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Mapping mental number line in physical space: Vertical and horizontal visual number line orientation in asymptomatic individuals with HIV

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INTRODUCTION

The human immunodeficiency virus (HIV) crosses the blood-brain barrier and affects the brain early in the course of the disease (Avison et al., 2004; Gray et al., 1996; Power et al., 1993), causing neurochemical changes that alter functioning in selective populations of neurons (Kaul, Garden, & Lipton, 2001; Mattson, Haughey, & Nath, 2005).The neuropsychological and neuroimaging literature suggests that frontostriatal pathology is especially prominent in HIV (Chang et al., 2004; Chang et al., 2001; Ernst, Chang, Jovicich, Ames, & Arnold, 2002; Heaton et al., 1995; (Paul, Cohen, & Stern, 2003; Paul et al., 2007). The basal ganglia, in particular, are subject to pathology early in the course of the infection (Berger & Nath, 1997). There is evidence that blood-brain barrier disruption, resulting from direct infection or apoptotic changes in endothelial cells, may increase the viral burden in this region and allow entry of substances that are damaging for basal ganglia (Berger et al., 2000). HIV infection is also associated with tissue loss in frontal and parietal areas (Thompson et al., 2005). Neuroimaging studies of cognitive activation in HIV positive (HIV+) individuals have found increased activation in frontal and parietal cortical regions that are adjacent to those activated by the HIV negative (HIV−) control group (Chang et al., 2004; Chang et al., 2001; Ernst, Chang, Jovicich, Ames, & Arnold, 2002), that were interpreted in the context of compensatory activation induced by dysfunction of frontostriatal circuits in HIV+ individuals.

Recent neuroimaging studies have reported increased signal change in a cognitively intact HIV + group compared to the HIV− group in lateral frontal and posterior parietal areas (Castelo, Sherman, Courtney, Melrose, & Stern, 2006). These findings also support the idea that HIV-

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related brain changes extend beyond the frontostriatal circuits to their parietal projections. Neuropsychological studies of cognition in HIV have shown that asymptomatic HIV+ individuals exhibit cognitive deficits consistent with dysfunction of frontostriatal circuits (Bogdanova, Diaz-Santos, & Cronin-Golomb, 2007; Bornstein et al., 1993; Castelo, Courtney, Melrose, & Stern, 2007; Heaton et al., 1995) and parietal cortical areas (Bogdanova & Cronin-Golomb, 2005; Olesen, Schendan, Amick, & Cronin-Golomb, 2007).

Neuropsychological measures of number processing, according to neuroimaging studies, have been linked to bilateral fronto-parietal cortico-subcortical circuits (reviewed in Dehaene, Piazza, Pinel, & Cohen, 2003; Hubbard, Piazza, Pinel, & Dehaene, 2005), including parietal areas that are important for visuospatial processing (Dehaene, Spelke, Pinel, Stanescu, & Tsivkin, 1999). Deficits in number processing and spatial function arise from changes in the cortico-striato-thalamic circuit that includes the basal ganglia, which are subject to pathology early in the course of HIV, and their cortical projection areas, the dorsolateral prefrontal cortex (DLPFC) and the posterior parietal lobes. There has been a recent surge of interest in number processing studies in healthy adults (Gobel, Calabria, Farne, & Rossetti, 2006; Izard & Dehaene; Longo & Lourenco, 2007) and neglect patients (Cappelletti, Freeman, & Cipolotti, 2007; Doricchi, Guariglia, Gasparini, & Tomaiuolo, 2005; Priftis, Zorzi, Meneghello, Marenzi, & Umilta, 2006; Rossetti et al., 2004; Zorzi, Priftis, Meneghello, Marenzi, & Umilta, 2006), significantly extending our understanding of numerical cognition, in particular mental number line and spatial representation of a number. To our knowledge, there are no published studies assessing numerical cognition in HIV.

In the present study we used a series of neuropsychological measures to investigate numerical and visuospatial processing in the early asymptomatic stage of HIV. This study examined the relation between numerical distance estimation and spatial orientation in asymptomatic HIV+ individuals.

Mental Number Line

Galton (1880) first introduced the concept of the spatial representation of numbers similar to a mental number line. Since then, there have been many behavioral, neuroimaging and lesion studies investigating the mechanisms underlying numerical processing and the abstract concept of a mental number line.

Luria (1945, 1962) demonstrated that lesions to the parietal area lead to number processing deficits based on a disorder of spatial synthesis, or a disturbance of the category of direction of space. When parietal systems of the brain are damaged, the spatial reference system, essential for calculation, is lost. Impairment of the spatial coordinate system with respect to numbers is manifested in the deterioration of a number’s decimal structure. With respect to calculation, the impairment of the spatial coordinate system is demonstrated by spatial errors on a mental number line. According to Luria’s model, we can expect that parietal lesions would lead to the impairment of the concept of number as well as a specific spatial impairment in number processing.

Restle (1970) suggested that the representation of numbers could be spatially organized along a mental number line, a concept that recently has been expanded and popularized by Dehaene. Dehaene’s triple-code model (Dehaene, 1992; Dehaene & Cohen, 1997) postulates that a magnitude code is subserved by the parietal lobes, and that numbers are represented as a distribution of activation on an oriented number line. Recent reports suggest that number magnitudes are represented spatially along a continuous analogue mental line, with smaller numbers located to the left and larger numbers to the right of the line (reviewed in Hubbard et al., 2005).

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The left-to-right orientation of the mental number line is currently a subject of investigation in the numerical cognition literature. Dehaene, Bossini, and Giraux (1993), and Dehaene, Dupoux, and Mehler (1990) demonstrated the SNARC effect (Spatial Numerical Association of Response Codes), the observation that individuals respond to smaller numbers faster with their left hand, and to larger numbers faster with their right hand. This phenomenon was observed even on a task that did not require processing the magnitude of the number stimuli, such as indicating whether the number was even or odd. The SNARC effect provides further evidence for the spatial nature of mental number representation and suggests left-to-right number organization on a horizontally oriented mental number line.

Neural Mechanisms for Mental Number Line

While exact neural mechanisms involved in number line processing remain unknown, some studies suggest that mental number line orientation relies mostly on parietal areas (Hubbard et al., 2005), whereas others suggest that mental number line orientation relies on spatial working memory mechanisms involving frontal areas (Doricchi et al., 2005). Several studies indicate that numerical quantity judgments, used in mental number bisection tasks, involve activation of the intraparietal sulcus (horizontal segment) bilaterally, the left precentral gyrus, and prefrontal areas (Dehaene, Molko, Cohen, & Wilson, 2004; Dehaene et al., 2003; Walsh, 2003). Repetitive transcranial magnetic stimulation (rTMS) studies provide further insight into the mechanisms of mental number line processing. Gobel and colleagues (2006) used rTMS over parietal and occipital areas in healthy individuals during a mental number bisection task. Performance during control trials was similar to performance reported in physical line bisection where participants underestimated the midpoint of the numerical interval (that is, exhibited leftward bias). rTMS over the right posterior parietal cortex produced a significant rightward shift of the perceived midpoint of the numerical interval, simulating ‘spatial’ neglect in healthy subjects. rTMS over the occipital cortex did not produce any effect on bisection performance. The study provided further evidence for spatial representation of a mental number line and for the involvement of the right posterior parietal cortex in the spatial representation of numbers.

Physical Line Orientation

Right posterior parietal cortex has been implicated in physical line bisection, a task frequently used in numerical cognition studies. Neuroimaging (Fink et al., 2000) and patient (Doricchi & Angelelli, 1999) studies showed that physical line bisection is associated with processing by the inferior and superior parietal lobes. Additionally, a neuroimaging (fMRI) study of physical line bisection judgment (Landmark task) indicated that processing horizontal and vertical physical lines activates anatomical networks in the right inferior parietal cortex (Fink, Marshall, Weiss, & Zilles, 2001). The study reported no significant interaction between the physical line bisection judgment task and stimulus orientation, suggesting that the activation of inferior parietal cortex during the Landmark task reflects visuospatial judgment irrespective of line orientation.

Relation between Spatial and Numerical Cognition

The studies of the SNARC effect provided evidence for spatial-numerical interactions (reviewed in Hubbard et al., 2005) Moreover, Caessens, Hommel, Reynvoet, and van der Goten (2004) demonstrated that the SNARC effect or spatial-numerical interaction occurs regardless of input or output modality. This study measured the spatial-numerical interaction without using visual digit presentation. Participants were presented with visual stimuli (arrows, then colors) and were asked to respond verbally with ‘one’ or ‘two.’ The automatic activation of numerical information interfered with participants’ responses to the orientation of an arrow.

Lesion studies provide additional evidence for the close relation between spatial and numerical domains (Benton, 1992; Mayer et al., 1999; Roux, Boetto, Sacko, Chollet, & Tremoulet, 2003). The classic case of Gerstmann's syndrome (Gerstmann, 1940) showed that the combination of number processing and spatial deficits are frequently observed in patients with lesions of the parietal lobes, specifically in the left angular gyrus. Disorders such as acalculia, agraphia, finger agnosia and right-left confusion typically associated with left angular lesions share close anatomical and possibly functional neural networks (Roux et al., 2003)

Neglect Research

Studies of patients with left hemispatial neglect provide further insight into our understanding of spatial and numerical cognition. Neglect patients typically bisect horizontal lines to the right of the veridical center, showing rightward bias, whereas healthy individuals exhibit systematic leftward bias, or pseudoneglect, on a physical line bisection task (Bowers & Heilman, 1980). Recent studies of neglect that used the mental number line bisection task in horizontal orientation also showed that neglect patients exhibit rightward bias on bisection, whereas healthy participants demonstrate leftward bias. Zorzi, Priftis, and Umiltà (2002) found that neglect patients produce errors on a mental number line bisection task, similar to the errors usually observed on a physical line bisection task (see also Priftis et al., 2006; Zorzi et al., 2006). Longo and Lourenco (2007) reported leftward bias (pseudoneglect) in both mental number line and physical line bisection in young healthy participants, and found that the magnitude of pseudoneglect in these tasks correlated across participants. The investigators concluded that hemispheric asymmetries in spatial attention apply to both physical and mental numerical space.

Attention-Orienting Bias

The imbalance of attention distribution produces ipsilesional (rightward) bias in neglect patients, whereas healthy participants may exhibit a "culture-induced" leftward orienting on tasks that require reading, writing and numerical processing. In our culture we orient to the left when we are about to start reading, writing a word or writing down a multi-digit numeral, as our writing and our attentional scanning habits are organized in the left-to-right direction (Fias & Fischer, 2005; Opfer & Thompson, 2006). We can hypothesize that on a task that requires estimation of numerical distance (for instance, place "7" on a horizontally presented visual [physical] number line from "0" to "10"), we orient to the left first in an attempt to "measure" the distance from the starting point of "0" to the required "7." It seems equally plausible that our attention is directed towards the left when we estimate the numerical distance on a mental number line, similar to the visual number line. The evidence for this is derived from the SNARC studies. The SNARC studies also demonstrated that American children do not show a SNARC effect until age nine (Berch, Foley, Hill, & Ryan, 1999), which is determined by their educational experience. Additionally, the SNARC studies showed a reversed effect in adult [Iranian] individuals whose first language was Arabic, and who write from right-to-left (Dehaene et al., 1993; reviewed in Hubbard et al., 2005)

Priftis et al. (2006) reported dissociations between implicit and explicit processing of the mental number line in neglect patients. Here, patients with left neglect (right hemisphere damage) performed a mental number bisection task and a modified version of the SNARC task. Results revealed a neglect effect on the mental number bisection task only. The investigators linked the impaired performance in mental number bisection to an attention-orienting bias during active exploration or manipulation of the number line.

The neglect literature has also established a dissociation between visual numerical and non-numerical representations of space (reviewed in Bisiach & Vallar, 2000; Rossetti et al., 2004; Zorzi et al., 2006). Zorzi et al. (2006) investigated the spatial representation of numerical and non-numerical sequences in neglect patients. Patients were asked to complete the bisection of visual lines and the mental bisection of number intervals, letter intervals, and month intervals. There was a rightward bias on visual line and similarly on mental number interval bisection, but no effect on non-numerical sequences. The investigators concluded that the spatial layout for numerical representations on a mental line is number specific and does not apply to all ordered sequences. The study confirmed their earlier isomorphism hypothesis (Zorzi et al., 2002), which postulated that the mental number line organization strongly resembles the structure of a physical line.

A recent study of neglect patients (Cappelletti et al., 2007) examined the orientation of mental number lines and physical line bisection. In this study, all five patients with neglect exhibited a rightward bias for physical and horizontally oriented mental number lines. Three of the patients also demonstrated an upward bias for vertically oriented mental number lines, while two showed no bias. The investigators concluded that horizontal and vertical neglect can associate or dissociate in neglect patients, suggesting partially independent mechanisms for processing horizontal and vertical mental number lines.

Though neglect has been most often described in the horizontal dimension, it can be manifested in all three dimensions: horizontal (lateral), radial (near-far), and vertical (altitudinal) (Kageyama, Imagase, Okubo, & Takayama, 1994; Kori & Geldmacher, 1999; Vallar, Guariglia, Magnotti, & Pizzamiglio, 1995). Moreover, the processing of horizontal and vertical physical lines activates the same anatomical networks in the right inferior parietal cortex (Fink et al., 2001).

Physical Number Line

Our preliminary study of asymptomatic HIV+ and healthy matched individuals examined physical number line orientation (a pencil-and-paper task to assess visual number line orientation) in two dimensions, horizontal and vertical, and found that each group exhibited a similar bias on vertical and horizontal physical number line orientation (Bogdanova & Cronin-Golomb, 2005). Taken together, the findings from the studies of healthy and neurologically impaired adults, which showed the same directional bias for the mental number line and physical line bisection, lead us to hypothesize that (a) the physical number line will have numerical and spatial properties that are similar to those of the mental number line. Additionally, the studies of the SNARC effect that demonstrated similar spatial-numerical interactions regardless of input and output modality, and neglect studies allowed us to hypothesize that (b) the internal mental number line activated during these tasks can be applied (mentally rotated) in more than one dimension, and that (c) the physical number line will have similar numerical properties and spatial integrity in both horizontal and vertical orientations. Although no studies have investigated the neural basis of physical number line orientation, findings from previous studies allow us to hypothesize that (d) active direct exploration and manipulation of both physical and mental number lines will involve the same attentional orienting bias. We hypothesized that (e) operation within the physical number line may rely on neural networks involved in both physical line and abstract numerical (mental number line) orientation. Based on the previous studies that established a dissociation between visual numerical and non-numerical representations of space, and our own preliminary results, we predicted (f) a dissociation between the processing components of numerical distance (physical number line) and physical space (physical line bisection) in our HIV+ group, as we hypothesized that there is a differentiation between the neural networks involved in these processes. The neural areas implicated in mental number line processing, frontostriatal and parietal, present particular interest to our study of asymptomatic HIV+ individuals, as we attempt to explore the impact of HIV infection on the brain beyond well-studied frontostriatal circuits, specifically to include parietal-based spatial functions.

Present Study

We had two main aims of the present study. The first was to investigate the effect of HIV infection on cognitive function, in particular, the relation of numerical and spatial cognition in individuals with HIV in its early asymptomatic stage. Because frontostriatal circuitry is affected in HIV, and this circuitry includes projections to the parietal lobes, the expectation is that parietal-based numerical processing and visuospatial function should be impaired as a consequence of HIV. The second aim was to explore the underlying mechanisms for both physical and mental number orientation using several modes of presentation and response: mental number line bisection (verbal input and verbal output), physical number line orientation on visually-presented number lines (visual and verbal input, visuo-motor output), and physical line bisection (visual input, visuo-motor output). To further investigate the nature of the relation between numerical and spatial processing, the physical number line was presented in both horizontal and vertical orientation.

METHODS

PARTICIPANTS

Thirty-seven HIV+ participants (mean age: 46.9.5 ± 6.2 years; education: 14.6 ± 1.8 years) and 37 HIV− participants (mean age: 46.5 ± 6.6 years; education: 15.4 ± 2.0 years) were recruited from Boston area clinics and from the local community. Groups were matched on socio-demographic variables (see Table 1). Participants were required to be native speakers of English. Exclusionary criteria included co-existing serious chronic medical (including psychiatric or neurological) illness, use of psychoactive medications, score above 30 on the Beck Depression Inventory II, history of intracranial surgery, traumatic brain injury (loss of consciousness), alcoholism or other substance abuse in the past 12 months, or eye disease or abnormalities. Handedness was assessed with the Edinburgh Scale (Oldfield, 1971). The American modification of the National Adult Reading Test (ANART; Nelson, 1982) was given as a measure of premorbid intelligence.

Additional exclusionary criteria for HIV+ participants included complications of HIV infection that may have affected neurological systems (e.g., opportunistic infections such as toxoplasmosis or cryptococcal meninigitis). HIV+ participants were screened to rule out associated dementia through use of the HIV-Dementia Scale (Power, Selnes, Grim, & McArthur, 1995), with a score of 10 or below resulting in exclusion. Those participants with a remote substance abuse history were asked to report frequency (alcohol and drug) and means of administration. Data were collected with regard to each participant's complete medication regimen, including CD4 count, viral load, and anti-retroviral therapies.

HIV+ participants reported their most recent CD4 count and plasma viral load, and completed a detailed immunological history form documenting past and present substance use, including duration of use, as well as history of opportunistic infections, lowest CD4 count since infection, number of times CD4 count fell below 200, and a complete list of antiretroviral medications. We used this information to determine clinical staging as recommended by the CDC (1992). All HIV+ participants were Stage A. The mean CD4 count was 532.6 ± 235/mL and mean duration of HIV infection of 12.0 ± 6.1 years. Twenty-two patients had undetectable viral loads (<75 copies/mL), two patients had a low viral load (<400 copies/mL), and 13 patients had high viral loads (>400 copies/mL) (Table 1).

Screening measures—HIV+ participants' performance on the HIV Dementia Scale did not indicate cognitive impairments indicative of dementia (mean: 14.04 ± 1.47, range: 5, maximum score: 16). HIV+ and HIV− groups had similar estimated verbal IQ, as determined by the American National Adult Reading Test (ANART). These results indicate that the groups were well matched for overall premorbid cognitive ability.

PROCEDURES

Before participating, each individual provided informed consent in accordance with regulations of the Boston University Institutional Review Board. All participants were administered a series of neuropsychological tests sensitive to HIV-associated neuropsychological impairments. The number processing section included cognitive neuroscience-based and standard clinical neuropsychological measures chosen to assess a range of number processing abilities reflecting parietal-lobe functioning in persons with HIV. The neuropsychological tests were administered and scored according to standard procedures.

NEUROPSYCHOLOGICAL ASSESSMENTS

Attention and Executive Function

Digit Span and Spatial Span, Wechsler Memory Scale III: (WMS-III; Wechsler, 1997) are the standardized measures of efficiency of attention (Forward Span) and working memory (Backward Span) in verbal and nonverbal domains (Lezak, Howieson, & Loring, 2004). The standard total score was used for the group comparisons of Digit Span and Spatial Span. Additionally, Backward Span scores were used as measure of working memory.

The Trail Making Test: (Armitage, 1946) is a standardized test of psychomotor speed and executive functioning that consists of two subtests: Trails A and Trails B. Trails A is a test of simple attention and psychomotor speed, in which participants connect numbered circles in ascending order (1-2-3, etc). Trails B is a measure of combined visual search, psychomotor speed, and cognitive flexibility, assessing the ability to shift and maintain the response set, where participants sequentially alternate between alpha-numeric sequences (1-A-2-B, etc). Time to completion was used for the group comparisons.

Subtracting from 100 by 7's: (Luria, 1962) is a task of sequential arithmetic operation. A neuroimaging study (Rueckert et al., 1996) demonstrated bilateral prefrontal and posterior parietal cortex activation during silent subtraction by sevens in healthy adults. The task was presented verbally and required a spoken verbal answer. Time to completion was used for the group comparisons.

Controlled Oral Word Association Test: (Benton & Hamsher, 1989). This is a standardized test of verbal (phonemic) fluency. Participants were required to generate words beginning with a particular letter (F, A, S) and the total number correct was recorded.

Verbal Functioning

Similarities, Wechsler Adult Intelligence Scale III: (WAIS-III; Wechsler, 1997). This is the standard measure of abstract verbal reasoning, in which participants were required to identify categorical similarities between verbally presented pairs of objects or concepts. Total number of points was recorded.

The Boston Naming Test: (BNT) (Kaplan, Goodglass H., & Weintraub S., 1983) is a test of confrontation naming, in which the participant names 60 black and white line drawings of objects presented one at a time. The total number correct was recorded.

Number Processing

Number Reasoning Test: This is a shorter version of the Number Reasoning Test adapted from Langdon and Warrington (1997). This test consists of 10 graded-difficulty reasoning items. Each item consists of three numbers from a progressive series. They range in difficulty from a simple arithmetic series (i.e., 1, 2, 3, _) to a complex geometric series (2, 4, 8, _). The participant is required to select a fourth number to complete the series from a multiple choice of 4 numbers. There are two practice items. This number reasoning test minimizes demands on attentional and language skills. Total correct and time to completion were recorded and used for group comparisons.

Subtracting from 100 by 7's: This test is described above. The number of errors was recorded as the comparison between groups.

Mental Number Line Bisection: Participants are required to identify the midpoint of a pair of numbers (11–17; 23–29; etc). Errors and direction of deviations were recorded. Psychophysical evidence suggests that the mental representation of numbers has a spatial nature, possibly with a left–right orientation (Seron, Pesenti, Noël, Deloche, & Cornet, 1992). Zorzi et al. (2002) demonstrated right parietal involvement in a mental number bisection task. Their patients with right parietal lesions showed a spatial deficit in the line bisection task and a similar deficit when bisecting the mental number line.

Physical Number Line Orientation: This measure assesses visual number line orientation. In each of 10 trials per condition, the participant places a mark that corresponds to a spoken numeral (e.g., of the set 7, 16, 21, etc.; order randomized) on a horizontally or vertically oriented number line (from 0 to 100), one at a time, each on a separate page. Each line (20 cm in length) was printed in the center of a white 8 ½ × 11" paper. The page was placed in front of the participant, opposite the body midline (viewing distance about 50 cm). Accuracy was calculated as degree of deviation from the target placement. Direction of the deviations was also recorded.

Visuospatial Functioning

Physical Line Bisection: Ten horizontal lines of 1 mm width, and varying lengths, ranging from 80 to 170 mm, increasing in 10 mm increments, were presented in random order. Each line was printed in the center of a white 8 ½ ×11" paper. The page was placed in front of the participant, opposite the body midline (viewing distance about 50 cm). Participants were asked to mark the subjective center of each line using a pen. A percent deviation score was calculated for each line as 100 × ([measured left half − true half]/true half). Information regarding the direction of the deviations was also recorded. Sheppard, Bradshaw, and Mattingley (2002) examined line bisection judgments in another frontostriatal disorder, Tourette's syndrome. Their findings suggested a deficit in visuospatial attention consistent with dysfunction of frontostriatal circuitry in Tourette's syndrome. Similar findings have been reported in Parkinson's disease, which likewise is associated with frontostriatal dysfunction (Lee, Harris, Atkinson, & Fowler, 2001).

Raven's Coloured Progressive Matrices (RCPM): (Raven, 1965). This standard measure requires the performance of visual closure and spatial analogies, thereby assessing visuospatial skills and reasoning ability. The task is to choose one of six possible completions of an incomplete pattern matrix. All trials are untimed. Each subtest has 12 items; total score (the number correct out of 36 items) was recorded.

Visual Symbol Search Test: (Mesulam, 1985) provides a measure of visual scanning abilities and sustained attention. Participants search and cancel the target symbol in the non-verbal array. The time to completion was recorded and used for the group comparison.

Right-Left Orientation Subtests, Boston Visuospatial Quantitative Battery: (BVSQB; Goodglass & Kaplan, 1983). These tests (I. Body parts and II. Body parts + objects) assess right-left orientation with reference to the body parts (hand, knee, eye, etc.), and require the identification of right and left on 20 different body parts and objects drawn in various positions. The number of errors was recorded. Right-left discrimination may be disrupted by left posterior lesions (Lezak et al., 2004).

Drawing Subtest, BVSQB: (Goodglass & Kaplan, 1983). On the "Drawing to command" subtest the participant is required to draw six objects, one at a time. Total number of points was recorded. Visuo-constructional abilities are the most vulnerable to the injuries of both frontal and parietal lobes.

Rey-Osterrieth Complex Figure Drawing Test (ROCF): (Osterrieth, 1944). Constructional praxis, or the ability to copy or draw designs, was assessed with the copy condition of this standardized test of abstract figure drawing, which involves copying from the image presented in front of the participant. We employed the commonly-used 36-point scoring system evaluating the presence and accuracy of the 18 elements of the ROCF (Taylor, 1991), and a total score was recorded.

Memory

Verbal Memory Tests: ***Logical Memory Subtests, Wechsler Memory Scale III:*** (WMS-III; Wechsler, 1997). This test assesses the ability to learn and spontaneously recall details of narrative material presented orally in paragraphs immediately after presentation (Logical Memory 1 [LM1]) and after a 25 minutes delay (Logical Memory 2 [LM2]). Number correct on recognition trials was also recorded.

Visuospatial Memory Tests: ***Rey-Osterrieth Complex Figure Drawing Test:*** Same as above except participants were asked to recall the figure by re-drawing it immediately after copying (incidental) and again after 25 minutes (delayed recall). Total score was recorded.

Psychomotor Functioning

Purdue Pegboard Test: (Tiffin, 1968) is a measure of psychomotor speed, wherein participants fit small pegs into holes on a board, using the preferred, non-preferred, and finally both hands together to fill two rows (top to bottom) within a 30-second time period (described in Spreen & Strauss, 1998). Total number of pegs inserted was recorded for each condition. Patients with Parkinson's disease demonstrate impairment of bimanual movements on this test (Brown, Jahanshahi, & Marsden, 1993). We report bimanual scores.

RESULTS

This study used a within-subject design, with each participant receiving all assessments. For each analysis, the Bonferroni correction of alpha was applied when appropriate. Analyses of performance between right-handers (n=29) and left-handers/mixed handedness (n=8) in the HIV+ sample revealed no significant differences in neuropsychological profile or mood ratings. Data were accordingly collapsed across handedness. The left-handers/mixed hand preference subgroup was not included in the analysis of "number lines" because these tests are sensitive to handedness/cerebral asymmetry.

For clarity of presentation, results are divided into two sections. The first section presents findings regarding the effects of HIV+ on cognitive function. The second section specifically addresses performance on physical and mental number line orientation tasks, and the relation between numerical and spatial processing.

Effect of HIV+ on Cognitive Function

Neuropsychological Findings—To examine whether the HIV+ group exhibited cognitive deficits compared to the HIV− group, we conducted independent groups t-tests across neuropsychological assessments (see Table 2). Alpha was adjusted to *.002* (.05/25) to account for multiple comparisons. For all comparisons, the HIV+ group performed more poorly than the HIV− group. Significant group differences were found on measures of attention and executive function, number processing, visuospatial functioning, and visuospatial memory abilities. There were no significant differences observed for tests of verbal functioning, verbal memory, or psychomotor functioning. These findings support our hypothesis that deficits observed in HIV+ are specific to domains subserved by frontostriatal and parietal circuitry.

Visuospatial and Reasoning Abilities—Pearson correlations were performed to examine the relation between visuospatial abilities (RCPM) and number reasoning (Number Reasoning Test), and visuospatial (RCPM) and verbal reasoning (WAIS-III Similarities) in each group. As predicted, performance on the RCPM significantly correlated with the Number Reasoning Test (time) in the HIV− group [$r(35) = -.39$, $p < .04$], and the Number Reasoning Test (total score) in the HIV+ group [$r(35) = .42$, $p < .028$], demonstrating that the two types of reasoning abilities are functionally related. There were, however, no significant correlations between WAIS-III Similarities and the RCPM in either group (HIV−, $r = .23$, $p > .27$; HIV+, $r = .37$, $p > .06$) supporting the lack of a relation between visuospatial and verbal reasoning abilities.

Number Line Exploration

Physical and Mental Number Line Orientation—Pearson correlations were performed to investigate hypotheses pertaining to the relation between physical and mental number line processing abilities in HIV− and HIV+ individuals. These findings are summarized in Table 3. As depicted under the heading "Degree of Bias," the Horizontal Physical Number Line (% dev) was positively correlated with the Vertical Physical Number Line (% dev) for both the HIV− [$r(30) = .52$, $p < .003$] and HIV+ [$r(27) = .47$, $p < .012$] groups. This supports the hypothesis that the physical number line has similar numerical and spatial properties in both horizontal and vertical orientations.

To demonstrate that the physical number line has numerical and spatial properties similar to those of the mental number line, Pearson correlations were performed between performance on the Horizontal Physical Number Line (% dev) and the Mental Number Line Bisection (errors) tasks for both groups. Results indicated a significant positive correlation for the HIV − group [$r(30) = .41$, $p < .032$] and no correlation for the HIV+ group [$r(27) = -.05$, $p = .80$]. The lack of a correlation in the HIV+ group demonstrates the dissociation between the physical and mental number line processing in this sample.

The correlation between Horizontal Physical Number Line (% dev) and Physical Line Bisection (% dev) was positive for the HIV− group [$r(30) = .59$, $p < .001$], with no correlation for the HIV+ group [$r(27) = -.01$, $p = .96$]. Combined with the results above, a clear pattern emerges. For the HIV− group, results support the hypotheses that active direct exploration and manipulation of both physical and mental number lines involves the same attentional orienting bias, and operation within the physical number line may rely on neural networks involved in both physical and mental number line orientation. Lack of a correlation for the HIV+ group is evidence supporting a dissociation in this group between physical and mental number line orientation.

As depicted in Table 3 under the heading "Direction of Bias," Pearson correlations for the HIV − group revealed significant relations between Horizontal Physical Number Line (leftward bias) and Vertical Physical Number Line (downward bias: $r(30) = .47$, $p < .014$), Mental

Number Line Bisection (leftward bias: $r(30) = .41$, $p < .034$), and Physical Line Bisection (leftward bias: $r(30) = .53$, $p < .004$), suggesting that the internal mental number line mechanism was activated during these tasks, and that it can be mentally rotated in more than one dimension. Similar results were not found for the HIV + group (correlations of $r(27) = .27$, $p = .17$, $r(27) = .14$, $p = .50$, and $r(27) = -.07$, $p = .73$, respectively), demonstrating the selective impact of HIV+ on spatial and numerical cognition. Overall and as predicted, both groups demonstrated leftward bias (pseudo-neglect) on the Horizontal Physical Number Line Orientation task, with the HIV+ group exhibiting significantly greater leftward bias [$t(59) = -3.74$, $p < .001$] than the HIV− group.

Mental Number Line Bisection—To explore the contribution of the frontostriatal and parietal areas implicated in mental number line processing, we performed Pearson correlations between Mental Number Line Bisection performance and measures of verbal working memory (WMS-III Digit Span Backward), spatial working memory (WMS-III Spatial Span Backward), and visuospatial functions (i.e., reasoning – RCPM, left-right orientation – BVSQB R-L Orientation). As depicted in Table 4, there were different patterns of performance for the two groups: Mental Number Line Bisection (errors) significantly correlated with performance on tests of both verbal and spatial working memory in the HIV− group, whereas the HIV+ group showed significant correlations between the number of errors and performance on measures of visuospatial abilities. These results support frontostriatal and parietal network involvement in mental number line orientation, and point to a dissociation between the processing components of numerical distance (working memory and spatial processing) in HIV.

Physical Number Lines—To further investigate the nature of the relation between different processing components involved in the Physical Number Line task (numerical, spatial, and executive [mental manipulation/rotation] processing), we examined performance on the Horizontal and Vertical Physical Number Lines. As expected, there was a significant correlation between performance on the Horizontal Physical Number Line task and the Number Reasoning task for both HIV− [$r(30) = .44$, $p < .016$] and HIV+ groups [$r(27) = .54$, $p < .003$], demonstrating that both visually presented numerical tasks involve the activation of a mental number line. There were no correlations between the Physical Number Lines (both Vertical and Horizontal) and working memory tasks (WMS-III Digit [all *r's* < .05, *p's* > .78] and Spatial Spans [all *r's* < .23, *p's* > .20]) for the HIV− group. The HIV+ group showed a significant correlation between the Vertical Physical Number Line task and the Backward Spatial Span [$r(27) = -.43$, $p < .023$], as well as Trails B [$r(27) = -.39$, $p < .049$]. Additionally, the HIV+ group showed a significant correlation between the Horizontal Physical Number Line task and the Visual Symbol Search Task, a test of visual scanning and sustained attention [$r(27) = .60$, $p < .001$]. These results show that in the HIV+ group, unlike the HIV− group, visuospatial and executive components influence Physical Number Line processing, demonstrating the vulnerability and breakdown of these systems in HIV.

Additional correlations revealed significant relations between the degree of deviation on the Vertical Physical Number Line task and the performance (number of errors) on the Mental Number Line Bisection task in the HIV+ group [$r(27) = .46$, $p < .019$], and also between downward bias on the Vertical Physical Number Line task and leftward bias on the Mental Number Line Bisection task in the HIV+ group [$r(27) = .66$, $p < .001$]. There was also a predicted correlation in the HIV+ group between the Vertical Physical Number Line task and visuospatial reasoning (RCPM) [$r(27) = -.44$, $p < .023$]. These correlations were not observed in the HIV− group (all *r*'s < .15, *p*'s > .43). These results point to greater specific visuospatial and executive involvement in HIV+, and suggest that an additional spatial processing component may be involved in this task, such as mental manipulation or rotation of the stimuli.

Physical Line Bisection—As expected, there were no correlations between performance on the Physical Line Bisection task and Mental Number Line Bisection task for either group (all r's < .22, p's > .27). In contrast to the results of Mental Number Line Bisection task, there were no correlations between performance on the Physical Line Bisection task and working memory tasks (WMS-III Backward Digit and Spatial Spans) for either group (all r's < .21, p's > .30). These findings suggest differential contributions of visuospatial and executive processing components to these two bisection tasks.

Cognitive Functioning and HIV Markers—In line with our prediction of the impact of HIV infection on number processing, significant correlations were noted between CD4 count and performance on the Number Reasoning task (total correct) [$r(35) = .43$, $p < .007$], and between disease duration (years) and performance on the Mental Number Line Bisection task (errors) [$r(27) = .45$, $p < .008$) for the HIV+ participants. There were no correlations between performance on any of the neuropsychological measures and viral load (all p's > .05).

DISCUSSION

We examined cognitive performance in individuals with asymptomatic HIV, specifically number processing and its relation to visuospatial processing. Our findings demonstrated the effect of HIV infection on cognition. First, the results of this study showed HIV-related changes in multiple cognitive domains on the early, asymptomatic stage of the disease. Second, the specific affected domains included executive function, visuospatial functioning, and number processing, which is reflective of frontostriatal and parietal dysfunction associated with HIV. Third, our results demonstrated that HIV-related damage to the brain can produce selective disruption of fronto-parietal cortico-subcortical neural pathways underlying numerical processing. Finally, our findings show that HIV infection can alter the spatial representation of numerical distance in asymptomatic HIV+ participants.

Our findings also address several aspects of number processing and visuospatial function. They provide evidence for the spatial organization of the mental number line. As well, the results demonstrate that the physical number line preserves the integrity of its spatial organization regardless of the actual physical space coordinates. Whether the number line is horizontally or vertically presented, it can be similarly navigated, as all participants exhibited similar underestimation of the numerical distance, i.e. leftward bias (for horizontal presentation) and downward bias (for vertical presentation), which may represent pseudo-neglect under both conditions. The results imply a dissociation between the processing components of numerical distance (Horizontal Number Line) and physical space (Line Bisection), suggesting differentiation between the neural networks involved in number line and physical line orientation. In HIV, this finding provides evidence for selective disruption of fronto-parietal cortico-subcortical neural pathways underlying numerical distance processing.

Neuropsychological Findings

The asymptomatic HIV+ participants exhibited specific cognitive deficits in the executive, number processing, and visuospatial domains. These results are in accord with recent studies implicating frontostriatal and parietal regions in HIV (see Introduction). Verbal processing domains remained intact in our asymptomatic HIV+ group, thereby providing additional support for the specificity of the brain regions affected by HIV. These findings expand our understanding of the impact of HIV on cognition and indicate that HIV infection affects brain functioning subserving these domains in the early, asymptomatic stage of the disease.

Relation of Spatial and Numerical Cognition

The impact of HIV on the neural mechanisms underlying visuospatial functioning led us to hypothesize that number processing, with its close functional relation to the spatial domain, would also be affected by HIV. Supporting this hypothesis, the HIV+ group's performance on visuospatial and number processing tasks was significantly slower and was characterized by a higher number of errors compared to the HIV− group. Correlational analyses revealed close relations between number processing and visuospatial performance in both groups. These findings demonstrate the impact of HIV on spatial and numerical cognition, and provide additional evidence for the functional relation between these domains in healthy adults. Furthermore, these results support our hypothesis that HIV infection affects numerical cognition and visuospatial functioning on early stages of the disease, due to the impact of HIV on frontostriatal circuits and their parietal cortical projections.

Number Lines

To further investigate the nature of the relation between numerical and visuospatial cognitive domains, we explored the concept of mental number line and its relation to visuospatial processing. We examined number line orientation in several modalities: mental number line bisection, number line orientation on visually presented physical number lines (horizontal and vertical), and [visual] physical line bisection.

The issue of left-to-right mental number line orientation is still debated in the field of numerical cognition. While some studies presented evidence of left-to-right organization of the horizontal mental number line (reviewed earlier), other investigators proposed an independent, vertical mental number line with bottom-to-top organization (Cappelletti et al., 2007). Cappelletti (2007) reported a dissociation between horizontal and vertical mental number line bisection in neglect patients, and suggested that there may be separate internal horizontal and vertical mental number line representations analogous to physical horizontal and vertical lines.

The previous research on the SNARC effect, studies of neglect patients, and our preliminary study led us to hypothesize that the internal (mental) number line can be applied (or mentally rotated) along vertical and horizontal dimensions, while preserving its numerical integrity and spatial organization. To test this hypothesis, we presented the visual physical number lines along two dimensions: horizontal and vertical. The results confirmed our prediction that participants would exhibit the same directional bias on mental and physical number lines in the vertical as well as the horizontal orientation. Both groups underestimated numerical distance, showing leftward and downward bias on the horizontal and vertical visual number lines, respectively. These results are in accordance with Longo and Lourenco (2007), who demonstrated that pseudoneglect can be observed in representational spaces, such as the mental number line. Our study examined physical number line processing in asymptomatic HIV+ and healthy HIV− individuals using horizontal–vertical orientations. The results of the present study support our hypothesis of the unity of the internal mental number line that can be applied to multiple dimensions (vertical and horizontal in this study) while preserving its spatial and numerical integrity, and provide support to the notion of the spatial representation of the mental number line.

For the HIV+ group there was also a significant correlation between leftward bias on the Mental Number Line and downward bias on the Vertical Visual Number Line. These findings further support our hypothesis that the internal mental number line preserves its numerical properties and spatial integrity in both vertical and horizontal orientations, and support the spatial-numerical interaction representation of the mental number line.

As expected, there were significant relations between the Horizontal Physical Number Line task and Number Reasoning task for both HIV− and HIV+ groups, as both tasks involve the activation of a mental number line while processing visually presented numerical tasks. The lack of a correlation between the Vertical Physical Number Line task and Number Reasoning task may be attributed to the additional visuospatial processing component involved in this task (Vertical Physical Number Line), such as mental manipulation or rotation of the stimuli. The observed correlation between the Vertical Physical Number Line and a visuospatial reasoning task (RCPM) in the HIV+ group provides additional evidence to that assumption, and points to greater specific visuospatial and executive involvement in HIV. Additionally, the HIV+ group showed a significant correlation between the Horizontal Physical Number Lines and the Visual Symbol Search task (a test of visual scanning and sustained attention), which further confirms the vulnerability of spatial and executive processing components in HIV.

A different pattern of performance of the HIV+ group (as compared to HIV− group) on the Vertical Physical Number Line Orientation task provides evidence that despite a strong correlation between vertical and horizontal physical number line tasks and the mental number line task, the internal mental number line activation and manipulation in horizontal orientation involves an additional processing component, similar to mental manipulation/rotation and subserved by frontostriatal and parietal networks.

Taken together, our findings provide support for the isomorphism hypothesis of internal mental number line organization, which postulates that the mental number line organization strongly resembles the structure of a physical line. Our results also suggest an additional processing component involved in the vertical number line orientation, providing partial support for the interpretation of the reported dissociation between horizontal and vertical neglect (Cappelletti et al., 2007).

It is of interest that the HIV+ group showed significantly greater leftward bias than the HIV− group, which is in accord with the recent neuroimaging findings. Neuroimaging studies (fMRI) demonstrating increased brain activation during cognitive tests in asymptomatic HIV+ individuals have suggested that early injury to the neural substrate may necessitate increased usage of brain reserve to maintain normal cognitive function (Chang et al., 2001; Ernst et al., 2002). More recent neuroimaging studies suggest that the HIV+ group may over-activate the “challenged” neural network/s in order to compensate for the (mild) deficit (Daselaar, Prince, & Cabeza, 2004), and demonstrate altered activation of frontal and parietal areas in HIV+ individuals with neuropsychological performance within normal limits (Castelo et al., 2006).

Physical Line Bisection

Our healthy HIV− participants showed similar leftward bias (pseudoneglect) on physical line bisection and on mental number line bisection tasks, which is consistent with recent findings of Gobel et al. (2006) and Longo and Lourenco (2007) in healthy adults. The observed correlation between directional bias on physical line bisection and on mental number line bisection tasks shows a close functional relation between spatial and numerical processing and again supports the notion for the spatial representation of the mental number line. The HIV− group showed significant positive correlation between the degree of deviation on Physical Line Bisection and Horizontal Visual Number Line tasks. HIV− participants also showed a significant correlation in regard to leftward bias on these tasks.

HIV+ participants exhibited similar (leftward) bias on both the Physical Line Bisection and Mental Number Line Bisection task. The observation that the HIV+ group also did not demonstrate a close relation between physical line bisection and physical number lines or mental number line biases provides evidence for the dissociation between the number line (both physical and mental) and physical line orientation in the HIV+ group.

As expected, there were no correlations between performance on Physical Line Bisection and working memory tasks for both groups. There was however, a significant correlation between Physical Line Bisection and Trails B, a measure of combined visual search, psychomotor speed, and cognitive flexibility, for the HIV+ group. This finding once again highlights the involvement of a visuospatial component, in particular visual search, in HIV.

Our results demonstrate a dissociation between the processing components of numerical distance and physical space, suggesting differentiation between the neural networks involved in number line and physical line orientation. These findings provide evidence for selective disruption of neural pathways underlying numerical distance processing in HIV, in particular, frontostriatal and parietal circuits.

Mental Number Line

Previous research (Doricchi et al., 2005) indicated that mechanism of mental number line bisection processing is different from that of physical line bisection. The investigators suggested that the navigation along the mental number line and its bisection relies on spatial working memory mechanisms, supported by prefrontal areas.The investigators argued that pathological bias was due to the damage to the ventrolateral prefrontal cortex, which has been implicated in the short-term processing of contralateral spatial positions (Rizzuto, Mamelak, Sutherling, Fineman, & Andersen, 2005). Our findings are in accord with the previous research, as the HIV− group in our study showed a significant correlation between performance on tests of working memory and the Mental Number Line Bisection task but not the Physical Line Bisection task.

The two groups showed different patterns of performance on the Mental Number Line Bisection task. While the HIV− group's performance significantly correlated with tests of verbal, spatial and number–related working memory, the HIV+ group's performance revealed a significant correlation with the number–related working memory test and measures of visuospatial abilities. These results show a dissociation between the processing components of numerical distance in HIV (working memory components and spatial processing), and suggest frontal and parietal network involvement in mental number line orientation.

The observed significant correlation between spatial reasoning and number reasoning abilities in both groups, and lack of significant correlations between verbal and spatial reasoning in either group, provide further support for close and distinctive functional relations between numerical and visuospatial processing.

Conclusions

There have been significant advances in the last several years in our understanding of cognition in HIV, with most research focusing on functions that are dependent upon the integrity of frontostriatal systems. Our study has documented functional deficits in visuospatial and number processing, suggesting involvement beyond frontostriatal regions to include parietal cortex. These findings support our recent studies of visuospatial dysfunction in asymptomatic HIV+ patients (Bogdanova & Cronin-Golomb, 2005; Olesen et al., 2007), while extending our understanding to the domain of number processing.

This investigation addressed several aspects of number processing and visuospatial function besides disease-related effects. Our findings provided evidence for the spatial organization of the mental number line, and showed that direct exploration of both physical and mental number lines involves the same attentional orienting bias in healthy adults. They suggested that the physical number line orientation relies on neural networks involved in both physical line and mental number line bisection. The results demonstrated that the internal mental number line preserves its numerical and spatial integrity in both the vertical and horizontal physical dimensions. They further revealed a dissociation between the processing components of numerical distance and physical space, suggesting differentiation between the neural networks involved in number line and physical line orientation. In regard to HIV, these findings show that HIV-related damage to the brain can alter the spatial representation of numerical distance, providing evidence for selective disruption of frontal and parietal pathways underlying numerical distance processing in HIV.

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REFERENCES

Armitage SG. An analysis of certain psychological tests used for the evaluation of brain injury. Psychological Monographs 1946;60(1, Serial No. 277)

Benton AL. Gerstmann's syndrome. Arch Neurol 1992;49(5):445–447. [PubMed: 1580804]

Benton, AL.; Hamsher, Kd. Multilingual Aphasia Examination. Iowa City, Iowa: AJA Associates; 1989.

Berch DB, Foley EJ, Hill RJ, Ryan PM. Extracting parity and magnitude from Arabic numerals: developmental changes in number processing and mental representation. J Exp Child Psychol 1999;74 (4):286–308. [PubMed: 10552920]

Berger JR, Nath A. HIV dementia and the basal ganglia. Intervirology 1997;40(2–3):122–131. [PubMed: 9450229]

Berger JR, Nath A, Greenberg RN, Andersen AH, Greene RA, Bognar A, et al. Cerebrovascular changes in the basal ganglia with HIV dementia. Neurology 2000;54(4):921–926. [PubMed: 10690987]

Bisiach, E.; Vallar, G. Unilateral neglect in humans. In: Boller, F.; Grafman, J., editors. Handbook of neuropsychology. Amsterdam: Elsevier; 2000. p. 459-502.

Bogdanova, Y.; Cronin-Golomb, A. Abstract Viewer/Itinerary Planner. Washington, DC: Society for Neuroscience Program No. 877.31; 2005. Numerical cognition in HIV.

Bogdanova, Y.; Diaz-Santos, M.; Cronin-Golomb, A. Relationship of alexithymia to cognition in asymptomatic individuals with HIV. Abstracts, International Neuropsychological Society 35th Annual Meeting; 2007.

Bornstein RA, Nasrallah HA, Para MF, Whitacre CC, Rosenberger P, Fass RJ. Neuropsychological performance in symptomatic and asymptomatic HIV infection. AIDS 1993;7(4):519–524. [PubMed: 8507418]

Bowers D, Heilman KM. Pseudoneglect: Effects of hemispace on a tactile line bisection task. Neuropsychologia 1980;18(4–5):491–498. [PubMed: 6777712]

Brown RG, Jahanshahi M, Marsden CD. The execution of bimanual movements in patients with Parkinson's, Huntington's and cerebellar disease. J Neurol Neurosurg Psychiatry 1993;56(3):295–297. [PubMed: 8459247]

Caessens B, Hommel B, Reynvoet B, van der Goten K. Backward-compatibility effects with irrelevant stimulus-response overlap: the case of the SNARC effect. J Gen Psychol 2004;131(4):411–425. [PubMed: 15523822]

Cappelletti M, Freeman ED, Cipolotti L. The middle house or the middle floor: Bisecting horizontal and vertical mental number lines in neglect. Neuropsychologia 2007;45(13):2989–3000. [PubMed: 17640687]

Castelo JM, Courtney MG, Melrose RJ, Stern CE. Putamen hypertrophy in nondemented patients with human immunodeficiency virus infection and cognitive compromise. Arch Neurol 2007;64(9):1275–1280. [PubMed: 17846265]

Castelo JM, Sherman SJ, Courtney MG, Melrose RJ, Stern CE. Altered hippocampal-prefrontal activation in HIV patients during episodic memory encoding. Neurology 2006;66(11):1688–1695. [PubMed: 16769942]

CDC. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults; Morbidity and Mortality Weekly Report. 1992. p. 1-19.

Chang L, Lee PL, Yiannoutsos CT, Ernst T, Marra CM, Richards T, et al. A multicenter in vivo proton-MRS study of HIV-associated dementia and its relationship to age. Neuroimage 2004;23(4):1336–1347. [PubMed: 15589098]

Chang L, Speck O, Miller EN, Braun J, Jovicich J, Koch C, et al. Neural correlates of attention and working memory deficits in HIV patients. Neurology 2001;57(6):1001–1007. [PubMed: 11571324]

Daselaar SM, Prince SE, Cabeza R. When less means more: deactivations during encoding that predict subsequent memory. Neuroimage 2004;23(3):921–927. [PubMed: 15528092]

Dehaene S. Varieties of numerical abilities. Cognition 1992;44(1–2):1–42. [PubMed: 1511583]

Dehaene S, Bossini S, Giraux P. The mental representation of parity and numerical magnitude. J. Exp. Psychol. Gen 1993;122:371–396.

Dehaene S, Cohen L. Cerebral pathways for calculation: double dissociation between rote verbal and quantitative knowledge of arithmetic. Cortex 1997;33(2):219–250. [PubMed: 9220256]

Dehaene S, Dupoux E, Mehler J. Is numerical comparison digital? Analogical and symbolic effects in two-digit number comparison. J Exp Psychol Hum Percept Perform 1990;16(3):626–641. [PubMed: 2144576]

Dehaene S, Molko N, Cohen L, Wilson AJ. Arithmetic and the brain. Curr Opin Neurobiol 2004;14(2):218–224. [PubMed: 15082328]

Dehaene S, Piazza M, Pinel P. Three parietal circuits for number processing. Cognitive Neuropsychology 2003;20:487–506.

Dehaene S, Spelke E, Pinel P, Stanescu R, Tsivkin S. Sources of mathematical thinking: behavioral and brain-imaging evidence. Science 1999;284(5416):970–974. [PubMed: 10320379]

Doricchi F, Angelelli P. Misrepresentation of horizontal space in left unilateral neglect: role of hemianopia. Neurology 1999;52(9):1845–1852. [PubMed: 10371533]

Doricchi F, Guariglia P, Gasparini M, Tomaiuolo F. Dissociation between physical and mental number line bisection in right hemisphere brain damage. Nat Neurosci 2005;8(12):1663–1665. [PubMed: 16261135]

Ernst T, Chang L, Jovicich J, Ames N, Arnold S. Abnormal brain activation on functional MRI in cognitively asymptomatic HIV patients. Neurology 2002;59(9):1343–1349. [PubMed: 12427881]

Fias, W.; Fischer, MH. Spatial representation of numbers. In: Campbell, JID., editor. Handbook of Mathematical Cognition. New York: Psychology Press; 2005. p. 43-54.

Fink GR, Marshall JC, Shah NJ, Weiss PH, Halligan PW, Grosse-Ruyken M, et al. Line bisection judgments implicate right parietal cortex and cerebellum as assessed by fMRI. Neurology 2000;54 (6):1324–1331. [PubMed: 10746605]

Fink GR, Marshall JC, Weiss PH, Zilles K. The neural basis of vertical and horizontal line bisection judgments: an fMRI study of normal volunteers. Neuroimage 2001;14(1 Pt 2):S59–S67. [PubMed: 11373134]

Galton F. Visualised numerals. Nature 1880;21:252–256.

Gerstmann J. Syndrome of finger agnosia, disorientation for right and left, agraphia, acalculia. Arch. Neurol. Psychol 1940;44:398–408.

Gobel SM, Calabria M, Farne A, Rossetti Y. Parietal rTMS distorts the mental number line: Simulating `spatial' neglect in healthy subjects. Neuropsychologia 2006;44(6):860–868. [PubMed: 16260006]

Goodglass, H.; Kaplan, E. Vol. 2nd ed. Philadelphia: Lea and Febiger; 1983. The assessment of aphasia and related disorders.

Heaton RK, Grant I, Butters N, White DA, Kirson D, Atkinson JH, et al. The HNRC 500--neuropsychology of HIV infection at different disease stages. HIV Neurobehavioral Research Center. J Int Neuropsychol Soc 1995;1(3):231–251. [PubMed: 9375218]

Hubbard EM, Piazza M, Pinel P, Dehaene S. Interactions between number and space in parietal cortex. Nat Rev Neurosci 2005;6(6):435–448. [PubMed: 15928716]

Izard V, Dehaene S. Calibrating the mental number line. Cognition In Press, Corrected Proof :1106.

Kageyama S, Imagase M, Okubo M, Takayama Y. Neglect in three dimensions. Am J Occup Ther 1994;48 (3):206–210. [PubMed: 8178913]

Kori A, Geldmacher DS. Three-dimensional neglect phenomena following right anterior choroidal artery infarction. J Int Neuropsychol Soc 1999;5(6):567–571. [PubMed: 10561938]

Langdon DW, Warrington EK. The abstraction of numerical relations: a role for the right hemisphere in arithmetic? J Int Neuropsychol Soc 1997;3(3):260–268. [PubMed: 9161105]

Lee AC, Harris JP, Atkinson EA, Fowler MS. Evidence from a line bisection task for visuospatial neglect in left hemiparkinson's disease. Vision Res 2001;41(20):2677–2686. [PubMed: 11520513]

Lezak, MD.; Howieson, DB.; Loring, DW. Neuropsychological assessment. Vol. fourth ed.. New York: Oxford University Press; 2004.

Longo MR, Lourenco SF. Spatial attention and the mental number line: Evidence for characteristic biases and compression. Neuropsychologia 2007;45(7):1400–1407. [PubMed: 17157335]

Luria, AR. K patologii schetnih operacii [Pathology of calculation]. Moscow: Academy of Pedagogical Science Press; 1945.

Luria, AR. Visshie Korkovie Funkcii Cheloveka [Higher Cortical Functions in Man]. Moscow: Moscow University Press; 1962.

Mayer E, Martory MD, Pegna AJ, Landis T, Delavelle J, Annoni JM. A pure case of Gerstmann syndrome with a subangular lesion. Brain 1999;122(Pt 6):1107–1120. [PubMed: 10356063]

Mesulam, M-M. Attention, confusional state, and attention. In: Mesulam, M-M., editor. Principles of behavioral neurology. Philadelphia: F.A Davis Company; 1985.

Nelson, HE. National Adult Reading Test (NART): Test manual. Windsor, U.K.: NFER-Nelson; 1982.

Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 1971;9(1):97–113. [PubMed: 5146491]

Olesen PJ, Schendan HE, Amick MM, Cronin-Golomb A. HIV infection affects parietal-dependent spatial cognition: Evidence from mental rotation and hierarchical pattern perception. Behavioral Neuroscience 2007;121(6):1163–1173. [PubMed: 18085869]

Opfer, JE.; Thompson, CA. Even early representations of numerical magnitude are spatially organized: Evidence for a directional magnitude bias in pre-reading preschoolers; Paper presented at the XXVIII Cognitive Science Society; 2006.

Osterrieth PA. Le test de copie d'une figure complexe. Archives de Psychologie 1944;30:206–356.

Paul R, Cohen R, Stern R. Neuropsychiatric and neurobehavioral functioning in human immunodeficiency virus. CNS Spectrums 2003;7(12):8600–8866.

Paul R, Yiannoutsos CT, Miller EN, Chang L, Marra CM, Schifitto G, et al. Proton MRS and Neuropsychological Correlates in AIDS Dementia Complex: Evidence of Subcortical Specificity. J Neuropsychiatry Clin Neurosci 2007;19(3):283–292. [PubMed: 17827413]

Power C, Selnes OA, Grim JA, McArthur JC. HIV Dementia Scale: a rapid screening test. J Acquir Immune Defic Syndr Hum Retrovirol 1995;8(3):273–278. [PubMed: 7859139]

Priftis K, Zorzi M, Meneghello F, Marenzi R, Umilta C. Explicit versus implicit processing of representational space in neglect: dissociations in accessing the mental number line. J Cogn Neurosci 2006;18(4):680–688. [PubMed: 16768369]

Raven, JC. Guide to using the Coloured Progressive Matrices. London: H.K. Lewis; 1965.

Restle F. Speed of adding and comparing numbers. Journal of Experimental Psychology 1970;83(2):274–278.

Rizzuto DS, Mamelak AN, Sutherling WW, Fineman I, Andersen RA. Spatial selectivity in human ventrolateral prefrontal cortex. Nat Neurosci 2005;8(4):415–417. [PubMed: 15768035]

Rossetti Y, Jacquin-Courtois S, Rode G, Ota H, Michel C, Boisson D. Does action make the link between number and space representation? Visuo-manual adaptation improves number bisection in unilateral neglect. Psychol Sci 2004;15(6):426–430. [PubMed: 15147498]

Roux FE, Boetto S, Sacko O, Chollet F, Tremoulet M. Writing, calculating, and finger recognition in the region of the angular gyrus: a cortical stimulation study of Gerstmann syndrome. J Neurosurg 2003;99 (4):716–727. [PubMed: 14567608]

Rueckert L, Lange N, Partiot A, Appollonio I, Litvan I, Le Bihan D, et al. Visualizing cortical activation during mental calculation with functional MRI. Neuroimage 1996;3(2):97–103. [PubMed: 9345480]

Seron X, Pesenti M, Noël MP, Deloche G, Cornet JA. Cognition 1992;44:159–196. [PubMed: 1511585]

Sheppard DM, Bradshaw JL, Mattingley JB. Abnormal line bisection judgements in children with Tourette's syndrome. Neuropsychologia 2002;40(3):253–259. [PubMed: 11684158]

Spreen, O.; Strauss, E. A compendium of neuropsychological tests: Administration, norms and commentary. Vol. 2nd ed.. New York: Oxford University Press; 1998.

Taylor, LB. Scoring criteria for the ROCF. In: Spreen, O.; Strauss, E., editors. A compendium of neuropsychological tests: administration, norms, and commentary. New York: Oxford University Press; 1991.

Thompson PM, Dutton RA, Hayashi KM, Toga AW, Lopez OL, Aizenstein HJ, et al. Thinning of the cerebral cortex visualized in HIV/AIDS reflects CD4+ T lymphocyte decline. Proc Natl Acad Sci U S A 2005;102(43):15647–15652. [PubMed: 16227428]

Tiffin, J. Purdue Pegboard: Examiner Manual. Chicago: Science Research Associates; 1968.

Vallar G, Guariglia C, Magnotti L, Pizzamiglio L. Optokinetic stimulation affects both vertical and horizontal deficits of position sense in unilateral neglect. Cortex 1995;31(4):669–683. [PubMed: 8750025]

Walsh V. Cognitive neuroscience: numerate neurons. Curr Biol 2003;13(11):R447–R448. [PubMed: 12781156]

Wechsler, D. Vol. 3d ed.. San Antonio: The Psychological Corporation; 1997. The Wechsler Memory Scale-III Manual.

Zorzi M, Priftis K, Meneghello F, Marenzi R, Umilta C. The spatial representation of numerical and non-numerical sequences: Evidence from neglect. Neuropsychologia 2006;44(7):1061–1067. [PubMed: 16356515]

Zorzi M, Priftis K, Umilta C. Brain damage: neglect disrupts the mental number line. Nature 2002;417 (6885):138–139. [PubMed: 12000950]

Table 1

Participant demographic and immunological characteristics, group means (SD). Demographic data are presented for all participants, and immunological data are presented for HIV+ participants.

	HIV−	HIV+	*p*
DEMOGRAPHIC DATA			
N	37	37	
Age (years)	46.5 (6.6)	46.9 (6.2)	.76
Years of education	15.4 (2.0)	14.6 (1.8)	.09
Men: Women	21:16	28:9	
Right: Left/Mixed Handedness	32:5	29:8	
ANART	122.5 (7.5)	121.2 (6.9)	.49
IMMUNOLOGICAL DATA			
Years since diagnosis		12.02 (6.1)	
CD4 count (copies/mL)			
Group average		532.6 (235.1)	
# of times below 200		0.9 (2.0)	
Viral load			
Undetectable (<75 copies/mL)		N=22	
Low (<400 copies/mL)		N=2	
High (>400 copies/mL)		N=13	

p-values reflect results of independent sample t-tests.

All HIV+ participants were Stage A as determined by the CDC (1993) guidelines.

Table 2

Neuropsychological performance; raw score mean values (SD).

Measure (raw score)	**HIV−**	**HIV+**	***p***
Attention & Executive Function			
WMS-III Digit Span (total)	21.94 (5.3)	17.29 (4.0)	***.0001****
WMS-III Spatial Span (total)	16.71 (2.4)	13.16 (2.6)	***.0001****
Trails A (time in sec)	28.65 (9.5)	41.71 (16.6)	***.0001****
Trails B (time in sec)	56.58 (16.4)	89.54 (45.6)	***.0001****
Subtracting by 7's (time in sec)	48.25 (25.7)	85.74 (59.0)	***.001****
FAS (total)	51.7 (14.8)	39.97 (13.4)	***.002****
Verbal Functioning			
WAIS-III Similarities (total)	28.33 (4.0)	26.59 (3.6)	*.069*
BNT (total)	56.33 (3.2)	53.52 (4.2)	*.042*
Number Processing			
Number Reasoning Test (total correct)	11.34 (0.7)	10.54 (1.0)	***.0001****
Number Reasoning Test (time)	47.2 (18.8)	67.7 (23.1)	***.001****
Subtracting by 7's (errors)	0.61 (1.0)	2.54 (2.8)	***.0001****
Mental Number Line Bisection (errors)	0.93 (1.3)	3.0 (1.9)	***.0001****
Horizontal Physical Number Line (%dev)	27.06 (13.8)	49.36 (27.7)	***.0001****
Vertical Physical Number Line (%dev)	27.21 (12.2)	39.57 (14.9)	***.001****
Visuospatial Functioning			
Physical Line Bisection (%dev)	19.50 (7.8)	23.9 (7.8)	*.134*
RCPM (total)	34.67 (1.5)	30.78 (4.6)	***.0001****
Visual Symbol Search Test (time in sec)	71.61 (20.3)	95.82 (30.3)	***.001****
BVSQB R-L Orientation (errors)	1.72 (1.7)	4.14 (3.5)	***.0001****
BVSQB Drawing (total)	10.98 (1.9)	7.87 (3.2)	***.0001****
ROCF Copy (total)	31.89 (4.3)	29.25 (5.3)	*.025*
Memory			
Verbal Memory			
WMS LM 1 Immediate recall (total)	47.91 (5.5)	42.74 (9.0)	*.097*
WMS LM 2 Delayed recall (total)	30.45 (7.3)	24.94 (7.0)	*.056*
WMS LM Recognition (total)	27.25 (2.8)	26.39 (2.8)	*.419*
Visuospatial Memory			
ROCF Immediate recall (total)	20.41 (7.1)	14.93 (6.9)	***.002****
ROCF Delayed recall (total)	20.35 (6.0)	15.35 (7.2)	***.002****
Psychomotor Functioning			
Purdue Pegboard (total)	13.39 (2.3)	11.63 (1.9)	*.008*

p-values reflect results of independent sample *t*-tests, *alpha* was adjusted using Bonferroni correction to .002.

Table 3

Horizontal Visual Number Line correlations with the Vertical Visual Number Line, Mental Number Line, and Physical Line Bisection.

	HIV −	HIV+
DEGREE OF BIAS	Horizontal Physical Number Line (%dev)	
Vertical Physical Number Line (% dev)	***.52*** **	***.47*** **
Mental Number Line Bisection (errors)	***.41*** *	*−.05*
Physical Line Bisection (% dev)	***.59*** **	*−.01*
DIRECTION OF BIAS	*Horizontal Physical Number Line (leftward bias)*	
Vertical Physical Number Line (downward bias)	***.47*** **	*.27*
Mental Number Line Bisection (leftward bias)	***.41*** *	*.14*
Physical Line Bisection (leftward bias)	***.53*** **	*−.07*

* $p < .05$

** $p < .01$: %dev = % deviation from the target number or true midline.

Table 4

Correlations between number of errors on the Mental Number Line Bisection task and performance on measures of verbal working memory (WMS-III Digit Span), spatial working memory (WMS-III Spatial Span), and visuospatial functions (reasoning, RCPM; visual right-left orientation, BVSQB R-L orientation).

	Mental Number Line Bisection (errors)	
	HIV−	**HIV+**
WORKING MEMORY		
Digit Span Backward (total)	***−.44****	*−.02*
Spatial Span Backward (total)	***−.45****	*−.09*
VISUOSPATIAL FUNCTIONS		
Spatial Reasoning (RCPM, total)	*−.32*	***−.46****
BVSQB R-L Orientation (time)	*−.19*	***−.46****

* $p < .05$