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Neuroimaging

Thinner temporal and parietal cortex is related to incident clinical progression to dementia in patients with subjective cognitive decline

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Abstract

Introduction: We aimed to investigate if thinner cortex of the Alzheimer's disease (AD)-signature region was related to clinical progression in patients with subjective cognitive decline (SCD).

Methods: We included 302 SCD patients with clinical follow-up (≥1 year) and three-dimensional T1 magnetic resonance imaging. We estimated AD-signature cortical thickness, consisting of nine frontal, parietal, and temporal gyri and hippocampal volume. We used Cox proportional hazard models (hazard ratios and 95% confidence intervals) to evaluate cortical thickness in relation to clinical progression to mild cognitive impairment (MCI) or dementia.

Results: After a follow-up of the mean (standard deviation) 3 (2) years, 49 patients (16%) showed clinical progression to MCI (n = 32), AD (n = 9), or non-AD dementia (n = 8). Hippocampal volumes, thinner cortex of the AD-signature (hazard ratio [95% confidence interval], 5 [2–17]) and various AD-signature subcomponents were associated with increased risk of clinical progression. Stratified analyses showed that thinner AD-signature cortex was specifically predictive for clinical progression to dementia but not to MCI.

Discussion: In SCD patients, thinner regional cortex is associated with clinical progression to dementia.

Keywords: Subjective cognitive decline; Cortical thickness; MRI; Cognitively normal; Cognitive complaint; Dementia; MCI; Alzheimer's disease cortical signature

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1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by behavioral changes and gradual decline of cognitive function and daily functioning [1]. Atrophy, particularly of the medial temporal lobe, is the magnetic resonance imaging (MRI) hallmark of dementia due to AD [2,3]. It has been suggested that a specific pattern of regional atrophy in the temporal, parietal, and frontal gyri, which has been coined as the cortical AD-signature, shows changes very early in the disease process [4,5]. Moreover, cortical thinning of the AD-signature region in cognitively normal elderly has been suggested to predict AD dementia due to as early as a decade before diagnosis [6].

Cognitively normal memory clinic patients who perceive subjective cognitive decline (SCD), are at a threefold increased risk of clinical progression to dementia [7–11]. In an effort to explore the earliest signs of AD, a framework has been proposed that provides a common concept and terminology for studying subjective experience of cognitive decline [12].

Memory clinic–based studies have demonstrated decreased gray matter volumes [13–15] and cortical thinning [16] in medial temporal regions in SCD compared with healthy controls. It is still unclear, however, whether such smaller brain structures are related to clinical progression over time in SCD patients. Therefore, we investigated whether baseline cortical thickness is related to incident clinical progression in patients with SCD in a tertiary referral center. More specifically, if thinner cortex of the AD-signature in cognitively intact patients with self-perceived memory complaints is associated with increased risk of mild cognitive impairment (MCI) or dementia over time.

2. Methods

2.1. Study population

We included 302 SCD patients from the Amsterdam Dementia Cohort [17,18] according to the following inclusion criteria: availability of brain MRI and clinical follow-up ($\geq$1 year). Patients were referred by a general practitioner or local hospital (according to Dutch healthcare system regulations) and subsequently visited our memory clinic between 2000 and 2012. At baseline, all patients underwent a standardized dementia screening, including extensive neuropsychological assessment, physical, and neurologic examination as well as laboratory tests and brain MRI. Patients were labeled as having SCD when they presented with cognitive complaints, and results of clinical assessments were within normal range. Patients were excluded if criteria for MCI, dementia, or any other neurologic or major psychiatric (e.g., major depression) disorders known to cause cognitive complaints were met (at baseline) during a multidisciplinary consensus meeting according to international research consensus criteria [12]. In addition, we offered patients a lumbar puncture for research purposes. We determined β-amyloid1–42 and total tau in cerebrospinal fluid (CSF) using sandwich enzyme-linked immunoassays (Innogenetics, Belgium) [19,20].

Follow-up took place by annual visits to our memory clinic in which medical history, neuropsychological assessment, and general physical and neurologic examination were repeated. The primary outcome in this study was clinical progression, which was defined as progression to MCI, AD, or another type of dementia as diagnosed at follow-up by an interdisciplinary consensus meeting based on international diagnostic or research consensus criteria [21–26]. In this study, for subjects who progressed to MCI, we further determined the MCI subtype (amnestic, multidomain, or nonamnestic) based on the neuropsychological evaluation at the time of clinical progression. Our neuropsychological test battery included tests that measured cognitive functioning in the domains of memory, attention, executive functioning, and language [17]. For the memory domain, we used the Dutch version of the Rey Auditory Verbal Learning Test (RAVLT) direct and delayed recall and visual association task A. For attention we used digit span forward, Trialmaking Test-A (TMT-A), and Stroop 1 and 2. For the executive function domain, we used Trialmaking Test-B (TMT-B), digit span backward, and Stroop color-word test. For the language domain, we used category fluency animals and visual association task naming. The medical ethics committee of the VU University Medical Center approved the study. All patients provided written informed consent for their clinical data to be used for research purposes.

2.2. MRI acquisition

Structural MRI was performed at the first visit to the memory clinic using 1.0 T (n = 182) Siemens Magnetom Impact (Siemens, Erlangen, Germany) and 3.0 T (n = 120) Signa HDxt (General Electric, Milwaukee, WI) scanners.

For cortical thickness estimations, three-dimensional (3D) T1-weighted images were acquired using the following sequences: magnetization-prepared rapid acquisition gradient-echo (MPRAGE) on 1.0 T (168 slices, matrix = 256 × 256, voxel size = 1 × 1 × 1.5 mm^3, echo time = 7 ms, repetition time = 15 ms, inversion time = 300 ms, and flip angle, 15°) and Fast Spoiled Grass Sequence with Inversion Recovery-Prepared (IR-FSPGR) on 3.0 T (176 slices, matrix = 256 × 256, voxel size = 1 × 0.9 × 0.9 mm^3, echo time = 3 ms, repetition time = 7.8 ms, inversion time = 450 ms, and flip angle 12°). In addition, the scan protocol included T2-weighted images and fluid attenuated inversion recovery. A standard circular head coil was used. Motion was restricted using expandable foam cushions. Scans with movement or any other image (reconstruction) artifacts were excluded (1.0 T, n = 5; 3.0 T, n = 7). T1-weighted images acquired on 3.0 T were corrected for gradient nonlinearity in all three directions.