A systematic review of locus coeruleus degeneration detected by neuromelanin sensitive MRI technique in patients with Alzheimer's disease

Yuqing Chen[1], Teng Chen[2], Ruihua Hou[3]

1 School of Clinical Medicine, Addenbrooke's Hospital, University of Cambridge, Cambridge, UK ; 2 Department of Neurosurgery, Qilu Hospital of Shandong University, Jinan, Shandong, China
3 Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, Southampton, UK

Background

The locus coeruleus(LC) is a bilateral nucleus located in the dorsal pontine tegmentum and is the major source of noradrenaline(NA), which plays a key role in cognition. While cognitive decline in Alzheimer disease(AD) has primarily been related to dysfunction within the cholinergic system in the nucleus basalis, there is considerable research evidence indicating extensive LC degeneration in AD, with some suggesting that it is among the earliest pathologies. Therefore, the early vulnerability of the LC to AD is of considerable clinical significance, as this raises the possibility that changes of the LC activity may provide early detection markers for diagnosis as well as early intervention targets to delay AD progression. However, the contribution of LC degeneration to cognitive decline in the development of AD has been underappreciated due to methodological difficulties, with most evidence coming from animal and post-mortem studies. The absence of reliable non-invasive direct measures of the LC remains the biggest challenge. Recent research indicates that LC visibility is driven by neuromelanin content of noradrenergic neurons and the intrinsic neuromelanin-sensitive MRI technique enables direct visualisation of the LC.

Aims & Research Question

Can locus coeruleus degeneration be detected by neuromelanin sensitive MRI technique in patients with Alzheimer's disease?

Methods

A systematic search of the literature was performed on electronic databases including PubMed, Web of Science, and Embase. Human imaging studies employing neuromelanin-sensitive MRI technique to measure LC degeneration were included in this review. Screening, data extraction, and quality assessment were undertaken following PRISMA guidelines for preferred reporting of systematic reviews.

Results

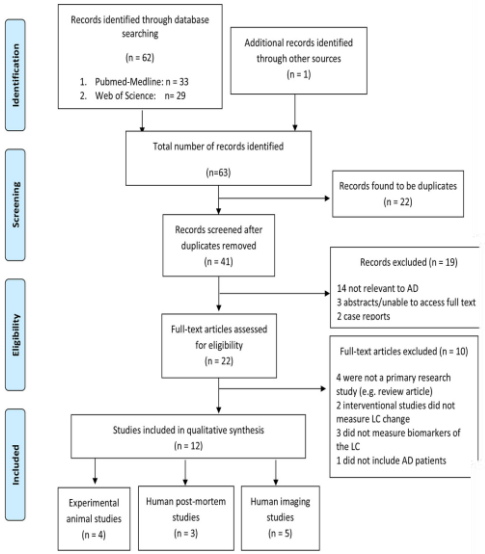
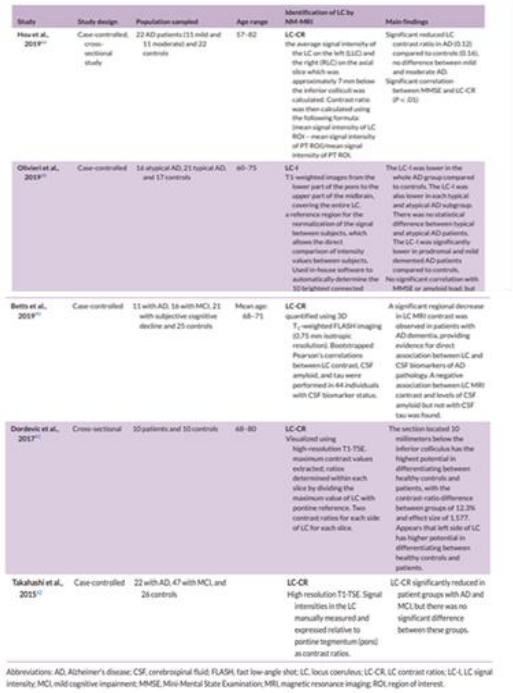


Figure 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram of study selection

Table 1 Data extraction table of human NM-MRI studies



Study	Study design	Population sampled	Age range	Identification of LC by NM-MRI	Main findings
Hou et al., 2019[41]	Case-controlled, cross-sectional study	22 AD patients (11 mild and 11 moderate) and 22 controls	57–82	LC-CR: the average signal intensity of the LC on the left (LLC) and the right (RLC) on the axial slice which was approximately 7 mm below the inferior colliculi was calculated. Contrast ratio was then calculated using the following formula: (mean signal intensity of LC ROI − mean signal intensity of PT ROI)/mean signal intensity of PT ROI.	Significant reduced LC contrast ratio in AD (0.12) compared to controls (0.16); no difference between mild and moderate AD. Significant correlation between MMSE and LC-CR ($P < .01$)
Olivieri et al., 2019[42]	Case-controlled	16 atypical AD, 21 typical AD, and 17 controls	60–75	LC-I: T1-weighted images from the lower part of the pons to the upper part of the midbrain, covering the entire LC. a reference region for the normalization of the signal between subjects, which allows the direct comparison of intensity values between subjects. Used in-house software to automatically determine the 10 brightest connected	The LC-I was lower in the whole AD group compared to controls. The LC-I was also lower in each typical and atypical AD subgroup. There was no statistical difference between typical and atypical AD patients. The LC-I was significantly lower in prodromal and mild demented AD patients compared to controls. No significant correlation with MMSE or amyloid load. but
Betts et al., 2019[43]	Case-controlled	11 with AD, 16 with MCI, 21 with subjective cognitive decline and 25 controls	Mean age: 68–75	LC-CR: quantified using 3D T_1-weighted FLASH imaging (0.75 mm isotropic resolution). Bootstrapped Pearson's correlations between LC contrast, CSF amyloid, and tau were performed in 44 individuals with CSF biomarker status.	A significant regional decrease in LC MRI contrast was observed in patients with AD dementia, providing evidence for direct association between LC and CSF biomarkers of AD pathology. A negative association between LC MRI contrast and levels of CSF amyloid but not with CSF tau was found.
Dordevic et al., 2017[44]	Cross-sectional	10 patients and 10 controls	68–80	LC-CR: Visualized using high-resolution T1-TSE. maximum contrast values extracted; ratios determined within each slice by dividing the maximum value of LC with pontine reference. Two contrast ratios for each side of LC for each slice.	The section located 10 millimeters below the inferior colliculus has the highest potential in differentiating between healthy controls and patients, with the contrast-ratio difference between groups of 12.3% and effect size of 1.577. Appears that left side of LC has higher potential in differentiating between healthy controls and patients.
Takahashi et al., 2015[45]	Case-controlled	22 with AD, 47 with MCI, and 26 controls		LC-CR: High resolution T1-TSE. Signal intensities in the LC manually measured and expressed relative to pontine tegmentum (pons) as contrast ratios.	LC-CR significantly reduced in patient groups with AD and MCI, but there was no significant difference between these groups.

Abbreviations: AD, Alzheimer's disease; CSF, cerebrospinal fluid; FLASH, fast low-angle shot; LC, locus coeruleus; LC-CR, LC contrast ratios; LC-I, LC signal intensity; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; ROI, region of interest.

Results

Recent advances in neuroimaging have offered the opportunity for direct visualisation of LC degeneration. Five studies were found from the literature search, which all used neuromelanin-sensitive MRI. All these images were analyzed, and contrast ratios or intensities compared. This was performed by manually defining regions of interest and use of a reference region for the normalisation of the signal between subjects. LC-CR/LC-I were found to be significantly reduced in patient groups with AD compared to the healthy control group in all six studies. These results provide strong evidence for a direct association between LC MRI contrast using in NM-MRI imaging and CSF biomarkers of AD pathology. These findings also mimic what has been observed in post-mortem studies, which show a reduction in LC cell count in AD brains compared to those without cognitive impairment. Studies also sought to determine the location of the highest LC/Pons ratio within the LC demonstrating promise as a tool to aid AD Diagnosis.

Conclusions

The current systematic review strongly supports the use of the neuromelanin-sensitive MRI technique to detect the LC degeneration as a biomarker for AD neuropathology. Future research are warranted to characterize how LC signals evolve at different stages of AD, which could lead to novel intervention approaches to delay or prevent cognitive decline.