Resting state functional connectivity in a triple-transgenic mouse model of Alzheimer’s Disease: preliminary results

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Purpose Alzheimer’s disease (AD) is characterized by two hallmark lesions: diffuse and neuritic plaques, which are predominantly composed of the amyloid β-peptide; and neurofibrillary tangles, consisting of filamentous aggregates of hyperphosphorylated tau protein. The triple-transgenic mouse model of AD (3×TgAD) shares amyloid and tau pathologies, and cognitive deficits similar to human AD patients (1), and has been valuable in studying the pathophysiology and progression of AD.

Human neuroimaging studies suggest that brain regions associated with Aβ deposition and cortical atrophy in AD patients overlap remarkably well with the so-called default mode network (DMN), indicating that compromise in spontaneous activity within the DMN may serve as a biomarker for diagnosis and for monitoring the progression of AD (2-4). Interestingly, DMN is not unique to humans, as it has also been described in non-human primates (5) and rats (6,7). The existence of DMN in mice has not been demonstrated due to technical challenges. In the present study, we aimed to identify the mouse DMN and to investigate its potential dysregulation in a 3×TgAD mouse model.

Materials and Methods A total of nine 3×TgAD mice (age 12-14 mo) and six age-matched control mice were used in this study. The anesthesia protocol was adapted from Lu et al (6). Data were acquired on a Bruker 9.4T scanner using a 72 mm volume resonator for RF excitation and a single-turn surface coil for signal reception. A special mouse holder was constructed so that the mouse brain was positioned in the center of the surface coil with minimal distance from coil surface, maximizing signal-to-noise ratio. Scan parameters: single-shot gradient echo EPI, TR/TE=1000/15 ms, 15 slices, slice thickness = 0.6 mm, matrix size = 64×64, FOV = 2.5×2.5 cm². Data were analyzed using the AFNI framework. Group ICA was performed with the MELODIC package in FSL.

Results Data from both AD and control mice were grouped together to perform gICA analysis. Figure 1 shows two distinct connectivity patterns based on component maps. Figure 1A illustrates functional connectivity in bilateral whisker barrel cortices; Figure 1B shows a component with a complex connectivity pattern that involves bilateral orbital, prelimbic, cingulate (Cg1/Cg2), restrosplenial, and parietal association areas. This pattern is generally similar to the rat DMN (6) except that it does not include temporal association cortex and dorsal hippocampus (see discussion).

A recent 2DG study reported that 12-month old 3×TgAD mice had reduced basal glucose uptake in a number of brain regions, including restrosplenial cortex and anterior cingulate cortex (8). Motivated by this study, we placed a seed in Cg1/Cg2 and performed whole brain functional connectivity analysis with this seed; data from AD mice and control mice were subject to two-tailed student t-tests. AD mice showed lower connectivity than control mice in insular/piriform cortices and bilateral temporal association cortices (Fig 2). Seeding in restrosplenial cortex did not reveal any significant difference between the two groups.

Discussion Our results, though preliminary, are encouraging in the following two aspects: i) the DMN appears to be detectable in the mouse brain; ii) connectivity between components of the DMN appears to be compromised in 3×TgAD mouse. These results, if confirmed with a larger sample size, could potentially pave the way for elucidating the cellular and molecular mechanisms responsible for perturbed DMN connectivity in AD, and for evaluating potential interventions.

From a mouse imaging technology perspective, shimming is a major challenge in EPI at high field; this issue is particularly important in mouse brain imaging, given the small size and high field strength. Distortion and signal drop in temporal association cortices and entorhinal/perirhinal cortices were particularly severe, posing a special challenge for image registration. Stronger shimming (>5 A amplifier) and third order shimming may be necessary for mouse EPI imaging at 9.4T.

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