Technical Report # KU-EC-08-3:
Analysis of Metric Distances and Volumes of Hippocampi Indicates
Different Morphometric Changes over Time in Dementia of
Alzheimer Type and Nondemented Subjects

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Abstract

In this article, we analyze the morphometry (shape and size) of hippocampus in subjects with very mild dementia of Alzheimer’s type (DAT) and nondemented controls and how the morphometry changes over a two-year period. Morphometric differences with respect to a template hippocampus were measured by the metric distance obtained from the Large Deformation Diffeomorphic Metric Mapping (LDDMM) algorithm which was previously used to calculate dense one-to-one correspondence vector fields between the shapes. LDDMM assigns metric distances on the space of anatomical images thereby allowing for the direct comparison and quantization of morphometric changes. We characterize what additional information the metric distances provide in terms of size and shape given the volume measurements of the hippocampi. Moreover, we demonstrate how metric distances can be used in cross-sectional, longitudinal, and left-right asymmetry comparisons. We perform a principal component analysis on metric distances and hippocampus, brain, and intracranial volumes. We use repeated measures ANOVA models to test the main effects of and interaction between the diagnosis, duration, and hemisphere factors to see which factors significantly explain the differences in metric distances. When a factor is found to be significant, we use classical parametric and non-parametric tests to compare the metric distances for that factor. The analysis of metric distances is then used to compare the effects of aging in the hippocampus. At baseline, the metric distances for demented subjects are found not to be significantly different from those for nondemented subjects. At follow-up, the metric distances for demented subjects were significantly larger compared to nondemented subjects. The metric distances for demented subjects increased significantly from baseline to follow-up but not for nondemented subjects. We also demonstrate that metric distances can be used in a logistic regression model for diagnostic discrimination of subjects. We compare metric distances with the volumes and obtain similar results in cross-sectional and longitudinal comparisons. In classification, the model that uses volume, metric distance, and volume loss over time together performs better in detecting DAT. Thus, metric distances with respect to a template computed via LDDMM can be a powerful tool in detecting differences in shape in cross-sectional as well as longitudinal studies.

1 Introduction

Numerous post-mortem studies have shown that neurofibrillary tangles and amyloid plaques characteristic of Alzheimer’s Disease (AD) are prominent within the hippocampus of individuals with mild dementia of the Alzheimer’s type (DAT) and that the distribution of these neuropathological markers becomes more widespread to include several regions of the neocortex as the disease process progresses [1-7]. The accumulation of neurofibrillary tangles and amyloid plaques characteristic of AD are associated with neuronal damage and death [8]. Furthermore, macroscopic gray matter losses from the accumulation of microscopic scale neuronal destruction are detectable in living subjects using currently available magnetic resonance (MR) imaging. Specifically, volume losses within the hippocampus [9-14] have recently been reported in subjects with mild-to-moderate AD. In an unusual study where the antemortem MR scans and post-mortem material was available for the same subjects, hippocampal volume losses were shown to be powerful antemortem predictors of AD neuropathology [15]. Progressive atrophy of the entire brain has been observed in AD cases [16]. However, due to the complexity of the human brain and the non-uniform distribution of AD neuropathology early in the course of disease, detailed examination of specific brain regions known to be affected early in the AD disease process (e.g., hippocampus) may be preferred for distinguishing preclinical and very mild forms of AD from normal aging [17-19].

Methods developed in the field of Computational Anatomy (CA) that enable quantification of brain structure volumes and shapes between and within groups of individuals with and without various neurological diseases have emerged from several groups in recent years [20-25]. Based on the mathematical principles of general pattern theory [18, 19, 23, 26, 27], these methods combine image-based diffeomorphic maps between MR scans with representations of brain structures as smooth manifolds. Because of their high repeatability and sensitivity to changes in neuroanatomical shapes, they can be especially sensitive to abnormalities of brain structures associated with early forms of AD. Using such methods, we previously demonstrated that the combined assessment of hippocampal volume loss and shape deformity optimally distinguished subjects with very mild DAT from both elder nondemented subjects and younger healthy subjects [10]. These methods also allowed us to demonstrate that hippocampal shape deformities associated with very mild DAT and nondemented aging were distinct [28]. These methods were also extended to quantify changes in neuroanatomical volumes and shapes within the same individuals over time [29]. Other longitudinal neuroimaging analysis of hippocampal structures in individuals with AD have also emerged [30-41].
An important task in CA is the study of neuroanatomical variability. The anatomical model is a quadruple \((\Omega, \mathcal{G}, \mathcal{I}, \mathcal{P})\) consisting of \(\Omega\) the template coordinate space (in \(\mathbb{R}^3\)), defined as the union of 0, 1, 2, and 3-dimensional manifolds, \(\mathcal{G} : \Omega \leftrightarrow \Omega\) a set of diffeomorphic transformations on \(\Omega\), \(\mathcal{I}\) the space of anatomies is the orbit of a template anatomy \(I_0\) under \(\mathcal{G}\), and \(\mathcal{P}\) the family of probability measures on \(\mathcal{G}\). In this framework, a geodesic \(\phi : [0, 1] \rightarrow \mathcal{G}\) is computed where each point \(\phi_t \in \mathcal{G}, t \in [0, 1]\) is a diffeomorphism of the domain \(\Omega\). The evolution of the template image \(I_0\) along path is given by \(\phi_t I_0 = I_0 \circ \phi_t^{-1}\) such that the end point of the geodesic connects the template \(I_0\) to the target \(I_1\) via \(I_1 = \phi_t I_0 = I_0 \circ \phi_t^{-1}\). Thus, anatomical variability in the target is encoded by these geodesic transformations when a template is fixed.

Furthermore, geodesic curves induce metric distances between the template and the target shapes in the orbit as follows. The diffeomorphisms are constructed as a flow of ordinary differential equations \(\phi_t = v_t(\phi_t)\), \(t \in [0, 1]\) with \(\phi_0 = \text{id}\) the identity map, and associated vector fields, \(v_t, t \in [0, 1]\). The optimal velocity vector field parameterizing the geodesic path is found by solving

\[
\hat{v} = \arg \inf_{v: \phi = \int_0^1 v_t(\phi_t) dt, \phi_0 = \text{id}} \int_0^1 \|v_t\|^2_{\mathcal{V}} dt \text{ such that } I_0 \circ \phi_t^{-1} = I_1, \tag{1}
\]

where \(v_t \in \mathcal{V}\), the Hilbert space of smooth vector fields with norm \(\|\cdot\|_{\mathcal{V}}\) defined through a differential operator enforcing smoothness. The length of the minimal length path through the space of transformations connecting the given anatomical configurations in \(I_0\) and \(I_1\) defines a metric distance between anatomical shapes in \(I_0\) and \(I_1\) via

\[
d(I_0, I_1) = \int_0^1 \|\hat{v}_t\|^2_{\mathcal{V}} dt, \tag{2}
\]

where \(\hat{v}_t\) is the optimizer calculated from the Large Deformation Diffeomorphic Metric Mapping (LDDMM) algorithm [42]. Here, the metric distance does not have any units. The construction of such a metric space allows one to quantify similarities and differences between anatomical shapes in the orbit. This is the vision laid out by D’Arcy W. Thompson almost one hundred years ago. Figure 1 exemplifies the change in the metric distance during the evolution of the diffeomorphic map from the template shape to the target shape.

The notion of mathematical biomarker in the form of metric distance can be used in different ways. One is to generate metric distances of shapes relative to a template [42, 43]. Another is to generate metric distances between each shape within a collection [44]. The latter approach allows for sophisticated pattern classification analysis; it is however computationally expensive. We present an analysis based on the former approach which could provide a powerful tool in analyzing subtle shape changes over time with considerably less computational load. This approach may allow detecting the subtle morphometric changes observed in the hippocampus in DAT subjects in particular for those previously analyzed [29, 45]. These studies compared rates of change in hippocampal volume and shape in subjects with very mild DAT and matched (for age and gender) nondemented subjects. The change in hippocampal shape over time was defined as a residual vector field resulting from rigid-body motion registration, and changes in patterns along hippocampal surfaces were visualized and analyzed via a statistical measure of individual and group change in hippocampal shape over time and used to distinguish between the subject groups. Hence the motivation to analyze LDDMM generated metric distances between binary hippocampus images at baseline and at follow-up with respect to the same template hippocampus image. That is, the template was compared again, and not propagated between time points. One might wonder why we do not track changes within a subject directly, rather than via a reference template, as it could give a more sensitive measure of shape change since the small difference in shape would make finding correspondence more accurate. Although we have considered doing this, the difficulty is that since the template (or origin) is different for each longitudinal computation, how to correctly perform statistical comparison of group change is not completely settled. This is actively being developed by using the concept of “parallel transport” [46, 47]. In this study, we compute and analyze metric distances based on the data used in [29].

We briefly describe the data set in Section 2.1, computation of metric distances via LDDMM in Section 2.2, statistical methods we employ in Section 2.3, and results and findings in Section 3, which include descriptive summary statistics of the metric distances, comparison of metric distances of hippocampi of non-demented subjects and subjects with very mild dementia, correlation between metric distances, comparison of distributions of metric distances, and discriminative power of metric distances. We perform similar analysis on hippocampal volumes in Section 4, compare volumes and LDDMM distances in Section 5, and analyze annual
percentage rate of change in volumes and distances in Section 6. In the final section, we discuss the use of metric distances for baseline-followup studies, group comparisons, and discrimination analysis.

2 Methods

2.1 Subjects and Data Acquisition

Detailed description of subjects can be found in [29] where 18 very mild DAT subjects (Clinical Dementia Rating Scale, CDR0.5) and 26 age-matched nondemented controls (CDR0) were each scanned approximately two years apart. Clinical Dementia Rating (CDR) Scale assessments which detect the severity of dementia symptoms were performed annually in all subjects by experienced clinicians without reference to neuropsychological tests or in-vivo neuroimaging data. The experienced clinician conducted semi-structured interviews with an informant and the subject to assess the subject’s cognitive and functional performance; a neurological examination was also obtained. The clinician determined the presence or absence of dementia and, when present, its severity with the CDR. Overall CDR scores of 0 indicate no dementia, while CDR scores of 0.5, 1, 2, and 3 indicate very mild, mild, moderate and severe dementia, respectively [48]. CDR assessments have been shown to have an inter-rater reliability of $\kappa = 0.74$ (weighted kappa coefficient [49] $\kappa$ of 0.87) [50], and this high degree of inter-rater reliability has been confirmed in multi-center dementia studies [51]. Elderly subjects with no clinical evidence of dementia (i.e., CDR0 subject) have been confirmed with normal brains at autopsy with 80% accuracy; i.e., approximately 20% of such individuals show evidence of AD [52]. CDR0.5 subjects have subtle cognitive impairment, and 93% of them progress to more severe stages of illness (i.e., CDR > 0.5) and show neuropathological signs of AD at autopsy ([53], [54], and [52]). Although elsewhere the CDR0.5 individuals in our sample may be considered to have MCI [55], they fulfill our diagnostic criteria for very mild DAT and at autopsy overwhelmingly have neuropathologic AD [56]. A summary of subject information is listed in Table 1.

The scans were obtained using a Magnetom SP-4000 1.5 Tesla imaging system, a standard head coil, and a magnetization prepared rapid gradient echo (MPRAGE) sequence. The MPRAGE sequence (TR/TE - 10/4, ACQ - 1, Matrix - 256 $\times$ 256, Scanning time - 11.0 min) produced 3D data with a 1 $mm$ $\times$ 1 $mm$ in-plane resolution and 1 $mm$ slice thickness across the entire cranium.

A neuroanatomical template was produced using an MR image from an additional elder control (i.e., CDR0 or non-demented) subject (male, age = 69). The choice and a detailed description of the template is provided in [57]. The subject selected to produce this template was obtained from the same source as the other subjects in the study, but was not otherwise included in the data analysis. Data used are the left and right hippocampal surfaces in the template scan created from expert-produced manual outlines using methods previously described [28,58], and the left and right hippocampal surfaces of each subject generated at baseline and follow-up. These surfaces were converted to binary hippocampus volumetric images by flood filling the inside of the surface and giving it label 1, and the outside of the surface was labeled as 0, or background. Each individual hippocampal surface was first scaled by a factor of 2 and aligned with the template surface, which was also scaled by a factor of 2, via a rigid-body rotation and translation before converting to volumetric binary images. In [58] we showed that mapping accuracy could be enhanced at higher resolution because of smaller voxels – voxels at the periphery of the structure (i.e., surface) account for much more of the structural volume at 1 $mm^3$ voxel resolution versus 0.5 $mm^3$. Since then we have adapted this as part of the standard mapping procedure. These surfaces were then converted into binarized image of dimension $64 \times 112 \times 64$ with voxel resolutions of 0.5 $\times$ 0.5 $\times$ 0.5 $mm^3$, followed by smoothing by a Gaussian filter of $9 \times 9 \times 9$-voxel window and one voxel standard deviation to smooth out the edges for LDDMM, which was then applied to each template-subject pair to compute metric distances, $d_k^t$, $d_k^f$($k = 1, \ldots, 44$), in each hemisphere at baseline ($b$) and at follow-up ($f$) as illustrated in Figure 2.

Controlling for brain size is important because people with bigger brains tend to have bigger hippocampus and we want our results to not reflect that very interesting fact: we inherently correct for brain size by first rigid-aligning the subject brain to the prototype brain prior to LDDMM. Segmentation of hippocampal MRI shapes across subjects, especially in diseased states, is a challenging problem. However the accuracy of the segmentation is not the point of this paper and has been demonstrated before [10, 57, 58].
In addition to the metric distances, our data set also consists of the following variables: gender, age, education in years (these variables are used for controlling the confounding effects of these factors on hippocampus morphometry, so the subjects are taken to be similar or evenly distributed in these variables). Furthermore, we have brain and intracranial volumes at baseline and follow-up, and hippocampus volumes for left and right hippocampi at baseline and follow-up.

2.2 Computing Metric Distance via Large Deformation Diffeomorphic Metric Mapping

Metric distances between the binary images and the template image are obtained by computing diffeomorphisms between the images. Computation and analysis of these diffeomorphic mappings have been previously described [57]. Diffeomorphisms are estimated via the variational problem that, in the space of smooth velocity vector fields \( V \) on domain \( \Omega \), takes the form [42]:

\[
\hat{v} = \arg \min_{v: \phi_t = v(\phi_t)} \left( \int_0^1 \|v_t\|^2 dt + \frac{1}{\sigma^2} \|I_0 \circ \phi_t^{-1} - I_1\|^2 \right).
\] (3)

The optimizer of this cost generates the optimal change of coordinates \( \varphi = \phi_t^{\hat{v}} \) upon integration \( d\phi_t^v / dt = \hat{v}_t \), where the subscript \( v \) in \( \phi^v \) is used to explicitly denote the dependence of \( \phi \) on the associated velocity field \( v \). Enforcing a sufficient amount of smoothness on the elements of the space of \( V \) of allowable velocity vector fields ensures that the solution to the differential equation \( \dot{\phi}_t = v_t(\phi_t) \), \( t \in [0,1] \), \( v_t \in V \) is in the space of diffeomorphisms [59, 60]. The required smoothness is enforced by defining the norm on the space \( V \) of smooth velocity vector fields through a differential operator \( L \) of the type \( L = (-\alpha \Delta + \gamma)^\sigma I_{n \times n} \)

where \( \alpha > 1.5 \) in 3-dimensional space such that \( \|f\|_V = \|Lf\|_{L_2} \) and \( \|\cdot\|_{L_2} \) is the standard \( L_2 \) norm for square integrable functions defined on \( \Omega \). The gradient of this cost is given by

\[
\nabla_v E_t = 2 \hat{v}_t - K \left( \frac{2}{\sigma^2} |D\phi_{t,1}^\hat{v}| \nabla J_t^0 (J_t^0 - J_t^1) \right)
\] (4)

where \( J_t^0 = I_0 \circ \phi_t \) and \( J_t^1 = I_1 \circ \phi_t^{-1} \), \( |Dg| \) is the determinant of the Jacobian matrix for \( g \) and \( K \) is a compact self-adjoint operator \( K : L_2(\Omega, R^d) \rightarrow V \) uniquely defined by \( < a, b >_{L_2} = < Ka, b >_V \) such that for any smooth vector field \( f \in V, K(L^1 L) f = f \) holds. The metric distance is then calculated via Equation (2).

2.3 Statistical Methods

First, we investigate what LDDMM metric distance measures and how it is related to hippocampus, brain, and intracranial volumes. That is, as a compound measure of morphometry, how much of the metric distance is related to shape and size and how it is associated with the volume, which is mostly a measure of size. Along this line, we provide the correlation between volume and metric distance measures by the pairs plots at baseline and follow-up of left and right hippocampi. Furthermore, we perform a principal component analysis (PCA) on metric distance and volumes to characterize the major traits these quantities measure. Then we provide a statistical methodology for the analysis of LDDMM distances. We compute and interpret simple summary statistics, such as, mean, standard deviation (SD), minimum, first quartile (Q1), median, third quartile (Q3), and maximum for \( d_k^{(b,f)} \). Then we apply repeated measures analysis of metric distances with diagnosis group as main effect and timepoint as the repeated factor, side (i.e., hemisphere) as main effect and timepoint as the repeated factor, and diagnosis group as main effect and side-by-timepoint as the repeated factor, since there are within-subject dependence of metric distances for left and right hemispheres and at baseline and follow-up. We apply four possible competing models each assuming a different variance-covariance structure to obtain the model that best fit to our data set. The first model assumes compound symmetry, in which the diagonals (i.e., the variances) are equal, and so are the off diagonals (i.e., the covariances). The other three models assume unstructured, autoregressive (AR), and autoregressive heterogeneous variances, respectively. In the unstructured model, each variance and covariance term is different, in the AR model, the variances are assumed to be equal but the covariances change by time, and in the ARH model, the variances are also different and the covariances change by time. The corresponding variance-covariance (Var-Cov) structures
For post-hoc comparison of CDR0.5 vs CDR0, our null hypothesis for the comparison of diagnosis groups, CDR0 and CDR0.5, is $H_0 : \mu_{\text{CDR}0} = \mu_{\text{CDR}0.5}$ for each baseline left, baseline right, and follow-up left, follow-up right hippocampi. For the $t$-test, among the underlying assumptions are the normality of the distributions and homogeneity of the variances of the independent samples. We employ Lilliefors’ test of normality [65]; and Brown and Forsythe’s (B-F) test (i.e., Levene’s test with absolute deviations from the median) for homogeneity of the variances [66]. If there is lack of significant deviation from normality of distribution of a metric distance for a group, we will state it as “the metric distances for the group can be assumed to come from a normally distributed population”, henceforth.

We compare metric distances at baseline and follow-up. The LB-CDR0.5 metric distances and LF-CDR0.5 metric distances are dependent as they come from the same person at baseline and follow-up. Likewise for LB-CDR0 and LF-CDR0 pairs. Hence our null hypothesis for the comparison of baseline and follow-up groups is $H_0 : \delta(B, F) = 0$ where $\delta(B, F)$ is the mean difference of metric distances between hippocampi at baseline and follow-up for each of CDR0 left, CDR0 right, CDR0.5 left, CDR0.5 right hippocampi. We also compare the metric distances for the left and right hippocampi are dependent (for each left-right hippocampi pair comes from the same subject). Hence our null hypothesis for the comparison of left and right metric distances is $H_0 : \delta(L, R) = 0$ where $\delta(L, R)$ is the mean difference of metric distances between left and right metric distances for each of CDR0 baseline, CDR0 follow-up, CDR0.5 baseline, CDR0.5 follow-up hippocampi.

We also calculate and interpret correlation coefficients between metric distances. Since metric distances of all groups can be assumed to have normal distribution based on Lilliefors’ test of normality, we use Pearson’s correlation coefficient, denoted $r_P$, between baseline and follow-up (overall and by diagnosis group) and for the left and right hippocampi and the corresponding tests of $H_0 : r_P = 0$ vs $H_a : r_P > 0$ for inference [67,68].

We also estimate the empirical cumulative distribution functions (cdf) of the metric distances and compare them by Kolmogorov-Smirnov (K-S) test, Cramér’s test, and Cramér-von Mises test. The null hypothesis for the comparison of cdfs of the metric distances per diagnosis groups, CDR0 and CDR0.5, is $H_0 : F_{\text{CDR}0} = F_{\text{CDR}0.5}$ for each baseline left, baseline right, follow-up left, follow-up right hippocampi. For calculation of the critical value of Cramér’s test the kernel $\phi_C(x) = \frac{\sqrt{x}}{2}$ (which is recommended for location alternatives) is used. The estimated $p$-values are based on $\alpha = 0.05$ and 10000 ordinary bootstrap replicates.

We apply logistic discrimination with metric distances and other variables, since the diagnosis have only two levels, namely CDR0 and CDR0.5. We use logistic regression to estimate or predict the risk or probability of having DAT using metric distances, together with side (i.e., hemisphere) and timepoint (baseline vs follow-up) factors. In other words, we model the probability that the subject is CDR0.5 given the metric distance of the subject for left or right hippocampus at baseline or follow-up. In standard logistic regression the model-parameters are obtained via maximum likelihood estimators. For more on logistic regression and logistic discrimination, see [69] and [70], respectively. We consider the logistic model with the response where (i.e., the probability that the subject is diagnosed with CDR0.5). First we model with one predictor variable at a time from side, timepoint, and metric distance, etc., if the variable is not significant at .05 level, we omit that variable from further consideration. We consider the full logistic model with the response $\logit p = \log [p/(1 - p)]$ where $p = P(Y = 1)$ (i.e., the probability that the subject is diagnosed with CDR0.5); the remaining variables with all possible interactions as the predictor variables. On this full model, we choose a reduced model by AIC in a stepwise algorithm, and then use stepwise backward elimination procedure on the resulting model [64]. We stop the elimination procedure when all the remaining variables are significant at $\alpha = 0.05$ level.

Based on the final model with significant predictors, we apply logistic discrimination. In logistic discrimination the log-odds-ratio of the conditional classification and therefore indirectly the conditional probabilities of being CDR0.5 and CDR0 are modeled. In general, if this estimated probability is larger than a prespecified probability $p_o$, the subject is classified as CDR0.5, otherwise the subject is classified as CDR0 (i.e., normal).
This means our decision function reduces to
\[
\hat{p}_k = P(Y = 1 | d_{ijk}) \begin{cases} > p_o \Rightarrow \text{classify } CDR0.5, \\ \leq p_o \Rightarrow \text{classify } CDR0, \end{cases}
\]
where \(p_o\) is usually taken to be 0.5. This threshold probability \(p_o\) can also be optimized with respect to a cost function which incorporates correct classification rates, sensitivity, and/or specificity [71].

We apply the same analysis procedure on hippocampal volumes to compare the results with LDDMM metric distances. Furthermore, we find the differential volume loss and metric distance change by using the annual percentage rate of change (APC) in volume and metric distance (see [71] for APC in volume for entorhinal cortex). We also consider the logistic discrimination models that incorporate volume and metric distance together and APC in volumes and metric distances together.

3 Analysis of LDDMM Distances of Hippocampi

3.1 Preliminary Analysis of LDDMM Distances and Other Variables

The summary measures for the variables are provided in Table 1. Observe that the subjects are evenly distributed in terms of gender, years of education, scan intervals, and age for the diagnostic groups. The brain and intracranial volumes are much larger in scale, then come the hippocampal volumes, and then the metric distances. Notice that brain and hippocampal volumes all decrease by time and are smaller in CDR0.5 subjects compared to CDR0 subjects. On the other hand, the metric distances tend to increase by time and are larger for the CDR0.5 subjects. Also presented in Table 1 are the \(p\)-values for Lilliefor’s test of normality and Wilcoxon rank sum test for differences between the diagnostic groups. Notice that most variables can be assumed to follow a Gaussian distribution, but since a few fails to do so, we apply the Wilcoxon rank sum test instead of Welch’s \(t\)-test. The diagnostic groups do not significantly differ in age, education, brain and intracranial volumes. Furthermore, among the metric distances, we see that only right follow-up metric distances are significantly different between the diagnostic groups.

We present the pairs plot (scatter plot of each pair) of continuous variables in Figure 3 and also calculate the correlation coefficients between each pair of the variables (not presented). We observe that age and education are not significantly correlated with any of the other variables. Hence we discard them in our prospective analysis (except for logistic discrimination). We observe significant correlation between each pair of hippocampal volumes, and between each pair of brain and intracranial volumes. The metric distances are only moderately correlated with each other. Hippocampal volumes are mildly correlated with brain and intracranial volumes. The same holds for the metric distances but to a lesser extent.

Summary statistics of population mean, standard deviation (SD), minimum, first quartile \((Q_1)\), median, third quartile \((Q_3)\), and maximum for \(d_{ik}^{(b,f)}\) are presented in Table 1.

Baseline metric distances seem to be different in distribution (location and spread) from follow-up metric distances follow-up distances being larger than baseline distances for both left and right hippocampi; likewise left metric distances seem to be different from right metric distances with right distances being larger than left for both baseline and follow-up. Let LDB be the metric distances for left hippocampi at baseline, LDF be the metric distances for left hippocampi at follow-up. Let RDB and RDF be similarly defined for right hippocampi. One-tailed \(t\)-tests revealed that the order of these measures is LDB < LDF < RDF < RDB with all inequalities being significant at .05 level. This implies that the morphometric differences of left hippocampi with respect to the left hippocampus of the template subject at baseline are significantly smaller than those at follow-up, i.e., at baseline, left hippocampi are more similar to the left template hippocampus, and by follow-up left hippocampi tend to become more different in morphometry (shape and size) from the template hippocampus. This is not surprising, as the template hippocampus is one from the baseline hippocampi. That is the template was based on a baseline scan. Although this should seem to be irrelevant in view of the wide age variation, it is not the age that is the main point here, when baseline and follow-up are compared, we use matched pair (i.e., dependent) tests, which would reveal differences that would otherwise be concealed by the independent two-sample tests. For example, when all the subjects age about two years, their morphometric alterations accumulate to render their relative difference from the template more significant.
The right hippocampi reveal similar morphometric differences and change over time. Furthermore, we observe that the morphometric difference of right hippocampi from the right template hippocampus is significantly larger compared to the morphometric difference of left hippocampi from the left template at both baseline and follow-up. The summary statistics (means and standard deviations (SD)) for left and right metric distances by group are provided in Table 1.

Observe that CDR0 distances are smaller than CDR0.5 distances at baseline and at follow-up for both left and right hippocampi. This suggests that the morphometric differences of CDR0 hippocampi with respect to the template hippocampus are smaller than those of CDR0.5 hippocampi. This is not surprising, considering the template hippocampus being one of the CDR0 hippocampi. Furthermore, the standard deviations of the distances for CDR0 subjects tend to be smaller than those of CDR0.5 subjects. That is, the morphometric variability of CDR0 hippocampi with respect to the template hippocampus is smaller than that of CDR0.5 hippocampi. The statistical significance of these results will be provided in the following sections.

See also Figure 4 for the (jittered) scatter plots of the metric distances by group, where the crosses are centered at the mean distances and the points are jittered (scattered) along the horizontal axis in order to avoid frequent point concurrence and tight clustering of points, thereby making the plot better for visualization.

3.2 Principal Component Analysis for the Volumes and Metric Distances

The volumes and metric distances measure different but related aspects of morphometry, so some of the variables are highly correlated with each other (see Figure 3). We perform principal component analysis (PCA) to obtain a set of uncorrelated variables that hopefully represent some identifiable aspect of the morphometry. See [70,76] for more on PCA. When we perform PCA of metric distances and volumes of left hippocampi at baseline with eigenvalues based on the covariance matrix, we observe that the first principal component (PC) accounts for almost all the variation (see Table 2). Considering the variable loadings in Table 2, we see that PC1 is the head size component, PC2 is the contrast between brain and intracranial volumes, PC3 is the hippocampus size, and PC4 is the metric distance component. However, the volumes are in \( \text{mm}^3 \) and metric distances are unitless, hence the data are not to scale. In particular, the brain and intracranial volumes have the largest variation in the data set, hence dominate the PCs. To remove the influence of the scale (or unit), we apply PCA with eigenvalues based on the correlation matrix (i.e., PCA on the standardized variables). The importance scores of principal components and variable loadings from the PCA of metric distances and volumes of left hippocampi at baseline and follow-up with eigenvalues based on the correlation matrix are presented in Table 3. Notice that with the correlation matrix, the first three PCs account for almost all the variation in the variables. Comparing the variable loadings, PC1 seems to be the head size component, PC2 is the hippocampus shape, PC3 is the hippocampus size and the contrast between hippocampus and head size, and PC4 is the contrast between brain and intracranial volume. The PCA on variables for right hippocampi yields similar results (see Table 4).

The variable loadings in the PCA of variables at baseline and follow-up suggest that brain and intracranial volumes are mostly measures of head size, metric distance is mostly a measure of hippocampus shape and partly is a measure of head and hippocampus size, and hippocampus volume is mostly a measure of hippocampus size and partly related to hippocampus shape and head size. That is, volumes and the metric distance convey information that is related but not identical. Volumes mostly emphasize the size differences, while metric distances emphasize the shape differences. Hence, one should use both of them in morphometric analysis of brain tissues.

3.3 Repeated Measures Analysis of LDDMM Distances

Due to within-subject dependence of metric distances for left and right hemispheres and for baseline and follow-up measures, we apply repeated-measures analysis with group and side as main effects and timepoint as the repeated factor, and group as main effect and side-by-timepoint as the repeated factor (see below). For the left data, metric distances at baseline for CDR0.5 subjects are labeled as LB-CDR0.5, at follow-up are labeled as LF-CDR0.5. CDR0 individuals are labeled as LB-CDR0 and LF-CDR0 accordingly. Similar labeling is done for the right metric distances. Hence, we have four measurements for each subject, so repeated measures analysis can be performed on our data set.
3.3.1 Modeling LDDMM Distances with Group as Main Effect with Compound Symmetry in Var-Cov Structure

For the repeated measures ANOVA with group as main effect and compound symmetry repeated over time, for each subject, we will denote diagnosis, timepoint, and hemisphere factors as numerical subscripts for convenience. The corresponding model is

\[ d_{ijk} = \mu + \alpha_i^D + \alpha_j^T + \alpha_{ij}^{DT} + \varepsilon_{ijk} \]  

(6)

where \( d_{ijk} \) is the distance for subject \( k \) with diagnosis \( i \) (\( i = 1 \) for CDR0; 2 for CDR0.5) at timepoint \( j \) (\( j = 1 \) for baseline; 2 for follow-up), \( \mu \) is the overall mean, \( \alpha_i^D \) is the effect of diagnosis level \( i \), \( \alpha_j^T \) is the effect of timepoint level \( j \), \( \alpha_{ij}^{DT} \) is the diagnosis-by-timepoint interaction, i.e., part of the mean distance not attributable to the additive effect of diagnosis and timepoint, and \( \varepsilon_{ijk} \) is the error term. The Var-Cov structure for the error term is

\[ \text{Var}(\varepsilon_{ijk}) = \sigma^2 \text{ and } \text{Cov}(\varepsilon_{ijk}, \varepsilon_{ij'k}) = \sigma^2_T. \]

Notice that the effect of side (left or right) is ignored in this model. There is no significant group main effect \( (F = 3.36, df = 1,42, p = 0.0739) \). However, the within group time-point main effect \( (F = 11.16, df = 1,130, p = 0.0011) \) and the group-by-timepoint interaction \( (F = 4.84, df = 1,130, p = 0.0295) \) are both significant, which imply that the two groups should be compared at the different time points. In Figure 5, we present the interaction plots for diagnosis over time, where the end points of the line segments are located at the mean metric distances at baseline and follow-up years. We see that both lines increase over time, but are not parallel; the increase of the line for CDR0.5 group is steeper.

3.3.2 Modeling LDDMM Distances with Side as Main Effect with Compound Symmetry in Var-Cov Structure

For the repeated measures ANOVA with side as main effect and compound symmetry repeated over time, the corresponding model is

\[ d_{ijk} = \mu + \alpha_i^S + \alpha_j^T + \alpha_{ij}^{ST} + \varepsilon_{ijk} \]  

(7)

where \( d_{ijk} \) is the distance for subject \( k \) with side \( i \) (\( i = 1 \) for left; 2 for right) at timepoint \( j \) (\( j = 1 \) for baseline; 2 for follow-up), \( \mu \) is the overall mean, \( \alpha_i^S \) is the effect of side level \( i \), \( \alpha_j^T \) is the effect of timepoint level \( j \), \( \alpha_{ij}^{ST} \) is the side-by-timepoint interaction, and \( \varepsilon_{ijk} \) is the error term. The Var-Cov structure for the error term is

\[ \text{Var}(\varepsilon_{ijk}) = \sigma^2 \text{ and } \text{Cov}(\varepsilon_{ijk}, \varepsilon_{ij'k}) = \sigma^2_T. \]

Notice that the effect of diagnosis (CDR0 or CDR0.5) is ignored in this model. The side and timepoint main effects are both significant \( (F = 20.25, df = 1,129, p < 0.0001) \) and \( (F = 12.51, df = 1,129, p = 0.0006) \), respectively, but side-by-timepoint interaction is not significant \( (F = 1.85, df = 1,129, p = 0.1766) \). Consequently, we see that the lines are parallel but far apart, the main effect of side comparison is meaningful and about the same at each timepoint. Moreover, the sides do change in morphometry over time. In Figure 5, we see that both lines increase over time and are parallel, but the slope for right side seems to be steeper, which will eventually make the slope estimates significantly different.

3.3.3 Modeling LDDMM Distances with Group, Side, and Group-by-Side Interaction

Looking at models including only the main effects of side or group separately does not answer all our questions. We would also like to know, for example, if the metric distances of left hippocampi of CDR0.5 subjects are different from those of left CDR0 subjects. In order to address these types of questions we need to look at a model that includes the interaction of diagnosis and side. First, we need to model the Var-Cov structure for the repeated measures for each subject. We have four correlated measures per subject, namely LDB, LDF, RDB, and RDF. Below is the estimated Var-Cov matrix for these variables:

\[
\begin{bmatrix}
0.46 & 0.35 & 0.18 & 0.02 \\
0.35 & 0.60 & 0.24 & 0.18 \\
0.18 & 0.24 & 0.45 & 0.23 \\
0.02 & 0.18 & 0.23 & 0.44
\end{bmatrix}
\]
We start with compound symmetry for our model, and then try unstructured, autoregressive (AR), and autoregressive heterogeneous (ARH) Var-Cov structures. The variances (in the diagonal) suggest heterogeneity between them, and also, covariances seem to differ. This suggests that either an unstructured or ARH model might fit this data best. See Table for the comparison of model selection criteria such as AIC, BIC, and Log-likelihood and likelihood ratio test p-value.

The most promising model is the unstructured model based on likelihood ratio test, since -2 Log Likelihood scores are significantly smaller than the -2 Log Likelihood scores of other models. However, BIC and AIC favor the model with the AR variance-covariance structure. Besides, the log-likelihood approach gives the second smallest -2 Log Likelihood score for this model. Hence, we choose the model with AR variance-covariance structure. The corresponding model is

\[ d_{ijkl} = \mu + \alpha_i^S + \alpha_j^D + \alpha_k + \alpha_{ij}^{ST} + \alpha_{ik}^{ST} + \alpha_{jk}^{DT} + \sigma^2 + \varepsilon_{ijkl}, \]

where \( d_{ijkl} \) is the distance for subject \( l \) for side \( i \) (1 for left; 2 for right) with diagnosis \( j \) \((j = 1 \text{ for CDR0}; 2 \text{ for CDR0.5})\) at timepoint \( k \) \((k = 1 \text{ for baseline}; 2 \text{ for follow-up})\), \( \mu \) is the overall mean, \( \alpha_i^S \) is the effect of side level \( i \), \( \alpha_j^D \) is the effect of diagnosis level \( j \), \( \alpha_k \) is the effect of timepoint level \( k \), \( \alpha_{ij}^{ST} \) is the side-by-diagnosis interaction, \( \alpha_{ik}^{ST} \) is the side-by-timepoint interaction, \( \alpha_{jk}^{DT} \) is the diagnosis-by-timepoint interaction, \( \sigma^2 \) is the side-by-diagnosis-by-timepoint interaction, and \( \varepsilon_{ijkl} \) is the error term. The Var-Cov structure for the error term is

\[
\text{Cov}(\varepsilon_{ijkl}, \varepsilon_{ij'k'l'}) = \begin{bmatrix}
\sigma^2 & \sigma^2 & \sigma^2 & \sigma^2 \\
\sigma^2 & \sigma^2 & \sigma^2 & \sigma^2 \\
\sigma^2 & \sigma^2 & \sigma^2 & \sigma^2 \\
\sigma^2 & \sigma^2 & \sigma^2 & \sigma^2 
\end{bmatrix}.
\]

The three way interaction of side-by-group-by-timepoint is not significant \((F = 0.50, df = 1, 168, p = 0.4823)\), and neither are the two way side-by-group \((F = 0.76, df = 1, 168, p = 0.3860)\), and side-by-timepoint interactions \((F = 2.25, df = 1, 168, p = 0.1359)\). On the other hand, the group-by-timepoint interaction is significant \((F = 8.47, df = 1, 168, p = 0.0041)\). The main effects of side, group, and timepoint are all significant \((F = 6.12, df = 1, 168, p = 0.0143; F = 4.05, df = 1, 168, p = 0.0457; \text{and} F = 19.52, df = 1, 168, p < 0.0001, \text{respectively})\), but due to interaction, the main effect for diagnosis \((\text{i.e.}, \text{group})\) is close to clinically meaningless; i.e., the groups should be compared at each time point instead of an overall comparison of group means. But, the main effects of timepoint and side being significant is interpretable between baseline and follow-up.

Below we perform various post-hoc tests to see which groups are significantly different or significantly change over time. To accomplish this, we test for differences at each timepoint, between baseline and follow-up, and between left and right distances.

### 3.4 Post-Hoc Comparison of LDDMM Distances of CDR0.5 vs CDR0 Hippocampi

For the \( p \)-values regarding the comparison of independent groups, see Table. The significant values at \( \alpha = 0.05 \) are marked with *. None of the distance groups deviate significantly from normality (all \( p \)-values greater than 0.10). That is, distance distribution of each group can be assumed to come from a Gaussian distribution. Moreover, LB-CDR0.5 and LB-CDR0 distances can be assumed to have equal variances \((p = 0.2948)\), and so can RB-CDR0.5 and RB-CDR0 \((p = 0.2273)\). But, the variance of LF-CDR0 distances is significantly smaller than that of LF-CDR0.5 distances \((p = 0.0294)\), and similarly for RF-CDR0 versus RF-CDR0.5 \((p = 0.0262)\). Therefore, for comparisons at baseline, we can use the \( p \)-values from the \( t \)-tests [68], while for follow-up comparisons, it is more appropriate to use the \( p \)-values from Wilcoxon rank sum tests [67].

Observe that RF-CDR0.5 mean distances are significantly larger than RF-CDR0 mean distances at .05 level \((p = 0.0106)\), and LF-CDR0.5 distances are significantly larger than LF-CDR0 distances at 0.10 level \((p = 0.0813)\). On the other hand, LB-CDR0.5 and LB-CDR0 distances are not significantly different \((p = 0.5362)\), and likewise for RB-CDR0.5 and RB-CDR0 distances \((p = 0.8176)\). This implies that at baseline, the morphometric differences of CDR0.5 and CDR0 hippocampi with respect to the template hippocampus are about same, which might indicate no significant shape differences in the left and right hippocampi due to dementia. However, since the metric distances do not necessarily provide direction in either shape or
size, this is not a decisive implication. At follow-up, left and right hippocampi of CDR0.5 subjects tend to significantly differ in morphometry from the template compared to those of CDR0 subjects. Moreover, this significance emanates over time; that is, right hippocampi of CDR0.5 subjects tend to undergo more alteration in morphometry compared to those of CDR0 subjects over time.

3.5 Comparison of Baseline and Follow-up Metric Distances

For the comparison of dependent groups by paired difference method, see Table 7. The paired differences in Table 7 can all be assumed to be normal based on Lilliefors’s test of normality. Hence, we use the more powerful $t$-test for paired differences [68].

Observe that LB-CDR0.5 metric distances are significantly smaller than LF-CDR0.5 distances at $\alpha = .05$ ($p = 0.0259$). Likewise for RB-CDR0 vs RF-CDR0.5 distances ($p = 0.0002$). That is, CDR0.5 hippocampi tend to become more different in morphometry from the template, which implies that for both left and right distances there is significant change in morphometry (perhaps reduction in size) of CDR0.5 hippocampi over time. In fact, significant volume reduction over time is detected [29]. The morphometric changes in CDR0.5 right hippocampi from baseline to follow-up is barely significantly larger than those of CDR0.5 left hippocampi ($p = 0.0445$). The associated $p$-value here is obtained by testing the difference sets (LB-CDR0.5)-(LF-CDR0.5) versus (RB-CDR0)-(RF-CDR0.5) using the usual paired $t$-test. On the other hand, only RB-CDR0 is almost significantly less than RF-CDR0 at .05 level ($p = 0.0621$), which implies there is not strong evidence for shape change in control subjects over time, but some weak evidence for mild change in right hippocampi can be detected as a result of aging. Furthermore, the morphometric changes in CDR0 right hippocampi from baseline to follow-up are not significantly different from those of CDR0 left hippocampi ($p = 0.3817$).

The morphometric changes in CDR0.5 left hippocampi from baseline to follow-up are not significantly different from those of CDR0 left hippocampi ($p = 0.1337$), while the morphometric changes in CDR0.5 right hippocampi from baseline to follow-up are significantly larger from those of CDR0 right hippocampi ($p = 0.0074$). Therefore, over time, DAT influences the morphometry of right hippocampi more compared to left hippocampi.

3.6 Comparison of LDDMM Distances of Left and Right Hippocampi

As for left vs right comparisons, LB-CDR0.5 and RB-CDR0.5 distances are not significantly different from each other ($p = 0.3046$), LF-CDR0.5 distances are significantly smaller than RF-CDR0.5 distances at .05 level ($p = 0.0179$), the same holds for LB-CDR0 vs RB-CDR0.5 ($p = 0.0215$) and LF-CDR0 vs RF-CDR0 ($p = 0.0021$) comparisons. This implies that at baseline morphometric differences of CDR0.5 left hippocampi from the left template are about the same as those of CDR0.5 right hippocampi from the right template. On the other hand at follow-up, morphometric differences of CDR0.5 left hippocampi are smaller than those of CDR0.5 right hippocampi. At baseline and follow-up, morphometric differences of CDR0 left hippocampi from the left template are smaller than those of CDR0 right hippocampi. That is, CDR0 left hippocampi are more similar in morphometry to the left template when compared to CDR0 right hippocampi to the right template. These distance comparisons for left versus right hippocampi would imply left-right morphometric asymmetry, only if the left and right hippocampi of the template subject were very similar (up to a reflection). Otherwise, these comparisons are only suggestive of morphometric differences from the respective hemisphere (side) of the hippocampi.

3.7 Analysis of the Correlation between Metric Distances of Dependent Hippocampi

Correlation coefficients between metric distances for baseline and follow-up (overall and by group) and for the left and right hippocampi are provided in Table 8 and Table 9, respectively, where Pearson’s product-moment correlation coefficient is denoted as $r_p$, Spearman’s rank correlation coefficient is denoted as $\rho_S$, and Kendall’s rank correlation coefficient is denoted as $\tau_K$ [67, 68]. The corresponding null and alternative hypotheses are
\[ H_0 : \text{correlation} = 0 \quad \text{vs} \quad H_a : \text{correlation} > 0. \]

The values in the parentheses right of the correlation coefficients are the corresponding p-values. The significant p-values at level \( \alpha = 0.05 \) are marked with an asterisk (*). Since all groups can be assumed to be normal, the more powerful Pearson’s correlation test will be used for inference.

Notice that from the correlation analysis of baseline vs follow-up, we see that the overall distances, L-CDR0, and R-CDR0 are significantly correlated at 0.05 level. But LB-CDR0 and LF-CDR0 are significantly correlated at 0.05 level based on Pearson’s test, and Spearman’s test, and at 0.10 by Kendall’s tests. However, RB-CDR0 and RF-CDR0 are significantly correlated at 0.10 level by only Pearson’s test. This implies that except for the CDR0 right hippocampi, the distances tend to increase at baseline together with distances at follow-up. That is, as the morphometric differences from the template hippocampus increase at baseline, so do the differences from the template at follow-up (except for CDR0 right hippocampi).

Notice also that from the correlation analysis of left and right distances, we observe that overall left and right at baseline (LDB and RDB) distances are significantly correlated at 0.05 level, but LDF and RDF are correlated at 0.05 level by Pearson’s test only, and 0.10 by Spearman’s test. And LB-CDR0 and RB-CDR0 have significant correlation structure at 0.05 level. However, the correlation coefficients are not that large, which suggests mild correlation between left and right metric distances. That is, as the morphometric differences of left hippocampi from the left template increase, differences of right hippocampi from the right template tend to increase slightly.

### 3.8 Comparison of Distributions of the Metric Distances

The samples (groups) should be independent for these tests to be valid, so we only compare LB-CDR0.5 vs LB-CDR0, RB-CDR0.5 vs RB-CDR0, LF-CDR0.5 vs LF-CDR0, and RF-CDR0.5 vs RF-CDR0. The corresponding p-values for the two-sided and one-sided cdf comparison tests are provided in the Table 10 where \( p_{KS} \) is the p-value for the two-sided K-S test, with (l) and (g) are abbreviations of first cdf less than the second and first cdf greater than the second, respectively, \( p_C \) is the p-value for Cramér’s test, and \( p_{CvM} \) is the p-value for Cramér-von Mises test [65, 72].

Notice that at \( \alpha = 0.05 \) level, the cdf of RF-CDR0.5 distances is significantly smaller than the cdf of RF-CDR0 distances (\( p = 0.0259 \) for K-S test). That is, RF-CDR0.5 metric distances are stochastically larger than RF-CDR0 right metric distances. In other words, RF-CDR0.5 hippocampus shapes are more likely to be different than the template hippocampus compared to RF-CDR0 hippocampus shapes. Furthermore, the cdf of LF-CDR0.5 distances is significantly smaller than the cdf of LF-CDR0 distances (\( p = 0.0004 \) by K-S test and \( p = 0.0495 \) by Cramér’s test); that is, LF-CDR0.5 metric distances are stochastically larger than LF-CDR0 metric distances. See Figure 7 for the corresponding cdf plots. Observe that these results are in agreement with the ones in Table 10.

### 3.9 Logistic Discrimination with Metric Distances

We model the probability that the subject has CDR0.5 given the hippocampal LDDMM distances of the subject for left and right hippocampi at baseline and follow-up. First we consider the full logistic model (designated as \( M_l(D) \)) with the response logit \( \logit p = \log \left[ \frac{p}{1 - p} \right] \) where \( p = P(Y = 1) \) (i.e., the probability that condition of the subject is CDR0.5); side, timepoint, and distance with all possible interactions are the predictor variables. When the stepwise model selection procedure is applied, the resulting model is logit \( p_k = \beta_0 + \beta_1 d_{ijk} \) where \( p_k \) is the probability of subject \( k \) having DAT and \( d_{ijk} \) the distance for subject \( k \) with diagnosis \( i \) (1 for CDR0 and 2 for CDR0.5) at timepoint \( j \) (1 for baseline and 2 for follow-up), \( \beta_0 \) is the intercept and \( \beta_1 \) is the slope of the fitted line. However, the graph of the proportions of CDR0.5 subjects for grouped metric distances in Figure 5 suggests that the relationship is a quadratic one (in fact, we found that the higher order distance terms are not significant). That is, the analysis of deviance table indicates that only the linear and quadratic terms are significant (\( p = 0.001 \) and \( p = 0.010 \)). So the resulting model is

\[
M_{lin}(D): \logit p_k = \beta_0 + \beta_1 d_{ijk} + \beta_2 d_{ijk}^2
\]

where \( \beta_2 \) is the coefficient of the quadratic term.
Using this logistic classifier with $p_0 = 0.5$, we obtain classification summary matrix A in Table 11 for the 176 hippocampi MRI images in this data set. The labels on the left margin show the groups to which the hippocampi MRIs are classified into, while the top margin shows the groups from which these MRI images come. Observe that 95 out of 104 (91%) of the hippocampus MRIs from CDR0 subjects would be classified correctly and 20 out of 72 (28%) of the hippocampus MRIs from CDR0.5 subjects are classified correctly.

However, in this logistic discrimination procedure, we treat each hippocampus from left, right, baseline or follow-up hippocampi as a distinct subject. From a clinical point of view, each subject has four hippocampus MRIs in this study, and one MRI classified as CDR0.5 would suffice to classify the subject as CDR0.5, while all four MRIs should be classified as CDR0 for the subject to be classified as CDR0. With this classification rule, we obtain the classification matrix B in Table 11. Notice that 18 out of 26 (69.2%) of the CDR0 subjects would be classified correctly and that 10 out of 18 (55.6%) of the CDR0.5 subjects are classified correctly.

Moreover, when we use $d_i^{RB}$ and $d_i^{RF}$ one at a time in a logistic model, we see that only the model

$$M_{III}(D): \logit p_k = \beta_0 + \beta_1d_{ik}^{RB} + \beta_2(d_{ik}^{RF})^2$$

has significant coefficients for the distance terms. Using this logistic model in the logistic classifier, we get the classification matrix C in Table 11. Notice that 22 out of 26 (85%) of the CDR0 subjects would be classified correctly and that 8 out of 18 (44%) of the CDR0.5 subjects are classified correctly.

The above classification matrices are almost the same with leave-one-out cross-validation with logistic discrimination (not presented).

We also calculate the sensitivity and specificity of the classification procedures summarized in Table 12. Sensitivity is the proportion of subjects that are classified to be CDR0.5 (i.e., positive) of all CDR0.5 subjects. That is, sensitivity is defined as $P_{sens} = \frac{T_{CDR0.5}}{N_{CDR0.5}} \times 100\%$ where $T_{CDR0.5}$ is the number of correctly classified CDR0.5 subjects and $N_{CDR0.5}$ is the total number of CDR0.5 subjects in the data set (i.e., $N_{CDR0.5} = 18$ in our data). Notice that the higher the sensitivity, the fewer real cases of AD go undetected. Specificity is the proportion of subjects that are classified CDR0 (i.e., negative, control, or healthy) of all CDR0 subjects; that is $P_{spec} = \frac{T_{CDR0}}{N_{CDR0}} \times 100\%$ where $T_{CDR0}$ is the number of correctly classified CDR0 subjects and $N_{CDR0}$ is the total number of CDR0 subjects in the data set (i.e., $N_{CDR0} = 26$ in our data). Notice that the higher the specificity, the fewer healthy people are labeled as sick. The correct classification rates, sensitivity and specificity percentages for the classification matrices A-D are presented in Table 12. Observe that best classification performance is with the logistic model $M_{III}(D)$ in Equation (10) with one CDR0.5-labeled hippocampus enough to label the subject to have CDR0.5 (see matrix C in Table 11). Furthermore, in these classification procedures, specificity rates are (significantly) larger than the sensitivity rates.

We could also change the threshold probability $p_o$ in Equation (5). The correct classification rates, sensitivity, and specificity percentages with models $M_{I}(D) - M_{IV}(D)$ and $p_0 \in \{1/2, 18/44\}$ are presented in Table 13. Observe that with $p_o = 1/2$ the best classifier is based on $M_{III}(D)$ and with $p_o = 18/44$ the best classifier is based on $M_{IV}(D)$. Setting $p_o = 18/44$ (the proportion of CDR0.5 subjects in the data set) we get higher sensitivity rates than those with $p_o = 1/2$. However, as $p_o$ decreases, the correct classification rate and specificity tend to decrease.

One can optimize the threshold value of $p_o$ in Equation (5) to maximize the correct classification rates and minimize the misclassification rates using an appropriately chosen cost function. For example one can consider the cost function

$$C_1(p_o, w_1, w_2) = -(T_{CDR0} - F_{CDR0})^{w_1}(T_{CDR0.5} - F_{CDR0.5})^{w_2},$$

where $w_1 \leq w_2$ are positive odd numbers, $F_{CDR0}$ is the number of CDR0.5 subjects classified (falsely) as CDR0 and $F_{CDR0.5}$ is the number of CDR0 subjects classified (falsely) as CDR0.5. Notice that minimizing
on the right side. Repeated-measures ANOVA showed both significant change over time (within group, F = 98.97, df = 1, 42, p < .0001) and significant time-group interaction (F = 7.81, df = 1, 42, p = 0.0078) in the hippocampal volumes. The time-group interaction persisted when covaried with baseline total cerebral brain volume (p = 0.0066) or with baseline total intracranial volume (p = 0.0077). In order to take into account variations in between-visit intervals (mean 2.11 ± 0.47 years), scan interval was also used as a covariate in the volumes comparison. Again, the significant time × group interaction after covarying for scan intervals (p = 0.015) persisted.

4 Analysis of Hippocampal Volumes

The LDDMM distance gives one number reflecting the global size and shape. Volume measurements were presented in detail in [29]. The LB-CDR0 subjects had an average hippocampal volume of 2081 (± 354) mm³ while RB-CDR0 subjects had 2600 (± 481) mm³. The LB-CDR0.5 subjects had an average hippocampal volume of 1717 (± 224) mm³ and RB-CDR0.5 had 2186 (± 370) mm³. On the other hand, LF-CDR0 subjects showed a volume reduction of 82 mm³ (4.0%, NS) and RF-CDR0 subjects showed a reduction of 142 mm³ (5.5%, NS) where NS stands for “not significant”. LF-CDR0.5 subjects had hippocampal volume reduction of 164 mm³ (8.3%, p = 0.03) and RF-CDR0.5 subjects had reduction of 236 mm³ (10.2%, p = 0.05) on the right side. Repeated-measures ANOVA showed both significant change over time (within group, F = 98.97, df = 1, 42, p < .0001) and significant time-group interaction (F = 7.81, df = 1, 42, p = 0.0078) in the hippocampal volumes. The time-group interaction persisted when covaried with baseline total cerebral brain volume (p = 0.0066) or with baseline total intracranial volume (p = 0.0077). In order to take into account variations in between-visit intervals (mean 2.11 ± 0.47 years), scan interval was also used as a covariate in the volumes comparison. Again, the significant time × group interaction after covarying for scan intervals (p = 0.015) persisted.

4.1 Repeated Measures Analysis of Hippocampal Volumes

We repeat the same modeling procedure of Section 3.1 on the hippocampal volumes. For modeling hippocampal volumes using the repeated measures ANOVA with group as main effect and compound symmetry in Var-Cov structure and volume measurements repeated over time for each subject, the model is

\[ V_{ijk} = \mu + \alpha_i^D + \alpha_j^T + \alpha_{ij}^{DT} + \epsilon_{ijk}, \tag{14} \]

where \( V_{ijk} \) is the volume for subject \( k \) with diagnosis \( i \) at timepoint \( j \), \( \mu \) is the overall mean, \( \alpha_i^D \) is the effect of diagnosis level \( i \), \( \alpha_j^T \) is the effect of timepoint level \( j \), \( \alpha_{ij}^{DT} \) is the diagnosis-by-timepoint interaction, i.e., part of the mean volume not attributable to the additive effect of diagnosis and timepoint, and \( \epsilon_{ijk} \) is the error term. Notice that the effect of side (left or right) is ignored in this model. There is significant group main effect (F = 17.54, df = 1, 42, p = 0.0001) and within group time-point main effect (F = 9.87, df = 1, 130, p = 0.0021) but the group-by-timepoint interaction is not significant (F = 0.84, df = 1, 130, p = 0.3624). This implies that the main effect of group comparison is meaningful and about the same at each timepoint. Moreover, the groups do change in morphometry over time.
For modeling volumes using the repeated measures ANOVA with side as main effect and compound symmetry in Var-Cov structure and volume measurements repeated over time, the corresponding model is

\[ V_{ijk} = \mu + \alpha^S_i + \alpha^T_j + \alpha^{ST}_{ij} + \varepsilon_{ijkl}, \tag{15} \]

where \( V_{ijk} \) is the volume for subject \( k \) for side \( i \) (1 for left; 2 for right) at timepoint \( j \), \( \mu \) is the overall mean, \( \alpha^S_i \) is the effect of side level \( i \), \( \alpha^T_j \) is the effect of timepoint level \( j \), \( \alpha^{ST}_{ij} \) is the side-by-timepoint interaction, and \( \varepsilon_{ijkl} \) is the error term. Notice that the effect of diagnosis (CDR0 or CDR0.5) is ignored in this model. The side and timepoint main effects are both significant (\( F = 377.21, df = 1,129, p < .0001 \) and \( F = 38.31, df = 1,129, p < .0001 \), respectively), but side-by-timepoint interaction is not significant (\( F = 1.84, df = 1,129, p = 0.1769 \)). Consequently, we conclude that the lines that join mean volumes in the interaction plot are parallel and far apart, the main effect of side comparison is meaningful, and about the same at each timepoint. Moreover, the left and right hippocampi do change in morphometry over time.

For the model that includes the diagnosis, side, and diagnosis-by-side interaction, we use the same model selection criteria in Section 3.1.3. We find that the most promising model based on likelihood ratio test, BIC, and AIC is the one with unstructured Var-Cov matrix. The corresponding model with significant terms at \( \alpha = .05 \) level is

\[ V_{ijkl} = \mu + \alpha^S_i + \alpha^D_j + \alpha^T_k + \alpha^{ST}_{ik} + \alpha^{DT}_{jk} + \varepsilon_{ijkl}, \tag{16} \]

where \( V_{ijkl} \) is the volume for subject \( l \) for side \( i \) with diagnosis \( j \) at timepoint \( k \), \( \mu \) is the overall mean, \( \alpha^S_i \) is the effect of side level \( i \), \( \alpha^D_j \) is the effect of diagnosis level \( j \), \( \alpha^T_k \) is the effect of timepoint level \( k \), \( \alpha^{ST}_{ik} \) is the side-by-timepoint interaction, \( \alpha^{DT}_{jk} \) is the diagnosis-by-timepoint interaction, and \( \varepsilon_{ijkl} \) is the error term. The (unstructured) Var-Cov structure for the error term is

\[ \text{Cov}(\varepsilon_{ijkl}, \varepsilon_{i\ell,j\ell,k\ell}) = \begin{bmatrix} \sigma^2 & \sigma^2 & \sigma^2 \\ \sigma^2 & \sigma^2 & \sigma^2 \\ \sigma^2 & \sigma^2 & \sigma^2 \end{bmatrix}. \]

The main effects of side, group, and timepoint are all significant (\( F = 120.10, df = 1,170, p < .0001; F = 25.25, df = 1,170, p < .0001; \) and \( F = 89.53, df = 1,170, p < .0001 \), respectively). But due to interaction, the main effect for diagnosis (i.e., group) is close to clinically meaningless, i.e., the group means should be compared at each time point or hemisphere instead of comparing the overall means of the groups. But, the main effects of group and side being significant are interpretable between baseline and follow-up.

### 4.2 Post-Hoc Comparison of Hippocampal Volumes for Differences in Group, Time, and Hemisphere

We repeat the analysis procedure of Section 3 on hippocampal volumes also. We find that left hippocampus volumes are significantly smaller than the right hippocampus volumes at both baseline and follow-up years (i.e., there is significant volumetric left-right asymmetry in hippocampi); baseline volumes are larger than follow-up volumes for both left and right hippocampi (i.e., there is significant reduction in volume by time) (\( p < .0001 \) for each comparison). The means and standard deviations of the volumes for left and right hippocampi of each group are provided in Table 1. We observe the same trend in the overall comparison for each group also. However, left-right volumetric asymmetry significantly reduces by time in CDR0.5 group (\( p = .0407 \)); but the same holds only barely in CDR0 group (\( p = .0524 \)). The level of left-right volumetric asymmetry is about the same in both CDR0 and CDR0.5 groups at baseline (\( p = .3495 \)) and follow-up (\( p = .4853 \)). The volumes decrease significantly by time in CDR0 group for both left and right hippocampi (\( p < .0001 \) for both); the same holds for CDR0.5 group also (\( p = .0001 \) for both). The volumetric reduction is significantly larger in CDR0.5 right hippocampi compared to CDR0.5 left hippocampi (\( p = .0407 \); but the same holds only barely in CDR0 group (\( p = .0524 \)). On the other hand, the volumetric reduction is significantly larger in CDR0 left hippocampi compared to CDR0 left hippocampi (\( p = .0108 \); the same holds for right hippocampi also (\( p = .0418 \)). The variances of volumes are not significantly different for (LB-CDR0.5, LB-CDR0), (RB-CDR0.5, RB-CDR0), and (RF-CDR0.5, RF-CDR0) groups, but volumes of LF-CDR0 hippocampi are significantly larger than LF-CDR0.5 hippocampi (\( p = .0268 \)). The CDR0.5 volumes are significantly smaller than CDR0 volumes in left hippocampi at baseline (\( p = .0001 \)) and follow-up (\( p < .0001 \), and for right hippocampi at baseline (\( p = .0071 \)) and follow-up (\( p = .0001 \)). The CDR0.5 volumes
are stochastically smaller than CDR0 volumes for left hippocampi at baseline ($p = .0007$) and follow-up ($p = .0003$), and for right hippocampi at baseline ($p = .0064$) and follow-up ($p = .0028$).

### 4.3 Logistic Discrimination with Hippocampal Volumes

We apply the logistic discrimination methods of Section 3.7 on hippocampal volumes. First we consider the full logistic model (designated as $M_I(V)$) with side, timepoint, and volume with all possible interactions being the predictor variables. We apply the same stepwise elimination procedure as in Section 3.7 and get the following reduced model:

$$M_{II}(V): \logit p_l = \beta_0 + \alpha_k^S + \beta_1 V_{ijkl},$$

(17)

where $p_l$ is the probability of subject $l$ having DAT and $V_{ijkl}$ the volume for subject $l$ with diagnosis $i$ ($i = 1$ for CDR0 and 2 for CDR0.5) at timepoint $j$ ($j = 1$ for baseline and 2 for follow-up) with side $k$ ($k = 1$ for left and 2 for right), $\beta_0$ is the overall intercept, $\alpha_k^S$ is the effect of side level $k$, and $\beta_1$ is the slope of the fitted line.

However, as we have seen in Section 3.1.3, due to group-by-timepoint interaction, we need to consider diagnosis groups at each time point. When we use $V_{kl}^L$ and $V_{kl}^F$ one at a time in a logistic model, we see that the model

$$M_{III}(V): \logit p_l = \beta_0 + \alpha_k^S + \beta_1 V_{kl}^F,$$

(18)

has the most significant coefficients for the volume terms.

Moreover, when we use $V_{kl}^{LB}$, $V_{kl}^{LF}$, $V_{kl}^{RB}$, and $V_{kl}^{RF}$ one at a time in a logistic model, we see that the following model has the best fit.

$$M_{IV}(V): \logit p_l = \beta_0 + \beta_2 V_{kl}^{LF}$$

(19)

The classification rates are presented in Table 13. Observe that with $p_o = 1/2$ the best classifier is based on model $M_{II}(V)$ and with $p_o = 18/44$ the best classifier is based on model $M_{IV}(V)$. Furthermore, as $p_o$ decreases from 1/2, sensitivity increases but the correct classification rate and specificity decreases. We use the cost function $C_1(p_o, w_1, w_2)$ with $w_1 = w_2 = 1$ and with $w_1 = 1$ and $w_2 = 3$ to calculate the optimal $p_o$ values for each of the models $M_I(V) - M_{IV}(V)$. Observe that with $w_1 = w_2 = 1$ the best classifier is based on model $M_{IV}(V)$ and with $w_1 = 1$ and $w_2 = 3$ the best classifier is based on model $M_{III}(V)$. We find the optimal $p_o$ values based on the cost function $C_2(p_o, \eta_1, \eta_2)$ with $\eta_1 = \eta_2 = 0.5$ and with $\eta_1 = .3$, $\eta_2 = 0.7$ for each of models $M_I(V) - M_{IV}(V)$. With $\eta_1 = \eta_2 = 0.5$ the best classifier is based on model $M_{IV}(V)$ and with $\eta_1 = .3$, $\eta_2 = 0.7$ the best classifier is based on model $M_I(V)$. Observe that from $\eta_1 = \eta_2 = 0.5$ to $\eta_1 = .3$, $\eta_2 = 0.7$, sensitivity increases, correct classification rate and specificity tend to decrease.

### 5 Comparison of Hippocampal Volumes and Metric Distances

Although volume is a measure of size and metric distance is a measure of overall morphometric difference from a template, the repeated measure analysis and post-hoc analysis of volumes and metric distances provide similar results. The main difference is that volumes tend to decrease, while LDDMM distances tend to increase by time.

The logistic discrimination models are similar, except model $M_{IV}(D)$ for metric distances contains right follow-up distances, while model $M_{IV}(V)$ for volumes contains left follow-up volumes. The classification performances with $p_o = 1/2$ and $p_o = 18/44$ suggest that volume models have better performance than the metric distance models (see Tables 13 and 15). Using the optimal $p_o$ values with the cost functions $C_1(p_o, w_1, w_2)$ and $C_2(p_o, \eta_1, \eta_2)$, the classification performances are significantly different for models $M_I(V) - M_{IV}(V)$ of volumes and $M_I(D) - M_{IV}(D)$ metric distances. Comparing Tables 13 and 15 we see that logistic discrimination with volumes has better performance.

We apply the logistic discrimination using both volume and metric distance as predictors. The models we consider are the full logistic model (designated as model $M_I(V, D)$) with side, timepoint, volume, and metric distances with all possible interactions being predictor variables. We apply the same stepwise elimination procedure as in Section 3.7 and get

$$M_{II}(V, D): \logit p_l = \beta_0 + \alpha_k^S + \beta_1 V_{ijkl} + \beta_2 d_{ijkl}^D + \beta_3 V_{ijkl} d_{ijkl}$$
where \( p_i \) is the probability of subject \( l \) having DAT and \( V_{ijkl} \) the volume and \( d_{ijkl} \) the distance for subject \( l \) with diagnosis \( i \) (\( i = 1 \) for CDR0 and 2 for CDR0.5) at timepoint \( j \) (\( j = 1 \) for baseline and 2 for follow-up) with side \( k \) (\( k = 1 \) for left and 2 for right), \( \beta_0 \) is the overall intercept, \( \alpha_k^S \) is the effect of side level \( k \), \( \beta_1 \) is the coefficient for volume, \( \beta_2 \) is the coefficient for ninth power of the distance, \( \beta_3 \) is the coefficient for the interaction between volume and distance. When we use baseline or follow-up measures one at a time in a logistic model, we see that the model

\[
M_{III}(V,D): \logit p_l = \beta_0 + \alpha_k^S + \beta_1 V_{ijkl} + \beta_2 (d_{ijkl}^F)^5
\]

has the most significant coefficients. When we use side-by-timepoint combinations one at a time in a logistic model, we see that the following model has the best fit:

\[
M_{IV}(V,D): \logit p_l = \beta_0 + \beta_1 (d_{ijkl}^F)^3 + \beta_2 V_{ijkl}^{LF}.
\]

The corresponding classification rates are presented in Table 16. Observe that considering metric distance and volume together in the logistic discrimination procedure with the cost functions \( C_1(p_o, w_1, w_2) \) and \( C_2(p_o, \eta_1, \eta_2) \), we get better classification rates compared to logistic models with only one of metric distance or volume being the predictors.

### 6 Annual Percentage Rates of Change in Hippocampal Volumes and Metric Distances

Our volume and LDDMM metric comparisons are cross-sectional or longitudinal by construction. However these measures might need to be adjusted for anatomic variability, since intersubject variability might add substantial amount of noise to volume or distance measurements at baseline or follow-up. There is no simple way to correct for this noise in practice. Differential volume loss or distance change over time might be self-correcting for such variability. For example, entorhinal cortex volume loss over time was shown to be a better indicator for DAT than cross-sectional measurements [73].

#### 6.1 Annual Percentage Rate of Change in Hippocampal Volume

The hippocampal volume change over time can be written as the following annual percentage rate of change (APC) [73]:

\[
V^{APC} = \frac{V_k^b - V_k^f}{V_k^b} \times 100 \%, \tag{20}
\]

where \( T \) is the interscan interval in years (\( T \approx 2 \) in our data).

For modeling annual percentage rate of change in volume \( V^{APC} \) using the repeated measures ANOVA with group as main effect and compound symmetry in Var-Cov structure and \( V^{APC} \) measures repeated over side for each subject, the model is

\[
V_{ijkl}^{APC} = \mu + \alpha_i^D + \alpha_j^S + \alpha_{ij}^{DS} + \varepsilon_{ijkl}, \tag{21}
\]

where \( V_{ijkl}^{APC} \) is the APC in volume for side \( j \) of subject \( k \) with diagnosis \( i \), \( \mu \) is the overall mean, \( \alpha_i^D \) is the effect of diagnosis level \( i \) (\( i = 1 \) for CDR0; 2 for CDR0.5), \( \alpha_j^S \) is the effect of side level \( j \) (\( j = 1 \) for left and 2 for right), \( \alpha_{ij}^{DS} \) is the diagnosis-by-side interaction, and \( \varepsilon_{ijkl} \) is the error term. The diagnosis main effect is significant (\( F = 18.62, df = 1, 84, p < .0001 \)) but neither side main effect (\( F = 0.72, df = 1, 84, p = .3754 \)) nor diagnosis-by-side interaction is significant (\( F = 0.11, df = 1, 84, p = 0.7384 \)). Consequently, we conclude that the lines that join the mean \( V^{APC} \) values in the interaction plot are parallel and far apart, the main effect of diagnosis comparison is meaningful, and about the same at each hemisphere. The post hoc comparison of \( V^{APC} \) values indicate that the APC in CDR0.5 volumes are significantly larger than APC in CDR0 volumes (\( p = .0001 \)).

We apply the logistic discrimination methods of Section 3.7 on APC in hippocampal volumes. First we consider the full logistic model (designated as \( M_I \) (\( V^{APC} \))) with side and APC in volume with all possible
interactions being the predictor variables. We apply the same stepwise elimination procedure as in Section 3.7 and get

\[ M_{II} (V^{APC}) : \logit p_k = \beta_0 + \beta_1 V^{APC}_{ijk} + \beta_2 (V^{APC}_{ijk})^3 \]  

(22)

where \( p_k \) is the probability of subject \( k \) having DAT.

Furthermore, when we use \( V^{APC,L}_{ijk} \) and \( V^{APC,R}_{ijk} \) as predictors in a logistic model, we see that the following model has the best fit.

\[ M_{III} (V^{APC}) : \logit p_k = \beta_0 + \beta_1 V^{APC,L}_{ijk} + \beta_2 V^{APC,R}_{ijk} + \beta_3 (V^{APC,L}_{ijk})^2. \]  

(23)

The classification rates with \( p_o = 1/2 \) and \( p_o = 18/44 \) and optimal \( p_o \) values with respect to the cost functions are presented in Table 17. Observe that the classifier using the cost function \( C_2(p_o, \eta_1, \eta_2) \) with \( \eta_1 = .3, \ \eta_2 = .7 \) in model \( M_I (V^{APC}) \) has the best performance. Comparing Tables 15 and 16 we observe that correct classification rates, sensitivity, and specificity percentages with the classifiers based on APC in volume are about the same as those with volume only. Unlike the findings of [73] hippocampal volume loss over time is not a better indicator for DAT than cross-sectional measurements. On the other hand, the classifier based on volume and distance together performs better compared to models based on only one of volume, distance, or APC in volume values.

6.2 Annual Percentage Rate of Change in LDDMM Metric Distance

The hippocampal LDDMM metric distance change over time can be written as the following annual percentage rate of change:

\[ D^{APC} = \frac{d^T_k - d^b_k}{d^b_k \times T} \times 100\%. \]  

(24)

Notice that to make APC in metric distance positive, we take the difference \( d^T_k - d^b_k \) as opposed to the order in the APC in volume definition. For modeling \( D^{APC} \) using the repeated measures ANOVA with group as main effect and compound symmetry in the Var-Cov structure and \( D^{APC} \) measures repeated over side for each subject, the model is

\[ D^{APC}_{ijk} = \mu + \alpha^D_i + \alpha^S_j + \alpha^{DS}_{ij} + \varepsilon_{ijk}, \]  

(25)

where \( D^{APC}_{ijk} \) is the APC in LDDMM metric distance for side \( j \) of subject \( k \) with diagnosis \( i \). The other terms are as in Equation (21). The diagnosis main effect is significant \( (F = 4.75, \ df = 1, 84, \ p = .0320) \) but neither side main effect \( (F = 2.29, \ df = 1, 84, \ p = .1338) \) nor diagnosis-by-side interaction is significant \( (F = 0.87, \ df = 1, 84, \ p = .3532) \). Consequently, we conclude that the lines that join the means in the interaction plot are parallel and far apart, the main effect of diagnosis comparison is meaningful, and about the same at each hemisphere. The APC in CDR0.5 LDDMM distances is significantly larger (in absolute value) than APC in CDR0 distances \( (p = .0036) \).

We apply the logistic discrimination methods of Section 3.7 on APC in hippocampal LDDMM distances. First we consider the full logistic model (designated as \( M_I (D^{APC}) \)) with side and APC in distance with all possible interactions being the predictor variables. We apply the same stepwise elimination procedure as in Section 3.7 and get

\[ M_{II} (D^{APC}) : \logit p_k = \beta_0 + \beta_1 D^{APC}_{ijk}. \]  

(26)

Furthermore, when we use \( D^{APC,L}_{ijk} \) and \( D^{APC,R}_{ijk} \) as predictors in a logistic model, we see that the following model has the best fit.

\[ M_{III} (D^{APC}) : \logit p_k = \beta_0 + \beta_1 D^{APC,R}_{ik}. \]  

(27)

The classification rates with \( p_o = 1/2 \) and \( p_o = 18/44 \) and optimal \( p_o \) values with respect to the cost functions are presented in Table 18. Observe that these classifiers have relatively poor performance. Comparing each of Tables 13 and 18 we observe that the classifiers with the optimal \( p_o \) values have much larger sensitivity rates but this increase comes at the expense of substantial decrease in correct classification rate and specificity. Hence hippocampal LDDMM change over time is not a better indicator for DAT than cross-sectional distance comparisons.
6.3 Annual Percentage Rate of Change in Hippocampal Volume and Metric Distances

We apply the logistic discrimination based on distance and APC in volumes. First we consider the full logistic model (designated as $M_I(V^{APC}, D)$) with side and APC in volume, and distances with all possible interactions being the predictor variables. We apply the same stepwise elimination procedure as in Section 3.7 and get

$$M_{III}(V^{APC}, D) : \logit p_k = \beta_0 + \beta_1 V_{ik}^{APC} + \beta_2 (V_{ijk}^{APC})^3 + \beta_3 (\delta_{ik}^F)^2.$$  (28)

Furthermore, when we use and left and right measures as predictors in a logistic model, we see that the following model has the best fit.

$$M_{III}(V^{APC}, D) : \logit p_k = \beta_0 + \beta_1 V_{ik}^{APC,L} + \beta_2 V_{ik}^{APC,R} + \beta_3 \delta_{ik}^{RF}.$$  (29)

The classification rates with $p_o = 1/2$ and $p_o = 18/44$ and optimal $p_o$ values with respect to the cost functions are presented in Table 19. With the cost function $C_1(p_o, w_1 = 1, w_2 = 1)$, the best classifier is based on $M_{III}(V^{APC}, D)$ for which the optimal threshold value is $p_o \approx .37$, the correct classification rate is 80%, sensitivity is 78%, and specificity is 81%. Likewise, with the cost function $C_1(p_o, w_1 = 1, w_2 = 3)$, the best classifier is based on $M_I(V^{APC}, D)$ for which the optimal threshold value is $p_o = .56$, the correct classification rate is 80%, sensitivity is 78%, and specificity is 81%. On the other hand, with cost function $C_2(p_o, \eta_1 = .5, \eta_2 = .5)$ the best classifier is based on $M_{IV}(V, D)$ for which the optimal threshold value is $p_o = .64$, the correct classification rate is 84%, sensitivity is 72%, and specificity is 92%. With cost function $C_2(p_o, \eta_1 = 3, \eta_2 = .7)$, the best classifier is again based on $M_{IV}(V, D)$ for which the optimal threshold value is $p_o = .56$, the correct classification rate is 80%, sensitivity is 78%, and specificity is 81%. Comparing Tables 16 and 19, we observe that the classifiers based on metric distance and volume usually perform better compared to the classifiers based on metric distance and APC in volume. Comparing Table 17 and 19, we observe that adding the metric distance to the logistic model with APC in volume improves the classification performance. Hence the model with hippocampal volume loss over time and metric distance is a better indicator for DAT compared to either variable used separately in logistic discrimination.

We also apply the logistic discrimination based on volume, distance, and APC in volumes. First we consider the full logistic model (designated as $M_I(V, V^{APC}, D)$) with side, volume, and APC in volume, and distances with all possible interactions being the predictor variables. We apply the same stepwise elimination procedure as in Section 3.7 and get

$$M_{III}(V, V^{APC}, D) : \logit p_k = \beta_0 + \beta_1 V_{ik}^B + \beta_2 V_{ijk}^{APC} + \beta_3 (V_{ijk}^{APC})^3 + \beta_4 (\delta_{ijk}^F)^3.$$  (30)

Furthermore, when we use and left and right measures as predictors in a logistic model, we see that the following model has the best fit.

$$M_{III}(V, V^{APC}, D) : \logit p_k = \beta_0 + \beta_1 V_{ik}^{RF} + \beta_2 \delta_{ik}^{LF} + \beta_3 V_{ik}^{APC,R} + \beta_4 (V_{ik}^{APC,L})^3 + \beta_5 (\delta_{ik}^{RF})^3.$$  (31)

The classification rates with $p_o = 1/2$ and $p_o = 18/44$ and optimal $p_o$ values with respect to the cost functions are presented in Table 20. With the cost function $C_1(p_o, w_1 = 1, w_2 = 1)$, the best classifier is based on $M_{III}(V, V^{APC}, D)$. Comparing Table 20 with Tables 13, 14, 17, 18, 16 and 19, we observe that the classifiers based on metric distance, volume, and APC in volumes usually perform better compared to the classifiers based on other models. Hence the model with volume, hippocampal volume loss over time, and metric distance is a better indicator for DAT compared to other models based on subsets of these variables.

7 Discussion and Conclusions

In this study, we used the Large Deformation Diffeomorphic Metric Mapping (LDDMM) algorithm to generate metric distances between hippocampi in groups of subjects with and without Dementia of Alzheimer’s type (DAT) in its mild form (labeled as CDR0.5 and CDR0 patients, respectively) at baseline and at follow-up. The subjects in this paper have been previously analyzed using related but different tools. As a single scalar
measure, volumes were used for diagnosis group comparisons at baseline and follow-up [29] and displacement momentum vector fields based on LDDMM were used for discrimination [57]. But the metric distances computed from LDDMM has not hitherto been used in diagnosis group analysis. The metric distance gives a single number reflecting the global morphometry (i.e., the size and shape) while volume measurements only provide information on size. So metric distances provide morphometric information not conveyed by volume whereas momentum vector fields also provide local information on shape changes. Further, the morphometric information conveyed by the metric distance depends on the choice of the template, while the morphometric information conveyed by momentum vector fields is independent of the template chosen. That is, although the vector fields change when the template changes, the morphometric information they convey is the same.

Previously, it has been shown that hippocampal volume loss and shape deformities observed in subjects with DAT distinguished them from both elderly and younger control subjects [10]. The pattern of hippocampal deformities in subjects with DAT was largely symmetric and suggested damage to the CA1 hippocampal subfield [74]. Hippocampal shape changes were also observed in healthy elderly subjects, which distinguished them from healthy younger subjects. These shape changes occurred in a pattern distinct from the pattern seen in DAT and were not associated with substantial volume loss [75].

Furthermore, Wang et al. [45] analyzed the baseline hippocampi of the same data set and showed that the very mild DAT subjects showed significant inward variation in the left and right lateral zones (LZ) the left and right intermediate zone (IMZ), but not in the left and right superior zones (SZ) as compared to CDR0 subjects. In their logistic regression analysis, inward variation of the left and right LZ or IMZ by 0.1 mm relative to the average of the nondemented subjects increased the odds of the subject being a very mild DAT subject rather than being a nondemented subject. The odds ratios for the left and right SZ were not significant. These results represented a replication of their previous findings [10] and suggest that inward deformities of the hippocampal surface in proximity to the CA1 subfield and subiculum can be used to distinguish subjects with very mild DAT from CDR0 subjects [45]. However, although momentum vector fields obtained by the LDDMM algorithm can be used to detect such local (i.e., location specific) morphometric changes (as in the CA1 subfield), metric distance does not provide such local information, hence fails to indicate any type of laterality differences.

The main results in this paper are that although metric distances did not detect any significant difference in morphometry at baseline (see Table 7), follow-up metric distances for the right hippocampus in CDR0.5 (i.e., mildly demented) subjects are found to be significantly larger than those in CDR0 (i.e., non-demented) subjects (see Table 7). Wang et al. also analyzed the velocity vector fields for the baseline hippocampi of the same data set and found that the left hippocampus in the DAT group shows significant shape abnormality and the right hippocampus shows similar pattern of abnormality [57]. Again, the reason for the metric failing to detect such abnormality in the baseline hippocampi is that metric distance is a compound and oversummarizing measure of global morphometry. From baseline to follow-up, metric distances for CDR0.5 subjects significantly increase while those in CDR0 subjects do not (see Table 7). That is, the morphometry (shape and size) of hippocampus in CDR0.5 subjects changes significantly over time, but not in CDR0 subjects. Atrophy – over two years – might occur with aging, and this is captured by metric distances (see Table 7). However the increase in the metric distances in CDR0 subjects is not found to be statistically significant.

Such differences in morphometry between diagnosis groups or morphometric changes over time can be detected by metric distances computed via LDDMM and could potentially serve as a biomarker for the disease. Previously, the volumes and velocity vector fields associated with the same data set (i.e., baseline and follow-up of both groups) were also analyzed and it was found that hippocampal volume loss over time was significantly greater in the CDR0.5 subjects (left = 8.3%, right = 10.2%) than in the CDR0 subjects (left = 4.0%, right = 5.5%) (ANOVA, $F = 7.81, p = 0.0078$). Using singular-value decomposition and logistic regression models, [45] quantified hippocampal shape change across time within individuals, and this shape change in the CDR0.5 and CDR0 subjects was found to be significantly different (Wilks’ $\lambda$, $p = 0.014$). Further, at baseline, CDR0.5 subjects, in comparison to CDR0 subjects, showed inward deformation over 38% of the hippocampal surface; after 2 years this difference grew to 47%. Also, within the CDR0 subjects, shape change between baseline and follow-up was largely confined to the head of the hippocampus and subiculum, while in the CDR0.5 subjects, shape change involved the lateral body of the hippocampus as well as the head region and subiculum. These results suggest that different patterns of hippocampal shape change in time as well as different rates of hippocampal volume loss distinguish very mild DAT from healthy aging [29].
In regard to statistical analysis, as a compound but brief measure of morphometry, metric distances can thus serve as a first step to identify the morphometric differences, and can be used as a pointer to which direction a clinician or data analyst could go. The importance of the CDR0 versus CDR0.5 contrast analyzed here is that it tests a necessary but not sufficient condition for the eventual goal of discriminating CDR0s who subsequently convert to CDR0.5, from CDR0s who subsequently stay CDR0. As subjects are followed longitudinally and some convert, we have shown that cross-sectional measures of the hippocampal structure can be used to predict those who convert. Metric distances may also be used in this way. When baseline and followup of converted and nonconverted nondemented subjects were analyzed, it was found that the inward variation of the lateral zone and left hippocampal volume significantly predicted conversion to CDR0.5 in separate Cox proportional hazards models. When hippocampal surface variation and volume were included in a single model, inward variation of the lateral zone of the left hippocampal surface was selected as the only significant predictor of conversion. The pattern of hippocampal surface deformation observed in nondemented subjects who later converted to CDR0.5 was similar to the pattern of hippocampal surface deformation previously observed to discriminate subjects with very mild DAT and nondemented subjects. These results suggest that inward deformation of the left hippocampal surface in a zone corresponding to the CA1 subfield is an early predictor of the onset of DAT in nondemented elderly subjects [74]. This appears to contradict our finding that the morphometric changes in CDR0.5 right hippocampi from baseline to follow-up is significantly larger than those of CDR0.5 left hippocampi ($p = 0.044$). The morphometric changes in CDR0 right hippocampi from baseline to follow-up are not significantly different from those of CDR0 left hippocampi ($p = 0.382$). The morphometric changes in CDR0.5 left hippocampi from baseline to follow-up are not significantly different from those in CDR0 left hippocampi ($p = 0.134$), while the morphometric changes in CDR0.5 right hippocampi from baseline to follow-up are significantly larger than those of CDR0 right hippocampi ($p = 0.007$). Therefore, over time, DAT may alter the (global) morphometry of the right hippocampus. However, note that the finding in [74] are concerned with changes in (local) subregions of hippocampi, while metric distance is concerned with overall morphometric changes. That is, DAT might implicate CA1 of the left hippocampi, yet the overall change in morphometry of right hippocampi might be more substantial. Moreover, in [74] the converted (from CDR0 to CDR0.5) subjects were analyzed separately, which we do not consider such conversion in our analysis. Also, metric distance results agree with the volume comparisons of [29], hence volume (i.e., scale) might be highly dominating the morphometric changes in the hippocampi. In other words, the significant volume reduction in left and right hippocampi might dominate the change in shape, when morphometry is measured by metric distances. To remove the size influence so as to measure the shapes only, one can perform scaling on the hippocampi and then apply LDDMM to normalize the size differences.

Differences and changes (over time) in morphometry can also be used for diagnostic discrimination of subjects in non-demented or demented groups. Many discrimination techniques such as Fisher’s linear discriminant functions, support vector machines, and logistic discrimination can be applied to the metric distances, together with other qualitative variables. In this study we applied logistic discrimination based on metric distances, as logistic regression not only provides a means for classification, but also yields a probability estimate for having DAT. Furthermore, one can optimize the threshold probability for a particular cost function for the entire training data set, or by a cross-validation technique. The correct classification rate of the hippocampi was about 70% in our logistic regression analysis. In [57] PCA of the initial momentum of the same data set led to correct classification of 12 out of 18 (i.e., 67% of the) demented subjects and 22 out of 26 (i.e., 85% of the) control subjects. Metric distances can be used to distinguish AD from normal aging quantitatively; however, to be able to use it for diagnostic purposes, the method should be improved to a greater extent.

We perform a principal component analysis on metric distances and hippocampus, brain, and intracranial volumes. Considering the variable loadings, we conclude that volumes are mostly measures of size and partly related to shape, while the metric distance is mostly a measure of shape and partly related to size.

We also compare the cross-sectional, longitudinal, and discrimination results of LDDMM distances with those of volumes. We observe that cross-sectional and longitudinal analysis give similar results, although metric distances increase and volumes decrease by time. The metric distance, being an extremely condensed summary measure give very similar results as the hippocampal volume. That is, neither volume nor metric distance discriminated left baseline (LB), right baseline (RB), or left followup (LF) between CDR0 and CDR0.5; volume reduction and metric distances differences are both significant for CDR0.5 subjects, but neither of them are significant for CDR0 subjects; and ANOVA suggested a significant diagnosis group-by-timepoint interaction for both measures. On the other hand, we obtain better classification results with using volumes
compared to metric distances. When volume and LDDMM distances are used together, the classification results improve compared to results based on volume or distance only. Furthermore, the differential volume and distance changes are measured by annual percentage rate of change (APC) for the two year period in the study. Similar to the results of [71], we found that APC in volumes may be a good indicator for early stage of DAT. However, APC in LDDMM distances do not provide a good performance in classification of CDR0 versus CDR0.5 hippocampi. Comparing the discrimination results, we found that the classifier based on volume, distance, and APC in volume has the best performance. Hence these measures may constitute a reliable biomarker when used together.

In conclusion, we have presented detailed statistical analysis of metric distances computed with LDDMM and show that this is potentially a powerful tool in detecting morphometric changes between diagnosis groups or changes in morphometry over time. Furthermore, we avoid the single subject analysis, which might be of greater interest clinically. Metric distances depend on the choice of template anatomy used. However, in this article we do not address the issue of template selection for optimal differentiation between hippocampus morphometry.

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**Tables and Figures**
### I- Summary Information of Subjects

| Gender (M/F) | Age (years) | Scan interval (years) (Min-Max) | Education (years) (mean ± SD) |
|-------------|-------------|---------------------------------|-------------------------------|
| CDR0        | 12/14       | 75.2±7.0                        | 2.2 [1.4-4.1]                 |
| CDR0.5      | 11/7        | 75.7±4.4                        | 2.0 [1.0-2.6]                 |
| overall     | 23/21       | 75.4±6.1                        | 2.1 [1.0-4.1]                 |

#### II- Summary Statistics for Metric Distances at Baseline and Follow-up

| Left-d^L_k (LDB) | Mean ± SD | Min | Q_1 | Median | Q_3 | Max |
|------------------|-----------|-----|-----|--------|-----|-----|
| CDR0             | 3.40 ± 0.68 | 1.97 | 3.00 | 3.30   | 3.65 | 5.08 |
| CDR0.5           | 3.57 ± 0.77 | 2.26 | 2.99 | 3.48   | 4.02 | 6.03 |
| overall          | 3.65 ± 0.67 | 1.73 | 3.32 | 3.53   | 4.09 | 4.98 |

| Right-d^L_k (LDF) | Mean ± SD | Min | Q_1 | Median | Q_3 | Max |
|-------------------|-----------|-----|-----|--------|-----|-----|
| CDR0              | 4.05 ± 0.67 | 2.96 | 3.72 | 3.95   | 4.34 | 5.71 |
| CDR0.5            |           |     |     |        |     |     |
| overall           |           |     |     |        |     |     |

#### III- Mean ± SD Values of Brain and Intracranial Volumes

| BV1 | BV3 | ICV1 | ICV3 |
|-----|-----|------|------|
| CDR0 | 1006892 ± 104214.0 | 1003319.4 ± 101129.0 | 1407972 ± 156067.1 | 1464494 ± 177496.0 |
| CDR0.5 | 1003850 ± 92293.4 | 993380.8 ± 95425.0 | 1408507 ± 134912.6 | 1454966 ± 138931.2 |
| overall | 1005647 ± 98408.2 | 999253.6 ± 97828.6 | 1408191 ± 146140.3 | 1460596 ± 161152.7 |

#### IV- Mean ± SD of Hippocampal Volumes

| LB | LF | RB | RF |
|----|----|----|----|
| CDR0 | 2081.4 ± 354.8 | 2081.4 ± 354.8 | 2081.4 ± 354.8 | 2081.4 ± 354.8 |
| CDR0.5 | 1717.6 ± 224.8 | 1717.6 ± 224.8 | 1717.6 ± 224.8 | 1717.6 ± 224.8 |
| overall | 1932.6 ± 354.8 | 1932.6 ± 354.8 | 1932.6 ± 354.8 | 1932.6 ± 354.8 |

#### V- Mean ± SD of Metric Distances

| LB | LF | RB | RF |
|----|----|----|----|
| CDR0 | 3.34 ± 0.62 | 3.41 ± 0.54 | 3.63 ± 0.57 | 3.83 ± 0.47 |
| CDR0.5 | 3.48 ± 0.76 | 3.82 ± 0.98 | 3.68 ± 0.81 | 4.37 ± 0.78 |
| overall | 3.40 ± 0.68 | 3.57 ± 0.77 | 3.65 ± 0.67 | 4.05 ± 0.67 |

Table 1: Summary information of subjects (I); summary statistics for metric distances at baseline and follow-up, where SD stands for standard deviation, Q_1 and Q_3 stand for the first and third quartiles (II); means and SDs of brain and intracranial volumes by diagnosis group (III); means and SDs of hippocampal volumes by diagnosis group (IV); and means and SDs of metric distances by diagnosis group (V). p_L: p-value based on Lilliefors’s test of normality, p_W: p-value based on Wilcoxon rank sum test. NA: not applicable; BV1 (BV3): brain volume at baseline (followup); ICV1(ICV3): intracranial volume at baseline (followup); LB: left baseline; LF: left followup; RB: right baseline; and RF: right followup.
### Table 2: The importance of principal components and variable loadings from the principal component analysis of metric distances and volumes of left hippocampi at baseline with eigenvalues based on the covariance matrix.

| Importance of Components | PC1  | PC2  | PC3  | PC4  |
|-------------------------|------|------|------|------|
| Prop. Var               | .9877| .0123| ~ 0.0| ~ 0.0|
| Cum. Prop.              | .9877| ~ 1.0| ~ 1.0| 1.0  |

| Variable Loadings       | PC1  | PC2  | PC3  | PC4  |
|-------------------------|------|------|------|------|
| HLV                     | ~ 0.0| ~ 0.0| 1.00 | ~ 0.0|
| HLM                     | ~ 0.0| ~ 0.0| ~ 0.0| 1.00 |
| BV                      | .55  | ~ .83| ~ 0.0| ~ 0.0|
| ICV                     | .83  | .55  | ~ 0.0| ~ 0.0|

PCi stands for principal component i for i = 1, 2, 3, 4; Prop.Var: proportion of variance explained by the principal components; Cum.Prop: cumulative proportion of the variance explained by the particular principal component; HLV: volume of left hippocampus at baseline; HLM: metric distance of left hippocampus at baseline; BV: brain volume at baseline; ICV: intracranial volume at baseline.

### Table 3: The importance of principal components and variable loadings from the principal component analysis of metric distances and volumes of left hippocampi at baseline and followup with eigenvalues based on the correlation matrix.

| Importance of Components | Baseline | Followup |
|-------------------------|----------|----------|
| Prop. Var               | .57      | .54      |
| Cum. Prop.              | .57      | .57      |

| Variable Loadings       | Baseline | Followup |
|-------------------------|----------|----------|
| HLV                     | .37      | .41      |
| HLM                     | .22      | .41      |
| BV                      | .64      | .65      |
| ICV                     | .63      | .64      |

HLV: volume of left hippocampus; HLM: metric distance of left hippocampus; BV: brain volume; ICV: intracranial volume. The other abbreviations are as in Table 2.

### Table 4: The importance of principal components and variable loadings from the principal component analysis of metric distances and volumes of right hippocampi at baseline and followup with eigenvalues based on the correlation matrix.

| Importance of Components | Baseline | Followup |
|-------------------------|----------|----------|
| Prop. Var               | .54      | .57      |
| Cum. Prop.              | .54      | .57      |

| Variable Loadings       | Baseline | Followup |
|-------------------------|----------|----------|
| HRV                     | .35      | .50      |
| HRM                     | ~ 0.0    | ~ 30.0   |
| BV                      | .66      | .58      |
| ICV                     | .66      | .57      |

HRV: volume of right hippocampus; HRM: metric distance of right hippocampus; BV: brain volume; ICV: intracranial volume. The other abbreviations are as in Table 2.
Table 5: The Var-Cov structures for the repeated measures ANOVA analysis on the metric distances; $\sigma^2$ is the common variance term, $\sigma^2_i$ is the variance for repeated factor $i$, $\sigma_{ij}$ is the covariance between repeated factors $i$ and $j$, and $\rho$ is the correlation coefficient for first order in an autoregressive model.

| Model | Var-Cov   | df | AIC  | BIC  | Log Likelihood | Test | L.Ratio | p-value |
|-------|-----------|----|------|------|----------------|------|---------|---------|
| 1     | CS        | 10 | 362.8| 394.1| -171.4         | —    | —       | —       |
| 2     | UN        | 18 | 352.9| 409.1| -158.4         | 1 vs 2| 25.9    | 0.0011  |
| 3     | ARH       | 13 | 350.9| 391.5| -162.5         | 1 vs 3| 17.92   | < 0.0001|
| 4     | AR        | 10 | 347.1| 378.4| -163.6         | —    | —       | —       |

Table 6: Model selection criteria results for models with compound symmetry (CS), unstructured (US), autoregressive (AR), and autoregressive heterogeneous (ARH) Var-Cov structures. $df$ = error degree of freedom, AIC = Akaike information criteria, BIC = Bayesian information criteria, L.Ratio = likelihood ratio.

Table 7: The p-values based on independent sample t-test (top) and Wilcoxon rank sum test (middle) for both left and right metric distances and p-values based on paired t-tests for both left and right metric distances (bottom). Notice that we use t-tests when the assumptions (such as normality or homogeneity of variances hold), otherwise we use Wilcoxon test. Significant p-values at 0.05 level are marked with an asterisk (*).

Table 8: The correlation coefficients and the associated p-values for the one-sided (correlation greater than zero) alternatives. $r_P$ = Pearson’s correlation coefficient, $\rho_S$ = Spearman’s rank correlation coefficient, and $\tau_K$ = Kendall’s rank correlation coefficient. Significant p-values at 0.05 level are marked with an asterisk (*).
Correlation Coefficients of Distances of Left vs Right Hippocampi

| Groups               | \(r_p\)     | \(\rho_s\)  | \(\tau_K\) |
|----------------------|-------------|-------------|-------------|
| LDB, RDB             | 0.4017 (.0034*) | 0.27 (.0382*) | 0.1749 (.0471*) |
| LDF, RDF             | 0.3441 (.0111*) | 0.2009 (.0952) | 0.1241 (.1175) |
| LB-CDR0.5, RB-CDR0   | 0.3312 (.0492*) | 0.3813 (.0277*) | 0.2191 (.0582) |
| LF-CDR0.5, RF-CDR0.5 | 0.1033 (.3078)  | 0.0400 (.4225) | 0.0340 (.4039) |
| LB-CDR0, RB-CDR0     | 0.3312 (.0492*) | 0.3813 (.0277*) | 0.2191 (.0582) |
| LF-CDR0, RF-CDR0     | 0.1033 (.3078)  | 0.0400 (.4225) | 0.0340 (.4039) |

Table 9: The correlation coefficients and the associated \(p\)-values for the one-sided (correlation greater than zero) alternatives. \(r_p\), \(\rho_s\), and \(\tau_K\) stand for Pearson’s, Spearman’s, and Kendall’s correlation coefficients, respectively. Significant \(p\)-values at 0.05 level are marked with an asterisk (*).

| Groups               | \(p_{KS}\) (2-s) | \(p_{KS}\) (l) | \(p_{KS}\) (g) | \(p_C\) | \(p_{CvM}\) |
|----------------------|------------------|----------------|----------------|--------|-----------|
| LB-CDR0.5, LB-CDR0   | .6932            | .364           | .5706          | .4325  | .5112     |
| RB-CDR0, RB-CDR0     | .8997            | .5204          | .5875          | .6084  | .7098     |
| LF-CDR0.5, LF-CDR0   | .1208            | .0604          | .5706          | .0495* | .0665     |
| RF-CDR0.5, RF-CDR0   | .0517*           | .0259*         | .9365          | .0095* | .0235*    |

Table 10: The \(p\)-values for the K-S, Cramér’s, and Cramér-von Mises tests. \(p_{KS}\) (2-s), \(p_{KS}\) (l), and \(p_{KS}\) (g) stand for the \(p\)-values based on K-S test for the two sided alternative, first cdf less than the second, and first cdf greater than the second alternatives, respectively, \(p_C\), and \(p_{CvM}\) stands for the \(p\)-values for Cramér’s test and Cramér-von Mises test, respectively. Significant \(p\)-values at 0.05 level are marked with an asterisk (*).

| Truth     | CDR0 | CDR0.5 | Total |
|-----------|------|--------|-------|
| Predict A |      |        |       |
| CDR0      | 95   | 52     | 147   |
| CDR0.5    | 9    | 20     | 29    |
| Total     | 104  | 72     | 176   |

| Truth     | CDR0 | CDR0.5 | Total |
|-----------|------|--------|-------|
| Predict B |      |        |       |
| CDR0      | 18   | 8      | 26    |
| CDR0.5    | 8    | 10     | 18    |
| Total     | 26   | 18     | 44    |

| Truth     | CDR0 | CDR0.5 | Total |
|-----------|------|--------|-------|
| Predict C |      |        |       |
| CDR0      | 22   | 8      | 30    |
| CDR0.5    | 4    | 10     | 14    |
| Total     | 26   | 18     | 44    |

| Truth     | CDR0 | CDR0.5 | Total |
|-----------|------|--------|-------|
| Predict D |      |        |       |
| CDR0      | 22   | 10     | 32    |
| CDR0.5    | 4    | 8      | 12    |
| Total     | 26   | 18     | 44    |

Table 11: The classification matrices using metric distances in logistic regression with threshold \(p = 0.5\): A = classification matrix of all hippocampi using logistic model \(M_{II}(D)\) using hippocampal LDDMM metric distances in Equation (9); B = classification matrix of subjects using logistic model \(M_{II}(D)\) in Equation (9) with one hippocampus MRI classified as CDR0.5 being sufficient to label CDR0.5; C = classification matrix of subjects using logistic model \(M_{III}(D)\) in Equation (10) that only uses follow-up hippocampus MRIs and one hippocampus sufficient to label CDR0.5; D = classification matrix of subjects using logistic model \(M_{IV}(D)\) in Equation (11) that only uses follow-up right hippocampus MRIs.

|          | A     | B     | C*    | D     |
|----------|-------|-------|-------|-------|
| \(P_{CCR}\) | 65%   | 64%   | 73%   | 68%   |
| \(P_{sens}\) | 28%   | 26%   | 56%   | 44%   |
| \(P_{spec}\) | 91%   | 69%   | 85%   | 85%   |

Table 12: The correct classification rates (\(P_{CCR}\)), sensitivity (\(P_{sens}\)), and specificity (\(P_{spec}\)) percentages with \(p_0 = 0.50\) for the classification procedures A-D in Table 11. The model with the best classification performance is marked with an asterisk (*).
Table 13: The correct classification rates ($P_{sens}$), sensitivity ($P_{sens}$), and specificity ($P_{spec}$) percentages for the classification procedures based on models $M_I(D) - M_{IV}(D)$ using hippocampal LDDMM metrics and volumes with threshold probabilities $p_o = 1/2$ and $p_o = 18/44$ (top); with optimum threshold values $p_o = p_{opt}$ based on the cost function $C_1(p_o, w_1, w_2)$ with $w_1 = w_2 = 1$ and $w_1 = 1, w_2 = 3$ (middle); and with optimum threshold values $p_o = p_{opt}$ based on the cost function $C_2(p_o, \eta_1, \eta_2)$ with $\eta_1 = 0.5$ and $\eta_1 = 0.3, \eta_2 = 0.7$ (bottom). The model with the best classification performance is marked with an asterisk (*).

Table 14: The p-values based on independent sample t-test (top) and Wilcoxon rank sum test (middle) for both left and right hippocampus volumes and p-values based on paired t-tests for both left and right hippocampus volumes (bottom). Significant p-values at 0.05 level are marked with an asterisk (*).
Table 15: The correct classification rates ($P_{CCR}$), sensitivity ($P_{sens}$), and specificity ($P_{spec}$) percentages for the classification procedures based on models $M_I(V) - M_{IV}(V)$ using hippocampal LDDMM metrics and volumes with threshold probabilities $p_o = 1/2$ and $p_o = 18/44$ (top); with optimum threshold values $p_o = p_{opt}$ based on the cost function $C_1(p_o, w_1, w_2)$ with $w_1 = w_2 = 1$ and $w_1 = 1$, $w_2 = 3$ (middle); and with optimum threshold values $p_o = p_{opt}$ based on the cost function $C_2(p_o, \eta_1, \eta_2)$ with $\eta_1 = \eta_2 = 0.5$ and $\eta_1 = 3$, $\eta_2 = 0.7$ (bottom). The model with the best classification performance is marked with an asterisk (*).

| $p_o = 1/2$ | $p_o = 18/44$ |
|-------------|----------------|
| $p_{opt}$   | $p_{opt}$      |
| $P_{CCR}$   | $P_{CCR}$      |
| $P_{sens}$  | $P_{sens}$     |
| $P_{spec}$  | $P_{spec}$     |

Using optimum $p_o$ based on cost function $C_1(p_o, w_1, w_2)$ with $w_1 = w_2 = 1$ and $w_1 = 1$, $w_2 = 3$

| $p_{opt}$ | $p_{opt}$ |
|-----------|-----------|
| $P_{CCR}$ | $P_{CCR}$ |
| $P_{sens}$| $P_{sens}$|
| $P_{spec}$| $P_{spec}$|

Using optimum $p_o$ based on cost function $C_2(p_o, \eta_1, \eta_2)$

| $\eta_1 = \eta_2 = 0.5$ | $\eta_1 = 3$, $\eta_2 = 0.7$ |
|--------------------------|-------------------------------|
| $p_{opt}$                | $p_{opt}$                     |
| $P_{CCR}$                | $P_{CCR}$                     |
| $P_{sens}$               | $P_{sens}$                    |
| $P_{spec}$               | $P_{spec}$                    |

Table 16: The correct classification rates ($P_{CCR}$), sensitivity ($P_{sens}$), and specificity ($P_{spec}$) percentages for the classification procedures based on models $M_I(V, D) - M_{IV}(V, D)$ using hippocampal LDDMM metrics and volumes with threshold probabilities $p_o = 1/2$ and $p_o = 18/44$ (top); with optimum threshold values $p_o = p_{opt}$ based on the cost function $C_1(p_o, w_1, w_2)$ with $w_1 = w_2 = 1$ and $w_1 = 1$, $w_2 = 3$ (middle); and with optimum threshold values $p_o = p_{opt}$ based on the cost function $C_2(p_o, \eta_1, \eta_2)$ with $\eta_1 = \eta_2 = 0.5$ and $\eta_1 = 3$, $\eta_2 = 0.7$ (bottom). The model with the best classification performance is marked with an asterisk (*).
| $p_o = 1/2$ | $p_o = 18/44$ |
|-----------------|-----------------|
| $M_1 (V^{APC})$ | $M_1 (V^{APC})$ |
| $M_{II} (V^{APC})$ | $M_{II} (V^{APC})$ |
| $M_{III} (V^{APC})$ | $M_{III} (V^{APC})$ |
| $P_{CCR}$ | 75% | 64% | 73% | 73% |
| $P_{sens}$ | 72% | 61% | 61% | 61% |
| $P_{spec}$ | 77% | 92% | 85% | 81% |

Using optimum $p_o$ based on cost function $C_1(p_o,w_1,w_2)$ with $w_1 = w_2 = 1$ and $w_1 = 1, w_2 = 3$:

| $p_{opt}$ | $M_1 (V^{APC})$ | $M_{II} (V^{APC})$ | $M_{III} (V^{APC})$ |
|-----------|----------------|-----------------|-----------------|
| $P_{CCR}$ | .55-.55 | .38-.39 | .27-.28 |
| $P_{sens}$ | 72% | 72% | 78% |
| $P_{spec}$ | 85% | 81% | 73% |

Using optimum $p_o$ based on cost function $C_2(p_o,\eta_1,\eta_2)$ with $\eta_1 = \eta_2 = 0.5$ and $\eta_1 = 3, \eta_2 = 0.7$:

| $p_{opt}$ | $M_1 (V^{APC})$ | $M_{II} (V^{APC})$ | $M_{III} (V^{APC})$ |
|-----------|----------------|-----------------|-----------------|
| $P_{CCR}$ | .54-.55 | .82-.85 | .61-.69 |
| $P_{sens}$ | 72% | 56% | 56% |
| $P_{spec}$ | 85% | 100% | 100% |

Table 17: The correct classification rates ($P_{CCR}$), sensitivity ($P_{sens}$), and specificity ($P_{spec}$) percentages for the classification procedures based on models $M_1 (V^{APC}) - M_{III} (V^{APC})$ using APC in hippocampal volumes with threshold probabilities $p_o = 1/2$ and $p_o = 18/44$ (top); with optimum threshold values $p_o = p_{opt}$ based on the cost function $C_1(p_o,w_1,w_2)$ with $w_1 = w_2 = 1$ and $w_1 = 1, w_2 = 3$ (middle); and with optimum threshold values $p_o = p_{opt}$ based on the cost function $C_2(p_o,\eta_1,\eta_2)$ with $\eta_1 = \eta_2 = 0.5$ and $\eta_1 = 3, \eta_2 = 0.7$ (bottom). The model with the best classification performance is marked with an asterisk (*).

| $p_o = 1/2$ | $p_o = 18/44$ |
|-----------------|-----------------|
| $M_1 (D^{APC})$ | $M_1 (D^{APC})$ |
| $M_{II} (D^{APC})$ | $M_{II} (D^{APC})$ |
| $M_{III} (D^{APC})$ | $M_{III} (D^{APC})$ |
| $P_{CCR}$ | 59% | 61% | 61% | 64% |
| $P_{sens}$ | 27% | 28% | 28% | 72% |
| $P_{spec}$ | 81% | 85% | 85% | 46% |

Using optimum $p_o$ based on cost function $C_1(p_o,w_1,w_2)$ with $w_1 = w_2 = 1$ and $w_1 = 1, w_2 = 3$:

| $p_{opt}$ | $M_1 (D^{APC})$ | $M_{II} (D^{APC})$ | $M_{III} (D^{APC})$ |
|-----------|----------------|-----------------|-----------------|
| $P_{CCR}$ | .45 | .45-.46 | .41 |
| $P_{sens}$ | 66% | 66% | 66% |
| $P_{spec}$ | 61% | 61% | 73% |

Using optimum $p_o$ based on cost function $C_2(p_o,\eta_1,\eta_2)$ with $\eta_1 = \eta_2 = 0.5$ and $\eta_1 = 3, \eta_2 = 0.7$:

| $p_{opt}$ | $M_1 (D^{APC})$ | $M_{II} (D^{APC})$ | $M_{III} (D^{APC})$ |
|-----------|----------------|-----------------|-----------------|
| $P_{CCR}$ | .45 | .45-.46 | .32 |
| $P_{sens}$ | 66% | 66% | 89% |
| $P_{spec}$ | 69% | 69% | 46% |

Table 18: The correct classification rates ($P_{CCR}$), sensitivity ($P_{sens}$), and specificity ($P_{spec}$) percentages for the classification procedures based on models $M_1 (D^{APC}) - M_{III} (D^{APC})$ using APC in hippocampal LD-DMM metric distances with threshold probabilities $p_o = 1/2$ and $p_o = 18/44$ (top); with optimum threshold values $p_o = p_{opt}$ based on the cost function $C_1(p_o,w_1,w_2)$ with $w_1 = w_2 = 1$ and $w_1 = 1, w_2 = 3$ (middle); and with optimum threshold values $p_o = p_{opt}$ based on the cost function $C_2(p_o,\eta_1,\eta_2)$ with $\eta_1 = \eta_2 = 0.5$ and $\eta_1 = 3, \eta_2 = 0.7$ (bottom). The model with the best classification performance is marked with an asterisk (*).
Table 19: The correct classification rates (P_{CCR}), sensitivity (P_{sens}), and specificity (P_{spec}) percentages for the classification procedures based on models $M_I (V^{APC}, D) - M_{III} (V^{APC}, D)$ using metric distance, and APC in hippocampal volumes with threshold probabilities $p_o = 1/2$ and $p_o = 18/44$ (top); with optimum threshold values $p_o = p_{opt}$ based on the cost function $C_1(p_o, w_1, w_2)$ with $w_1 = w_2 = 1$ and $w_1 = 1$, $w_2 = 3$ (middle); and with optimum threshold values $p_o = p_{opt}$ based on the cost function $C_2(p_o, \eta_1, \eta_2)$ with $\eta_1 = \eta_2 = 0.5$ and $\eta_1 = 0.3$, $\eta_2 = 0.7$ (bottom). The model with the best classification performance is marked with an asterisk (*).
Using optimum \( p_o \) based on cost function \( C_1(p_o, w_1, w_2) \) with

\[
\begin{array}{cccc}
\eta_1 = \eta_2 = .5 & \eta_1 = .3, \eta_2 = .7 \\
\hline
M_I (V, V^{APC}, D) & M_{II} (V, V^{APC}, D)^* & M_{III} (V, V^{APC}, D) & M_I (V, V^{APC}, D) \\
\hline
\end{array}
\]

Using optimum \( p_o \) based on cost function \( C_2(p_o, \eta_1, \eta_2) \) with

\[
\begin{array}{cccc}
\eta_1 = \eta_2 = .5 & \eta_1 = .3, \eta_2 = .7 \\
\hline
M_I (V, V^{APC}, D) & M_{II} (V, V^{APC}, D)^* & M_{III} (V, V^{APC}, D) & M_I (V, V^{APC}, D) \\
\hline
\end{array}
\]

Table 20: The correct classification rates (\( P_{CCR} \)), sensitivity (\( P_{sens} \)), and specificity (\( P_{spec} \)) percentages for the classification procedures based on models \( M_I (V, V^{APC}, D) - M_{III} (V, V^{APC}, D) \) using metric distance, and APC in hippocampal volumes with threshold probabilities \( p_o = 1/2 \) and \( p_o = 18/44 \) (top); with optimum threshold values \( p_o = p_{opt} \) based on the cost function \( C_1(p_o, w_1, w_2) \) with \( w_1 = w_2 = 1 \) and \( w_1 = 1, w_2 = 3 \) (middle); and with optimum threshold values \( p_o = p_{opt} \) based on the cost function \( C_2(p_o, \eta_1, \eta_2) \) with \( \eta_1 = \eta_2 = 0.5 \) and \( \eta_1 = .3, \eta_2 = 0.7 \) (bottom). The model with the best classification performance is marked with an asterisk (*)
Figure 1: Change in metric distance during diffeomorphic flow from template ($I_0$) to target ($I_1 = \phi_1 I_0 = I_0 \circ \phi_1^{-1}$).
Figure 2: Generation of metric distances $d_{k}^{(b,f)}$ for subjects $k = 1, \ldots, 44$ at baseline ($b$) and at follow-up ($f$).
Figure 3: Pairs plots of the continuous variables for the hippocampi at baseline and follow-up. HLV: volume of left hippocampus; HRV: volume of right hippocampus; HLM: metric distance for left hippocampus; HRM: metric distance for right hippocampus; BV: brain volume; ICV: intracranial volume. The numbers 1 and 3 stand for year 1 (i.e., baseline) and year 3 (i.e., follow-up), respectively.
Figure 4: Scatter plots of the metric distances for the left and right distances at baseline and follow-up. The metric distances are jittered for better visualization and the crosses represent the mean distance values.

Figure 5: The left interaction plot is for diagnosis levels over the timepoint levels (the effect of sides is ignored). The slope (i.e., the rate of change in morphometry for CDR0.5 subjects) is significantly larger than that of CDR0 subjects. The right interaction plot for side levels over the timepoint levels (the effect of diagnosis is ignored). The slopes seem to not significantly differ between Left and Right hippocampi.
Figure 6: Interaction plots for diagnosis levels over the timepoint levels for left and right metric distances. Although the slopes are different for both left and right hippocampi, the difference in the right seems to be much larger.

Figure 7: Empirical cdfs of the metric distances for the CDR0.5 vs CDR0 Left and Right hippocampus at follow-up.
Figure 8: Fitted probability for having mild dementia (CDR0.5) and observed proportion in metric distances with model (9) (top-left); model (10) (top-right); and model (11) (bottom),