Diffusion Tensor Imaging of Rat Model of Obsessive-Compulsive Disorder

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Introduction

The localization of cognitive domains can be achieved by functional imaging modalities such as fMRI, PET and MEG. It was recently shown that voxel-wise correlation between high resolution quantitative structural MRI (e.g. diffusion tensor imaging indices, DTI) and various behavioral measures allows brain localization of cognitive performance. This approach hypothesizes that inter-subject behavioral variability is manifested by morphological tissue variability leading to functional differences. The power of this methodology was demonstrated on the memory cognitive domain, where DTI indices extracted from the hippocampus, septum, fimbria and amygdala were shown to be in correlation with learning and memory abilities.

In the present study we used the same technique to localize the behavioral manifestation of the signal attenuation (SA) rat model of obsessive-compulsive disorder (OCD). This model includes several phases. In the first phases the rats learn a basic relation between light, sound, lever pressing and collection of reward. During an extinction test, excessive lever-pressing is observed without the attempt to collect the reward. This behavior reflects the same behavioral disorder that is present in clinical OCD. In this study we used a voxel-wise approach to compare regional DTI indices differences between control and SA rats.

Methods

Twenty six Sprague-Dawly male rats were scanned in a 7T MRI system (Bruker, Germany) divided into two groups: a control group that does not develop compulsive lever pressing (regular extinction (RE) group) and a research group that does develop the compulsive behavior (signal attenuation (SA) group). The rats were scanned at 4 different time points: Once before, twice during and once after the behavioral paradigm.

The MRI protocol included diffusion weighted echo-planar imaging (DWI-EPI) with the following parameters: TR/TE=4000/25 ms, Δ/δ =10/4.5ms, 16 non-collinear gradient directions, 12 slices of 1.0 mm thickness and in-plane resolution of 0.2x0.2mm^2.

Image analysis included diffusion tensor imaging analysis of the DWI-EPIs to produce for each rat fractional anisotropy (FA) and apparent diffusion coefficient (ADC) maps. For statistical comparison between rats (voxel based morphometry) each rat brain volume was co-registered and normalized with template rat atlas. The registration and statistical analysis were performed using SPM2 (FIL, UCL, London, UK).

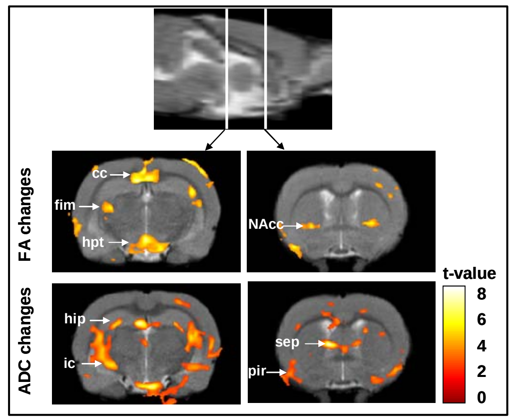

Figure 1: Statistical parametric maps of the FA (top row) and ADC changes between the SA and RE groups (superimposed on T2 weighted image) following the 2nd phase of the behavioral paradigm. The statistical threshold was set to p<0.005

Results and discussion

The behavioral paradigm includes 3 phases; at the first phase the rats (in both groups) are trained to link lever-pressing to a compound signal (light and sound) that is followed by a reward (food). At the second phase, for the SA group, the levers are removed from the operant box while the rats receive the compound signal without reward. At this phase the SA group develops the OCD-like behavior which is measured at the final phase. At the last phase, the rats undergo extinction test, where the levers are placed back in the operant box and still no reward is given following the compound signal. At this phase the rats in the SA group show excessive level pressing without attempt to collect a reward - this is the principle parameter for compulsive behavior in this model. The RE group undergoes the same test at this phase but does not show the compulsive behavior.

The rats were scanned before the behavioral paradigm and following each of the three phases. The most significant regional DTI changes were found following the second phase of the behavioral paradigm (where the SA group acquires the compulsive behavior). It was found that the FA index decreases in the SA compared with the RE group in the fimbria of hippocampus, accumbens shell and caudate/putamen regions (Figure 1). Both groups undergo the same FA changes in the following regions: hypothalamus, corpus callosum and piriform cortex. ADC analysis reports on ADC decrease in the same regions but also in the internal capsule, hippocampus, septum and multiple sub-regions within the caudate/putamen (Figure 1). Figure 2 show region of interest analysis for the fimbria of the hippocampus depicting the FA changes along the different MRI scans along the procedure. The differences between the groups become apparent at the 3rd MRI scan ($p<0.005$, paired t-test) following the signal attenuation phase, which afterwards an OCD-like behavior is observed. The difference becomes even larger following the final phase. Similar results are observed in the abovementioned regions.

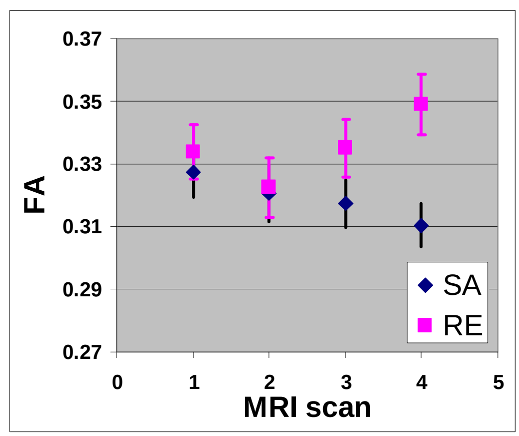

Figure 2: ROI analysis for the fimbria cluster in Figure 1 for all paradigm phases. The error bars represent standard error. Note that statistically difference between the two group is observed only at the 3rd and 4th MRI scans.

Conclusions

The results of this study suggest that diffusion tensor imaging can be used for localization of cognitive performance and disorders. It is also speculated that interplay between the limbic system (mainly hippocampus) and the ventral striatum lies in the basis of the pathology in the OCD animal model. The ADC and FA changes (both are reduced in the SA group) might indicate of microstrucutral morphological plasticity manifested by increase in tissue density and reduced fiber/dendrite organization.