Barriers to effective memory assessments for Alzheimer's diseases

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Abstract

Recently, Alzheimer's Disease International (ADI) stressed that around 75% of people living with dementia globally are still not receiving a diagnosis. In this commentary, I reflect on how efforts towards better cognitive assessments, particularly of memory, can be aligned and harmonised to contribute to such needs. I highlight some barriers that ongoing collaborations and trials are facing and their potential drivers. I suggest some strategies that can help overcome them and in so doing, integrate research agendas. We need to ignite the debate towards strategies that can help level the playfield to tackle AD with true global solutions.

Alzheimer's Disease International (ADI) recently reported that 75% of people living with dementia globally are not receiving a clinical diagnosis, being those from low and middle-income countries (LIMC) in a greater disadvantage [1]. Several barriers are identified in this report but one on which this commentary focusses is the lack of cognitive assessments that can be easily introduced in primary care settings, are informative about the underlying AD pathology so they are sensitive and specific to its insipient stages, and hold validity to support global strategies (e.g., culture-free) [2]. In this commentary, I will map such barriers to novel cognitive assessments which are meeting the above criteria and proving promising for the preclinical detection of AD. Considering the shift from cure to prevention of dementia, these would hold additional value in assisting the early diagnosis and selection of individuals who can benefit from novel interventions.

I will specifically address the assessment of memory which, despite growing evidence on the clinical heterogeneity of AD [3], remains the function most severely and earliest affected in its typical presentation variants[1] [4]. I will focus on the need of better theory driven assessments, the role of cultural diversity, heterogeneity, risk and protective factors, and the importance of harmonization and validation strategies to introduce novel assessment to global dementia initiatives. Our understanding of memory has grown dramatically since standardised tests currently available were developed. Memory functions have been fractioned in short-term (STM) and long-term memory (LTM), at the behavioural and neuroanatomical levels. Such evidence still points to the Medial Temporal Lobe (MTL) as the seat of the earliest pathological expression of AD. However, the hippocampus, which has for long been considered the earliest structure affected by AD and on which most of the above tests focus, has proved not to be [5-8]. Other regions within the MTL display AD pathology

[1] The author acknowledges that whereas the focus of this commentary is on enhancing memory assessments for AD, the disorder can manifest with decline in several other domains and therefore comprehensive assessments are normally needed to rule out alternative causes of cognitive and functional decline.

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earlier than the hippocampus (i.e., entorhinal, perirhinal, parahippocampal cortex) and their functions are becoming accessible through new theory driven tests [9, 10]. Nevertheless, by focusing only on MTL regions, we may still be missing functions supported by other brain regions which appear to be affected by AD in its very early preclinical stages (e.g., parietal cortex [11, 12], visual ventral stream [13, 14]). Such regions appear to support rather early cognitive functions linked to visual perception (e.g., integrative mechanisms linked to the formation and temporary retention of object's identity , [15, 16]) which are the building blocks of memory and when impaired, their impact may go unnoticed [17]. This evidence endorses the importance of pursuing domain-specific memory tests if we are to identify, via cognitive assessments, the earliest sub-clinical expressions of AD. Recent efforts are moving away from this notion perhaps driven by continuous disappointments caused by ineffective tests of specific cognitive functions [18, 19]. There is a surge of composite cognitive scores which are trying to address the sensitivity gap and the lack of effective cognitive outcome measures for clinical trials [20-22]. These however, will unlikely deliver effective assessments for the early detection of AD[2] which are urgently needed to support prevention strategies (see [23, 24] and Table 1, Strategies A-D)). **Barrier 1: Theory driven assessments**[3]**.**

In fact, prevention entails both early detection and effective treatments and both are currently lacking for AD. As highlighted by Logie et al. [2], features of effective cognitive tests for AD among others are (1) sensitivity, (2) specificity (relative to normal ageing and other dementias), and (3) cultural validity. The first two are relevant in light of the heterogeneity of the clinical presentation of AD and related dementias. The last one will play a key role in the development of global diagnostic strategies to meet the needs recently highlighted by ADI [1]. Recent diagnostic approaches, which focus on costly biomarkers [25, 26], are not to going to be readily and globally available any time soon [27]. We need affordable assessment (e.g., cognitive biomarkers) to screen individuals at risk who are seeking help [27, 28]. To that aim, we need to better understand the impact of risk and protective factors on memory and cognition across diverse populations [29, 30]. This is relevant because exposure to such factors varies greatly cross High and Low and Middle Income Countries (HIC, LMIC) and it can impact the development of cognitive and brain reserve (CBR) [31, 32]. In fact, models of CBR have been heavily influenced by evidence drawn from HIC. We need representative models that capture drivers of CBR and resilience in populations with limited resources and low socio-cultural backgrounds.

This call is timely because factors driving CBR, brain pathology in AD and cognitive impairments interact. Parra et al. [33-35] have investigated a memory function called Short-Term Memory Binding (STMB), which seems to fit the above criteria. STMB has proved

[2] Effective assessments for AD are expected to meet criteria for good cognitive markers (see [2] Logie RH, Parra MA, Della Sala S (2015) From Cognitive Science to Dementia Assessment. *Policy Insights from the Behavioral and Brain Sciences* **2**, 81-91.)

[3] For a cognitive test to be intelligible and interpretable, a sound and tenable theory needs to guide its development and aid the interpretation of its outcomes. This ensures the results from the novel tests can be analysed, interpreted, and communicated with more confidence and can further guide the refinement of such instruments. The two memory tests on which my commentary focuses (VSTMBT and FCSRT) are "neuroscience-informed measures" insofar as the constructs they assess are linked to functions that have been dissociated both behaviourally and neurally and such tests have sound psychometric properties.

sensitive and specific to AD [33, 34, 36, 37] and insensitive to the level of education or socio-cultural background of those assessed [38, 39]. The function does not rely on the hippocampus [40, 41] and is affected by AD before hippocampal related memory abilities decline [33, 42]. This evidence suits the model proposed by Didic et al [8] which is in line with the discussion above. It might be the case that early cognitive functions linked to visual perception and STM, which are sensitive to AD prior to its hippocampal stage, are less sensitive to socio-cultural factors which are known to greatly impact higher level cognitive abilities (i.e., episodic memory, learning, executive functions, etc.). Investigating this hypothesis is of a paramount importance because detecting AD in people with different levels of CBR is already posing significant challenges (see [29, 43] and Table 1, Strategies E-G).

Barriers 2: Considerations toward cultural diversity, heterogeneity, risk factors and BCR

Moreover, STMB correlates with Amyloid deposits in individuals who are in the preclinical stages of familial AD [44] and in the early prodromal stages of sporadic AD [45] before any overt neurodegeneration is observed. This association has been found with other domain-specific memory tests (e.g., Memory Capacity Test [46], recently renamed as The Memory Binding Test [47]). The underlying construct of both these two tests is memory binding. However, they tax two very different binding functions. The STMB test assesses a form of conjunctive binding responsible for holding integrated features (e.g., shape and colour) within object representations, whereas the FCSRT assesses a form or relational binding that supports the retention of associative memories such as semantic categories and exemplars (Fruit – Banana). Recent consensus [48] highlighted the need of investigating the complementary value of these promising tests. Studies following these recommendations have reported on the combined use of the Free and Cued Selective Reminding Test (FCSRT) and the visual STMB test (VSTMBT) [49, 50] with the former but not the latter being sensitive to normal ageing [51] and both being sensitive to AD [39]. There is a need of cohort studies with long follow up periods which can provide the context wherein such novel cognitive tests can be contrasted against pipeline biomarkers[25, 26], validated as disease markers, and further developed into cognitive biomarkers by combining them with novel technologies (e.g., [52, 53], see Table 1 Strategies H-J). **Barrier 3: Evidence from studies comparing the effectiveness of promising memory markers throughout the AD continuum assessed against pipeline biomarkers.**

Overcoming Barrier 3 is a key step to support dementia prevention strategies. We need tests that can help detect the transition from normal to abnormal ageing and also to monitor the disease progression and response to treatments. No one single memory test will likely achieve all these gaols. For instance the VSTMBT identifies impairments in healthy older adults who are free from symptoms or complaints ([54], full publication in preparation). Older adults with poor STMB functions showed a significant increase in Amyloid β relative to those whose STMB was normal. These groups could not be distinguished based on other traditional neuropsychological assessments or using neurodegeneration metrics (i.e., cortical thickness and grey matter volume). These findings though encouraging present us with further challenges. Based on traditional neuropsychological and clinical assessments we have been allocating older adults who do not provide signals of AD (or other dementias) to control groups. This can explain the heterogeneity that characterises “healthy” control groups and the limited value of norms drawn from such groups [55]. We need to better understand the

variability of dementia risk factors across HIC and LMIC [31] and the contributions of the environment to such a biological heterogeneity [56]. There is increasing awareness about this challenge and some strategies have been recently recommended (i.e., biomarker adjusted normative data) [57]. (See Table 1, Strategies K-N). **Barrier 4: Disentangling normal and abnormal ageing trajectories to create reliable normative samples.**

Another barrier we need to overcome is the limitations that predictive models of risk of dementia currently face. There are at least two factors relevant to cognitive outcome measures to consider here. One is the test used to inform such prediction models and the other is when, in the diseases continuum, evidence is first gathered with such tests (i.e., baseline). The diagram below try to illustrate the influence of these factors.

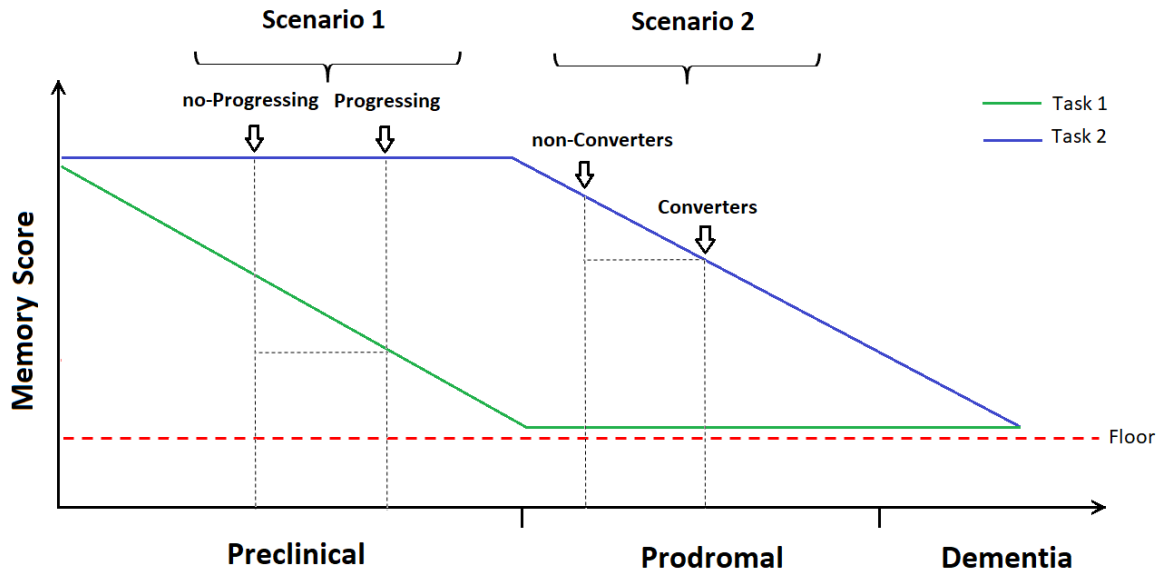

Figure 1. Hypothetical effectiveness of two memory tasks sensitive to two different stages of the AD continuum simultaneously used to gather baseline data at these stages. As Logie et al. [2] suggested, AD specific markers should avoid both ceiling (i.e., test too little taxing or insensitive to the early stages of AD e.g., Task 2 in Scenario 1) and floor effects (i.e., test too taxing or function severely affect by AD e.g., Task 1 in Scenario 2). Titration procedures can help address these limitations [2, 58].

Scenario 1 illustrates how a task sensitive to the preclinical stages (Task 1) would outperform a task that detects impairments in the MCI stages (Task 2) if baseline measures are obtained in the former stage. Scenario 2 shows a rather reverse picture. If Task 1 and 2 are administered at baseline during the MCI stages, the latter stands a better chance to discriminate between converter and non-converter MCI patients as the function assessed by the former would have likely declined to floor levels (see [44, 58] for evidence and further discussion and also [8] for a model supporting this notion).

This suggestion is far too simplistic as there are other factors that will need to be considered (e.g., disease severity at baseline, years to symptom onset, length of follow up, risk window, individual risk factors and comorbidities, cohort characteristics, just to mention a few). However, it presents two scenarios that seem to fit existing data [59, 60]. The notion that no

one-size-fits-all when it comes to prediction models for dementia is not new. Belleville et al [60] acknowledge that a cognitive toolkit intended to identify AD at the pre-dementia stage will need tasks that are early indicators and others that might suggest imminent progression. This model is compatible with this notion and further research will be required to unveil not only the "which" [8] but also the "when" in memory assessments for AD (See Table 1, Strategies O-Q). **Barrier 5. Predictive models relying on longitudinal data need to consider "which" memory function is assessed and "when" in the disease continuum baseline data is obtained.**

In this commentary, I have highlighted some important barriers current memory assessments for AD are facing. This list is non-exhaustive. There are other factors that undermine the effectiveness of available assessments. I have decided to highlight these five as they have figured prominently in studies and initiatives addressing global dementia needs [29, 43, 61]. As suggested by the recent ADI report, dementia is a condition that affects us all and therefore solutions to tackle it must suit us all. I finalise this commentary by suggesting some strategies which may help overcome the identified barriers and in so doing, help address the dementia challenge globally. My only expectation is that this will further stimulate ongoing debates and help level the playfield, so that we can all make "dementia research fit for the planet" [62].

Table 1. Barriers to effective memory assessment for AD and some suggested strategies.

Barrier	Strategy
Theory driven assessments	A. Zoom out to search for neural correlates of memory impairments outside the MTL B. Development of domain-specific memory assessments C. Search for subtle (i.e., deficits that are still unnoticed by affected individuals) rather than overt (i.e., deficits that cause complaints or interfere with people's abilities to perform daily living tasks) memory impairments. D. Address the psychometric limitations of Composite Scores [23, 24, 63]
Considerations toward cultural diversity, heterogeneity, risk factors and BCR	E. Development of tests insensitive to the cultural and socio-economic background of those assessed (e.g., visual rather than verbal formats [1, 64], early integrative cognitive functions[38]). F. Explore association between CBR and subtle cognitive deficits detected by tests compatible with strategies to address Barrier 1. G. Foster new cross-cultural collaborations towards the harmonization of assessments across HIC and LMIC [27, 29, 30, 61, 65]

Evidence from studies comparing the effectiveness of promising memory markers throughout the AD continuum assessed against pipeline biomarkers	H. Collaboration with cohort studies with long follow up periods (e.g., PREVENT [66], RedLAT [61], Cognitive reserve in a multiethnic cohort [67], just to mention a few. I. Validate memory markers for AD against pipeline biomarkers [25, 26] towards the development of cognitive biomarkers [27, 29, 30, 43] (see next) J. Explore the usefulness of cognitive tests combined with low-cost biomarkers (e.g., biofluids, Eye-tracking, Ocular Coherence Tomography, EEG) and validate these cognitive biomarkers against pipeline biomarkers [52, 68, 69]
Disentangling normal and abnormal ageing trajectories to create reliable normative samples	K. Continue the search for specific memory functions insensitive to normal ageing and sensitive to AD [2] L. Continue exploring the heterogeneity of cognitive trajectories in diverse older adults [55]. M. Improve understanding of the variability of dementia risk factors across HIC and LMIC and the links between environment and neurobiology [29, 56]]. N. Examine the need to adjust for biomarker status in cohort studies of healthy older adults (e.g., [66, 67, 70])
Predictive models relying on longitudinal data need to consider “which” memory function is assessed and “when” in the disease continuum baseline data is obtained	O. Develop theory-driven assessment protocols that incorporate state of the art cognitive and functional assessments that are well mapped onto the AD continuum [71]. P. Capitalise on secondary data approaches relying on datasets such as ADNI [72], API [73], DIAN[74], and Population Studies [62] Q. Develop AI models to identify domain-specific cognitive tests that can enhance both effectiveness of assessments and precision medicine [28, 63]

The Visual Short-Term Memory Binding Test (VSTMBT) can be accessed for free on this page: https://www.strath.ac.uk/research/subjects/psychology/cognition/appliedcognitionlab/visualshort-termmemorybindingtestvstmbt/. Relevant publications reporting on sensitivity, specificity and where these tests stand regarding the identified barriers can be found in the above suggested webpage (see also Martínez et al. [75] for a recent review on these

methodologies). Feel free to contact the author who was involved in the development of the VSTMBT for advice, and guidance and further information.

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