Methodologies for investigating the locus coeruleus in-vivo using ultra high-field MRI

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Abstract

Background: One of the first brain regions to accumulate hyperphosphorylated tau is the locus coeruleus (LC), where post-mortem studies have shown LC volume loss as early as Braak stage 0. Methods have been developed to investigate the integrity of the LC in-vivo in order to aid early detection of individuals at risk for neurodegenerative disease. Some post-mortem data suggests deterioration of the rostral LC with age; however, discrepancies exist between in-vivo findings concerning the structural integrity of the LC across the lifespan, likely due to different methodologies and samples used. This study aims to compare different methods of LC delineation in-vivo across the entire adult lifespan to the golden standard of post-mortem histology.

Method: The study comprised 100 cognitively normal participants with a wide age span (30-87 years). Using high-resolution 7T imaging, we investigated both a univariate and multivariate template-guided process to delineate the LC in-vivo. These template processes involved using ANTs image registration software to warp individual images to a common template space based on the LC-signal sensitive magnetization transfer turbo flash (MT-TFL) images (univariate) or a combination of MT-TFL images and T1-weighted structural images (multivariate). After template creation, the LC was delineated by four independent investigators and the resulting LC mask was applied to each individual image. We also investigated manual delineation of the LC at the individual level as a method. Regression models were constructed to investigate the slice-by-slice association between LC signal intensity and age while correcting for sex differences.

Results: Preliminary results suggest no association between age and integrity of the LC in either of the tested methods after correction for multiple comparisons.

Discussion: Preliminary results do not show a decrease in LC integrity with age, but rather a lack of age-related decline. This may be due to the limitations of the methods applied. Manual delineations are sensitive to rater bias, while the template creation process is prone to inaccurate registrations and optimization of the template creation process is needed. Further analyses will include the addition of a machine learning based method to delineate the LC as well as an automated cluster-based thresholding method.