**Functional Connectivity Changes of the Locus Coeruleus in Alzheimer’s Disease**

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Abstract

Growing evidence indicates neurone loss in the Locus Coeruleus (LC) in patients with Alzheimer’s Disease (AD). The wide projection and rich connectivity of the LC with multiple brain regions and its interaction with different neural networks suggests the importance of investigating the functional connectivity of the LC, an area of research which has been less studied. The primary aim of this study was to test for differences in functional connectivity of the LC between AD subjects and matched controls using neuromelanin-sensitive MRI (NM-MRI). The secondary aim of this study was to investigate the change in the resting state networks in AD. Pre-processing of the fMRI and structural MRI data from 23 AD subjects and 23 Controls was completed using the FMRIB Software Library (FSL). The images were skull-stripped, registered, and normalised. LC masks were created from the NM-MRI also using FSL. The subsequent data was processed using the CONN toolbox. Seed-to-voxel and ROI-ROI analysis were used to produce connectivity maps and comparisons were conducted between AD and Controls, Left and Right LC, Mild and Moderate AD, and resting state networks. In comparison to Controls, AD subjects had reduced LC connectivity in the subcallosal (p-FDR=0.016417), increased LC connectivity in the right supramarginal and postcentral gyri (p-FDR=0.000002), and reduced connectivity in the default mode network (p-FDR=0.000286) and sensorimotor network (p-FDR=0.027524). The left LC in the AD subjects had a decreased number of significant connections to the amygdala and vermis, compared to the right LC. The number of significant LC connections decreased with progression from controls to mild AD to moderate AD. This study provides new evidence of reduced LC connectivity in AD patients and asymmetrical reduction in the LC skewed towards the left LC. LC connectivity reduction could indicate pathogenesis and progression of AD, aiding prediction of disease progression and development of novel intervention targets.

Key Words

Locus coeruleus, functional, connectivity, Alzheimer’s Disease, default mode network, sensorimotor network, visual network, structural MRI, functional MRI, neuromelanin-sensitive MRI