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Motor cortex hypointensity on susceptibility-weighted imaging: a potential imaging marker of iron accumulation in patients with cognitive impairment

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Abstract

Purpose To assess the prevalence and characteristics of motor cortex hypointensity on 3-T susceptibility-weighted imaging (SWI) in patients with cognitive impairment and examine its clinical significance.

Methods The institutional review board approved this retrospective study and waived the requirement for informed consent. A total of 127 patients with a clinical diagnosis of probable Alzheimer's disease (AD) ($n = 32$) or mild cognitive impairment (MCI) ($n = 95$) and 127 age- and sex-matched control subjects underwent 3-T brain magnetic resonance imaging. SWI was analyzed for both subjective visual scoring and the quantitative estimation of phase shift in the posterior bank of the motor cortex. A multivariate logistic regression analysis was performed to identify clinical and imaging variables associated with motor cortex hypointensity on SWI.

Results Motor cortex hypointensity on SWI was observed in 94/127 cognitively impaired patients (74.0%) and 72/127 control subjects (56.7%) ($p = 0.004$). Age was the only variable that was significantly associated with motor cortex hypointensity in patients with cognitive impairment (odds ratio, 1.15; 95% confidence interval, 1.065–1.242; $p < 0.001$). The quantitative analysis confirmed a significant increase in phase shifting in the posterior bank of the motor cortex in patients with positive motor cortex hypointensity on SWI ($p < 0.001$).

Conclusion Motor cortex hypointensity on SWI was more frequently found in patients with cognitive impairment than in age-matched controls and was positively associated with age. Thus, it may be a potential imaging marker of iron accumulation in patients with MCI or AD.

Keywords Dementia · Alzheimer's disease · Cognitive dysfunction · Magnetic resonance imaging · Susceptibility-weighted imaging · Iron

Introduction

In the late 1990s, motor cortex hypointensity on T2-weighted or fluid-attenuated inversion recovery (FLAIR) imaging was reported as a useful imaging finding for diagnosing amyotrophic lateral sclerosis (ALS); however, this imaging finding was later reported in the aging brain and in Alzheimer's disease (AD) [1–4]. Additionally, motor cortex hypointensity has been significantly associated with aging, cardiovascular risk factors, and cerebrovascular disease [1]. The pathological mechanism underlying this finding is thought to increase regional iron deposition, which induces susceptibility changes on T2 and FLAIR imaging [5].

Susceptibility-weighted imaging (SWI) uses tissue magnetic susceptibility differences to generate contrast and is well known for its increased sensitivity for detecting iron content and other substances affecting the local magnetic field [6]. In patients with ALS, motor cortical hypointensity was more sensitively detected by SWI than by T2- or T2*-weighted imaging, and accordingly, SWI is emerging as a new diagnostic tool for detecting motor cortex hypointensity [7–9].

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However, the presence of motor cortical hypointensity on SWI has not been fully studied in healthy individuals and in individuals with neurodegenerative diseases, and its clinical significance and diagnostic utility remain to be determined.

In the present study, we hypothesized that motor cortex hypointensity on SWI would appear more frequently in patients with cognitive impairment than in normal healthy subjects, similar to previously reported findings on T2 and FLAIR imaging, and we aimed to find possible clinical variables associated with motor cortex hypointensity on SWI. Hence, we explored the prevalence of motor cortex hypointensity on SWI in patients with cognitive impairment and investigated relevant clinical associations.

Materials and methods

Study population

This retrospective study was approved by the local institutional review board, and the requirement for informed consent was waived. A review of our institution's database identified a total of 318 patients who underwent brain magnetic resonance imaging (MRI) for the evaluation of subjective cognitive decline between January and December of 2013. Of these patients, we excluded 50 who had other forms of dementia, 5 with inadequate image acquisition, 18 with unavailable Neuropsychological Screening Battery results, and 13 with comorbid brain pathology (five of the patients had superficial siderosis; one, old infarction; three, intracranial hemorrhage; and four, brain tumors). The remaining 232 patients had a clinical diagnosis of probable AD or mild cognitive impairment (MCI) based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders (4th edn.), the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA), and McKhann et al. [10] and Petersen et al. [11]. From the same period, we also identified 228 individuals who underwent brain MRI with the same protocol for evaluation of headache or syncope but were found to have no clinical or imaging abnormalities. Among this cohort, we finally selected 127 age- and sex-matched subjects from each group using the case-control matching procedure of MedCalc (version 9.3.6.0; MedCalc Software, Mariakerke, Belgium).

We assessed basic demographic characteristics, other medical conditions (including vascular risk factors), laboratory test results, global cognitive assessments (Clinical Dementia Rating Scale Sum of Boxes, Mini-Mental Status Examination, and Geriatric Depression Scale scores), and brain MRI scans.

Image acquisition

All patients underwent MRI using a 3-T unit (Skyra; Siemens Medical Solutions, Erlangen, Germany) with a 20-channel head coil. All patients had undergone axial turbo spin echo T2-weighted imaging with the following parameters: repetition time (TR) = 4450 ms, echo time (TE) = 81 ms, flip angle = 150°, bandwidth (BW) = 362 Hz/pixel, matrix size = 512 × 358, field of view (FOV) = 22 × 22 cm^2, slice number = 28, ~; and corontal 3D T1-weighted magnetization-prepared rapid acquisition of gradient echo sequences with the following parameters: TR = 1900ms, TE = 2.4ms, flip angle = 9°, BW = 190Hz/pixel, matrix size = 256 x 216, FOV = 23 x 19.4 cm , slice number = 240, slice thickness = 0.9mm and no gap = 2.0 mm; axial FLAIR with the following parameters: TR = 9000 ms, TE = 95 ms, flip angle = 150°, BW = 206 Hz/pixel, matrix size = 320 × 188, FOV = 22 × 22 cm^2, slice thickness = 5.0 mm, and gap = 2.0 mm; and coronal 3D T1-weighted magnetization-prepared rapid acquisition of gradient echo sequences with the following parameters: TR = 1900ms, TE = 2.4ms, flip angle = 9°, BW = 190Hz/pixel, matrix size = 256 x 216, FOV = 23 x 19.4 cm^2, slice number = 240, slice thickness = 0.9 mm and no gap. SWI was implemented using a 3D gradient echo sequence with the following parameters: TR = 29 ms, TE = 20 ms, flip angle = 15°, BW = 120 Hz/pixel, matrix size = 512 × 256, FOV = 22 × 22 cm^2, slice number = 72, slice thickness = 2.0 mm, and no gap. The total acquisition time of SWI was 3.13 min with an acceleration factor of 2.

Analysis of motor cortex hypointensity

All SWI data were visually evaluated in a regular clinical setting by two neuroradiologists with 18 years and 3 years of experience, respectively. Each evaluation was independent, and the raters were blinded to diagnoses. Visual rating scores were assigned for the posterior bank of the motor cortex using a 3-point scoring system, similar to what has been reported in recent studies of ALS: a score of 0 (absent) was assigned when any part of the motor cortex did not differ from the neighboring cortices, a score of 1 (mild to moderate) was assigned when any part of the motor cortex appeared to be slightly more hypointense than the neighboring cortices, and a score of 2 (marked) was assigned when any part of the motor cortex appeared to be much more hypointense than the neighboring cortices (Fig. 1) [9, 12]. The central sulcus was used as an anatomical landmark to identify the motor cortex.

Quantitative regional assessment of iron content

A region of interest (ROI)–based quantitative analysis of regional iron content was performed on phase images. Freehand ROIs were manually drawn by an experienced

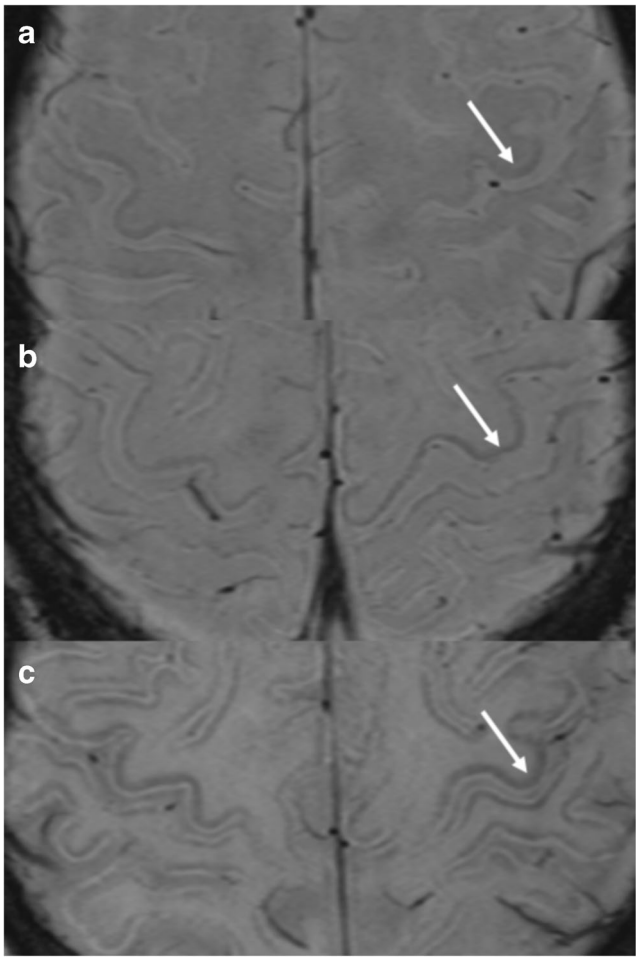

Fig. 1 Visual scoring of motor cortex hypointensity on susceptibility-weighted imaging. Sample images for absent (score 0) (**a**), mild-to-moderate (score 1) (**b**), and severe (score 2) (**c**) ratings are shown

neuroradiologist. Phase values were obtained for four structures in the left hemisphere including the gray matter of the precentral cortex, postcentral cortex, medial frontal cortex, and frontal deep white matter, with care to exclude adjacent cortical vessels (Fig. 2). To normalize phase values between subjects, phase shifts between cortical gray matter and deep white matter were calculated for each region and expressed in radians [13]. To obtain inter-rater and intra-rater reliability, the two experienced neuroradiologists independently placed the ROIs for 30 randomly selected cases 4 weeks after the initial ROI analysis.

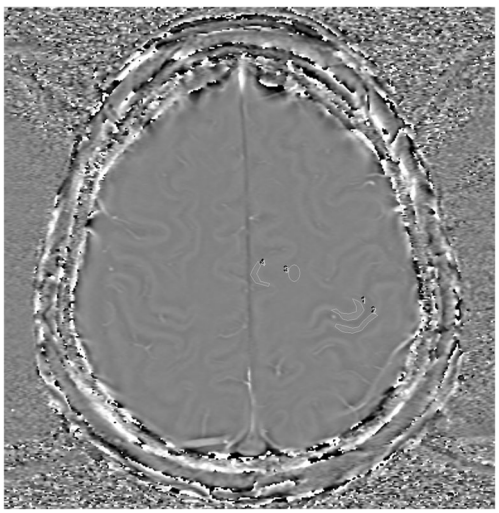

Fig. 2 Axial phase image showing the regions of interest used in the quantitative analysis. *1* Precentral cortex, *2* postcentral cortex, *3* frontal white matter, *4* medial frontal cortex

Analysis of vascular risk factors

White matter hyperintensity (WMH) was defined as lesions of white matter hyperintensity on FLAIR images according to the Standards for Reporting Vascular Changes in Neuroimaging criteria and graded according to the Fazekas scale as deep WMH (0 = absent, 1 = punctate, 2 = early confluent, and 3 = confluent) and periventricular WMH (0 = absent, 1 = caps or pencil-thin lining, 2 = smooth halo, and 3 = irregular WMH extending into the deep white matter). A total Fazekas score was calculated by adding the periventricular and deep WMH scores, and a total score > 3 was designated as WMH positive [14, 15]. Lacunes were defined as small lesions (3–15 mm in diameter) that were hypointense on T1-weighted images and hyperintense on T2-weighted images and had perilesional halos on FLAIR images [15]. Microbleeds were defined as a small signal void (≤ 10 mm in diameter) with associated blooming on T2*-weighted images. The presence and number of WMH, lacunes, and microbleeds were recorded as previously described [15].

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS, version 24.0 for Windows; Chicago, IL) and MedCalc (version 9.3.6.0; MedCalc Software, Mariakerke, Belgium). For the analysis, an image score of 0 was considered as the absence of motor cortex hypointensity on SWI, and scores of 1 and 2 were considered to indicate the presence of motor cortex hypointensity on SWI.

First, we compared baseline demographic and clinical characteristics between cortical SWI-positive and SWI-negative groups. Continuous variables (presented as the mean and range) were compared using independent *t* tests, and categorical variables (presented as the frequency and percentage) were compared using chi-square tests or Fisher's exact tests. Inter-rater agreement for the visual scoring of motor cortex hypointensity on SWI was determined statistically. To investigate independent factors associated with motor cortex hypointensity on SWI, variables yielding p values < 0.1 in either independent *t* tests or chi-square tests were included in a multivariate logistic analysis. Then, multiple logistic

regression analysis was performed using the enter method including age, systolic blood pressure, APOE-ε4 status, and lacunes as factors. To measure the inter-rater agreement of visual assessment of motor cortical hypointensity, we obtained weighted kappa values. We assessed inter-rater and intra-rater reproducibility on all phase shift measures using the intraclass correlation coefficient (ICC). p values < 0.05 were considered to be statistically significant.

Results

Characteristics of the study population

Of the 127 cognitively impaired patients (27 men and 100 women; mean age 69.2 years, range 46–91 years), 95 had MCI (17 men and 78 women; mean age 68.5 years, range 46–91 years) and 32 had AD (10 men and 22 women; mean age 71.3 years, range 47–86 years). The age- and sex-matched control group (27 men and 100 women; mean age 69.1 years, range 46–90 years) and the cognitively impaired patient group did not differ in terms of sex ($p = 1.000$) and age ($p = 0.08$). Baseline population characteristics of the cognitively impaired patients are summarized in Table 1.

Visual rating measurements

Among the cognitively impaired patients, 94/127 (74.0%) were classified as positive and 33/127 (26.0%) were classified as negative for motor cortex hypointensity. Among the patients with positive cortical hypointensity, 22/94 (23.4%) had AD and 72/94 (76.6%) had MCI. In the negative group, 10/33 (30.3%) had AD and 23/33 (69.7%) had MCI. There was no significant difference in the disease distribution according to the status of motor cortex hypointensity ($p = 0.432$). The mean age of the patients in the positive group was significantly higher than that in the negative group (mean age 70.7 years [range 54–91 years] vs. mean age 65.1 years [range 46–82 years], respectively; $p = 0.001$; Table 1). There were no other significant between-group differences in gender, educational years, presence of hypertension, diabetes mellitus, dyslipidemia, history of smoking, CVA, heart disease, trauma, depression, systolic blood pressure, level of serum HbA1c (%), serum glucose level, 25-OH vitamin D, and APOE4 allele carrier status (Table 1).

In the control group, there were 72 patients (56.7%) with positive motor cortex hypointensity and 55 patients (43.3%) with negative motor cortex hypointensity. The mean age of control subjects in the positive group was significantly higher than that in the negative group (mean age 71.0 years [range 53–90 years] vs. mean age 66.6 years [range 46–83 years], respectively; $p = 0.003$).

The incidence of positive motor cortex hypointensity was significantly higher in cognitively impaired patients than in control subjects (74.0% vs. 56.7%, $p = 0.004$). The frequency of negative motor cortex hypointensity decreased as age increased in both cognitively impaired patients and control subjects. Severe motor cortex hypointensity (score 2) was only found in the cognitively impaired group (0% of the control group vs. 11.0% of the cognitively impaired group, $p < 0.001$) (Fig. 3a, b).

Quantitative measurement

Table 2 shows mean phase shifts for the motor cortex, sensory cortex, and medial frontal cortex in cognitively impaired patients and control subjects. Among the cognitively impaired patients, larger mean phase shifts for the motor cortex were identified in the positive motor cortex hypointensity group than in the negative motor cortex hypointensity group (mean phase shift 119.5 rad [range 66.7–213.2 rad] vs. mean phase shift 94.8 rad [range 46.3–169.8 rad], respectively; $p < 0.001$). There were significant group differences for the sensory and medial frontal cortices as well ($p = 0.003$ and $p = 0.029$, respectively).

Furthermore, we compared the phase shifts of the cognitively impaired patient group and the control group and found that only the motor cortex showed a significant difference between the groups (mean phase shift 121.6 rad [range 46.3–213.2 rad] vs. mean phase shift 113.1 rad [range 69.8–186.4 rad], respectively; $p = 0.01$). The sensory cortex and the medial frontal cortex did not show any significant differences (mean phase shift 97.3 rad [range 42.6–166.6 rad] vs. mean phase shift 91.8 rad [range 38.2–181.8 rad], respectively; $p = 1.000$, and mean phase shift 72.7 rad [range 15.6–178.3 rad] vs. mean phase shift 71.1 rad [range 21.6–157.8 rad], respectively; $p = 0.605$).

Multiple logistic regressions for positive motor cortical hypointensity in cognitively impaired subjects

Age ($\beta = 0.14$; odds ratio, 1.15; 95% confidence interval, 1.065–1.242; $p < 0.001$) was the only variable independently associated with motor cortex hypointensity on SWI in the cognitively impaired subjects (Table 3). Cox-Snell R^2 and Nagelkerke R^2 values were 0.182 and 0.274, respectively.

Sensitivity and specificity analysis

The visual assessment of hypointensity scores in the motor cortices of the absent (grade 0) group compared to the present (grade 1 and grade 2) group showed a sensitivity of 74.0% and a specificity of 45.7% for differentiating cognitively impaired patients from control subjects.

Table 1 Baseline characteristics of the cognitively impaired patient population

Characteristics	Total ($n = 127$)	Motor cortex hypointensity (−) ($n = 33$)	Motor cortex hypointensity (+) ($n = 94$)	p value
Age (years)	69.2 ± 8.4	65.1 ± 9.3	70.7 ± 7.6	0.001*
Gender (M:F)	27:100	4:23	29:71	0.136
Educational year	8.8 ± 5.5	8.4 ± 5.7	9.0 ± 5.4	0.627
Hypertension, *n* (%)	46/126 (36.5)	9/33 (27.3)	37/93 (39.8)	0.200
Diabetes mellitus, *n* (%)	24/126 (19.0)	4/33 (12.1)	20/93 (21.5)	0.238
Dyslipidemia, *n* (%)	43/126 (34.1)	10/33 (30.3)	33/93 (35.5)	0.590
Smoking, *n* (%)	6/126 (4.8)	0/33 (0.0)	6/93 (6.5)	0.339
History of CVA, *n* (%)	8/126 (6.3)	0/33 (0.0)	8/93 (8.6)	0.110
History of heart disease, *n* (%)	16/126 (12.6)	4/33 (12.1)	12/93 (12.9)	1.000
History of trauma, *n* (%)	8/126 (6.3)	1/33 (3.0)	7/93 (7.5)	0.680
History of depression, *n* (%)	19/125 (15.2)	5/33 (15.2)	14/92 (15.2)	0.993
Systolic blood pressure	124.4 ± 13.7	120.6 ± 11.3	125.7 ± 14.2	0.074
HbA1c (%)	5.9 ± 0.6	5.9 ± 0.8	5.9 ± 0.5	0.772
Serum glucose	106.1 ± 29.4	100.9 ± 21.8	108.0 ± 31.6	0.297
25-OH vitamin D (ng/ml)	20.0 (14.7–26.5)	18.7 (13.9–27.2)	20.3 (14.7–26.8)	0.581
APOE4 allele carrier, *n* (%)	30/99 (30.3)	11/24 (45.8)	19/75 (25.3)	0.057
MMSE	23.2 ± 5.4	22.6 ± 6.1	23.4 ± 5.1	0.484
CDR	0.5 ± 0.3	0.5 ± 0.3	0.5 ± 0.2	0.676
CDRSOB	2.2 ± 1.7	2.4 ± 2.2	2.1 ± 1.5	0.483
GDepS	4.6 ± 3.7	5.0 ± 3.7	4.4 ± 3.6	0.461
GDS	3.3 ± 0.8	3.3 ± 0.8	3.3 ± 0.9	0.474
WMH, *n* (%)	49/127 (38.6)	10/33 (30.3)	39/94 (41.5)	0.256
Lacunes	0.6 ± 1.5	0.3 ± 0.7	0.7 ± 1.7	0.058
Microbleeds	3.0 ± 12.5	1.4 ± 4.1	3.5 ± 14.3	0.398

Inter-rater agreement

There was good inter-rater agreement for the identification of motor cortex hypointensity ($\kappa = 0.820$; 95% confidence interval, 0.700–0.940; $p < 0.001$).

For the 30 cases measured by two raters, there was excellent inter-rater reproducibility in the phase shift measurement of the motor cortex (ICC = 0.884; 95% confidence interval, 0.757–0.945). The inter-rater reproducibility was good in the sensory cortex (ICC = 0.675; 95% confidence interval, 0.316–0.845) and medial frontal cortex (ICC = 0.699; 95% confidence interval, 0.367–0.857) measurements. For the 30 cases measured twice by the same rater, there was good to excellent intra-rater reproducibility in the phase shift measurement of the motor cortex (ICC = 0.926; 95% confidence interval, 0.845–0.965), sensory cortex (ICC = 0.645; 95% confidence interval, 0.253–0.831), and medial frontal cortex (ICC = 0.733; 95% confidence interval, 0.440–0.873).

Discussion

In the present study, we qualitatively and quantitatively assessed motor cortex hypointensity in patients with cognitive impairment using 3-T SWI. We found that cortical hypointensity was more frequently observed in patients with cognitive impairment than in age- and sex-matched controls and was significantly associated with age.

Motor cortex hypointensity was first observed and proposed as a diagnostic imaging biomarker in patients with ALS, with a prevalence of 50% to 100% in these patients [7, 9, 16–18]. Here, we found that motor cortex hypointensity was also highly prevalent in patients with cognitive impairment (74.0%) on 3-T SWI, indicating that this imaging finding is not specific to ALS, consistent with the findings of other T2-weighted and FLAIR imaging studies [1, 2, 4, 5]. Notably, in our AD population, the prevalence of motor cortex hypointensity on SWI was higher (22/32, 68.8%) than that previously reported in T2 imaging studies (43.8–50.0%) [5, 19]. This can be attributed to the increased sensitivity of SWI for detecting small amounts of magnetically susceptible substance deposition compared to conventional T2-weighted imaging [7].

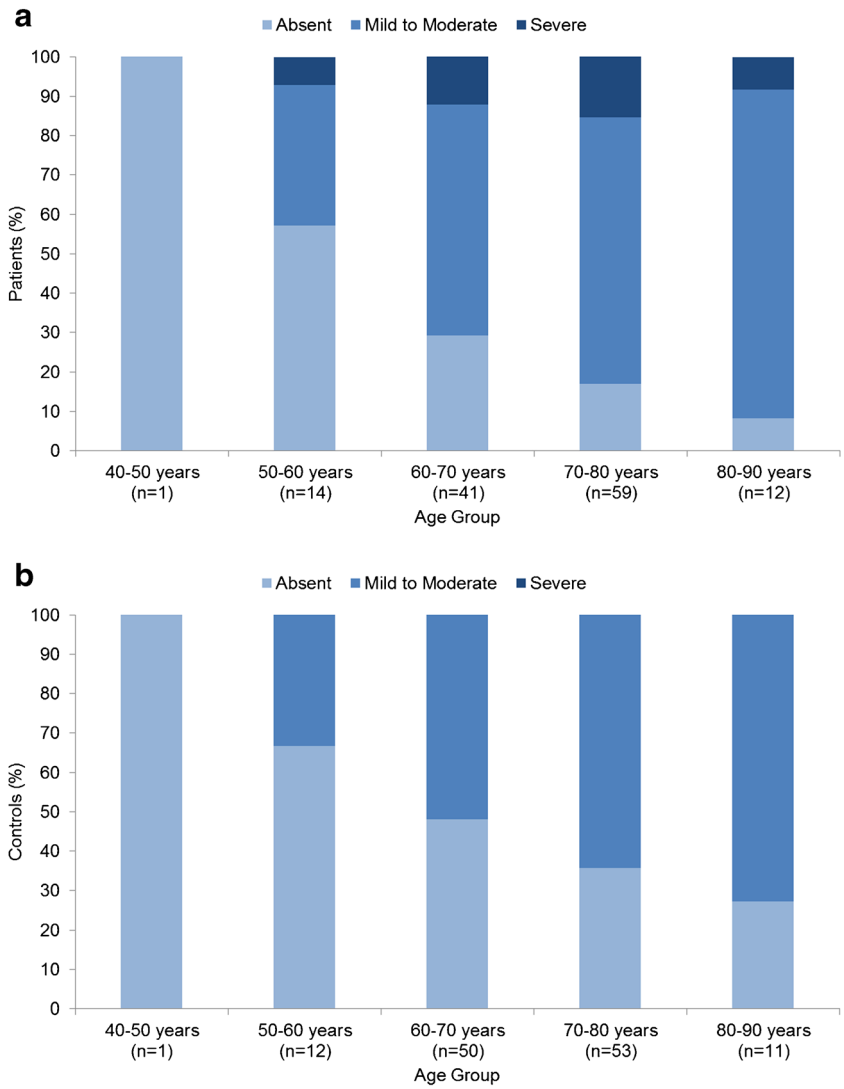

Fig. 3 Distribution of patients by age group and motor cortex hypointensity score in cognitively impaired patients (**a**) and control subjects (**b**)

Motor cortex hypointensity on SWI has been associated with the accumulation of iron in microglia in the middle and deep layers of the motor cortex on the histopathology of specimens from patients with ALS and was explained as reflecting abnormal iron homeostasis inducing excessive oxidative stress [17, 20, 21]. Recently, iron accumulation has received much attention as an emerging biomarker and a modulator of disease progression in the many neurodegenerative diseases including AD [22–24]. In patients with AD, ultra-high-field T2*-weighted imaging has successfully shown cortical susceptibility changes and iron has been reported as an important source for susceptibility changes in the cortex, which are

Table 2 Mean phase shifts and standard deviations for the cortical subregions in patients with cognitive impairment and control subjects with or without motor cortex hypointensity on susceptibility-weighted imaging

Region (rad)	Patients with cognitive impairment			Controls		
	Motor cortex hypointensity (−) ($n = 33$)	Motor cortex hypointensity (+) ($n = 94$)	p value	Motor cortex hypointensity (−) ($n = 55$)	Motor cortex hypointensity (+) ($n = 72$)	p value
Motor cortex	94.8 ± 24.7	119.5 ± 25.5	< 0.001	111.5 ± 22.2	129.4 ± 24.5	< 0.001
Sensory cortex	80.0 ± 19.9	96.0 ± 27.4	0.003	88.9 ± 23.7	103.8 ± 27.2	0.002
Medial frontal cortex	62.9 ± 29.2	73.9 ± 23.2	0.029	67.6 ± 19.6	76.5 ± 25.3	0.032

Table 3 Multivariate logistic regression analysis of motor cortex hypointensity (score 1 and score 2) on susceptibility-weighted imaging in patients with cognitive impairment

Characteristics	β coefficients	Odds ratio	95% CI	p value
Age	0.140	1.150	1.065–1.242	< 0.001
Systolic blood pressure	0.007	1.007	0.962–1.053	0.768
APOE4 allele carrier	− 0.459	0.634	0.202–1.989	0.434
Lacune	0.008	1.008	0.638–1.591	0.973

spatially correlated with changes in cortical iron accumulation [25]. In line with the observations in ultra-high-field MRI, we also found a higher incidence of positive motor cortex hypointensity on SWI in our cognitively impaired patient population, compared with that of the control population using 3-T MRI and believe that it was due to cortical iron accumulation associated with cognitive impairment. In a previous study, cortical iron accumulation was positivity correlated with the amount of beta-amyloid plaques and tau load, but currently, it is uncertain whether iron accumulation is the cause, coincidence, and/or consequence of amyloid or tau pathology [26].

In our study, age was the only clinical variable that was significantly and independently associated with motor cortex hypointensity on SWI in patients with cognitive impairment, consistent with several previous studies [1, 2, 4, 5]. Moreover, we also observed that the frequency of motor cortex hypointensity increases with age in both cognitively impaired patients and controls. This is not surprising, as increased iron accumulation is a hallmark of the aging brain, and increasing motor cortex hypointensity has already been reported as a result of age-related iron deposition in neurologically normal subjects [4, 27]. However, even in the age-matched comparison, we found there is a higher frequency of cortical iron accumulation in the cognitively impaired patient group and the degree of iron accumulation, considering the incidence of grade 2 score in each group is more severe in the cognitively impaired patients than in the control patients. Therefore, our observation indicates that motor cortex hypointensity on SWI may reflect a combination of pathologic age- and disease-related iron accumulation in AD and MCI patients, rather than age-related iron accumulation alone [24]. In this context, motor cortex hypointensity on SWI on 3-T MRI can be a useful and easily accessible in vivo imaging marker of iron accumulation in cognitively impaired subjects, which may reflect other aspects of disease besides beta-amyloid plaque or tau load.

Previous publications have shown diffuse cortical susceptibility in AD subjects [13, 27], while we only reported visible SWI change of the motor cortex. At baseline, the distribution of iron is different in each cortical field and the motor cortex is the area with the highest iron content [28]; therefore, when accelerated iron accumulation occurs in the motor cortex of cognitively impaired patients, it may be sufficient to cause visible susceptibility changes, while the changes in the other cerebral cortices are not. Even though this study focused on the motor cortex, we also found significant increases in phase shift in the sensory and medial frontal cortex in cognitively impaired patients compared with controls, which accords with previous results. Thus, the presence of motor cortical hypointensity may reflect more diffuse neurodegenerative changes related to cognitive impairment, even though it was only prominent in the motor cortex on our visual assessment.

This study has several limitations. As mentioned above, the absence of a direct correlation between amyloid and tau deposition and motor cortex hypointensity hampers an exact understanding of the true nature of motor cortex hypointensity. Second, we were not able to include patients with ALS in this study. A further study including ALS, AD, and control group subjects may clarify the clinical implications of this motor cortical hypointensity sign. Finally, because we obtained single-echo 3D gradient echo images for SWI, we were able to use only phase images for the measurement of local susceptibility change, which reflects the burden of susceptibility changes but can also be affected by non-local phase problems. For future studies, the use of quantitative susceptibility mapping from multi-echo 3D gradient echo images may offer more accurate susceptibility distribution of local field and validation of motor cortical hypointensity on SWI [29]. Furthermore, this study was only performed using one MR scanner; a validation study using multiple MR scanners is necessary to apply this imaging finding as a clinical in vivo imaging marker of iron accumulation.

In conclusion, motor cortical hypointensity on SWI does not appear to be a specific imaging finding for ALS. It may be more frequently observed in patients with AD and AD-related cognitive decline than in age-matched controls and is positively associated with age. Motor cortical hypointensity on SWI can be a potential imaging marker of pathologic iron accumulation in patients of MCI and AD, which can reflect another aspect of disease pathology besides beta-amyloid plaque or tau load.

Compliance with ethical standards

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Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies 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. For this type of study formal consent is not required.

Informed consent For this type of retrospective study formal consent is not required.

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