Brief Report

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Potential Utility of Practice Effects in Preventive Trials

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By the time an individual fulfills clinical criteria for Alzheimer's disease (AD) dementia, extensive and likely irreversible neurodegeneration has already occurred. While we might be able to slow disease progression at this late stage, there is minimal likelihood of completely restoring brain and cognitive function once extensive neurodegeneration is present. Accordingly, most clinical trials for AD have shifted toward the prodromal (before dementia) or even the preclinical (before symptom onset) phase of the disease. With this shift towards AD prevention, new challenges have emerged, the most important of these being i) to better identify individuals on the path to AD dementia and ii) to develop optimal outcome measures that can capture the earliest changes related to AD.

Studies involving individuals with autosomal dominant forms of AD (ADAD) suggest that disease-related changes occur in a predictable order, with a reduction of cerebrospinal fluid (CSF) amyloid levels appearing 25 years before expected symptom onset, accumulation of brain amyloid deposition assessed using positron emission tomography (PET) imaging and hippocampal volume loss 15 years before expected symptom onset, and memory deficits 10 years before expected symptom onset (1). While the time course of sporadic AD might be slightly different and more variable from one individual to another than what is found in ADAD, the order of biomarker changes in both forms of the disease is hypothesized to be very similar (2, 3). Based on this assumption, an international working group convened by the National Institute on Aging and the Alzheimer's Association (NIA-AA) proposed a conceptual framework to define the preclinical (4) and the prodromal (5) phases of AD. Both phases are characterized by the presence of amyloidosis, which can be found alone (preclinical stage 1), and in association with neurodegeneration (preclinical stage 2), subtle cognitive decline (preclinical stage 3) and/or mild cognitive impairment (MCI, prodromal stage), reflecting increasing disease severity.

Assessing the presence of amyloidosis using PET imaging or CSF assays might therefore be the optimal approach for identifying individuals in the preclinical and prodromal phases of the disease. When used alone however, these expensive and somewhat invasive procedures must be performed on a substantial number of individuals, as only about a third of cognitively normal older adults and half of individuals with MCI exhibit amyloidoisis (6). More importantly, because amyloid accumulation starts about two decades before dementia onset (1, 7), enrolling participants in prevention trials based solely on markers such as amyloid status may result in heterogeneous samples that include some individuals close to symptom onset while others remain decades away. Those who are close to symptom onset often show cognitive and functional decline, while those who are decades away are less likely to decline over a relatively short follow-up. Accordingly, effects of preventive interventions may not be apparent in individuals who are decades away from symptom onset, especially when conventional cognitive and functional outcomes are used. There is therefore a crucial need to develop better approaches for identifying individuals on the path to AD dementia who are at a similar severity stages.

Practice effects as a potential pre-screening tool for AD preventive trials

Practice effects are defined as improvement on cognitive test performance resulting from learning during repeated testing. On memory tests, for instance, individuals should remember certain portions of the test if the content remains the same at each assessment. While practice effects are often thought of as potential confounders in longitudinal studies, an absence of practice effects may actually be an indicator of cognitive dysfunction in the earliest phase of AD. Indeed, an absence of improvement in test scores may be one of the earliest detectable signs of cognitive deficit, since before showing detectable performance reduction between two identical testing sessions, an individual should first stop improving despite test repetition. In a recent study, Duff and collaborators (8) assessed short-term practice effects by repeating the same cognitive evaluations one week apart in nine cognitively normal older adults and 18 individuals with MCI. In addition, these authors assessed amyloid burden measured with

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a single 18F-Flutemetamol PET evaluation. In keeping with previous studies, they found that increased amyloid burden was related to poorer cognition in non-demented individuals (9, 10). Interestingly, a reduction of practice effects was also related to increased amyloid burden, even after controlling for baseline cognitive performance. Previous studies had also suggested that an absence of practice effect could predict a worse prognosis in individuals with MCI (11, 12). A lack of practice effects might therefore help identify the best candidates for clinical trials targeting non-demented individuals.

Diminished long-term practice effects, measured over the course of one year, have further been observed in cognitively normal individuals positive for either amyloid or neurodegeneration (13). While diminished practice effects might not be specific to amyloidosis, they may at least help identify individuals who are free from amyloid and neurodegeneration. This last group is at very low risk of AD dementia and represents ~40% of cognitively normal older adults (14, 15). Importantly, assessing both practice effects and cognitive decline could also provide information on disease progression (or staging) in the pre-clinical phase of the disease. Indeed, individuals with evidence of amyloid deposition only (NIA–AA criteria preclinical stage 1) show diminished practice effects, while individuals with evidence of both amyloid and neurodegeneration (NIA–AA criteria preclinical stage 2) show a reduction in cognitive performance after the one-year follow-up (13).

Practice effects testing could therefore be seen as inexpensive pre-screening tool to identify individuals to be screened for amyloidosis. Based on current literature, limiting amyloid screening to individuals showing diminished practice effects could reduce the overall number of individuals to be screened and therefore save a substantial amount of time and money. When combined with amyloid assessment, differentiating an absence of practice effects from clear cognitive decline might provide further information on preclinical disease severity.

Taking advantage of practice effects when measuring cognitive outcomes in prevention trials

During the dementia stage of AD, a drug must demonstrate efficacy on both cognitive and functional outcomes to satisfy the U.S. Food and Drug Administration requirements. Before the onset of dementia, and particularly in the preclinical phase of the disease, it may be unrealistic to require alteration in functional abilities because individuals are usually far from the onset of functional disability. Cognitive outcomes, on the other hand, have been suggested to be sensitive and appropriate outcome measures in preventive trials (16). Even if assessing cognition as an outcome in asymptomatic individuals might also seem counterintuitive, as previously mentioned, cognitive decline can be detected about a decade before dementia onset in both ADAD and sporadic AD (1, 17). Cognitive outcomes may therefore be sensitive to tracking preclinical AD decline and therefore could serve as a primary endpoint in preventive trials (18).

To avoid practice effects, many clinical trials use alternate test versions to assess cognitive change over time. Based on the studies presented above, we suggest avoiding this practice in preventive trials since change in practice effects could be one of the earliest detectable change in cognition. Assessing practice effects as an outcome could be particularly important for therapies targeting individuals at the very early stage of AD pathogenesis (NIA–AA criteria stage 1). Indeed, while no cognitive decline might be evident at this early stage of AD, improvement in cognitive performance could still be observed in the treatment group. Based on this improvement, a trial could be considered successful, or this improvement could justify the need to extend the length of the cognitive follow-up. In situations where an absence of practice effects would not be used as a trial pre-screening inclusion criteria, differences in practice effects between the treatment vs non-treatment groups could also be seen as a positive outcome even in the absence of clear cognitive decline in the non-treatment group.

To be accepted as an endpoint in trials enrolling clinically normal individuals, strong evidence that practice effects changes are clinically meaningful will be needed. For instance, work supporting the idea that an absence of practice effects predicts later cognitive and functional decline would strengthen the idea that practice effects can help detect the earliest disease stages. Preventive trials designed to take advantage of practice effects would however need to be extremely careful and select cognitive tests that are adapted for asymptomatic individuals to avoid possible ceiling effects.

Conclusions

Low-cost tools that can help identify individuals in the prodromal or the preclinical phase of AD are needed. While practice effects assessment alone will never be sufficient for identification of individuals in the preclinical or prodromal phase of the disease, it could help pre-screen individuals to be tested for amyloid positivity. Assessing practice effects could also help estimate disease severity in the pre-dementia phase of the disease since individuals in the earliest stages of AD tend to show diminished practice effects while individuals in more advanced stages tend to show cognitive decline or even mild cognitive impairment. Enrolling individuals who are at similar distance from disease onset expression would seem crucial for diminishing inter-individual variability and therefore increasing chances of detecting treatment effects. Finally, practice effects could have

some validity as an end-point in preventive trials since they might help detect the earliest AD-related cognitive changes.

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