

# Drug Development in Alzheimer's Disease— The Role of Default Mode Network Assessment in Phase II

Jeffrey Cummings,<sup>1</sup> Kate Zhong,<sup>2</sup> and Dietmar Cordes<sup>1</sup>

1. Cleveland Clinic Lou Ruvo Center for Brain Health, Las Vegas, NV, US; 2. Global Alzheimer's Platform, Washington, DC, US

DOI: <https://doi.org/10.17925/USN.2017.13.02.67>

Alzheimer's disease (AD) is rapidly becoming more common as the global population ages. New treatments are needed and new approaches to drug development are warranted. The phase II challenge for AD treatment development programs is how to provide proof-of-concept (POC) of the candidate agent without a large long trial equivalent to phase III. We propose that the available data support measures of the default mode network (DMN) using functional magnetic resonance imaging (fMRI) as demonstrating the effect of treatment on cognitive circuits critical to human cognition. Improved DMN function with symptomatic cognitive enhancing agents or decreased deterioration of DMN function compared to placebo in trials of disease-modifying agents would support POC and allow progression to phase III with greater confidence.

## Keywords

Alzheimer's disease, functional MRI, default mode network, disease-modifying therapy, cortical circuits

**Disclosure:** Jeffrey Cummings has provided consultation to Abbvie, Acadia, Actinogen, Alzheon, Avanir, Axovant, Biogen, Boehringer-Ingelheim, Bracket, Dart, Eisai, Genentech, Kyowa, Lilly, Lundbeck, Medavante, Merck, Orion, Otsuka, Pfizer, QR, Roche, Suven, and Takeda pharmaceutical and assessment companies. Kate Zhong is employed by Global Alzheimer's Platform. Dietmar Cordes reports no disclosures. This article is a short opinion piece and has not been submitted to external peer reviewers. No funding was received in the publication of this article.

**Acknowledgment:** Jeffrey Cummings acknowledges support of a COBRE grant from the NIH/MIGMS (P20GM109025) and Keep Memory Alive.

**Authorship:** All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship of this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval to the version to be published.

**Open Access:** This article is published under the Creative Commons Attribution Noncommercial License, which permits any noncommercial use, distribution, adaptation, and reproduction provided the original author(s) and source are given appropriate credit.

**Received:** May 9, 2017

**Published Online:** June 28, 2017

**Citation:** *US Neurology*, 2017;13(2):67–9

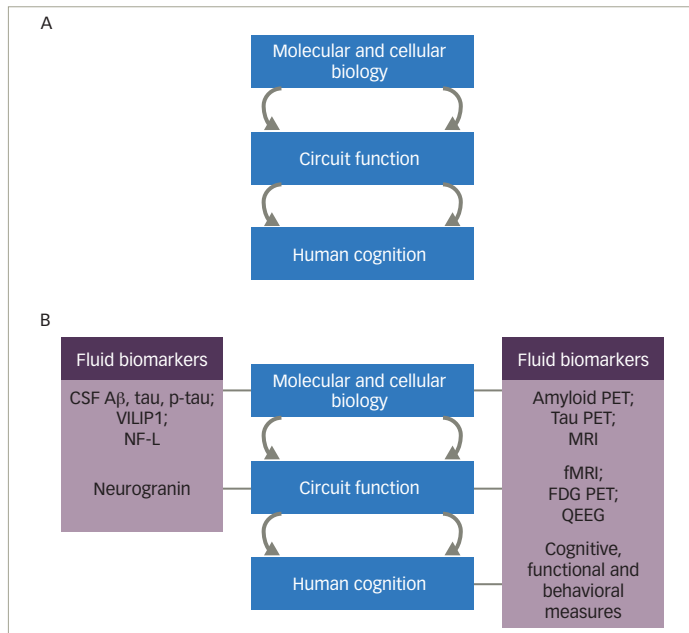
**Corresponding Author:** Jeffrey Cummings, Cleveland Clinic Lou Ruvo Center for Brain Health, 888 West Bonneville Ave, Las Vegas, NV 89106. E: cumminj@ccf.org

Alzheimer's disease (AD) is approaching epidemic proportions as the world's population ages and the number of victims of this age-related disorder soars.<sup>1</sup> At the same time that this tsunami of affected individuals looms, there has been little progress in developing new therapies, either symptomatic drugs to relieve the symptoms of AD or disease-modifying therapies (DMTs) to prevent, delay onset, or slow progression. No new novel treatment of AD has been approved since 2003 and 100% of DMTs in development have failed.<sup>2</sup>

Drug development progresses from preclinical studies in animals to phase I trials involving normal volunteers, to phase II "learning" trials in small populations of AD patients, to phase III confirmatory trials that demonstrate safety and efficacy prior to seeking marketing approval and making treatments widely available to patients. Phase II establishes proof-of-concept (POC) and determines the optimal doses to be included in phase III trials.<sup>3</sup> Phase III is the longest phase of drug development, includes the largest number of patients, and consumes the largest share of resources. Thus, only agents that have demonstrated POC efficacy in phase II should be advanced to phase III. Stopping development of ineffective drugs in phase II will save resources that can be devoted to other projects and will save exposing patients to drugs and side effects in futile trials. Many drugs that have failed and many in the current AD pipeline have not shown POC in phase II before proceeding to phase III. A high failure rate can be anticipated among these agents.

A critical aspect of phase II POC is target engagement and proof of mechanism. *Figure 1* shows how advances in understanding the biological underpinnings of human cognition can be applied to clinical trials to achieve POC in phase II. There is an ascending hierarchy of brain function from cells and cell processes, to circuit integration underlying cognitive function. In AD, amyloid-beta protein (A $\beta$ ) and phosphorylated tau protein aggregate and form neuritic plaques and neurofibrillary tangles, respectively. Protein oligomerization and aggregation lead to cell death, inflammation, and apoptosis.<sup>4</sup> Several biomarkers have been identified that provide insight into these events in the basic biology of AD. Brain imaging relevant to this level of understanding includes amyloid positron emission tomography (PET), tau PET, and atrophy as measured by magnetic resonance imaging (MRI). Fluid biomarkers reflective of these events include cerebrospinal fluid (CSF) A $\beta$ , CSF total tau protein, CSF phosphorylated tau (p-tau) protein, visinin-like protein 1 (VILIP1), and neurofilament light chain protein.<sup>5,6</sup> CSF A $\beta$  production and clearance can be measured using stable isotope labeled kinetics (SILK) techniques.<sup>7</sup>

**Figure 1: Biological underpinnings of human cognition (A) and changes in biological underpinnings of human cognition in Alzheimer's disease and biomarkers that assist in measuring these alterations (B)**



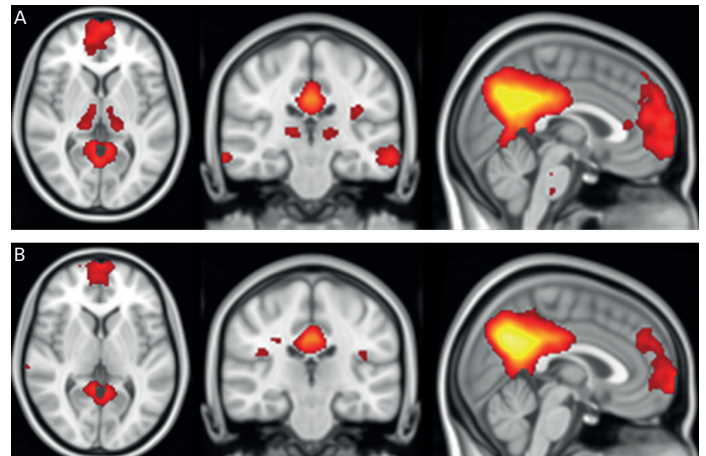
Aβ = amyloid beta-protein; CSF = cerebrospinal fluid; FDG = fluorodeoxyglucose; fMRI = functional magnetic resonance imaging; MRI = magnetic resonance imaging; NF-L = neurofilament light; p-tau = phosphorylated tau protein; PET = positron emission tomography; QEEG = quantitative electroencephalography; VILIP1 = visinin-like protein 1.

Human cognition depends on intact cortical circuitry and assessment of circuits may provide insight into drug effects at this critically important level of central nervous system (CNS) organization.<sup>8</sup> Circuit function can be assessed with functional MRI (fMRI), fluorodeoxyglucose (FDG) PET, and quantitative electroencephalography (QEEG).<sup>9-11</sup>

The technique that most clearly assesses circuit function is fMRI. Task-free resting state fMRI reveals a posterior default mode network (DMN) and an anterior salience network (SN). The DMN comprises a temporal-parietal-hippocampal network associated with memory and visuospatial function; the SN includes frontal structures relevant to social-emotional function. In AD, the posterior DMN is preferentially affected, reflecting the temporal-parietal patho-geography of the major histologic changes. DMN connectivity to posterior hippocampus and medial cingulo-parieto-occipital regions is diminished and SN connectivity is intensified.<sup>12</sup> DMN changes are sensitive to the pathology of AD, present in prodromal AD,<sup>13</sup> and anticipate cognitive abnormalities in individuals genetically predisposed to development of AD.<sup>14</sup> Resting state measures show improved hippocampal connectivity in mild AD following treatment with donepezil that correlates with commonly used clinical trial measures.<sup>15</sup> Figure 2 shows regions of DMN activity in normal elderly and in patients with prodromal AD (defined as mild cognitive impairment in amyloid-positive individuals).

These studies suggest that fMRI DMN provides insight into drug effects often currently lacking in phase II development programs. They may be relevant to both DMTs and symptomatic cognitive enhancing therapies.

**Figure 2: Default mode network in healthy elderly (A) and patients with prodromal Alzheimer's disease (B)**



Note the smaller regions of activity in B compared to A (Figure courtesy of Zhengshi Yang, Cleveland Clinic Lou Ruvo Center for Brain Health).

Abnormalities are detectable early, suggesting that they can be used in prevention trials of at-risk individuals and treatment trials of persons with prodromal AD or mild AD dementia. They are sensitive measures, allowing POC trials to be completed in shorter periods of time with smaller sample sizes than conventional phase II trials. Correlations with cognitive measures suggest that drugs or drug doses not improving DMN function in trials of cognitive enhancing agents or not preserving the function better than placebo in DMT trials are unlikely to produce a cognitive benefit in longer larger trials. Resting state measures are collected without asking participants to perform cognitive tasks and may be applicable to trials involving individuals across a broad range of severity and in global settings. Standard protocols will be required for multi-site trials, but relatively few specialized sites may be needed for POC studies.

An unresolved conundrum for phase II of drug development is whether to require demonstration of cognitive benefit.<sup>16</sup> Trials designed to show robust clinical benefit must be large and long and therefore are similar or identical to trials required for phase III. Taking time to determine clinical responses consumes patent life, making long phase II trials untenable. This has led some sponsors to skip phase II, proceeding directly from animal studies and human safety trials to phase III. Within this paradigm, there is relatively little opportunity to understand the candidate treatment, explore dose relationships, accrue safety data, or collect biomarker data possibly predictive of phase III efficacy. Phase II trials measuring amyloid or tau burden or CSF measures involving Aβ, tau, and p-tau may take longer to demonstrate and, even if positive but insufficient to affect circuit function, might not accurately forecast clinical benefit. DMN measure relates directly to cognitive function and may optimize demonstration of POC in phase II.

The fMRI technique has not been established as a surrogate measure that predicts clinical outcomes. We suggest that the current data warrant further investigation and that development programs explore the potential utility of DMN measures to assess drug and dose effects systematically and to determine if this approach, when incorporated in phase II, allows better prediction of phase III outcomes. □

1. Alzheimer's Association, 2016 Alzheimer's disease facts and figures, *Alzheimers Dement*, 2016;12:459–509.
2. Cummings JL, Morstorf T, Zhong K, Alzheimer's disease drug-development pipeline: Few candidates, frequent failures, *Alzheimers Res Ther*, 2014;6:37.
3. Ator MA, Mallamo JP, Williams M, Overview of drug discovery and development, *Curr Protoc Pharmacol*, 2006;9.9.1–26.
4. Masters CL, Bateman R, Blennow K, et al., Alzheimer's disease, *Nat Rev Dis Primers*, 2015;1:150–56.
5. Brier MR, Gordon B, Friedrichsen K, et al., Tau and Abeta imaging, CSF measures, and cognition in Alzheimer's disease, *Sci Transl Med*, 2016;8:338ra66.
6. Zetterberg H, Skillback T, Mattsson N, et al., Association of cerebrospinal fluid neurofilament light concentration with Alzheimer disease progression, *JAMA Neurol*, 2016;73:60–7.
7. Holtta M, Dean RA, Siemers E, et al., A single dose of the gamma-secretase inhibitor semagacestat alters the cerebrospinal fluid peptidome in humans, *Alzheimers Res Ther*, 2016;8:11.
8. Canter RG, Penney J, Tsai LH, The road to restoring neural circuits for the treatment of Alzheimer's disease, *Nature*, 2016;539:187–96.
9. Carbonell F, Charil A, Zijdenbos AP, et al., Hierarchical multivariate covariance analysis of metabolic connectivity, *J Cereb Blood Flow Metab*, 2014;34:1936–43.
10. Sperling RA, Dickerson BC, Pihlajamaki M, et al., Functional alterations in memory networks in early Alzheimer's disease, *Neuromolecular Med*, 2010;12:27–43.
11. Zippo AG, Castiglioni I, Integration of (18)FDG-PET metabolic and functional connectomes in the early diagnosis and prognosis of the Alzheimer's disease, *Curr Alzheimer Res*, 2016;13:487–97.
12. Zhou J, Greicius MD, Gennatas ED, et al., Divergent network connectivity changes in behavioural variant frontotemporal dementia and Alzheimer's disease, *Brain*, 2010;133:1352–67.
13. Sorg C, Riedl V, Muhlau M, et al., Selective changes of resting-state networks in individuals at risk for Alzheimer's disease, *Proc Natl Acad Sci U S A*, 2007;104:18760–5.
14. Filippini N, Macintosh BJ, Hough MG, et al., Distinct patterns of brain activity in young carriers of the APOE-epsilon4 allele, *Proc Natl Acad Sci U S A*, 2009;106:7209–14.
15. Goveas JS, Xie C, Ward BD, et al., Recovery of hippocampal network connectivity correlates with cognitive improvement in mild Alzheimer's disease patients treated with donepezil assessed by resting-state fMRI, *J Magn Reson Imaging*, 2011;34:764–73.
16. Cummings JL, Optimizing phase II of drug development for disease-modifying compounds, *Alzheimers Dement*, 2008;4(Suppl. 1):S15–20.