Direct estimation of patient attributes from anatomical MRI based on multi-atlas voting

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MRI brain atlases are widely used for automated image segmentation, and in particular, recent developments in multi-atlas techniques have shown highly accurate segmentation results. In this study, we extended the role of the atlas library from mere anatomical reference to a comprehensive knowledge database with various patient attributes, such as demographic, functional, and diagnostic information. In addition to using the selected (heavily-weighted) atlases to achieve high segmentation accuracy, we tested whether the non-anatomical attributes of the selected atlases could be used to estimate patient attributes. This can be considered a context-based image retrieval (CBIR) approach, embedded in the multi-atlas framework. We first developed an image similarity measurement to weigh the atlases on a structure-by-structure basis, and then, the attributes of the multiple atlases were weighted to estimate the patient attributes. We tested this concept first by estimating age in a normal population; we then performed functional and diagnostic estimations in Alzheimer's disease patients. The accuracy of the estimated patient attributes was measured against the actual clinical data, and the performance was compared to conventional volumetric analysis. The proposed CBIR framework by multi-atlas voting would be the first step toward a knowledge-based support system for quantitative radiological image reading and diagnosis.

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of simple anatomy-pathology correlations challenging. Through past clinical experience and research, loose relationships between brain pathology and anatomical features have been established. For example, hippocampal atrophy is often used as an indicator of Alzheimer’s disease, and frontotemporal dementia usually accompanies atrophy of the frontal and temporal lobes. However, such correlations may not be strong enough to be reliably perceived by subjective evaluations.

In conventional image analysis, the patient populations are first homogenized into specific dementia groups based on clinical symptoms (e.g., MCI, AD, etc.), and then, voxel-based analysis is performed to identify certain anatomical features that differentiate the population from a control group. The challenges faced by clinicians are fundamentally different as the patient population is inherently heterogeneous both in the anatomical and clinical domains, and the initial stratification of patients is often unknown. In addition, patients may have a heterogeneous “nature” and “degree” of pathologies that co-exist in multiple “locations.” Thus, to support clinical image reading, it is an important effort to develop and test tools that can detect not only abnormalities (with respect to age-matched controls), but also apply past knowledge to individual patients and provide a quantitative and systematic evaluation of their anatomical states.

In the past, CBIR has been attempted for several radiological images, such as lung CT and mammography (Muller et al., 2004). For brain MRI, Coupe et al. (2012) devised a simultaneous segmentation and grading approach, which graded the test subjects based on several pre-selected structures, according to their similarity to the corresponding structures in the training subjects. This approach has been shown to provide respectable accuracy (up to 90% success rate) in discriminating AD patients and normal controls. The performance was superior or equivalent to other recent studies for AD classification, e.g., single-atlas based studies by Cuingnet et al. (2011) (88.5% accuracy) and Liu et al. (2012) (90.8% accuracy), or multi-atlas based studies by Koikkalainen et al. (2011) (86.0% accuracy) and Min et al. (2014) (91.64% accuracy), just to name a few from the extensive literature about AD studies. The analysis in Coupe et al. (2012), however, was based on a hypothesis that the pre-selected structures (the hippocampus and the entorhinal cortex) carry key anatomical features for AD patients. This is a valid assumption for pre-stratified AD populations, but, for clinical patient populations with heterogeneous pathology, identifying key brain anatomical locations would be an important initial step, as the abnormality is region specific to each disease (or functional deficit) category.

This paper shares the same fundamental concept as the pioneering work by Coupe et al., but employs a unique framework of multiple-atlas brain segmentation to evaluate the anatomy of the entire brain. In atlas-based segmentation approaches (Collins et al., 1995; Dawant atlas brain segmentation to evaluate the anatomy of the entire brain. work by Coupe et al., but employs a unique framework of multiple-category. To first demonstrate the proof-of-principle using the age estimation, which can be validated by the known age. Then, we used MCI and AD cases from the Alzheimer’s disease Neuroimaging Initiative (ADNI) to evaluate the performance in estimating both the functional deficits, such cognitive scores, and diagnostic categories (NC, MCI, or AD) of these patients. The accuracy was then measured by comparing the estimated and actual clinical data from the ADNI database. If the MAV estimation works, it would estimate AD patients as “highly demented” based on the anatomical features of medial temporal lobe structures, as the atrophy of these structures has been repeatedly identified as key discriminating features of AD in past morphometric studies. This paper describes the results of this unique MAV approach for direct estimation of the patients’ diagnostic attributes in the context of Alzheimer’s disease.

2. Methods and materials

2.1. Subjects

2.1.1. Subjects used for age estimation

The age-specific, multi-atlas dataset consisted of T1-weighted images of healthy controls from a pediatric population (4–12 yr, 20 atlases), a mid-age population (20–50 yr, 20 atlases), and an elderly population (60–80 yr, 20 atlases). Another 10 atlases from each age group were used as test subjects. The atlases are a subset of the MriCloud atlas repository (https://braingps.mricloud.org/atlasrepo), which were segmented to 289 structures with extensive manual correction. All images were acquired on Philips 3 T scanners, with image resolution in the range of 1.0 × 1.0 × 1.0 mm to 1.0 × 1.0 × 1.2 mm.

2.1.2. Subjects used for dementia estimation

The dementia-specific, multi-atlas consisted of T1-weighted images from the ADNI database (http://adni.loni.usc.edu/), with 20 atlases from the Alzheimer’s disease (AD) population, 20 from the Mild Cognitive Impairment (MCI) population, and 20 from the normal elderly controls. Another 90 subjects (n = 30 in each group) chosen from ADNI as test subjects (Table 1). We estimated the diagnostic categories, as well as the functional attributes of the dementia patients, and we chose one of the most widely used cognitive scores—the Alzheimer’s Disease Assessment Scale-cognitive subscales with 11 items (ADAS.11) (Llano et al., 2011)—as the functional measure. The patient information, including the ADAS.11 scores are summarized in Table 1. Other functional measurements, such as The Mini Mental State Examination (MMSE), can be calculated in the same way.

The ADNI data included data acquired from Philips, SIEMENS, and GE scanners at 1.5 T and 3 T. We used an even number of subjects from each protocol in each group (control, MCI, and AD) for both the training and testing datasets (Table 1). Our analysis, therefore, contains effects from image protocol differences. In our previous paper (Liang et al., 2015), we evaluated the protocol effects on our pipeline, and found that the pipeline could robustly detect age-dependent anatomical changes regardless of the wide variety of protocols, including the different scanner fields and manufacturers. We evaluated the effect of scan protocol on
the estimation of patient attributes, as described in Section 2.3.4. We believe the inclusion of various MPRAGE protocols (all provided by the manufacturers) in this study was highly important to ensure that the observed biological effects would not be erased in practice when different imaging protocols are used.

2.2. Algorithms

2.2.1. Multi-atlas segmentation framework

In multi–atlas based segmentation, the parcellation profiles of the target image from each atlas, after registration, are combined according to certain atlas-weighting and fusion schemes. The registration in this study was achieved first by affine transformation, and then iterative Large Deformation Diffeomorphic Metric Mapping (LDDMM) (Christensen et al., 1996; Grenander and Miller, 1998; Miller et al., 1993), along with iterative inhomogeneity corrections. The concept of multi–atlas approach assumes that the warping of a single atlas to the target image is not always perfect. Although LDDMM ensures preserved topology and invertible transformation from an atlas to the target, if the anatomical differences are large, it could lead to a highly stretched transformation.

Let \( I_t \) be the target image, \( I^i_t \) (\( i = 1, 2, \ldots, N \)) be the atlas images after warping to the target image, and \( L^i_t \) be the label images associated with the warped atlases. We used a weighted voting approach (Artaechevarria et al., 2009; Isgum et al., 2009; Sabuncu et al., 2010) for label fusion:

\[
\hat{p}(I | I_t) = \sum_{i=1}^{N} w^i_{\lambda}(x) \cdot p(l | I_t, L^i_t)
\]

where \( p(l | I_t, I^i_t) \) is the estimated probability of voxel \( x \) being labeled \( l \) in the target image, and \( i = 1, 2, \ldots, L \), with \( L \) the total number of labels. \( p(l | I | I^i_t) = 1 \) when \( L^i_t(x) = l \) and \( p(l | I_t, L^i_t) = 0 \) otherwise. \( w^i_{\lambda}(x) \) represents the atlas-weighting term that measures the similarity between the target and atlas \( i \) at voxel \( x \), with \( \sum_{l=1}^{L} w^i_{\lambda}(x) = 1 \). When \( p(l | I | I^i_t) \) is binary, as it is used in this study, Eq. (1) reduces to a weighted majority voting scheme. The atlas-weighting used in this study is described in the next section. The final segmentation can be obtained by the Bayes maximum a posteriori (MAP) estimation, \( L^i_t(X) = \text{argmax}_{l=1, \ldots, L} p(l | I_t, I^i_t) \).

2.2.2. Atlas-weighting strategy

Atlas-weighting is the key component in MAV-based disease estimation. We assign atlas-weightings to each individual structure, based on the intensity similarity, on a label-by-label basis, as opposed to a voxel-by-voxel based approach. The similarity is measured based on the local intensity match along the boundary of each structural label between the target and the warped atlases. Namely, a tentative, “atlas-specific” boundary is casted from the atlas to the target first and the degree of matching, based on the similarity of the voxel intensity along the atlas-specific boundary, is evaluated. This process is repeated for each atlas and the weighting was judged based on similarity. We choose the boundary voxels rather than all voxels in the label, assuming the image intensities inside the structure are relatively homogeneous and the boundary voxels are more sensitive to the structural similarity.

| Group | No. | Usage | Age (years) | Diagnosis (ADAS.11) | Number of subjects from P1.5/P3/S1.5/S3/G1.5/G3 |
|-------|-----|-------|-------------|---------------------|-----------------------------------------------|
| Control | 20 | Atlas | 70.8 ± 8.3 | 4.53 ± 2.20 | 3/4/3/4/3/3 |
| Control | 30 | Test | 71.6 ± 2.5 | 6.57 ± 3.49 | 5/5/5/5/5/5 |
| MCI | 20 | Atlas | 73.1 ± 9.5 | 11.75 ± 2.81 | 3/4/3/4/3 |
| MCI | 30 | Test | 71.4 ± 8.7 | 12.78 ± 4.07 | 5/5/5/5/5/5 |
| AD | 20 | Atlas | 70.7 ± 11.0 | 17.05 ± 3.99 | 3/4/3/4/3 |
| AD | 30 | Test | 69.7 ± 12.3 | 20.67 ± 5.05 | 5/5/5/5/5/5 |

Let \( N^i = [x_1, x_2, \ldots, x_L] \) be a vector of voxels in a local neighborhood patch of radius \( r \) centered on a boundary voxel \( x \), then the similarity measure \( s^i_{\lambda}(x) \) of a warped atlas \( i \) is computed by

\[
s^i_{\lambda}(x) = \text{corr} \left( \tilde{p}^i_{\lambda}(N^i), I_t(N^i) \right)
\]

where \( \text{corr}(\cdot) \) is the Pearson correlation coefficient \( \text{corr}(bA(N^i), I_t(N^i)) = \frac{E[(bA(N^i) - \mu bA(N^i))(I_t(N^i) - \mu I_t(N^i))]}{\sqrt{\text{Var}(bA(N^i)) \cdot \text{Var}(I_t(N^i))}} \) with \( E \), \( \mu \), and \( \sigma \) being the expectation, mean, and standard deviation operations, respectively. \( s^i_{\lambda}(x) \) is a signed quantity with negative values indicating anti-correlation. We assume anti-correlations rarely occur in practice, as we use the atlas and target images from the same modality, which are sufficiently co-registered to each other. In case of anti-correlation, a negative \( s^i_{\lambda}(x) \) value would indicate very low similarity.

Since the similarity is measured based on the warped atlases that are already transformed through a large deformation to match the target image, in order to properly weigh the patient attributes that are associated with the un-deformed atlases in their native space, we include a deformation cost in the atlas-weighting. The LDDMM provides a structure-preserving diffeomorphism \( \psi \) between the atlas and target images by solving \( \dot{\psi} = v \psi, r \in [0, 1] \), with \( v_0 = \psi_0 \), and minimizing \( \int_{\mathcal{T}} \int_{\mathcal{T}} ||\mathcal{T} - \mathcal{T} \psi^{-1}||_2^2 + \int_{\mathcal{T}} ||v_0||_2^2 dt \), where \( \mathcal{T} \) is the time-dependent velocity vector field of the flow of the deformation, \( \psi_0 \) is the diffeomorphism at time \( t \), \( \psi_t \) denotes the first-order differentiation of \( \psi_t \), and \( \int_{\mathcal{T}} ||v_0||_2^2 dt \) represents the integration of the norm of \( v_0 \) over the entire velocity field, \( V \). (Christensen et al., 1996; Grenander and Miller, 1998; Miller et al., 1993, 2015). The deformation energy at individual voxels can be approximated by the determinant of the Jacobian matrix of the LDDMM transformation \( \mathcal{J}(x) \). We calculate the deformation cost using a negative exponential functional of this quantity, \( \phi \mathcal{J}(x) = \exp\left(-\mathcal{J}(x)^2\right) \), for each atlas \( bA_i \) at voxel \( x \), such that the larger the deformation, the smaller the \( \phi \mathcal{J}(x) \). In the boundary-based atlas-weighting, we obtain \( \phi \mathcal{J}(x) \) at each boundary voxel along an atlas label, and the dot product of \( s^i_{\lambda}(x) \cdot \phi \mathcal{J}(x) \) summed over all boundary voxels gives the weighting of atlas \( bA_i \) for this label.

\[
w^i_{\lambda}(l) = \sum_{x \in bA_i} s^i_{\lambda}(x) \cdot \phi \mathcal{J}(x)
\]

where \( w^i_{\lambda}(l) \) is the atlas-weighting of label \( l \) in atlas \( i \), and \( bA_i(l) \) denotes the boundary of label \( l \) in the warped atlas \( i \).

There are slight differences in the use of atlas-weighting for segmentation and MAV purposes. In segmentation, the atlas fusion is performed per spatial location and all voxels within the same label of an atlas receive the same weighting; whereas, for the MAV-based direct estimation of patient attributes, the voting is performed per structure. In both cases, the atlas-weightings are normalized such that \( \sum_{l=1}^{L} w^i_{\lambda}(l) = 1 \). In all cases, we used a combined weighting based on the similarity of the deformed atlas and the deformation cost for direct estimation of patient attributes; whereas, for segmentation purposes, we used only the similarity of the deformed atlas in atlas-weighting, \( w^i_{\lambda}(l) = \sum_{x \in bA_i(l)} s^i_{\lambda}(x) \), as the deformation cost is not related to the segmentation.
2.2.3. MAV-based patient attribute estimation

Given the demographic or clinical information, $D(l_i)$, that is associated with atlas $i$, the same type of information about the target subject can be inferred by

$$D(l | x) = \sum_{i=1}^{N} D(l_i) \cdot w_i(l)$$

(4)

where $D(l_i)$ is the demographic or clinical estimation of structure $l$ in a target subject. In the age estimation test, $D(\cdot)$ will be the age measure, and in the functional estimation of the dementia patients, $D(\cdot)$ will be the ADAS.11 score.

We can also estimate the diagnostic categories of the dementia patients based on the probability of the target subject belonging to normal elderly, MCI, or AD groups. The can be achieved by summing over the weightings of the atlases associated with the specific diagnostic groups, after normalizing the sum of all atlas weights to unity.

$$p(G_j | l) = \sum_{i \in G_j} w_i(l)$$

(5)

where $p(G_j | l)$ is the probability of the target belonging to atlas group $G_j$ in terms of label $l$, with $j = 1, 2, \ldots, J$ (the number of diagnostic groups).

2.3. Performance evaluation and statistical tests

2.3.1. Correlation between the estimated and clinically measured patient attributes

In the age estimation test, the ages estimated from the test subjects ($n = 30$) on individual structures were compared with the subjects' actual ages by linear regression. The estimation of functional deficits in the dementia population was similarly evaluated by linear regression between the estimated ADAS.11 scores and the clinically measured ADAS.11 in the ADNI subjects ($n = 90$). The $R^2$ was used to evaluate the goodness-of-fit of the linear regression, and the $p$-value from the $t$-statistics was used to evaluate the significance of linear regression with False Discovery Rate (FDR) [Benjamini and Hochberg, 1995] correction. The linear correlations between volumes of each structure and age or ADAS.11 were also computed for comparison. The volumes were obtained using a multi-atlas segmentation pipeline, as described in Section 2.2.1 and the proposed atlas-weighting in Section 2.2.2.

2.3.2. Group differences

To assess the significance of the estimated ADAS.11 among ADNI groups, a one-way analysis of variance (ANOVA) was performed among the AD/MCI/NC test subjects ($n = 30$ each), and the $p$-values from ANOVA tests were obtained and corrected by FDR for multiple ROI comparisons. The same ANOVA test was also performed on the volumetric measurements.

2.3.3. Feature extraction and classification accuracy

In addition to the regional presentation of patient attributes estimated from the MAV diagram, the regional features can also be combined to classify the disease categories. We compared the classification performance using the volumetric measurements, estimated ADAS.11 scores, and the estimated diagnostic category probabilities based on Eq. (5). In order to use the three types of categorical probabilities (AD/MC/NC) for feature selection and classification purposes, we integrated them into a single dementia probability measurement with a simple linear combination: $p(Dementia | l) = p(G_{AD} | l) \times 1.0 + p(G_{MCI} | l) \times 0.5 + p(G_{NC} | l) \times 0.0$, for structure $l$ of target image $l$.

To extract the most discriminative features from the high-dimensional feature vector (volumes or dementia probabilities estimated from 289 brain structures), we tested two approaches using the training data (atlases, $n = 20$ per group): 1) the top one or top 20 structures that showed the most prominent group difference, based on the $p$-values from the ANOVA tests; 2) the LASSO method (least absolute shrinkage and selection operator) [Tibshirani, 1996], which is a regression analysis method that selects the best subset of variables to enhance prediction accuracy. In our study, we performed LASSO using a regression model between the pre-determined diagnostic category (response variable) and the volumes, estimated ADAS.11 scores, or dementia probabilities from each structure (covariates). The LASSO method determines the optimal number of structures when the mean square fitting error is minimum. The regional features selected by the top one or top 20 criteria or LASSO were then fed into a linear discriminant analysis (LDA) classifier, using a leave-one-out cross validation approach on the ADNI test subjects ($n = 90$). The sensitivity, specificity, and overall accuracy of two-category (AD/NC) or three-category (AD/MCI/NC) classifications were evaluated. The LASSO and LDA were performed using R packages [https://cran.r-project.org/].

2.3.4. Evaluation of protocol effect

We evaluated the effect of scan protocol by including the protocol type (six types of protocols used in ADNI data acquisition) as another factor in addition to the estimated ADAS.11 scores, and tested its significance among the three groups, using two-way ANOVA followed by FDR correction. The protocol effect was statistically significant only in two of the 289 brain segments (left fusiform gyrus and left subcortical white matter of the inferior temporal gyrus).

3. Results

3.1. Framework of multi-atlas voting

The concepts of the two approaches are summarized in Fig. 1. The first approach that is illustrated in the blue dashed box is based on MAV, as described above. In this approach, the patient attributes (age as an example) are obtained directly from the process of the multi-atlas pipeline and the resultant segmentation is merely a proof of procedural accuracy (as long as the segmentation is accurately performed, the segmentation results are discarded). The second approach, as illustrated in the yellow dashed box, is a more conventional method, in which the segmentation results (e.g., volumes) are compared with population-based regression for indirect estimation of the patient’s age. The population-based regression between the volume and patient attributes must be established beforehand as a priori knowledge for the estimation of any new patients.

3.2. Testing of regional feature estimation using age

We used age estimation as a proof-of-concept of the MAV approach. Because we knew the exact age of each subject, we could evaluate the accuracy of the age estimation. The estimation was performed in each test subject ($n = 30$) on a structure-by-structure basis according to Eq. (4). The linear regression between the estimated ages and actual ages showed significant linear correlation (family-wise $p < 0.01$) in a majority of the structures (214 out of 289). Fig. 2 shows the correlation plots in several cortical, subcortical gray matter, and white matter regions. The subcortical structures and deep white matter structures demonstrated high correlation between the estimated age (y-axes) and the actual age (x-axes), with $R^2$ values around 0.7. The correlation with cortical structures was relatively weak, with $R^2$ around 0.3–0.5. The $R^2$ values and the slopes of linear regression were mapped to the T1-weighted images, and masked by a family-wise $p$-value threshold of 0.01 (Fig. 3). The $R^2$ maps indicated that the age estimation is most precise in the subcortical gray matter, the anterior deep white matter, and the cerebellum. Some peripheral white matter tracts and gyri in the posterior and superior brain did not show significant correlation. The slopes of the linear regression, which represent the systematic bias between...
the estimated and actual ages, suggested high estimation accuracy in the thalamus and midbrain structures and a higher degree of bias in the peripheral structures. Fig. 3C demonstrates the regional age estimation across the brain in several representative individuals at 7, 22, 41, 63, and 80 years of age. A clear increase in the estimated age was observed from the pediatric to the elderly brains. Regional variations were present, especially in the middle-age range.

We compared the age estimation by the MAV with a simple volume-based approach. The linear correlation between volumes and ages reached significance (family-wise p < 0.01) in 174 out of 289 structures.
Fig. 2B compares the volume-to-age linear correlation in the same structures as the MAV-based correlation plots in Fig. 2A. The $R^2$ values of volume-based and multi-atlas-based linear regression are directly compared in all 289 structures in Fig. 4. In the subcortical gray matter and deep white matter, the MAV-based age estimation outperformed volume-based estimation; whereas, in the cortical structures, the $R^2$ of volume-based correlation was relatively higher. With the MAV-based approach, 48 structures reached $R^2 > 0.7$, among which several subcortical gray matter, deep white matter, and ventricle structures showed $R^2$ values of 0.8 or higher, while there were only six structures that reached $R^2 > 0.7$ with the volume-based approach. In 200 of the 289 structures, the MAV-based age prediction gave higher $R^2$ values than the volume approach.

3.3. Estimation of the functional states in the dementia population

We estimated the cognitive assessment (ADAS.11 score) of the ADNI subjects using the disease-specific, multi-atlas library according to Eq.
We first examined the group average ADAS.11 scores estimated in the normal elderly, MCI, and AD test subjects (n = 30 in each group, presented as group mean ± standard deviation), in the structures that showed the most significant group difference. The order of the structures was determined based on their p-values (from low to high) from one-way ANOVA followed by FDR correction. *p < 0.001, **p < 1×10^{-5}. Abbreviations: CGH - cingulum (hippocampal part); CL - claustrum; Hippo - hippocampus, Amyg - amygdala; PHG - parahippocampal gyrus; Fx/ST - fornix/stria terminalis; BasForeBr - basal forebrain.

(4). We first examined the group average ADAS.11 scores estimated in the normal elderly, MCI, and AD test subjects (n = 30 each). Fig. 5A–B shows the top eight brain regions with the largest group differences in terms of the volumes (Fig. 5A) or estimated ADAS.11 (Fig. 5B), ranked according to the p-values from one-way ANOVA (after FDR correction). The two charts shared similarities: six of the eight detected structures

![Graphs showing the relationship between estimated ADAS.11 scores and clinically measured scores in various brain regions.](image-url)

Fig. 6. (A) Linear regression between the estimated ADAS.11 scores (y-axes) and clinically measured scores (x-axes) of 90 test subjects in several structures with the highest R², including the left and right hippocampus, amygdala, left parahippocampal gyrus and left entorhinal cortex. (B) Linear regression between the structural volumes (y-axes) and ADAS.11 score (x-axes) in the same structures. The R² and p-values of the linear regression are denoted in each graph.
were limbic gray matter structures, including the left and right amygdala, the left hippocampus, and the left parahippocampal gyrus, as well as limbic white matter structures, including the cingulum and the fornix/stria terminalis. Overall, fewer structures showed significant group differences (family-wise $p < 0.01$) using volumetric measurement (18 out of 289 structures), compared to those using estimated ADAS.11 (67 out of 289 structures).

Linear correlation between the estimated ADAS.11 scores ($y$-axes) and the clinically measured scores ($x$-axes) was plotted in Fig. 6A for several structures that showed the strong correlations according to the $R^2$. The left and right amygdala showed highest correlation ($R^2 = 0.48$ and 0.42), followed by the left and right hippocampus ($R^2 = 0.4$). These structures are known to be most affected in Alzheimer’s patients. In comparison, the correlations between volumes and measured ADAS.11 were lower in these structures ($R^2 < 0.2$, Fig. 6B); whereas the highest volume-based $R^2$ were found in the left claustrum ($R^2 = 0.29$). The $R^2$ maps in Fig. 7A showed significant correlations between the estimated and measured ADAS.11 (familywise $p < 0.01$) in multiple subcortical gray matter structures, including the caudate, the thalamus, and the basal forebrain; the white matter structures, including the internal capsule, the cingulum, and the corpus callosum; the lateral ventricle; and selected cortical regions, especially in the temporal lobes. Lateralization was observed in some structures toward the left hemisphere. The slopes of the linear regression (Fig. 7B) were highest in the hippocampus and the inferior lateral ventricle.

3.4. Testing of disease classification

The diagnostic categories (AD/MCI/NC) were predicted using three types of MRI markers – the conventional structural volumes, the dementia probabilities (as described in Section 2.3.3) and the ADAS.11 scores estimated from MAV. The results are summarized in Table 2. In this analysis, the classification accuracy was tested using the most discriminating structures, based on their significance in differentiating the AD/MCI/NC groups, or based on the LASSO analysis using the training (atlas) data. For the group difference ranking, we used the top one or top 20 structures of the total of 289 structures from both the volume or dementia probability markers for classification, while LASSO determined an optimal number of 22 structures from the volume marker, 40 structures from dementia probability estimations, and 26 structures from the estimated ADAS.11 scores. Table 3 lists the top 20 structures selected from each approach. As expected, the limbic structures in the medial temporal lobes dominated the list. For the volumetric markers, the left cingulum, which gave the most significant group differences, was used as the single feature for classifying AD/MCI/NC, which resulted in an overall accuracy of 0.53. The combination of the features based on the ranking or LASSO improved the overall accuracy to 0.58 and 0.61, respectively. The use of dementia probability estimated from MAV further improved the overall accuracy to 0.63, 0.69, and 0.82 for a single structure (left amygdala), combinations by ranking, and LASSO, respectively. The classification performance using the estimated ADAS.11 scores were in-between the performances of the volume and dementia probability markers, with an accuracy of 0.56, 0.61, and 0.69 for a single structure (left amygdala), the group difference ranking, and LASSO, respectively. In addition, we performed classification using the clinically measured ADAS.11 scores, which resulted in an accuracy of 0.79. If the estimation was limited to AD vs NC (MCI data excluded), the accuracy was 0.85–0.88 with volumetric markers, 0.9–0.92 with dementia probability estimation, and 0.88–0.92 with the estimated ADAS.11 scores. The AD/NC classification was 100% correct using the clinically measured ADAS.11 scores.

4. Discussion

4.1. Concept of multi-atlas voting for disease estimation

MRI atlases are commonly used for automated image segmentation (Chupin et al., 2009; Collins et al., 1995; Dawant et al., 1999; Fischl et al., 2002; Joshi et al., 2004; Rohlfing et al., 2004), and provide pre-segmented maps as a priori knowledge about the shapes and locations of the structures to guide the segmentation. The use of multiple atlases yields robust and accurate segmentation (Artaechevarria et al., 2009; Heckemann et al., 2006; Jia et al., 2012; Klein et al., 2005; Lotjonen et al., 2010), as the rich anatomical information from multiple atlases offers the flexibility to accommodate the diverse anatomy of the patient population. The end-goal of the atlas- or multi-atlas-based approaches is typically to obtain accurate segmentation, from which information about volumes, intensities, or shapes of the segmented structures can be extracted (Heckemann et al., 2008; Koppel et al., 2008; Mori et al., 2013; Tustison et al., 2014). Much of the previous effort has been focused on improving the segmentation accuracy through advanced image registration (Cholpouri et al., 2007; Klein et al., 2009; Lotjonen et al., 2009) or atlas weighting and fusion strategies (Langerak et al., 2010; Sabuncu et al., 2010; Tang et al., 2013; van Rikxoort et al., 2010; Wang et al., 2013; Warfield et al., 2004).

An interesting aspect of these studies is that the determination of the structural volumes is usually NOT the ultimate goal of the study; instead, the raw volume numbers must be interpreted to extract clinically useful information. For example, the structural volumes are compared between control and patient groups (and thus, can serve as a biomarker for diagnosis) or correlate with brain function measures (and thus, can be used to infer the functional loss). Therefore, the volume information

![Fig. 7](https://example.com/fig7.png) Whole-brain mapping of the $R^2$ (A) and linear correlation coefficients (B) of the linear regression between the estimated ADAS.11 and clinically measured score in each structure, overlaid on a T1-weighted image. Only structures with significant linear regression (family-wise $p$-value < 0.01) are shown.
Table 2
The sensitivity, specificity, and overall accuracy of the LDA classification results. Three types of biomarkers were evaluated — the structural volumes, the dementia probabilities, and the ADAS.11 score estimated based on the multi-atlas voting approach. Three feature extraction approaches based on the group difference rank (top one and top 20) and LASSO were tested, for each of the markers. We performed both three-group (AD/MCI/NC) and two-group (AD/NC) classification. In addition, we tested the classification results using the clinically measured ADAS.11 score. In the three-group classification, sensitivity and specificity were determined for each group. The overall accuracy is the percentage of true-positive plus true-negatives.

| Measurement          | Feature selection | Classification groups | Sensitivity   | Specificity | Overall accuracy |
|----------------------|-------------------|-----------------------|---------------|-------------|------------------|
| Single structure     | Left cingulum     | AD/MCI/NC             | 0.73/0.27/0.60 (AD/MCI/NC) | 0.80/0.73/0.77 | 0.53             |
|                      |                   | AD/NC                 | 0.80          | 0.90        | 0.85             |
|                      |                   | AD/MCI/NC             | 0.77/0.47/0.50 | 0.80/0.75/0.82 | 0.58             |
|                      |                   | AD/NC                 | 0.83          | 0.83        | 0.83             |
|                      |                   | LASSO (22 structures)  | 0.70/0.43/0.70 | 0.87/0.73/0.82 | 0.61             |
|                      |                   | AD/NC                 | 0.93          | 0.83        | 0.88             |
|                      | Left amygdala     | AD/MCI/NC             | 0.83/0.40/0.67 | 0.80/0.80/0.85 | 0.63             |
|                      |                   | AD/NC                 | 0.97          | 0.83        | 0.90             |
| Dementia probability | Group difference rank (top 20) | AD/MCI/NC             | 0.63/0.63/0.80 | 0.87/0.77/0.90 | 0.69             |
|                      |                   | AD/NC                 | 0.93          | 0.90        | 0.92             |
|                      |                   | LASSO (40 structures)  | 0.83/0.73/0.90 | 0.95/0.87/0.92 | 0.82             |
|                      |                   | AD/NC                 | 0.87          | 0.93        | 0.90             |
|                      | Left amygdala     | AD/MCI/NC             | 0.73/0.27/0.67 | 0.83/0.72/0.78 | 0.56             |
|                      |                   | AD/NC                 | 0.97          | 0.83        | 0.90             |
| Estimated ADAS.11    | Group difference rank (top 20) | AD/MCI/NC             | 0.67/0.47/0.70 | 0.83/0.73/0.85 | 0.61             |
|                      |                   | AD/NC                 | 0.90          | 0.93        | 0.92             |
|                      |                   | LASSO (22 structures)  | 0.77/0.63/0.67 | 0.92/0.73/0.88 | 0.69             |
|                      |                   | AD/NC                 | 0.93          | 0.87        | 0.90             |
| Measured ADAS.11     | None              | AD/MCI/NC             | 0.73/0.63/1.0  | 0.88/0.87/0.93 | 0.79             |
|                      |                   | AD/NC                 | 1.00          | 1.00        | 1.00             |

is an intermediate marker to infer more clinically meaningful information about the patients, such as diagnosis, prognosis, and functional risk factors.

The proposed MAV-based approach tries to directly estimate the clinically meaningful information from the knowledge database (atlas libraries) without going through the volume measurement step, which is naturally incorporated in the multi-atlas selection processes. The approach assumes that certain individual traits, such as demographics, functions, and diagnostics, have specific anatomical signatures (shape and intensity) at certain anatomical locations. Through the searching (weighting) for proper atlases based on anatomical similarity, the MAV approach attempts to retrieve non-image individual traits. For the anatomical similarity criteria, intensity-based atlas-weighting is widely used, e.g., the intensity differences, cross-correlation, or mutual information (Maes et al., 1997), Shaped-based averaging (Rohlfing and Maurer, 2007) is also an option, which requires an initial segmentation of the target image. The deformation energy transformation between the atlases and targets can also be used (Rohlfing et al., 2004), as

Table 3
The structures selected for classification from the volumetric marker and dementia probability estimation, based on the group difference rank or LASSO method. Note that, in the group difference rank, the top 20 structures were chosen for classification; while LASSO method used 22 structures from the volumetric measurements and 40 structures from the dementia probabilities, and only the first 20 structures with the highest regression coefficients (absolute value) are shown here.

| Volume-based measurement | Group difference rank | LASSO | Dementia probability-based measurement | Group difference rank | LASSO |
|-------------------------|-----------------------|------|----------------------------------------|-----------------------|------|
| Left cingulum           | Left caudatum         | Left amygdala | Left parahippocampal gyrus | Left amygdala         | Left parahippocampal gyrus |
| Left claustrum          | Right caudatum        | Left hippocampus | Right basal forebrain | Right hippocampus     | Right basal forebrain |
| Right hippocampus       | Left pontine crossing tract | Right amygdala | Left hippocampus | Left amygdala         | Left parahippocampal gyrus |
| Left amygdala           | Right caudate tail    | Left hippocampus | Left amygdala | Left hippocampus | Left amygdala |
| Left parahippocampal gyrus | Left hippocampus   | Left caudate tail | Left hippocampus | Left hippocampus | Left hipocampus |
| Left fornix/stria terminalis | Right hippocampus | Right amygdala | Right hippocampus | Left enteronhrial cortex | Left enteronhrial cortex |
| Right amygdala          | Left parahippocampal gyrus | Right amygdala | Right amygdala | Right amygdala | Right amygdala |
| Left caudatum           | Left gyrus rectus     | Left fornix/stria terminalis | Left ECCL | Left fornix/stria terminalis | Left ECCL |
| Right hippocampus       | Left fornix/stria terminalis | Left entorhinal cortex | Right fornix/stria terminalis | Right fornix/stria terminalis | Right fornix/stria terminalis |
| Right fornix/stria terminalis | Left subcortical white matter of the lingual gyrus | Right fornix/stria terminalis | Left subcortical white matter of the lingual gyrus | Right fornix/stria terminalis | Right fornix/stria terminalis |
| Left cerebral peduncle  | Left anterior part of the periventricular white matter | Right fornix/stria terminalis | Right fornix/stria terminalis | Right fornix/stria terminalis | Right fornix/stria terminalis |
| Left inferior fronto-occipital fasciculus | Left occipital lateral ventricle | Right fornix/stria terminalis | Right fornix/stria terminalis | Right fornix/stria terminalis | Right fornix/stria terminalis |
| Left pontine crossing tract | Left superior frontal gyrus/pole | Right fornix/stria terminalis | Right fornix/stria terminalis | Right fornix/stria terminalis | Right fornix/stria terminalis |
| Left basal forebrain    | Left inferior fronto-occipital fasciculus | Right fornix/stria terminalis | Right fornix/stria terminalis | Right fornix/stria terminalis | Right fornix/stria terminalis |
| Left pontine crossing tract | Left parietal sulci | Right fornix/stria terminalis | Right fornix/stria terminalis | Right fornix/stria terminalis | Right fornix/stria terminalis |
| Left inferior cerebellar peduncle/pons | Left hippocampus | Right fornix/stria terminalis | Right fornix/stria terminalis | Right fornix/stria terminalis | Right fornix/stria terminalis |
| Right substantia nigra  | Left subcortical white matter of the middle frontal gyrus | Right fornix/stria terminalis | Right fornix/stria terminalis | Right fornix/stria terminalis | Right fornix/stria terminalis |
| Right thalamus          | Right inferior lateral ventricle | Right fornix/stria terminalis | Right fornix/stria terminalis | Right fornix/stria terminalis | Right fornix/stria terminalis |
less deformation indicates higher similarity between the images in the native space. The similarity-based atlas-weighting can be evaluated on a global scale, such as the whole brain (Aljabar et al., 2009), or on localized scales, such as the voxels and structures (Wu et al., 2007). Artaechvarria et al. showed that locally defined weights improved the segmentation compared to the global approach (Artaechvarria et al., 2009).

In this study, we computed the atlas-weighting on a structure-by-structure basis to reflect the local pathology. Our strategy is to focus on the boundary voxels of each structural label, trying to search for images with similar anatomical features for not only the shape of the structure of interest, but also for the surrounding anatomical features. For example, the medial, lateral, and dorsal surfaces of the hippocampus are surrounded by the ventricles. In normal healthy brains, large portions of the ventricles in the dorsal and lateral surfaces are closed (invisible on MRI with 1 mm resolution) and the adjacent white matter tissues seem attached to the hippocampus, while these ventricle spaces enlarge and become visible in patients with severe brain atrophy. The boundary-based similarity-matching method could be sensitive to these surrounding anatomical features. This is significantly different from volume-based analysis, in which the anatomical features of the hippocampus would be contracted into one number.

4.2. Results of age-estimation

We first tested the efficacy of the MAV approach using age-dependent anatomical changes. The age estimation tested in this study may not have high clinical relevance, but as we knew the exact age, it was an ideal model with which to test the accuracy of our approach. The majority of the brain structures showed a high correlation between the estimated and actual ages, especially in the subcortical gray matter and the deep white matter (R² = 0.7–0.8). There was an overestimation of age in the pediatric population and an underestimation for the elderly population, leading to a regression slope of <1. This was likely due to a boundary problem, e.g., for a four-year-old test subject, only atlases with four-year-olds and older were available for the age estimation, thus leading to the overestimation of the age. The spatial difference in the R² maps and correlation slopes showed that the estimation accuracy and precision varied from structure to structure.

In majority of the anatomical areas, the atlas-voting approach had better estimation performance compared to volume correlation (Fig. 4). We attributed the better performance to the better ability of the atlas-voting to extract local anatomical features. There are two ways to interpret the regional variability of the estimation power. First, it is possible that certain anatomical regions have more age-dependent changes. Second, the employed tools may not be sensitive to changes in certain brain regions. The results in Fig. 4 could have been affected by both factors. For example, MAV achieved higher age-estimation accuracy for the subcortical gray matter and deep white matter structures, which tend to have simpler anatomical boundaries; but age estimation accuracy was not as good for the cortical gyri, as it is extremely difficult to achieve accurate boundary-to-boundary registration between atlases and targets. The atlas-voting strategy is still a field of active research and further investigation may be needed to achieve better performances.

4.3. Estimation of clinical attributes

In conventional multi-atlas brain segmentation studies, demographic and clinical information from the atlases is usually not available or is unused once satisfactory segmentation accuracy is achieved. In this study, we proposed a multi-atlas voting approach that enabled us to retrieve such information from the atlas database and use it to estimate the unknown attributes of new patients. In other words, each atlas is considered a classifier, and the opinions from multiple classifiers are rated and fused to reach a final decision. In this respect, the meaning of the multi-atlas library changes. If in segmentation accuracy is the only goal, a question like, “what is the minimum number of atlases that would be required to achieve accurate segmentation?” is meaningful, but if the multi-atlas library is considered a knowledge database from which we want to extract patient attributes, it needs to be enriched by cases with various anatomical and pathological conditions, as well as comprehensive demographic and clinical information.

The multi-atlas voting estimation of brain function (ADAS.11 score) demonstrated that the structures with the discriminating power were concentrated in the limbic structures of the medial temporal lobes, such as the amygdala, the hippocampus, the entorhinal cortex, the parahippocampal gyrus, the cingulum, and the fornix. Similar to the age estimation, the direct estimation of the functional outcome using the MAV provided demonstrated higher estimation accuracy compared to the conventional volume-functional correlation approach.

4.4. Diagnostic classification and comparison with existing studies

The diagnostic classification results in Table 2 also point out that the direct estimation of the diagnostic category or ADAS.11 scores by MAV outperformed the volume marker. The overall accuracy to differentiate the AD and NC was 0.90–0.92, based on the best discriminating structure or the optimized combination of the structures. The list of the discriminating structures and the AD-vs-NC discriminating power reported in this study are highly similar to those reported previously (Chupin et al., 2009; Cuignet et al., 2011; Gerardin et al., 2009; Koikkalainen et al., 2011; Liu et al., 2012; Min et al., 2014), which reported AD/NC classification accuracies between 86–92%, confirming the validity of the proposed multi-atlas voting approach. The estimation accuracy deteriorated to 0.63–0.82 for multi-class estimation (AD/MCI/NC). This was somewhat expected because the accuracy of a diagnosis based on cognitive assessment is not perfect; a definitive diagnosis of dementia cases can be achieved only by postmortem histology. In fact, even using the clinically measured ADAS.11 score, the multi-category classification accuracy was only 0.79 (Table 2). The performance of the multi-class classification by MVA was equivalent to or exceed the state-of-the-art algorithms. For example, in the computer-aided diagnosis of dementia (CADDementia) challenge (Bron et al., 2015), the best-performing algorithm yielded an accuracy of 63.0% in classifying AD/MCI/NC, among 29 competitors (accuracy ranging from 32% to 63%). It is also encouraging that the MAV-based approach achieved higher clinical correlation and classification accuracy than the conventional volume-based analysis with the same data and under the same multi-atlas framework. By adopting more advanced machine-learning methods, or even combining the structural volume or clinical data, it is possible that we can further improve the classification performance, but this is beyond the scope of the current proof-of-principle study. It should also be noted that classification is not the only goal of computer-aided diagnosis. Instead, quantitative descriptions of the regional features—the foci and vulnerable regions of a particular disease, such as the regional variations demonstrated in Figs. 5–7—are similarly important to clinical image readings. The functional attributes, such as cognitive and behavioral evaluations, estimated from the MRI (e.g., ADAS.11 score in this study) can also provide valuable characterization of the disease status besides categorical diagnosis.

The concept of our approach shared similarity with that of Coupe et al. (2012), who developed a technique known as scoring by non-local image patch estimator (SNIPE) for simultaneous segmentation and grading of structural MRI for Alzheimer’s patients. Similarly, the authors determined an AD/NC grading measurement based on the anatomical similarity between the test subject and the training dataset in a few selected structures, and they concluded that the best classification accuracy can be achieved by combining volumetric and grading information from the hippocampus and entorhinal cortex. Despite the similarity in the ways that training data (in our case, atlases) are conceived, our work is also different from the previous work in several ways. First,
our approach was incorporated into a general framework of a multi-atlas method that can be potentially applied to any type of dementia without a priori knowledge about the affected structures, which is a feature highly important for clinical applications. In Coupe’s approach, two structures (the hippocampus and the entorhinal cortex) that are most appropriate for estimating the likelihood of AD are pre-selected and manually defined in the “training” data. In the present study with the AD patients, the MAV method evaluated 289 structures defined in the atlases and could correctly identify the limbic structures as the most discriminating structures (Table 3). The overall accuracy for AD estimation was 0.90, replicating the results by Coupe et al. Another major difference from the previous work lies in the algorithm to measure anatomical similarity. In Coupe et al. (2012), the authors developed a voxel-based approach using the intensity difference within a local patch, centered on each voxel between test and training image; whereas, in our study, we developed a label-by-label procedure that integrated the local correlation of the boundary voxels along a label. In the MAV framework, it is possible to incorporate various types of similarly measure, and thus, it would be interesting future study to compare the different types of similarity functions.

4.5. Evaluation of anatomical patterns for disease classification

In the previous sections, the performance of the MAV approach was evaluated for each anatomical structure independently. An interesting question is whether we can evaluate the properties of a group of structures as a disease-specific anatomical feature. To test this idea, we evaluated the estimation accuracy for the clinical scores and disease categories between a single (the best discriminating structure) vs a group of structures. To select a group of structures, we tested the top 20 structures in the discriminating power ranking and the LASSO analysis. As shown in Table 2, the results using a test data set showed consistent improvement using the multi-structure anatomical features. For future clinical applications with heterogeneous pathological conditions, this could be an important research direction.

4.6. Limitations and future directions

One limitation of this study is that we tested only the MAV method in relatively well-characterized Alzheimer’s disease for proof-of-concept purposes. The results of this study showed that the accuracy of this new approach was comparable to or slightly better than the conventional volume-based analyses. However, this is only the first step toward our long-term goal to evaluate the efficacy of the tools that emulate the thought process of radiologists through the CBIR approach. Our results for the region-specific estimation of functional deficits and the categorical classification in AD, without a priori knowledge about the locations of the abnormalities, demonstrated the potential to use this approach for different types of neurodegenerative diseases or for an assortment of dementia pathology. To be truly useful as a tool to support clinical evaluation of patient images, atlases with various types of pathology (e.g., AD, Lewy bodies, Parkinson’s, frontotemporal dementia, vascular dementia, etc.) need to be included in the knowledge database (atlases) and the diagnostic specificity needs to be tested. Another important future direction is to incorporate non-anatomical features (demographic information, lab tests, clinical data, etc.) in the diagnostic estimator. Ultimately, the diagnostic or functional estimation are useful only if these factors can contribute to the prediction of clinically important functional deficits or treatment efficacy, which will require longitudinal data for validation. This proof-of-concept study is, thus, only the initial step in the development of clinically useful tools.

5. Conclusion

We proposed a novel MAV diagram to directly retrieve non-imaging patient attributes, in which the clinical information from multiple atlasts were weighted and fused to estimate the patient’s diagnosis. We demonstrated the performance of this approach in age estimation, as well as in the estimation of functional deficits and diagnostic categories in Alzheimer’s disease. Although MAV is a markedly different concept than conventional volume-based anatomical analyses, our results indicated that MAV can classify patients with the comparable accuracy and detect structures that are known to be affected by AD, indicating the proof-of-principle of this new approach.

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Conflict of interest

MS and MIM own “AnatomyWorks”. MS is its CEO. This arrangement is being managed by the Johns Hopkins University in accordance with its conflict of interest policies.

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