Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring 1 (2015) 14–23

Hippocampal subfield surface deformity in nonsemantic primary progressive aphasia

Adam Christensen[a,*], Kathryn Alpert[a], Emily Rogalski[b], Derin Cobia[a], Julia Rao[b], Mirza Faisal Beg[c], Sandra Weintraub[a,b,d], M.-Marsel Mesulam[a,b,d], Lei Wang[a,e]

[a]*Division of Clinical Psychology, Department of Psychiatry and Behavioral Sciences, Northwestern University, Feinberg School of Medicine, Chicago, IL, USA*
[b]*Cognitive Neurology and Alzheimer's Disease Center, Northwestern University, Feinberg School of Medicine, Chicago, IL, USA*
[c]*School of Engineering Science, Simon Fraser University, BC, Canada*
[d]*Department of Neurology, Northwestern University, Feinberg School of Medicine, Chicago, IL, USA*
[e]*Department of Radiology, Northwestern University, Feinberg School of Medicine, Chicago, IL, USA*

Abstract

Background: Alzheimer neuropathology is found in almost half of patients with nonsemantic primary progressive aphasia (PPA). This study examined hippocampal abnormalities in PPA to determine similarities to those described in amnestic Alzheimer disease.
Methods: In 37 PPA patients and 32 healthy controls, we generated hippocampal subfield surface maps from structural magnetic resonance images and administered a face memory test. We analyzed group and hemisphere differences for surface shape measures and their relationship with test scores and *APOE* genotype.
Results: The hippocampus in PPA showed inward deformity (CA1 and subiculum subfields) and outward deformity (CA2–4 + dentate gyrus subfield) and smaller left than right volumes. Memory performance was related to hippocampal shape abnormalities in PPA patients, but not controls, even in the absence of memory impairments.
Conclusions: Hippocampal deformity in PPA is related to memory test scores. This may reflect a combination of intrinsic degenerative phenomena with transsynaptic or Wallerian effects of neocortical neuronal loss.

Keywords: Frontotemporal dementia; Lobar degeneration; Multiatlas mapping; Structural magnetic resonance imaging (MRI); Memory; Neuroanatomy; Primary progressive aphasia (PPA); Alzheimer's disease (AD)

1. Introduction

The clinical course of primary progressive aphasia (PPA) is characterized by the initial progressive loss of language abilities and relative preservation of other cognitive functions, such as episodic memory [1]. There are three subtypes of PPA, each based on the most prominent type of language deficit in the clinical profile [2], but the preservation of memory is most easily demonstrated in nonsemantic PPA subtypes, namely, the agrammatic and logopenic variants, because they have relatively preserved language comprehension. Neuropathologically, PPA is heterogeneous: although the amyloid plaques and neurofibrillary tangles of Alzheimer's disease (AD) are predominant in the brains of some PPA patients, frontotemporal lobar degeneration (FTLD) pathology is predominant in others

Disclosures: Mr. Christensen: None, Ms. Alpert: None, Dr. Rogalski: NIH grant during the course of the study DC008552, R01 NS075075, Dr. Cobia: None, Dr. Rao: None, Dr. Beg: None, Dr. Weintraub: NIH grant during the course of the study DC008552, R01 NS075075, AG13854, Dr. Mesulam: None, Dr. Wang: None.

*Corresponding author. Tel.: +1-312-503-3981; Fax: +1-312-503-0527.
E-mail address: adam.a.christensen@gmail.com

http://dx.doi.org/10.1016/j.dadm.2014.11.013

[3–5]. Post-mortem studies have revealed that the prevalence of AD pathology in nonsemantic PPA subtypes ranges from 30% to 60% [4–7], and is highest in the logopenic subtype [4,6,8]. Although a significant accumulation of neurofibrillary AD pathology can be seen in the hippocampus/entorhinal cortex of PPA patients, its entorhinal-to-neocortical ratio is lower in PPA when compared with this ratio in post-mortem analysis of individuals with the more typical amnestic dementia of AD [3].

Medial temporal neurofibrillary pathology is the most characteristic feature of AD pathophysiology [9,10]. In AD associated with the amnestic dementia of the AD type (DAT), the neurofibrillary tangles accumulate in the entorhino-hippocampal complex at the earliest stages of the disease, even before symptom onset [11–13], and lead to regional atrophy of hippocampal subfields [14] and entorhinal [15] cortices as the disease progresses. In DAT, deficits in visual and verbal memory are known to correlate with both post-mortem neuropathological measures [16] and in vivo atrophy of the entorhinal cortex and hippocampus [11].

Although neuroimaging has revealed atrophy of the left hemisphere language network in PPA [17], less consistency is found in the hippocampus. For example, van de Pol et al. [18] found no significant hippocampal atrophy in patients with progressive nonfluent aphasia, but Gorno-Tempini et al. [19] found atrophy of the anterior left hippocampus in a nonsemantic logopenic subtype. A study of nine patients with nonsemantic progressive nonfluent aphasia and 21 controls found no overall total hippocampal volume difference between groups, although the left was smaller than the right in the patient group [20]. Using spherical harmonics, the same study found inward deformity in the patients' left hippocampus relative to the controls. These studies tended to have small sample sizes and all but one study examined only volumes but not shape, factors that may have contributed to inconsistent results.

The goal of this study was to compare the shape of the hippocampal surface, including its subfields, between PPA subjects and matched controls. We predicted a spectrum of hippocampal deformity in PPA based on the fact that some might have AD neuropathology, whereas others might not. We also predicted a greater degree of deformity in the left hippocampus, reflective of the left hemispheric focus of PPA. Study methodology involved a new multiatlas FreeSurfer-initiated Large-Deformation Diffeomorphic Metric Mapping (ma-FSLDDMM) procedure for the mapping of the hippocampal structure, and the assessment of nonverbal memory to correlate with hippocampal morphology. ma-FSLDDMM was based on our previously published single-atlas technique (sa-FSLDDMM) [21,22], for automated brain segmentation in high-resolution structural scans which combined initial FreeSurfer segmentation of gray and white matter structures (http://surfer.nmr.mgh.harvard.edu) with a smoothed approximation via Large-Deformation Diffeomorphic Metric Mapping (LDDMM) [23]. Compared with single-atlas methods, approaches that combine maps from multiple atlases that best match any individual subject's scan features have been shown to improve segmentation accuracy and reduce biases [24]. We chose the nonverbal Faces subtest in the Wechsler Memory Scale III (WMS-III) [25] to assess episodic memory. Although even an apparently nonverbal memory test can elicit internal verbalization [26], this choice avoided the pitfalls of using story or word-list recall to test episodic memory in patients with PPA [19,27]. Finally, the ε4 allele of the apolipoprotein ε (*ApoE*) gene has been revealed as a risk factor for amnestic but not aphasic dementias [28]. Because the genotype does not predict AD pathology in PPA, we hypothesized that the presence of the *ApoE* ε4 allele would not influence a patient's hippocampal shape or memory performance.

2. Methods

2.1. Participants and assessments

The present study consisted of the analysis of data derived from a larger PPA Research Program at Northwestern University Feinberg School of Medicine, and included 37 PPA and 32 control participants. The protocol for recruitment, comprehensive assessment of language and nonlanguage cognitive functions, magnetic resonance imaging (MRI) scanning, and *ApoE* genotyping was approved by the Institutional Review Board of Northwestern University; informed consent was obtained before evaluation.

All participants were right-handed. Diagnoses were established by consensus from experienced clinicians (MM, SW) according to previously published criteria [2] based on clinical interview, cognitive testing with the Uniform Data Set of the National Institute on Aging Alzheimer Disease Centers program [29], and review of prior diagnostic tests such as MRI and Positron Emission Tomography (PET) scans. *ApoE* genotyping was completed at Northwestern University using previously described methods [28]. PPA participants had obtained the diagnoses of PPA-G (nonfluent, agrammatic) and PPA-L (logopenic) variants, referred to in this article as nonsemantic variants. Aphasia severity was assessed using the Aphasia Quotient score from the Western Aphasia Battery [30] containing subtests of auditory comprehension, naming, repetition, and spontaneous speech.

Episodic memory was assessed using the WMS-III Faces subtest of visual-nonverbal recognition memory [25]. A similar test, the Warrington Recognition Memory Test (RMT), which assesses the immediate recognition of both words and faces, has been shown to be sensitive to hippocampal damage [31]. The WMS-III Faces test was chosen because of the addition of a delayed recognition condition, whereas the RMT tests only immediate