Neurobiology of Aging xxx (2014) 1–9

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

Relevance of parahippocampal-locus coeruleus connectivity to memory in early dementia

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ARTICLE INFO

Article history:
Received 13 February 2014
Received in revised form 10 October 2014
Accepted 30 October 2014

Keywords:
Locus coeruleus
Resting-state
Connectivity
Memory
Alzheimer's disease
MRI
Functional reorganization
Compensation
Consolidation
Retrieval
Parahippocampal gyrus
Medial temporal lobe

ABSTRACT

Neuropathology suggests an important role for the locus coeruleus (LC) in Alzheimer's disease (AD) pathophysiology. Neuropathology and structural damage in the LC appears to be one of the earliest changes. We hypothesize that reduced functional integration of the LC reflected by lower brain functional connectivity contributes to early memory dysfunction. To test this, we examined resting-state functional connectivity from the LC in 18 healthy older individuals and 18 mildly cognitively impaired patients with possible AD. Connectivity measures were correlated with memory scores. The left LC showed strong connectivity to the left parahippocampal gyrus that correlated with memory performance in healthy persons. This connectivity was reduced in aMCI patients. Lateralization of connectivity-memory correlations was altered in less impaired aMCI patients: greater right LC-left parahippocampal gyrus connectivity was associated with better memory performance, in particular for encoding. Our results provide new evidence that the LC, in interaction with the parahippocampal gyrus, may contribute to episodic memory formation. They suggest functional impairment and the possibility that associated compensatory changes contribute to preserved memory functions in early AD. Structural and functional LC-related measures may provide early AD markers.

1. Introduction

Alzheimer's disease (AD) is the most common form of dementia, characterized by behavioral and emotional problems and memory impairment progressing to more global cognitive dysfunction. With progression, these deficits increasingly impair performance of daily life activities and reduce quality of life of patients and caregivers. There is a growing interest in understanding the neuropathologic genesis of specific symptoms contributing to the developing dementia syndrome, to develop new methods of diagnosis, monitoring, and treatment.

The amyloid cascade hypothesis dominant in AD research (Korczyn, 2008) has suggested that the accumulation of amyloid plaques is a crucial etiopathogenic factor causing AD. This is supported by data confirming that amyloid plaques and neurofibrillary tangles are neuropathologic hallmarks of AD (Braak and Braak, 1991). Based on studies that often only considered the cerebrum, it is generally accepted that neurofibrillary tangle formation occurs in a well-defined order, starting in the medial temporal lobe (MTL) early in the disease and subsequently progressing toward the neocortical areas (Braak and Braak, 1991). By contrast, amyloid plaques first affect the posterior association cortices. The MTL areas might be affected, but this is not common in the early stages of AD (Braak and Braak, 1991; Thal et al., 2002).

However, Braak and Del Tredici (2012) have proposed an alternative novel disease model of AD (Braak and Del Tredici, 2012; Braak et al., 2011). In Braak and Del Tredici (2012), a large postmortem sample was examined, including the myelencephalon or metencephalon parts of the brain (Braak et al., 2011). Tau pathology was found in the locus coeruleus (LC), before any clinical symptoms or concomitant cerebral amyloid pathology was evident. Although tau and amyloid pathology has previously been observed in the brainstem nuclei of demented patients (Parvizi et al., 2001), this

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http://dx.doi.org/10.1016/j.neurobiolaging.2014.10.041

was the first study reporting tau pathology so early and focally in cognitively healthy individuals. This led the authors to formulate the novel hypothesis that the pathologic process of AD is initiated by tau pathology in the LC, which is then transported via anatomically connected neurons to the MTL to trigger subsequent neuropathologic changes associated with amyloid deposition (Braak and Del Tredici, 2012).

The locus coeruleus complex (LCC) is a group of small nuclei (Berridge and Waterhouse, 2003) situated deep in the pons and is the sole source of noradrenalin to most brain regions, including the MTL. Noradrenalin facilitates the interactions between networks or brain areas involved in several cognitive functions, and the LCC plays an important role in cognitive functions, including memory consolidation and retrieval (Sara, 2009).

Only a handful of structural imaging studies have investigated the LC with aging and AD. Neuronal loss and atrophy of the LC occurs during aging (Shibata et al., 2006) is an early event in AD and correlates with cognitive performance (Grudzien et al., 2007; Weinshenker, 2008). However, to date, the functional connectivity of the LCC in humans and its relevance to memory processes in early AD are unexplored. The aim of this study is to explore resting-state functional connectivities of the LCC and their relationship to episodic memory processes in patients with possible AD.

2. Methods

2.1. Participants

Eighteen patients with amnestic mild cognitive impairment (mean age: 65.1 years ± 4.5 standard deviation [SD]) were recruited from the Memory Clinic of the Academic Hospital Maastricht. These aMCI patients were matched for age and education with 18 cognitively healthy older participants (mean age: 64.6 years ± 3.4 SD) who displayed no signs of cognitive decline. Patients were included if they met the following criteria: diagnosis of mild cognitive impairment established by a clinical expert (Frans R. Verhey) with at least an impairment in the memory domain (−1.5 SD), according to the Petersen criteria (Petersen and Negash, 2008), the presence of cognitive complaints and a Clinical Dementia Rating score of 0.5 (Morris, 1993). These patients are from here on referred to as aMCI patients.

The control participants were recruited by means of advertisements in local newspapers. Control subjects were required to have a Clinical Dementia Rating of 0, no cognitive complaints and no evidence of cognitive deficits on testing. Hypertensive status was recorded based on the medical history (coded as yes or no). Only right-handed male individuals were included in both the patient and control groups to avoid uncontrolled lateralization effects. Participants were excluded from the study if they had a history of psychoactive medication use, abuse of alcohol or drugs, past or present psychiatric or neurologic disorders (i.e., epilepsy, stroke, Parkinson's disease, multiple sclerosis, brain surgery, brain trauma, electroshock therapy, heart disease, or brain infections), presence of depressive symptoms as indicated by the Hamilton Depression Rating Scale (HDRS; score ≥17; Hamilton, 1960) or contraindications for scanning. A neuroradiologist reviewed the MR images to ensure absence of clinically relevant neuropathology. Two control participants were excluded from this study because of structural brain abnormalities and were replaced.

The local Medical Ethics Committee approved the study and written informed consent was obtained from all participants in accordance to the 1964 Declaration of Helsinki and its later amendments.

2.2. Biomarker status

MTL atrophy was assessed blinded to group adherence by using a qualitative visual rating scale (Scheltens et al., 1992). Rating was performed on coronal T1-weighted images using a 5-point scale (medial temporal lobe atrophy scores), ranging from 0 (no atrophy) to 4 (severe atrophy) based on the height of the hippocampal formation and surrounding cerebrospinal spaces. According to recent work from our group, patients with an medial temporal lobe atrophy score of 3 or more (left and right scores summed) were considered as positive for AD risk (Clerx et al., 2013b). In our control group, 1 person had a score of 3, whereas none of the control participants had a score above 3. In the aMCI group, 16 of 18 patients (89%) had a score equal to or higher than 3, the other 2 aMCI patients had a score of 2. This indicates that the patients included in this study have most likely cognitive deficits because of AD pathology. According to recent criteria (Albert et al., 2011), these aMCI patients can be termed as prodromal AD patients.

Additionally, we also traced the left and right hippocampus and parahippocampal gyrus using the in-house developed software package General Image Analysis Tools (Gronenschild et al., 2010), which allows tracing of regions of interest in a triplanar and rotatable 3D surface-rendered view and calculation of gray matter volumes of interest. Both raters were blind to the demographic and cognitive characteristics of the participants. Intrarater reliability was determined by the intraclass correlation coefficient (>0.90) (Shrout and Fleiss, 1979). Tracing of the parahippocampal gyrus was performed on every coronal slice on which the hippocampus was visible. The subiculum was taken as the dorsal border and the collateral sulcus as the ventral border. The volume of the hippocampus included the hippocampus proper (including the dentate gyrus), the alveus, and the subiculum. The anterior and posterior borders were based on both sagittal and coronal sections of the brain. Significant group differences were found for the right parahippocampal gyrus ($p < 0.001$).

2.3. Procedures and neuropsychological assessment

Participants were invited twice. On the first day, the Hamilton Rating Scale Assessment (HDRS) was taken and a neuropsychological assessment took place, to confirm memory impairments in the patient group and to select a control group without cognitive problems. The tests were presented in the same order for each participant. The neuropsychological assessment included the Mini-Mental State Examination (Folstein et al., 1975), verbal fluency task (Van der Elst et al., 2006c), letter-digit substitution test (Van der Elst et al., 2006b), Stroop Color Word Task (Van der Elst et al., 2006d), verbal word learning task (WLT) (5 learning trials, delayed recall and recognition) (Van der Elst et al., 2005), and concept shifting task (Van der Elst et al., 2006a). Participants were familiarized with the magnetic resonance imaging (MRI) environment via a dummy scan session. The actual MRI scanning session took place during the second visit (at most 3 days later).

2.4. MRI acquisition

The MRI examination was performed using a 3.0 T whole-body MR system (Philips Medical Systems, Best, the Netherlands). Anatomic images were acquired with a T1 sequence: repetition time (TR) = 8 ms, echo time (TE) = 3.7 ms, fractional anisotropy (FA) = 8°, field of view (FOV) = 240 × 240 mm^2, voxel size = 1 mm isotropic, matrix size = 240 × 240, and number of slices = 180. Functional scans were collected using a T2* echo planar imaging sequence: TR = 2000 msec, TE = 35 msec, FA = 90°, FOV = 224 × 224 mm^2, voxel size = 3.5 mm isotropic, matrix size = 64 × 64, and