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Clinical Study

Structural neuroimaging correlates of cognitive status in older adults: A person-oriented approach

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ABSTRACT

Person-oriented approaches to clinical research aim to uncover subgroups of patients with different patterns of clinically relevant variables. Such approaches, however, are not yet widely employed in clinical neuroimaging research. This paper demonstrates an accessible approach to person-oriented research using model-based clustering in high-dimensional structural neuroimaging data. Cortical thickness measurements for 369 older adults (182 women, 187 men) were obtained from the Alzheimer's Disease Neuroimaging Initiative. Model-based cluster analysis was performed on these imaging variables and then validated using variables that were not used in the clustering process. Variable selection identified two specific regions that contributed to cluster formation: the left and right entorhinal cortices. Two subgroups were uncovered: a "typical" cluster with higher entorhinal thickness (M = 3.59 mm, 95% confidence interval = 3.57, 3.62), and an "atypical" cluster with relatively lower thickness (M = 2.84 mm, 95% confidence interval = 2.75, 2.92). Members of the atypical cluster also had lower hippocampal volumes, memory scores, and executive function scores, and were also more likely to be clinically classified as cognitively impaired. These findings demonstrate the utility of model-based clustering of structural neuroimaging data in studies of ageing. The role of the entorhinal cortices in cluster formation is consistent with the known pathological substrate of Alzheimer's disease. The entorhinal cortices are implicated in the early genesis of the disease and atrophy of these regions is strongly associated with the cognitive phenotype. Overall, this approach can be readily applied to future neuroimaging investigations.

1. Introduction

Analytical approaches to human inquiry can be classified as either variable or person oriented. The aim of variable-oriented research is to identify relationships between variables, such as the relationship between a clinical variable (for example, diagnostic status) and a neuroimaging marker (for example, grey matter volume). In this approach, the individual is viewed as a "data carrier", and the interest is in the inter-relations between the variables at the aggregate level [1]. This approach is typical for the analysis of neuroimaging data, where techniques such as group comparisons, correlations, and the general linear model predominate. In contrast, the aim of person-oriented research is to identify patterns or groupings of individuals under the assumption that the study sample might be drawn from multiple populations. Statistical techniques such as cluster analysis are typical for this approach to research.

Person-oriented approaches are yet to be employed extensively in neuroimaging research. One reason for this involves the high-dimensional nature of neuroimaging data. Cortical thickness data, for example, typically contains >100 datapoints for each participant [2]. While there are now techniques readily available to analyse such data in a person-oriented framework, they have yet to permeate into the neuroimaging community. The aim of this paper is to introduce the concept of person-oriented research in neuroimaging, and demonstrate its application to high-dimensional structural imaging data. Readily available software packages are used [3,4], which make the uptake of this approach relatively straightforward.

Von Eye and Bogat [5] describe three criteria for person-oriented research. First, an underlying assumption of the analysis is that the sample was drawn from more than one population.

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[1] Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-cont.

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Statistical techniques are used to identify different groups within the data that are characterised by different patterns of variables. The second criterion involves the validation of the different groupings. To avoid circularity, it is essential to use variables that were not used to form the groupings. In the case of neuroimaging data, phenotypic data are often suitable candidates. Finally, the groupings must be interpreted in the context of a theory. In the case of neuroimaging in neurodegenerative disease, the known pathological substrate provides this context.

This study used data from a large Alzheimer's disease (AD) study containing participants with varying degrees of cognitive function. The advantage of using this population is that there are likely to be structural changes in some participants, driving cluster formation [6]. The known pathological substrate of the disease provides a framework for interpreting the findings, and the associated measures of cognitive impairment provide a means of validating the cluster solution. As described in detail below, this study used a stepwise variable selection approach to reduce the number of variables used for clustering. Cluster analysis was then performed using a validated model-based approach [7]. These approaches overcome the challenges of high-dimensional data and facilitate the objective selection of the number of clusters to extract [8]. This approach has been successfully applied in the analysis of high-dimensional genetic data [9]. Given the known distribution of pathology in AD, it was predicted that clustering information will be encoded in the mesial temporal, parietal, and posterior cingulate structures [10–12]. Groups with greater atrophy were expected to have lower scores on cognitive measures, and would be more likely to carry a clinical diagnosis of cognitive impairment.

2. Material and methods

2.1. Participants

The data used in this study were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. The ADNI was launched in 2003 by the USA National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the Food and Drug Administration, private pharmaceutical companies and non-profit organisations, as a US$60 million, 5 year public–private partnership. The primary goal of ADNI has been to test whether serial MRI, positron emission tomography, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early AD. Determination of sensitive and specific markers of 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. ADNI is the result of efforts of many co-investigators from a broad range of academic institutions and private corporations, with subjects recruited from over 50 sites across the USA and Canada. The initial target for ADNI was to recruit 800 adults, age 55 to 90 years, to participate in the research, approximately 200 cognitively normal older individuals to be followed for 3 years, 400 people with MCI to be followed for 3 years and 200 people with early AD to be followed for 2 years (for more information, see www.adni-info.org).

The ADNI database was queried for all participants who underwent structural imaging at the 12 month timepoint. This timepoint was chosen essentially arbitrarily, except with the aim of maximising the number of patients included in the analysis. Only patients with complete demographics, cognitive, and neuroimaging data were included. Cases that failed strict quality control procedures were excluded. The study sample comprised 369 participants (182 women, 187 men). One hundred and nineteen (32.2%) were classified as having no dementia, 223 had questionable dementia (60.4%), 23 had mild dementia (6.2%), and four had moderate dementia (1.1%). Full subject characteristics are shown in Table 1.

Table 1
Participant characteristics from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database

Measure	Mean (95% CI)	Min	Max
Age, years	72.59 (71.88, 73.31)	56	90
MMSE	27.73 (27.44, 28.03)	13	30
ADAS-Cog	8.84 (7.85, 9.12)	1	38
FAQ	3.19 (2.63, 3,75)	0	29
Memory composite	0.53 (0.45, 0.61)	−2.58	2.77
Executive function composite	0.49 (0.40, 0.59)	−2.19	2.57

ADAS-Cog = Alzheimer's Disease Assessment Scale, CI = confidence interval, FAQ = Functional Assessment Questionnaire, max = maximum, min = minimum, MMSE = Mini Mental Status Examination.

2.2. Neuroimaging data

Structural neuroimaging data were downloaded from the ADNI database. Cortical thickness estimates were performed by investigators at The University of California, San Francisco, USA (full details of this analysis are available on the ADNI website: http://adni.loni.usc.edu/methods/mri-analysis). Non-accelerated T1 structural images (either multiplanar reconstruction or inversion recovery spoiled gradient echo) were analysed following preprocessing that included gradient warping, B1 correction, and N3 inhomogeneity correction. Cortical thickness estimates were obtained using the open source FreeSurfer software (version 5.1) [13]. Quality control procedures were followed, and only metrics that passed were included in the analysis. Mean thickness measurements for 34 cortical regions were extracted for each hemisphere [14]. Hippocampal volume measurements computed by the FreeSurfer subcortical pipeline were also downloaded in order to validate the clustering solution. Estimates of intracranial volume were also obtained from the FreeSurfer output.

2.3. Clinical variables

A number of clinical variables were extracted in order to validate the clustering solution and to characterise the resulting subgroups. These include the Mini Mental Status Examination [15], a cognitive screening measure where higher scores indicate better cognitive function. Another screening measure, the Alzheimer's Disease Assessment Scale [16] was also used. On this scale, higher scores indicate greater impairment. The Functional Assessment Questionnaire [17] provided a measurement of impairments in activities of daily living, where higher scores indicate greater impairment. For diagnostic characterisation, the Clinical Dementia Rating scale [18] was used. This clinician-rated scale classifies patients as either having no dementia, questionable dementia, mild dementia, or moderate dementia. Validated composite scores of memory and executive function were used, and are described in detail elsewhere [19,20].

2.4. Variable selection and model-based clustering

Variable selection was performed using the *clustvarsel* package in the R environment [3]. This package implements the variable selection procedure first described by Raftery and Dean [21] and subsequently extended by Maugis and colleagues [22,23]. Briefly, the algorithm begins with a set of variables and then assesses a new variable for exclusion or removal based on the Bayesian information criteria (BIC). This process is repeated until a final set of