Improved MR-Morphometry analysis techniques: What do they detect in the Schizophrenic Brain?

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Introduction

There is a present debate whether in schizophrenic patients there is a progressive degeneration that might be attenuated by antipsychotic treatment. Existing longitudinal imaging studies have produced conflicting findings probably due to the heterogeneity of samples, treatment effects as well as different methodological approaches. Additionally it is not yet completely understood how far the reported MRI volume changes actually reflect neurodegeneration or if they rather show short term changes in perfusion or other physiological alterations in brain tissue [1]. To investigate this question more thoroughly we tried to compare brain volumes in well-defined schizophrenic patients before and under standardized antipsychotic treatment to healthy controls using two different types of analyses: Voxel-based morphometry (VBM) which is sensitive to small changes in gray matter concentration, and tensor-based morphometry (TBM) which detects volume changes on a mesoscopic scale. To investigate short term effects like alterations in perfusion on VBM and TBM in healthy subjects, we studied in addition the acute influence of a single dose of intravenously applied haloperidol which is known from PET Studies to decrease rCBF in the prefrontal cortex.

Methods

We studied a group of ten first-episode neuroleptic naïve schizophrenic patients (DSM IV, paranoid subtype) before and after 16.0 months of olanzapine treatment (∅ 11,6 mg) with MRI as well as a ten age- and sex-matched healthy controls. An additional group of 9 healthy neuroleptic-naïve male controls was studied before, 2 h and 24 h after haloperidol (i.v. 5 mg/70 kg). Anatomical 3-D T1-weighted high resolution images were acquired (1.5T). For VBM data were transformed (affine) to Talairach space and segmented (SPM02). New template and a-priori images – one for each subject – were created. The original data was normalized nonlinearly to these templates and segmented using the new a-priori images. The partitioned images for grey matter (GM), white matter (WM) and CSF were smoothed and analyzed voxelwise applying ANOVA for repeated measurement including factor group. For TBM, after affine normalization, each subjects second dataset was normalized to the first using a highly nonlinear warping algorithm. The resulting vector fields were extracted and Jacobian images computed which were smoothed and tested voxelwise.

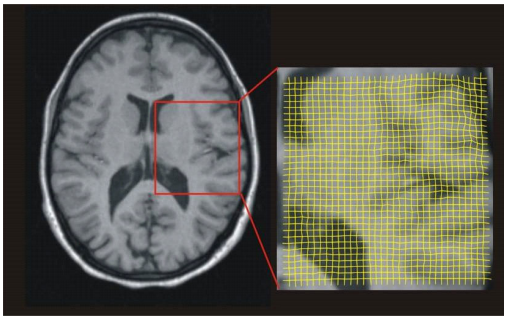

Fig. 1: Deformation Field mapping two volumes from the highly nonlinear normalization procedure.

Results

As expected no volume change was observed for the healthy control subjects with either method. With VBM significant ($p<0.05$ FDR-corrected) reduction of cortical GM concentration of patients compared to controls was found most pronounced in the left frontal cortex . No changes were found for WM and CSF. TBM showed comparable volume reductions but also reduced volume in the inferior temporal and the fusiform gyri and in large areas of the cerebellum as well as a ventricular enlargement. Comparing patients and controls cross-sectional using VBM showed a trend of increased frontal grey matter in patients at the first measurement($p<0.05$ uncor), which disappeared at the second measurement. The haloperidol group of healthy subjects showed a significant ($p<0.001$ uncorr.) volume reduction in the left frontal cortex 2 and 24 h after drug intake.

Conclusion

VBM and TBM are both highly sensitive methods for detecting alterations in brain tissue. Using highly nonlinear normalization algorithms, TBM is especially able to detect even small longitudinal changes. This could be shown in FE schizophrenic patients under atypical antipsychotics indicating a progressive volume loss of frontal cortical GM. Whole brain composition measurement showed no significant differences. Cross-sectional VBM, however, showed at the same time an unexpected trend for increased fronto-temporal GM volume in FE patients in the acute psychosis. Based on previous PET data [2] we hypothesize that there might be an apparent increased cerebral volume in our acutely psychotic patients due to increased perfusion caused by a hyperfrontal metabolic state. This hypothesis is endorsed by the significant volume reduction, that we have seen with the same methods after a single dose of haloperidol in healthy subjects, which is known - due to PET studies - to decrease perfusion in the frontal cortex. Based on our findings we caution investigators involved in MRI studies to suspect the reported volume changes in schizophrenic patients as being related to neurodegeneration. Variations in MRI measurements can also reflect differences in changes in tissue perfusion due to antipsychotics or other changes that make up living brain.

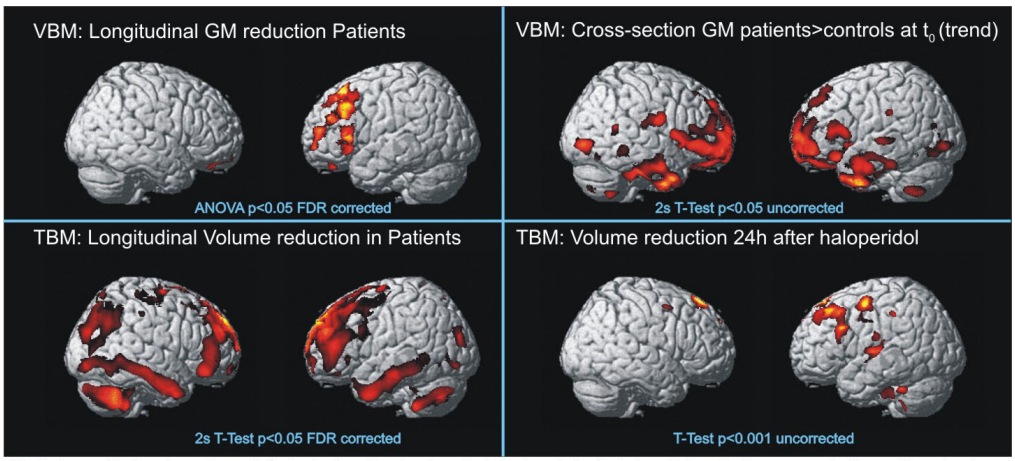

Fig. 2: Areas of brain volume change in first-episode schizophrenic patients, and controls after haloperidol application measured with voxel-based and tensor-based volumetry.

References

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