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Magnetization transfer imaging abnormalities in schizophrenia: A replication based on methodological scepticism

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Magnetization transfer ratio (MTR) imaging is a MR technique that estimates the concentration of macromolecules in tissues. Like diffusion-weighted techniques, it can detect microstructural abnormalities in brain tissue. Here, we focus on studies such as Foong et al. 2001, which using a statistical parametric mapping (SPM) analysis on MTR images claimed to have detected abnormalities in a sample of schizophrenic subjects. Our replication is based on a sample of 35 schizophrenic patients and 107 normal subjects, and was planned with the aim of showing that the findings of Foong et al. are artefactual using statistical methodology.

Foong et al. found several foci of reduced MTR in the grey matter close to the surface. After selecting arbitrarily the first 25 and 30 images of the schizophrenic and normal samples to replicate the size of Foong's study, and smoothing to the same kernel width of 10mm., we found a very similar distribution of reduced signal, significant, as in Foong, at cluster level (figures will be shown).

However, things can go wrong when using SPM on structural images. Ratios like MTR cannot be distributed normally. Since the statistic used for control of familywise error (FWE) rates are based on the distribution of maxima/minima, small changes of the distributional tails such as skewness and kurtosis affect the statistic much more than in the univariate case, even after smoothing (we will show a small simulation for the sceptical reader). Using the 107 normal subjects in our sample, we will show that the distribution of MTR images is highly kurtotic and somewhat skewed. A reason of particular concern is the hull of very unstable strong signal surrounding the brain parenchyma in MTR images. Although RON stripped the skull of the images, some of these voxels may have smeared the signal in the interior of the brain after smoothing.

To counter the effect of nonnormality, we computed the test using the Mann-Whitney rank test, with the ranks computed voxel-by-voxel. FWE-corrected thresholds were computed using permutation as in Holmes et al. 1996. To our surprise, we found that the results were very similar to the SPM analysis (and hence Foong's), showing that non-normality was not affecting the parametric test much.

To counter the effects of voxels outside the brain parenchyma, we replaced voxels classified with a probability of 0.15 or more as CSF by the segmentation procedure of SPM5 with random values with mean and variance as estimated from the values in other volumes where the same voxel had been classified as grey or white matter. Voxels where there were less than 28 values to compute this estimate were excluded. We found again that the areas of reduced signal persisted, although some of the grey matter was no longer available to analysis.

Smoothing the volumes prior to analysis as usual in SPM smooths not only the random error, as specified in the random field model, but also the fixed signal. Unlike

functional MRI, there is no reason in structural imaging to believe that the altered signal is spatially smooth. Hence, we reduced the smoothing kernel to 3mm., and applied the rank-test/permutation procedure to avoid random field theory and distributional assumptions. The higher-resulution maps of reduced MTR signal show that affected areas are mostly thin stripes in white matter running close to the gray matter in the cortex. The cerebellar white matter and the vermis also appears to be affected (all findings FWE-corrected). Unexpectedly, we found a patch of prefrontal cortex (grey matter) where schizophrenics had increased MTR signal (FWE-corrected), but the meaning of this isolated finding is uncertain.
Our findings indicate that the changes found by Foong et al. are robust, against our initial expectation. However, we found evidence for reduced signal in white matter and not grey matter as concluded by Foong et al.

References: ·

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