A Neuropsychological Perspective on Defining Cognitive Impairment in the Clinical Study of Alzheimer's Disease: Towards a More Continuous Approach

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Abstract

The global fight against Alzheimer's disease (AD) poses unique challenges for the field of neuropsychology. Along with the increased focus on early detection of AD pathophysiology, characterizing the earliest clinical stage of the disease has become a priority. We believe this is an important time for neuropsychology to consider how our approach to the characterization of cognitive impairment can be improved to detect subtle cognitive changes during early-stage AD. The present article aims to provide a critical examination of how we define and measure cognitive status in the context of aging and AD. First, we discuss pitfalls of current methods for defining cognitive impairment within the context of research shifting to earlier (pre)symptomatic disease stages. Next, we introduce a shift towards a more continuous approach for identifying early markers of cognitive decline and characterizing progression and discuss how this may be facilitated by novel assessment approaches. Finally, we summarize potential implications and challenges of characterizing cognitive status using a continuous approach.

1. Introduction

As the leading cause of dementia, Alzheimer's disease (AD) is currently understood to be a continuous process of gradual cognitive decline, starting with a preclinical phase that lasts perhaps 30 years or more, and during which neuropathological changes occur in the absence of *overt* clinical symptoms [1-5]. Despite this very long prodromal phase of the disease, most clinicians and researchers frequently categorize older adults in binomial terms, as cognitively healthy versus impaired. This lumping of individuals into either healthy or impaired (with a frequently used middle category of 'mild cognitive impairment') may be useful for a host of practical reasons, such as the facilitation of clinical treatment decision-making, but such imprecise categorization has also long influenced the design of clinical research.

In current clinical neuropsychology practice, an individual's cognitive status is typically determined by defined cut-off criteria on one or more cognitive tests at a single time point (e.g., Jak/Bondi criteria) [6, 7], as well as by the presence or absence of imaging, genetic, or other biomarkers of disease [8]. This approach has subsequently influenced the role of cognitive assessment in AD research and clinical trials, in terms of screening and monitoring of cognitive status, as well as for targeting specific groups for recruitment (i.e., cognitively impaired vs. cognitively healthy). To illustrate this point, a recent PubMed search (April, 2020) with the key terms ["cognitively normal" OR "cognitively healthy"] AND ["cognitively impaired"] AND ["Alzheimer's disease" OR dementia"] yielded over 25,000 reference citations just over the past five years. In clinical research, categorizing individuals at baseline as either cognitively healthy or impaired allows for more straightforward statistical approaches to data analysis, smaller sample-sizes [9], and easier application of diagnostic nosologies [10, 11]. However, this almost certainly leads to a loss of a large amount of information, as the transitions between baseline cognitive performance, age-related amnestic changes, and disease-related decline can be subtle and difficult to measure with precision using single time-point testing. With the growing older adult population and rising rates of AD, it is

crucial to better understand the pitfalls and potential alternatives to this approach, and the role of clinical neuropsychology in the future of AD research needs to be reexamined.

Theories and definitions of normal cognitive aging, such as those established by Salthouse [12] and Lidenberger & von Oertzen [13], are now shifting as a result of our improved understanding of amyloid β (Aβ) deposition and other neuropathological changes that may occur with aging in the absence of clinical symptoms or measurable cognitive or functional decline. In a recently longitudinal analysis of cognitively normal older adults, Harrington and colleagues [14] found that estimates of age-related change in verbal memory and working memory were related to undetected preclinical AD (positive Aβ PET scan). In fact, no age-related decline in verbal memory or working-memory was observed after controlling for Aβ status and progression to MCI or dementia, calling into question the long-standing conceptualization of normal aging as involving decline across most domains of cognitive function [15]. However, given that a majority of cognitively normal older adults evidence AD neuropathological changes at death [16, 17], we must consider whether or not it would be meaningful and clinically appropriate to characterize so many older adults as having preclinical AD, implying that they are aging 'abnormally'. Moreover, while the pathologies associated with various dementia etiologies have been important for determining trajectories and profiles of cognitive decline in old age, Boyle and colleagues have argued that over two-thirds of clinically diagnosed AD cases are attributable to heterogeneous, nonspecific neuropathologies, suggesting that other disease and protective factors are important and have yet to be explained [18, 19].

With these questions likely to be debated for years to come, it is important in the meantime for neuropsychologists to examine how our characterization of the cognitive features of AD can be adjusted for improved harmonization with a biomarker-based disease framework and improved detection of subtle cognitive changes during earlier stages of AD. This work would also be important for molecular biomarker researchers – the current view that AD has a clinically silent incubation time over decades might not be entirely correct (it is biologically implausible, for sure); maybe plaque pathology rather directly induces energy-consuming synaptic and neuronal network changes for

which plasticity mechanisms can compensate rather well over some time before a critical stage of breakdown is reached and the symptoms become clinically overt. Whilst currently available cognitive tests might not be able to identify this type of AD pathology-induced subtle network challenge, a continuous approach based on new assessment methods might. The need of more sensitive and specific cognitive tests has only been made more apparent by the roll out of the 2018 NIA-AA research framework, which proposes defining AD based on biomarker proxies for pathology, and provides an independent classification system for cognitive impairment [20]. The framework is not intended for clinical use, but as a research-only model to open the door for progressive, biomarker-driven directions in the field. However, the inherent disconnect with clinical practice and diagnosis raises questions about the utility and relevance of future research structured on this framework, especially when it comes to treating the clinical symptoms of the disease.

Even without formal changes to the clinical criteria for diagnosing MCI and AD, at this time clinicians and researchers are grappling with how to address the preclinical stage of AD. Discordance between results obtained from biomarker testing and a neuropsychological evaluation can be confusing for both providers and patients [21]. For example, someone may be told that they are cognitively normal, but have biomarker-confirmed AD. Additionally, within subjects discrepancies between clinical categorization (e.g., cognitively normal) and AD biomarker status (biomarker-positive) may affect the outcomes of clinical trials involving cognitively normal individuals as a control group, given evidence that approximately 30% of such individuals likely have elevated cerebral Aβ [22]. We have the sometimes fuzzy category of subjective cognitive decline where individuals may be AD biomarker-positive or –negative, and more or less close to the cutoffs for cognitive abnormality. Finally, we have a group of individuals who are in the gray zone of biomarker results where it is hard to determine if a patient has or does not have AD pathology. Again, longitudinal change over time (a year?) may help determine what is going on in these particular individuals.

Perhaps one solution for neuropsychologists to consider involves changing our current approach to defining cognitive health to reflect the more continuous nature of the clinical syndrome and cognitive symptoms of the disease when possible. The present article aims to provide a critical examination and discussion of how we define cognitive impairment in the context of aging and AD. We intend to 1) address the pitfalls of current methods for defining cognitive impairment as a distinct dichotomy within the context of clinical research; 2) propose a shift towards a continuous approach based on new assessment methods for identifying early predictors of cognitive decline and characterizing progression; and 3) discuss potential implications and challenges of characterizing cognitive decline on a continuum in the context of AD research.

2. Current approach: conceptual issues and challenges

Definitions and interpretations of cognitive decline can vary widely. For example, cognitive decline during older age is perceived differently across cultures, as illustrated by the finding that African-Americans may be more likely to attribute memory loss and other AD-related symptoms to natural aspects of aging as opposed to pathological processes [23, 24]. This is one of many reasons why African-American older adults may not be seen by clinicians until later in the disease course and have different experiences with AD diagnosis and care. Clinical disciplines may also vary in their approaches to defining cognitive health. Neurologists may assess cognitive health with a combination of neurological examination, brief cognitive screening measures, and neuroimaging, whereas clinical neuropsychologists primarily rely on multi-domain cognitive assessments and family and patient reports of cognitive and functional changes. As a consequence, the training background of the clinician who sees the patient will influence the manner by which cognitive functioning is defined.

In addition to these broader challenges in defining and approaching cognitive health, operationalizing AD-specific cognitive impairment and distinguishing it from age-related cognitive changes remains particularly difficult because the clinical picture of AD can be quite heterogeneous [25, 26]. Though we continue to treat cognitively normal aging and cognitive dysfunction as distinct

constructs, and there is no universal consensus on the actual definition of cognitive health, nor any single validated approach to capturing this complex construct. To illustrate this challenge for our field, we first review the complexities inherent in relying on 'traditional' neuropsychological approaches to diagnosing MCI and AD, including the use of cross-sectional normative data to gauge individual impairment, followed by the inclusion of subjective complaints in defining cognitive health.

The use of normative data. Neuropsychological test results are often interpreted based on available cross-sectional normative data with adjustment for age, sex, and sometimes education. The reliance on historical normative data obtained from cross-sectional samples carries some serious limitations. First, it has been shown that cognitive test performance is cohort-dependent. That is, a healthy 50-year-old person performs differently on a test *now* than a healthy 50-year-old person would have performed on the same test twenty years ago [27]. Interestingly, Dodge and colleagues also showed that this effect remained present after adjusting for the higher educational level of more recent cohorts. As a result, the 'average performance' on a given test may drift over time and, consequently, normative data become rapidly outdated. In addition, even after correction for years of education, it remains difficult to capture cognitive decline among highly educated individuals who likely possess substantial cognitive reserve [28]. That is to say, their current baseline test scores may still fall well within the education-adjusted range even when they report a (subtle) decline compared to their previous level of functioning, thereby underestimating the clinical decline that is taking place. There also exists a major and well-established problem when applying normative data to both highly educated and less educated individuals, as both ends of the spectrum are generally poorly represented in normative samples and therefore test results are difficult to interpret in those groups. Indeed, norms are typically based on relatively homogeneous participant samples, and may not generalize to other populations that differ across a number of other key individual variables as well (e.g., socioeconomic status, ethnicity, cultural heritage, language fluency). With the rapid growth of our aging populations worldwide and increasing numbers of the 'oldest-old', additional issues come to light such as known ethno-racial disparities in the prevalence of AD [29]. Despite this growing

concern, we nonetheless continue to have limited reference data for ethno-racial minorities [30] and the oldest-old segment of our population, though recent efforts have been made to address these gaps [31-33]. The collection of a sufficient amount of data to provide reliable norms – for a sufficient selection of cognitive tests that we commonly rely on – and for each specific sub-population and across the full age-range, is a complex and expensive undertaking. Moreover, the normative data derived from such a massive project would likely become outdated within two decades and as newer generations of neuropsychological instruments are developed.

The role of subjective cognitive decline in defining cognitive health. The process of differentiating between normal cognitive health, mild cognitive impairment (MCI), and AD dementia has typically relied in part on subjective reports of the person's daily functioning from both the person and/or their caregiver(s) [34]. Subjective cognitive decline (SCD), generally defined as the perception of worsening cognitive performance in the absence of objectively observed cognitive deficits, may be both a normal part of cognitive aging as well as an important feature of early pathological changes in cognitive function [35-37]. In the clinical staging scheme proposed in the NIA-AA research framework [20], subjective complaints are described as a possible clinical feature of preclinical AD Stage 2, reflecting that, in the context of research focused on the earliest stages of AD, the utility and role of subjective reporting is not yet clear. This is in part because it has been difficult to craft sensitive and broadly applicable clinical criteria or metrics in order to assess SCD [38, 39]. Currently, there are a variety of differing measures and labels to capture the phenomenon, making it challenging to compare data across studies and to investigate whether SCD is an early, reliable marker of declining cognitive health due to a neurodegenerative disease [40]. Adding a further complication, SCD often worsens with stress and commonly co-occurs with anxiety and depression [41]. While anxiety and depression have been associated with increased risk for AD, they are by no means specific to AD and are known to have independent deleterious effects on memory and other cognitive functions for individuals throughout the lifespan [42, 43]. Another complicating issue is that the setting in which participants are seen strongly influences whether SCD is a risk factor for

developing dementia [44]. The utility of SCD in defining and assessing cognitive health is therefore not surprisingly a topic of some debate, and more research is needed [38]. Comparing SCD reports with AD biomarkers, ideally in longitudinal studies, may be the most productive approach to deciphering the predictive utility of SCD across the clinical AD spectrum [45-50]. Recent progress in this direction has shown that SCD distinguishes between Aβ(+) and Aβ(-) older adults beyond the predictive utility of *APOE* genotype across several large community-based cohorts of older adults [51], suggesting that SCD is an important component of cognitive change on the AD continuum which should by factored into the AD research frameworks.

The field of neuropsychology has made significant strides in addressing the above challenges, such as developing more inclusive normative datasets [52], and forming working groups that establish standards to unified approaches to constructs such as SCD in the context of the AD continuum [20, 38]. However, our reliance on norms and cross-sectional cut-offs to determine cognitive dysfunction has remained essentially unchanged over the past 50 to 75 years. As the larger field of AD research is growing rapidly and has become intensely interdisciplinary, neuropsychology must develop a more flexible, progressive approaches to defining cognitive dysfunction, which can synergistically improve the value of discoveries made across disciplinary boundaries.

3. Defining cognitive health using repeated assessments

To tackle the aforementioned challenges, we advocate against grouping individuals as cognitively normal versus impaired at the time of a screening or baseline examination. Rather, we believe that a "best practice" is to measure cognitive performance using multiple repeated assessments. The latter approach enables the identification of 'progression markers' as cognitive decline captured by within-person change scores. The use of progression markers to define cognitive decline in MCI and dementia screening has several advantages as compared to current approaches most often applied in neuropsychology. Multiple repeated assessments may reduce noise from various sources of error associated with single time point assessment, thereby providing a more reliable and ecologically valid

method to evaluate one's cognitive health status [53]. This point was well illustrated in a study by Darby and colleagues, in which only a minority of participants were *consistently* diagnosed as having MCI on the basis of assessments at multiple time points [54]. Additionally, since within-person measurement will mostly rely on individuals' raw test scores, the availability of normative data is no longer a prerequisite to benchmark one's performance. Hence, the within-person measurement would be more cross-culturally applicable and less sensitive to age and education. Furthermore, within-person comparisons can be a promising method to detect accelerated cognitive change due to pathological processes that is distinct from ongoing 'age-related' changes [55]. The greater sensitivity of this approach has also been suggested by studies on preclinical AD showing that in older adults who do not meet criteria for MCI, abnormally high Aβ manifests only as longitudinal cognitive decline and not as cognitive impairment at baseline (e.g., [14]). Measuring progression markers may therefore be especially useful to apply to the measurement of subjective changes in order to evaluate individuals who report decline compared to their previous level of functioning but whose 'objective' performance still falls within the normal range according to available reference data. In these cases, multiple repeated assessments may allow for the detection of subtle changes associated with the earliest stages of neurodegenerative disease. However, utilizing a multiple time point assessment approach also raises several challenges, such as the fact that it is time-consuming. Furthermore, it assumes that the within-person variance is equal across age, education and cross-cultural groups, which might not always be the case. In the next section, we aim to discuss several approaches to address these challenges, including the implementation of new neuropsychological tools and strategies for repeated neuropsychological assessment in the clinical study of aging and AD.

4. Novel neuropsychological methods to characterize early cognitive decline

One promising new direction for neuropsychological assessment methodology involves a shift toward digital assessment tools [56]. Digital scoring software has the potential to capture

performance information with improved sensitivity and specificity and can rapidly compute a range of normed scores. These features are particularly attractive for the detection of subtle, early cognitive changes associated with preclinical stage of AD, which may not otherwise be detected by the examiner. Numerous digital cognitive test batteries, such as the NIH Toolbox and Cambridge Neuropsychological Test Automated Battery (CANTAB) [57] as well as standalone tests, such as the (e.g., DCTclock [58]) and have been developed for face-to-face administration in clinical and research settings [59]. Unsupervised online neuropsychological testing such as the Cogstate Brief Battery has been used in several AD clinical trials. More recently, the Online Repeated Cognitive Assessment [60] tool used for repeated assessment has been found to be sensitive to detect cognitive changes during the preclinical stage of AD, using metrics such as learning curves across multiple days of assessment [61]. Mobile versions of existing cognitive tests, as well as novel tasks designed specifically for mobile use, have also been developed in recent years [62-65], including from academic research programs such as the Center For Healthy Aging at Penn State [66], the Harvard Aging Brain Study [67], the Dominantly Inherited Alzheimer Network (DIAN) Observational Study, [68] and Oxford University [69]. Smartphone-based assessment comes with several unique challenges (e.g., variable device specifications, privacy, popup notifications), but have the potential to reduce patient burden by avoiding the need for lengthy in clinic testing. Conducting brief assessments via mobile device also has the potential to improve the ecological validity of cognitive tests by allowing patients to complete them in their typical environments across different time points [66]. While empirical support for mobile app assessment tools is still limited, recent initiatives, such as the NIA Mobile Toolbox, aim to bring open source and easily accessible mobile assessment tools to wider scientific and clinical audiences in the next few years, which may help accelerate validation studies.

Another solution for improving the sensitivity of assessment may involve new approaches to analyzing cognitive data from existing assessment measures. The issue of within subject variability is particularly relevant in the context of preclinical AD assessment, where cognitive changes may be quite subtle, and it becomes even more important when assessments are repeated over time to

capture disease progression. Mobile assessments have an advantage in this regard. New "burst" testing (i.e., multiple brief assessments completed over a period of several days) approaches provide multiple data points that can be averaged to generate more reliable indicators of cognitive performance. Statistical methods, such as the Dunlap's *d* test for assessing within-subjects change, may thus be useful for the creation of new indices of cognitive progression [70, 71]. Asken and colleagues [72] have recently proposed a Discrepancy-based Evidence for Loss of Thinking Abilities (DELTA) score as a new method for characterizing cognitive change on a continuous spectrum. Using ADNI data, they derived regression-based normative reference scores using age, sex, years of education, and word-reading ability from cognitively normal participants. DELTA scores were then calculated to reflect the degree of discrepancy between predicted and observed scores. This approach was validated against longitudinal Clinical Dementia Rating Scale scores and AD biomarkers and was found to have a positive predictive value greater than 0.9, suggesting that this could be an elegant and accurate method for capturing cognitive function on a continuum when longitudinal data is available.

One other statistical strategy to increase the responsiveness of measurement instruments involves the use of item response theory (IRT) analysis as a scoring technique. IRT links responses for a specific set of items to an underlying construct resulting in a latent trait score, assuming that items contribute differently to this latent trait score [73]. That is to say, the IRT model takes into account that some items may be more difficult to 'endorse' than others given someone's latent trait. Compared to classic scoring methods, such as a creating simple sum score, a latent trait based IRT score maximizes the sensitivity of responses and results in greater accuracy in the assessment of change over time[74]. Therefore, IRT is highly recommended for use when investigating an individual's change or 'growth' over time or the effectiveness of clinical interventions [75, 76]. In a simulation study [77], IRT based techniques for analyzing repeatedly measured multi-item questionnaire data yielded a more accurate evaluation of change over time than using sum scores. This was due to the fact that sum scores resulted in an overestimation of within person variance.

Finally, studies have also shown that IRT is superior to classical test theory methods in measuring individual change [78, 79].

The study of practice effects (sometimes also called learning effects) is another potential method for the evaluation of repeated neuropsychological measurements. Practice effects are improvements in cognitive test performance due to repeated evaluation with the same or similar test materials [80]. It has been shown that subjects with late-life cognitive disorders show reduced practice effects as compared to their healthy peers [81]. Furthermore, diminished practice effects may predict future decline, a future diagnosis of MCI, and greater brain-related pathology [82-84]. Hassenstab and colleagues [85] showed that reduced practice effects on episodic memory tests were already detectable in subjects with preclinical AD, and that the magnitude of these practice effects was inversely related to risk of progression. All together, these findings suggest that 'not able to gain from (short-term) repeated measurement' may be a better progression marker especially in early stages of AD. However, there is not much evidence yet that supports the use of practice effects on an individual level, and this warrants further investigation.

Lastly, developing and validating methods that re-interpret existing data from traditional tests may yield novel outcomes that can be used as progression markers. For example, Wouters and colleagues showed that IRT might improve the accuracy and precision of the Mini-Mental State Examination and Alzheimer's Disease Assessment Scale - Cognitive subscale [86]. Another example of applying IRT analysis on existing data included a study by Gross and colleagues, which they used data from two large AD research cohorts to derive an 'AD severity measure' that was based on latent trait modeling of cognitive tests. They showed that this latent trait measurement model provided a good approach for grading AD severity in preclinical and prodromal stages of AD [87]. An alternative approach includes performing a discrepancy analysis between two test scores, such as an inhibition versus a switching test, or a visuospatial versus verbal memory test, has been shown to be a promising technique for identifying cognitively normal elderly who are genetically at risk for AD [88, 89]. Another example came from a recent study which showed that distinguishing semantically

related vs. unrelated intrusions on the California Verbal Learning test was found to be informative for predicting progression in early AD [90].

5. Novel biomarker tests to facilitate the determination of AD pathology in cohort studies

Aβ pathology can be measured using two broadly interchangeable biomarkers: cerebrospinal fluid (CSF) Aβ42/Aβ40 ratio and amyloid positron emission tomography (PET) (PMID: 30537535). In parallel with Aβ accumulation, CSF concentrations of total and phosphorylated tau increase, likely indicating an Aβ-related change in tau metabolism resulting in increased secretion of tau from affected neurons (PMID: 28054371). This tau dysfunction eventually manifests itself as tangle pathology, which can be visualized using tau PET imaging, and then neuronal cell loss, i.e., neurodegeneration, which correlates more closely with cognitive decline (PMID: 30529601). Magnetic resonance imaging of the brain is the gold standard neurodegeneration marker in AD, especially when longitudinal imaging data can be obtained. CSF neurofilament light (NfL) concentration is the best established fluid biomarker for neurodegeneration (PMID: 30967444). During the past few years, reliable blood tests for Aβ pathology (plasma Aβ42/40 ratio), tau pathology (plasma P-tau181) and neurodegeneration (plasma NfL) have been developed and validated (PMID: 32251378). These will hopefully prove useful in cohort studies aimed at defining cognitive health using novel neuropsychological measures in future studies.

6. Discussion

In the previous section, we described several promising methods and approaches that can complement traditional neuropsychological assessments in order to characterize cognitive progression markers. These markers of cognitive decline could reflect the continuous nature of cognitive aging more reliably as compared to static, single time-point testing that lumps people into either cognitively healthy or impaired. The use of cognitive progression markers may be particularly relevant for individuals in an early, transitional phase of cognitive decline without objectifiable

cognitive impairment, or “Stage 2” as described in the clinical staging scheme of the NIA-AA 2018 AT(N) framework [20]. These Stage 2 individuals are considered an important and clinically relevant population, and they have become the main target population of secondary AD prevention trials [91]. However, identifying individuals in this ‘transitional stage’ remains challenging with the current neuropsychological paradigms relying on cross-sectional, single time-point testing [92]. Longitudinal assessment to monitor for cognitive progression markers could aid the identification of Stage 2 individuals, especially in combination with disease-specific biomarker information. This approach will both advance clinical trial screening procedures, leading to more successful enrollment of Stage 2 participants, and will also aid the detection of individuals with early cognitive decline in the memory-clinic.

Interdisciplinary harmonization of cognitive progression markers with biomarker models such as the AT(N) framework or other disease models of dementia may aid in the detection of preclinical AD and thereby the screening for (secondary) prevention clinical trials. However, methodological changes within neuropsychology that reexamine theories of cognitive aging and creatively test alternative approaches to assessment are also needed [93, 94]. For example, Snyder and colleagues recently described the rationale for administering a pharmacologic stress test (subcutaneous injection of scopolamine hydrobromide) to transiently impair cholinergic tone in at-risk cognitively normal adults [95]. This stressor appears to unmask otherwise subclinical disease-related symptomatology and these transient impairments were predictive of Aβ PET imaging results for the same individuals [96]. Although this pharmacologic stress test may allow for screening of individuals likely to have preclinical AD, other emerging non-pharmacologic cognitive stress test approaches may prove to be similarly useful [97].

The use of multivariate diagnostic algorithms is another multimodal approach that has recently been explored. Combining the predictive power of cognitive and biomarker data may be particularly useful for differentiating healthy aging from the preclinical AD stage [98].This was also shown by a study from Rhodius-Meester and colleagues showing that a combination of diagnostic

tests (cognitive tests, MRI, and CSF) may help to identify individuals with SCD at risk of progression [99]. Yet still, many newer algorithms being developed do not include cognitive data [100]. This again points to the need for newer, more sensitive cognitive tools that are easy to administer and repeat as part of a larger, multi-modal assessment approach. Overall, one of the larger challenges with using an algorithmic approach to diagnosis is the participant burden and costs associated with collecting multiple forms of data, often through procedures that are invasive (e.g., CSF collection) and not easily accessed or expensive (e.g., Aβ PET).

Challenges and potential limitations. By moving away from the oft relied on dichotomous "lumping" approach to cognitive aging assessment, there is much to be gained by characterizing cognitive decline as points along a continuum. However, transitioning to an approach that involves characterization of change on a continuum creates both methodological and practical challenges, as well as limitations that are not easily addressed. Included among those methodological challenges are the reliability and longitudinal validity of the measurement instruments that are used as progression markers. Those measurement properties are not self-evident, and are often questionable or not investigated. Another challenge relates to the use of progression markers on group level versus on a case-by-case or individual level. For example, there is currently not much evidence that supports the diagnostic relevance of diminished practice effects on an individual level. Lastly, this raises the question of what the ideal time frame for longitudinal assessments should be to reliable classify individuals as either normal or impaired. From the patient perspective, not being able to receive immediate diagnostic feedback following an initial examination of memory problems could lead to heightened feelings of uncertainty and anxiety. Further, even with brief assessments over short time-intervals, repeated measures are more time-, labor- and cost-intensive than single-time testing, and this is especially problematic when participants are lost to follow-up. Adherence is a major issue in implementing mobile phone assessments, and for both online and mobile phone assessment, and involvement of the target population in developing these tests, is crucial. Relying on multiple assessments may therefore be less suitable for individuals who are already on the more

impaired part of the spectrum, as in those cases a single cognitive screening visit will be sufficient to establish a diagnosis or screen for participation in a clinical trial. In fact, neuropsychological tests have proven to show high sensitivity and specificity for establishing a dementia diagnosis [101].

Based on these methodological and practical issues, we argue that multiple assessments are currently of particular relevance for defining 'cognitive health' and subtle cognitive impairments in early clinical stages of AD, and particularly in a research setting. If this development could go hand-in-hand with the analytical and clinical validation of the novel blood tests for AD pathology, longitudinal studies of the interplay between cognitive function and AD-related brain changes would become feasible.

7. Conclusion

In summary, we propose to move away from approaching cognitive health as a distinct dichotomy based on single-time point cognitive testing. Instead, we propose a transition to a more flexible model of cognitive change on a continuum, particularly as a means to improve future clinical trials design, by further development and use of 'cognitive progression markers.' In this article, we summarized several neuropsychological approaches and methods to define these progression markers, any or all of which may provide a better reflection of the slow and continuous nature of cognitive aging. An important advantage of using cognitive progression markers is their reduced reliance on normative datasets in cognitive testing, though normative data still play a role in determining what amount of change is considered normal (the recently proposed DELTA score approach, previously discussed, is one example). Additionally, the use of multi-time point assessment allows for within-subject analysis of cognitive change, which is more informative and clinically relevant in early stages of cognitive decline. It will also move our field away from the inherent ambiguity and challenges in defining the exact nature of what is 'normal' vs. 'impaired' cognitive aging. A challenge remains in finding solutions or new methods that could work for both clinical researchers, practitioners and patients and their caregivers. Neuropsychological paradigms that

reliably assess clinically meaningful cognitive progression need to be further validated in order to apply them in clinical research and practice.

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Conflicts of interest

HZ has served at scientific advisory boards for Denali, Roche Diagnostics, Wave, Samumed and CogRx, has given lectures in symposia sponsored by Fujirebio, Alzecure and Biogen, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program.

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