



# Diagnostic manifestations of total hemispheric glucose metabolism ratio in neuronal network diaschisis: diagnostic implications in Alzheimer's disease and mild cognitive impairment

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## Abstract

**Purpose** We tested the hypothesis that lateralized hemispheric glucose metabolism may have diagnostic implications in Alzheimer's disease (AD) and mild cognitive impairment (MCI).

**Methods** We performed FDG-PET/CT in 23 patients (mean age 63.7 years, range 50–78, 17 females) diagnosed with AD ( $n = 15$ ) or MCI ( $n = 8$ ) during a six-month period in 2014. Ten neurologically healthy individuals (HIs) (mean age 62.5 years, range 43–75, 5 females) served as controls. A neuroimaging expert provided visual assessment of diaschisis. The total hemispheric glucose metabolism ratio (THGr) was calculated, and with area-under the curve of receiver operating characteristics (AUC-ROC) we generated a “Network Diaschisis Test (NDT)”.

**Results** The qualitative detection of cerebral (Ce) and cerebellar (Cb) diaschisis was 7/15 (47%), 0/8 (0%), and 0/10 (0%) in AD, MCI, and HI groups, respectively. Median cerebral THGr was 0.68 (range 0.43–0.99), 0.86 (range 0.64–0.98), and 0.95 (range 0.65–1.00) for AD, MCI, and HI groups, respectively ( $p = 0.04$ ). Median cerebellar THGr was, respectively, 0.70 (range 0.18–0.98), 0.70 (range 0.48–0.81), and 0.84 (range 0.75–0.96) ( $p = 0.0138$ ). A positive NDT yielded a positive predictive value of 100% for the presence of AD or MCI and a 86% negative predictive value for healthy brain. Moreover, the diagnostic manifestation of THGr between MCI and AD led to a positive predictive value of 100% for AD, but a negative predictive value of 42.9% for MCI.

**Conclusion** Patients with AD or MCI had more pronounced diaschisis, lateralized hemispheric glucose metabolism and lower THGr compared to healthy controls. The NDT distinguished AD and MCI patients from HIs, and AD from MCI patients with a high positive predictive value and moderate and low negative predictive values. THGr can be a straightforward source of investigating neuronal network diaschisis in AD and MCI and in other cerebral diseases, across institutions.

**Keywords** Diaschisis · Neuronal network · FDG-PET/CT · Alzheimer's disease · Mild cognitive impairment

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## Introduction

A loss or change in the function of neurons triggered by distant brain damage has been known as diaschisis since the first description by von Monakow in 1914 [1]. This neurological alteration can be visualized as asymmetrical glucose metabolism in the brain by PET of 2-[<sup>18</sup>F] fluoro-2-deoxy-D-glucose (FDG) uptake. The symptoms of an underlying impairment of brain connectivity have been linked to the focal lesions caused by apoplexy [2, 3], tumours [4, 5], and trauma [6]. Basal ganglia or thalamic diaschisis have also been reported in Alzheimer's disease (AD) [7] and may be present in other dementias associated with the regional decline of cerebral glucose metabolism [8]. Mapping neuronal networks and synaptic interconnections are of fundamental importance in cognitive neuroscience and neuropsychology. Studies of human brain networks and the identification of variable neuronal architectures are the goals of programs such as the Human Connectome Project [9, 10]. Connectivity is the driver of brain energy turnover in neuronal networks, as shown by "resting state" network activity recorded by functional MRI (fMRI). The fMRI signals, in turn, can be related to glucose metabolic rates in the brain measured by FDG-PET [11, 12], and asymmetrical changes in the glucose metabolism of fore- and hind-brain have been detected in patients with AD [7]. Whether this lateralized disconnection in AD is primarily due to diaschisis, rather than local differences in the degree of pathology, is uncertain. Indeed, the presence of lateralized glucose metabolism as an indication of hemispheric diaschisis in patients with AD supports the hypothesis of AD as a syndrome of disconnection [13, 14]. The total hemispheric glucose metabolism ratio (THGr) is an index of the degree of hemispheric lateralization of brain glucose metabolism. The methodology provided evidence of cerebral and cerebellar diaschises in patients afflicted by stroke [15] and glioma [16], yielding prognostic information in the latter. Further, cognitive decline in stroke patients with thalamocortical diaschisis has been associated with lateralized hemispheric glucose metabolism [16, 17]. Quantification of glucose metabolism in the neuronal network of the brain may bear evidence of early intra- or interhemispheric disconnectivity related to various conditions including the onset of the AD [7]. Here, we tested the hypothesis that lateralized hemispheric glucose metabolism may have diagnostic implications in AD or mild cognitive impairment (MCI).

## Material and methods

We analyzed clinical data of 41 patients admitted to the Dementia Clinic of Odense University Hospital during the first six months of a single year as part of an investigation of the clinical relevance of FDG-PET/CT in all patients referred

to the clinic. For greater homogeneity of patient material, the inclusion criterion for the study was a final ICD-10 diagnosis of either MCI or AD. Thus, we excluded 18 patients with a final diagnosis of depression ( $n = 3$ ), psychiatric disorder ( $n = 5$ ), other types of dementia ( $n = 6$ ) or other neurological diagnosis ( $n = 4$ ). The remaining 23 patients underwent standard clinical examinations including history taking, blood sampling, structural imaging with CT or MRI and neuropsychological testing in addition to the exploratory FDG-PET/CT scan that was performed contributing to a final diagnosis. Ten healthy individuals (HIs) were recruited independently by public advertisement, all of them without known cognitive deficits, severe brain trauma, neurological disease, addiction, or medication use affecting the central nervous system. These HIs served as the age-matched control group with similar gender distribution, and as such, they had one FDG-PET/CT examination.

The study was approved by the Danish Data Protection Agency (J.nr. 2014-41-3474) and the Danish Patient Safety Authority (J.nr.3-3013-2055/1). The data collection was approved by the Danish National Committee on Health Research Ethics (no. s-20120056) and registered at [ClinicalTrials.gov](https://www.clinicaltrials.gov) (NCT01724749). Also, an approval from an ethical standards committee to conduct this study was received, and all subjects signed an informed consent.

## Cognitive rating scales

The patients were assessed for their cognitive state with the Mini-Mental State Examination (MMSE) and the Cambridge Cognitive Capacity Scale (CAMCOG) at the Dementia Clinic of Odense University Hospital. Both tests were paper-based. These tests both have individualised cut-off values as a recommendation for the diagnosis of early-stage dementia, as shown in a study performed in Odense [18]. If there was any doubt about the diagnosis, further neuropsychological examination was performed.

## Imaging data acquisition protocol

Patients and control subjects fasted for six hours before injection of FDG. Then they rested supine on the tomograph bed in a dark and quiet room with their head immobilised in a dedicated headrest. Participants rested for 10 min before the tracer was injected intravenously using a mean dose of 200 MBq of FDG for patients and of 4 MBq/kg body weight for control subjects. The images were obtained with a General Electric Discovery PET/CT 690 or 710 scanner with an acquisition protocol in which each frame had 47 slices (3.3 mm) and a dual field of view of 250 × 250 mm (matrix 256 × 256 pixels). We applied CT-derived attenuation and iteratively reconstructed the data using time-of-flight ordered subset expectation maximisation. The data from 52 to 67 min were summed

and used for analysis. Similarly, the data from 45 to 60 min were summed and used for analyses of the HI scans. Images were normalized, and standardised uptake values (SUV) were calculated.

### Visual assessment of PET images

The PET images were visually assessed for hemispheric diaschisis by a nuclear medicine physician specialised in neuroimaging. This qualitative assessment was blinded for the THGr outcome. Each image was assessed for hemispheric diaschisis using the following scale for cerebrum and cerebellum: - = symmetric and/or probably symmetric transhemispheric glucose metabolism; + = probably asymmetric transhemispheric glucose metabolism; ++ = asymmetric transhemispheric glucose metabolism.

### Quantitative PET analysis

For quantitative analysis of the cerebral FDG-PET images, we used the THGr method described by Segtnan et al. in patients with glioma [16]. Each hemisphere was segmented with ROVER software (ABX, Radeberg, Germany). The highest glucose metabolism index was identified by a top-down thresholding procedure in each hemisphere. Each PET brain scan was manually divided into four volumes of interest, one for each cerebral (Ce) and cerebellar (Cb) hemisphere. After finding the SUVmax value for each global hemisphere in the four volumes of interest, we applied a threshold-based segmentation to each hemisphere: cerebral lower threshold = SUVmax (for global hemisphere) – 3 SUV units, and cerebellar lower threshold = SUVmax (for global hemisphere) – 2 SUV units. The total hemispheric glucose metabolism (THG) (segmented volume  $\times$  partial volume corrected SUVmean) was computed using the segmented voxels in each hemisphere. The “top-down” SUV thresholds have been previously determined in glioma patients with cerebro-cerebellar diaschisis [16]. Hence, we wanted to test the same thresholds in AD and MCI brains suspicious of having diaschisis. The hemisphere with the lowest THG was indexed to the contralateral hemisphere, with the resulting THG ratio ranging between zero and one; the latter indicating symmetrical hemispheric glucose metabolism. The segmented volume value was low in some patients ( $n=6$  in the cerebrum,  $n=4$  in the cerebellum) possibly creating a systematic bias of imbalanced glucose metabolism between hemispheres (low THGr). In order to minimize this bias in patients (marked with ‘a’ in Table 1) we did the following: we titrated the “top-down” thresholding with one SUV unit at a time until the THG value, as a minimum, exceeded 100 SUV units (THG) in cerebrum or 50 SUV rates (THG) in cerebellum; due to the observation that the healthy controls did not have volumes below these rates.

### Statistical analysis

Pairwise correlations between THGr, MMSE, and CAMCOG scores were assessed with Spearman’s rho. In a hierarchical testing procedure, the Kruskal-Wallis test was used to identify statistically significant differences of THGr between AD and MCI patient groups and HIs. To this end, the global hypothesis of any differences between the three groups was tested first; if rejected, pairwise comparisons between the three groups followed. We used ROC analysis to ascertain the THGr as a potential diagnostic predictor differentiating AD or MCI from HI by interpreting the AUC-ROC and to establish if the THGr value could differentiate the AD and MCI groups from each other by using ROC-derived optimal cut-off points. The latter was indicated by the point on the ROC curve being closest to (0,1) [19]. Moreover, by using the ROC-derived THGr thresholds, we generated  $4 \times 4$  tables (Tables 2 and 3). In these tables, the THGr values for both hindbrain and forebrain in each patient were given, according to the ROC thresholds. In our previous study performed in patients with specific cerebrocerebellar diaschisis inflicted by glioma, the THGr method yielded findings of prognostic value [16]. Here, we adopted the less restrictive term network diaschisis to indicate that disorders of connectivity are known now to affect multiple clusters of networks potentially. Positive and negative predictive values were supplemented with Wilson score-based 95% confidence intervals. Level of significance was 5%. STATA/IC 13.1 software (StataCorp, College Station, Texas 77,845 USA) was used for all statistical analyses.

### Results

We included the FDG-PET/CT brain images of 23 patients (17 females) with a final diagnosis of AD ( $n=15$ ) or MCI ( $n=8$ ), aged 50 to 78 years (mean age 63.7 years). The AD and MCI patients had a mean MMSE score of 20.5 (range: 11–30) and 24.9 (range: 16–29), and a mean CAMCOG score of 70.0 (range: 40–98) and 83.8 (range: 60–98), respectively. Ten age-matched HIs aged 43 to 75 years (mean age 62.5 years) were also included (5 females). The clinical and imaging characteristics of the AD and MCI patients are listed in Table 1.

### Visual PET analysis correlated to diagnosis and quantitative analysis

Qualitative examination of the FDG-PET scans detected diaschisis in the hemispheric networks of forebrain and hindbrain in 47% (7/15) of AD patients and 0% of MCI patients and HIs. The independent visual detection rate of diaschisis in the hemispheric network of hindbrain was 47% (7/15), 12.5% (1/8), and 0% (0/10) in patients with AD and MCI, and in HIs,

**Table 1** Cerebral and cerebellar total hemispheric glucose metabolism ratio (THGr) and visual assessment of diaschisis in patients with mild cognitive impairment (MCI) and Alzheimer’s disease (AD)

Age (years)	D	MMSE	CAMCOG	Cerebrum			Cerebellum		
				THGr	Visual	HL <sup>a</sup>	THGr	Visual	HL <sup>a</sup>
72	MCI	27	98	0.64	–	R	0.76	–	R
77	MCI	24	86	0.88	–	R	0.55	–	L
64	MCI	26	86	0.77	–	R	0.71	+	R
62	MCI	29	95	0.84	–	R	0.81	–	R
66	MCI	21	60	0.98	–	R	0.72	–	R
78	MCI	27	88	0.76	–	L	0.48	–	R
59	MCI	16	66	0.97 <sup>a</sup>	–	L	0.68	–	R
50	MCI	29	91	0.96	–	L	0.49 <sup>a</sup>	–	L
54	AD	24	84	0.99 <sup>a</sup>	+	L	0.94	–	R
69	AD	15	N/A	0.80 <sup>a</sup>	++	L	0.98	+	R
53	AD	26	84	0.56	++	R	0.94	–	L
63	AD	20	73	0.48 <sup>a</sup>	++	L	0.87	+	R
62	AD	17	54	0.87	–	R	0.66	–	R
59	AD	14	51	0.68	++	L	0.75	++	R
61	AD	27	82	0.97 <sup>a</sup>	++	L	0.77	–	R
55	AD	30 <sup>b</sup>	98	0.64	–	L	0.58 <sup>a</sup>	–	R
64	AD	24	71	0.87	–	L	0.83 <sup>a</sup>	–	R
64	AD	20	74	0.93	+	R	0.18	–	R
67	AD	15	58	0.91	+	R	0.70 <sup>a</sup>	+	R
74	AD	27	84	0.55	–	L	0.65	–	L
58	AD	11	40	0.64 <sup>a</sup>	+	R	0.55	+	R
68	AD	14	52	0.53	++	R	0.37	++	L
58	AD	23	75	0.43	++	L	0.55	+	R

D diagnosis, MMSE Mini-Mental State Examination, CAMCOG Cambridge Cognitive Capacity scale, AD Alzheimer’s disease, MCI mild cognitive impairment, HL hemisphere with lowest glucose consumption, R right, L left; N/A not applicable; – symmetric and/or probably symmetric transhemispheric glucose metabolism transhemispheric; + probably asymmetric transhemispheric glucose metabolism, ++ asymmetric transhemispheric glucose metabolism

<sup>a</sup>“Top-down” thresholding was used (see section Materials and methods, Quantitative PET analysis)<sup>b</sup> Further neuropsychological testing showed impaired memory

respectively. Hemispheric diaschisis in the forebrain network was qualitatively detected in 73% (11/15) of AD patients compared to 0% of MCI patients and HIs. The qualitative confirmations of hemispheric diaschisis are listed in Table 1 and

displayed in Figs. 1 and 2. Network diaschisis was qualitatively present in 60% (3/5) of the patients when both hindbrain and forebrain THGr were low (i.e., less than ROC threshold 0.76(Ce) and 0.71(Cb)). On the other hand, if only THGr(Cb)

**Table 2** NDT. Diagnostic implications of cerebral and cerebellar total hemispheric glucose metabolism ratio (THGr) for discrimination between patients with Alzheimer’s disease (AD) or mild cognitive impairment (MCI) and healthy individuals (HI)

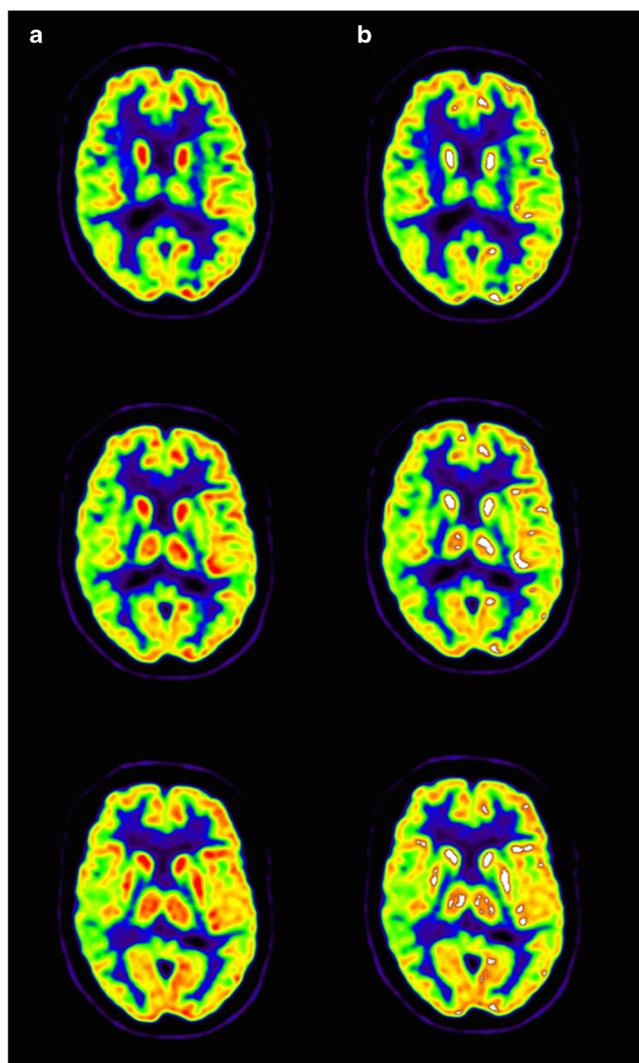
Test interpretation	Test <sup>a</sup> cerebrum	Test <sup>a</sup> cerebellum	AD	MCI	HI	Diagnostic manifestation (95% CI)
<b>Negative</b> Both tests above threshold	Above	Above	1	–	6	NPV 85.7% (48.7–97.4)
<b>Positive</b> One or both tests below the threshold	Below	Above	4	1	3	PPV 62.5% (30.6–86.3)
	Above	Below	3	3	1	PPV 85.7% (48.7–97.4)
	Below	Below	7	4	–	PPV 100% (74.1–100)
<b>Total</b>	–	–	15	8	10	–

AD Alzheimer’s disease, CI confidence interval, MCI mild cognitive impairment, HI healthy individual, NPV negative predictive value, PPV, positive predictive value<sup>a</sup> The cut-off points for THGr in cerebrum and cerebellum were obtained by ROC analysis. Dichotomization for cerebral THGr: above=>0.91 and below =< 0.91; dichotomization for cerebellar THGr; above=>0.79 and below =< 0.79

**Table 3** NDT: Diagnostic implications of cerebral and cerebellar total hemispheric glucose metabolism ratio (THGr) for discrimination between Alzheimer's disease (AD) and mild cognitive impairment (MCI)

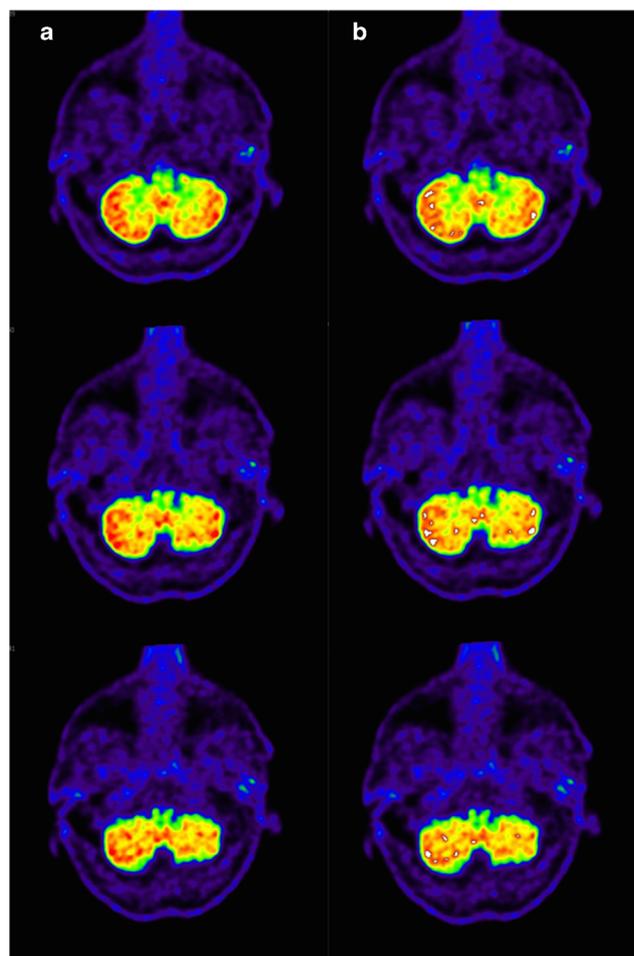
Test Interpretation	Test <sup>a</sup> Cerebrum	Test <sup>a</sup> Cerebellum	AD	MCI	Diagnostic manifestation (95% CI)
<b>Negative</b> Both tests above threshold	Above	Above	4	3	NPV 42.9% (15.8–75.0)
<b>Positive</b> One or both tests below the threshold	Above	Below	3	4	PPV 42.9% (15.8–75.0)
	Below	Above	3	1	PPV 75% (30.1–95.4)
	Below	Below	5	–	PPV 100% (56.6–100)
<b>Total</b>	–	–	15	8	–

AD Alzheimer's disease, CI confidence interval, MCI mild cognitive impairment, NPV negative predictive value, PPV positive predictive value. <sup>a</sup>The cut-off points for THGr in cerebrum and cerebellum, were derived from ROC analysis, respectively dichotomization for cerebral THGr: above = > 0.76 and below = < 0.76, and dichotomization for cerebellar THGr: above = > 0.71 and below = < 0.71



**Fig. 1** FDG-PET scan and three consecutive transaxial images in an Alzheimer's disease patient. Visual assessment detected right-sided hemispheric diaschisis (a). Quantitative analysis was performed, and neurons with the highest indexed glucose metabolism (white pixels) were segmented (b), yielding a cerebral total hemispheric glucose metabolism ratio of 0.56

was low, cerebellar hemispheric diaschisis would be visually detected in 36% (4/11), and if only THGr(Ce) was low, hemispheric diaschisis in forebrain would be visually detected in 67% (6/9).



**Fig. 2** FDG-PET scan and three consecutive transaxial images in an Alzheimer's disease patient. Visual assessment detected left-sided hemispheric diaschisis (a). Quantitative analysis was performed, and neurons with the highest indexed glucose metabolism (white pixels) were segmented (b), yielding a cerebellar total hemispheric glucose metabolism ratio of 0.38

## Quantitative PET analysis

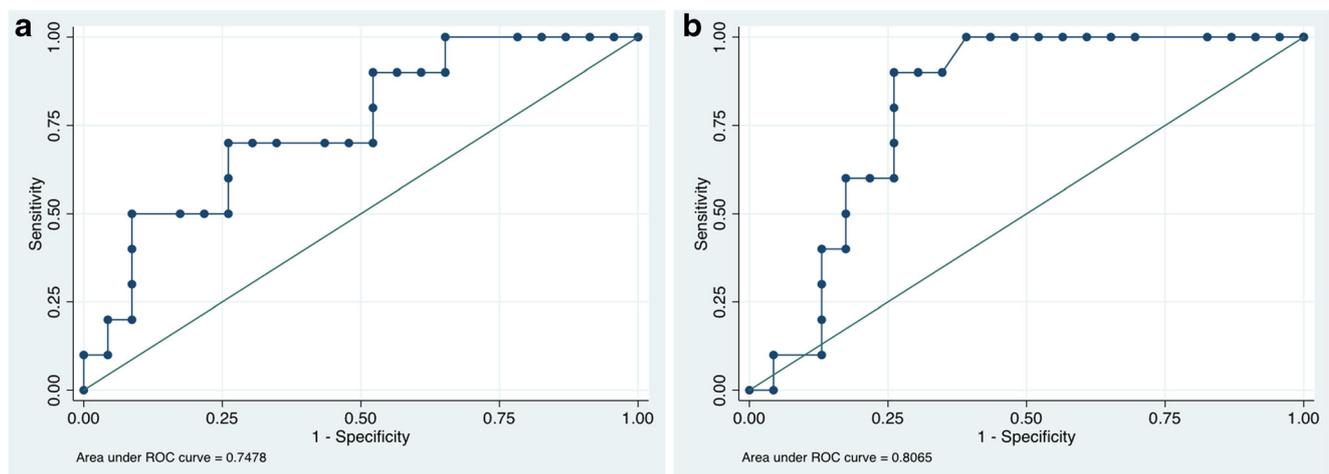
Lateralized glucose metabolism in the forebrain neuronal network estimated with cerebral THGr(Ce) reached a median of 0.68 (range 0.43–0.99), 0.86 (range 0.64–0.98), and 0.95 (range 0.65–1.00) for patients with AD and MCI, and for HIs, respectively ( $p = 0.04$ ). There were statistically significant differences between THGr(Ce) values of AD and HI ( $p = 0.02$ ). However, no statistical difference was found between THGr(Ce) of the AD and MCI ( $p = 0.15$ ) nor between MCI and HI ( $p = 0.21$ ). Table 1 lists the THGr(Ce) values. Cerebral THGr segmentation is displayed in Fig. 1. The optimal ROC cerebral THGr threshold for differentiating AD and MCI from HI was THGr(Ce) = 0.91 (AUC = 0.75, 95% CI 0.57–0.93; Fig. 3). The optimal cerebral THGr(Ce) threshold for differentiating AD from MCI patients was THGr(Ce) = 0.76 (AUC = 0.68, 95% CI 0.47–0.91). There was no statistically significant correlation between MMSE score and the cerebral THGr value ( $\rho = 0.031, p \approx 0.89$ ). Similarly, none was found between the CAMCOG score and the cerebral THGr value ( $\rho = -0.0136, p \approx 0.95$ ).

Lateralized glucose metabolism in the hindbrain neuronal network estimated with cerebellar THGr reached a median THGr(Cb) of 0.70 (range 0.18–0.98), 0.70 (range 0.48–0.81) and 0.84 (range 0.75–0.96) for patients with AD and MCI, and HIs, respectively ( $p = 0.01$ ). Table 1 lists the THGr(Cb) values. The cerebellar THGr segmentation is displayed in Fig. 2. There were statistically significant differences between THGr(Cb) values of AD patients and HI ( $p = 0.048$ ) and between MCI patients and HIs ( $p = 0.01$ ). However, no statistically significant difference was found between THGr(Cb) in AD and MCI patients ( $p = 0.48$ ). The optimal ROC-derived cerebellar THGr threshold for

differentiating AD/MCI from HI was THGr(Cb) = 0.79 (AUC = 0.81, 95% CI 0.66–0.96; Fig. 3). The optimal ROC-derived cerebellar THGr threshold for differentiating AD from MCI was THGr(Cb) = 0.71 (AUC = 0.40, 95% CI 0.17–0.65). There was no statistically significant correlation between MMSE score and the cerebellar THGr value ( $\rho = 0.134, p = 0.55$ ). Similarly, none was found between the CAMCOG scores and the cerebellar THGr value ( $\rho = 0.0600, p = 0.79$ ).

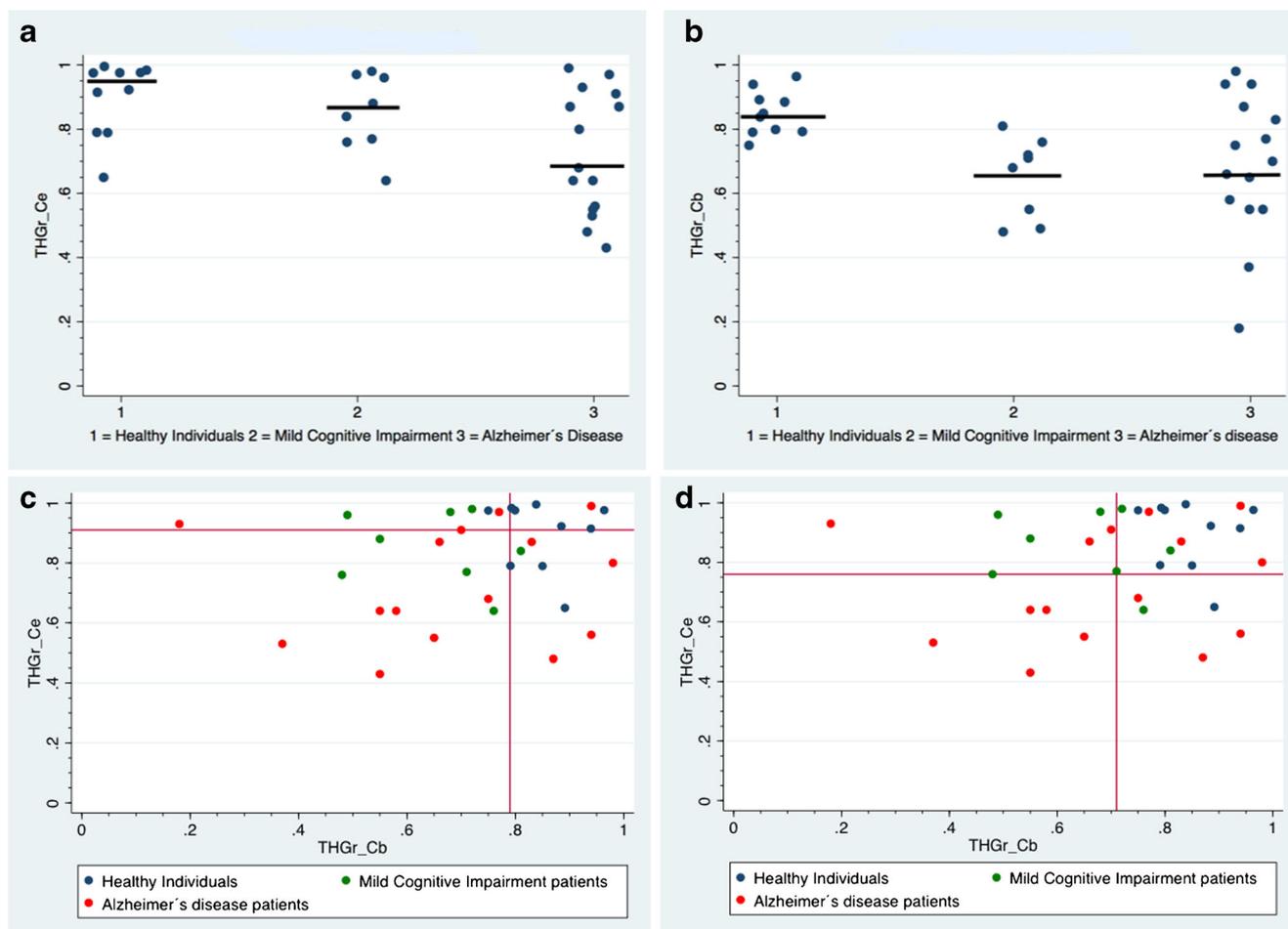
## Combined quantitative analyses for forebrain and hindbrain

ROC derived optimal thresholds for differentiation between AD or MCI, and HI brains were 0.91 and 0.79 for THGr(Ce) and THGr(Cb), respectively. Lower THGr indicated imbalanced hemispheric glucose metabolism and network diaschisis (Fig. 4). Thus, the THGr(Ce) and THGr(Cb) values that exceeded the thresholds (as a negative test) indicated a negative predictive value of 85.7%. When both tests failed to reach the thresholds, it was considered as a positive test for diaschisis in the human brain neuronal network, i.e., a positive NDT, with a positive predictive value of 100% for AD or MCI. Intermediate results of the diagnostic test had 62.5% and 85.7% positive predictive values for dementia (Table 2). For differentiation between MCI and AD, ROC analysis revealed optimal thresholds of THGr(Ce) at 0.76 and THGr(Cb) at 0.71. When both THGr values were below the thresholds, they represented a positive predictive value of 100% for AD. However, both THGr(Ce) and THGr(Cb) values exceeding the thresholds had a negative predictive value of 42.5% in differentiating MCI from AD (Table 3). Figure 4 graphically displays the results presented in Tables 2 and 3, respectively.



**Fig. 3** Total hemispheric glucose metabolism ratio (THGr) in the forebrain (a) and hindbrain (b) was tested as a diagnostic marker in dementia patients (Alzheimer's disease and mild cognitive impairment)

and compared to healthy individuals. AUC-ROC values were 0.75 and 0.81 for, respectively, cerebral and cerebellar THGr



**Fig. 4** Cerebral (a) and cerebellar (b) total hemispheric glucose ratio (THGr) in healthy individuals and patients with Alzheimer's disease and mild cognitive impairment. Optimal THGr thresholds were derived

from AUC-ROC analysis and used in a NDT. This test differentiated healthy from dementia brain (c) and Alzheimer's disease from mild cognitive impairment (d)

## Discussion

This study showed that qualitative assessment of FDG-PET images could detect the presence of cerebellar and cerebral hemispheric diaschisis in patients with the AD. Also, it was revealed that THGr is a quantitative measure that reflects a hemispheric imbalance of glucose metabolism in the cerebellum and cerebrum of patients with MCI and AD. With a single exception, we did not find diaschisis by qualitative assessment in the brain of MCI patients. The NDT differentiated AD and MCI brains from HI brains as well as AD from MCI brains with superior diagnostic value. However, the specificity of the test for the latter was poor.

### Cerebral Diaschisis

We showed that HIs had balanced hemispheric glucose metabolism (a median quantitative value close to unity). In contrast, we found that imbalanced hemispheric glucose metabolism strongly distinguished healthy brains from brains

afflicted by AD or MCI. The median values of THGr(Ce) were lower in patients with AD than MCI. Also, qualitative assessment showed more pronounced hemispheric diaschisis in patients with AD compared to patients with MCI. Due to the progressive nature of AD, we suggest that hemispheric diaschisis and lateralized glucose metabolism of forebrain potentially foreshadow MCI and that a decline of THGr(Ce) reflects active progression to AD.

It has been argued that MCI patients who later develop AD ("converters"), have a significantly lower relative cerebral glucose metabolic rate (rCMRglc) compared with non-converters. The reduction is more pronounced in some brain regions such as the hippocampal and parahippocampal loci and in parietal and posterior cingulate gyri than in others that gradually may cause a more severe asymmetry in converters than in non-converters. Intriguingly, the observed changes in converting MCI patients seem to continue in tandem with disease progression towards AD [20]. Evidence also suggests that progressive hypometabolism seen in the brain areas of converters may result from the disconnection from the CA1

area of the hippocampus that also has the highest burden of neurofibrillary tangles. This burden supports the diaschisis hypothesis and is consistent with functional MRI findings [21]. No clear explanation exists for why glucose metabolism lateralizes in MCI and AD, but studies show that the default mode network with its elevated activity under “resting” conditions and links to precuneus and entorhinal cortex, specifically is affected by AD pathology [22, 23].

Mesulam et al. reviewed 58 autopsies of patients with primary progressive aphasia (PPA), of whom 45% were found to have AD, and showed that loss of neurons and brain atrophy evolve asymmetrically in all pathologies of PPA including AD, not only at disease onset but also as the disease progresses. As a cardinal feature of neurodegeneration in AD, the asymmetry cannot be explained exclusively by the cellular or molecular pathology as it has also been noted in other pathologies [24].

The present results added value to the concept of asymmetry of neurodegeneration in AD not only in cerebrum but also in the cerebellum. Moreover, our results showed that hemispheric glucose metabolism detected with FDG-PET might be a marker of asymmetric neurodegeneration also in MCI. The basal ganglia and thalami of patients with AD or MCI, in general, had a higher index of glucose metabolism compared to the cortex. The finding is consistent with the common observation of reduced glucose consumption in patients with AD or MCI, in addition to the hemispheric imbalance revealed by the THGr index [25–28]. Also, while the decline of metabolism initially may affect only one hemisphere, it progresses to involve both hemispheres but to different degrees. The imbalanced hemispheric glucose metabolism is then the result of either loss of functional connections inter and/or intra-hemispheric, the localized onset of AD pathology or both.

### Cerebellar diaschisis

Cerebellar THGr indices were significantly lower both in MCI and AD patients compared to HIs, which is surprising as cerebellum is distant to the cerebrum, where AD and MCI pathology is thought to develop first. The observation of a lateralized decline of hemispheric glucose metabolism indices in the cerebellum may reflect the loss of connections between fore- and hindbrain. Impaired activity of the cerebello-thalamic tract may, in turn, lower the activity of the striato-thalamo-cortical loop [29]. The impairment may indicate that a whole-brain connectome, including the infratentorial brain parenchyma, is affected in AD and MCI which is also shown by Guo et al. [30]. Disconnection of neuronal networks, labelled as diaschisis, may explain the simultaneous cerebral and cerebellar involvement in AD casting doubt on the use of cerebellum as a reference region. Indeed, the results showed that the use of cerebellum as a reference region for forebrain FDG accumulation is not robust. Hence, our findings contrast

the evidence from amyloid markers that reveal only negligible cerebellar plaques, and markers of the density of the 18 kDa translocator protein that used cerebellar SUV ratios as the reference for forebrain pathology in AD [31, 32].

### Quantification and visual assessment of network diaschisis

The qualitative detection rate of diaschisis and the quantitative hemispheric glucose metabolism ratio had a lower association in cerebrum and cerebellum than those noted in a previous study of patients with glioma [16]. We speculate that either the overall decline of glucose metabolism in AD and MCI makes it more difficult to qualitatively and quantitatively detect the diffuse pathology of diaschisis, or that the unilateral nature of a glioma lesion facilitates the visual detection of diaschisis. Although there may be an imbalance of glucose metabolism in AD and MCI patients, it may be widely distributed to an extent that interferes with the visual detection of the lateralized disconnectivity. Thus, it is crucial to further improve the THGr method to raise the sensitivity of detection of imbalanced hemispheric glucose metabolism. We also showed that the greater the imbalance between hemispheric glucose consumption in both cerebrum and cerebellum, the higher the likelihood of AD and MCI compared to HI. Further, visually detected network diaschisis, i.e., diaschisis in both the hemispheric neuronal networks of forebrain and hindbrain, was confirmed only in AD patients. The results heighten the importance of assessing the entire neuronal network of the brain in AD and MCI to acquire a better understanding of the disease.

### Strengths and weaknesses

Our study had several limitations. There is no consensus in the literature on whether diaschisis is caused by vascular or metabolic disturbances in the brain, or both. We used the material presented here only to investigate the metabolic manifestation of diaschisis and not to evaluate any potential vascular component. Until now, there is no gold standard for detection of diaschisis in patients, or a definition of pathological asymmetry of metabolism in the human brain, caused by diaschisis. Our inability to compare our results to a well-defined gold standard is an inherent weakness of the study. The sample size was suitable only for preliminary evaluation of an investigative approach to the quantification of diaschisis, and further studies with larger numbers of patients is needed to validate the diagnostic accuracy of the test, as well as the presence of network diaschisis. As an example of the latter, there was one outlier in the healthy control THGr(Ce) values. Visual examination detected a different size of the two hemispheres in this healthy individual. Larger cohorts of healthy individuals are needed to be evaluated with THGr and the NDT. For materials

larger than ours, indifference curves or other methods may be applied for the further development of the ROC-derived THGr thresholds for diagnostic use [33]. As stated in the methods section, some THGr measurements were semi-automated, which is a subject for further development and improvement; hence the authors regard it as a weakness that the THGr method could not be fully automated in the presented material.

When we designed the THG ratio and NDT methods, we used a non-parametric statistical approach, in contrast to the commonly used Statistical Parametric Mapping of neuroimaging studies. Although non-parametric statistics is a simpler statistical method, compared to SPM, we regard the choice a methodological strength: The biology, presence, and potential effects of diaschisis in humans is still unknown, and statistical presumptions may clutter an investigation into the unknown. Moreover, the non-parametric statistical design of the NDT allows the model to accommodate new evidence from new and different studies. As we do not know the distribution of the data from future studies, non-parametric statistics is better suited to a median that is expected to be more representative. The outlier from the healthy controls is an example of the reason that non-parametric statistics is better suited to explorations of diaschisis when the populations underlying the extracted materials generally are small. Hence, we designed an approach that may be expanded according to the data that are collected. In the light of the observations that diaschisis is detected in more than 15 different brain disorders, it is necessary to promote methods that are dynamic rather than rigid. For this purpose, non-parametric statistics are known to be more robust, with fewer assumptions to satisfy. Moreover, to our knowledge, this is the first study to report detection of diaschisis in MCI with a non-parametric statistically quantitative approach.

It is important to note that the present study aimed to test the hypothesis that hemispheric diaschisis and lateralized hemispheric glucose metabolism are present in patients with MCI and AD and that it is possible to quantify the network diaschisis with the method first presented in patients with glioma [16]. It should also be noted that the optimal ROC-derived THGr thresholds in dementia were different from the THGr thresholds derived in the glioma material. Whether to use different THGr thresholds and/or optimise ROC thresholds to heighten the predictive value for each different brain disease suspected of diaschisis is a subject for investigation in future studies, as larger materials are needed, and preferably from other brain disorders as well. Finally, as an argument to why we can use AUC-ROC in our material, we quote Altman [34] to the effect that “the ROC curves, being based only on sensitivity and specificity, takes no account of the prevalence of the disease being tested for”. Moreover, diaschisis might be a reversible neurological sign [35], thus the THGr calculations may also have value in monitoring treatments, such as when exercise is being used as therapy in patients with MCI [36].

We age-matched the control group to avoid having to test for age-related metabolic changes, but it is of interest in larger materials of healthy individuals to investigate the presence of metabolic diaschisis as a function of age. The method presented here is the result of four years of meticulous trial and error experiments, and we regard this meticulous effort of quantification of diaschisis as a strength. For a systematic review on diaschisis, we currently have collected data for the exploration of more than 3000 patients investigated for diaschisis. More than half of the included studies ( $n = 95$ ) have a patient populations of fewer than 21 individuals. Hence, we regard it an additional strength that the present study concerns a population of more than 21 patients. Moreover, the systematic review disclosed more than 30 different variations of diaschisis detected in neuroimaging studies, including, e.g., thalamic diaschisis, transhemispheric diaschisis, and callosal diaschisis, etc. The quantitative methodology we have presented segments every voxel in all four hemispheres and calculates an asymmetry index with a non-parametric statistical approach. To our knowledge, this has not been done before. We regard it therefore as a further strength that our meticulous method targets all 30 variation of diaschisis, bringing them jointly into the concept of network diaschisis.

## Conclusion

In conclusion, using FDG-PET and THGr, we showed that patients with AD or MCI have lateralized glucose metabolism in both forebrain and hindbrain correlating with neuronal network diaschisis. The NDT was able to discriminate AD or MCI patients from healthy individuals and AD from MCI patients with a high positive predictive value. However, the negative predictive value was lower. THGr can be a straightforward source of investigating neuronal network diaschisis in AD and MCI and in other cerebral diseases, across institutions.

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## Compliance with ethical standards

**Conflict of interest** All authors declare that they have no conflict of interest.

**Ethical approval** All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or National Research Committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent** Informed consent was obtained from all individual participants for whom identifying information is included in this article.

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