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Geodesic distance on a Grassmannian for monitoring the progression of Alzheimer's disease

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ABSTRACT

We propose a geodesic distance on a Grassmannian manifold that can be used to quantify the shape progression patterns of the bilateral hippocampi, amygdalas, and lateral ventricles in healthy control (HC), mild cognitive impairment (MCI), and Alzheimer's disease (AD). Longitudinal magnetic resonance imaging (MRI) scans of 754 subjects (3092 scans in total) were used in this study. Longitudinally, the geodesic distance was found to be proportional to the elapsed time separating the two scans in question. Cross-sectionally, utilizing a linear mixed-effects statistical model, we found that each structure's annualized rate of change in the geodesic distance followed the order of AD > MCI > HC, with statistical significance being reached in every case. In addition, for each of the six structures of interest, within the same time interval (e.g., from baseline to the 6th month), we observed significant correlations between the geodesic distance and the cognitive deterioration as quantified by the ADAS-cog increase and the MMSE decrease. Furthermore, as the disease progresses over time, this linkage between the inter-shape geodesic distance and the cognitive decline becomes considerably stronger and more significant.

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative brain disorder that is mainly characterized by both memory loss and cognitive decline and which usually succeeds from mild cognitive impairment (MCI). MCI is considered as an intermediary stage between normal aging and dementia. Patients who have reached this MCI stage are known to incur a very high risk of progressing to probable AD (Morris et al., 2001). From observations of this progression, we know that the medial temporal lobe (MTL) structures of the human brain, including the hippocampus, the amygdala, and the entorhinal cortex, are affected the earliest and the most severely in the neuropathology of AD (Hyman et al., 1984), exhibiting significant degrees of atrophy that occur at elevated rates in both MCI and AD compared to those induced by normal aging (Du et al., 2001; Jack et al., 1997; Krasuski et al., 1998; Laakso et al., 1995). Due to the spatial adjacency of the lateral ventricle (LV) to those MTL structures, LV enlargement is a consistent observation across a variety of AD studies (Chetelat and Baron, 2003; McKhann et al., 1984; Ridha et al., 2008). Such an exploration of the MTL structures and the LV in the neuropathology of AD has largely been facilitated by the advent of modern magnetic resonance imaging (MRI) techniques.

With the development of specialized, geometry-based, mathematical tools that can be utilized in the analysis of MRI, in conjunction with traditional volumetric analysis, shape analyses of MTL structures and of the LV have gained substantial popularity in the investigation of AD, with a large number of innovative results being obtained by multiple research groups (Apostolova et al., 2006; Csernansky et al., 2005; Frisoni et al., 2008; Miller et al., 2015; Qiu et al., 2009; Scher et al., 2007; Tang et al., 2014, 2015a, 2015b, 2015c; Thompson et al., 2004). In contrast to the volumetric measurement, shape morphometrics can not only quantify brain tissue loss but also characterize more detailed localized morphometric abnormality patterns.

The general approach in shape analysis is to identify a localized morphometric quantity (a scalar or a vector at each vertex of the structural surface of interest), such as the vertex-wise surface area and

Abbreviations: AD, Alzheimer's Disease; MCI, Mild Cognitive Impairment; HC, Healthy Control; MTL, Medial Temporal Lobe; LV, Lateral Ventricle; MRI, Magnetic Resonance Imaging; ROI, Region of Interest; ADAS-cog, Alzheimer's Disease Assessment Scale-Cognitive Behavior Section; MMSE, Mini Mental State Examination; ADNI, Alzheimer's Disease Neuroimaging Initiative; CDR, clinical dementia rating; CDR-SOB, clinical dementia rating scale sum of boxes

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the vertex-wise deformation factor, and to perform statistical analyses (cross-sectional or longitudinal) on that vertex-based quantity. An alternative approach is to identify a metric (distance) between two shapes upon which statistical analyses, such as cross-sectional group comparisons, disease-versus-normal classifications, and regressions, can then be conducted. A variety of shape metrics have been proposed and applied in brain morphometry analyses, such as the diffeomorphic metric distance in the setting of large deformation diffeomorphic metric mapping (Ceyhan et al., 2012; Feng et al., 2013; Miller et al., 2002; Yang et al., 2012) and the Wasserstein Distance (Su et al., 2015).

Over the past few decades, researchers have actively pursued the modeling of shapes that are invariant under a given type of transformation by building a shape space (Bryner et al., 2014; Dryden, 1998; Fletcher et al., 2009; Jayasumana et al., 2013; Kendall, 1984; Le and Kendall, 1993; Lele and Richtsmeier, 2001; Pennec et al., 2006; Small, 1996; Swann and Olsen, 2003; Younes, 2012). A space formed from shapes that are invariant under such a carefully-defined group of transformations has the underlying geometrical structure of a manifold. For example, when considering affine transformations, the shape space is a Grassmannian manifold and a shape thus becomes a point on this Grassmannian manifold (Begelfor and Werman, 2006; Gui et al., 2016; Patrangenaru and Mardia, 2003; Sepiashvili et al., 2003; Srivastava et al., 2005; Turaga et al., 2011). In fact, in our approach, we will focus on shapes distorted by affine transformations, since affine transformations well approximate the general projective transformations, and we will study the shape space in the framework of Grassmannian manifolds. For any individual MRI scan, we can represent any one of its anatomical regions of interest (ROIs), such as the left hippocampus, with a set of N landmarks. We refer to these N landmarks as the configuration of that anatomical ROI. This configuration may change when the MRI scans are taken from different viewpoints. In longitudinal studies, for it to be feasible to compare different scans of the same individual, we must factor out the distortions within the configurations of the anatomical ROI induced by the particular viewpoint from which that MRI scan was acquired. We model these distortions with affine transformations that may account for, say, rotation, stretching, scaling, or other effects. As such, the affine-invariant geometric structure extracted from the configuration of an anatomical ROI in an MRI scan is defined as the shape of that ROI. By making this identification, we have guaranteed that the shape remains the same regardless of viewpoint. We recall that the shape, as a point on the Grassmannian, is a vector space. In fact, under this definition, the shape of a specific anatomical ROI can be represented as a 3-dimensional linear subspace in $\mathbb{R}^N$, and thus a point on the Grassmannian $Gr(3, N)$. To compare the shapes of a specific ROI across longitudinal time points, we need to introduce a measure of similarity (or dissimilarity). If we were comparing the shapes in the standard Euclidean space $\mathbb{R}^3$, then a reasonable similarity measure would be the Euclidean distance between the landmark sets configuring different scans. Given that the shapes representing different longitudinal scans are now points on the Grassmannian, we adopt, as the distance between two shapes, the distance between the two points on our Grassmannian manifold. A variety of such metrics exist, such as the Procrustes distance (Turaga et al., 2011), the Projection metric (Edelman et al., 1998), and the Binet-Cauchy metric (Wolf and Shashua, 2003). In this work, we adopt a geodesic-based distance (Gui et al., 2016) and explore its practical application to the comparison of ROI shapes across longitudinal time points. We will demonstrate the applicability of this geodesic distance as a similarity (or dissimilarity) measure in the analysis of structural shape variation over time and the relative impact of disease states upon the patterns thereof.

In summary, we investigate the use of a geodesic distance defined on the Grassmannian manifold to study, both longitudinally and cross-sectionally, the shape of the hippocampus, the amygdala, and the LV in both hemispheres along with its relevance to the progression of AD. The primary goal of this paper is to quantitatively assess whether or not the rates of change in this geodesic distance vary significantly as a function of disease severity during the progression towards AD. In addition to these cross-sectional comparisons, we also examine the potential of using this geodesic distance on the Grassmannian as a surrogate biomarker of AD. A biomarker would not be useful in clinical applications if it could not be significantly linked with cognitive declines (Black, 1999). Therefore, we statistically quantify how the changes in this geodesic distance between shapes of a structure of interest link with changes in cognitive measures.

We utilize two of the most prominent cognitive measures in the study of AD, the Alzheimer's Disease Assessment Scale-Cognitive Behavior Section (ADAS-cog) (Rosen et al., 1984) and the Mini Mental State Examination (MMSE) (Folstein et al., 1975). ADAS-cog measures a number of cognitive domains, including components of memory, language, and praxis; it is scored from 0–70 with higher values indicating greater cognitive impairment. MMSE provides a continuous scale to assess primary cognitive functions that are affected by the dementia of the Alzheimer type, including orientation, registration, attention, recall, language and constructional praxis. The MMSE score ranges from 0–30 and, in contrast to ADAS-cog, lower MMSE scores indicate more severe cognitive impairment.

In this study, we use data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) study, including a total of 210 healthy control (HC) subjects, 369 MCI subjects, and 175 AD subjects at baseline, each with a sequential MRI dataset obtained over 6- or 12-month intervals within a follow-up period of 6–36 months, resulting in a total of 3092 scans included in the analysis. From this data we aim to extract the following results: (1) the mean and standard deviations of the geodesic distance, for the shape of each of the six structures of interest (left and right hippocampus, amygdala, and lateral ventricle), between the baseline shape and that of each follow-up scan as computed across the subjects of each of the three clinical groups, allowing direct longitudinal and cross-sectional comparisons; (2) the outcome of group comparisons, in terms of each structure's rate of change in the geodesic distance, between HC and MCI as well as HC and AD via a linear mixed-effects statistical model; (3) the annualized rates of change in the geodesic distance for each structure of interest, in each of the three groups, as estimated from the linear mixed-effects model after removing co-variate effects; (4) the statistical associations (in terms of both strength and significance) between the geodesic distance and changes in the two AD-related cognitive measure (ADAS-cog and MMSE) within 6 months, 12 months, 18 months, 24 months, and 36 months from the baseline for each of the six structures of interest within the whole group (all three cohorts combined). We also quantitatively evaluate the computational efficiency of obtaining this geodesic distance as a potential surrogate biomarker for AD.

2. Material and methods

2.1. Alzheimer's Disease Neuroimaging Initiative

Data used in preparation of this manuscript were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the Food and Drug Administration, private pharmaceutical companies and non-profit organizations, as a $60 million, 5-year public-and-private partnership. The primary goal of ADNI has been to test whether serial MR imaging, positron emission tomography, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials.

The Principal Investigator of this initiative is Michael W. Weiner,