as being in an early stage of the disease because they were not diagnosed with AIDS; most of them (all except 3 participants) had a CD4 count above 200, and all were asymptomatic for CNS effects.

Nine of the HIV-positive participants were on antiretroviral therapy that included a combination of drugs. Two participants were taking only nucleoside reverse transcriptase inhibitors. The remaining 3 participants did not take any antiretroviral medication.

Table 1  
Participant Characteristics

Variable	Group	<i>M</i>	<i>SD</i>	Range	<i>F</i>	<i>p</i>
Demographics						
	Age	HIV+ 46.4 HIV- 47.0	7.4 7.1	35–58 30–56	0.03	<i>ns</i>
Education	HIV+ 14.4 HIV- 14.8	2.2 1.9	12–18 12–18	0.16	<i>ns</i>	
	Clinical tests					
BNT	HIV+ 52.9 HIV- 53.8	6.2 5.7	38–60 39–59	0.56	<i>ns</i>	
	Hooper	HIV+ 25.6 HIV- 25.7	2.5 3.9	22.5–30 15.5–29.5	0.47	<i>ns</i>
JLO		HIV+ 6.9 HIV- 2.3	4.1 1.9	0–17 0–7	3.27	.001
	Road-Map	HIV+ 6.1 HIV- 1.6	5.1 2.3	0–16 0–7	9.28	.008
HDS		HIV+ 13.2	2.6	9.5–16		

Note. BNT = Boston Naming Test (*df* = 1, 24); Hooper = Hooper Visual Organization Test (*df* = 1, 24); JLO = Judgement of Line Orientation Test (*df* = 1, 23); Road-Map = Money Road Map Test (*df* = 1, 23); HDS = HIV Dementia Scale.

Five HIV-positive participants were currently taking antidepressant medication. One was taking medication for treatment of anxiety. None of the HIV-negative participants were currently taking any psychoactive drugs.

### *Neuropsychological Assessment*

The participants were assessed with four standard neuropsychological tests (see Table 1). The neuropsychological tests were chosen on the basis of their relative requirements for visuospatial and verbal processing. We did not expect any group differences in performance on the verbal naming task but included this task to confirm that the impairments related to HIV infection were specific to visuospatial abilities and not simply reflecting general cognitive dysfunction.

The Standardized Road-Map Test of Direction Sense (Money, 1976) examines right-left orientation and spatial navigation. A drawing of a small map of a city was presented to the participant on a sheet of paper. The examiner traced a predefined route in the city, and following the same route, the participant was asked to indicate the direction taken at each turn (right or left). The participant was not allowed to turn the paper, which forced him to create a mental representation of the direction to be taken. The Hooper Visual Organization Test (Hooper, 1983) assesses visuospatial ability and object categorization. The task is to categorize objects that have been cut up and rearranged by mentally putting the pieces together and naming the whole object. Benton's Judgment of Line Orientation test (JLO; Benton, Varney, & Hamsher, 1978) examines the ability to judge the orientation of lines that are presented at various angles. The Boston Naming Test (BNT; Kaplan, Goodglass, & Weintraub, 1983) is a test of confrontation naming, which requires naming 60 two-dimensional (2D) line drawings of objects that are presented one at a time. The number of errors was used in the analyses for the Road-Map and the JLO tests. For the Hooper test and the BNT, the number of correct answers was analyzed.

In addition to the neuropsychological tests, we screened for HIV-associated dementia in the HIV-positive group using the HIV Dementia Scale (Power, Selnes, Grim, & McArthur, 1995).

### *Materials*

*MR task.* Details of the MR task used in this study have been provided elsewhere (Amick et al., 2006). Participants compared two figures presented on a computer screen and decided whether the figures were exactly the same or different (i.e., mirror images; see Figure 1). In order to judge whether the figures were the same, it was necessary to mentally rotate one of the figures into the position of the other figure. The images were line drawings of objects and hands that had been rotated along two orthogonal axes in either 2D or three-dimensional (3D) space. Around each axis, the object or hand was rotated in nine different spatial rotations ranging from 20° to 180° in 20° increments.

The task included two blocks of 144 trials each: one block of object stimuli and one block of hand stimuli. For each trial, pairs of stimuli were presented simultaneously on the computer screen. One stimulus was presented in a circle on the left side on the screen. The second stimulus was a rotated version of either exactly the same figure or a mirror image of the figure and was presented

in a circle to the right on the screen. The participants judged whether this figure was the same as or different from the figure to the left.

*HPP task.* The stimuli for the HPP task (see Figure 2) were similar to those used in Lamb, Robertson, and Knight (1989). Stimuli were presented in the center of the computer screen and consisted of multiple small (local) uppercase letters that were arranged to form one large (global) uppercase letter. The task was to decide whether the target letter, *H* or *S*, was present at either level of the figure. The large letters were 7.4 times taller than the small letters. All letters were 1.5 times as high as they were wide. Stimuli were black on a white background. The hierarchical figures were formed from the letters *H* and *S*, which were the target letters, and *A* and *E*, which were foil letters. Each stimulus contained one of the target letters and one of the foil letters.

### *Procedures*

*General procedures.* The testing took place in a noise-isolated room that had a mean luminance of 17.1 cd/m<sup>2</sup>. Stimuli were presented on a 17-in. (43.18 cm) Studio Display color monitor controlled by a Mac Power G3 computer running SuperLab Pro stimulus presentation software (Version 1.74 for Macintosh, Cedrus Corporation, San Pedro, CA). Responses were collected using a response box (Cedrus Corporation, Model 610). The participant was seated in front of the computer screen with his chin upon a chin rest such that the eye-to-monitor distance was about 72 cm for the MR task and 79 cm for the HPP task. For the MR task, the visual angle subtended by the stimuli was ~5°. For the HPP task, the local letters subtended approximately 1.2° visual angle vertically and 0.8° horizontally. Global letters subtended about 6.6° of visual angle vertically and 4.3° visual angle horizontally. All participants received the same standardized instructions for all tasks.

There was no time limit for the response in either the MR or the HPP task. Participants were instructed to respond as quickly and as accurately as possible, emphasizing that accuracy was more important than speed. The stimuli remained on the screen until a response was given. RTs and the number of errors were recorded and analyzed. The order of presentation of the MR and HPP tasks was counterbalanced across participants within each group.

*MR procedures.* A stimulus pair appeared on the computer screen. The participant responded by pressing either of two buttons on the response box. The *S* button was pressed if the images were judged to be the same, and the *D* button was pressed if they were judged to be different.

Practice sessions (18 trials) including hand or object stimuli were administered before each test session. The examiner explained the task and corrected the performance until it was clear that the participant had understood the instructions and was performing the task accordingly. Participants were not allowed to use their hands to facilitate the judgments on the hand trials.

The order of presentation of the two blocks, including object and hand stimuli, was counterbalanced across participants and is referred to as *List*. There were two different orders of presentation of the stimuli within the blocks (*Order*) to control for the order of different configurations, rotation angles, and mirror and identical images. Each block was administered following either of the two orders of presentation. If one participant received hands in the first

block, following Order 1, and objects in the second block, following Order 2, then the next participant would receive objects in the first block, following Order 1, and hands in the second, following Order 2.

**HPP procedures.** Each trial started with a 500-ms tone followed by the presentation of a hierarchical pattern. The response was given by pressing the *H* or *S* key on the response box. The task was divided into three blocks with 128 trials in each block. The first and the last blocks included attention biasing toward either the local or the global level, according to the procedures used in Robertson et al. (1988). In the global-bias condition, the targets appeared at the global level on 75% of the trials and at the local level on 25% of the trials. The opposite was true for the local-bias condition. In the middle block (no-bias condition), 50% of the targets appeared at the local level and 50% at the global level. In the no-bias condition, there were never more than four targets of the same letter consecutively following each other. Short (<5 min) neuropsychological tests (BNT and Hooper) were administered between consecutive blocks in order to minimize any possible biasing effects from one block to the next.

Two practice sessions were administered prior to the first block, as in Lamb et al. (1989). The first practice session (24 trials) included a feedback text line indicating whether the response was correct or not. The second practice session (48 trials) was similar to the actual test and did not include feedback.

The order of conditions (i.e., global, local, and no-bias condition) was counterbalanced across participants and is referred to as *List*. Two lists were used (Block1/Block2/Block3): global-bias/no-bias/local-bias and local-bias/no-bias/global-bias. There were three different orders of presentation of trials within each condition (*Order*) that allowed for counterbalancing the order of local and global targets across participants.

## Results

### General Analyses

For data from each individual, extreme RT values, which were defined as those more than two standard deviations above each participant's mean, were excluded before entering the data into the analyses. In addition, participants who had extreme values relative to their respective group mean values for each task were excluded from the analyses. For the MR task, participants were excluded from analyses if their mean RT for each stimulus type was more than two standard deviations above the group mean and/or if their accuracy was less than 75%. For the HPP task, participants were excluded from analyses if they had extreme RTs (more than two standard deviations above the group mean) on both global and local hierarchical levels within each condition (local, global, and no-bias trials). We calculated effect sizes using Cohen's *d*.

The scores on the HIV Dementia Scale are reported in Table 1; data from 1 participant were not available. Excluding the 2 participants with marginal scores of 9.5 from the MR and HPP analyses did not change the pattern of significant results. Consequently, their data were included in the analyses.

### MR Analyses

One HIV-negative participant who had extreme RTs on both object and hand trials was excluded from the analyses of RTs. One

HIV-positive participant was excluded from the analysis of RTs on hand trials. All participants scored over 75% correct, our criterion for inclusion, a cut-off chosen on the basis of prior MR research with similar methods (Amick et al., 2006; Ganis et al., 2000; Kosslyn et al., 1998) and ensuring the high accuracy required for valid RT measures.

To increase power, we collapsed dependent measures into three levels of rotation: low (20°–60° rotation), medium (80°–120°), and high (140°–180°). The number of errors was the primary dependent measure, as we found this to be the most informative in our prior research with patients with PD (Amick et al., 2006). Analyses of RTs on correct trials were also included to identify group differences in processing speed.

An omnibus three-way repeated measures analysis of variance (ANOVA) had within-subjects factors of Stimulus (hands, objects) and Rotation (low, medium, high) and a between-subjects factor of Group (HIV-positive, HIV-negative). Because our prior study with PD patients found group differences with hands but not objects (Amick et al., 2006), contrast ANOVAs also assessed MR effects for each stimulus separately in two-way mixed, repeated measures ANOVAs with the Rotation and Group factors.

We computed the slopes and intercepts of the best fitting lines of the MR functions (Shepard & Cooper, 1982). The slopes represent the change in errors and RTs per degree of rotation. The steeper the slope, the stronger is the effect of MR. Group differences in slopes would indicate that there is a difference in core MR processes. The intercepts represent information about more general processes, such as encoding of the stimulus and response preparation. We analyzed group differences in the slopes and intercepts for each stimulus type separately by using ANOVAs with the Group factor.

**Depth MR.** There were no group differences in the numbers of errors on 2D and 3D figures ( $p > .05$ ). The data were collapsed across depth for subsequent analyses.

**List and Order MR.** Some List and Order effects were significant for the analyses of object trials. Subsequent analyses included these between-subjects factors.

### MR Results

**Objects and hands: Errors.** The number of errors was higher on object than on hand transformations, and the amount of rotation had a larger effect on transformations of objects compared to those of hands (see Figures 3A and B). The omnibus three-way ANOVA showed significant main effects of Stimulus,  $F(1, 18) = 49.5$ ,  $p < .001$ , and Rotation,  $F(2, 36) = 31.99$ ,  $p < .001$ , and a significant interaction between Stimulus and Rotation,  $F(2, 36) = 7.77$ ,  $p = .002$ . Between groups, the effect of rotation, regardless of stimulus, was greater in the HIV-positive group than in the HIV-negative group, suggesting a general impairment on MR. This was seen as a significant interaction between Group and Rotation,  $F(3, 36) = 5.28$ ,  $p = .01$ , but not between Group and Stimulus,  $F(2, 36) = 0.03$ ,  $p = .87$ . There was no three-way interaction,  $F(2, 36) = 0.85$ ,  $p = .44$ , and no main effect of Group,  $F(1, 18) = 0.27$ ,  $p = .61$ .

**Objects and hands: RTs.** Participants in both groups had slower RTs for object than for hand transformations, and RTs increased with rotation angle (see Figures 3C and D). There were significant effects of Stimulus,  $F(1, 16) = 36.50$ ,  $p < .001$ , and

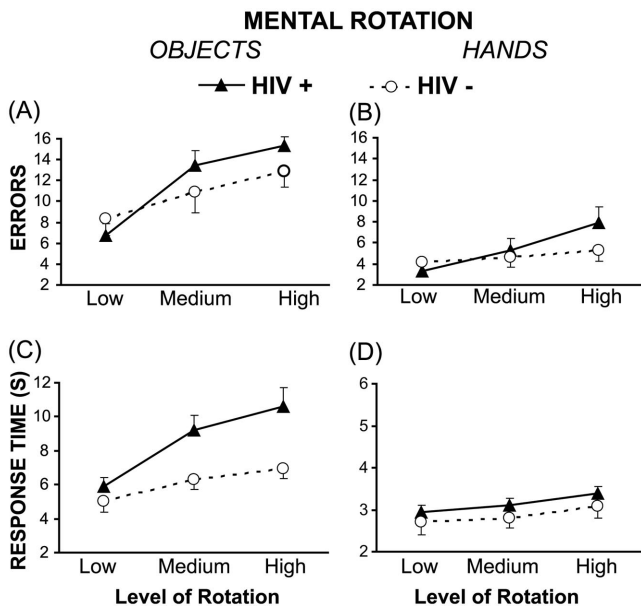


Figure 3. Mean number of errors (Figures 3A and 3B) and response times in seconds (Figures 3C and 3D) on mental rotation of objects (Figures 3A and 3C) and hands (Figures 3B and 3D) for the HIV-positive and HIV-negative groups. Nine rotational angles were collapsed into three levels of rotation: low (20°, 40°, 60°), medium (80°, 100°, 120°), and high (140°, 160°, 180°). Error bars show the standard error of the mean.

Rotation,  $F(2, 32) = 21.80, p < .001$ , and a significant interaction between Stimulus and Rotation,  $F(3, 32) = 16.26, p < 0.001$ . HIV-positive participants were significantly slower than the HIV-negative group and showed a stronger rotation effect with objects. There were significant interactions between Rotation and Group,  $F(3, 32) = 3.41, p = .045$ , and Stimulus, Rotation, and Group,  $F(4, 32) = 3.75, p = .034$ ; in addition, there was a trend toward a main effect of Group,  $F(1, 16) = 3.32, p = .09$ . A Huynh-Feldt correction for violation of sphericity assumption applied to all results ( $\epsilon = 1.000, p < .05$ ).

**Objects and hands: Slopes and intercepts.** The slopes showed that the effect of rotation was larger on object trials than on hand trials and larger for the HIV-positive group than for the HIV-negative group.

The slopes and intercepts for the error curves on object and hand trials were compared between the groups in two separate ANOVAs, one for slopes and one for intercepts. The analysis of slopes showed significant effects of Stimulus,  $F(1, 18) = 9.51, p = .006$ , and Group,  $F(1, 18) = 17.25, p = .001$ . There was a trend showing an effect of Stimulus on the intercepts for the error curves,  $F(1, 18) = 4.07, p = .059$ .

Similarly, we compared the groups for slopes and intercepts for the RT curves. There was a significant effect of Stimulus,  $F(1, 16) = 19.47, p < .001$ , and interaction between Group and Stimulus,  $F(1, 16) = 4.53, p = .049$ , reflecting a steeper slope for the HIV-positive than for the HIV-negative group on object trials but not on hand trials. There was a trend showing a main effect of Group,  $F(1, 16) = 4.00, p = .063$ . The analysis of intercepts showed a significant effect of Stimulus,  $F(1, 16) = 7.97, p = .012$ .

**Objects: Errors and RTs.** HIV-positive participants showed a stronger effect of rotation on object trial errors and RTs compared

to the HIV-negative group. There was a significant effect of Rotation on errors,  $F(2, 36) = 36.33, p < .001, d = 0.67$ , and on RTs,  $F(2, 34) = 21.33, p < .001, d = 0.56$ . The main effect of Group was not significant for errors,  $F(1, 18) = 0.22, p = .64, d = 0.012$ , but there was a trend for RTs,  $F(1, 17) = 3.54, p = .08, d = 0.17$ . There was a significant interaction between Group and Rotation on errors,  $F(3, 36) = 4.31, p = .021, d = 0.19$ , and on RTs,  $F(3, 34) = 4.36, p = .021, d = 0.20$ ; for RTs, a Huynh-Feldt correction for violation of the sphericity assumption applied ( $\epsilon = 1.000, \text{all } p\text{s} < .05$ ).

**Objects: Slopes and intercepts.** HIV-positive participants had steeper object MR slopes than did the HIV-negative group, as shown by Group effects for the slopes for both errors,  $F(1, 18) = 7.82, p = .012, d = 0.72$ , and for RTs,  $F(1, 17) = 5.16, p = .036, d = 0.54$ . There were no group differences in the intercepts ( $p > .05$ , for both errors and RTs).

**Hands: Errors and RTs.** The ANOVA of hand trials did not reveal any significant group differences in performance. There was a significant effect of Rotation on both errors,  $F(2, 36) = 6.68, p = .003, d = 0.27$ , and on RTs,  $F(2, 32) = 9.21, p = .001, d = 0.37$ , but no significant main effect of Group; errors:  $F(1, 18) = 0.24, p = .63, d = 0.013$ ; RTs:  $F(1, 16) = 0.68, p = .42, d = 0.041$ . There was a trend toward an interaction between Group and Rotation for errors,  $F(3, 36) = 2.41, p = .10, d = 0.12$ , and no effect for RTs,  $F(3, 32) = 0.04, p = .96, d = 0.003$ , suggesting some impairment with hands as well, given that the omnibus did not show any group and stimulus interactions.

There were no group differences in RTs and errors for any level of rotation (univariate ANOVAs, all  $p\text{s} > .25$ ).

**Hands: Slopes and intercepts.** A clear impairment on hand MR, in addition to that found for object MR, was shown by the slope of errors. The MR slope for errors was steeper in the HIV-positive group than in the HIV-negative group, which was seen as a significant main effect of Group for the slopes of errors,  $F(1, 18) = 4.90, p = .04, d = 0.50$ , but not slopes of RTs,  $F(1, 16) = 0.06, p = .81, d = 0.00$ . There were no group differences in the intercepts ( $p > .05$ , for either errors or RTs).

### HPP Analyses

The average number of errors was very low ( $\leq 2$  errors on each condition), precluding detailed analysis by accuracy. The main dependent variable, therefore, was RT. Data were excluded from 1 HIV-negative participant who had extreme RTs in all conditions and from 1 HIV-positive participant who had extreme RTs in the global-bias condition. We performed the analyses using mean values. Separate analyses that used the medians showed no significant difference in the results. The first 10 trials in the biased conditions were meant to prime the participant for the biasing condition, and therefore were not included in the analyses.

The effect of biasing was analyzed in an omnibus, three-way mixed, repeated measures ANOVA with Bias (global bias, local bias) and Level (global targets, local targets) as within-subjects factors and Group as the between-subjects factor.

Difference scores were calculated for each participant by subtracting RTs on trials with local targets from RTs on trials with global targets (i.e., global-local). These scores reveal the effect of biasing. Compared to trials without biasing, the difference score would be more positive on local-bias trials (i.e., faster RTs for

local targets) and more negative on global-bias trials (i.e., faster RTs for global targets; Robertson et al., 1988). We analyzed the difference scores for each group separately using one-sample *t* tests to examine the effect of biasing. We analyzed group differences in the effect of biasing using univariate ANOVAs.

Some List effects were significant in the omnibus, three-way ANOVA. The List effect was related to a practice effect such that RTs were faster when a task was performed last in the session. List was included as a between-subjects factor in all analyses. The order of stimulus presentation did not significantly change the results, and Order was not included as a factor in subsequent analyses.

### HPP Results

*No bias.* Under no-bias conditions, HIV-positive participants performed similarly to the HIV-negative group (see Figure 4). The omnibus ANOVA of RTs on no-bias trials showed no main effect of Level or Group,  $F(1, 21) < 0.90, p > .50, d < 0.03$ , for both analyses, and no interaction between Group and Level,  $F(2, 21) = 2.01, p = .17, d = 0.087$ .

There was no significant difference in the RTs toward local and global targets in either group; HIV-negative:  $F(1, 9) = 0.91, p = 0.37, d = 0.09$ ; HIV-positive:  $F(1, 12) = 1.81, p = .20, d = 0.13$ , and no significant group differences in the difference scores,  $F(1, 21) = 2.01, p = .17, d = 0.09$ .

*Global and local biasing.* Under biasing conditions, HIV-positive participants showed abnormal global biasing (see Figure 4). The omnibus three-way ANOVA of RTs on biased trials showed no main effect of Group, Level, or Bias,  $F(1, 20) < 1.7, p > .20, d < 0.08$ , for all analyses. Significant interactions were found between Bias and Level,  $F(2, 20) = 28.63, p < .001, d = 0.60$ , and Bias, Level, and Group,  $F(3, 20) = 5.78, p = .026, d = 0.22$ .

Analyses of difference scores showed that only the HIV-positive participants were significantly affected by the global biasing, though the HIV-negative group was marginally affected; for one-sample *t* tests within each group, HIV-negative:  $F(1, 9) = 3.66, p = .09, d = 0.29$ ; HIV-positive:  $F(1, 11) = 11.41, p = .006, d = 0.51$ . Neither group was significantly affected by the local biasing, though the HIV-negative group was marginally affected; HIV-

negative:  $F(1, 9) = 3.48, p = .10, d = 0.25$ ; HIV-positive:  $F(1, 12) = 0.16, p = .69, d = 0.01$ , and there were nearly identical RTs between groups under local-bias conditions (see Figure 4). The more striking result is that HIV-positive participants showed a larger effect of global biasing than did the HIV-negative group, which reflected slower RTs toward targets at the local level for the HIV-positive than for the HIV-negative participants. The difference scores on global-bias trials in the HIV-positive group were significantly more negative compared to the equivalent scores in the HIV-negative group,  $F(1, 20) = 4.63, p = .044, d = 0.19$ . For the local-bias condition, there was no significant group difference in RTs occurring at the local or global level,  $F(1, 21) = 0.08, p = .78, d = 0.004$ .

### Neuropsychological Assessment

Results from the neuropsychological assessments are reported in Table 1. Data were not available for 1 HIV-negative participant on two neuropsychological tests; the demographics of the groups remained comparable after removal of this participant. Significant group differences were found on two of the three visuospatial tests: Road-Map (equal variances not assumed, Levene's test) and JLO but not Hooper. As expected, there were no group differences on the BNT.

### General Discussion

Overall, the results show that HIV infection was associated with significant impairment on parietal-dependent visuospatial tasks. For MR, results revealed impaired processes related to the MR of hands and objects. This was seen as a stronger effect of rotation on performance in the HIV-positive group compared to the HIV-negative group, which was supported by group differences in the MR slopes, though most consistently for objects. On the HPP task, HIV-positive participants benefited from global biasing but not in a normal way, because they were slower than the HIV-negative group to respond to targets at the local level under this globally biased condition. The finding of visuospatial deficits based on the MR and HPP results was further supported by group differences on two of three standard neuropsychological tasks of visuospatial function. The pattern of impairments indicates that HIV infection is associated with dysfunction of visuospatial abilities that have been shown in prior neuroimaging and neuropsychological research to depend primarily upon the posterior inferior parietal cortex, which suggests that these brain structures are affected by the virus.

Next, we relate prior research on the brain basis of MR and HPP to the present findings in order to suggest avenues for future research on how the virus may influence parts of the CNS involved in spatial cognition. Further research, especially neuroimaging with HIV-positive individuals, will be necessary to identify definitively which brain regions are responsible for the changes in spatial cognition that we observed in HIV-positive individuals.

### MR and the Parietal Lobes

HIV infection was found to be related to deficits in core MR processes. Steeper slopes of the linear MR curves were found for object and hand errors and object RTs in the HIV-positive group

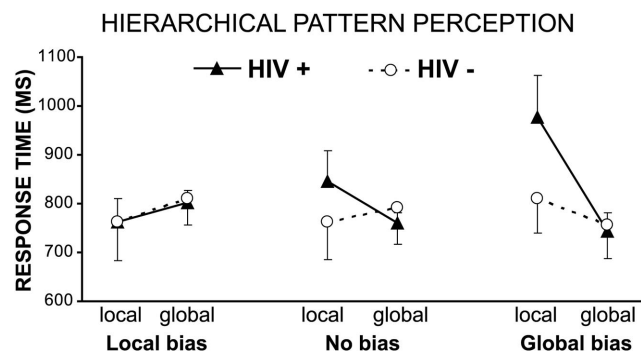


Figure 4. Mean response times for the HIV-positive and HIV-negative groups on the local bias, no bias, and global bias conditions. Response times to targets occurring at the local and global levels are presented for each condition. Error bars show the standard error of the mean.

than in the HIV-negative group. These findings demonstrate that dysfunction in core MR processes in HIV-positive individuals impairs their accuracy on MR with both objects and hands and their speed of MR with objects. For both groups, performance was better on the MR of hands than of objects, as found previously (Amick et al., 2006; Vingerhoets, de Lange, Vandemaele, Deblaere, & Achten, 2002).

The regions around the ventral caudal intraparietal sulcus and the ventral premotor cortex are considered the critical structures for object MR, with the occipitoparietal part of the frontoparietal network mediating the linear scaling of performance with rotation and thus being responsible for the steepness of the MR curve (Alivisatos & Petrides, 1997). MR of hands recruits additional regions of primary, supplementary and premotor cortex, middle frontal gyrus and somatosensory parietal cortex, relative to object MR (Kosslyn et al., 1998). Consequently, our findings of impaired MR slopes in the HIV-positive group lead us to hypothesize that the dysfunctional regions responsible for these performance changes include brain structures around the ventral caudal intraparietal sulcus.

Although parietal areas may be more crucial to the MR of objects than of hands (Parsons, 2003), the primary motor cortex has been shown to play a causal role in the MR of hands, increasing the RTs (but not errors) at all rotations (Ganis et al., 2000). For hand trials, we speculate that the frontal and motor regions additionally recruited for hand MR (Kosslyn et al., 1998) can compensate for impaired spatial transformation processes in the intraparietal region. This may explain how RTs on the hand MR task were spared in the HIV-positive patients; consistent with a relatively spared primary motor contribution to hand MR speed, we found no overall RT difference between groups on hand MR.

Our findings from standard neuropsychological assessments further support our proposal that HIV results in dysfunction of intraparietal regions that support spatial cognition. The HIV-positive group showed poor performance on the JLO, which involves activity in areas around the intraparietal sulcus (Ng et al., 2000), and on the Road-Map, on which MR is required (Rainville, Marchand, & Passini, 2002). Differences in verbal and nonspatial compared to spatial demands on these tests may explain why HIV was found to impair performance on the Road-Map and the JLO but not on the Hooper test or the BNT. The JLO may depend more on spatial processing than does the Hooper test, which also assesses visual organization, object categorization, and naming. Intact performance on the confrontation naming task of the BNT supports the specificity of a visuospatial impairment in HIV. The present findings support the use of the Road-Map and the JLO in the clinic to evaluate visuospatial deficits related to the asymptomatic phase of HIV infection.

#### *HPP and Lateral Inferior Parietal Cortex*

On the HPP task, HIV-positive individuals shifted attention normally between targets at the global and local levels under the no-bias condition, indicating preserved perception of hierarchical visuospatial patterns in HIV. Compared to the HIV-negative group, global biasing had an abnormally adverse effect on local targets in the HIV-positive group, who responded slower to targets at the local level relative to the HIV-negative group, whereas RTs were comparable between groups to global targets at the biased

global level. This finding suggests an impairment specific to targets at the local level, consistent with our finding also of a local biasing effect in the HIV-negative group but not in the HIV-positive group. The HPP task with no-, global-, and local-bias conditions was used previously to assess the effect of HIV infection in symptomatic, asymptomatic, and control groups (Martin et al., 1995). They found that asymptomatic HIV-positive patients showed a greater RT cost of attention to the global level on perceiving local level targets than did the control group, consistent with this finding in our results. Unlike in our study, however, they also found a similar cost under local bias conditions, but this could be related to their inclusion of many HIV-positive participants with a history of intravenous drug use.

HPP mainly depends upon the lateral posterior cortex around the temporal–parietal junction, with greater right hemisphere involvement for global-level processing and greater left hemisphere involvement for local-level processing (Han et al., 2004; Robertson et al., 1988; Yamaguchi et al., 2000), but does not depend upon the dorsolateral prefrontal cortex (Robertson et al., 1991). Shifting attention to the global or local level requires the left rostral inferior parietal lobule (Robertson et al., 1988). We hypothesize that dysfunction in the lateral inferior parietal cortex may be responsible for impaired local-level processing related to HIV infection, especially when attention is biased away from the local level.

#### *Role of Basal Ganglia and Posterior Parietal Cortex in HIV and Spatial Cognition*

The basal ganglia are crucial to MR (Harris, Harris, & Caine, 2002) and are affected by HIV (Berger & Arendt, 2000; Ragin et al., 2005). The frontostriatal circuitry has been proposed to be a primary target for HIV in the brain. Evidence that frontostriatal circuitry contributes to the hand MR and Road-Map tasks comes from studies on patients with PD (Amick et al., 2006) and Huntington's disease (Bylsma, Brandt, & Strauss, 1992), respectively. In a study using methods nearly identical to those of the present study, Amick et al. (2006) found that PD patients were impaired on MR of hands, as we found in HIV-positive patients, but they were not impaired on MR of objects, unlike our HIV-positive group. It seems that although the basal ganglia are affected in both PD and HIV, the neural dysfunction leading to their spatial problems is somewhat distinct.

The visuospatial problems we found in asymptomatic HIV-positive participants suggest that processing in posterior parietal regions is dysfunctional even at the earliest stage of the disease. This dysfunction could be due to the virus directly affecting parietal neurons, or an indirect product of parietal connections with basal ganglia or frontal lobe structures, which are also thought to be affected by the virus, as we reviewed. For example, a parietal–basal ganglia loop may be responsible for spatial dysfunction, as suggested by work in monkeys, which has shown that posterior intraparietal sulcus regions potentially homologous to the regions implicated in human object MR studies have projections to the head of the caudate and receive output projections from the substantia nigra pars reticulata (Clower, Dum, & Strick, 2005; Middleton & Strick, 2000a, 2000b; Yeterian & Pandya, 1995).

## Conclusion

We studied HIV-positive individuals in the asymptomatic phase of HIV infection, and we observed cognitive problems specifically related to the core spatial transformation processes underlying MR of objects and hands. HPP performance revealed spatial cognitive problems related to HIV infection that are unlikely to depend upon the dorsolateral prefrontal cortex or frontostriatal circuits. Other brain functions may be spared: RT slopes on MR of hands, which involves motor functions and transformations, were normal, and normal performance was found on neuropsychological tasks that may depend more on nonspatial object cognition or language processes. We propose the hypothesis that HIV-related visuospatial problems result from neural dysfunction in the inferior parietal cortex and/or impaired function in subcortical structures connected with these parietal areas. Our results suggest that the parietal cortex is affected by the HIV disease process before effects develop in the frontal and motor cortical areas. Numerous studies (e.g., Castelo et al., 2006; Chang et al., 2001; Hall et al., 1996; Harrison et al., 1998) that have found frontostriatal circuitry to be the central target for HIV in the brain have included participants who were in a more severe stage of the disease than were our participants. Future studies are needed that compare performance on tasks of visuospatial abilities and tasks of motor and executive function in HIV-positive individuals at various stages of the disease. Neuroimaging studies with HIV patients will be particularly important in order to further specify which brain regions are affected by the virus.

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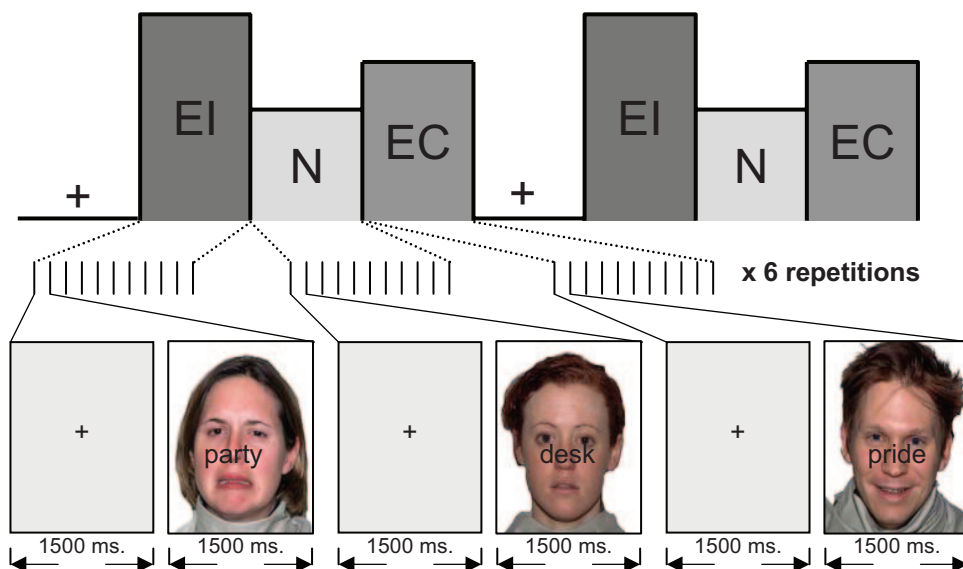
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### Correction to Haas, Omura, Constable, and Canli (2007)

In the article “Emotional Conflict and Neuroticism: Personality-Dependent Activation in the Amygdala and Subgenual Anterior Cingulate,” by Brian W. Haas, Kazufumi Omura, R. Todd Constable, and Turhan Canli (*Behavioral Neuroscience*, 2007, Vol. 121, No. 2, pp. 249–256), there was an error in the text of Figure 1 on p. 250. Above the image of the third person, “x?6repetitions” should have appeared as “x 6 repetitions.” See corrected figure below.



**Figure 1.** Schematic representation of an experimental paradigm. Stimuli were either emotionally incongruent (EI), neutral (N), or emotionally congruent (EC). Stimuli were presented in a total of 6 blocks of 10 trials for each condition. Each trial consisted of a 1,500 ms presentation of a fixation cross followed by a 1,500 ms presentation of the stimulus. Emotional conflict was assessed by comparing the blood oxygen level-dependent (BOLD) signal obtained during EI trials relative with the BOLD signal obtained during EC trials.