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Hippocampo-Horn Percentage and Parietal Atrophy Score for Easy Visual Assessment of Brain Atrophy on Magnetic Resonance Imaging in Early- and Late-Onset Alzheimer's Disease

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Abstract.
Background: Magnetic resonance imaging (MRI) visual scales of brain atrophy are important for differential diagnosis of dementias in routine clinical practice. Atrophy patterns in early- and late-onset Alzheimer's disease (AD) can be different according to some studies.
Objective: Our goal was to assess brain atrophy patterns in early- and late-onset AD using our recently developed simple MRI visual scales and evaluate their reliability.
Methods: We used Hippocampo-horn percentage (Hip-hop) and Parietal Atrophy Score (PAS) to compare mediotemporal and parietal atrophy on brain MRI among 4 groups: 26 patients with early-onset AD, 21 younger cognitively normal persons, 32 patients with late-onset AD, and 36 older cognitively normal persons. Two raters scored all brain MRI to assess reliability of the Hip-hop and PAS. Brain MRIs were obtained from Alzheimer's Disease Neuroimaging Initiative (ADNI) database.
Results: The patients with early-onset AD had significantly more pronounced mediotemporal and also parietal atrophy bilaterally compared to the controls (both $p < 0.01$). The patients with late-onset AD had significantly more pronounced only mediotemporal atrophy bilaterally compared to the controls ($p < 0.000001$), but parietal lobes were the same. Intra-rater and inter-rater reliability of both visual scales Hip-hop and PAS were almost perfect in all cases (weighted-kappa value ranged from 0.90 to 0.99).
Conclusion: While mediotemporal atrophy detected using Hip-hop is universal across the whole AD age spectrum, parietal atrophy detected using PAS is worth rating only in early-onset AD. Hip-hop and PAS are very reliable MRI visual scales.

Keywords: Early-onset Alzheimer's disease, hippocampo-horn percentage, late-onset Alzheimer's disease, mediotemporal atrophy, parietal atrophy score, parietal atrophy, reliability

[1]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: https://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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INTRODUCTION

Brain magnetic resonance imaging (MRI) can support the diagnosis of Alzheimer's disease (AD) [1]. Tissue loss in the mediotemporal area is typical for late-onset AD (patients older than 65 years) [2–13]. Distribution of atrophy in patients with early-onset AD (individuals younger than 65 years) is not so obvious. More pronounced atrophy of the parietal lobes with less affected mediotemporal region could be more typical for these younger patients based on some studies [14–17].

Atrophy of brain structures can be assessed on MRI using quantitative techniques such as manual or automatic segmentation [2, 8, 18–21]. Accuracy and objectivity of these approaches are main adv antages. However, automatic segmentation requires specialized software and manual segmentation is time-consuming. These quantitative techniques detect well-known mediotemporal atrophy in patients with AD and also parietal atrophy (smaller precuneus and cingulate gyrus) more typical for patients with early-onset AD [22, 23].

MRI visual scales represent easier and faster option to evaluate brain atrophy and thus are more suitable for routine clinical practice [24–26]. Their possible disadvantage can be lower reliability compared to quantitative methods, because evaluations are performed by different raters who can have different experience. Previous studies using MRI visual scales achieved comparable results as studies with quantitative techniques mentioned above [27–30]. The most used visual scales are Scheltens scale for the mediotemporal atrophy and Koedam scale for the parietal atrophy. However, these visual scales may be complicated and time consuming for routine clinical practice.

The aim of our study was to assess parietal and mediotemporal atrophy in patients with early- and late-onset AD using our simple MRI visual scales. We also wanted to evaluate reliability of these scales. The Parietal Atrophy Score (PAS) for evaluation of the parietal region was introduced in our previous reports [31–33]. Hippocampo-horn percentage for evaluation of the mediotemporal atrophy was developed based on our previous findings [2, 3].

We assumed that we will be able to determine and confirm different atrophy patterns in early- and late-onset AD using our new and simple MRI visual scales which could be suitable for routine clinical practice. We believed that these results could be useful in differential diagnosis of neurodegenerative dementias especially AD in clinical field.

MATERIALS AND METHODS

Visual scale of mediotemporal atrophy

Hippocampo-horn percentage (Hip-hop) is based on determining the ratio between the hippocampal area and the sum of the hippocampal area and the temporal horn area of the lateral ventricle in percentages on one suitable MRI slice which is clearly defined and is easy to find. The suitable slice is defined as the first coronal MRI slice in the antero-posterior direction where amygdala is no longer visible. Our recent paper describes a detailed explanation how to select this optimal slice for Hip-hop determination [3]. Hip-hop can theoretically range between 0% (total atrophy – hippocampus is not visible) and 100% (completely spared structure of the hippocampus), 20–90% in real clinical practice. More detailed Hip-hop scoring instructions are summarized in the Supplementary Material.

Visual scale of parietal atrophy

The PAS is based on evaluation of atrophy degree in three parietal lobe structures: sulcus cingularis posterior, precuneus and parietal gyri. Each structure is ranked separately left and right 0 (no atrophy), 1 (borderline finding) or 2 (prominent atrophy). The degree of atrophy in each structure is evaluated on MRI coronal slices in the range of whole parietal lobes. Evaluation of the PAS in antero-posterior direction begins from first slice where cerebellar hemispheres are visible and continues until parietooccipital sulcus first appears. PAS is determined from a combination of atrophy degrees separately in the left and right hemisphere according to specific rating criteria and can be quantified 0 (parietal lobe without atrophy), 1 (border-line atrophy) or 2 (prominent atrophy of the parietal lobe) [31–33]. PAS scoring instructions are summarized in Supplementary Material.

Alzheimer's Disease Neuroimaging Initiative

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu), more specifically from ADNI-1, ADNI-GO and ADNI-2 study. The ADNI was launched in 2003 as a public-private partnership, led by Principal Investi-

gator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial MRI, positron emission tomography, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment and early AD.

Participants and MRI protocol

Diagnoses of AD were established by ADNI according to the neurological examination, cognitive tests and using the biomarkers of AD. We selected AD patients with mild impairment of cognitive functions (Mini-Mental State Examination (MMSE) 22 ± 4). Cognitively normal subjects were defined as those with normal neurological examination and normal cognitive test (MMSE 29 ± 1). We divided our participants into those with younger age (< 65 years) and ones older than 65 years.

We created four groups: 1) patients with late-onset AD (AD patients older than 65 years), 2) older cognitively normal subjects, 3) patients with early-onset AD (AD patients younger than 65 years), and 4) younger cognitively normal subjects.

We first compared mediotemporal and parietal atrophy using our MRI visual scales (Hip-hop, PAS) between patients with late-onset AD and older cognitively normal elderly subjects, patients with early-onset AD and younger cognitively normal persons.

In the second step we compared atrophy between older and younger cognitively normal persons, patients with late- and early-onset AD.

Correlation of the Hip-hop and PAS with age was calculated using all cognitively normal subjects (older and younger group together).

Detailed participant's characteristics are visualized in Table 1. Patients with early- and late-onset AD were age-matched with cognitively normal subjects in both cases. Patients with early- and late-onset AD had equal cognitive impairment according to MMSE scores.

Brain MRI of these patients were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. 94% patients were examined by the following imaging protocol: Acquisition Plane = sagital; Acquisition Type = 3D; Coil = PA; Field Strength = 1.5 tesla; Flip Angle = 8.0 degree; Manufacturer = SIEMENS; Matrix X = 192.0 pixels; Matrix Y = 192.0 pixels; Matrix Z = 160.0; Mfg Model = SonataVision; Pixel Spacing X = 1.25 mm; Pixel Spacing Y = 1.25 mm; Pulse Sequence = IR/GR; Slice Thickness = 1.2 mm; TE = 3.54 ms; TI = 1000.0 ms; TR = 2400.0 ms; Weighting = T1.

Characteristics of raters and reliability assessment (intra- and inter-rater agreement)

Rater 1 was a neurologist with 6-year experience in the assessment of brain atrophy using MRI visual scales. He rated all brain MRI twice with an interval 2 years between evaluations to evaluate intra-rater agreement. The rater was blinded for clinical information (diagnosis, age), for his previous rating and for the rating of second rater. This rater achieved very good intra- and inter-rater agreement with other experienced evaluators in our previous study about the PAS reliability [31]. First scoring of this rater was used to assess differences in brain atrophy between 4 groups.

Rater 2 was a medical doctor and PhD student with 3-year experience in the assessment of brain atrophy using MRI visual scales. She rated all brain MRI first to assess inter-rater agreement with rater 1. She rated 40 brain MRI (10 from each group) after 6 weeks to assess intra-rater agreement. Rater 2 was also blinded for clinical information (diagnosis, age), for her previous rating and for the rating of the first rater. Rater 2 also achieved very good intra- and inter-rater agreement with another evaluators in our previous study about the PAS reliability [31].

Table 1
Characteristics of participants

	LOAD	OCN	LOAD versus OCN	EOAD	YCN	EOAD versus YCN
Number of subjects	32	36	n.a.	26	21	n.a.
Mean age (y)	80	80	n.s.	63	64	n.s.
MMSE (points)	22 ± 4	29 ± 1	$p < 0.001$	22 ± 4	29 ± 1	$p < 0.001$
Sex (male/female)	19/13	14/22	n.a.	14/12	11/10	n.a.

LOAD, patients with late-onset Alzheimer's disease; EOAD, patients with early-onset Alzheimer's disease; OCN, old cognitively normal subjects; YCN, young cognitively normal subjects; MMSE, Mini-Mental State Examination; n.s., not significant; n.a., not available/applicable.

Statistical analysis

Statistical analysis was performed using software Statistica and Medcalc. We used non-parametric Mann-Whitney U test to compare Hip-hop and PAS scores between the groups.

We also performed Receiver Operating Characteristic (ROC) analysis to determine specificity and sensitivity of our visual scales in diagnosis of early- and late-onset AD.

Kappa statistics was used to assess intra-rater and inter-rater agreement (reliability).

Spearman's rank correlation coefficient was used to assess correlation of the PAS and Hip-hop with age.

RESULTS

Comparison of Hip-hop and PAS scores between the patients with AD and the cognitively normal subjects

Patients with late-onset AD had significantly more pronounced mediotemporal atrophy compared to cognitively normal subjects using Hip-hop. No significant difference was found in atrophic changes of the parietal lobes using PAS between these groups (Table 2).

Patients with early-onset AD had significantly more pronounced mediotemporal atrophy using Hip-hop and also parietal atrophy using PAS compared to cognitively normal persons (Table 2).

Comparison of Hip-hop and PAS scores between older and younger cognitively normal persons and between the patients with early- and late-onset AD

Older cognitively normal persons had significantly more pronounced mediotemporal atrophy bilaterally compared to the younger cognitively normal subjects, but parietal lobes were the same (Table 2).

Patients with early-onset AD had significantly more pronounced parietal atrophy bilaterally compared to the patients with late-onset AD (Table 2). Patients with late-onset AD had more pronounced mediotemporal atrophy bilaterally compared to the younger patients (Table 2).

Table 2
Comparison of Hip-hop and PAS scores among patients with late- and early-onset AD and younger and older cognitively normal subjects

	OCN Median (IQR)	LOAD Median (IQR)	LOAD versus OCN p value	YCN Median (IQR)	EOAD Median (IQR)	EOAD versus YCN p value	OCN versus YCN p value	LOAD versus EOAD p value
Hip-hop right	78% (20%)	40% (30%)	$p<0.000001$	90% (10%)	70% (40%)	$p<0.0001$	$p<0.001$	$p<0.0001$
Hip-hop left	80% (20%)	38% (28%)	$p<0.000001$	80% (10%)	80% (30%)	$p<0.01$	$p<0.01$	$p<0.00001$
SCP right	1 (2)	0 (1)	n.s.	0 (1)	1 (1)	$p<0.001$	n.a.	
PRE right	0,5 (1)	0 (1)	n.s.	1 (1)	1 (1)	n.s.		
PG right	1 (1)	1 (1)	$p<0.05$	1 (1)	2 (1)	$p<0.01$		
PAS right	1 (1)	1 (2)	n.s.	1 (2)	2 (0)	$p<0.01$	n.s.	$p<0.001$
SCP left	1 (2)	0 (1)	$p<0.01$	0 (0)	1 (1)	$p<0.0001$	n.a.	
PRE left	0,5 (1)	0 (1)	n.s.	1 (1)	1 (1)	$p<0.01$		
PG left	1 (1)	1 (1)	n.s.	1 (1)	2 (1)	$p<0.01$		
PAS left	1 (1)	0,5 (2)	n.s.	1 (2)	2 (1)	$p<0.001$	n.s.	$p<0.001$

LOAD, patients with late-onset Alzheimer's disease; EOAD, patients with early-onset Alzheimer's disease; OCN, old cognitively normal subjects; YCN, young cognitively normal subjects; Hip-hop, Hippocampal-Horn percentage; PAS, Parietal Atrophy Score; SCP, sulcus cingularis posterior; PRE, precuneus; PG, parietal gyri; n.s., not significant; n.a., not available.

Table 3
Sensitivity and specificity of Hip-hop and PAS in diagnosis of early- and late-onset AD

	OCN versus LOAD			YCN versus EOAD		
	Cut-off	Sensitivity	Specificity	Cut-off	Sensitivity	Specificity
Hip-hop left	≤60%	88%	83%	≤75%	62%	91%
Hip-hop right	≤60%	84%	92%	≤70%	58%	100%
PAS left	≤0	50%	78%	>1	73%	71%
PAS right	≤0	44%	78%	>1	77%	62%

LOAD, late-onset Alzheimer's disease; EOAD, early-onset Alzheimer's disease; OCN, old cognitively normal subjects; YCN, young cognitively normal subjects; Hip-hop, Hippocampal-Horn percentage; PAS, Parietal Atrophy Score.

Correlation of the Hip-hop and PAS with age in cognitively normal subjects

We found significant negative correlation between the Hip-hop and age on the right ($r = -0.43$, $p < 0.001$) and also on the left ($r = -0.34$, $p < 0.01$).

Correlation between the PAS and age was not significant on the right ($r = 0.11$, $p = 0.40$) or on the left ($r = 0.22$, $p = 0.07$)

Sensitivity and specificity of Hip-hop and PAS in diagnosis of early- and late-onset AD

Hip-hop achieved high specificity and sensitivity in diagnosis of late-onset AD. Specificity of the Hip-hop in diagnosis of early-onset AD was also high, but sensitivity was lower (Table 3).

PAS achieved good specificity and sensitivity in diagnosis of early-onset AD. Specificity of the PAS in diagnosis of late-onset AD was also quite good, but sensitivity was low (Table 3).

Hip-hop is significantly better visual scale in diagnosis of late-onset AD compared to PAS according to the comparison of the areas under receiver operating characteristic curves (Table 4). We did not find significant difference between Hip-hop and PAS in diagnosis of early-onset AD (Table 4).

Reliability of Hip-hop and PAS

Intra-rater agreement of the neurologist and the medical doctor in Hip-hop and PAS were almost perfect in all cases. Inter-rater agreement between the neurologist and the medical doctor in Hip-hop and PAS were also almost perfect in all cases. Weighted-kappa values are summarized in Table 5.

We also used first scoring of Rater 2 (medical doctor) to assess differences among our four groups: patients with late-onset AD, older cognitively normal subjects, patients with early-onset AD, and younger cognitively normal subjects. The results calculated from medical doctor scoring matched the results calculated from neurologist scoring, which are used in our manuscript. Significant differences in mediotemporal and parietal atrophy were between patients with early-onset AD and controls. Significant difference was only in mediotemporal and not parietal atrophy between patients with late-onset AD and controls. Results of comparison of late- and early-onset AD patients, and older and younger cognitively normal subjects were also same when we used scoring of Rater 2 in statistics.

DISCUSSION

Our results with the PAS and Hip-hop in AD patients with mild impairment of cognitive functions confirmed the hypothesis based on some previous studies that mediotemporal atrophy is typical for both late- and early-onset AD, but less pronounced in these younger patients [14–17]. Parietal atrophy seems to be more typical for patients with early-onset AD compared to late-onset AD [14–17, 22, 27].

We proved that our simple MRI visual scales Hip-hop and PAS are very reliable with almost perfect

Table 4
Comparison of areas under receiver operating characteristics curves of PAS and Hip-hop in late- and early-onset AD

		Hip-hop right	PAS right	Comparison of AUC	Hip-hop left	PAS left	Comparison of AUC
OCN versus LOAD	AUC	0.93	0.60	$p < 0.0001$	0.93	0.63	$p < 0.0001$
YCN versus EOAD	AUC	0.85	0.71	n.s.	0.76	0.76	n.s.

LOAD, patients with late-onset Alzheimer's disease; EOAD, patients with early-onset Alzheimer's disease; OCN, old cognitively normal subjects; YCN, young cognitively normal subjects; n.s., not significant; Hip-hop, Hippocampo-horn percentage; PAS, Parietal Atrophy Score; AUC, Area Under the ROC Curve; ROC, Receiver Operating Characteristic.

Table 5
Intra-rater and inter-rater agreement in Hip-hop and PAS expressed as weighted-kappa value

	weighted-kappa value for Hip-hop right/left	weighted kappa value for PAS right/left	weighted-kappa value for Hip-hop right/left	weighted kappa value for PAS right/left
Rater	neurologist 1. rating	neurologist 1. rating	medical doctor 2.rating	medical doctor 2. rating
neurologist 2. rating	0.97 / 0.96	0.95 / 0.97	n.a.	n.a.
medical doctor 1. rating	0.94 / 0.93	0.90 / 0.96	0.94 / 0.91	0.91 / 0.99

Hip-hop, Hippocampo-horn percentage; PAS, Parietal Atrophy Score; n.a., not available.

intra-rater and inter-rater agreement. These results are even better than reliability results of PAS from our previous study [31]. We think that explanation of this improvement can be effect of learning. Both raters in our current study also participated in reliability assessment of the PAS in our previous paper and have gained more experience with this visual scale.

The results (differences in atrophy between our four groups) calculated from medical doctor scoring matched the results calculated from neurologist scoring, which are used in our manuscript and mentioned above. The results are consistent because inter-rater reliability of our visual scales was almost perfect.

Moreover, Hip-hop and PAS are used only in coronal MRI slices, which can spare the time during atrophy evaluation in routine clinical practice. PAS has been recently introduced in our studies [31–33]. This is the first report of Hip-hop estimated in an optimal coronal MRI slice described in the recent paper [3]. We consider our new easily applicable and very reliable visual scales as the main strengths of our study.

Some limitations of our study should be mentioned. Diagnoses of AD were not confirmed at autopsy. However, diagnoses were established based on clinical examination with support of novel biomarkers of AD. Presence of atypical forms of AD in our sample from ADNI is unknown. They can have different atrophy patterns. We did not use a quantitative method to support accuracy of our visual scales in this study. We do not have clear explanation why the atrophy of sulcus cingularis left and parietal gyri right was significantly more pronounced in older cognitively normal subjects compared to the patients with late-onset AD. PAS should be used mainly for diagnosis of early-onset AD.

Mediotemporal atrophy assessed using Hip-hop is more pronounced in older cognitively normal subjects according to the correlation of the Hip-hop with age and comparison of older and younger cognitively normal group. This should be taken into account during evaluation in clinical practice. Our control groups of cognitively normal persons were age-matched with AD patients. It means that our results should not be influenced by this phenomenon. Parietal atrophy assessed using PAS was not different between older and younger controls. Correlation of the PAS with age also was not significant. This confirms results with the PAS from our previous study [32]. It could mean that more pronounced atrophy in this region is probably not accompanied with normal aging and should be considered as pathologic.

Hip-hop can support the diagnosis of both early- and late-onset AD. PAS can support mainly the diagnosis of early-onset AD. Hip-hop seems to be better visual scale in diagnosis of late-onset AD compared to PAS because parietal atrophy is negligible and comparable in these older AD patients and controls [33]. PAS could be useful in differential diagnosis between frontotemporal lobar degeneration (FTLD) and early-onset AD. Mediotemporal atrophy is typical for these early-onset dementias, but parietal atrophy is not typical for FTLD where frontal lobes are usually more affected [34–38].

Different patterns of brain atrophy in early- and late-onset AD may be related to different clinical presentations of these subtypes. Recent episodic memory is usually mostly affected in patients with late-onset AD (greater hippocampal atrophy). Atypical clinical forms with early decline in other cognitive abilities, e.g. visuospatial functions are more frequent in patients with early-onset AD (greater parietal atrophy) [39–41].

We believe that Hip-hop and PAS could be useful tools in differential diagnosis of neurodegenerative dementias especially AD in routine clinical practice.

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SUPPLEMENTARY MATERIAL

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