Volumetric Changes in the Monkey Cerebral Cortex Following Prolonged Voluntary Ethanol Drinking

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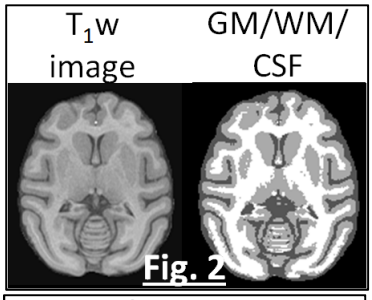
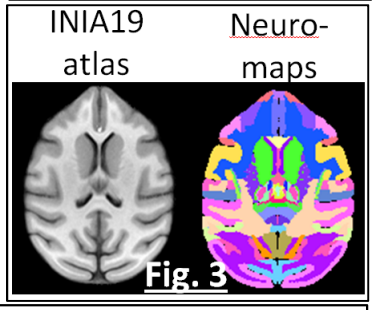
Introduction Magnetic resonance imaging (MRI) studies have documented consistent patterns of volumetric reductions in cerebral cortex of chronic heavy ethanol drinkers relative to non-heavy drinkers [1-3]. This finding prompts several questions related to the role of brain structural changes in brain functional deficits related to ethanol exposure, and the cellular anatomical source of observed structural changes. Such questions require systematic study of animal model systems, because ethical and technical constraints preclude the study of the effect of ethanol on the human brain. Neuroanatomical and behavioral similarities of rhesus macaques (*Macaca mulatta*) to human make the rhesus monkey a useful model of human alcoholism. A previously developed experimental procedure for studying drinking in monkeys (Fig. 1, [4,5]), involving a 3-month induction period followed by a period in which animals are given free access to ethanol, has been shown to generate a wide array of drinking behaviors, including animals that drink in excess of 3 g/kg/day of ethanol (for comparison 0.25 g/kg is a standard 1-drink equivalent). The drinking procedure is amenable to adaptation for longitudinal assessment of brain volume changes by MRI. Here we report that cerebral cortical volumetric changes similar to those observed in human alcoholics are observed in heavy-drinking monkeys.

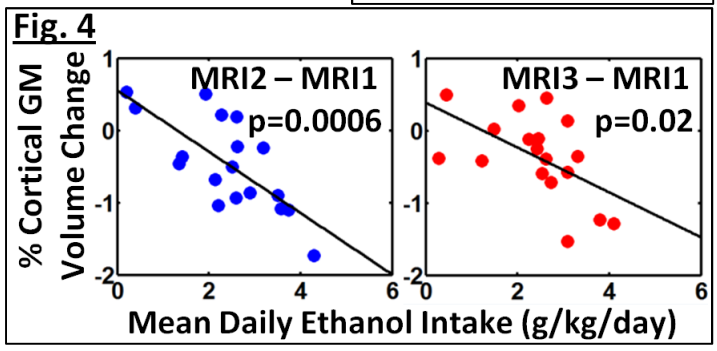
Methods Eighteen young to middle age adult (7.8 ± 1.6) male rhesus macaque monkeys underwent the longitudinal, voluntary drinking and MRI experiment outlined in Fig. 1. T_1 -weighted (MP-RAGE) MRI data was acquired as previously described [6,7] using a 3T Siemens Magnetom trio MRI system at 3 time points: prior to ethanol exposure, after 6 months, and after 1 year of voluntary drinking. Image segmentation into gray matter (GM), white matter (WM), and cerebral spinal fluid (CSF) components utilized the FAST tool from the FMRIB software library (fsl.fmrib.ox.ac.uc.uk/fsl) as exemplified for one animal in Fig. 2. Further subdivision of the cerebral cortex was facilitated through construction of the INIA19 brain template, and its merging with the NeuroMaps parcellation system (Fig. 3, [7]).





Results The monkey cerebral cortical volume, expressed as a percentage of the intracranial volume, decreases in a manner that is proportional to mean daily ethanol intake (MDI). In Fig. 4, the differences in percent cerebral cortical volume are plotted vs. MDI following 6 months (MRI2 - MRI1 vs. MDI: ρ=-0.73, p=0.0006, left panel) and 12 months (MRI3 - MRI1 vs. MDI: ρ=-0.55, p=0.02, right panel) voluntary drinking. Analyses of individual cortical areas revealed largest volumetric changes within the parietal lobe and within allocortical areas.

Conclusions Similar to humans, nonhuman primates that voluntarily drink large amounts of ethanol undergo brain structural changes, in which the volume of cerebral cortical GM is reduced compared with the ethanol-naïve volume. These results support the position that at least some of the brain volume shrinkage observed in chronic alcoholics is related to alcohol consumption and not simply a premorbid condition. Due to the ability to quantify ethanol intake precisely during the voluntary drinking phase of the experiment, the magnitude of the volume reduction can be related to the daily ethanol exposure in this study, and volumetric changes are found to be proportional to intake. Given the close similarity of this animal model system to many aspects of human drinking, we anticipate that further characterization of the brains of animals that undergo these experimental procedures (e.g. by histological examination) will genrate insights related to the biological mechanisms underlying neuroimaging findings in human alcoholics.



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