Brainstem specific warping improves locus coeruleus functional imaging in humans

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Introduction

The locus coeruleus (LC), a specific brainstem structure containing noradrenergic neurons [1], has recently attracted much interest because the LC is involved in attention processes and attention modulations [2]. The accurate localisation of LC activity with functional imaging in group studies was questioned since the LC is anatomically difficult to localise on standard functional (EPI) or structural (T_1-weighted) MR images. We aim to show here that standard EPI-based normalisation leads to approximate alignment of the LC across subjects, and that using a T_1-based brainstem specific normalisation leads to an accurate match of the group averaged LC localisation.
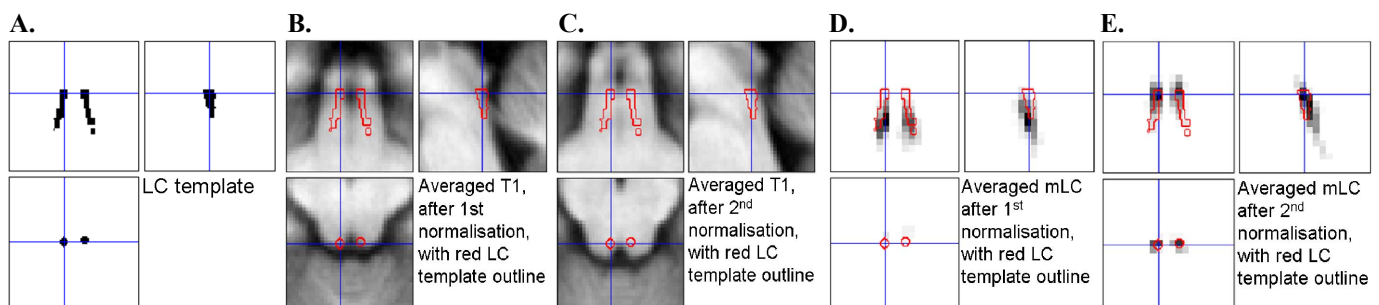
Material and methods

Data: Twenty healthy human subjects were scanned on a Siemens Allegra 3T scanner. For each subject a series of images were acquired: a temporal series of low-resolution functional images (EPI, 64x64x32 voxels, 3.4x3.4x3.9 mm^3), one high-resolution T_1-weighted structural image (MDEFT, 176x240x256 voxels, 1x1x1 mm^3) and a high-resolution T_1-turbo spin echo image (T_1-TSE, 400x512x10 voxels, 0.4x0.4x3 mm^3). The neuromelamin produced by the noradrenergic neurons in the LC shows a brighter intensity than the surrounding tissue in the T_1-TSE images, allowing the LC to be precisely and individually localised.

Methods: Before any processing, an expert manually delineated the bilateral LC volumes on the T_1-TSE image of each subject and saved it as a "masked-LC" image (mLC). Using the SPM5 software, each individual dataset was processed as follows: 1) The EPI time series is realigned to account for subject's movement and a mean-EPI image is created. 2) The T_1, T_1-TSE and mLC are coregistered to the mean-EPI. 3) First normalisation step: the mean-EPI is used to estimate the normalisation parameters (affine and non-linear warping, EPI template) to warp the individual EPI images and the coregistered T_1, T_1-TSE and mLC images into MNI space. 4) Second normalisation step: the warped T_1 image is used to estimate the parameters of a brainstem specific normalisation step (affine transform only, T_1 template and a template space brainstem mask) [3] to "brainstem-normalise" the warped T_1, T_1-TSE and mLC images. Importantly both normalisation steps are based on simple functional (EPIs) and structural (T_1) images. The T_1-TSE and mLC images are simply brought along as indicators of the true LC localisation within each subject. Finally, after both normalisation steps, the warped 20 T_1 and mLC images were averaged together. These average images reflect the variability across subjects in overall brain, brainstem and LC anatomy after each normalisation step. Then the averaged warped mLC images (1 or 2 normalisation steps) are compared to an LC template (Fig. A) obtained in an independent study with T_1-TSE data and an LC specific normalisation procedure [4].

Results and conclusions

The first normalisation step ensures an overall match between the subjects' brain anatomy. Consequently the averaged brainstem area is rather smooth (Fig. B) and the averaged mLC only approximately matches the LC template (Fig. D). After the second normalisation step, the brainstem area is better matched across subjects (Fig. C), at the cost of larger mismatch for the other structures. Importantly the averaged mLC image now matches closely the LC template (Fig. E) even though the mLC images were obtained using only EPI and T_1 based normalisation. In conclusion, a brainstem specific normalisation step can lead to an accurate anatomical alignment and localisation of the LC structure across subjects. This improved match effectively leads to an increased sensitivity in LC activation detection [5].

A. LC template

B. Averaged T1, after 1st normalisation, with red LC template outline

C. Averaged T1, after 2nd normalisation, with red LC template outline

D. Averaged mLC after 1st normalisation, with red LC template outline

E. Averaged mLC after 2nd normalisation, with red LC template outline

References

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