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Featured Article

Staging of amyloid β, t-tau, regional atrophy rates, and cognitive change in a nondemented cohort: Results of serial mediation analyses

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Abstract

Introduction: Current models posit a sequence of amyloid β (Aβ), tau, atrophy, and cognitive change leading to Alzheimer's disease, but ambiguities remain. We examined these sequences via serial mediations.

Methods: We studied normal controls, early mild cognitive impairment, and late mild cognitive impairment individuals from the Alzheimer's Disease Neuroimaging Initiative 2 database for the mediation of baseline cerebrospinal fluid Aβ effects on 2-year cognitive change via regional longitudinal atrophy rate (AR) alone or AR and tau.

Results: In normal controls, Aβ correlated directly with regional ARs and memory loss, with no mediations. In early mild cognitive impairment, tau and lateral temporal ARs serially mediated the influence of Aβ on memory while Aβ affected memory via hippocampal AR. Late mild cognitive impairment consistently showed serial mediations of tau followed by atrophy. However, Aβ effects on memory also continued to be specifically mediated by medial temporal ARs without intermediate tau.

Discussion: Biomarker sequences vary by region and disease state, suggesting the need to refine current cascade models.

Keywords: Alzheimer's disease; MCI; Amyloid β; Tau; Cognitive aging; Longitudinal atrophy

1. Background

Recent biomarker cascade models [1–3] depict biomarker evolution as a sequence of sigmoid abnormality curves, in which amyloid β (Aβ) abnormality precedes abnormality in tau, which in turn leads to elevated brain degeneration and accelerated cognitive decline (changes in cognition [ΔCog]). The earliest model [1] featured a strict succession of abnormality curves, with Aβ always in the lead, but a later refinement acknowledged that preexisting tau abnormality might occur before Aβ while still remaining below threshold levels of detection [2]. Alternatively, a combined neurodegeneration category of tau with other markers—magnetic resonance imaging (MRI) atrophy and [18]fluorodeoxyglucose (FDG) measures of hypometabolism—might exist in levels that are barely detectable before Aβ abnormality [3]. Although these models acknowledge that tau may be independently deposited in brainstem, locus coeruleus, and medial temporal lobe regions (MTL), all models nonetheless make explicit predictions about

[1]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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biomarker sequences. The first is that Aβ is the necessary inducer of increasingly elevated tau/neurodegeneration [3]. Second, to the extent that Alzheimer's disease (AD)–related brain atrophy and FDG decline can be distinguished from effects of aging [3], these will not occur without abnormal tau. Finally, cognitive decline will not be present without abnormal neurodegeneration (see Fig. 5 in [2] and Fig. 2A–C in [3]). These predictions therefore posit a very clear ordering, in which the only possible deviation may be the presence of age-related medial temporal tau or neurodegeneration before Aβ abnormality.

There have been several studies investigating the sequential predictions of these models [4–9]. The main difficulty for definitive verification is that there does not exist a dataset with sufficiently long follow-up to monitor longitudinal changes, given that the buildup of brain Aβ is postulated to take decades [10]. In response, studies to date have relied implicitly or explicitly on the concept of mediation—the direct effects of baseline Aβ on cognition could be largely explained or attenuated by one or more intervening variables such as tau, MRI atrophy, or FDG—using cross-sectional or longitudinal study designs.

Mediation effects have been inferred using hierarchical models [4,5], in which variables are successively introduced one at a time to see if they diminish the effects of variables which were significant in a preceding model. Alternatively, an explicit mediation model incorporating a pathway of the form A → B → C (see Fig. 1C in [11]) estimates whether the product of the effects A → B times B → C significantly reduces the direct unmediated effect A → C. Studies using explicit modeling have investigated the roles of cortical atrophy [8], regional atrophy and FDG [7] or regional baseline and change in FDG [6] as mediators of effects of Aβ or tau on cognitive change.

The full sequential hypothesis of Aβ → tau → atrophy → ΔCog has been previously investigated [5]. These authors found partial support for the full sequence but also some unexpected deviations. For example, cerebrospinal fluid (CSF) Aβ and tau had independent effects on hippocampal baseline volume and longitudinal atrophy as well as on ventricle baseline volume and longitudinal enlargement. Meanwhile, CSF tau had an independent effect on baseline cognition. The study of the partial sequence Aβ → tau → atrophy for hippocampus, precuneus, and (as a control) the precentral gyrus [4] also found some deviations; for example, in normals, Aβ directly predicted hippocampal atrophy without the mediation of tau. Meanwhile, all the explicit mediation studies [6–8] found regionally significant mediation effects of regional cortical atrophy [7,8] or FDG decline [6,7] for the effects of baseline Aβ or tau on cognition.

This brief survey of current literature suggests that a systematic study of the full biomarker sequence, including regional variation of atrophy rates in different diagnostic categories, may be useful to clarify the extent of applicability for the posited succession of events [1–3]. Serial mediation models—incorporating pathways of the format A → B_1 → B_2 → C and all possible subpathways (see [11], Fig. 1D)—offer the means to simultaneously test alternative mediations of the effects of Aβ on ΔCog via selected regional atrophy, with and without the influence of tau, and of tau, independent of regional atrophy. This allows evaluation of competing hypotheses. By comparison, previous mediation studies [6–8] did not incorporate all these factors and thus provided only partial tests of the full biomarker cascade, whereas the hierarchical model analysis [5] examined only a few regions of interest (ROIs). Our models included 2-year atrophy rates of 10 selected brain regions known to be involved in early tau deposition independent of Aβ [12,13] as well as of others known to be associated with the trajectory of cognitive decline in AD [7,14–17].

2. Methods

2.1. Study design

Data were obtained from the database of the Alzheimer's Disease Neuroimaging Initiative (ADNI) (adni.loni.usc.edu). The National Institute of Aging, the National Institute of Biomedical Imaging and Bioengineering, the Food and Drug Administration, private pharmaceutical companies, and nonprofit organizations launched ADNI in 2003 as a public-private partnership. The primary goal of ADNI has been to test whether serial MRI, positron emission tomography, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early AD.

The principal investigator of ADNI is Michael Weiner, MD, VA Medical Center and University of California, San Francisco. For current information on ADNI, see www.adni-info.org.

2.2. Study participants

The study population was drawn from nondemented participants in the ADNI-2 database (Table 1). Inclusion/exclusion criteria are described at www.adni-info.org. Briefly, subjects in ADNI-2 are between the ages of 55 and 90 years at enrollment, have completed at least six years of education, and are free of any significant neurological disease other than AD. Normal controls (CNs) are distinguished from MCI categories by the Clinical Dementia Rating [18] score of 0 versus 0.5, respectively. The early mild cognitive impairment (EMCI) group differed from late mild cognitive impairment (LMCI) group only based on education-adjusted scores for the delayed paragraph recall subscore on the Wechsler Memory Scale–Revised Logical Memory II [19]; EMCI subjects were intermediate between normal subjects and LMCI.

Owing to the longitudinal aims of our analysis, we selected subjects from the ADNI-2 database having baseline CSF Aβ and total tau (t-tau) measurements together with baseline and 2-year cognitive measurements and structural MRI scans. Selection was made *a priori* from ADNI-2 subjects based on the availability of complete data including longitudinal imaging and measures of cognition.