Structural Abnormalities Revealed by T2-Weighted and Manganese-Enhanced MRI in Methylazoxymethanol Acetate-Treated Rats: Relevance as a Translational Biomarker for Schizophrenia

C-L. Chin[1], P. Curzon[2], A. E. Tovcimak[1], B. F. Cox[1], L. E. Rueter[2], M. W. Decker[2], G. B. Fox[1], and A. M. Basso[2]

[1]Advanced Technology, Abbott Laboratories, Abbott Park, IL, United States, [2]Neuroscience Research, Abbott Laboratories, Abbott Park, IL, United States

Introduction Schizophrenia is a complex disorder that can have a genetic and/or environmental etiology. Clinically, schizophrenia is characterized by three subsets of symptoms that are classed as positive (e.g. delusions, hallucinations; impulsive activity), negative (e.g. affective flattening, alogia, avolition, social withdrawal), and cognitive (e.g. disorganized thought, attentional, and speech processes) [1]. Although the etiology of schizophrenia remains elusive, structural and functional neuroimaging as well as the advance of new animal models have been providing great insights into its underlying pathophysiology [2, 3]. Herein, using T_2-weighted and manganese-enhanced MRI (MEMRI) [4, 5] we aimed to investigate cytoarchitectural and morphological changes in methylazoxymethanol acetate (MAM)-treated rats – a neurodevelopmental model of schizophrenia [6, 7] – and to further evaluate the feasibility of translating these imaging data to schizophrenia patients.

Materials and Methods Pregnant SD dams (Charles River, Portage, MI) were acquired on gestational day (GD) 10. On GD17, dams were administered saline or 25 mg/kg MAM i.p. Female offspring were weaned on postnatal day (PD) 21 and housed individually (n=11, saline-treated; n=8, MAM-treated) and later imaged on PD 45. Prior to imaging, rats were i.c.v. cannulated under isoflurane anesthesia. For MEMRI, $MnCl_2$ (Sigma-Aldrich, St. Louis, MO) was dissolved in saline and injected via an i.c.v. cannula (0.08M, 5µL), 24-h before imaging. Rats were anesthetized and imaged using a 7T MRI scanner (Bruker Biospin, Karlsruhe, Germany) with a T_1-weighted (TR/TE = 600/10 ms, NA=16), or T_2-weighted (TR/TE =3200/75ms, RARE factor = 8, NA=8) pulse sequence at a pixel size = 250 × 250 μm^2 and slice thickness = 1.25 mm. Volumetric analysis was conducted using AFNI [8].

Results and Discussion Enlargement of ventricles is one of the most consistently replicated pathological findings in schizophrenia [2]. Our results indicated that volumetric analysis revealed a significant increase in the size of lateral ventricles ($p<0.001$) and third ventricle ($p<0.05$) in MAM-treated rats compared to vehicle controls (Fig. 1A and Fig. 2). Conversely, hippocampal volume significantly decreased ($p<0.001$) in MAM-treated rats (Fig. 1B and Fig. 2), which is in agreement with cortical thickness thinning reported from previous studies [6, 7]. Since the limbic system plays an important role in emotional behavior and declarative memory [9], the structural abnormalities observed in the current study may partly explain the cognitive and behavioral deficits observed in MAM-treated animals [6, 7]. Previously, other investigators have demonstrated cytoarchitecture enhancement in brain regions, such as the olfactory bulb, hippocampus, or cerebellum, using MEMRI with either systemic [4, 5] or intracerebral [10, 11] administration of $MnCl_2$. Here, we extended this approach to the MAM rat model of schizophrenia. Interestingly, despite the significant reduction in hippocampal volume in rats exposed to MAM, signal enhancement calculated from the hippocampus was not significantly changed from controls, indicating functional activity of excitable neurons remains uncompromised on PD45. In addition, signal enhancement was lower in MAM-treated rats in brain regions distant to the $MnCl_2$ injection site (e.g. cerebellum, brainstem; not shown here), implying slower axonal transport along hippocampal projection pathways [5, 10] in the diseased state. In summary, structural abnormalities observed in a neurodevelopmental model of schizophrenia are readily imaged using MRI. These techniques may therefore provide translational tools for assessing novel treatments for schizophrenia.

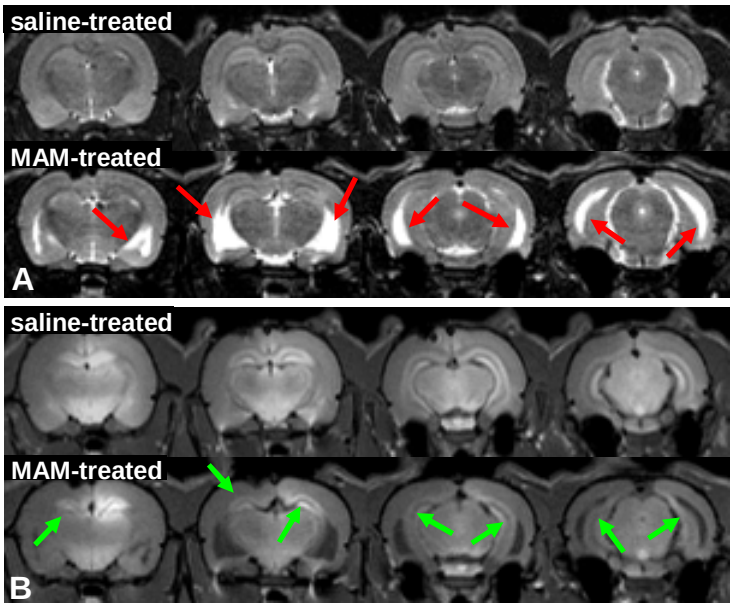

FIG 1. Representative T_2-weighted (A) and manganese-enhanced (B) MR images obtained from saline-treated and MAM-treated rats. Enlargement of ventricle volume (red arrows) and reduction in hippocampus volume (green arrows) are clearly shown.

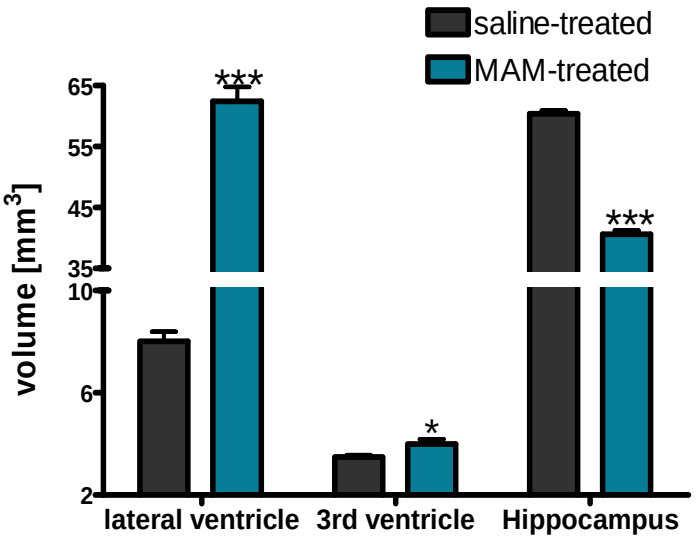

FIG 2. Volumetric analysis of lateral and 3rd ventricles as well as hippocampus (mean ± SEM) of saline-treated (n=11) and MAM-treated rats (n=8). Significant changes in cerebral structures in MAM-treated were observed. (*$p<0.05$, ***$p<0.001$, *t*-test)

References **1** Carpenter WT *et al*, NEJM 330, p681 (1994). **2.** Shenton ME *et al*, Schizophrenia Research 49, p1 (2001). **3**. McGuire P *et al*, TIPS 29, p91 (2008). **4**. Silva AC *et al*, NMR BioMed 17, p532 (2004). **5.** Pautler RG *Methods Mol Med*, 124, p636 (2006) **6**. Flagstad *et al*, Neuropsychopharmacology 29, p2052 (2004). **7**. Moore H *et al*, Biol Psychiatry 60, p253 (2006). **8**. Cox RW, Comput Biomed Res, 29, p162 (1996). **9**. Squire LR *et al*, Science, 253, p1380 (1991). **10**. Watanabe T *et al*, NeuroImage, 22, p860, (2004). **11**. Allegrini PR *et al*, NMR BioMed, 16, p252 (2003).