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Serial Susceptibility Weighted MRI measures brain iron and microbleeds in dementia

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Abstract

A new iron sensitive MR sequence (susceptibility weighted imaging – SWI) enabling the simultaneous quantitation of regional brain iron levels and brain microbleeds (BMB) has been acquired serially to study dementia. Cohorts of mildly cognitively impaired (MCI) elderly (n=73) and cognitively normal participants (n=33) have been serially evaluated for up to 50 months. SWI phase values (putative iron levels) in 14 brain regions were measured and the number of brain microbleeds (BMB) were counted for each SWI study. SWI phase values showed a left putaminal mean increase of iron (decrease of phase values) over the study duration in 27 participants who progressed to dementia compared to Normals (p=0.035) and stable MCI (p=0.01). BMB were detected in 9 of 26 (38%) of MCI participants who progressed to dementia and are a significant risk factor for cognitive failure in MCI participants (risk ratio = 2.06 (95% confidence interval 1.37–3.12)). SWI is useful to measure regional iron changes and presence of BMB, both of which may be important MR based biomarkers for neurodegenerative diseases.

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“Disclosure Statement”

None of the authors, with the exception of Dr. Haacke, have any actual or potential conflicts of interest with regard to this work. Dr. Haacke is a consultant to the Siemens Corporation and has patent applications related to the SPIN program. His academic institution, the MRI Institute for Biomedical Research, does not have any financial or ownership interests that directs into the topic of this manuscript. None of the other authors have any relationship to the Siemens Corporation or any financial interest or any conflict of interest for this work.

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Keywords

brain; microbleeds; susceptibility weighted imaging; dementia; amyloid angiopathy; cognitive impairment; putaminal iron; globus pallidus iron

1. Introduction

Until the advent in the 1980s of magnetic resonance brain imaging (MRI), studies of the aging human brain and its diseases were essentially post-mortem associations. [1,2] MRI opened new venues for studies of brain aging, permitting not only structural evaluations but more importantly the potential for longitudinal studies of specific neuroanatomical structures.[3] Furthermore, the discovery that T2 weighted (T2W) brain MR imaging could detect and estimate regional patterns of iron deposition stimulated an intensive search for new MR sequences to provide biomarkers to monitor iron-related neurodegenerative diseases.[4] Though brain iron is known to occur excessively in a variety of neurodegenerative disorders and is implicated in free radical mediated oxidations, the mechanisms and kinetics of its accumulation, as well as, its source remain speculative.[5,6] Longitudinal studies with a new MR sequence, susceptibility weighted imaging (SWI), allows simultaneous assessment of regional brain iron deposition [7] and the detection of iron rich brain microbleeds (BMB) – a documented biomarker for cerebrovascular disease.[8] Furthermore, SWI has shown greater sensitivity than conventional gradient recalled echo T2* weighted (T2* GRE) imaging for BMB detection, identifying more and smaller lesions in both cerebral amyloid angiopathy (CAA) and brain trauma cases.[9–13]

On MR images, paramagnetic blood products cause well documented signal decreases in T2* GRE and T2 weighted (T2W) spin echo images, an effect that has been widely used to study brain iron. Though there are numerous reports of brain iron quantitation using MRI [14–21], there are no universally accepted methods or standards. Our group has compared the effectiveness of SWI to other MR brain iron quantitation methods and has established baseline phase values as putative markers for regional brain iron levels.[7,19,22]

This study reports the first application of serial SWI to use phase changes as a marker for regional brain iron changes in a prospective study of sporadic late-onset dementia extending over 5 years. We also report on the appearance of BMB as detected on SWI which appeared in a subset of this population during the course of this study.

2. Methods

2.1 Participant selection

Over a 5-year period, 1,348 individuals from several local communities were screened to recruit elderly cognitively normal and mild cognitively impaired (MCI) study participants. Inclusion and exclusion criteria defined by the Mayo Clinic Group [23] were used in the screening process. All Normals were without objective or subjective memory deficits and within normal limits on neuropsychological testing (Global Clinical Dementia Rating (CDR) of 0, CDR memory component of 0 and a sum of CDR boxes of 1 or less at baseline).[24] All MCI participants fulfilled the Mayo Clinic criteria for classification as MCI-multiple domain impairment, i.e.: i) A memory complaint confirmed by Logical Memory testing or reports of the informant and a CDR of 0.5. ii) Normal activities of daily living. iii) Normal general cognitive function iv) Abnormal memory for age as measured by standard scores and education. v) A global CDR of 0.5 and no clinically determined dementia.

Participants in the study have been evaluated cognitively (bi-yearly) and radiologically (every 9–14 months) for up to 5 years. Cognitive tests were scheduled in proximity to MR evaluations. All participants gave informed consent and all studies were approved by the Loma Linda University Institutional Review Board.

2.2 Cognitive testing

Cognitive tests included: videotaped CDR with informant, Logical Memory I, II, Word Fluency: Phonemic and Semantic, Wisconsin Card Sorting Test, Trail Making Test A&B, Boston Naming Test, Draw-A-Clock, and Geriatric Depression Scale. North American Adult Reading Test and Depression Features Battery Version II were given during initial assessment. Results of imaging and cognitive studies were reviewed bimonthly and, if neurologic assessment indicated development of a disorder other than AD, the subject was removed from the study. Results of neuropsychological tests were considered abnormal if below 1.5 standard deviations (SD) on normative data based on age and education. The diagnosis of dementia was based on clinical judgment, a consensus conference, NINCDS-ADRDA criteria, and a Sum of Boxes (SOB) on a CDR ≥ 3.5 . [24]

2.3 MR imaging

MR acquisitions were performed on a 1.5T MR scanner (Vision, Siemens Medical Solutions) and included: sagittal magnetization prepared rapid gradient echo (T1-3D MPRAGE), axial T2 weighted fast spin echo (T2-FSE), fluid attenuated inversion recovery (FLAIR), 2D T2* weighted gradient recalled echo acquisition (T2* GRE) and 3D whole brain SWI.

SWI is a fully flow-compensated, three-dimensional (3D), high-resolution, gradient-echo sequence used to collect magnitude and phase data with each slice. To obtain SWI phase measurements, phase images were high-pass-filtered and processed region by region offline with a custom Visual C++ software program (SPIN, Signal Processing in NMR). [25] This software was also used to obtain SWI images, by multiplying magnitude images with filtered phase images to enhance the susceptibility effect and then performing a minimum intensity projection (mIP) reconstruction to produce various slice thicknesses (4 – 10 mm) in order to better visualize connectivity of the microvasculature to BMB. Imaging acquisition parameters for SWI used in-plane resolution 0.5 mm $\times$ 1.0 mm (interpolated to 0.5 mm $\times$ 0.5 mm); 2 mm thick, field-of-view = 256 mm $\times$ 256 mm; matrix = 256 $\times$ 512, 48 slices; TE = 40 ms; TR = 57 ms; and FA = 15 degrees. Phase units were expressed as Siemens normalized units as discussed previously. [7] Imaging parameters for the 2D T2* GRE sequence used for comparison to SWI were in-plane resolution 0.5 mm $\times$ 1.0 mm (interpolated to 0.5 mm $\times$ 0.5 mm); 4 mm thick, field-of-view = 256 mm $\times$ 256 mm; matrix = 256 $\times$ 512, 24 slices; TE = 18 ms; TR = 500 ms; and FA = 15 degrees.

2.4 ROI regional tissue iron determinations

Phase images from whole brain SWI were used to quantitatively measure iron in 14 different regions of interest (ROIs) in both cerebral hemispheres. Methods for drawing ROIs in each cerebral hemisphere, post-processing for phase measurements, and baseline phase data for the ROIs have been given in previous publications. [7,22,26] Bilateral ROIs assayed included: motor cortex grey matter (GM), cerebral white matter subjacent to motor cortex (WM), cerebrospinal fluid in the sulcus next to the motor cortex (CSF), caudate nucleus (CN), paracingulate gyrus (PG), thalamus (T), total putamen (P), globus pallidus (GP), red nucleus (RN), (RN-nonvascular), (RN-vascular), substantia nigra (SN), (SN-pars reticularis), (SN-pars compacta). A demonstration of ROI placement for serial putaminal studies is shown in Figure 1. Phase measurements obtained from SWI filtered phase data were described in normalized units as supplied by the manufacturer and were inversely associated with putative iron values. As demonstrated previously in phantoms, measurements in an ROI of at least 100 pixels

enabled a determination of changing iron levels of 3 $\mu\text{gm Fe/gm brain}$ ($p=0.01$). [7] To check reproducibility of phase measurements, studies were processed at both participating sites with excellent interobserver agreement (intraclass coefficient (ICC) of 0.94 determined on 43 test cases). [7]

2.5 Brain microbleed (BMB) identification

BMB were defined for this study as homogeneous signal losses (≤ 10 mm outer diameter (O.D.)) without vessel continuity. BMB identification and counting has a wide reported interrater reliability. [27] SWI scans were evaluated for BMB by four trained readers all blinded to clinical status using an identical protocol. The readers have had over 4 years experience evaluating SWI images for BMB using this protocol. Differences in BMB counts were resolved by a senior neuroradiologist (DK). Signal voids mimicking BMB, e.g. subarachnoid pial sulcal vessels, end-on vascular voids, rare angiomatous malformations as well as symmetrical focal basal ganglia iron deposits were excluded.

2.6 Statistical Methods

All data were entered into a relational database application (Access) and cross-verified. Numeric data was checked for normality. For comparing mean phase values, independent t-tests were used for between-group comparisons and paired t-tests were used to detect mean hemispheric differences and changes between first and last measures. The unadjusted risk ratios (RR) were determined from a contingency table. A 95% confidence interval (CI) for risk of dementia associated with BMB is presented. Logistic Regression was used to derive age adjusted Odds Ratios (OR) for progression to dementia associated with phase values. Age adjusted group-by-time changes in SWI phase values associated with cognitive status, were evaluated using the linear mixed model (SAS 9.2). All results assume an $\alpha = 0.05$. All reported p-values are 2-tailed.

3. Results

3.1 Enrollment and grouping

Of the 1,348 individuals screened, 112 participants were enrolled and initially classified into two groups according to cognitive status as normal ($n=39$) and MCI ($n=73$). Cognitive endpoints were defined as Normal, MCI, or Dementia and were assigned for each participant at the time of their last imaging study. Participants were classified into three groups based on their baseline and endpoint cognitive status and whether they stayed in the study long enough to obtain at least two SWI studies which were needed for serial iron analysis.

Group 1 (Normals; $n=33$) included participants who were classified as “normal” both neurologically and cognitively at baseline and “normal” at the time of the last MRI evaluation. Of the 39 initially enrolled, 37 remained at normal cognitive status for the entire study and 2 progressed to MCI and/or dementia and were therefore included in the MCI and Dementia groups. Four Normals left the study after only 1 MRI due to cancer (1) or the study ended before another SWI could be obtained (3). Note that ten of the participants classified into the Normal group were initially evaluated as MCI, however, they were reclassified to the Normal group since they were scored as normal in at least 3 subsequent cognitive evaluations (minimum of 3 and maximum of 7) over a range of 18 to 52 months.

Group 2 (MCI; $n=23$) included participants who were classified as MCI ($n=73$) or Normal ($n=1$) at baseline and remained at MCI status for the last MRI evaluation. Of the 73 initially enrolled, 46 remained at MCI status for the entire duration of the study while 27 progressed to dementia and were included in the Dementia group. Twenty-four of the remaining 46 MCI left the study or were excluded after only 1 imaging study due to co-morbidity (2), claustrophobia

(1), loss of care support, transportation or moved (6), pacemaker insertion (1), no longer wanted to participate (3) or the study ended before another SWI could be obtained (11). One MCI died with autopsy-proven progressive supranuclear palsy and SWI findings reported.[10] The high morbidity and dropout rate of the MCI subjects has been noted by others and is a problem inherent to the clinical syndrome.[28,29]

Group 3 (Dementia; n=27) included participants who were classified as MCI (n=26) or Normal (n=1) at baseline and progressed to dementia when evaluated for the last MRI study. The MCI who progressed to dementia did so at a progression rate of 0.15 per person-year of follow-up (95% CI: 0.09 to 0.21). Two participants from the Dementia group left the study or were excluded after only 1 useable imaging study due to loss of care support/moved (1) or no-longer willing to participate (1). The clinical picture of dementia in all of the cases was diagnosed as typical “Alzheimer’s disease” by experienced gerontologists and neurologists. The cognitive outcomes of our community-based MCI and control elderly cohorts over the 5.0 years (mean = 2.7 y) of the study conform with previous reports.[23]

3.1 Group description

Demographic data and neuropsychological profiles on the three groups whose cohorts are described in the above paragraphs are given in Table 1. No significant group differences were seen with respect to gender or years of education which may have influence on cognitive evaluations. The age at enrollment was significantly different between groups ($p < 0.001$). Post hoc tests showed that the mean age of Normals was significantly lower than the Dementia group ($p < 0.001$), but not the MCI group ($p = 0.056$) and the MCI and Dementia groups were not significantly different ($p = 0.14$). The median number of cognitive evaluations and imaging studies obtained for each participant were similar for all three groups (Table 2). Participants received more cognitive evaluations during the study than MRI evaluations due to cost and scheduling issues. Normal participants stayed in the study longer (median of 35 months) compared to MCI (21 months) and demented (26 months) participants (Table 2). The time between MRI studies ranged from a minimum of 6 months up to 35 months, however, the median was similar for all three groups (Table 2). Only subjects with two or more scans have results reported and the times between scans are given in Table 2. The median interval in months for the “normals” was 14, MCI subjects 13, and demented 12.5.

3.2 Changes in regional iron levels over time

Of the 14 different regions evaluated, several regions in the right (WM, PG, CN, T, SN-pars reticularis) and left (P GP, RN-vascular) cerebral hemispheres showed a pattern of a subtle but not statistically significant decrease in SWI phase values in the Dementia cohort compared to MCI or Normals. These findings agree with previous reports of hemispheric asymmetries in iron content with the left hemisphere showing increased levels.[21] We have found, however, that after evaluation of the iron content of all ROIs only the left putamen showed a significant difference in mean SWI phase values between groups at baseline (ANOVA; $p = 0.043$). A linear mixed model was then used to compare group-by time effects on phase values in the left putamen Figure 2 shows a significant left putaminal decrease of SWI phase values over the 50 month study duration in the 27 participants who progressed to dementia compared to Normals ($p = 0.035$) and MCI ($p = 0.01$). Kinetics of iron uptake are based on the change in phase units over time with a decrease in SWI phase units representing an increase in iron levels.[7] The stable MCI cohort had no change in putaminal iron over the course of the study compared to a small increase in iron for the Normals and a greater increase in the Dementia cohort.

3.3 Probability of dementia based on putaminal iron levels

We used logistic regression models to determine if left putaminal SWI phase data related to iron levels was predictive for progression to MCI status and found that age produced a higher

and significant odds ratio (Odds ratio (OR) = 1.16; $p=0.002$) than baseline phase values (OR=0.991; $p=0.093$) when used in the same model. Age was included since the mean age between Normals (74.9 ± 7.8 ; $n=33$) and all MCI (80.8 ± 4.9 ; $n=49$) at baseline was significantly different ($p<0.001$). When baseline left putaminal phase values were used separately as an independent variable for the model, an odds ratio close to one was determined (OR= 0.989; $p=0.02$). The results of these analyses show that age is a stronger predictor of dementia than putaminal phase values.

3.4 Number and regional distribution of BMB

Of the 33 normal participants, none were found to have BMB during the course of the study. Of the 23 in the MCI group, SWI detected one participant with greater than 1 BMB at entry which was still detectable 51 months later at the time of the last MRI. In the group that progressed to dementia, 8 of 26 had greater than 1 BMB at entry (range 2–69; median, 22) and an additional participant was found to have 5 at the time of their second SWI study obtained 8 months later. No BMB were detected in the remaining 15 in the demented group during the course of the study. The number of BMB increased in all 9 participants during the course of the study to a much greater extent in some than others (range of increase: 1–141; median, 16). Two participants showed a reduction of BMB at their last scan suggesting resorption of BMB during the course of the study. Among those classified as MCI at baseline, the Relative Risk (RR) for development of dementia associated with BMB >1 at any time is 2.06 (95% CI, 1.37–3.12).

As shown in Figure 3, significantly more BMB were detected with SWI in the right cerebral hemisphere than the left ($p\text{-value} = 0.02$, Wilcoxon Signed Ranks Test). The BMB are clustered primarily subcortically in the posterior parietal (23%), temporal (13%), frontal (15%), and occipital lobes (38%). The following BMB size distributions were found: 1–3 mm O.D. (95%), 4–5 mm O.D. (3%) > 5 but <10 mm O.D. (2%). An illustration of BMB as seen on SWI from one of the participants in the Dementia group is shown in Figure 4A and is compared to a T2* GRE image (Figure 4B).

3.5 Probability of dementia based on presence of BMB

Logistic regression was also used to determine whether the presence of BMB can predict whether the participants in our study in the MCI group will progress to dementia. When the presence or absence of BMB was included as an independent variable in the model to compare MCI ($n=23$) to Dementia ($n=26$), we found a significant odds ratio of 11.6 ($p=0.026$), however, the presence of BMB is significant only when the logistic regression model is not adjusted for age. When age and presence of BMB are included in the model, the odds ratio for neither variable was significant (OR=1.16 and 7.7, respectively; $p=0.07$ for each). The results of these analyses show an increased risk for progression to dementia when BMB are detected on SWI, however, a larger number of participants will need to be included to prove significance when adjusted for age due to the strong association of increased age and dementia.

4. Discussion

We report the first longitudinal study of sporadic late onset dementia development focused on changes in regional brain iron. Using SWI we found a significantly increased rate of iron uptake in the left putamen in participants who progressed from MCI to dementia during the course of this study compared to participants in the stable MCI group or Normals. These findings are consistent with previous reports of findings noted in elderly depression. Increasing left putaminal iron levels as determined qualitatively by T2 weighted MRI hypointensity have been described in a well controlled study of clinically depressed elderly patients.[30] It is now appreciated that clinical depression commonly precedes and may overlap with Alzheimer's

type dementia development.[31,32] Our observations of increasing left putaminal iron are consistent with other neuroimaging studies that have associated iron increases with greater left sided basal ganglia pathology.[33] Normal aging is associated with an irregular, uneven gradient of symmetric putaminal iron deposition extending from postero-lateral to antero-medial with uneven borders.[22,34] Though increases in brain iron are clearly associated with aging and neurodegenerative diseases, the source of iron as well as mechanisms responsible for enhanced uptake remain unresolved.[35–38] The assumption that excessive ferrous iron, a redox-active metal, mediates indiscriminate free radical based oxidative damage to tissue is widely accepted and has found a basis for metal chelation as a therapeutic strategy.[39,40]

We also show the presence of BMB in participants who progressed to dementia, distributed primarily in the parieto-occipital lobes of the right cerebral hemisphere. Brain hemosiderin deposits secondary to BMB have been considered inert biomarkers, however, there is now MRI evidence for their dynamism and resolution.[41] Blood extravasation into brain precipitates a marked inflammatory response characterized by microglial activation, rapid degradation of hemoglobin to hemosiderin with release of free iron, and immediate and long-term neurotoxic effects.[42,43] The observation of a lateralized deep gray matter accumulation of iron in the face of progressing and resolving microhemorrhages has its counterpart with other iron associated neurodegenerative processes e.g. multiple sclerosis plaques (MS) and global hypoxia-ischemia.[44,45] It has been suggested that iron accumulation in the basal ganglia in MS may arise from either a disturbance in the neuronal transport of free iron, blocking iron outflow from the striatum or conversely, an accelerated transport of hemosiderin derived iron into the putamen.[44]

We found that participants with BMB are twice as likely to progress to dementia than those without BMB. The relation of radiologically identified BMB to cognitive loss, risks of future bleeding, and the diagnosis of cerebral amyloid angiopathy or hypertension is becoming increasingly recognized.[46–48] A possible source for the increased brain iron noted in a host of neurodegenerative diseases is that resulting from unrecognized microhemorrhages.[49] The total blood volume of BMB and the pathobiology responsible for blood extravasation is now receiving increased attention.[27,50,51] Although it is unlikely that the number of BMB detected in this study and/or their breakdown alone is sufficient to account for the total increased iron accumulation measured in the demented group of participants, the BMB detected may be a small percentage of the actual number present. It is known that pericapillary heme deposits are widespread in the brains of elderly and AD subjects and that most BMB are too small to be identified by either conventional MRI or SWI and often escape notice in routine neuropathological examination.[49,52]

Of great interest is the fact that a steady increase in iron levels in several regions predominately in the deep brain is noted along with a predominance of BMB only in the demented cohort. Both GABA and dopaminergic neurons have been implicated in iron transport to and from distal sites and deep central gray matter.[53,54] It is speculated that overloading axonal and neuronal iron transport mechanisms could play a significant role in neurodegenerative processes by causing regional iron catalyzed oxidative stress e.g. putaminal degeneration - a feature of another iron metabolic disturbance - aceruloplasminemia.[55] BMB secondary to head trauma, many too small to be recognized by conventional MRI, could be setting the stage for overloading deep nuclear brain iron (e.g. substantia nigra, basal ganglia) and predispose to further neurodegenerative processes such as that occurring in Parkinson's disease. SWI studies at higher field strengths may provide more sensitivity by both recognizing smaller BMB as well as the iron content in projecting neuronal tracts.

SWI detects significantly more and smaller BMB than conventional T2* GRE sequences.[9–13] The limit of resolution possible for detecting BMB has not been fully explored, particularly

utilizing the higher field MR scanners currently available. Previous reports of the localization and topography of BMB have not described a predominant right hemisphere localization.[27, 51,56–58] This may be due to limited visualization from using conventional T2* GRE imaging. Over 95% of the SWI identified BMB in our series are 1 to 3 mm in outer diameter which may require the increased sensitivity of SWI in order to detect. In addition, all 9 of the demented cases with BMB in our series have a significantly greater clustered posterior right-sided distribution, a finding that has also been observed during routine screening with SWI in our Geriatric Clinic.[9] This is significant since clustered hemorrhagic lesions found preferentially in the temporal or occipital lobes have been regarded as diagnostic evidence of probable CAA.[59] The vulnerability of vessels that results in BMB and the significance of regional distribution in relation to dementia merits further study.

There are several unique features to this study. For the first time, a community-based cohort with an at-risk group for sporadic late-onset dementia has had an extended longitudinal assessment of regional iron levels and BMB using SWI. We have identified a subset of dementing elderly with BMB associated with progressively increasing iron levels in the left putamen. SWI enhanced BMB detection may be an important biomarker for projected immunotherapy for AD since this treatment modality can aggravate the microvascular fragility associated with CAA.[60] In conclusion we have shown that SWI is useful to measure regional iron changes and presence of BMB, both of which may be important MR based biomarkers for neurodegenerative diseases.

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Scan 1: 4/29/2003

Scan 3: 5/27/2004

Scan 4: 6/9/2005

Figure 1.

Representative serial SWI scans (3 of 7) on an MCI subject progressing to dementia with the left putamen outlined. Putaminal phase measurements in this case showed a progressive increase in iron as well as BMB (Subject P4 in Fig. 3). Note the reproducible axial registration of the head in the scanner to enable consistent putaminal outlining.

Figure 2.

Graph showing greater SWI phase decreases in the left putamen (increased iron uptake) in the Dementia group over time compared to MCI and Normals. Significance between groups determined with a mixed model linear regression. (SAS)

Figure 3. Distribution of BMB counts between right and left cerebral hemispheres in participants with BMB in Dementia Group (9 cases). The X-axis represents the number of BMB averaged over the course of the study.

Figure 4.

A and B. Comparison of SWI (A) and T2* GRE (B) images of a demented participant taken on the same day for BMB detection. This case is an example of the right hemispheric predominance of BMB found in our study. In comparable 4 mm thick slices, SWI detects 14 BMB of varying sizes clustered in the right parieto-occipital region (**4A**) whereas GRE-T₂* provides less discrete resolution (arrow) without visualization of smaller lesions (**4B**).

Table 1
Demographics of three cohorts at entry. Data reported as number (%) or mean (range)

	Normal (n = 33)	MCI (n = 23)	Demented (n=26)	p-value
Sex,				
Female	19	8	14	0.219
Male	14	15	12	
Age at enrollment (years)	71.2 (42.4)	75.5 (54-84)	78.9 (64-87)	<0.001
Education (years)	14.6 (11-20)	14.7 (9-20)	13.4 (6-20)	0.138
Ethnicity	27 (81.8)	20 (87.0)	23 (88.5)	NA
Non-Hispanic White	1	-	1	
African American	2	3	2	
Hispanic	2	-	-	
American Indian	2	-	-	
Other	1	-	-	

Table 2

Evaluations performed and time in study

	Normal (n=33)	MCI (n=23)	Demented (n=26)
Number of Evaluations	Median (Range)	Median (Range)	Median (Range)
Cognitive	7 (3–10)	5 (2–8)	5 (2–12)
MRI Studies	3 (2–5)	3 (2–5)	3 (2–6)
Months in Study	35 (12–52)	21 (11–51)	26 (6–49)
Months between MRI Evaluations	14 (9–35)	13 (7–23)	12.5 (6–18.5)
Person years (events) *	118.25	62.58	67.75

* Based on time of entry for last cognitive evaluation