

Functional MRI and neural responses in a rat model of Alzheimer's disease

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INTRODUCTION:

Alzheimer's disease (AD) is a neurodegenerative disease categorized by progressive loss of memory and other cognitive functions. AD is characterized by increased levels of amyloid β peptide (A β) plaques and neurofibrillary tangles in the brain that are associated with neuronal damage [1-2] and vascular toxicity [3-6]. Based on the hypothesis that amyloid plaques found throughout the cerebral cortex can affect every cortical functions and presumably not affect subcortical function in the AD brain, we investigated alterations of functional responses in an AD rat model. High-field fMRI and multi-unit activity (MUA) measurements were applied to characterize brain functions from cortical and subcortical regions in a non-transgenic rat model of AD comparing to age matched healthy control group of rats.

MATERIALS and METHODS:

Animal preparation: Experiments conducted on artificially ventilated (70% N₂O / 30% O₂) adult male Long Evans (250-350 g; Charles River, Wilmington, MA) and Alzheimer's rats (250-350g; Taconic Farms Inc, NY). We used Samaritan Alzheimer's Rat Model from Taconic Farms (surgery model # FAB). The detailed description of the FAB surgical procedures can be found elsewhere (www.taconic.com; [surgery model# FAB](#)). During the animal preparation 2% isoflurane was used for induction. Intraperitoneal line was inserted for administration of α -chloralose (46 \pm 4 mg/kg/hr) and D-tubocurarine chloride (1 mg/kg/hr). An arterial line was used for monitoring physiology (blood pH, pO₂, pCO₂) throughout the experiment.

Forepaw stimuli (2mA, 0.3 ms, 3Hz): Stimulation was achieved by insertion of thin needle copper electrodes under the skin of the forepaw. **fMRI**

(n=10): All fMRI data were obtained on a modified 11.7T Varian horizontal-bore spectrometer using a ¹H surface coil (ϕ = 1.4 cm). The images were acquired with gradient echo EPI sequence (TR/TE = 1000/15) [7].

Neural activity

measurements (n=10): The rat

was placed in a stereotaxic holder on a vibration-free table inside a Faraday cage. Tiny burr holes above the contralateral somatosensory regions [4.4 mm lateral and 1.0 mm anterior to bregma] and bilateral ventral posterior lateral (VPL) thalamic nuclei [3.0 mm lateral and 3.0 mm posterior to bregma] were drilled and tungsten microelectrodes (FHC Inc, Bowdoinham, ME) were inserted up to layer 4 for S1_{FL} and 5 mm ventral for the thalamic nuclei (VPL) with stereotaxic manipulators (Kopf). Neural (multi unit activity: MUA) data

from cortical and thalamic regions were acquired with high impedance electrodes, and the signals from the regions were normalized to the initial peak response during forepaw stimulation. All signals were then digitized (>20 kHz) with a μ -1401 interface using Spike2 software (CED, Cambridge, UK). Multi-unit activity was processed using a RMS (root mean square) approach [7].

RESULTS AND DISCUSSION: Forepaw stimulation induced changes in somatosensory activation was measured in AD rats and compared the results with age and species matched healthy controls. Electrical stimulation of the forepaw (2mA, 3Hz, 0.3 ms) led to evoked BOLD and neural (MUA) responses in the contralateral somatosensory cortex (S1_{FL}) and the thalamus (VPL). In AD brain we noted more than 50% smaller BOLD activation patterns in S1_{FL} (Fig.1A-B), and moreover, the dynamics of MUA was significantly attenuated (Fig.1C). However evoked BOLD and MUA responses in VPL were unaltered in AD rats (Fig.1D-F). These results suggest that cortical energy metabolism in Alzheimer's rats is significantly reduced, presumably due to increased levels of A β plaques and neurofibrillary tangles, as compared with the normal control rats. In future studies, application of calibrated fMRI to extract cerebral metabolic rate of oxygen consumption (CMR_{O2}) can help to better understand the relationship between neural activity, cerebral blood flow and metabolic changes in normal and disease states. These studies may have implications for understanding altered brain function in human Alzheimer's disease.

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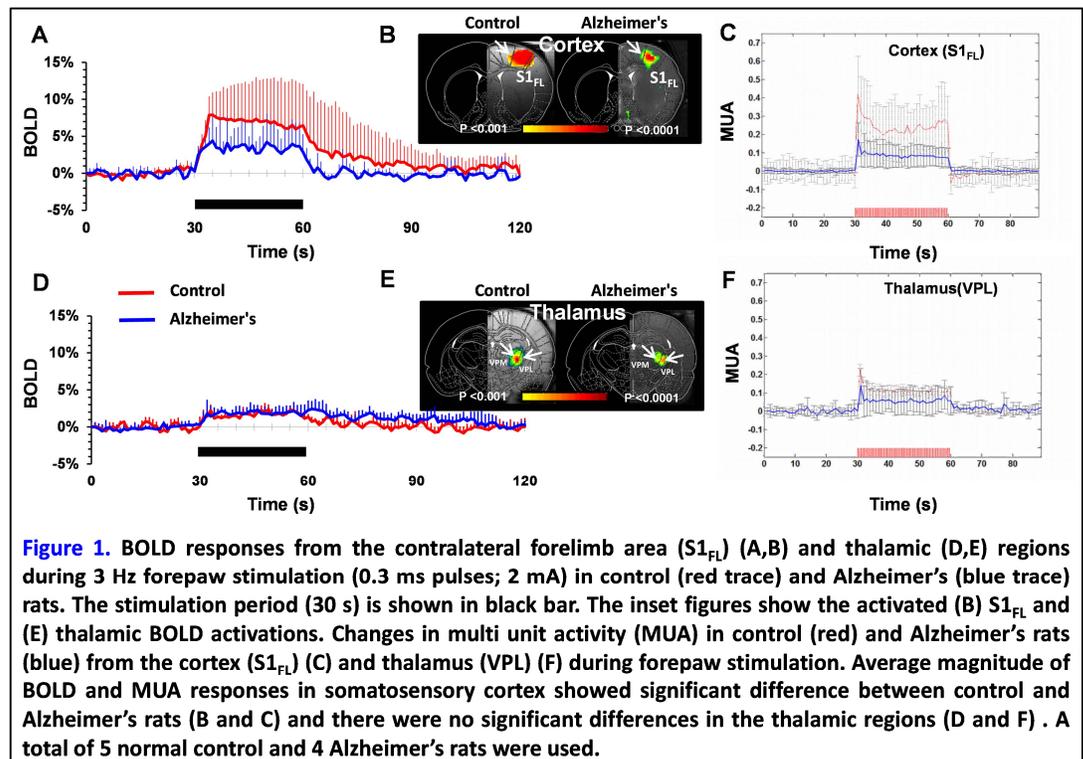


Figure 1. BOLD responses from the contralateral forelimb area (S1_{FL}) (A,B) and thalamic (D,E) regions during 3 Hz forepaw stimulation (0.3 ms pulses; 2 mA) in control (red trace) and Alzheimer's (blue trace) rats. The stimulation period (30 s) is shown in black bar. The inset figures show the activated (B) S1_{FL} and (E) thalamic BOLD activations. Changes in multi unit activity (MUA) in control (red) and Alzheimer's rats (blue) from the cortex (S1_{FL}) (C) and thalamus (VPL) (F) during forepaw stimulation. Average magnitude of BOLD and MUA responses in somatosensory cortex showed significant difference between control and Alzheimer's rats (B and C) and there were no significant differences in the thalamic regions (D and F). A total of 5 normal control and 4 Alzheimer's rats were used.