MRI-Based Pattern Recognition Methods for Dementia Diagnostics

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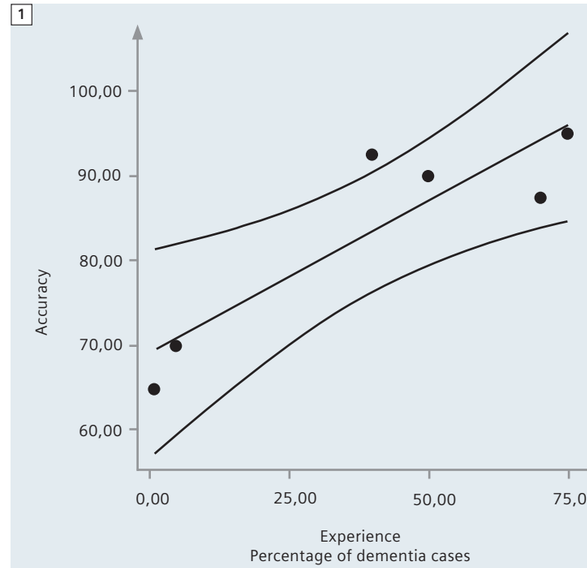
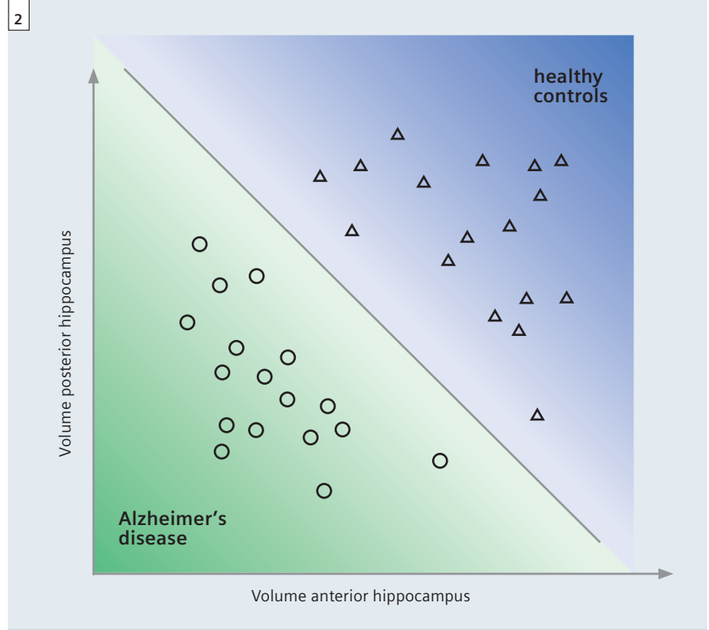
It is estimated that the number of people that will suffer from dementia by 2020 will be more than 40 million, with an increasingly higher proportion coming from developing countries [8]. Historically, brain imaging with CT or MRI has largely been used to rule out alternative and especially structural causes of the dementia syndrome. This approach is consistent with established diagnostic consensus criteria such as those published by the NINCDS-ADRDA [14]. Recently, there has been a realisation that MRI may add positive predictive value to a diagnosis of Alzheimer's disease (AD) [9]. Several studies demonstrate that using MRI to evaluate atrophy of temporal lobe structures can contribute to diagnostic accuracy [2, 22], but these findings have yet to be applied to routine clinical radiological practice, let alone in the general practice or internal medicine setting [22]. Recent developments in machine-learning analysis methods and their application to neuroimaging [4–7, 10, 11, 13, 15, 18–21] are very encouraging in relation to the levels of diagnostic accuracy achievable in individual patients. These multivariate methods promise fully-automated, standard PC-based clinical decisions, unaffected by individual neuroradiological expertise which strongly affects diagnostic accuracy (Fig. 1). They are sufficiently sensitive to successfully separate those with mild cognitive impairment (MCI [16]) from the cognitively normal [3] or identify those cognitively normal subjects who will convert to MCI [4]. So far, computational anatomy has been used to characterise differences between the brains of patients and normal age-matched volunteers at the group level. What is needed in the clinical setting is a diagnostic method applicable to each and every individual. Multivariate classification methods such as linear support vector machines (SVM) integrate information from the whole brain. In the context of machine learning, individual MR images are treated as points located in a high dimensional space. Figure 2 illustrates this procedure in an imaginary two-dimensional space: In this example the two groups to be classified are represented by circles and triangles. It can be seen that the groups cannot be separated on the basis of values along one dimension only and that only a combination of the two leads to adequate separation. The space used for classifying image data is of much higher dimension; the total number of dimensions is determined by the numbers of voxels in each MR image. Related methods have been introduced to aid in breast cancer screening where they are applied to 2D X-rays and are now part of the diagnostic workup. With the advent of faster computer hardware, an accurate spatial transformation of the individual scan to a standard template is possible within minutes.



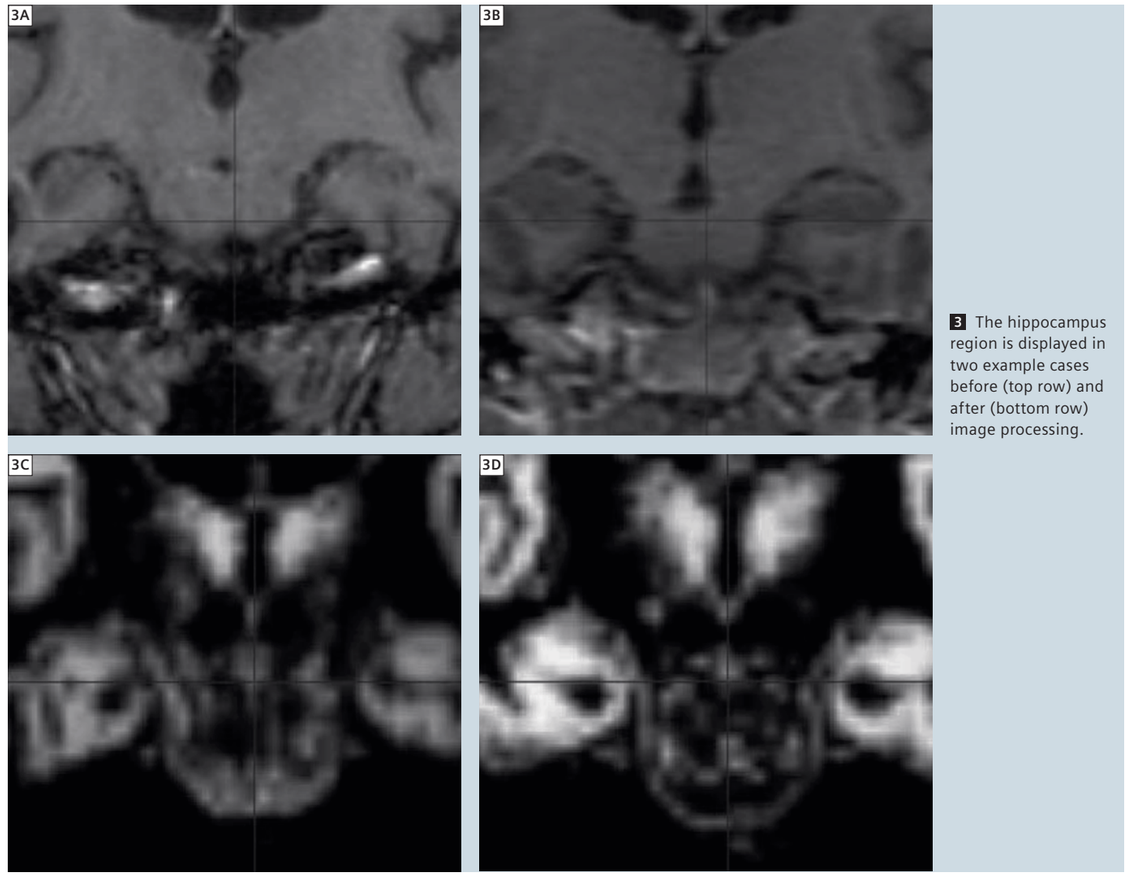
1 Shows an increasing accuracy of radiologists more experienced in the diagnosis of dementia [10].



2 Concept of multivariate classification methods in a 2D example.

Image processing pipeline

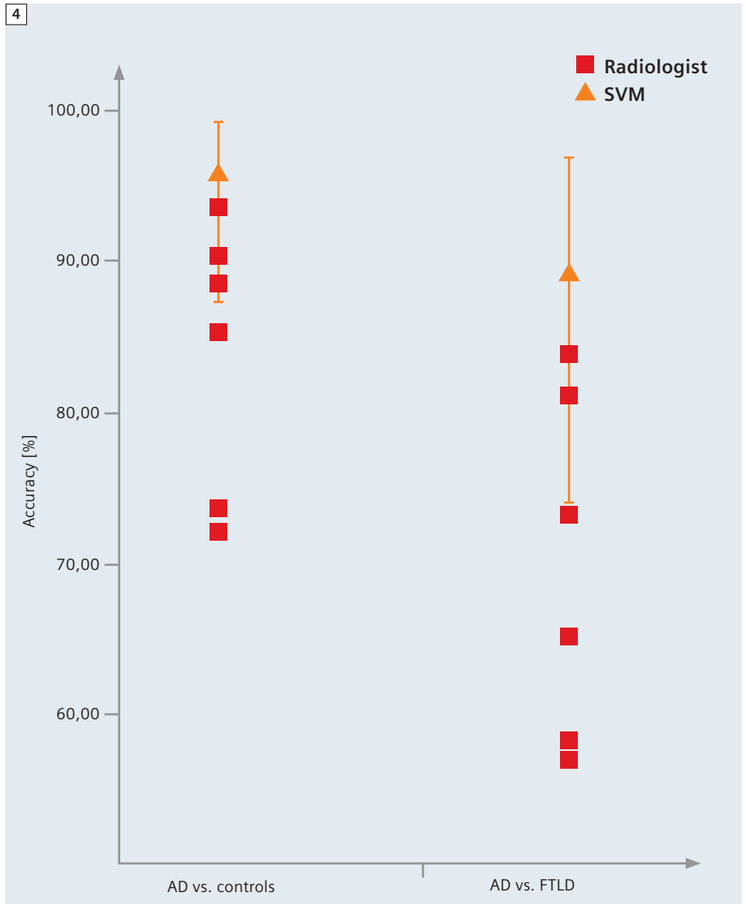
To apply classification methods successfully it is critical to extract relevant information from the MRI-scan. Figure 3 magnifies the hippocampus area in



3 The hippocampus region is displayed in two example cases before (top row) and after (bottom row) image processing.

two example cases. An observer with some experience may well be able to identify the more atrophic medial temporal lobe areas in figure 3C. Looking at the same images from the feature extraction perspective, it becomes obvious that there are substantial differences between both images, (e.g. regarding brightness, anatomy of the ventricles or differences in non-brain structures) that are unrelated to the diagnostic problem. Those are therefore a source of noise.

Several strategies exist to reduce noise and extract relevant information. Most include a segmentation into grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF) followed by a spatial normalisation of the GM segment to a template. A separate 'modulation' step [1] ensures that the overall amount of each tissue class remains constant after normalization. The bottom row in figure 3 depicts the same two cases as the top row but after applying the preprocessing steps. The brightness of a voxel now codes the local GM volume and the reduced brightness in figure 3C can easily be identified by an automated method.



4 Diagnostic accuracy of radiologists compared to an SVM when separating Alzheimer's Disease (AD) from either healthy controls or cases with fronto-temporal lobar degeneration (FTLD).

Applying the support vector machine

In practical terms, a linear kernel matrix is created from normalised GM segmented images. To this end, each MRI scan undergoes a pair-wise multiplication with all other scans. Each element in the kernel matrix is therefore a dot product of two images. Intuitively, the kernel matrix can be viewed as a similarity measure among subjects belonging to a characterised group. Each scan is effectively treated as coordinate in a high dimensional space and the location is determined by the intensity value at each voxel. The images do not span the whole high dimensional space, but rather cluster in subspaces containing images that are very similar. This is one reason why image normalization into a standard space is an important preprocessing step. Good spatial normalization will tighten clustering and reduce dimensionality.

The use of a support vector machine (SVM) for image classification is an example of a linear discrimination. In the basic model it is a binary classifier, which means it divides the space into which the MR images are distributed into two classes by identifying a separating hyper-plane. In a simple two dimensional space, the boundary is represented by a line, but is called a hyperplane in higher dimensional space. Fisher's linear discriminate analysis or linear perceptrons can both identify linear discriminant hyperplanes. However, the motivation behind using an SVM is that it uses the principle of 'structural risk minimization', which aims to find a hyperplane that maximizes the distance between training classes (see Figure 2). Intuitively, it can be seen that the optimal separating hyperplane (OSH) produced by an SVM is defined by those voxels that are closest to the separating boundary between them, i.e., the voxels that are most ambiguous. These voxels are called the 'support vectors'. Voxels that are further away from a separating boundary are distinctively different, hence are not used to calculate the OSH. This fact suggests that adding more images to a training set will have little effect on an OSH if they are distant from it.

After training, an OSH contains learned differences between classes – in our case, AD and control images. That information is then used to assign any new image to its appropriate class (leave-one-out method). This procedure iteratively leaves successive images out of training for subsequent class assignation until each had been used in this way. This validation procedure ensures that a trained SVM can generalize and be used on scans that have never been presented to the SVM algorithm previously.

Clinical applications

We have recently shown that mild to moderately affected individuals with AD and controls can be correctly assigned to their respective group with an accuracy of 95% and a sensitivity of 100%, even when scans come from different scanners to those used to generate the discriminant model that differentiates the categories [11]. A similar accuracy was found when diagnosing two forms of dementia, AD and fronto-temporal lobar degeneration (FTLD), using such computer-based analyses [11]. This performance compares well to that achieved by experienced neuroradiologists [10] (see figure 4). Our preliminary analysis indicates that around 20 subjects per diagnostic group are required to achieve reasonably good performance [12].

Roadmap for future developments

These results have a number of implications that suggest a general adoption of computer-assisted methods for MRI scan-based dementia diagnosis should be seriously considered. The most important of these are:

a) improving diagnosis in places where trained neuroradiologists or cognitive neurologists are scarce;

b) increasing speed of diagnosis without compromising accuracy by eschewing lengthy specialist investigations; and

c) recruitment of clinically-homogeneous patient populations for pharmacological trials. The following steps should be taken before wide application:

1. Establishment of precise classification techniques with well-established test criteria such as sensitivity and specificity values for each disease and the question under study.
2. Creation of a large database with cases from a high number of disorders diagnosed with certainty.
3. Further optimisation of the ability to combine data from different scanners. Despite encouraging results, scanner differences have effects on imaging [17] and should be corrected if possible.
4. Comparison of present gold standard methods for MRI-based classification methods and examination of combinations of methods.
5. Conclusion as to whether classification methods are capable of creating new gold standards, given limited resources.
6. Implementation of all required image processing steps on the MRI console to facilitate integration into the clinical workflow.

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