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Original Article

Poor Aerobic Fitness May Contribute to Cognitive Decline in HIV-infected Older Adults

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ABSTRACT: The HIV-infected older adult (HOA) community is particularly vulnerable to cognitive impairment. Previous studies in the general older adult population have reported that lower scores on tests of cognitive function often correlate negatively with aerobic fitness [5-7]. HIV-infected individuals have significantly reduced aerobic fitness and physical function compared to HIV-uninfected individuals. Determining important correlates of cognitive ability may be beneficial in not only detecting precursors to future cognitive impairments, but also target areas for interventions. The purpose of this study was to investigate the relationship between cognitive ability and aerobic fitness in HIV-infected older adults. We conducted a cross-sectional study of HOA on antiretroviral therapy (ART) >50 years of age. Domain specific cognitive function was assessed by means of a neuropsychological battery. Aerobic fitness (VO_{2peak}) was assessed using a graded, progressive treadmill test. Thirty-seven HOA on ART (mean±SD: age 59±6years, BMI 28±5, CD4 663±337 cells/ml, duration since HIV diagnosis 17±7 years; 81% males) completed the cognitive tests. Several domains of cognition were significantly associated with VO_{2peak} by Spearman correlation analysis ($p<0.05$). By step-wise adjusted regression VO_{2peak} was most frequently and significantly related to many cognitive domains such as verbal and visual memory, visual perception, and language ($p<0.05$). We found that participants with higher Vo_{2peak} were less likely to have more severe forms of HIV-associated neurocognitive disorders (HAND) such as mild neurocognitive disorder (OR=0.65; p=0.01) and HIV-associated dementia (OR=0.64; p=0.0006). In HOA and in conclusion, aerobic fitness is related to cognitive performance on various tasks. The likelihood of cognitive impairment increased with lower fitness levels. Therefore, increased fitness may serve an important factor in maintenance of cognition and neural integrity for aging HIV-infected individuals. Future prospective and large scale studies are needed to evaluate the effect of fitness and vascular stiffness and function on cognition and brain structure among HOA.

Key words: HIV, older adults, aerobic fitness, cognition

The number of older adults with the human immunodeficiency virus (HIV) has markedly increased in the last 20 years; an increase which is largely attributed to the success of antiretroviral therapy (ART) [1,2]. Despite the effectiveness of ART, a significant number of HIV-infected patients continue to experience mild or asymptomatic cognitive impairments [3]. The HIV-infected older adult (HOA) community is particularly vulnerable to cognitive impairment and its related adverse outcomes such as dementia, loss of independence and increased nursing home admissions. Moreover, HIV-associated neurocognitive disorders

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(HAND) are particularly known to be a significant burden to the healthcare system, caregivers, and HIV-infected individuals themselves as they adversely impact quality of life (QOL) [4].

Previous studies in older adults have demonstrated the interrelationship between aerobic fitness and cognitive ability [5-7]. These studies report that lower scores on tests of cognitive function often correlate negatively with aerobic fitness. While informative, these previous studies primarily focus on the general older adult population. Therefore, it remains uncertain whether the association between cognitive and physical fitness measures can also be observed in the HOA community. This is an important next step because HIV-infected individuals have significantly reduced aerobic fitness and physical function compared to HIV-uninfected individuals, and this population is at increased of risk of frailty and functional decline [8,9].

Determining important correlates of cognitive ability may be beneficial in not only detecting precursors to future cognitive impairments, but also target areas for interventions aimed at slowing the decline of cognitive function in HIV-infected patients. Ultimately, preserving cognitive function can go a long way in mitigating the decline of QOL in HOA. Therefore, the purpose of this study was to investigate the interrelationship of cognitive ability and aerobic fitness in HOA on ART.

METHODS

Subjects

We recruited HIV-infected patients from our hospital-based infectious disease clinic. Patients were eligible if they were greater than 50 years in age, on stable ART regimen for a 3 month period prior to enrollment, able to ambulate without assistive devices, and free of any AIDS defining illness (ADI) for a 6 month period prior to enrollment. Excluded were those with any of the following: severe cardiopulmonary illness, severe anemia, significant orthopedic or neuromuscular impairments, renal failure, cirrhosis, significant sensory impairments, untreated depression, unstable manic or psychotic disorder, and active malignancy. Patient medical history was primarily obtained from self-completed questionnaires and secondarily from electronic medical records. Participants who did not have CD4 cell count and HIV viral load documented for a 3 month period prior to enrollment provided blood samples as part of the research protocol. Informed consent was obtained from all participants prior to enrollment. The study was approved by the University of Rochester Medical Center's Research Subjects Review Board.

Table 1. Subject Characteristics

	n (%)	*M (SD)*	*Range*
Gender			
Female	7 (18.9)		
Male	30 (81.8)		
Race			
African American	10 (27.0)		
Hispanic	3 (8.1)		
White (not Hispanic)	24 (64.9)		
Age (years)		58.92 (5.62)	50 – 71
Education (years)		13.51 (3.01)	8 – 22
Body Mass Index (BMI)		28.36 (5.25)	19.1 – 44.3
Waist Circumference (cm)		105.26 (13)	81.3 –136
HIV Chronicity (years with HIV)		16.78 (7.04)	1 – 26
CD4 Count		663.27 (337.02)	226 – 1401
CD4 Nadir			
CD4 Count < 200	19 (57.6)		
CD4 Count ≥ 200	14 (42.4)		
Viral Load (<50), copies/ml	27 (72.9)		
Current PI Use	19(51.3)		
Current N(t)RTI Use	35(94.5)		
Diabetes Mellitus			
No	24 (64.9)		
Yes	13 (35.1)		
Hypertension			
No	17 (46.0)		
Yes	20 (54.0)		
History of Myocardial infarction			
No	34 (91.9)		
Yes	3 (8.1)		
Hyperlipidemia			
No	15 (40.5)		
Yes	22 (59.5)		
COPD / Asthma			
No	32 (86.5)		
Yes	5 (13.5)		
Depression			
No	29 (78.4)		
Yes	8 (21.6)		
Smoking (present)			
No	23 (62.2)		
Yes	14 (37.8)		

PI, Protease Inhibitors; N(t)RTI, Nucleoside/Nucleotide Reverse Transcriptase Inhibitors

Cognitive Assessment

The cognitive battery included sensitive measures of cognitive domains frequently affected in HAND and allowed us to classify our participants according to recently published consensus criteria for HAND [10].

Reasoning Speed. We used the abbreviated California Computerized Assessment Package [11] in which participants view a stream of briefly presented single digits on a computer monitor and respond to task-specific digits with a button press. The test provides measures of simple reaction time, choice reaction time, simple serial pattern matching, and a more difficult version of serial pattern matching.

Attention and Concentration. We used the Wechsler Adult Intelligence Scale-III (WAIS-III) Digit Span subtest [12] to measure immediate attention span. Participants are read increasingly longer sequences of digits, which they repeat verbatim for Digits Forward or in reverse order for Digits Backward. The highest span length achieved represents immediate and complex attention capacity.

Executive, Response Inhibition and Cognitive Flexibility. The Delis-Kaplan Executive Function System (DKEFS) Color-Word Interference Test [13] is a variant of the Stroop procedure and was used to measure response inhibition. This test consists of four separately administered conditions in which the participant 1) names color patches, 2) reads color words printed in black ink, 3) names the ink color in which color words are printed and, 4) switches between naming dissonant ink colors and reading the conflicting words. Conditions three and four are measures of response inhibition and cognitive flexibility.

Language. The DKEFS Verbal fluency subtest [13] was used to measure oral language generation. Participants complete three conditions of the test in which they must rapidly generate words to phonemic cues (Letter Fluency), semantic cues (Category Fluency), and alternate between two categories when generating words (Category Switching). The Category Switching task is also a measure of cognitive flexibility and scores on this task were considered under executive function.

Memory. The Hopkins Verbal Learning Test (HVLT) [14] was used to measure verbal encoding, learning, retrieval, and retention. This test consisted of a list of 12 words from three categories, and was presented to the subject over three learning trials. Participants were required to recall as many as possible words after each trial. Delayed free recall was assessed 25-minutes later. Immediately after the delayed recall trial, a forced-choice recognition test which included the 12 target words plus 12 distractor words (six semantically-related and six semantically-unrelated) was administered. The Rey-Osterrieth Complex Figure Test (RCFT) [15] was used to assess visual short term memory. In the copy condition, participants copied as accurately as possible, a complex drawing consisting of 18 details. After a filled 3-minute delay, participants were required to reproduce the figure from memory. They were not informed of the short-term recall trial beforehand. The drawings were scored for accuracy of detail placement according to a standardized scoring system [15].

Visuoperceptual and Visuospatial. The Hooper Visual Organization Test (HVOT) [16] was used to measure visual perceptual organization. In this 30-item test, participants are required to mentally rotate and rearrange component pieces of a common object illogically arranged on a card. The copy condition of the Rey Complex Figure Test described above was included as a measure of visuospatial construction.

Anthropometric Variables

Body mass index (BMI) was calculated as weight (kilograms)/height^2 (meters). Waist circumference, a measure of central adiposity, was computed as the average of two measurements performed by a single evaluator who placed a tape measure snugly around the bare abdomen halfway between the anterior superior iliac crest and the lowest portion of the 12th rib while the subject was standing.

Assessment of Aerobic Fitness

Peak aerobic capacity ($VO_{2\ peak}$) was assessed during graded treadmill walking. Warm-up was at 0% grade, at the fastest comfortable walking speed, and varied from 3–5 minutes to produce approximately 70% of each participant's peak heart rate. Speed was held constant and treadmill incline was increased by 2% every 2 minutes. As a safety measure, participants could lightly hold a handrail to maintain balance. The test was terminated when participants became too fatigued to continue. Cardiorespiratory data were collected continuously during treadmill testing using a computerized system. The highest average O_2 uptake from four consecutive fifteen second periods was designated the $VO_{2\ peak}$. This protocol provides a very accurate measure of $VO_{2\ peak}$ and has been successfully used in our previous studies [7,9,17,18].

Activities of Daily Living (ADL)

Information about the ability to perform ADLs was collected by using the Functional Status Questionnaire (FSQ), a standardized, validated instrument that evaluates difficulty in performing nine ADLs with a score range of 0-36 [9,17].

HAND Classification

Each participant's cognitive test scores were compared to age- and where available, education- and sex-adjusted normative data to determine impairment. We used the HAND definitions proposed by Antinori and colleagues [10] to classify each participant into the categories of normal, Asymptomatic Neurocognitive Impairment (ANI), Mild Neurocognitive Disorder (MNC), or HIV-associated Dementia (HAD). Performance 1.5 SD below normative values for each cognitive domain was considered impaired. A score of 32 or lower on FSQ represented impaired ADL [17].

Table 2. Mean and Standard Deviation for Study Tests (N = 37)

Test	*M (SD)*	*Range*
Reasoning Speed		
CalCap Simple Reaction Time	450.94 (125.64)	282 – 761
CalCap Choice Reaction Time	464.60 (51.86)	362 – 587
CalCap Sequential Reaction Time 1	600.74 (107.83)	359 – 817
CalCap Sequential Reaction Time 2	693.66 (93.49)	433 – 858
Language		
DKEF Letter Fluency	36.32 (9.85)	18 – 54
DKEF Category Fluency	33.35 (9.09)	20 – 59
Executive Function		
Category Switching Correct	11.22 (3.28)	4 – 19
Category Switching Accuracy	10.81 (3.48)	1 – 19
Color Word- Word Reading	35.68 (7.09)	25 – 63
Color Word- Color Naming	27.49 (6.25)	17 – 45
Color Word- Interference	72.32 (14.67)	44 – 112
Color Word- Switching	88.26 (28.15)	57 – 170
Attention		
Digit Span Forward Total Score	9.81 (2.50)	6 – 15
Digit Span Forward Longest Span	6.27 (1.39)	4 – 9
Digit Span Backward Total Score	5.51 (2.48)	2 – 12
Digit Span Backward Longest Span	4.16 (1.42)	2 – 8
Visual Perception		
Hooper Visual Organization Test Score	24.86 (3.63)	14 – 30
Visual Spatial		
RCFT Copy Score	32.07 (5.53)	14 – 36
Visual Memory		
RCFT Immediate Recall Score	16.80 (8.42)	0 – 34
Verbal Memory		
HVLT Total Recall Score	18.92 (5.43)	8 – 32
HVLT Delayed Recall Score	6.03 (2.54)	2 – 12
HVLT Retention Percent Score	77.54 (19.74)	40 – 125
HVLT Recog Discrim Index Score	8.46 (2.41)	0 – 12
Aerobic Fitness ($VO_{2\ peak}$) (ml/kg/min)	20.30 (6.37)	10 – 40
Functional Status Questionnaire	30.50 (3.20)	25 – 34

Statistical Analysis

Spearman correlations were first used to examine pair-wise relationships between dependent variables in each cognitive domain and the independent variables of age, education, waist circumference, BMI, number of years with HIV, CD4 count, CD4 nadir and VO_{2peak}. We used multiple regression techniques with stepwise variable selection to examine the joint effect of the independent variables on cognitive tests of each cognitive domain. In case of domains with multiple cognitive tests, we also applied principle component analysis to extract the major components, and then regressed the major component on the independent variables, to take account of small sample size and high correlations among cognitive tests from the same domains. Finally, logistic regression models were used to determine which independent variables best predicted our HAND classification (ANI, HAD and MNC vs. normal cognition). All data analyses were performed using SAS®/STAT software, Version 9.2 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Thirty-seven HOA on ART (mean±SD: age 59±6years, BMI 28±5, CD4 663±337 cells/ml, duration since HIV diagnosis 17±7 years; 81% males) completed the cognitive tests. Clinical characteristics of the subjects are shown in Table 1. Four subjects did not complete the exercise treadmill test and the FSQ because of scheduling difficulty. Descriptive statistics for the cognitive domain specific tests, VO_{2peak} and FSQ are presented in Table 2. Several domains of cognition were significantly associated with VO_{2peak} by Spearman correlation analysis (p<0.01 each) (Table 3).

Table 3. Correlation Matrix of Selected Independent Variables and Cognitive Domains

Spearman Correlation Coefficient & p-value	CD4 Count	CD4 Nadir	BMI	VO2 ml/kg	Age	Years HIV	Years Education	Waist Circum.
Reasoning Speed Sequential RT2 Mean	0.14	0.40** p=0.0383	-0.05	-0.08	0.03	0.33* p=0.0770	-0.14	-0.01
Language DKEF VF Category	0.20	-0.48*** p=0.0047	-0.14	0.63*** p<0.0001	-0.25	-0.05	0.41** p=0.0125	-0.15
Executive Function DKEF VF Cat Switch	0.09	-0.26	-0.19	0.50*** p=0.0030	-0.11	-0.04	0.36** p=0.0297	-0.16
Visual Perception HVOT	-0.07	-0.03	-0.26	0.46*** p=0.0078	-0.20	0.18	0.56*** p=0.0003	-0.23
Visual Memory RCFT Immediate	-0.06	-0.21	-0.11	0.57*** p=0.0006	-0.11	0.09	0.46*** p=0.0041	-0.02
Verbal Memory								
HVLT Total Recall	-0.002	-0.10	-0.22	0.54*** p=0.0013	-0.20	-0.06	0.33** p=0.0484	-0.14
HVLT Delayed Recall	-0.02	0.02	-0.09	0.59*** p=0.0003	-0.22	-0.05	0.25	-0.03
HVLT Retention Percent	-0.10	0.03	-0.06	0.48*** p=0.0044	-0.15	-0.09	0.16	-0.07
HVLT Recog Discrim Ind	-0.21	-0.003	-0.07	0.57*** p=0.0006	-0.15	0.09	0.25	0.07

Step-wise adjusted regression models revealed that VO_{2peak} was the most frequent independent variable associated with the cognitive measures (Table 4). VO_{2peak} explains a significant amount of variability in DKEF Category fluency of the Language domain (37% variance, p<0.001), and in DKEF Category Switch of the Executive domain (28%, p<0.01). On the Memory domain, it also accounts for 41% variability in HVLT Total Recall (p<0.001) and 47% variability in HVLT Recognition (p<0.001). VO_{2peak} explains 60% variability in Sequential Reaction Time 2 mean of the Reasoning Speed domain controlling for CD4 Nadir, BMI and number of years with HIV (p=0.0003), 40% variability in HVOT of the Visual Perception domain when controlling for number of years with HIV (p=0.0004), 50% variability in RCFT immediate of the Memory domain controlling number of years with HIV (p<0.0001), 53% variability in HVLT delayed recall (p<0.0001) and 21% variability in HVLT retention percent correct (p=0.0064) of the Memory domain. In the Memory domain, principal component analysis revealed factor loadings of 0.87, 0.95, 0.75 and 0.81 for HVLT Total Recall, HVLT Delayed Recall, HVLT Retention Percent Correct and HVLT Recognition, in order, which explain over 72% variability performance in this domain. VO_{2peak} together with CD4 Nadir accounts for 57% variability in these major Memory domain components.

On classifying HAND diagnosis we found that 9 subjects had normal cognitive function, 5 subjects had ANI, 7 subjects had MNC and 12 subjects had HAD. We further found that participants with higher VO_{2peak} were less likely to have more severe forms of HAND – i.e., MNC (OR=0.65; p=0.01) and HAD (OR=0.64; p=0.0006) (Figure 1).

Table 4. Association between Selected Independent Variables and Cognitive Domains in Stepwise Adjusted Linear Regression Models

β-Coefficient (p-value)	*CD4 Nadir*	*BMI*	*VO2 ml/kg*	*Years HIV*	*Waist Circum.*
Reasoning Speed ***Sequential RT2 Mean***	0.20231 (0.0006)	-9.90960 (0.0023)	-5.00016 (0.0520)	6.57549 (0.0022)	
Language ***DKEF VF Category***			0.88439 (0.0002)		
Executive Function ***DKEF VF Cat Switch***			0.25880 (0.0018)		
Visual Perception ***HVOT***			0.33929 (0.0002)	0.18829 (0.0305)	
Visual Memory ***RCFT Immediate***			0.92649 (<0.0001)	0.31551 (0.0820)	
Verbal Memory ***HVLT Total Recall***			0.57823 (<0.0001)		
HVLT Delayed Recall	0.00284 (0.0362)		0.28037 (<0.0001)		
HVLT Retention Percent	0.02158 (0.0852)		1.63900 (0.0027)		
HVLT Recog Discrim Ind			0.26223 (<0.0001)		0.0628 (0.0168)
Verbal memory (major component from PCA)	0.00113 (0.0265)		0.12344 (<0.0001)		

DISCUSSION

The results of this study demonstrated that aerobic fitness is predictive of cognitive ability on various tasks in HOA on ART. In fact, we found that HOA with lower aerobic fitness are more likely to have HAND compared with subjects who had higher aerobic fitness. Additionally, HOA with higher fitness tend to have no cognitive impairments. Therefore, these findings suggest an important function of maintaining a high level of aerobic fitness, as this may have neuroprotective effects for aging HIV-infected individuals.

Notably, this is the first study to examine the relationship between aerobic fitness and cognitive ability in HIV-infected individuals. In addition to confirming previous studies that have examined the relationship between aerobic fitness and cognitive ability in the general older population [5-7], this study observed a significant relationship between aerobic fitness and several cognitive domains such as verbal and visual memory, visual perception, and language, independent of age, adiposity, immune function, and duration of HIV disease.

In this study we observe evidence not only of more cognitive deficits among HOA, but also more cortically based deficits rather than the subcortical deficits typically reported for younger HIV-infected patients [19]. This qualitative change in the profile of cognitive deficits suggests that chronic ART may be involved in producing these deficits. Alternately, this may represent the evolution of cortical dementia in individuals who may already have the biological predisposition for this [20]. The results of the study also demonstrate that aerobic function is closely related to the cortical pattern of deficits rather than the classic (pre-ART era) subcortical attention/executive profile as described in the HIV literature [19]. Moreover, the findings of our study are also consistent with the notion that duration of HIV disease and CD4 nadir are important predictors of cognitive function in this population [3,21].

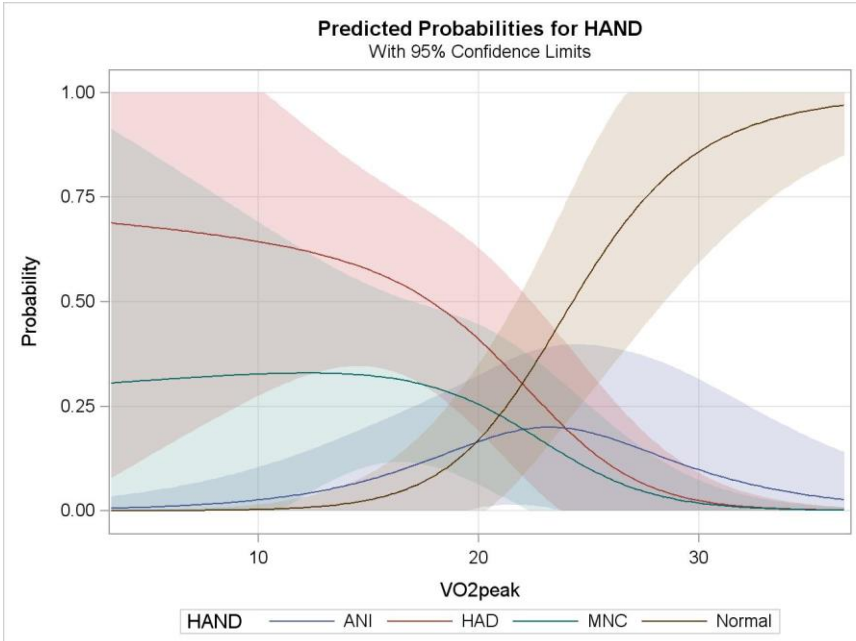

Figure 1. Predicted probabilities (with 95% Confidence Intervals) of cognitive impairment, based on aerobic fitness. Study participants were classified as cognitively normal, or as having a HAND diagnosis (ranging in severity from ANI [least severe], to MNC to HAD [most severe]. The curves demonstrate increasing probability of cognitive impairment with lower VO_{2peak} and increasing probability of better cognition with higher VO_{2peak}. The inflection point for classification appears to be around 22 ml/kg/min.

Previous studies have suggested a negative relationship between central obesity and cognitive impairment in HIV-infected and HIV-uninfected younger individuals [22,23]. The present study did not reveal such a relationship in HOA. Studies focusing on the general older adult population have been seen to be controversial [24], as a recent report demonstrated that the relation between central obesity and cognitive impairment diminishes with aging [25]. One possible reason that our study did not observe this relationship is because of the relatively small sample size. Nevertheless, our study results underscore that obesity does not prevent the benefits of fitness for cognition among HOA.

Our results suggest a causal link between vascular health and cognition in this population and a number of potential mechanisms may explain our findings. Vascular stiffening has been postulated to diminish cerebral perfusion and contribute to cognitive impairment independent of other risk factors [26]. It is well known that aerobic fitness correlates strongly with endothelial and vascular function [27-29]. Further, it is known that aerobic exercise training improves endothelial function and reduces vascular stiffening [30-32]. With respect to the HIV-infected community, there is emerging evidence that vascular stiffness and aging are accelerated with the presence of HIV infection because of the high prevalence of cardiovascular disease risk factors [33]. The biological effects of HIV and the metabolic perturbations associated with ART appear to accelerate vascular stiffening in HIV-infected patients [34,35]. Thus, vascular alterations and endothelial pathology may explain the relationship between fitness and cognition that we observed in our sample of HOA.

One weakness of this pilot study may be a sampling bias as only those who were willing and able to come to our facility participated in the study. In addition, the conclusions of our study were limited due to a small sample size. On the other hand, a major strength of our study is the comprehensive clinical and cognitive characterization of our study participants. Lastly, we realize that the cross-sectional design of this study can only identify associations. Nonetheless, at the very least, this pilot study offers interesting insight into the cognitive implications of low levels of aerobic fitness in HOA.

The findings of this study are important because aging with HIV is emerging as a critical issue in the developed world. HIV-infected individuals represent a new and relevant subset of the older adult population who are at increased risk of premature aging. The negative consequences of cognitive impairment not only increase the burden on clinical care, but also generate an increased demand for access to an overburdened health care system. To conclude, our study demonstrates that aerobic fitness is an important predictor of cognitive ability in the HOA population. Further, the study suggests that maintaining a high level of aerobic fitness may serve as an effective strategy in preventing cognitive impairment among HOA. Future prospective and large scale studies are needed to evaluate the effect of fitness and vascular stiffness on cognition and brain structure in HOA.

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Conflict of Interest

None.

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