Enhanced neurometabolic activity and neuroanatomical changes in visual area of rats prenatally exposed to MAM parallel schizophrenic symptoms

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Target Audience: Neuroscientists interested in the metabolic basis of schizophrenia.

Purpose: Schizophrenia is a debilitating neuropsychiatric disorder affecting ~1% of the world's population. Visual hallucination is one of the core positive symptoms of schizophrenia experienced by approximately one-third of patients. This key trait in patients has been associated with increased functional connectivity between visual cortex and hippocampus/amygdala detected by fMRI[1] and high white matter connectivity between hippocampal formation and visual areas measured by DTI[2] compared to patients without visual hallucinations. To investigate the metabolic and anatomic basis of these clinical markers of visual hallucination in schizophrenic patients, we applied ^{13}C MRS and DTI methods in a rat model of schizophrenia. The rats were treated with methylazoxymethanol acetate (MAM) on embryonic day 17. Although the MAM model is a well-validated neurodevelopmental model of schizophrenia, visual hallucination has been difficult to characterize. We hypothesized that if the MAM rat manifests the positive symptoms associated with visual hallucination then the somatosensory cortex, which is undisturbed in the schizophrenic model, will be used as a control region to evaluate metabolic changes in visual cortex.

Methods: MAM and SHAM (saline-treated control) Sprague-Dawley rats were obtained from Charles River. All experiments were performed on 52 - 78 days old rats under medetomidine anesthesia (0.05 mg//kg/h). MRI and MRS data were acquired at 9.4T and 11.7T respectively. Fractional anisotropy (FA) map was calculated from the DTI data obtained by the Stejskal-Tanner spin-echo diffusion weighted sequence (diffusion gradient = 5 ms, delay = 15 ms, TR=2000 ms, TE=25 ms). DTI data were registered to a high-resolution atlas using BioImage Suite. *In vivo* proton-observed carbon-edited (POCE) MRS data were acquired from a localized volume (9×1.5×6 mm^3) under continuous infusion of [1,6-^{13}C]-labeled glucose from a femoral vein. POCE data, localized to visual and somatosensory cortices, were analyzed to calculate rates of neuronal tricarboxylic acid (TCA) cycle flux ($V_{TCA,N}$) and glutamate-glutamine cycling ($V_{cyc(tot)}$).

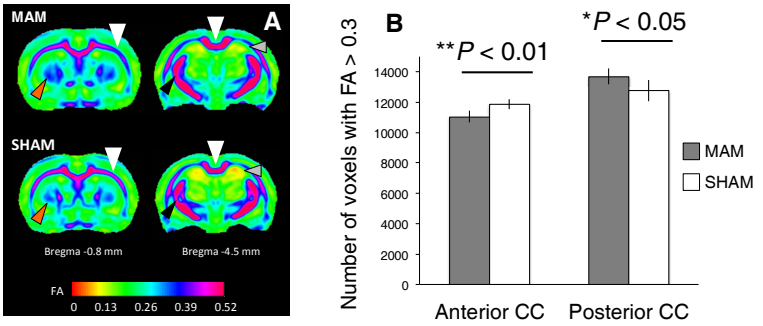

Figure 1. DTI results in MAM and SHAM rats (n = 6 for each group). (A) Representative slices of average FA maps. White, black, gray and orange arrowheads indicate CC, internal capsule, dorsal hippocampus and globus palllidus, respectively. (B) CC volumes represented as the number of voxels with high FA (> 0.30). Anterior and posterior CC correspond to slices at bregma -0.2 to -1.3 mm, including somatosensory area and bregma -3.6 to -5.8, including visual area, respectively, where clear differences in CC thickness were observed in average images. Bars represent standard deviations. Non-parametric *t*-test was used for statistical comparisons.

Results: Structural MRI revealed that MAM rats had thinner visual cortex (by ~0.3 mm) and enlarged lateral ventricles compared to SHAM rats as reported previously in this model[3,4], and are also symptomatic of schizophrenic patients[5,6]. The most notable alterations in FA were found in corpus callosum (CC). The MAM rats showed high and low FA in posterior (bregma -3.6 to -5.8 mm) and anterior (-0.2 to -1.3 mm) CC, respectively, compared to SHAM rats (Figure 1A). Quantification of the number of voxels with high FA (> 0.3) supported these observations (Figure 1B). In more posterior regions MAM rats again showed low CC FA, although the difference did not reach statistical significance. Visual cortex, internal capsule, dorsal hippocampus and globus pallidus of MAM rats also tended to have increased FA. *In vivo* POCE demonstrated that visual cortex of MAM rats had significantly higher $V_{TCA,N}$ and $V_{cyc(tot)}$ than that of SHAM rats (Figure 2A), whereas no significant differences were found in somatosensory cortex (Figure 2B).

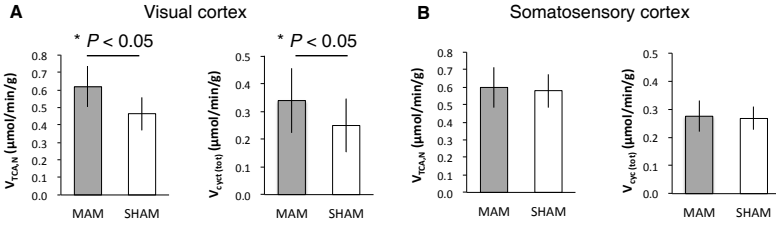

Figure 2. Neuronal TCA flux ($V_{TCA,N}$) and glutamate-glutamine cycling flux ($V_{cyc(tot)}$) obtained by *in vivo* POCE (n = 6 and 5 for MAM and SHAM) for (A) visual and (B) somatosensory cortices. Bars represent standard deviations. Student's *t*-test for statistics.

Discussion: Schizophrenia patients generally have low structural connectivity in widespread white matter regions compared to healthy controls, while there have been many conflicting reports on changes in functional connectivity[7]. Visual hallucinations, however, have been consistently related to increased connectivity in the visual pathway. In this study, visual area of MAM rats showed cortical thinning and increased neuronal energetics and activity, as reflected by $V_{TCA,N}$ and $V_{cyc(tot)}$, compared to the somatosensory area. Higher FA in posterior CC of MAM rats is indicative of increased myelination and could underlie the increased functional connectivity detected in patients[1,8]. These results are thus analogous to alterations observed in human schizophrenia patients with visual hallucinations. Interestingly a previous MAM rat study showed that the anterior CC had decreased FA[3], which is in agreement with results of this and other clinical studies[7].

Conclusion: The above findings suggest that gray/white matter changes and enhanced metabolic activity in the visual pathway may underlie schizophrenic symptoms of visual hallucination and encourage further studies on visual abnormalities of this model such as response to visual stimuli and connectivity of visual cortex with other brain regions. In addition, the interpretation of high gray matter FA is not straight forward although it has been associated with tissue compression due to structural changes[9]. Electrophysiological, functional and histochemical experiments will be useful to address these issues.

References:

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