Voxel-based morphometry in assessing a rat model of impulsivity: agreement with targeted Western blot analysis

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Introduction

Elucidating the neural and psychological substrates of impulsive behaviour in experiments is central to elucidating the aetiology of attention deficit hyperactivity disorder (ADHD) and co-morbid brain disorders such as drug addiction. Converging evidence implicates the fronto-striatal systems in the expression of impulsive behavioural phenotypes, including especially the ventromedial prefrontal cortex and nucleus accumbens (NAcc). Trait-like impulsivity is also associated with reduced dopamine D2/3 receptor availability in the ventral striatum (Dalley et al., 2007). The present study sought to investigate whether high impulsivity in rats is also accompanied by structural and molecular abnormalities in the fronto-striatal brain networks. High resolution MR images were acquired for 3D voxel-based morphometry (VBM) (Ashburner 2009) which was used to assess grey matter density in rats selected for extreme high and low impulsivity phenotypes on a 5-choice serial reaction time (5-CSRT) task. Guided by the results of VBM we also measured neuronal and glial markers in several brain regions of interest using Western blot analysis.

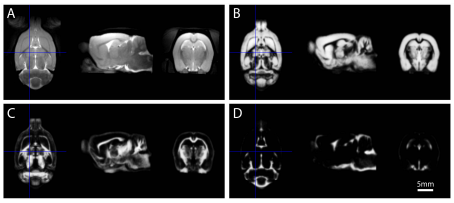


Fig 1 Rat brain atlas with GM, WM and CSF probability maps used for the VBM analysis.

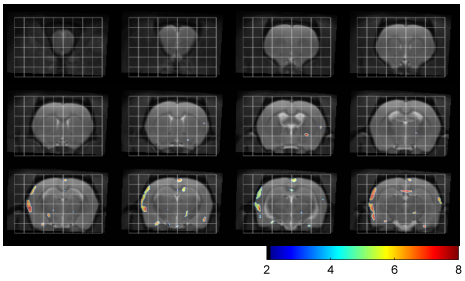


Fig 2a above: results showing areas of the brain where GM score negatively correlates with impulsivity scores, P_{FDR}-corrected < 0.05. Scale bar is T score.

Fig 2b: below top: section at level of nucleus accumbens (arrowhead, $p < 0.005$ uncorrected for illustration) showing asymmetrical effects in the NAcc core and the parietal cortex.

Methods

18 Lister-hooded rats (300-500g) were selected from their behaviour in the 5CSRT (6 low, 6 medium and 6 highly impulsive) and scanned using a 4.7T Bruker BioSpec 47/40 system. A RARE sequence was used to achieve 150µm^3 resolution in 1.5 hours (TR/TE 3500/43ms, ETL 16, FOV 38.4×38.4×14.4mm^3, matrix 256×256×96). Image analysis was performed using SPM5 (Ashburner 2005) and the SPMMouse animal toolbox (Sawiak 2009). Images were registered rigidly to a randomly selected image, all images were averaged and the resulting image used as an initial target for affine registration. Transformed images were used as the target for non-linear registration and averaged again, this resulting image was segmented into grey and white matter classes (GM/WM) and a class for cerebrospinal fluid (CSF) figure 1. These images were smoothed and used as tissue priors for the unified segmentation procedure of SPM5. Output GM maps were smoothed and analysed in a general linear model for correlation with premature responses from the 5CSRT. The false-discovery rate was used to control for multiple comparisons.

Results

Figure 2 shows the regions of the brain where GM scores from VBM correlate negatively with GM scores from VBM. A section at the level of the nucleus accumbens core (NAcc core) and parietal cortex is shown in figure 2b at a less stringent level for illustration, and all significant results are reconstructed in 3D in figure 3.

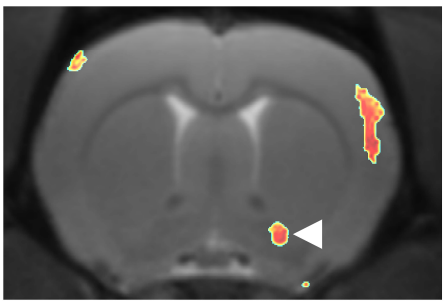
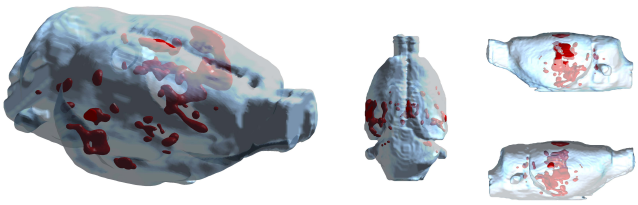


Fig 3: 3D reconstruction of the significant regions ($p < 0.05$ FDR corrected) shown inside the rat brain.

Conclusions

VBM allows assessment of the whole brain for differences with minimal user intervention. We have shown that MRI can detect areas of the brain where grey matter concentrations correlate significantly with measures of impulsivity. From this we conclude that trait-like impulsivity is associated with a significant reduction in grey matter in the core sub-region of the NAcc and fronto-parietal cortex. Furthermore, the extent of grey matter reduction in the NAcc core strongly predicts the level of impulsivity. These structural biomarkers are present mainly in the left hemisphere and loss of grey matter in the left NAcc core is accompanied by a striking reduction in GAD 65/67, the rate limiting enzyme involved in the production of GABA as measured by Western blot analysis. Collectively, these results indicate that trait-like impulsivity in rats may be caused by asymmetric morphological abnormalities in the NAcc core and parietal cortex and especially by GABA-ergic dysfunction in the NAcc.



References

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