Relating one-year cognitive change in mild cognitive impairment to baseline MRI features

Simon Duchesne a,b,⁎, Anna Caroli c,d, Cristina Geroldi c, D. Louis Collins e, Giovanni B. Frisoni c

a Radiology Department, Université Laval, Québec, Canada
b Centre de Recherche Université Laval Robert Giffard, Québec, Canada
c Laboratory of Epidemiology, Neuroimaging and Telemedicine, IRCCS San Giovanni di Dio, Fatebenefratelli, Brescia, Italy
d Medical Imaging Unit, Biomedical Engineering Department, Mario Negri Institute for Pharmacological Research, Bergamo, Italy
e Brain Imaging Center, Montreal Neurological Institute, McGill University, Montreal, Canada

ARTICLE INFO

Article history:
Received 15 August 2008
Revised 29 March 2009
Accepted 1 April 2009
Available online 14 April 2009

Keywords:
Mild cognitive impairment
MRI
High-dimensional analysis
Regression
Mini-Mental Score Examination

ABSTRACT

Background: We propose a completely automated methodology to investigate the relationship between magnetic resonance image (MRI) features and changes in cognitive estimates, applied to the study of Mini-Mental State Examination (MMSE) changes in mild cognitive impairment (MCI).

Subjects: A reference group composed of 75 patients with clinically probable Alzheimer’s Disease (AD) and 75 age-matched controls; and a study group composed of 49 MCI, 20 having progressed to clinically probable AD and 29 having remained stable after a 48 month follow-up.

Methods: We created a pathology-specific reference space using principal component analysis of MRI-based features (intensity, local volume changes) within the medial temporal lobe of T1-weighted baseline images for the reference group. We projected similar data from the study group and identified a restricted set of image features highly correlated with one-year change in MMSE, using a bootstrap sampling estimation. We used robust linear regression models to predict one-year MMSE changes from baseline MRI, baseline MMSE, age, gender, and years of education.

Results: All experiments were performed using a leave-one-out paradigm. We found multiple image-based features highly correlated with one-year MMSE changes (|r| > 0.425). The model for all N = 49 MCI subjects had a correlation of r = 0.31 between actual and predicted one-year MMSE change values. A second model only for MCI subjects with MMSE loss larger than 1 U had a pairwise correlation r = 0.80 with an adjusted coefficient of determination r² = 0.61.

Findings: Our automated MRI-based technique revealed a strong relationship between baseline MRI features and one-year cognitive changes in a sub-group of MCI subjects. This technique should be generalized to other aspects of cognitive evaluation and to a wider scope of dementias.

© 2009 Elsevier Inc. All rights reserved.

Introduction

Mild cognitive impairment (MCI) describes elderly individuals with memory complaints and objective cognitive impairment relative to subjects of similar age and education (Petersen et al., 2001). MCI individuals are considered an at-risk group for progression to dementia, in particular Alzheimer’s dementia (AD) (Dubois and Albert, 2004). Early detection of probable dementia in MCI subjects and/or prediction of the progression of MCI to probable dementia are critical issues facing clinicians. The main advantage of early detection or prediction of progression is the opening of a therapeutic window of opportunity otherwise not available.

MRI in AD and MCI

Neuroimaging, and in particular magnetic resonance imaging (MRI), is widely available, non-invasive, and holds considerable promise in the study of dementias and its putative prodromal stages (Chetelat and Baron, 2003). Standard T1, T2 and PD weighted MRI sequences acquired on clinical scanners of 1.0–3.0 T field strengths can image macroscopic disease-related effects such as changes in shape, size or image intensity of anatomical structures (Ashburner et al., 2003). It is clear however that these images lack the resolution to measure directly microscopic changes due to the disease in the cellular environment, and thus have a limit on the role they can play in helping to diagnose or predict the progression to probable dementias. Still, that role has shifted from finding exclusion criteria for other

Abbreviations: AD, Alzheimer’s Disease; CTRL, Control Subjects; MCI, Mild Cognitive Impairment; MRI, Magnetic Resonance Imaging; MMSE, Mini-Mental State Examination; VOI, Volume of Interest.

⁎ Corresponding author. Centre de Recherche Université Laval Robert Giffard, F-4415/2601 de la Canardière, Québec, QC, Canada. Fax: +1 418 663 9540.
E-mail address: duchesne@ieee.org (S. Duchesne).

1053-8119/5 – see front matter © 2009 Elsevier Inc. All rights reserved.
doi:10.1016/j.neuroimage.2009.04.023
possible causes of dementia to measuring disease-specific inclusion criteria that may identify the disease at a very early stage (Hansson et al., 2006; Dubois et al., 2007).

Computer-aided analysis techniques have been proposed to discover and study inclusion biomarkers via texture changes in signal intensity (Freeborough and Fox, 1998), grey matter concentrations differences (Frisoni et al., 2002; Kloppe et al., 2008; Fan et al., 2008), atrophy of subcortical limbic structures (Thompson et al., 2004; Frisoni et al., 2006; Csernansky et al., 2000) and general cortical atrophy (Thompson et al., 2003; Chan et al., 2003; Lerch et al., 2005). A recent and growing body of literature has used machine learning methods to extract high-dimensional features of interest from MRI, on which classification functions are built to assist in clinical diagnosis of probable AD or predict future clinical status for individuals with MCI (Kloppe et al., 2008; Fan et al., 2008; Lao et al., 2004; Duchesne et al., 2008; Davatzikos et al., 2008).

A new and valuable area of research for quantitative MRI resides in the analysis and prediction of change in non-MRI variables (Friston et al., 2008). For example, Ashburner (2007) attempted to predict subject age from morphological information. Nevertheless, to our knowledge there have been limited studies (Duchesne et al., 2005) on the predictive ability of MRI for cognitive change in the context of dementias. The underlying assumption being, in this case, that changes in neuropsychological or neurological functions under consideration have a morphological correlate detectable via structural MRI.

Progression of cognitive change

For practical purposes, the short-term (e.g. one year) progression of cognitive change in MCI patients is a continuous phenomenon. In those subjects, the distribution of change in a variable assessing cognitive status will not be dichotomous but rather multi-valued, either ordinal or continuous. On the other hand, only small fluctuations are expected for stable MCI subjects.

We have elected to choose as an example of cognitive test the Mini-Mental State Examination (MMSE) (Folstein et al., 1975), a well-known and widely used scale. Its usefulness in the study of AD is exemplified by Petrella et al., who suggested simple thresholds to differentiate between normality (MMSE = 30), mild impairment (23 < MMSE < 30) or possible dementia (MMSE < 23) (Petrella et al., 2003); such thresholds are useful but not definitive. With a retest interval of 1 to 2 years, normal subjects typically show a small amount of change (+/− 2 MMSE points) with 0.80 test–retest correlation (Strauss et al., 2006). It has been estimated that the value needed to detect a reliable change over a shorter interval (3 months) is +/− 2.73 points (Strauss et al., 2006). Thus, small fluctuations (+/− 2 MMSE points) are more than likely not representative of true cognitive change. Nevertheless, the MMSE is a cornerstone of cognitive batteries in the study of dementias and AD.

Hypothesis and objective

We propose a completely automated methodology that will test the hypothesis that future cognitive status is related to baseline MRI. The goal of this article is to assess the relationship between one-year MMSE changes and baseline MRI in a cohort of MCI research subjects.

Method

Our methodology is comprised of three steps that can be summarized as follows: (i) extraction of multidimensional image-based features within a large, non-specific Volume of Interest (VOI) on MRI; (ii) creation of a multidimensional image-based feature space from within a restricted feature set, selected with respect to the task of predicting cognitive change; and (iii) robust linear regression modeling using the restricted feature set to predict future changes.

The methodological details are elaborated in the following sections. The foundation for the technique was proposed originally in Duchesne et al. (2005, in press).

Ethics

All subjects provided written informed consent for the study and Review Boards from the participating institution approved the protocol.

Subjects

This is a retrospective study for which a total of 199 subjects were included. The first cohort, or reference group, consisted in 150 subjects: 75 patients with a clinical diagnosis of probable AD (33 F; 42 M) and 75 control subjects (CTRL) (37 F; 38 M) without neurologological or neuropsychological deficit. The probable AD subjects are individuals with mild to moderate probable AD (McKhann et al., 1984) recruited among outpatients seen at the Centro San Giovanni di Dio Fatebenefratelli — The National Center for AD (Brescia, Italy) between November 2002 and January 2005. History was taken with a structured interview from a knowledgeable informant (usually the patient’s spouse) and was particularly focused on those symptoms that might help in the differential diagnosis of the dementias in order to avoid contamination of non-AD dementias in the study group. Laboratory examinations included complete blood count, chemistry profile, thyroid function, B12 and folic acid, and EKG. A neurologist performed structured neurological examination and a geriatrician performed the physical examination. A comprehensive neuropsychological battery was also administered. The MRIs were not used for diagnosis except for the exclusion of secondary causes of cognitive deterioration.

CTRL subjects, age-matched to the probable AD group, were selected from an ongoing study of the structural features of normal aging at the same institution. This study recruits outpatients attending the Neuroradiology Unit of the Città’ di Brescia hospital (Brescia, Italy) aged 40 and older and undergoing brain MR scan for reasons other than cognitive impairment (usually headache and vertigo) and negative for major stroke, tumor, aneurysm, or other focal lesions. Incidental atrophy, white matter disease, and lacunes were not exclusionary criteria. Normality of cognitive functions was ascertained through neuropsychological evaluation and structured interview.

The second cohort, or study group, consisted in 49 MCI subjects (19 F; 30 M) taken from a prospective project on the natural history of MCI, carried out in the outpatients’ section of the Centro San Giovanni di Dio Fatebenefratelli (Brescia, Italy) memory clinic. The goal of this study is to relate MMSE changes to MRI features in this group.

Inclusion criteria into the prospective MCI study group were: (a) memory or other cognitive disturbances; (b) MMSE score ≥ 24; and (c) spared basic and instrumental activities of daily living or abilities firmly due to causes other than cognitive impairment. Exclusion criteria were: (a) dementia according to the Diagnostic Statistical Manual for Mental Disorders—fourth edition (DSM-IV) criteria; (b) age > 90 years; (c) depression or psychosis of juvenile onset; and (d) history or neurological signs of major stroke. At baseline all study subjects underwent: (a) a semi structured interview; (b) a neuropsychological examination; (c) a neuropsychological battery of tests assessing memory, executive and frontal functions, language and visuo-construcional abilities; and (d) an assessment of depressive symptoms (Center for Epidemiologic Studies Depression Scale (Radloff, 1977)).

MCI patients in the prospective project underwent a yearly follow-up visit, consisting of complete clinical and neuropsychological examination, from 1 to 4 years after enrolment. In those individuals that progressed to dementia, status was ascertained according to clinical diagnostic criteria for AD (McKhann et al., 1984), subcortical
vascular dementia (Erkinjuntti et al., 2000), dementia with Lewy bodies (McKeith et al., 2000), and fronto-temporal dementia (Knopman et al., 2005).

Within the larger prospective cohort of MCI patients enrolled from April 2002 to December 2006, we have retrospectively selected for this study all patients followed clinically a minimum of 48 months after their baseline MRI that either remained stable (N = 29) or progressed to probable AD (N = 20).

In keeping with our assumptions, we have studied only the relationships between baseline MRI and MMSE changes at one year in this cohort. The long-term, four-year clinical follow-up information was only used to select subjects in this study. The study of long-term MMSE changes, as well as that for individuals with dementias other than probable AD, fell outside of the chosen scope of this study.

Data

Age, gender, and years of education were recorded for each subject.

MRI data for all subjects were acquired in Brescia, Italy on a Philips Gyroscan 1.0 T scanner (Philips Medical, Best, Netherlands) using a T1-weighted fast field echo sequence (TR = 20–25 ms, TE = 4.9–6.9 ms, sagittal acquisition, 1 mm × 1 mm in-plane resolution, 1.3 mm slice thickness).

MRI feature extraction

The objective of this step is to extract salient image-based features from MRI for each subject in the reference and study groups. Since the feature extraction process is similar to that performed in other studies (Duchesne et al., 2008), albeit with some additional steps, only a brief description will be given here. First, raw scanner images were corrected for intensity inhomogeneities (Sled et al., 1998) and denoised using a non-local means algorithm (Coupe et al., 2008). The images were then linearly scaled in grey-level intensities across subjects to match the mean level of the reference image, registered into a standard target template space (Collins et al., 1994) optimizing global then local alignment between reference and subject via successive affine transformations, the first on the whole cerebrum and the second on the VOI. The data were then resampled onto a 1 mm³ isotropic grid (Mazziotta et al., 1995) and finally transformed into z-score maps. The two-step global registration process has been shown in other studies to reduce positional variability of the VOI (Duchesne et al., 2006), which serves to reduce variations that may propagate as unwanted noise in the morphometric modeling. Thus, the first feature of interest consists in the rasterized grey-level z-score maps of intensities from voxels within the VOI.

The VOI, identified on the reference image, measures n = 90 × 50 × 50 = 405,000 voxels and is oriented along the long axis of the hippocampus. It captures both hippocampi and neighboring medial temporal lobe structures that are known to be affected in early AD, such as the entorhinal, perirhinal and parahippocampal gyri, irrespective of normal inter- and intra-individual variability.

The target template consisted in a high-contrast, high-resolution image built from 27 averaged T1w MRI scans of the same individual (Collins et al., 1998) within a Talairach-like stereotactic space (Mazziotta et al., 1995). This approach has been explored with success elsewhere (Carmichael et al., 2005).

Nonlinear intensity-based image registration was then performed (Collins and Evans, 1997) to derive tissue deformation characteristics, in this case an estimate of local volume change, mapping the baseline image to the target template volume. The log-determinant of the Jacobian of the deformation fields was then computed. It represents a biologically meaningful quantity, as it is an indicative measure of local brain tissue volume difference when compared to the target volume.

Image processing for feature extraction was completed using the MINC image processing toolbox (http://packages.bic.mni.mcgill.ca).

Feature space creation and set selection

The next step in our methodology was the creation of a multidimensional feature space from reference group data, in which the study data was projected. Acting on these projected data, a restricted set of features, salient to our purpose of studying relationships between MRI features and cognitive change, was selected.

A schematic description of the processing steps that led to the selection of the restricted feature set is provided in Fig. 1. At the beginning a comparative, pathologically appropriate multidimensional eigenspace of image intensity and local volume change was built using the probable AD and CTRL reference group data. This space was created by uniting results from two distinct principal component analyses of (i) image intensity z-scores within the VOIs, as a proxy of local tissue composition (Figs. 1A,C); and (ii) image log-determinants of the Jacobian of the deformation field (mapping baseline MRI to target template volume), as a proxy of local tissue deformation (Figs. 1B,D). The reference eigenspace consisted in the ensemble of principal directions that contributed for 99.7% of the description of the total variance of the system of reference images after the PCA process. This ensemble of intensity and local volume change eigenvectors will be referred to as S. At that point the reference group data is no longer used in the methodology.

Projecting intensity and local volume change data from the MCI study group subjects within the multidimensional principal component eigenspace S (Fig. 1E) started the feature selection process. While a number of possible features can be calculated on the distribution of the projected data, our predictor is based on the position along the PCA axes or eigenvectors. The distribution of eigencoordinates along any principal component for a given population was assessed for normality with Shapiro–Wilke statistics. We elected to reduce the number of features from S to include in the model for prediction to reduce over-determination and over learning in the training set; the restricted set will be referred to as S*.

To this end, for each of the λ = 292 eigencordinate distributions we calculated the Pearson correlation coefficient r against the cognitive variable of interest (Figs. 1F,C), in our case one-year difference in MMSE scores for the selected MCI subjects. The process was completed by selecting eigenvectors from the global set S with average correlation r above a pre-selected threshold t into the restricted eigenvector set S*, thereby achieving our goal to select the most highly correlated features related to cognitive change.

Modeling

To relate one-year MMSE changes to MRI data for each of our study group subjects, a model was built from the restricted set S* of highly correlated features via robust linear regression (MATLAB Statistics Toolbox, The MathWorks, Natick, MA). At this point we also included age, sex, years of education, and baseline MMSE to the model set, all known to influence MMSE results (Strauss et al., 2006). The features were selected using the variables of interest in the context of a cross-validated procedure, discussed in the following section (‘Statistical independence and confidence’).

Iterative reweighted least square regression was chosen as a robust regression scheme. It works by assigning a weight to each data point automatically and iteratively. In the first iteration, each point is assigned equal weight and model coefficients are estimated using ordinary least squares. At subsequent iterations, weights are recomputed so that points farther from model predictions in the previous iteration are given lower weight. Model coefficients are then recomputed using weighted least squares. The process continues until the values of the coefficient estimates converge within a specified tolerance. A bisquare function with tuning constant was selected for weighting (MATLAB Statistics Toolbox, The MathWorks,
Fig. 1. Extracted image-based features (A,B) from reference subjects (probable AD, CTRL) are analyzed via principal components (C,D) to generate a multidimensional, pathology-specific reference space. Image-based features for the N = 49 MCI study subjects are then projected in the reference space (E); the resulting eigencoordinate distributions along each principal component are the independent variables used in the regression model, after a selection process to determine those with highest correlation to clinical scores (F,G).
Table 1
Demographic and MMSE information on reference and study subjects.

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Baseline age (years)</th>
<th>Baseline MMSE</th>
<th>One-year MMSE change</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reference group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probable AD (33 F; 42 M)</td>
<td>75</td>
<td>73.3 (8.4)</td>
<td>27.1 (1.7)</td>
<td>0.5 (2.1)</td>
</tr>
<tr>
<td>Control (37 F; 38 M)</td>
<td>75</td>
<td>73.3 (4.6)</td>
<td>27.1 (1.7)</td>
<td>0.5 (2.1)</td>
</tr>
<tr>
<td><strong>Study group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCI (19 F; 30 M)</td>
<td>49</td>
<td>67.9 (12.7)</td>
<td>27.1 (1.7)</td>
<td>0.5 (2.1)</td>
</tr>
<tr>
<td>p-value (reference vs. study)</td>
<td>0.0002</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sub-groups</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCI — true decliners (7 F; 9 M)</td>
<td>16</td>
<td>72.5 (4.1)</td>
<td>27.6 (1.0)</td>
<td>2.9 (1.0)</td>
</tr>
<tr>
<td>MCI — stable (12 F; 21 M)</td>
<td>33</td>
<td>65.8 (14.8)</td>
<td>26.9 (1.9)</td>
<td>-0.6(^{16}) (1.2)</td>
</tr>
<tr>
<td>p-value (true decliners vs. stable)</td>
<td>0.03</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Negative MMSE loss implies a gain in MMSE units at yearly retest.

Natick, MA). We did not perform a sensitivity analysis to changes in the weighting function or tuning constant.

For each model performed (see Experiments section), we report predicted values, residuals, correlation and adjusted correlation coefficients, and root mean square errors.

Statistical independence and confidence

In order to maintain statistical independence in the creation of the model and the generation of results, we resorted to a global leave-one-out approach. First, it should be restated that the reference group only served to generate an eigenspace of MRI features into which the MCI data was projected, and did not serve otherwise in the model creation. Next, for each of the MCI subjects, we started the feature selection process by removing this test subject from the pool altogether. Then, we proceeded with the feature selection process on the remaining, training subjects.

In order to further increase our confidence in the reliability of the feature selection, we elected to use a bootstrap procedure. Bootstrapping involves the generation of multiple versions of the training group, serving to ensure maximum learning efficiency from a limited dataset. Each bootstrap sample was of maximal size \( M = N - 1 \) (e.g. \( M = 48 \) in experiments on all \( N = 49 \) MCI subjects). Choosing \( n_{\text{boot}} \) random samples from the training dataset, allowing replacement, created multiple samples, each of dimension \( M \) equal to the dimension of the training dataset. Sampling with replacement means that every sample is returned to the data set after sampling, and thus a particular data point from the original data set could appear multiple times in a given bootstrap sample. When this is repeated a hundred or thousand times, we get independent pseudo-samples that behave similarly to the underlying distribution of the data. One would expect that variables that truly were correlated strongly with MMSE would be identified in a majority of the bootstrap samples, whereas noise variables would be identified in only a minority of samples. For our experiments, in each one of the \( n_{\text{boot}} = 1000 \) bootstrap samples, we calculated the correlation with MMSE, chose features of interest above the threshold \( r \), created the regression model using these features, and calculated the predicted response for the left-out test subject. The final reported result consists in the average predicted response over all \( n_{\text{boot}} = 1000 \) bootstraps.

Principal component analysis, linear modeling and prediction were performed using MATLAB (The MathWorks, Natick, MA). Statistical testing for group-wise differences was performed using JMP (SAS Institute, Cary, NC, USA).

Experiments

Experiments conducted included (1) descriptive analyses of individual features correlation with one-year MMSE change; (2) a predictive analysis of one-year MMSE change from baseline MRI for all MCI subjects; and (3) a predictive analysis of one-year MMSE change from baseline MRI based on MCI subjects with MMSE loss greater than 1 U (‘true decliners’).

Results

Descriptive analyses

Summary statistics about the reference and study groups can be found in Table 1. There were no statistical age differences between probable AD and CTRL in the reference group. The only statistically significant difference between the study (MCI) and reference subjects (probable AD, CTRL) was age, as can be expected (Student \( t \)-test; \( p = 0.0002 \)).

The distribution in MMSE changes at one year for MCI subjects can be found in Fig. 2. One notices that 16/49 were ‘true decliners’ (i.e. with loss greater than 1 U), and that 10 out of these 16 progressed to probable AD within 48 months. The only statistically significant difference between the ‘true decliners’ group and the remainder of the MCI subjects, albeit small, was age (Student \( t \)-test; \( p = 0.03 \)). PCA was used to reduce the dimensionality of the probable AD and CTRL reference data and generate two linear variation models of (a) image intensity, as a proxy of covarying tissue composition (146 intensity vectors) and (b) image local volume change, as a proxy of tissue deformations (146 determinant vectors) for the 150 subjects in the reference group. Our global multidimensional image-based feature space \( S \) was thus of size \( n = 292 \). As mentioned previously, these 292 variables explain 99.7% of the total variability in the probable AD and CTRL population samples. Shapiro–Wilke statistics confirmed that all features were normally distributed.

Individual features correlation analysis showed that baseline MMSE was moderately to weakly correlated with age and years of education (\( r = -0.40 \) (\( p = 0.004 \)), \( r = 0.16 \) (\( p = 0.3 \)), respectively) and that baseline MMSE, age, and years of education were moderately to weakly correlated with one-year MMSE change (\( r = 0.42 \) (\( p = 0.003 \)), \( r = -0.47 \) (\( p = 0.0007 \)), and \( r = -0.06 \) (\( p = 0.68 \)),
of residuals for this model is shown in (C).

Predictive analyses

Predictive analysis of one-year MMSE change from baseline MRI for all MCI subjects

With threshold $t = 0.300$ and $b_{\text{boot}} = 1000$, we used the technique mentioned above to generate linear regression models linking baseline MRI features to one-year MMSE changes for all $N = 49$ MCI subjects. The median number of variables retained per model was 25.

The pairwise correlation between actual and predicted baseline MMSE was $r = 0.31$ ($p = 0.03$), with an adjusted coefficient of determination $r^2 = 0.09$, RMSE = 1.33 and average residual 0.6 (2.1) in MMSE units (Fig. 3A).

Predictive analysis of one-year MMSE change from baseline MRI for MCI subjects with $\Delta$MMSE $\geq 2$

Given the known test–retest variability in MMSE, we conducted a second experiment whereby only MCI subjects with MMSE loss at one year larger than 1 MMSE unit would be included in the model (‘true decliners’; $n = 16$). When using a leave-one-out process to create a ‘true decliners’ model and test it on the same population, the median number of variables retained in the regression model was 12, with a pairwise correlation of 0.80 ($p < 0.0001$), an adjusted coefficient of determination $r^2 = 0.61$ with RMSE = 0.64 and average residual 0.02 (0.84) in MMSE units (Figs. 3B, C). This implies that in this sub-group baseline MRI explains 61% of the variance in the one-year MMSE change for these subjects.

Discussion

In keeping with the fact that short-term (e.g. one year) progression of cognitive change in MCI patients is a continuous phenomenon, we tested our hypothesis that baseline MRI features were related to one-year cognitive change. Our analyses demonstrated, in this limited sample, that while baseline MRI features moderately predict one-year MMSE changes in the general MCI population, they are more accurate in a population subset with reliable, significant decline.

Clinical aspects and limitations

The test–retest reliability of the MMSE has been discussed previously (Strauss et al., 2006). For our purposes, we will point to the fact that small changes (<2 points) within a time frame of one year are not considered reliable. Further, one must take into account the ceiling effect for the MMSE (maximum result = 30). Large year-to-year gains are clinically deemed less relevant than large losses, as the latter are intuitively expected to reflect the progression of disease, whereas the former are considered due to habituation and other effects. Considering the above, our finding of an increased relationship with morphological features at baseline in the 16 of the 49 MCI subjects with larger MMSE decline (10 of which progressed to probable AD) is commensurate with clinical impression, and indicative of the specificity and sensitivity of analyzing medial temporal lobe structures, primarily affected in AD (Braak and Braak, 1996). It points to the ability of MRI to detect morphological changes that predict further cognitive decline, putatively pointing to a pathological cause, even though we cannot dismiss that part of the effect may be due to ageing, as the ‘true decliners’ group is slightly older. However, the preponderance of subjects progressing to probable AD in this group is an argument in favor of a pathology-related cause.

For the present purposes, we have chosen to limit ourselves to studying the relationship between one-year MMSE changes with a single, cross-sectional MRI measurement in a selected population. The disadvantage of any cross-sectional approach is that the effect at hand may differ for individuals enrolled in the study or be confounded by another variable.

It is important to note that not all MCI patients progress to clinically defined AD, nor show MMSE decline at identical rates (Grundman et al., 2002). However, careful design and selection of the patient population have served to improve homogeneity of effect in the test population.

It is equally clear that the MMSE does not specifically test temporal lobe functions, but rather was designed as an overall cognitive test, thus resting on a global morphological substrate. Our choice of MMSE was primarily based on the fact that it is an extremely prevalent test.
and that memory declines first in the progression to clinically probable AD (Haxby et al., 1992). Future work should concentrate both on using a test that would be more focused on functions related to probable AD, for example the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005) and expanding the region of interest to analyze the global whole brain substrate. Additionally, the MCI cohort was restricted to cases whereby a 48-month longitudinal clinical assessment showed either cognitive stability or progression to probable AD. Further experiments need to be performed to determine if relationships exist between cognitive change and morphological features for other dementias. This is another argument for expanding the region of interest to encompass the whole cerebrum.

Finally, the choice of model for long-term prediction will need to be revisited, considering that (a) the rate of MMSE decline, along with regional and global atrophy, will not be linear for MCI patients over a long period, as reported in long-term AD follow-up data (Chan et al., 2003); and (b) the distribution of MMSE change (or other cognitive measures) will tend towards bi-modality, as some MCI patients remain stable while others progress towards dementia, most of them AD. Future work should therefore also include classification of the different types of dementias and different sub-types, and their own cognitive trajectories.

Overall, the presence of a relationship between baseline MRI features and future MMSE decline points to the ability to perform prediction of future cognitive status, which would benefit physicians in the management of patients with MCI.

Methodological aspects and limitations

As the reference group and the study group are composed of different subjects, there is no issue of over-determination in the creation of the reference space and subsequent projection of study group data.

The use of case resample bootstrap increases the efficiency of learning from a limited dataset. It also requires very minimal assumptions, and works with both parametric and non-parametric distributions. However, the method is not exact, does not provide general finite sample guarantees, and has a tendency to be overly optimistic.

The use of intensity features from MRI raises the question of calibration and normalization. Absolute intensities are rarely used in MRI, since they vary with machine calibration, shimming, and patient-induced variations (Deoni et al., 2005). We have tried to limit those variations by (1) using the same scanner for both reference and study groups in the study; (2) ensuring that the same quality assurance procedures were followed for each acquisition; (3) acquiring subject scans in random group order; and (4) using various post-processing techniques (intensity inhomogeneity correction, normalization, scaling, and z-scores) within the intensity space of the high-resolution reference target. Equally, the linear and nonlinear registration process will not capture all macroscopic changes. Point homology in nonlinear registration is of course approximate: in regions where there is complete homology, the displacement field will be nearly exact; and in regions where it is not, the result will be noisy. Further, PCA involves unsupervised consideration of variance; no knowledge of the association with pathology is employed. If the registration errors are a large component of the variance, then they will be selected by the PCA; if a useful pathology-related signal represents small relative variation then it will be ignored. The use of supervised selection (e.g. (Friston et al., 2008)) should reduce this effect.

Other statistical measures for the goodness-of-fit for the regression models could also be employed (e.g. F-tests).

Overall, the experimental results demonstrate the ability of the technique to discover relationships between baseline MRI intensity and local volume change features to one-year changes in a cognitive variable such as the MMSE.

Conclusion

We have proposed an automated analysis technique to find relationships between baseline MRI and one-year changes in MMSE scores, exemplified in a model that explains 61% of the variance of one-year MMSE change in true decliners. The ability of an independent, MRI-based technique to predict change in specific cognitive aspects, rather than simply classify or predict progression or non-progression to probable AD in a dichotomous manner, would help optimize individual patient management and longitudinal evaluation in a timely fashion. The technique can be generalized to include other neuroimaging modalities and be applied to cognitive or clinical scores other than MMSE and in a different context than AD research.

Authors’ contributions

• Guarantors of integrity of entire study, all authors;
• Study concepts and design, all authors;
• Literature research, S.D.;
• Clinical studies, A.C., C.G., G.B.F.;
• Data acquisition, A.C., C.G., G.B.F.;
• Methods, analysis and interpretation, S.D.;
• Statistical analysis, S.D.;
• Manuscript preparation, S.D.; revision/review, all authors; and
• Manuscript definition of intellectual content, editing, and final version approval: all authors.

Acknowledgments

This work was supported by the Programme de Soutien à la Recherche – Support aux Initiatives Internationales de Recherche et Innovation du Ministère du Développement Économique, de l’Innovation et de l’Exportation du Québec.


References


