Addressing positioning induced variabillity in VBM analyses

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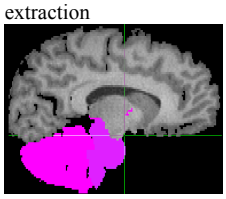
Introduction

Voxel Based Morphometry is an established method for assessing changes in brain anatomy in schizophrenia. Recent metanalytic studies, [3], using this approach have suggested the presence of reduced gray matter (GM) in relatively focal lateral and medial prefrontal and temporal cortical regions that are present at the first episode and which appear to become more extensive with illness progression. However there are a number of methodological concerns that impact the interpretation of studies using the VBM approach. Firstly, these studies have been cross-sectional rather than longitudinal, limiting the ability to infer that differences observed in different populations are due to illness progression rather than other factors that can lead to differences between early illness and chronic populations. The second relates to concerns regarding the interpretation of data analyzed using the VBM approach, in particular the observation that inter-individual and between group differences in the accuracy of normalization of GM to a standard template space can be a major source of variability.

In this work we compare a large group of First Episode Schizophrenia patients on admission to an early psychosis service to a group of controls, as well as a subgroup of subjects who were scanned a second time one year later. Attempting to strengthen our inference about the neurobiological significance of these results, we systematically examine the effects of an improved alignment procedure that can lead to enhanced registration accuracy and improve our ability to interpret group VBM differences in terms of regional GM reductions.

Figure 1:cerebellum + extraction



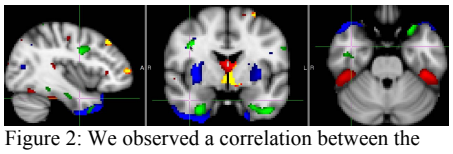


Figure 2: We observed a correlation between the brain's center of mass during acquisition and the GM intensity. Changes in the head position reflected unevenly across the brain (yellow +Y, red +Z, green

Methods

Subjects: Ninety first episode schizophrenia patients entering care in an early intervention service (the EDAPT clinic) and seventy demographically matched controls were included in this analysis. All diagnoses were made using the Structured Clinical Interview for DSM Disorders (SCID) and subjects were excluded if they had a history of neurological disorder, recent substance abuse or dependence, seizure disorder or ECT treatment. Control subjects with any Axis I disorder or a first degree relative with a history of psychosis were excluded. The MRI experiments were performed on a 1.5T GE Signa scanner running Signa LX software. A standard CP GE coil was used. The relevant sagittal SPGR parameters are spatial resolution 0.9x1.5X0.9 mm, 124 sagital slices, in-plane matrix size 256x256.

The standard FSL-VBM analysis is enhanced in several respects. First, the coarse brain delineation is further corrected for non-uniformity using the iterative enhancing of Vokurka algorithm. The images are further scaled (a linear transform in image space). In the end, FreeSurfer is used to exclude the brain stem and the cerebellum, in this way we reduce the registration related variability, and subsequently assumptions of the GLM are better fulfilled. The study template creation is an iterative process at step n spelling: align all brains to the template "n" then average them to construct the new template "n+1". The typical VBM uses as template "1" the MNI standard brain. This step is critical since the differences between the template and the individual brains are at a maximum at n=1, therefore the probability of landing in a local minimum, too. Observing that the relative positioning of the brain stem and cerebellum introduce a large amount of variability across brains, we decide to use a cerebrum-only template. Attempting to achieve this by iterating the straightforward process: "registration /cerebellum identification/re-weighting" was not satisfactory. Nevertheless, the approach becomes feasible when the FreeSurfer automated segmentation is used; an accurate delineation of the cerebrum as well as a accurate and consistent delineation of the Brain stem is possible using this software.

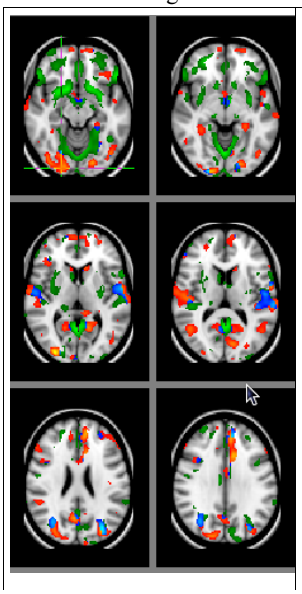


Figure 3: VBM analysis results (controls n=69,patients n=91)
Red Areas: greater in controls than patients independent of head position effects
Blue: areas where group differences are also potentially subject to confounds related to head position variation
Green: areas that do not show group differences but show correlations between gray matter density measures and head position variation
The Z-statistic images were threshold at z=2.35, then the FDR correction was applied (using the FSL cluster), only the cluster with $p < 0.05$ were kept.

Results

By running a GLM model with the MR image intensity as response and the brain's center of mass coordinates as explanatory variables, we are able to identify three classes of the results depicted in Figure 2. The surprising finding is the uneven reflection of the positioning in the image intensities. The fact that the temporal lobes are the most affected by the positioning of the brain is another manifestation of the difficulties raised by that brain region. In attempt to characterize better those dependencies, a full VBM analysis was performed with the added explanatory variables the head position. In Figure 3 the typical results of this are exemplified. The existence of regions in which the head positioning is a significant predictor suggests that head positioning should be included in the VBM model. In our work, the underling origin of those position dependent effects is indentified in the magnet specific static distortions.

References

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