CHARACTERISATION OF RAT MAM MODEL OF SCHIZOPHRENIA BY IN VIVO STRUCTURAL AND PHARMACOLOGICAL MRI

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Introduction Offspring of rats treated in utero with a DNA-alkylating agent MAM exhibit several cognitive and brain abnormalities typical of schizophrenia. The brains are overall smaller and ventricles enlarged, and there is an imbalance in the function of glutamatergic and dopaminergic systems, exemplified by hypersensitive behavioural responses to an NMDA antagonist phencyclidine and a dopamine agonist amphetamine2. The aim of this study was to test if the functional and structural brain abnormalities persist in the aged MAM rats.

Methods MAM or Sham (vehicle) treatment was administered to pregnant Sprague Dawley rat dams at E17 as previously described, resulting in a cohort of 16 MAM and 15 Sham male rats. Serial structural MRI (sMRI) of rat models (E17 Varian scanner, TSE T2W images, TR 60ms, FOV 40x40mm, 256x128, 44 slices, 0.6mm isotropic voxels, 72 volumes over time, 32 per volume) by imaging all rats continuously 15 minutes before and 45 minutes after NMDA antagonist ketamine (25mg/kg ip) injection. Data were pre-processed (realigned, normalised to template and Gaussian smoothed 2x in plane resolution) and statistically analysed (behavioural input function3, GLM, 2nd order) using SPM8 software (Wellcome Trust Centre for Neuroimaging). Prior to the final MRI, at 12 months of age, the rats were also tested for locomotor activity (LMA) in response to ketamine (25mg/kg ip) by video recording their activity for 90 minutes in 1300x1300x600mm activity chambers and computerised analysis (Ethovision) of the recordings, resulting in measure of distance travelled per minute. To avoid habituation, those rats that received ketamine in the LMA experiment received saline in MR scanner, and vice versa.

Results Body weights of MAM rats were significantly lower than from Sham rats in 3 months of age, whereas MAMs’ brains were significantly smaller at all time-points (1, 3, 6 and 12 months) by 11 – 14 % (p<0.001 throughout). Dorsal hippocampi were also smaller at all timepoints (p<0.01 at 1 and 3 mt, p<0.001 at 6 and 12 nt). During the early phase (1mt) there were significant differences in the thickness of the prefrontal, parietal and entorhinal cortices, whereas at 12 months prefrontal and parietal cortex remained smaller, but entorhinal cortex normalised (Fig 1). Behavioural testing revealed an increased locomotor activity in response to ketamine in MAM rats (P<0.01 MAM saline vs. MAM ketamine), in comparison to sham in which any increase in LMA was probably masked by ketamine-induced stereotypes (Fig 2). pMRI revealed widespread ketamine-induced BOLD changes in the sham rats, encompassing cingulate, prefrontal & retrosplenial cortex, striatum and thalamus, as we previously described. SPM difference maps, particularly when displayed at the lower p<0.05 threshold (not shown here) revealed an attenuated BOLD response in the striatum and an increase in the hippocampus and retrosplenial cortex (Fig 3) in MAM vs. Sham rats response to ketamine. Fig 1 Cortical thickness measures in MAM and Sham rats. 2 way repeated measures ANOVA with Bonferroni post-tests, P<0.05*,0.01**, 0.001***.

Conclusions Data reveal consistent and long-term structural changes in the brains of MAM rats, including shrinkage of the cortex as well as hippocampi, consistent with earlier reported finds for younger rats. The results also confirm that even in aged MAM rats, there is an enhanced behavioural response to ketamine. PhMRI results show a pattern of changes which likely reflect the underlying pattern of imbalance in glutamatergic and dopaminergic transmitter circuits. Increased ketamine-induced activation in the hippocampal areas may be indicative of the reduced glutamatergic activity in this model whereas a reduced caudate putamen activity could be linked to a dopaminergic increase, which has also been shown to attenuate BOLD response in this area. Structural and PhMRI of MAM model could be used to characterise the efficacy of putative antipsychotic therapies.