Tracking the limbic-frontal glutamate system associated with aged emotion regulation

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Introduction

Age-related neuronal loss may occur in certain brain regions as a result of chronic stress accumulation across the lifespan [1, 2]. Alternatively, neuronal loss or dysfunction associated with older age may be the result of mechanisms that affect all cells of the body. Evidence of frontal involvement in the regulation of emotion is further supported by imagining studies. For example, the anterior cingulate cortex (ACC), ventrolateral prefrontal cortex (VLPFC) and dorsolateral prefrontal cortex (DLPFC) have been found to activate with response inhibition during the cognitive-emotion interference tasks [3, 4, and 5]. These findings highlight the importance of functional connectivity within limbic-frontal circuitry during emotion regulation. The current study was designed to use functional Magnetic Resonance Imaging (fMRI) and proton MR spectroscopic imaging (1H-MRSI) techniques to explore the neurochemical mechanisms related to the brain functional changes in fear response in aging rats.

Methods

All imaging was performed on a 4.7T Bruker small animal magnet. In the baseline in vivo 1H-MRSI study, 3 old and 3 young male Long-Evans rats were secured into the restrainer under low dose isoflurane (1.0-1.2%) anesthesia with self respiration. Localized single voxels (3×3×3 mm) centered on the volume of interested regions in prefrontal cortex (PFC) and cingulate cortex were selected using PRESS sequence with TE of 15.5ms, TR of 1500 ms, data points of 1024, spectral bandwidth of 4006 Hz, and acquisition averages of 256. The fMRI study was conducted on 4 young (3-6 months) and 4 aged (18-24 months) Fischer 344 rats (300-400g). All rats were acclimated to a restraint system that allows us to image conscious animals (Insight Neuro-Imaging Systems, MA, and USA) and incorporates surface and volume coil electronics. The imaging included an anatomical scan (RARE, 3.0 x 3.0 cm^2 field of view, twelve 1.2 mm slices, TR = 2.0s, effective TE =12ms, Matrix = 256 x 256.), followed by a 10 minute functional scan (Spin Echo EPI with a 64 x 64 matrix, TR=2s, TE=55ms, Number of Repetitions = 301) which consisted of a 2 minute baseline, 3 minute exposure to a predator odor TMT(5-dihydro-2,4,5-trimethylthiazoline, extracted from fox feces/urine as an olfactory fear-eliciting cue in these studies to elicit unconditional fear) and five additional minutes after scent removal to ensure return to baseline.

Results

Fig 1 shows the absolute metabolite concentration of glutamate, choline metabolites (Cho), creatine metabolites (Cr), and the putative neuronal marker, N-acetyl-aspartate (NAA). There were no statistically significant differences between 3 young and 3 old rats in glutamate concentrations. Fig 2 shows the time course of the by Blood Oxygenation Level Dependent (BOLD) response in the two main regions of interest, i.e. the PFC and cingulate cortex in the group data from 4 young and 4 old rats. Old rats had a stronger response to the predator odor TMT than young rats. Significant activation of the frontal cortices was seen in response to TMT.

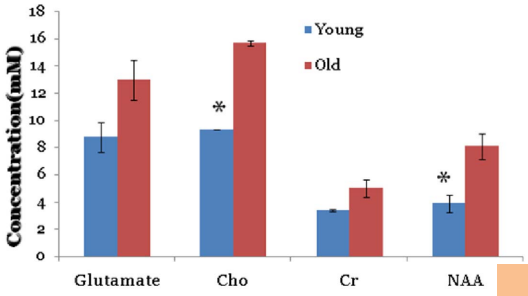
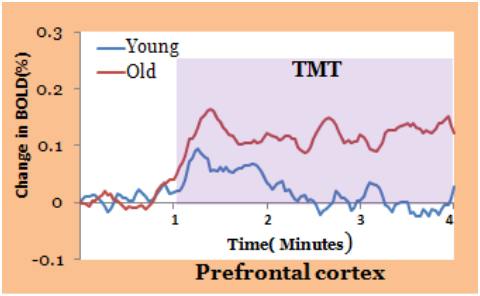
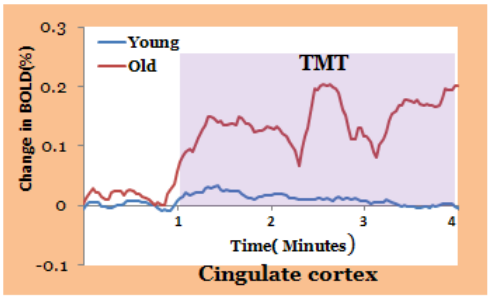


Figure 1 (left): The absolute metabolite concentrations were obtained from the right PFC and cingulate cortex of young and old rats (*p<0.05).

Figure 2 (below): Mean BOLD % change over time in PFC and cingulate cortex associated with the fear response in two groups. TMT was placed in the bore of the magnet at time point 1.





Discussion

Elucidation of the mechanisms underlying unconditioned fear in aged animal may assist in understanding phobias and aging-related increases in fear-related psychiatric disorders. A fuller understanding of the role of limbic-frontal glutamate systems in fear and fear learning may suggest novel pharmacological approaches to the treatment of clinical anxiety disorders.

References:

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