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Investigating Functional Impairment in Preclinical Alzheimer's Disease

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Very little is known about functional change in persons in the preclinical stage of AD. As currently conceptualized, functional impairment in Alzheimer's disease (AD) is the final and somewhat remote downstream outcome of a cascade of preceding pathophysiological and clinical events characterizing AD: amyloid deposition, neurodegenerative cellular, metabolic and network pathway changes, tissue loss and atrophy, and significant cognitive decline. Given this prevailing conceptual framework, possible functional change in preclinical AD, and related clinical trial methodology, have received relatively little attention. For example, the 2013 draft guidance of the FDA for treatment of early stage Alzheimer's disease anticipates that persons in the preclinical phase will only show subtle cognitive deficits "in the absence of any detectable functional impairment" (1), and that in these circumstances the field may be allowed to pursue valid and reliable cognitive assessments as a single primary efficacy measure (1).

This prevailing framework notwithstanding, a new perspective has recently begun to emerge concerning functional change and outcome measures in preclinical AD. The intriguing possibility that detectable functional change actually commences much earlier in the AD disease process, possibly as early as the preclinical stage, has recently been suggested (2, 3). In support of this proposition is the now well-established finding that functional impairment is clearly present in prodromal AD. Prior research by several groups (3–7) has shown that complex functional skills (Independent Activities of Daily Life, or IADLs) show impairment in patients with mild cognitive impairment (MCI) and continue to decline over time (5). In particular, financial capacity is a higher order functional skill that is highly sensitive and vulnerable to MCI and mild AD (4, 5, 8), which raises the possibility that measurable financial decline may also occur in persons with preclinical AD.

It should be noted that current diagnostic criteria for preclinical AD explicitly contemplate and posit incipient subtle cognitive changes emerging in the third or "late" stage of the preclinical phase (9). Consistent with this theoretical view, recent studies have shown

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episodic memory impairments in older individuals with abnormal levels of brain amyloid (10, 11). The presence of detectable albeit subtle cognitive impairments in individuals with preclinical AD raises the possibility that associated subtle changes in complex functional activities may also be present and detectable.

A critical factor here is the sensitivity of the functional measure employed. Detection of functional impairment in cognitively normal individuals with preclinical AD will require instruments sensitive to subclinical cognitive and functional changes. Informant report measures commonly used to characterize functional decline in late MCI and AD type dementia likely lack sensitivity to detect these very subtle functional changes. In contrast, performance based assessment measures may have sufficient sensitivity as they can support finely grained quantitative measurement using performance and task completion time variables.

In the author's view, in order to maximize detection of functional impairment in preclinical AD, proposed functional assessment measures should incorporate the following features:

1. Assess cognitively complex functional abilities relevant to independent living and sensitive to early decline in AD.
2. Assess the functional ability using an interval scaled, direct performance measure that evaluates performance variables in a highly detailed and granular manner.
3. Include time limitations for performance items in order to enhance item difficulty.
4. In addition to performance items, include task completion time variables in order to capture subtle processing speed changes.

Feature 1

Assess cognitively complex functional abilities relevant to independent living that are sensitive to early decline in AD.

Functional measures in preclinical AD should measure cognitively complex functional abilities relevant to independent living that will also have credibility to research participants and families, and clinicians and researchers. For example, financial capacity is a cognitively complex functional ability that is critical to independent functioning and that shows very early change and rapid decline in prodromal and clinical AD. The ability to manage finances is also an IADL that will likely have credibility as an outcome measure to older participants, family members, and other stakeholders.

Feature 2

Assess the functional ability using an interval scaled, direct performance measure that evaluates performance variables in a highly detailed and granular manner. In order to detect subtle subclinical functional change in preclinical AD, it is important to employ direct performance measures that are finely gradated and are interval scaled. Fine performance gradations together with interval scores can provide a level of quantitative precision that is needed to detect small signals in the data. Traditionally functional impairment in AD

dementia has been measured using self and informant report measures using diffuse, global rating scores and ordinal or categorical outcomes (eg., ratings such as “can do without help”, “can do with help”, “cannot do even with help”). Such global rating measures arguably lack the necessary gradation, precision and sensitivity to detect a small functional signal in preclinical AD.

Feature 3

Include time limitations for performance test items in order to enhance item difficulty.

In order to detect subtle subclinical functional change in preclinical AD, it is important to enhance item difficulty where possible. An easy and valuable way to increase performance item difficulty is to assign a time limit to completing individual performance items.

Feature 4

In addition to performance items, include task completion time variables in order to capture subtle processing speed changes.

In order to detect subtle subclinical functional change in preclinical AD, it is important to complement performance variables with task completion time variables. Timing variables offer an additional measurement dimension that is quantitatively precise (seconds of time) and that can tap subtle processing speed changes likely to be implicated in preclinical AD.

Proposed Financial Measure for Investigating Functional Change in Preclinical AD

Marson and colleagues at the University of Alabama at Birmingham (UAB) have empirically investigated financial capacity in MCI and AD for over a decade (4, 5, 8). They have found that financial capacity is very sensitive to AD type neurodegenerative change and believe that it is a good functional target for evaluation in preclinical AD.

The UAB group previously developed a clinical conceptual model of financial capacity and a related psychometric performance measure called the Financial Capacity Instrument (FCI) (4, 8). The FCI was designed for assessing dementia populations and has been used empirically to study declining financial skills in patient populations with MCI and dementia secondary to AD (4, 5, 8), and also in patient populations with MCI and dementia secondary to Parkinson’s disease (PD) (12). The FCI has also been used to identify cognitive correlates of financial skill impairment in MCI and AD (13), as well as in MRI imaging studies investigating structural brain changes linked to impaired financial skills in patients with MCI and AD (14, 15).

In an effort to detect financial changes present in earlier phases of AD, the UAB group recently developed a new functional assessment measure, the Financial Capacity Instrument —Short Form (FCI-SF) (16). The FCI-SF is a brief performance measure of financial skills derived from the FCI long form. Designed to be sensitive to financial declines associated with transition from MCI to mild AD type dementia, it focuses on more complex financial

skills and tasks. The FCI-SF measures constructs of financial conceptual knowledge, monetary calculation, use of a checkbook and register, and use of a bank statement. The FCI-SF also includes time limits on performance items, as well as multiple variables measuring time to completion of FCI-SF tasks. The FCI-SF takes 15 minutes or less to administer to cognitively normal older adults, and has a detailed well-operationalized scoring system. The author believes that the FCI-SF fulfills the four measure characteristics set forth above for an assessment measure sensitive to subclinical functional decline in preclinical AD.

A fuller description of the development and psychometric characteristics of the FCI-SF can be found elsewhere (16, 17).

Proposed Method to Investigate Functional Impairment in Preclinical AD

The sensitivity of functional assessment measures like the FCI-SF can be field tested in community samples of cognitively normal elderly positive for an AD biomarker. Such biomarkers include CSF positivity for abnormal levels of beta amyloid and/or tau, and PET neuroimaging such as PiB that shows positivity for abnormal brain levels of amyloid. Based on the distribution of the AD biomarker, cross-sectional older adult samples can be divided into biomarker positive and negative subgroups. For example, using PiB imaging, a sample can be divided into cognitively normal older adults with abnormal levels of amyloid deposition (A+) and cognitively normal adults without abnormal amyloid deposition (A−).

With the sample subdivided by biomarker status, one can then statistically compare the A+ and A− groups on study demographic factors, cognitive and personality variables, and on the selected functional measure's performance and task completion time variables.

One can next use logistic regression to develop a predictor model of study participants' amyloid status (positive/negative), and specifically examine how well the FCI-SF or other functional measure's significant performance and timing variables predict amyloid status in relation to the study's demographic, cognitive, and personality variables. This cross sectional model, together with data supporting measure sensitivity to longitudinal change, can help determine the suitability of the functional measure as a possible outcome measure in AD clinical and prevention trials.

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