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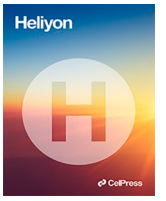

Altered metabolism in right basal ganglia associated with asymptomatic neurocognitive impairment in HIV-infected individuals

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ABSTRACT

Background: Only few studies have focused on the metabolite differences between asymptomatic neurocognitive impairment (ANI) and cognitively normal people living with HIV (PLWH). The current study aims to examine whether brain metabolisms in basal ganglia (BG) by magnetic resonance spectroscopy (MRS) were potential to discriminate ANI from cognitively normal PLWH.

Methods: According to neuropsychological (NP) test, 80 PLWH (37.4 ± 10.2 years) were divided into ANI group (HIV-ANI, n = 31) and NP normal group (HIV-normal, n = 49). Brain metabolisms by MRS from right BG were compared between groups, including *N*-acetylaspartate and *N*-acetyl aspartylglutamate (tNAA), creatine and phosphocreatine (tCr), and choline-containing compounds (tCho). A total value of three metabolites were introduced. All brain metabolisms were evaluated as its percentage of total. Furthermore, correlations between MRS and NP and clinical measures were evaluated. A logistic regression model was applied, and the AUC values for the model and the continuous factors were compared using receiver operating curve (ROC) analysis.

Results: Compared to HIV-normal group, tNAA/total was lower and tCr/total was higher in the HIV-ANI group ($P < 0.05$). Both tNAA/total and tCr/total values were correlated with NP score ($P < 0.05$), especially in verbal fluency, speed of information processing, learning, and recall ($P < 0.05$). The logistic model included BG-tCr/total, current CD4 and infection years of PLWH. The AUC value for the BG-tCr/total was 0.696 and was not significantly lower than that for logistic model ($P < 0.01$).

Conclusion: The altered brain metabolites in the right BG were found in the ANI group compared to PLWH with normal cognition, and further associated with NP deficits. The current findings indicated that brain metabolites assessed by MRS has the potential to discriminate ANI from cognitively normal PLWH.

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1. Introduction

Following central nervous system (CNS) opportunistic infection, HIV-associated neurocognitive disorder (HAND) was the second risk factor in people living with HIV (PLWH) in terms of mortality hazard ratio [1], which was closely related to worse medication adherence [2] and lower level of life quality [3,4]. Despite the successful application of antiretroviral therapy (ART) and the extended survival time [1,5], nearly half of PLWH are estimated to have HAND [6–9]. The overall HAND prevalence rate is similar to that in the pre-ART era [10], although asymptomatic neurocognitive impairment (ANI) becomes more common (23.5 %) than symptomatic HAND including mild neurocognitive disorder (13.3 %) and dementia (5.0 %) [7,11,12].

According to the updated criteria of HAND classification published in 2007 [13], ANI is characterized with impaired neurocognitive functions without obvious interference with daily functions [13]. Multiple studies have shown that, compared to PLWH with normal neuropsychological (NP) performance, PLWH with ANI had a two-fold to six-fold risk of developing into symptomatic HAND in four years [14–16]. Fortunately, ANI can be improved by intervention; NP function monitoring and routine screening of ANI in PLWH are therefore crucial for preventing severe outcomes [11].

In addition to NP tests, magnetic resonance spectroscopy (MRS) have revealed brain deficits associated with HIV infection or HAND [5,11,17–19], and may be a potential time-saving method in distinguishing ANI from NP normal PLWH. MRS measures various brain metabolites, including total *N*-acetyl-aspartate (tNAA) as a marker for neuronal density and viability, total choline (tCho) as an indicator of cell membrane turnover and gliosis, and total creatine (tCr) as a marker for cellular energy metabolism [20]. HIV virus can pass through the blood-brain barrier [21], destroy neurons and cause white matter demyelination and glial proliferation, resulting in abnormalities in brain tissue metabolites [22]. These changes of brain metabolites in PLWH may be related to neuronal damage (tNAA decrease), increased cellularity or increased cell membrane decomposition (tCho increase), and increased energy demand of cell maintenance (tCr increase) [23]. Hence, altered brain metabolite concentration in PLWH could reflect neurological abnormalities which were further related to decreased neurocognition [24].

Compared to healthy people, PLWH showed altered brain metabolites, especially tNAA [25–27] and glutamate [28]. Among subtypes of HAND, NAA concentration was reduced and correlated with NP scores in PLWH with dementia, and this reduction widely happened in basal ganglia (BG) [29–32]. Only one MRS study explored BG metabolism differences between ANI and NP normal PLWH, and reported lower BG-NAA in ANI patients [33]. However, the correlations between the altered brain metabolisms and NP deficits were not explored in that study.

In the current study, we aimed to investigate the altered brain metabolites in ANI patients comparing to PLWH with normal cognition, and further explore their relationships with NP deficits. We focused on the BG as metabolite alterations occur mainly in BG during early HIV infection [31], and it interacts with the cerebral cortex in various cognitive tasks, such as reinforcement learning and action selection [34,35]. We further focused on the right BG following the previous study [31]. Our previous studies on the same population also found that, there were more group differences in the right hemisphere, including disrupted resting-state functional connectivity [36] and morphological changes [37], not only between PLWH and normal subjects [36,37], but also between subgroups within PLWH [36]. Based on these right-lateralized findings, we speculated that HIV or HAND related metabolic changes in this cohort were more probable to be detected in the right hemisphere. We further hypothesized that alterations in right BG metabolites were related to the NP deficits in the ANI group, which may be potentially important imaging characteristics distinguishing ANI patients from PLWH with normal cognition.

2. Materials and methods

2.1. Participants

The current study was approved by the ethics committee of the Shanghai Public Health Clinical Center. All participants provided written informed consent prior to participation. Eighty younger and middle-aged PLWH were recruited from a cohort of more than 600 subjects paying regular visits to the Shanghai Public Health Clinical Center from 2015 to 2019. The main inclusion criterion was being more than 18 and less than 60 years old. HIV infection status was confirmed by detection of plasma HIV-RNA or by documented positive HIV enzyme-linked immunoassay. The exclusion criteria were as follows: 1) any pre-existing psychiatric or neurological disorder, active brain infection besides HIV, presence of brain neoplasm or space-occupying lesion, chronic seizures or head injury, or any contraindication to MRI; 2) history of drug or alcohol dependence according to medical records, or illicit drug use in the past six months; 3) any clinically significant abnormalities in conventional MRI, including T1-weighted, T2-weighted, and diffusion weighted imaging; 4) co-infection of hepatitis viruses B and C, pulmonary tuberculosis, and cryptococcosis. Demographic information including gender, age and education level, as well as infection history was collected from all subjects. All of them completed the Beck Depression Inventory and Patient's Assessment of Own Functioning, the latter of which assessed memory, language and communication, use of hands, sensory-perceptual abilities, higher level intellectual and cognitive functions, and work. All subjects underwent assessment of instrumental activities of daily living (IADLs) (modified version of the Lawton and Brody scale [38]), and none reported dysfunctions in daily activities. The clinical information related to HIV infection was collected from medical records, including time of diagnosis, ART onset time, CD4 and CD8 cell counts in medical history. All PLWH subjects were under viral suppression in peripheral blood.

2.2. Neuropsychological tests

Subjects were grouped into PLWH with ANI (HIV-ANI) and PLWH with normal cognition (HIV-normal) based on their performance

on NP tests, following the Frascati criteria [13]. Seven cognitive domains were assessed referring to the CNS HIV Antiretroviral Therapy Effects Research (CHARTER) study [6,39–41], including speed of information processing, learning and recall, abstraction or executive functioning, verbal fluency, attention or working memory, and motor. All tests were conducted in Mandarin using adapted Chinese versions, which have been used to assess cognitive impairments of HIV-infected individuals in China [40,42,43]. The NP norm of the current study was comprised of 708 urban dwelling participants from China (Beijing, n = 80; Hong Kong, n = 153; Shanghai, n = 72; and Kunming, n = 403). NP tests used in each cognitive domain were listed in Table 1.

Raw scores of NP tests were converted to T-scores adjusting for demographic characteristics, including age, years of education and gender. Demographically-corrected T-scores were converted to clinical ratings (CR) according to the following criteria: CR = 1 as T-score ≥55 (above average), CR = 2 as 45 ≤ T-score ≤54 (average), CR = 3 as 40 ≤ T-score ≤44 (low average), CR = 4 as borderline, CR = 4 as 35 ≤ T-score ≤39 (mild impairment), CR = 6 as 30 ≤ T-score ≤34 (mild to moderate impairment), CR = 7 as 25 ≤ T-score ≤29 (moderate impairment), CR = 8 as 20 ≤ T-score ≤24 (moderate to severe impairment), and CR = 9 as T-score ≤19 (severe impairment) [44].

2.3. MR imaging and spectroscopy

All MR scans were performed on a 3.0 T scanner (Ingenia, Philips Healthcare, Best, Netherlands) equipped with a 16-channel receive head coil. Before MRS examination, sagittal 3D T1-weighted images with 1 mm isotropic voxel size, axial T2-weighted and fluid-attenuated inversion recovery images, and diffusion-weighted images were obtained. These images were evaluated by two independent neuro-radiologists. Subjects with abnormal gray or white matter intensity and cerebral atrophy were excluded from further analysis.

The single-voxel MRS was done using the point resolved spectroscopy sequence. The data acquisition parameters were as follows: TR = 2000 ms, TE = 144 ms, number of acquisitions = 128, time of acquisition = 5 min. An isotropic expansion of 15 mm around the right BG was placed on the axial T2-weighted images to define the MRS volume of interest.

MRS spectra were processed using LCModel software (Version 6.3-1L), which analyzes an in vivo spectrum as a Linear Combination of Model in vitro spectra from individual metabolite solutions [45]. The LCModel basis set contained 17 different metabolites and the standard LCModel macromolecule peaks. Concentration and ratio values were included for statistical analysis only if their Cramér-Rao lower bounds were less than 15 % and the signal-to-noise ratios were greater than three [45]. Finally, we evaluated single-voxel MRS metabolites reflecting neuronal integrity and inflammation, including tNAA, tCho, and tCr. A total value of three metabolites was introduced, i.e., total = tNAA + tCho + tCr. The parameter for each brain metabolite was evaluated as its ratio against to the total value [46]. We used the total value instead of the tCr value as the metabolite reference to enable the quantification of tCr concentration [47], which was reported to reflect dementia severity [24] and might be closely related to ANI. A representative spectrum from right BG is shown from a single subject in Fig. 1.

2.4. Statistical analysis

Group differences on demographics, clinical information, and neurocognitive performances were statistically tested via two-sample *t*-tests and a Fisher's exact test (gender). Spearman's rank correlations were conducted to explore the relationships between global CR scores, domain CR scores, demographically corrected clinical measures and MRS metabolic values. We calculated the standardized mean difference (SMD) between HIV-ANI and HIV-normal groups using Cohen's *d*. Logistic regression analyses were performed to classify the HIV-ANI and the HIV-normal groups based on MRS metabolic measures, clinical characteristics, age, and years of education. A backward elimination process was used in accordance with the Akaike information criterion [48] to generate a parsimonious multivariable model. Receiver operating curve (ROC) analyses were conducted for the logistic regression model as well as for the continuous factors selected by the regression model. The ROC curves were compared using the Delong test. The area under the curve

Table 1
Neurocognitive tests used in the study.

Cognitive domain	Tests
Speed of information processing	WAIS-III Digit Symbol
	WAIS-III Symbol Search
	Trail Making Test (Part A)
Learning	Hopkins Verbal Learning Test-Revised
	Brief Visuospatial Memory Test-Revised
Memory	Hopkins Verbal Learning Test-Revised
	Brief Visuospatial Memory Test-Revised
Abstraction/Executive Functioning	Wisconsin Card Sorting Test-64 Card Version
	Halstead Category Test
	Trail Making Test (Parts A and B)
Verbal Fluency	Semantic Verbal Fluency (animals and actions)
Attention/Working Memory	WMS-III Spatial Span
	PASAT (1st channel only)
Motor	Grooved Pegboard (dominant and non-dominant hands

WAIS III = Wechsler Adult Intelligence Scale-III, WMS-III = Wechsler Memory Scaled-III, PASAT = Paced Auditory Serial Addition Task

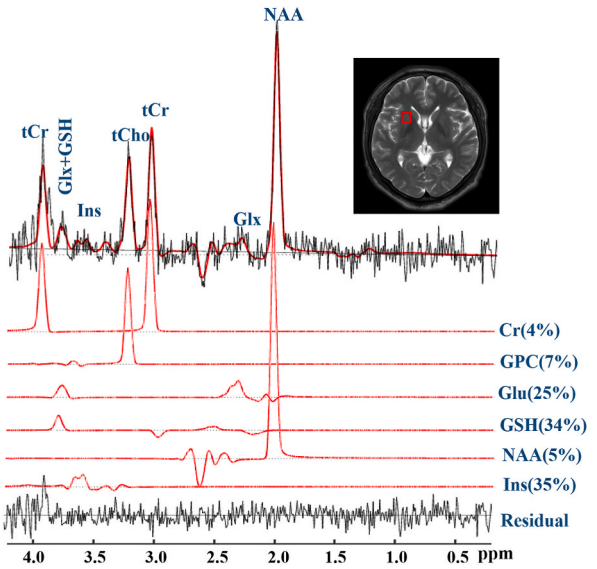

Fig. 1. An example of the voxel location used for brain MR spectroscopy in right basal ganglia (BG). An example of a spectrum from the BG in a 40-year-old HIV subject is shown with results from the LCModel analysis (red curves), including corresponding raw spectrum, superimposed LCModel fit, fit residual and selected metabolites with the estimated Cramér-Rao lower bounds in parentheses. Signals are assigned to *N*-acetylaspartate (NAA), *N*-acetyl aspartylglutamate (NAAG), creatine (Cr), phosphocreatine (PCr), glycerophosphocholine (GPC), phosphocholine (PCh), glutamine (Gln), glutathione (GSH) and myo-inositol (Ins). tNAA = NAA + NAAG; tCr = Cr + PCr; tCho = GPC + PCh.

(AUC) values were used to evaluate the predictive efficiency of the classifiers on distinguishing the HIV-ANI group from the HIV-normal group [49]. The cutoff values were defined by maximizing the Youden index. All univariate and multivariate analyses were performed using statistical computing and graphics software (R, version 3.4.2, R Foundation). A P value < 0.05 was considered statistically significant.

Table 2
Demographics and clinical characteristics.

Sample size (n)	HIV-ANI	HIV-normal	SMD[b]	*P*
	31	49		
Demography				
Gender (male, n, %)	29, 93.5 %	47, 95.9 %		0.638
Age (mean ± SD, years)	39.06 ± 12.715	35.53 ± 8.026	0.332	0.131
Education years (mean ± SD, years)	13.71 ± 2.795	14.20 ± 2.458	0.186	0.409
HIV Infection				
Infection years (mean ± SD, years)	6.89 ± 4.290	5.12 ± 3.495	0.452	0.064
ART years (mean ± SD, years)	5.59 ± 3.788	4.57 ± 3.270	0.289	0.239
Current CD4 (mean ± SD, cells/mm^3)	437.96 ± 157.805	509.78 ± 172.166	0.435	0.089
Nadir CD4 (mean ± SD, cells/mm^3)	190.44 ± 122.879	214.37 ± 144.305	0.179	0.485
Current CD8 (mean ± SD, cells/mm^3)	813.52 ± 312.730	883.41 ± 368.528	0.204	0.428
Nadir CD8 (mean ± SD, cells/mm^3)	505.36 ± 328.367	526.23 ± 309.882	0.065	0.793
Clinical Rating Scores of Neurocognitive Tests				
Motor (mean ± SD)	3.10 ± 1.938	2.10 ± 1.531	0.573	
Verbal fluency (mean ± SD)	2.65 ± 1.817	1.47 ± 0.739	0.851	
Attention/Working memory (mean ± SD)	3.26 ± 1.914	1.92 ± 1.170	0.845	
Speed of information processing (mean ± SD)	4.10 ± 1.886	2.31 ± 1.245	1.080	
Executive functioning (mean ± SD)	5.03 ± 1.643	2.67 ± 1.390	1.551	
Learning (mean ± SD)	3.81 ± 1.621	2.06 ± 1.107	1.261	
Recall (mean ± SD)	3.97 ± 1.871	2.06 ± 1.435	1.146	
Brain metabolites				
tNAA/Total[a] (mean ± SD)	0.54 ± 0.030	0.56 ± 0.029	−0.677	0.014*
tCr/Total (mean ± SD)	0.36 ± 0.026	0.34 ± 0.029	0.714	0.006*
tCho/Total (mean ± SD)	0.10 ± 0.013	0.10 ± 0.017	0.000	0.880

P values were calculated via Fisher's exact test and chi-square test for categorical variables and Wilcoxon rank sum test for continuous variables; *$P <$ 0.05.

[a] Total = tNAA + tCho + tCr.

[b] Standardized mean difference.

3. Results

Demographics and clinical characteristics are summarized in Table 2. All patients were receiving ART. Thirty-one HIV-infected individuals were classified as ANI (HIV-ANI), and 49 as PLWH with normal cognition (HIV-normal). There were no significant group differences in age, education, gender, current and nadir CD4, current and nadir CD8 ($P > 0.05$). Compared to the HIV-normal group, tNAA/total was significantly decreased in the HIV-ANI group (0.54 ± 0.030 vs. 0.56 ± 0.029, SMD = −0.677, $P = 0.014$), while tCr/total was significantly increased (0.36 ± 0.026 vs. 0.34 ± 0.029, SMD = 0.714, $P = 0.006$). No significant difference was found in tCho/total between the two groups (0.10 ± 0.013 vs. 0.10 ± 0.017, SMD = 0.000, $P = 0.880$).

Both tNAA and tCr values were correlated with the global CR score of cognitive impairment (tNAA/total, rho = −0.353, $P = 0.005$; tCr/total, rho = 0.391, $P = 0.002$) and GDS (tNAA/total, rho = −0.328, $P = 0.009$; tCr/total, rho = 0.354, $P = 0.004$). MRS measures were further correlated with domain CR scores of verbal fluency (tNAA/total, rho = −0.267, $P = 0.034$), speed of information processing (tCr/total, rho = 0.272, $P = 0.031$), learning (tNAA/total, rho = −0.408, $P < 0.001$; tCr/total, rho = 0.371, $P = 0.003$), and recall (tNAA/total, rho = −0.448, $P < 0.001$; tCr/total, rho = 0.470, $P < 0.001$). Results from correlation analyses are presented in Table 3.

Backward elimination was used to select significantly informative features associated with the risk of ANI (Table 4). The final logistic regression model indicated that the concentration of tCr in BG (P = 0.004), current CD4 (P = 0.018) and infection years (P = 0.009) in PLWH were significantly related to the diagnosis of ANI.

ROC analyses of the logistic regression model, tCr/total, current CD4 and infection years were performed to differentiate HIV-ANI from the HIV-normal group; the AUC values for the four types of differential diagnosis were 0.806, 0.696, 0.620, and 0.635, respectively. The cutoff value on the ROC curve was 0.397 for predictive probability using the logistic regression model (sensitivity, 72.0 %; specificity, 82.6 %), 0.354 for tCr/total (sensitivity, 56.0 %; specificity, 76.1 %), 374.000 cells/mm^3 for current CD4 (sensitivity, 48.0 %; specificity, 82.6 %), and 7.616 years for infection years (sensitivity, 48.0 %; specificity, 80.4 %). The ROC of the logistic regression model was comparable to tCr/total ($P = 0.070$), and significantly superior to that of current CD4 ($P = 0.014$) and infection years ($P = 0.016$) (Table 5 and Fig. 2).

4. Discussion

We investigated the BG metabolic alterations in PLWH with ANI comparing to PLWH with normal cognition, and explored the diagnostic value of the relevant MRS-based BG metabolite concentrations in distinguishing these two subgroups in PLWH. We found decreased tNAA and increased tCr in the right BG in PLWH with ANI. The altered brain metabolites were further associated with NP deficits, especially deficits in learning and recall. Furthermore, BG-Cr/total was an independent factor in classifying PLWH into ANI and cognitively normal groups. These findings suggested that even in well-treated PLWH with viral suppression, subgroups with impaired and normal cognition differ in brain metabolites. As ANI was defined as asymptomatic cognitive impairments with no interference with daily activity [13], these findings indicated that altered BG metabolites evaluated by MRS may precede symptomatic cognitive declines in PLWH, and more importantly, are potential imaging characteristics of ANI [13]. MRS-based evaluation of metabolite concentrations in BG, especially the BG-Cr concentration, can assist in the early detection of ANI and follow-up on changes in cognitive functions.

The main finding of the current study was increased tCr/total and decreased tNAA/total in the right BG in ANI when compared to PLWH with normal cognition. Cr widely exists in tissues with metabolic activity and plays a vital role in energy metabolism, storage, and transfer [50]. Hence, elevated Cr in PLWH indicated an increase in cell energy demand that compensate for increased cellular

Table 3
Correlation of brain metabolites with clinical and neurocognitive measures.

	tNAA		tCr		tCho	
	rho	*P*	rho	*P*	rho	*P*
Infection years	0.158	0.215	−0.175	0.169	0.038	0.765
ART years	0.152	0.236	−0.209	0.100	0.090	0.481
Current CD4	−0.017	0.894	−0.018	0.889	0.037	0.772
Nadir CD4	−0.109	0.396	0.029	0.823	0.141	0.270
Current CD8	−0.203	0.110	0.148	0.247	0.194	0.127
Nadir CD8	0.013	0.916	−0.075	0.557	0.139	0.277
Clinical rating scores of neurocognitive tests						
Global	**−0.353**	**0.005***	**0.391**	**0.002***	0.045	0.727
Learning	**−0.408**	**< 0.001*#**	**0.371**	**0.003***	0.162	0.205
Recall	**−0.448**	**< 0.001*#**	**0.470**	**< 0.001*#**	0.051	0.691
Verbal fluency	**−0.267**	**0.034***	0.206	0.105	0.083	0.519
Speed of information processing	−0.184	0.148	**0.272**	**0.031***	−0.100	0.436
Motor	0.031	0.811	0.032	0.803	−0.121	0.345
Attention/Working memory	−0.142	0.268	0.139	0.279	0.046	0.722
Executive functioning	−0.205	0.108	0.229	0.071	0.084	0.514

Spearman's rank correlations of clinical and neurocognitive measures with brain metabolism corrected for age, gender, and education years.
*$P < 0.05$; #$P < 0.05$ after Bonferroni correction.

Table 4
Backward stepwise logistic regression model to differentiate HIV-ANI from HIV-normal.

Feature	Estimate	Standard Error	*P*
(Intercept)	−12.106	4.339	0.005**
tCr/Total[a]	35.228	12.203	0.004**
Current CD4	−0.005	0.002	0.018*
Infection years	0.227	0.085	0.009**

[a] Total = tNAA + tCho + tCt; *$P < 0.05$. **$P < 0.01$.

Table 5
Comparison of ROC curves in differential diagnosis of HIV-ANI versus HIV-normal.

Feature Evaluated	AUC	(95 % CI)	Cut-off Value[b]	Sensitivity	Specificity	P[c]
Multivariate	0.805	(0.694, 0.890)	0.397	0.720	0.826	
tCr/Total[a]	0.696	(0.575, 0.799)	0.354	0.560	0.761	0.070
Current CD4	0.620	(0.497, 0.733)	374.000	0.480	0.826	0.014*
Infection years	0.635	(0.512, 0.746)	7.616	0.480	0.804	0.016*

*$P < 0.05$.
[a] Total = tNAA + tCho + tCr.
[b] The cutoff values of the ROC curves were the values of variables or the predicted probability of model with the maximum Youden index.
[c] The ROC curve for the multivariate model was compared with variables separately via Delong tests.

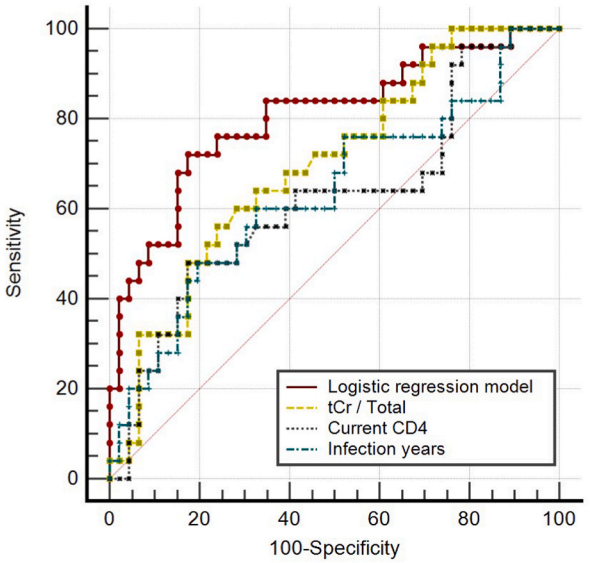

Fig. 2. Comparison of ROC curves in differential diagnosis of HIV-ANI versus HIV-normal. ROC curves of the logistic regression model, tCr/Total, current CD4 and infection years differentiating HIV-ANI from HIV-normal are presented. The diagonal line denotes reference.

workload, glial and neuronal cell injuries, as well as a surrogate for active gliosis [51]. Based on the classification model of HIV-ANI and HIV-normal groups, the relative concentration of tCr/total was an independent predictor of ANI in PLWH in addition to two clinical characteristics, the infection years and CD4 cell counts, suggesting the supplemental value of MRS examination in PLWH. Studies in animal models also showed that Cr concentration was sensitive to HIV-associated brain injuries [52]. Therefore, assessment of BG-Cr concentration can be beneficial to PLWH by detecting HIV-associated neurocognitive damages at an early stage.

NAA is synthesized in neuronal mitochondria, reflecting metabolic status of cell bodies and axons, and is considered a reliable indicator of neuronal integrity [47]. Decreased NAA indicated that there were neural damages in the BG of the ANI group. This finding was consistent with the multicenter longitudinal CHARTER study [33]. To our best knowledge, this was the only study in literature compared the MRS measures between ANI and NP normal PLWH. In that study, lower BG-NAA was associated with a higher likelihood of ANI; the differences in BG-NAA between ANI and NP normal PLWH persisted when the comparison was limited to subjects with viral suppression. It is worth mentioning that no significant group difference on BG-Cr was found in the CHARTER study. The discrepancy on the Cr finding in the two studies might be partly due to the different analytical methods for metabolite quantification: the CHARTER study used unsuppressed water signal as the internal reference, while our study used the combined signal of relevant metabolites. Future studies are needed to explore the influence of metabolite quantification methods on the current findings.

No BG-Cho difference was found between ANI and *N*P-normal PLWH in either the current study or the CHARTER study [33]. Cho is a cell membrane marker, which was increased in the BG of PLWH comparing to seronegative controls, indicating cell membrane disruption, cell proliferation, and active demyelination in PLWH [47]. The consistent findings of unchanged BG-Cho and altered BG-NAA in the ANI group comparing to *N*P-normal PLWH suggest that neuronal damages as indicated by abnormal NAA might be more relevant to cognitive dysfunctions than other HIV-associated brain cell damages.

Another finding in the current study was the association between altered brain metabolites and NP deficits in certain cognitive domains in PLWH with ANI or normal cognition. As the two PLWH subgroups were defined according to the overall cognitive performances, the correlations between the altered metabolite measures and the global CR were unsurprising. It is interesting that both increased tCr and decreased tNAA were significantly associated with greater impairments in learning and recall. Altered tCr and tNAA were also associated with impairments in speed of information processing and verbal fluency, respectively, although to a lesser extent. Similar correlations between brain metabolic levels and NP performances had been reported in previous studies [25,32]. A 3 T study reported decreased BG-NAA in PLWH with dementia comparing to other PLWH, and association of BG-NAA with speed of information processing [25]. A similar study reported associations of BG-myoinositol with speed of information processing and motor function in PLWH, although no associations of BG-NAA with NP scores were found [32]. A 7 T MRS study comparing PLWH with ANI and symptomatic HAND reported significant correlations between NAA concentration in the frontal white matter and various NP test performances, with no significant findings in BG metabolites [53]. Taken together, the association between BG-tCr and cognitive processing speed in PLWH we found in the current study was consistent with previous literatures. However, the altered BG metabolites in our study were not associated with motor function as previously reported [31]. Instead, they were associated with more complex cognitive functions such as learning, recall, and verbal fluency.

These discrepancies on altered metabolites and NP correlation findings are possibly due to several reasons. First, the current study only included PLWH with ANI and normal cognition, while previous studies included PLWH with dementia and PLWH with different levels of cognitive impairments. Thus, the deviations of NP performances in the whole PLWH sample were smaller in the current study, especially in the less complex cognitive domains such as motor, as reflected by SMD values. When comparing ANI with NP normal PLWH, the SMD of motor function was relatively smaller than other cognitive domains (0.573 vs. 0.845–1.551). Considering that the CR of motor function was larger than some other domains, it is possible that, although motor function was generally impaired in PLWH comparing to seronegative controls, it was not the main feature differing between cognitively normal or abnormal individuals within PLWH. Thus, no significant association was found between ANI-related BG metabolite alterations and ANI-unrelated motor functions in the current study. Second, our sample was characterized by younger age (35.3–39.06 y vs. 58.2–59.6 y in the 7 T study, 46.1–47.4 y in the 3 T study, respectively) and shorter infection duration (5.12–6.89 y vs. 19.2–19.9 y in 7 T study). Meanwhile, all subjects in our study were under viral suppression in peripheral blood, which was not the case in the previous two studies. These heterogeneities in study samples might partly explain the inconsistent findings on BG metabolites (no group difference was found in the 7 T study) and the cognitive domains associated with MRS measures (learning and recall ability in the current study vs. information processing speed in the 3 T study).

There were several limitations in the current study. First, we examined BG only to minimize the scanning time. We focused on the BG as previous studies suggested that metabolite alterations might be largely limited to the BG during the early stage of HIV infection [31]. We further focused on the right BG following the CHARTER study. Another reason was that our previous studies on the same population found more right-lateralized abnormalities which were associated with HIV infection or NP deficits in PLWH. The results of the current study might be biased due to the selection of brain region of interest. Future studies should include more target regions with potential metabolism differences between HIV-ANI and HIV-normal groups. Second, the sample sizes in the PLWH subgroups were relatively small. The ANI prediction model based on MRS metabolites and HIV-infection characteristics was not ready for clinical practice. Besides, due to the small sample size, confounding factors such as recent alcohol consumption and drug use were not considered in the current analysis. Multi-center and larger datasets are needed to further analyze the influence of confounding factors and improve the ANI prediction model in the future. Finally, the cross-sectional design of the present research was incapable of catching the dynamic process of HIV-related metabolic alterations. Longitudinal studies on PLWH with preclinical HAND are necessary.

5. Conclusions

The current study explored the BG metabolic differences between PLWH with ANI and PLWH with normal cognition using single-voxel MRS. Decreased tNAA and increased tCr in the right BG was found in the ANI group. The altered brain metabolites were further associated with NP deficits, especially deficits in learning and recall. These findings were in agreement with a large body of MRS studies on PLWH, most of which compared between PLWH and healthy controls or among PLWH with different levels of cognitive impairments. In sum, our study provided further evidence that altered BG metabolites were associated with HIV-related cognitive declines. More importantly, it suggested the possibility to distinguish ANI from cognitively normal PLWH by measuring brain metabolites via MRS, which is the first step in preventing adverse outcomes of HAND.

Author contributions

Y. Zhan and D-C. C.: participant recruitment, data collection, data analysis and manuscript writing. Y. L.: data analysis. Fengxiang S.: participant recruitment and data collection. Fei S: study design. Y. Zhang, P. S., and G. C.: participant recruitment and data collection. H. W.: results interpretation. Y. S.: study design, study conceptualization, project administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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