Clinical Morphometry

The application of advanced image analysis methods allows the clinician to use MRI scans to obtain quantitative measurements of tissue properties and compare these properties with normative values. These investigations can complement and enhance the standard visual inspection of MRI data, allowing for improved diagnosis, prognosis and overall patient management. They also provide an objective statistical framework for formal evaluation of the utility of different MRI-based imaging modalities. Traditional morphometric methods have typically required manual input from a trained operator. More recent methods are either completely or semi-automated. Automated methods allow for more extensive investigation of morphometric changes beyond a limited set of predefined brain regions, and overcome issues with test-retest variability, and, particularly in the clinical setting, bias due to lack of being blind to patient status. For use in the clinic, any technique should be assessed for sensitivity and specificity, preferably using methods that cover a range of sensitivity thresholds such as an ROC (receiver-operating characteristic) analysis. Clinical morphometric methods will be discussed in reference to investigations of neurological changes associated with epilepsy.

There are a number of image analysis techniques available for the clinical researcher. Some of the more widely used methods are listed below.

1. Hippocampal volumetry can be used to detect hippocampal atrophy. High resolution whole brain T1-weighted MRI is acquired, with coronal slices acquired orthogonal to the long axis of the hippocampus. The hippocampus may be segmented manually by a trained operator or automatically using software. A number of software based methods now exist for automated segmentation. The volume of the hippocampus is typically corrected for head size prior to comparison with a control cohort.
2. T2 relaxometry is used to detect changes in image intensity over the brain, indicative of tissue pathology. T2 weighted images are acquired over a range of echo times. Image intensity is fitted voxel-wise to an exponential decay equation and the decay constant (relaxation time) is mapped back onto the image. Regions of interest are placed by a trained operator and the average T2 value compared with controls.
3. Cortical thickness analysis can be used to locate cortical abnormalities. High resolution whole brain T1-weighted MRI is acquired. A series of image processing steps are applied to generate a map of the thickness of the cortex over the whole brain. Two methods are in common use; (i) surface based methods, which model the inner and outer surfaces of the cortical sheet (eg. Freesurfer), and (ii) voxel-based methods, which estimate cortical thickness directly from segmented gray matter (eg A Costa et al), giving a cortical thickness map in the same space as the original MRI scan. Coregistration methods can be used to allow vertex- or voxel-wise comparisons of cortical thickness with an appropriate control cohort.
4. Voxel-based morphometry is used to detect differences in gray matter distribution between groups of subjects. Gray matter is segmented, co-registered using a non-rigid registration method, and smoothed. Voxel-wise comparisons of gray matter concentration or density are then carried out.
5. Voxel-based T2 analysis applies the approach used in voxel-based morphometry to T2 relaxometry imaging data. The method allows for detection of pathological differences over the whole brain (gray matter and white matter), without the limitation to predefined regions, as is the case in T2 relaxometry.

Before a new image analysis method graduates from the research lab to the clinic, a formal investigation of the sensitivity and specificity of the method should be carried out on a relevant patient cohort and control group. The standard method for this assessment is known as receiver-operating characteristic (ROC) analysis. A curve is constructed by plotting the true positive rate versus false positive rate while varying the detection threshold. The area under this curve gives a measure of the quality of the method as a classifier. An area under the curve of 1 means the method is a perfect classifier; an area of 0.5 means the classifier is no better than flipping a coin.

Hippocampal volumetry is used clinically to detect atrophy associated with hippocampal sclerosis in temporal lobe epilepsy, with an aim to identifying a candidate temporal lobe for surgical resection [1]. Manual hippocampal segmentation has been shown to be superior to some publicly available automated hippocampal segmentation methods in temporal lobe epilepsy, particularly in pathological brains [2]. T2 relaxometry is a complementary...
approach to hippocampal volumetry in temporal lobe epilepsy that is useful for identifying a sclerotic hippocampus, and can also be used to probe surrounding structures such as the amygdala and anterior temporal lobe white matter[3–5]. Cortical thickness analysis has been shown to be useful for detection of subtle cortical dysplasia when attempting to identify the epileptogenic zone in intractable epilepsy [6]. Voxel-based morphometry is a similar technique to cortical thickness mapping that can identify subcortical as well as cortical gray matter changes [7]. Voxel-based T2 analysis has been used to demonstrate pathological damage in temporal lobe epilepsy in regions remote from the seizure focus [8], [9].

Application of morphometric image analysis methods to routine clinical imaging can enhance the standard radiological inspection of MRI scans. Some of the more venerable techniques, such as manual hippocampal volumetry and T2 relaxometry, have a reciprocal relationship with visual inspection; for example, hippocampal volumetry can be used as a training aid to establish normal limits for calling hippocampal atrophy in imaging centres that are not experts in diagnosis. A further benefit of hippocampal volumetry and T2 relaxometry are when hippocampal morphological or signal changes are bilateral. In the case of hippocampal volumetrics it should be noted that manual segmentation, in spite of the noted shortcomings, is currently probably superior to automated methods. Although some researchers have reported improved results using the automated approach, to the best of our knowledge there is no “out of the box” hippocampal segmentation software that has been shown to be superior to manual segmentation across imaging centres, image acquisition protocols and pathologies.

The more recent image analysis methods, such as cortical thickness mapping, voxel-based morphometry and voxel-based T2 relaxometry are yet to be widely deployed in the clinic. This is most likely due to a number of factors, including difficulty in implementing acquisition sequences and the additional time required for image processing. Some researchers have noted the relatively poor sensitivity of voxel-based morphometry, for detecting gray matter changes in individual patients [10], [11]. This is likely due in part to the dependence of the sensitivity of the technique to matching the spatial extent of the applied smoothing filter with the spatial extent of the lesion. Reduced sensitivity can result when this condition is not met. Improvements in statistical methods, particularly the use of multivariate statistics in which relationships between voxels/vertices are utilised, are likely to improve the ability of automated morphometric techniques to map anatomical changes in individual patients. Additional benefits for patient classification are likely to result from the investigation of higher order morphometric parameters, such as shape and texture measures [12], [13].

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