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Functional connectivity alterations in the noradrenergic system in patients with late-life major depression

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Background

•Neurodegenerative disorders are the most incapacitating and prevalent diseases in the elderly, and the first cause of dementia (1). Previous studies have associated initial pathological changes with Locus Coeruleus nucleus (LC) abnormalities (2). LC is involved in attentional function and is the major source of noradrenergic neurotransmission (3), targeting different cortical and subcortical brain regions (4).

•Structural alterations of the LC have previously been reported in neurodegenerative and psychiatric disorders (5). However, fewer studies have evaluated its functional alterations.

•In this study, **we investigated LC activity and functional connectivity during performance of an attentional oddball task in patients with disorders conferring an increased risk for developing neurodegenerative disorders, such as late-life major depression (MD) and mild cognitive impairment (MCI).**

Methods

•We assessed 20 patients with MD (mean age ± SD=67.05 ± 0.96, 13 females), 16 patients with MCI (mean age ± SD=71.13 ± 0.71, 10 females), and 26 healthy controls (HC) (mean age ± SD=67.42 ± 0.85, 16 females). All participants underwent a functional magnetic resonance assessment (in a Philips 3T Ingenia scanner) during the performance of a visual oddball task, where participants had to discriminate between standard and salient/oddball stimuli. Participants also underwent a T1-weighted neuromelanin-sensitive sequence for LC localization.

•Images were preprocessed and de-noised with the CONN fMRI Connectivity toolbox (6), implemented in MATLAB R2017b (Mathworks, Natick, MA, USA). Firstly, we assessed task-related activations with SPM12 software (http://www.fil.ion.ucl.ac.uk/spm/). In a second step, we performed a voxel-to-voxel functional connectivity analysis. Next, we used the result from the voxel-to-voxel analysis to perform a whole-brain seed-based modulation of functional connectivity analysis (i.e., Psychophysiological Interactions).

•All connectivity analyses were done with the CONN toolbox, and seed-based analysis results were subject to a family-wise error correction for multiple comparisons following a threshold-free cluster enhancement (TFCE) non-parametric test, using the TFCE Toolbox for SPM12 (http://www.dbm.neuro.uni-jena.de/tfce/).

Results

•At the behavioral level, groups showed significant differences in oddball task performance. Specifically, MCI patients showed more omission (p= 0.048, F= 3.210) and commission errors (p= 0.002, F= 7.239) than the other two groups. We did not observe, however, significant across-group differences in task-related activations.

•Conversely, patients with MD, in comparison with the other two groups, showed lower global connectivity degree during oddball stimuli detection in a cluster encompassing the right caudal LC (peak in x= 6, y= -38, z= -36; k_E= 11; TFCE= 53.16; p= 0.032) (Figures 1 and 2).

•Patients with MD showed a reduced functional connectivity between this right LC cluster and the right fusiform gyrus (FG) (TFCE= 602.65, p= 0.001, k_E= 1100), the left and right cerebellar hemispheres (TFCE= 485.47, p= 0.001, k_E= 449), and the left anterior cingulate cortex (ACC) (TFCE= 413.75, p= 0.001, k_E = 76) (Figure 3 a-e).

•Interestingly, in patients with MD the connectivity between the LC and the FG correlated negatively with the age at disorder's onset (p= 0.024, r= -0.503), while connectivity between the LC and the ACC showed also negative correlations in this same group with oddball task reaction time (p= 0.042, r= -0.471), the score in the Geriatric Depression Scale (p= 0.037, r= -0.468), and the number of previous depressive episodes (p= 0.037, r= -0.468) (Figure 3 f).

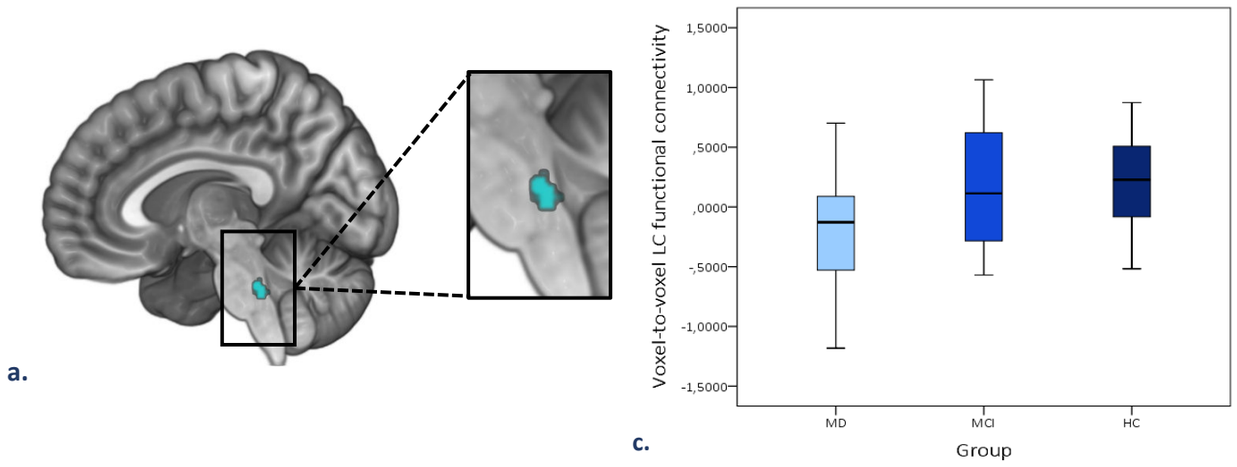

Fig 1. a) Sagittal view of the cluster showing a decreased voxel-to-voxel functional connectivity between the right caudal LC and the rest of the brain, observed in patients with MD compared to MCI and HC participants.

b) Basal view of this same result.

c) Box-plot of the differences across our three groups. Patients with MD showed a reduced LC voxel-to-voxel functional connectivity in comparison with MCI and HCs.

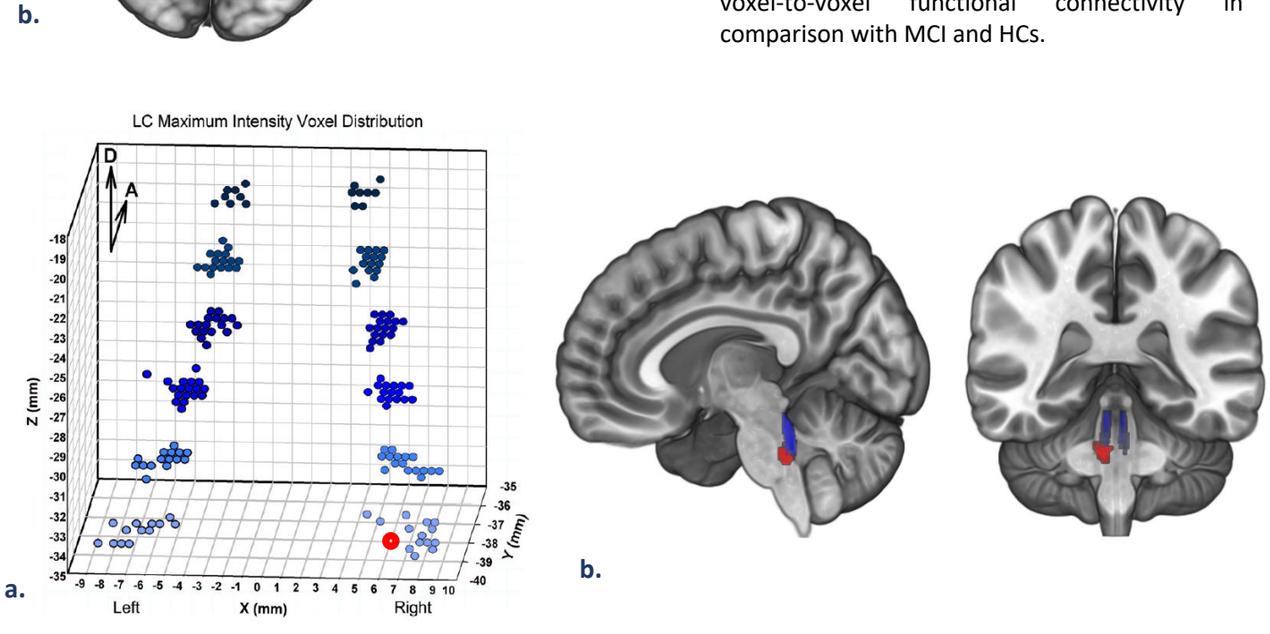

Fig 2. Localization of the voxel-to-voxel LC cluster overlaid onto a) a previously published LC coordinate map (7), and b) a LC map from the T1 neuromelanin-sensitive sequence obtained for the participants of our study. In both plots, LC voxel-to-voxel result localization is indicated in **red**.

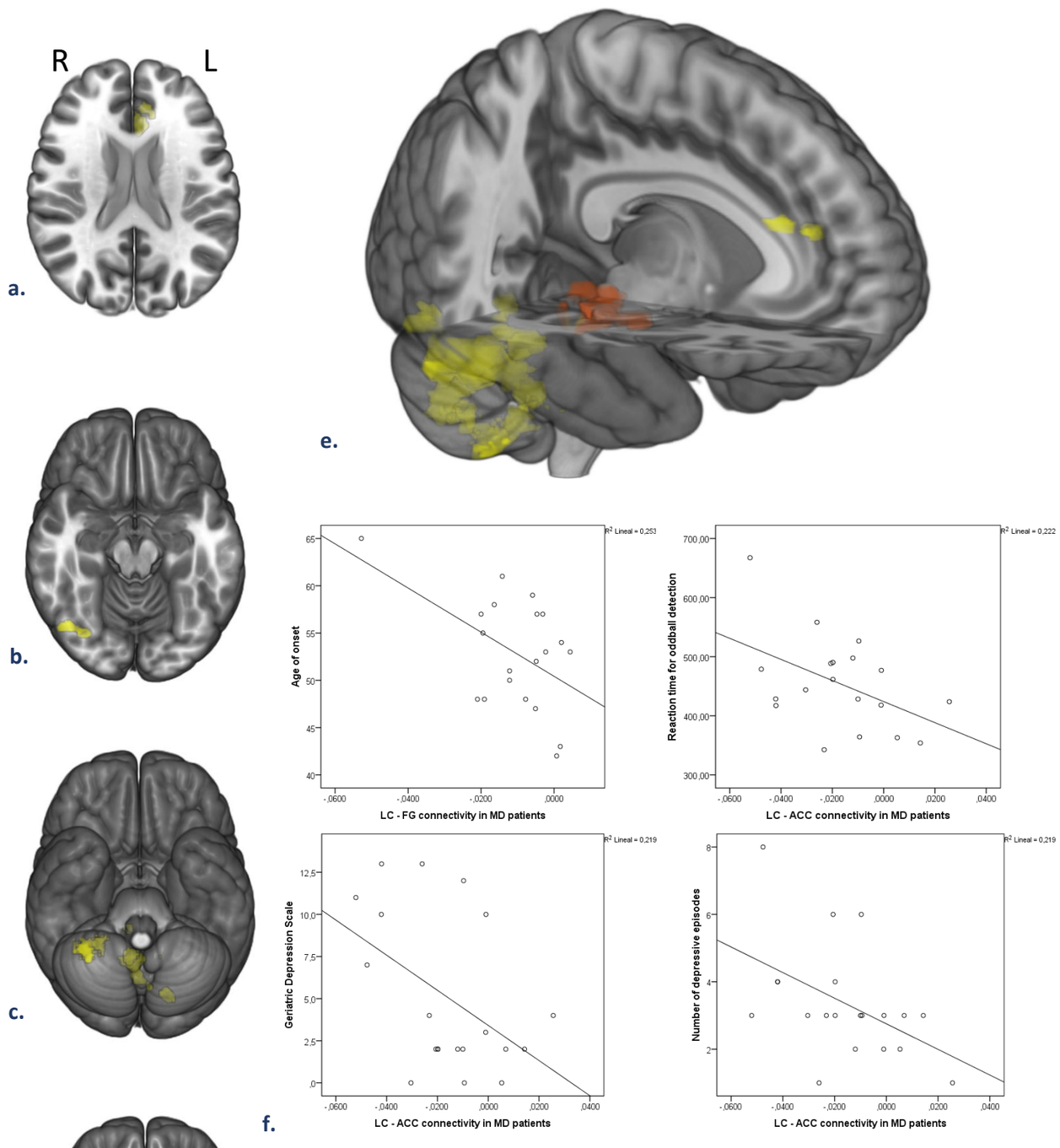

Fig 3. Decreased functional connectivity in patients with MD between the right LC and (a) the left anterior cingulate cortex, (b) the right fusiform gyrus, and (c - d) the left and right cerebellum (including the vermis).

(e) Overview of all the seed-based functional connectivity results.

(f) Correlations, in patients with MD, between LC-fusiform gyrus and LC-anterior cingulate cortex connectivity and different clinical and behavioral variables.

Conclusions

Reduced connectivity of the LC with the fusiform gyrus, the cerebellum and the anterior cingulate cortex during performance of an attentional task seems to specifically characterize patients with late-life MD, since this alteration was not observed in patients with MCI. Moreover, such finding was correlated with performance in oddball task, recurrence, late disorder's onset and a greater severity of depression symptoms, suggesting that it might be considered as an imaging marker for mood disorders detection and monitoring in elderly patients.

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