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Cortical phase changes measured using 7-T MRI in subjects with subjective cognitive impairment, and their association with cognitive function

Sanneke van Rooden[a,b]*†, Mathijs Buijs[a,b†], Marjolein E. van Vliet[a,b], Maarten J. Versluis[a,b], Andrew G. Webb[a,b], Ania M. Oleksik[c], Lotte van de Wiel[d], Huub A. M. Middelkoop[d], Gerard Jan Blauw[c,e], Annelies W. E. Weverling-Rynsburger[f], Jeroen D. C. Goos[g], Wiesje M. van der Flier[g,h], Ted Koene[g], Philip Scheltens[g], Frederik Barkhof[i], Ondine van de Rest[j], P. Eline Slagboom[k], Mark A. van Buchem[a,b] and Jeroen van der Grond[a,b]

Studies have suggested that, in subjects with subjective cognitive impairment (SCI), Alzheimer's disease (AD)-like changes may occur in the brain. Recently, an *in vivo* study has indicated the potential of ultra-high-field MRI to visualize amyloid-beta (Aβ)-associated changes in the cortex in patients with AD, manifested by a phase shift on T_2*-weighted MRI scans. The main aim of this study was to investigate whether cortical phase shifts on T_2*-weighted images at 7 T in subjects with SCI can be detected, possibly implicating the deposition of Aβ plaques and associated iron. Cognitive tests and T_2*-weighted scans using a 7-T MRI system were performed in 28 patients with AD, 18 subjects with SCI and 27 healthy controls (HCs). Cortical phase shifts were measured. Univariate general linear modeling and linear regression analysis were used to assess the association between diagnosis and cortical phase shift, and between cortical phase shift and the different neuropsychological tests, adjusted for age and gender. The phase shift (mean, 1.19; range, 1.00–1.35) of the entire cortex in AD was higher than in both SCI (mean, 0.85; range, 0.73–0.99; $p < 0.001$) and HC (mean, 0.94; range, 0.79–1.10; $p < 0.001$). No AD-like changes, e.g. increased cortical phase shifts, were found in subjects with SCI compared with HCs. In SCI, a significant association was found between memory function (Wechsler Memory Scale, WMS) and cortical phase shift ($\beta = -0.544$, $p = 0.007$). The major finding of this study is that, in subjects with SCI, an increased cortical phase shift measured at high field is associated with a poorer memory performance, although, as a group, subjects with SCI do not show an increased phase shift compared with HCs. This increased cortical phase shift related to memory performance may contribute to the understanding of SCI as it is still unclear whether SCI is a sign of pre-clinical AD. **Copyright © 2014 John Wiley & Sons, Ltd.**

Keywords: subjective cognitive impairment; Alzheimer's disease; brain imaging; phase; human 7-T MRI; AD pathology; cognition

* *Correspondence to: S. van Rooden, Department of Radiology, C3-Q, Leiden University Medical Center, PO Box 9600, 2300 RC Leiden, the Netherlands. E-mail: S.van_Rooden@lumc.nl*

a *S. van Rooden, M. Buijs, M. E. van Vliet, M. J. Versluis, A. G. Webb, M. A. van Buncem, J. van der Grond*
C. J. Gorter Center for High-Field MRI, Leiden University Medical Center, Leiden, the Netherlands

b *S. van Rooden, M. Buijs, M. E. van Vliet, M. J. Versluis, A. G. Webb, M. A. van Buncem, J. van der Grond*
Department of Radiology, Leiden University Medical Center, Leiden, the Netherlands

c *A. M. Oleksik, G. J. Blauw*
Department of Gerontology and Geriatrics, Leiden University Medical Center, Leiden, the Netherlands

d *L. van de Wiel, H. A. M. Middelkoop*
Department of Neuropsychology, Leiden University Medical Center, Leiden, the Netherlands

e *G. J. Blauw*
Department of Gerontology and Geriatrics, Bronovo Hospital, Den Haag, the Netherlands

f *A. W. E. Weverling-Rynsburger*
Department of Gerontology and Geriatrics, Diaconessen Hospital, Leiden, the Netherlands

g *J. D. C. Goos, W. M. van der Flier, T. Koene, P. Scheltens*
Alzheimer Center and Department of Neurology, Neuroscience Campus Amsterdam, VU University Medical Center, Amsterdam, the Netherlands

h *W. M. van der Flier*
Department of Epidemiology and Biostatistics, VU University Medical Center, Amsterdam, the Netherlands

i *F. Barkhof*
Department of Radiology, VU University Medical Center, Amsterdam, the Netherlands

j *O. van de Rest*
Division of Human Nutrition, Wageningen University, Wageningen, the Netherlands

k *P. E. Slagboom*
Department of Molecular Epidemiology, Leiden University Medical Center, Leiden, the Netherlands

† *These authors contributed equally to this work.*

Abbreviations used: *Aβ, amyloid-beta; AD, Alzheimer's disease; ANOVA, analysis of variance; CAMCOG, Cambridge Cognitive Examination; CSF, cerebrospinal fluid; GDS, Geriatric Depression Scale; GM, gray matter; HC, healthy control; MCI, mild cognitive impairment; MMSE, Mini Mental State Examination; NFT, neurofibrillary tangle; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association; PET, positron emission tomography; ROI, region of interest; SCI, subjective cognitive impairment; SD, standard deviation; TMT, Trail Making Test; WM, white matter; WMS, Wechsler Memory Scale.*

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INTRODUCTION

Subjective cognitive impairment (SCI) is common in the elderly and refers to a subjective decline in levels of cognitive functioning, which cannot be confirmed by neuropsychological evaluation (1). Longitudinal population-based studies have reported an association with future cognitive decline (2) and dementia (3). Moreover, neuroimaging studies have shown that, in subjects with SCI, Alzheimer's disease (AD)-like changes, such as loss of volume in the medial temporal lobe and hippocampus, may have already occurred before cognitive decline becomes evident (4–9). This suggests that the elderly with SCI may be at risk for the development of AD. Alternatively, cognitive complaints may be caused by other factors, such as depression, anxiety and quality of life (10–13).

Recently, it has been demonstrated that T_2*-weighted MRI at high field provides indirect evidence of the presence of AD pathology (14,15). This approach is based on the finding that, in autopsy material of patients with AD, amyloid-beta (Aβ) deposition and neurofibrillary tangles (NFTs), as well as tau deficiency, are found to co-localize with cortical iron accumulation (16–19). Based on the high sensitivity of T_2*-weighted MRI at 7 T in detecting small cerebral iron deposits (20,21), we have shown in a previous study that, in patients with AD, the magnitude of the observed cortical phase shift in T_2*-weighted phase images is correlated with global cognitive functioning, and demonstrates a high sensitivity in differentiating patients with AD from controls (14). Based on the fact that Aβ plaques and NFTs occur up to 10–20 years before cognitive decline can be measured (22), and the findings that SCI predicts the future diagnosis of AD (23,24), it could be hypothesized that, in subjects with SCI, differences in T_2*-weighted cortical phase shifts may already be present before cognitive decline can be determined.

The main aim of this study was to investigate whether cortical phase shifts on T_2*-weighted images at 7 T in subjects with SCI can be detected, suggesting the deposition of Aβ plaques and associated iron. The secondary aim was to investigate which cognitive domains are associated with cortical phase shifts in these subjects.

MATERIALS AND METHODS

Participants

This study was approved by the local institutional review board. In all cases, informed consent was obtained according to the Declaration of Helsinki (25). In total, 28 patients with AD, with a mean age of 71.2 years (range, 54–86 years; 18 men and 10 women), 18 subjects with SCI, with a mean age of 66.5 years (range, 49–85 years; 13 men and five women), and 27 healthy controls (HCs), with a mean age of 68.9 years (range, 52–80 years; 16 men and 11 women), were included.

Patients with AD and subjects with SCI were recruited from the memory clinic of the Leiden University Medical Center, the VU University Medical Center in Amsterdam, the Bronovo Hospital in The Hague and the Diaconessen Hospital in Leiden. Memory clinic patients were referred to the hospital by their general practitioner or a medical specialist. Prior to the 7-T study, all patients underwent a routine clinical protocol, comprising a whole-brain clinical MRI and a battery of neuropsychological tests measuring global cognitive functioning [Mini Mental State Examination (MMSE) (26) and Cambridge Cognitive Examination (CAMCOG) (27)], memory [Wechsler Memory Scale (WMS) (28) including digit span forward and backward (working memory)], executive function [Trail Making Test (TMT) part B (cognitive flexibility) (29) and STROOP card 3 (inhibition) (30)], psychomotor speed [TMT part A) (29)] and depression [abbreviated Geriatric Depression Scale (GDS) (31)]. A general medical and neurological examination was performed by a neurologist, psychiatrist or internist-geriatrician. Diagnosis was made in a multidisciplinary consensus meeting using the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for the diagnosis of probable AD (32). SCI was defined by the subjective feeling of memory decline for which these subjects (based on memory complaints) were referred to the memory clinic; however, subjects with SCI performed within the normal range on standard neuropsychological tests [i.e. criteria for mild cognitive impairment (MCI), dementia or other neurologic or psychiatric disorder were not fulfilled]. Participants with the diagnosis 'SCI' and 'probable AD', who were capable of giving informed consent (MMSE $\geq$ 19), were selected for inclusion. Patients with AD and subjects with SCI were selected for inclusion in the 7-T study either retrospectively within 1 year after attending the memory clinic, or otherwise prospectively.

HCs were recruited as part of the Leiden Longevity Study, the details of which have been described elsewhere (33). So as not to predispose for familial longevity, only partners of offspring were included. Subjects were included if they lived independently, were aged $\leq$85 years, had a body mass index between 23 and 35 kg/m^2, an MMSE $\geq$ 25 and a GDS $\leq$ 4. Individuals who were engaged in heavy/intense physical activity, had been immobile for longer than 1 week in the preceding 3 months, had shown psychiatric or behavioral problems, or had used either thyroid medication or immunosuppressants were excluded. Subjects were screened for cognitive deficits by an internist-geriatrician, and subjects with the following diseases were excluded: hemorrhagic and ischemic stroke, Parkinson's disease, dementia, MCI, diabetes type I or II, rheumatoid arthritis, polymyalgia rheumatica, cancer, heart failure and chronic obstructive pulmonary disease. Prior to the MRI scan, all subjects underwent cognitive testing, measuring global cognitive functioning (MMSE), working memory (digit span forward and backward), executive function [TMT part B (cognitive flexibility) and STROOP card 3 (inhibition)] and psychomotor speed (TMT part A).

MRI

Image acquisition

MRI was performed on a whole-body, human, 7-T MRI system (Philips Healthcare, Best, the Netherlands) using a quadrature transmit and 16-channel receive head coil. Participants were scanned using a two-dimensional, flow-compensated, transverse, T_2*-weighted gradient echo scan, including the frontal and parietal regions, which are most prone to Aβ deposition, with a total imaging duration of 10 min. Positioning of this stack of slices was planned within the frontal and parietal region above the occipital lobe, using the sagittal plane of the survey scan as a reference. The middle of the stack of slices was positioned through the corpus callosum, just above the thalamus. Imaging parameters were as follows: TR/TE = 1764/25 ms; flip angle, 45°; slice thickness, 1.0 mm with a 0.1-mm interslice gap; 20 slices; field of view, 240 × 180 × 22 mm^3; matrix size, 1024 × 768; in-plane spatial resolution, 0.24 × 0.24 mm^2. The bandwidth per pixel was 46 Hz, corresponding to a readout length of approximately 22 ms. The frequency- and phase-encoding directions were along the anterior–posterior and right–left axes, respectively. Shimming up

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to third order was performed using an image-based shimming approach (34). The phase images were subsequently unwrapped by high-pass filtering with a 92×92 kernel (35).

Image analysis

Phase values in the cortex were determined using the transverse two-dimensional T_2*-weighted gradient echo scans. The phase values of the cortical gray matter (GM) were determined on the unwrapped phase images in regions of interest (ROIs) in four different areas of the brain: frontal, parietal, left temporoparietal and right temporoparietal. Because of the laminar variation in the cortical areas (36), histograms perpendicular to the cortex within these regions were created to measure peak GM phase values, over at least 10 cortical regions per slice and per region. To correct for local macroscopic magnetic field inhomogeneities, subcortical white matter (WM) phase values were measured and used as an internal reference value. ROIs were selected containing only the GM or WM, avoiding blood vessels, cerebrospinal fluid (CSF), WM hyperintensities and other abnormalities which could influence the results. Phase values for GM and WM were measured in these four areas per MRI slice for every other slice (10 in total), resulting in 40 phase values for GM and WM separately per subject. The phase values of the different ROIs of the four regions were averaged. Per subject, the overall phase shift between cortical GM and subcortical WM (lobar cortical phase shift) was calculated for each region and expressed in radians. All phase values reported in our article represent these averages (14).

Statistics

Where appropriate, the data are expressed as the mean ± standard deviation. One-way analysis of variance (ANOVA) was used to assess differences in age, phase shift measurements and neuropsychological tests between patients with AD, subjects with SCI and HCs. *Post-hoc* independent-samples *t*-tests were used to assess differences in age, phase measurements and different neuropsychological test results between groups (two-sample comparison of means, two-sided test, equal variances were assumed). To evaluate differences in gender and education, chi-squared tests were performed. Univariate general linear modeling analysis was used to assess the association between diagnosis and cortical phase shifts, adjusted for age and gender. To determine the association between the different neuropsychological tests and phase shift in the cortex, linear regression analysis was used, correcting for age and gender in subjects with SCI. All statistical analyses were performed with the Statistical Package of Social Sciences (SPSS, version 20.0; SPSS, Chicago, IL, USA).

RESULTS

The characteristics of the participants, including the mean scores for different neuropsychological tests per group, are shown in Table 1. No differences in age, gender or education were found between the groups. A small difference in performance on the digit span backwards test (p = 0.024) and TMT part A (p = 0.042) between subjects with SCI and HCs was found. For the other tests, no differences between these groups were found. Patients with AD demonstrated an overall lower cognitive performance than subjects with SCI and HCs.

Figure 1 shows representative magnitude and phase images from a patient with AD, a subject with SCI and an HC. The mean phase shift of the entire cortex in patients with AD (mean, 1.19; range, 1.00–1.35) was higher than that for subjects with SCI (mean, 0.85; range, 0.73–0.99; adjusted for age and gender, $p < 0.001$) and HCs (mean, 0.94; range, 0.79–1.10; adjusted for age

Table 1. Mean baseline characteristics, mean scores with standard deviation (SD) and range of different neuropsychological tests of healthy controls (HC), subjects with subjective cognitive impairment (SCI) and patients with Alzheimer's disease (AD). In addition, significant p values between the groups are shown

	HC (SD; range) ($n = 27$)	SCI (SD; range) ($n = 18$)	AD (SD; range) ($n = 28$)
Age (years)	68.9 (8.1; 52–80)	66.5 (11.2; 49–85)	71.2 (8.4; 54–86)
Male/female	16/11	13/5	18/10
Education (median)	3.3 (3)	3.5 (3)	4.0 (4)
GDS	–	3.3 (2.6; 0–7)	3.3 (2.6; 0–9)
MMSE score	29.0 (1.1; 26–30)	28.3 (1.6; 25–30)	22.4 (2.0; 18–26)[b,d]
CAMCOG	–	92.7 (5.0; 86–100)	74.5 (8.4; 50–87)[d]
WMS	–	121.12 (15.2; 97–143)	91.1 (9.7; 74–103)[d]
Digit span forwards	5.8 (0.9; 5–7)	4.8 (0.8; 4–6)	5.2 (1.3; 3-8)
Digit span backwards	5.2 (1.0; 3–7)	3.8 (1.1; 2–5)[a]	3.6 (0.9; 2–5)[b]
TMT part A	35.0 (6.3; 28–46)	44.5 (15.9; 25–77)[a]	85.3 (80.4; 32–300)[a,c]
TMT part B	79.3 (25.9; 51–131)	100.5 (53.0; 44–208)	226.7 (90.4; 79–300)[b,d]
STROOP card 3	107.9 (31.6; 72–160)	132.3 (60.4; 83–300)	182.9 (70.2; 100–300)[a]

[a] $p < 0.05$ and
[b] $p < 0.001$: HC *versus* SCI or AD.
[c] $p < 0.05$ and
[d] $p < 0.001$: SCI *versus* AD.
CAMCOG, Cambridge Cognitive Examination; GDS, Geriatric Depression Scale; MMSE, Mini Mental State Examination; TMT, Trail Making Test; WMS, Wechsler Memory Scale. TMT part A and B and STROOP card 3 are given in seconds; other neuropsychological tests are given in points.

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and gender, $p < 0.001$). No AD-like changes, e.g. increased cortical phase shifts, were found in subjects with SCI compared with HCs. Parcellation into frontal, parietal and temporoparietal subregions did not yield different conclusions.

Table 2 shows the results of the linear regression analysis examining the association between the cortical phase shift of the whole brain (including all ROIs) and the scores of neuropsychological testing corrected for age and gender in subjects with SCI. A significant association was found between memory function (WMS) and the cortical phase shift ($\beta = -0.544$, $p = 0.007$). No significant association was found between other cognitive functions and the cortical phase shift. Parcellation into frontal, parietal and temporoparietal subregions showed a highly significant association between the cortical phase shift in the frontal region in subjects with SCI and memory function (WMS) ($\beta = -0.721$, $p < 0.0001$), and a less significant association with global cognitive functioning (MMSE) ($\beta = -0.519$, $p = 0.021$). Within the parietal region, a less significant association was also found with memory function (WMS) ($\beta = -0.406$, $p = 0.041$). It should be noted that these results were not corrected for multiple comparisons and therefore should be interpreted with care, especially those with moderate significance (i.e. 0.05–0.01).

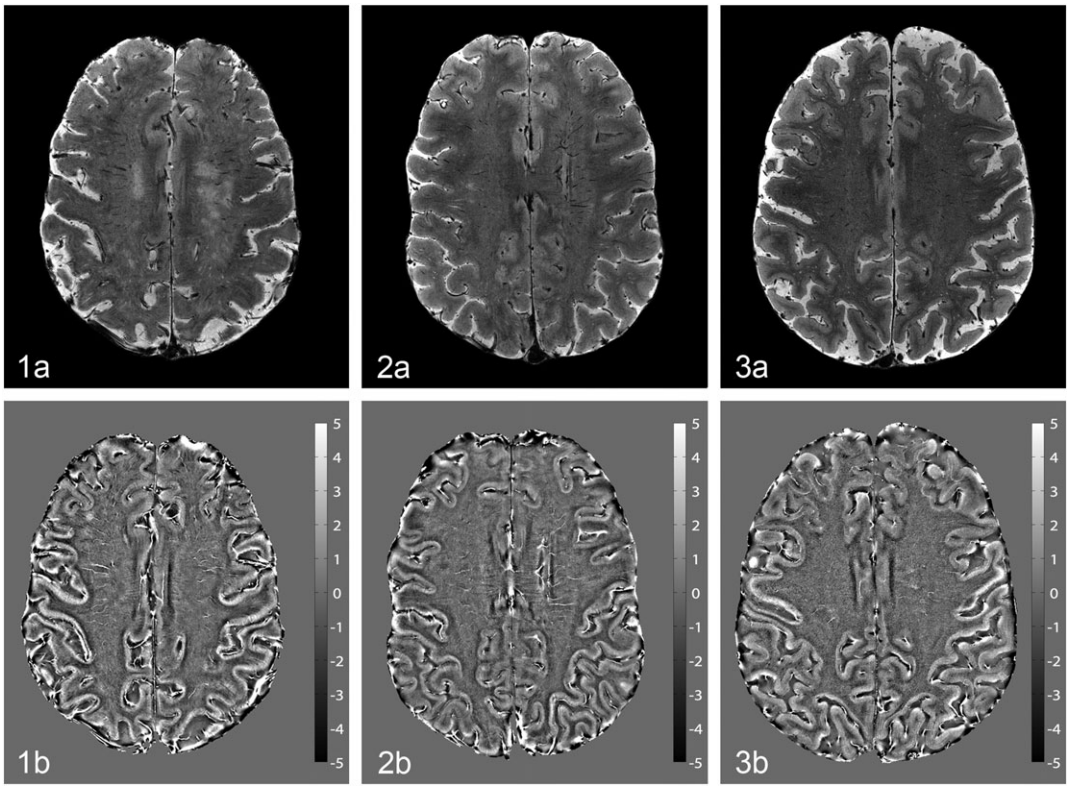

Figure 1. Representative magnitude (a) and phase (including a scale bar in hertz) (b) images acquired from a patient with Alzheimer's disease (1), a subject with subjective cognitive impairment (2) and a healthy control (3).

Table 2. β and p values correlating cortical phase shift with the scores of neuropsychological testing in subjects with subjective cognitive impairment, adjusted for age and gender

Cognitive domain	Cognitive test	β	Std. error *B*	Partial *r*	*P* value
Depression	GDS	–0.007	0.014	–0.009	0.991
Global cognitive functioning	MMSE	–0.238	0.011	–0.278	0.297
Global cognitive functioning	CAMCOG	–0.251	0.004	–0.300	0.320
Memory	WMS	–0.544	0.001	–0.667	0.007*
Psychomotor speed	TMT part A	0.616	0.002	0.445	0.096
Executive function (cognitive flexibility)	TMT part B	0.250	0.001	0.171	0.541
Executive function (inhibition)	STROOP card 3	–0.060	0.000	–0.068	0.863

CAMCOG, Cambridge Cognitive Examination; GDS, Geriatric Depression Scale; MMSE, Mini Mental State Examination; TMT, Trail Making Test; WMS, Wechsler Memory Scale.

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DISCUSSION

The major finding of this study is that, in subjects with SCI, an increased cortical phase shift measured with high-field MRI is associated with a poorer memory performance, although, as a group, subjects with SCI did not show an increased phase shift compared with HCs. The finding of an increased cortical phase shift being related to memory performance is important new information, as it is still unclear whether SCI represents a first stage of AD or a sign of pre-clinical AD, and results from previous studies are inconclusive with regard to the rate of decline and risk for conversion to AD dementia (1). Previous longitudinal and epidemiological studies have suggested that SCI is a precursor of AD (3,37,38), and therefore we hypothesized that we might find an increased phase shift, related to AD pathology, in subjects with SCI compared with controls, but that this phase shift would be lower relative to that of patients with AD. However, we did not find an increased cortical phase shift in subjects with SCI compared with HCs. Our findings might be explained by studies demonstrating that the majority of subjects with SCI do not develop AD, as there is only a 20% chance that SCI will progress to dementia in this group (39), and multiple factors contribute to the presence of cognitive complaints, such as depression, anxiety and quality of life (11–13). Moreover, SCI is a heterogeneous group in which some pre-AD subjects might show an increase in phase, whereas non-AD cognitive impairment is associated with a phase decrease, perhaps suggesting a different mechanism for this group.

Our study shows that the cortical phase shift, determined on T_2*-weighted MRI at 7 T, is associated with memory performance in subjects with SCI. In contrast, global cognition, executive function and psychomotor speed are not associated with the cortical phase shift in these subjects. Based on previous studies, we expected to find an association between the iron-sensitive phase shift and cognition (40). However, assuming that the cortical phase shift is an indirect marker of the amount of amyloid plaques, the association would be more complicated. Previous studies have shown that this association is not straightforward and is most probably influenced by the presence of NFTs, as discussed in a review by Nelson *et al*. (22). The dynamic biomarkers model of AD states that AD starts with an increase in Aβ in the brain, followed by the formation of NFTs and, at a later stage, memory is impaired when the amount of Aβ is still increasing (41). As we found an association between the cortical phase shift and memory, and no other cognitive domain, this implies that, in subjects with SCI, the cortical phase shift might be a marker to demonstrate very early changes in the brain related to memory function.

Our data demonstrate that subjects with SCI do not show AD-like phase changes in comparison with HCs. Although the SCI group performs slightly lower on the cognitive tests than the HC group, our results also show no highly significant differences in cognitive function between the groups. Several explanations for these findings are possible and are partly described above. If SCI is indeed an early AD stage, in which AD pathology is present without the presence of cognitive symptoms, as suggested by several studies, our data indicate that phase changes would only appear at a later stage of the disease when AD pathology is more severe and starts to have an effect on brain function. Another explanation for our results might be that SCI is not strongly associated with AD, as it is related to many factors other than AD, and only a small subset of the subjects with SCI develop AD (10–13,42). Alternatively, because phase changes are measured at a group level, it might be that, as most subjects with SCI do not develop AD, the differences between controls and subjects with SCI are too small to be significant. The investigation of cortical phase changes in longitudinal studies in subjects with SCI, MCI and AD to evaluate the possibility of detecting early AD pathology over time could provide more insight into SCI and the development of AD pathology, and the association with cortical phase changes and cognitive performance.

One overall limitation of this study is that phase measurements may partly be influenced by the geometry and orientation of the individual structures (21). To limit these effects as much as possible, all participants were positioned in the same manner and, for every subject, the phase measurements were performed in the same way and were averaged to cancel out the possible effects of geometry and orientation. Although it is most likely that the difference in phase shift between groups is mainly attributable to iron, other compounds may contribute to a change in phase shift, such as deoxyhemoglobin, myelin and proteins (36,43).

In conclusion, in this study, we have shown that patients with AD demonstrate an increased cortical phase shift, indicating greater iron accumulation, compared with HCs. Moreover, these cortical phase shifts are associated with decreased memory performance in subjects with SCI. Although previous studies have suggested that, in SCI, AD-like changes may occur before cognitive decline becomes manifest, our data do not show any signs of AD-like high-field T_2*-weighted cortical phase shifts at a group level in subjects with SCI.

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