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Commentary

Voxel-based morphometry in Alzheimer's patients

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Baxter et al. [7] examine the relationship between commonly used screening cognitive measures with gray and white matter integrity in patients with mild to moderate Alzheimer's disease (AD) using voxel-based morphometry (VBM). The severity of the cognitive impairment is hypothesized to be specific to regions that are affected in AD. Moreover, a correlation study is also performed which assesses the impact of the Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) and Mini Mental Status Examination (MMSE) tests commonly used for diagnosis of dementia. The authors discuss that the two tests correlate differently with volumetric imaging results because they might represent different neural mechanisms of changes observed in AD. Other groups have also studied anatomical changes in AD but, as the authors note, the focus appears to have been on grey matter integrity [6,10].

Voxel-based morphometry, a technique based on the magnetic resonance imaging (MRI) modality, has gained increasing popularity in the past decade or so. In simple terms, VBM involves the following steps. First, MRI scans from all subjects are normalized onto a stereotactic template and the individual 2-D image slices are used to reconstruct the image of the entire brain in 3-D. Then, the 3-D regions of interest (ROIs) are segmented and compared voxel-by-voxel to assess the difference between various groups [5]. A variation of VBM involves segmenting the 2-D MRI scans first and then reconstructing the 3-D image of only the ROI, which is computationally less intensive. VBM provides a means to explore structural changes in various parts of the brain by mapping statistical parameters to MRI scans. VBM is slowly developing into a tool of significant interest for ROI studies of the brain pertaining to various normal and abnormal mental states.

The *classical* ROI studies involve manual tracing of anatomical features of the brain. This manual tracing may also be computer-based but is not automated. However, recent advances in technology have led to novel techniques such as VBM which can be used for such volumetric studies (involving anatomical features) too. In that case, the only difference between a manual tracing-based ROI study and a VBM-based ROI study is the degree of automation. Therefore, we can see that VBM and ROI themselves are not two distinct modalities of investigation. Instead, VBM and manual tracing may be referred to as separate modalities. Our commentary is based on this broader sense of the term *ROI*. For example if we are studying grey matter distribution, then our region of interest would be all areas that show up as grey matter on an MRI scan. Alternatively, if we are interested in areas with increased blood flow in the brain in response to some cognitive task, then all areas that show increased blood flow on the fMRI scan will become our region of interest. Historically, this same

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concept is applied to specific anatomical structures in the brain to obtain anatomical ROIs.

VBM has been used in a number of investigations on patients with schizophrenia [15,16], epilepsy [17], autism [1], Kallmann's syndrome [11], chronic unipolar depression [12], speech and language disorder [14] and others. Yamasue et al. used VBM in nine victims of the Tokyo subway sarin attack with posttraumatic stress disorder (PTSD) and 16 matched victims of the same event without PTSD and found a significant gray-matter volume reduction in the left anterior cingulate cortex in victims with PTSD compare with those without PTSD [18].

Since the technique is still in its infancy, there are two primary problems that need to be resolved (also noted by the authors). The first problem stems from the fact that the shape and size of the human brain and its various components vary from subject to subject. Moreover, even for a single subject, images from any two MRI scanning sessions may not be directly comparable due to variability in the orientation of the head (position, rotation, and angle of inclination) and motion artifacts. Since these variations are intrinsic to the MRI technique on which VBM is based, they have to be statistically built into the experimental design to achieve accurate intra- and inter- subject comparability. Most often, this comparability is achieved by mapping the image of the brain on to a standard stereotactic template. This process is dubbed *registration*. Various registration functions including ones based on deformation and tensors have been used in order to model local changes in brain structure, but with limited success [2, 5,9,13].

The other problem is related to the techniques used by researchers for image smoothing and ROI segmentation into white matter, gray matter, and cerebrospinal fluid (CSF). Researchers in various fields, not just medical imaging and image processing, have been experimenting with smoothing and segmentation algorithms for decades. Although significant advancements have been made in this area, the results and therefore, the conclusions, are very subjective. This is especially true in the case of images of the brain where the amount of detail and complexity involved is very high. There are significant trade-offs at every step especially in the light of computational limitations. For instance, if a higher resolution image is used to obtain a better estimate of an ROI boundary, it comes at the cost of significantly increased imaging artifacts as well as computational burden. If the resolution is reduced, the risk of missing important details in the image is increased. Both cases may result in vastly inaccurate estimates of the size and shape of the ROI. This problem is exacerbated when automated algorithms are used because of their inability to incorporate human feedback. Therefore, most image analysis is still done simultaneously by automated algorithms quantifying various characteristics of the ROI as well as a skilled imaging specialist to ensure the accuracy of the procedure. Decisions regarding resolution, smoothing function, and segmentation algorithm are made on a case by case basis.

The issues discussed above lead to a large degree of variability between independently performed investigations. This causes problems in comparing the results of one study to another. Even within the scope of a particular study, there may be significant variations between results obtained from different images depending on the techniques used. Moreover, it must be kept in mind that conclusions from this study as well as other similar studies are based on differences between the test subjects and normal control subjects. The reliability of the selection of the control population can be an issue since the selection procedure is based on very subjective tests. If the control subjects are not selected carefully, this can add further variability in the experiment. In such a situation, how do we reach a consistent conclusion? In the face of the inherent variability in the experiments, the consensus seems to be that a large number of subjects should be used for the results to be statistically significant. Baxter et al. [7] use a total sample population of 30 subjects, out of which 15 were age and education matched controls with no history of neurological or psychological disorders or significant health problems. The sample size does not seem to be large enough to make general conclusions.

Baxter et al. [7] use a custom template based on their sample population for image registration. On the one hand, this ensures to some extent that age related changes in brain components are taken into consideration. On the other hand, it also ensures that the conclusions from this study are not directly comparable to a similar one performed on a different subject set. However, since this is a study of differences, such a technique is generally accepted. Overall, the conclusions from this study seem to be consistent with that reported in literature. Some new theories are hypothesized but need to be further explored before they can be conclusively accepted. The importance of the study lies primarily in improving the current understanding of AD and the diagnostic tools used in its assessment. The study is an example application of increasingly sophisticated image processing techniques and increas-

ing influence of computational neuroscience in dealing with neurological disorders [2–4].

The automated VBM procedure does take into consideration some major limitations of manual tracing-based ROI such as user bias, bias towards anatomical outlines of brain structures etc. However, just like any other modality, VBM suffers from certain limitations. Since the technology is still in its infancy, all of these limitations have not been addressed or resolved yet, and one has to be cautious about the general conclusions of the study. This is not a criticism of the work of Baxter et al. [7] which definitely takes advantage of the VBM technology to improve our understanding of the current state of the art. The significance of the conclusions reported may have been even lower if other methods were used. However, the shortcomings of VBM cannot be denied and are well documented in the literature [8]. Some of these concerns can be circumvented by designing the experiment carefully. Baxter et al. [7] themselves attempt to address some of these concerns, for example, by using a custom stereotactic template for registration. However, other concerns cannot be addressed at this point due to limitations on resolution, signal to noise ratio etc. of the underlying imaging modality. In some cases, VBM and *classical* ROI studies are used to complement each other with results from one corroborating those from the other.

Based on this discussion about the limitations of VBM, the authors believe that conclusions from any study using this modality should be interpreted with extreme caution. Although such studies are important for advancing our understanding, any claims based on these studies can be accepted conclusively only when:

1) The sample population investigated is sufficiently large (in addition to being well-designed)
2) The VBM study is supported by evidence from other comparable or complementary modalities.

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