Brain Ventricular Enlargement in the SAPAP3 Knockout Mouse Model of OCD

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Target Audience: Researchers interested in neuroanatomical studies of compulsive disorders.

Purpose: The lifetime prevalence of obsessive compulsive disorder (OCD) is about 2%, yet the etiology of OCD is not well understood. Defects in the basal ganglia have been proposed to play a key role [1]. This hypothesis is strengthened by our studies of SAPAP3 knockout mutant mice as a model of OCD [2]. SAPAP3 is a key scaffold protein for the assembly of the glutamatergic cortico-striatal synapses. Genetic deletion of the SAPAP3 gene in mice results in compulsive grooming behavior leading to facial hair removal and skin lesions, accompanied by anxiety-like behavior [2]. Biochemical and ex vivo electrophysiological studies reveal cortico-striatal synaptic defects in SAPAP3 mutant mice. Recent human genetic studies have also provided supporting evidence that SAPAP3 gene may be associated with obsessive compulsive spectrum disorders [3-6]. Enlarged ventricular volumes have been reported in pediatric OCD patients [7]. Accordingly, we sought to begin characterizing neuroanatomical deficits in SAPAP3 mutant mice by studying brain ventricular volumes, using ultra high magnetic field (9.4 Tesla) structural MRI scans.

Methods: Heterozygous SAPAP3 knockout mice were bred and genotyped to obtain wild type (WT,N=6, 2 males) and homozygous SAPAP3 knockouts (SAPAP3-/-, KO, N=6, 2 males). Mice were anesthetized with isoflurane (1.5%) and physiological parameters including rectal temperature and respiration rate were monitored and maintained throughout scans. Mice underwent structural MRI scans on a 9.4 Tesla Varian Direct Drive scanner with a 100 G/cm gradient system, using a custom-designed volume head coil. Imaging was performed using a fast spin echo sequence with acceleration factor=8, TR=4150 ms, and effective TE=55ms (13.75 ms × k0 = 4) in order to optimize T2 contrast. Other parameters were: in-plane FOV=16mm, matrix =256x256, slices=36, slice thickness=0.5mm, interleaved acquisition, averages=20 to preserve SNR (signal-to-noise-ratio), gap=0. Two dummy scans were acquired at the beginning of each acquisition to avoid transient effects (35 min total acquisition time). Images were acquired in the coronal plane with respect to the mouse brain. Images were visualized with fslview (FSL, FMRIB, Oxford, UK). Whole brains and ventricles (hyperintense in T2-weighted images) were manually outlined in each image by a rater blind to subject identity (WT or KO), and FSL command-line tools were used to measure total brain and ventricular masks. WT and KO whole brain and ventricular volumes were compared with t-tests (2-tailed).

Because ventricular volumes are known to increase in C57BL/6J mice during brain development [8], we also analyzed for an association between mouse age on the scan day and ventricular volume. All data presented are means ± Standard Deviations.

Results: Mean ages of WT and KO mice were statistically equivalent (98.5 ± 21.1 and 117.5 ± 23.7 days, respectively). Only one of the six KO mice exhibited skin lesions characteristic of prolonged compulsive grooming phenotype. Total brain volumes (TBV) for WT and KO mice were statistically equivalent (542.0 ± 35.4 and 546.5 ± 29.8 ul, respectively, Left Figure). By contrast, ventricular volumes for WT and KO mice were 10.6 ± 1.9 and 16.2 ± 3.8 ul, respectively, and on average were more than 50% larger in KO versus WT mice (unpaired 2-sided t-test t=3.2 (df=10), P <0.01). Middle and Right Figures, ventricles shaded unilaterally in red. When ventricular volumes were expressed as a fraction of TBV, WT and KO mice fractional volumes averaged 1.95 ± 0.38 and 2.97 ± 0.58 % of TBV, respectively (unpaired 2-sided t-test t=3.6, (df=10) P =0.005). We found no association between mouse age on the scan day and ventricular volume in either WT or KO mice.

Discussion: To our knowledge, these data represent the first structural neuroimaging abnormality reported in the SAPAP3 KO mouse model of OCD. The 50% ventricular enlargement we observed in KO versus WT mice substantially exceeds the ventricular volume increase reported to occur in C57BL/6J mice as they age from 12 to 24 weeks (5%), the age range of mice involved in this study [8]. The ventricular enlargement in KO mice is consistent with a study reporting increased ventricular volumes in pediatric OCD patients [7]. That human OCD study also reported finding striatal volume reductions. Because SAPAP3 KO mice have abnormal striatal synaptic ultrastructure at glutamatergic synapses [2], we plan to assess striatal volumes to determine whether they are abnormal in SAPAP3 KO mice and whether striatal structural abnormalities could contribute to the present observation of increased ventricular volume. We also plan to conduct longitudinal studies in younger KO mice to determine whether brain changes occur before compulsive grooming behavior emerges.

Conclusions: Ventricular enlargement in KO mice appeared in 5 of 6 mice before skin lesions were apparent, suggesting that neuroanatomical abnormalities precede onset of the severe behavioral phenotype. Accordingly, the SAPAP3 KO mouse model of OCD may be useful for detecting neurodevelopmental abnormalities that predict onset of compulsive behaviors. Since OCD in humans typically is not diagnosed and treated until nearly a decade after symptom onset [9], it is very difficult to characterize the neuroanatomical etiology of the disorder in humans. Accordingly, studies in animal models such as the SAPAP3 KO mouse, which is genetically predetermined to develop compulsive behaviors, may be key to developing imaging methods permitting early diagnosis and intervention of compulsive disorders, which in turn could improve clinical outcomes.