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KEY SYMPOSIUM

Multiple cognitive deficits during the transition to Alzheimer's disease

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Abstract. Bäckman L, Jones S, Berger A-K, Laukka EJ, Small BJ (Karolinska Institute, Stockholm, Sweden; and University of South Florida, Tampa, FL, USA) Multiple cognitive deficits during the transition to Alzheimer's disease (Key Symposium). *J Intern Med* 2004; **256**: 195–204.

The literature on cognitive markers in preclinical AD is reviewed. The findings demonstrate that impairment in multiple cognitive domains is typically observed several years before clinical diagnosis. Measures of executive functioning, episodic memory and perceptual speed appear to be most effective at identifying at-risk individuals. The fact that these cognitive domains are most implicated in normal cognitive aging suggests that the cognitive deficit observed preclinically is not qualitatively different from that observed in normal aging. The degree of cognitive impairment prior to the diagnosis of Alzheimer's disease (AD) appears to generalize relatively well across major study characteristics, including sample ascertainment procedures, age and cognitive status of participants, as well as time to diagnosis of dementia. In episodic memory, there is evidence that the size of the preclinical deficit increases with increasing cognitive demands. The global cognitive impairment observed is highly consistent with observations that multiple brain structures and functions are affected long before the diagnosis of AD. However, there is substantial overlap in the distribution of cognitive scores between those who will and those who will not be diagnosed with AD, hence limiting the clinical utility of cognitive markers for early identification of cases. Future research should consider combining cognitive indicators with other types of markers (i.e. social, somatic, genetic, brain-based) in order to increase prediction accuracy.

Keywords: Alzheimer's disease, preclinical, cognition, markers, transition, memory.

Background

This paper focuses on patterns of cognitive performance during the transition to Alzheimer's disease (AD). Specifically, we will provide a review of recent evidence pertaining to cognitive alterations in preclinical AD across (i) different cognitive domains, and (ii) major sample and task characteristics.

There is pervasive evidence for a performance decrement at a baseline assessment point amongst persons who are currently nondemented, but will receive an AD diagnosis after a follow-up interval [1]. That is, persons who will go on to be diagnosed with AD after a follow-up period exhibit poorer cognitive performance relative to persons who will not be diagnosed with dementia. Such preclinical deficits

have been observed across multiple cognitive domains, including episodic memory [2], executive functioning [3], verbal ability [4], visuospatial skill [5] attention [6] and perceptual speed [7]. Similar deficits have been observed for global indicators of cognitive functioning such as the Mini-Mental State Examination [8] and composite measures of cognitive ability [7]. It is of note that cognitive impairment in persons who will develop AD has been observed several years [9, 10], and in some cases even many decades [11, 12], prior to dementia diagnosis.

Despite the seemingly global cognitive impairment in preclinical AD, it has oftentimes been argued and occasionally empirically demonstrated that tasks assessing episodic memory (e.g. word recall, face recognition) are particularly useful in the preclinical detection of at-risk individuals [5, 9, 13]. To be sure, impairment of episodic memory functioning is expected in preclinical AD. It is well documented from both lesion and imaging research that the hippocampus and neighbouring regions are critically involved in the encoding, storage and retrieval of episodic information [14]. It is equally well documented from histopathology [15], structural imaging [16] and functional imaging [17] that the hippocampal complex is implicated long before the diagnosis of AD.

A global cognitive deficit in preclinical AD

However, close examination of the available evidence suggests that episodic memory does not have a unique status amongst cognitive measures in differentiating those who will develop AD versus those who will not. Specifically, effect-size measures such as Cohen's *d* [18] or η^2 as well as epidemiological indicators of differentiation (e.g. sensitivity and specificity) show strikingly similar accuracy in discriminating preclinical AD cases from controls for measures of episodic memory [2, 5, 9, 13, 19], executive functioning [3, 19, 20] and perceptual speed [3, 7, 21]. Somewhat smaller, albeit quite sizable, differences between cases and controls are typically observed for measures of verbal ability [4–6, 22, 23], visuospatial skill [3, 19, 24, 25] and attention [13, 26, 27]. The point that multiple cognitive functions are strongly implicated in preclinical AD is further substantiated by the observation that indicators of global cognitive ability appear to be equally impaired as specific measures of episodic memory, executive functioning and perceptual speed at identifying individuals in the preclinical phase of AD [7, 8, 27–29].

The notion of a multiple cognitive systems breakdown is consistent with data that conversion rates to AD over 3 years are considerably greater for persons with deficits in episodic memory and some other cognitive domain (e.g. verbal ability, visuospatial skill) at baseline than for those who have isolated memory impairment [30, 31]. As such, multiple cognitive deficits prior to the diagnosis of AD may be the more typical presentation of preclinical AD. Of further note is that the three specific cognitive domains that seem to best discriminate between cases and controls (i.e. episodic memory, executive functioning, perceptual speed) have also been implicated as particularly sensitive to the effects of normal aging [32–34]. These two sets of observations suggest continuity rather than discontinuity from normal aging to preclinical AD with regard to the patterns of cognitive impairment [35, 36].

Biological underpinnings

How then should we reconcile the apparent multiple cognitive systems breakdown in preclinical AD with extant knowledge concerning the biological basis of cognitive deficits in this phase of the disease? As noted, in searching for biological correlates of the cognitive impairment in preclinical AD, heavy emphasis has been placed on the medial – temporal lobe (MTL), with its obvious link to episodic remembering. However, recent brain imaging and histopathological evidence suggests that multiple brain structures and functions in addition to those related to the MTL may be affected before the diagnosis of AD. These findings include volume reductions of anterior cingulate and temporal sulcus [37], posterior cingulate and neocortical temporoparietal regions [38] and frontal regions [39]; decreased blood flow in posterior cingulate and precuneus [40], reduced glucose metabolism in temporoparietal regions [41]; and deposits of amyloid plaques in temporal [42] and frontal [43] cortex. In addition, more general alterations of brain functions in preclinical AD have been observed, including an increase of white matter hyperintensities [44] as well as a reduction of whole-brain glucose metabolism [45].

Thus, given that these studies indicate a rather widespread affection of brain structures and functions

in preclinical AD, it should come as no surprise that a similar extent of impairment is observed at the behavioural level. This point is further strengthened by recent evidence indicating strong relationships of volumetric measures of the whole brain and the temporal and frontal lobes to cognitive performance (e.g. memory, verbal skill, executive functioning) in mild cognitive impairment (MCI) and early AD, although no relationships were observed between regional brain damage and impairment of specific cognitive functions [46].

Study characteristics

Having established that impairment of many, if not most, higher-order cognitive functions in preclinical AD is a biologically plausible outcome, it is of interest to address the extent to which the magnitude of cognitive deficits is influenced by various sample and task characteristics. Here we will consider briefly four factors related to the nature of the study sample: (i) onset age of AD; (ii) length of the follow-up period between cognitive assessment and dementia diagnosis; (iii) sampling method (i.e. population-based versus convenience sample); and (iv) participant status {i.e. whether or not the sample was classified as cognitively impaired [e.g. MCI, cognitive impairment, no dementia (CIND)] at baseline}. This discussion will focus on episodic memory and global cognitive ability, because these two domains comprise a sufficient number of studies to make comparisons meaningful. In addition, for the domain of episodic memory we will also examine whether clear performance deficits in preclinical AD are more likely to occur for some task conditions than for others. In so doing, we will contrast studies involving (i) immediate versus delayed testing of memory, (ii) recall versus recognition, and (iii) verbal versus nonverbal materials.

The impressions from the available literature can be summarized as follows. First, baseline differences between cases and controls appear to be larger for earlier-onset cases than for later-onset cases. This pattern is evident when grouping the relevant studies into those that involve persons who received the dementia diagnosis before 75 years of age versus those who were diagnosed after 75 years of age, and it applies to both episodic memory [2, 19, 24, 25, 47–50] and global cognitive ability [8, 19, 24, 25, 28, 41, 51, 52]. This observation may reflect the fact that brain lesions are more widespread and severe amongst younger cases [53, 54], and could also be a result of lower performance amongst the controls for very old adults, restricting the room for further deterioration in preclinical AD [55, 56].

Not surprisingly, the magnitude of the preclinical cognitive deficit increases with decreasing time between baseline cognitive assessment and diagnosis. Again, this pattern holds for episodic memory [2, 6, 7, 22, 24, 27, 50, 57–59] and global cognitive ability [19, 41, 44, 51, 60–65] alike. Notwithstanding this pattern, it is of interest to note that the degree of cognitive impairment is quite sizable also for studies employing retest intervals of 5 years or longer [2, 6, 61, 63, 64]. This observation is interesting to view in the light of recent longitudinal evidence on the trajectory of cognitive decline in preclinical AD. In two studies, stability of cognitive impairment amongst incident AD patients was observed from 6 to 3 years prior to eventual diagnosis [2, 63]. In another study, disproportionate decline was seen amongst incident AD cases from 3.5 to 1.5 years before diagnosis [19]. Thus, these studies suggest that the preclinical period in AD is characterized by an early onset followed by relative stability until a few years before diagnosis when precipitous cognitive decline occurs [8, 16, 26].

Clear preclinical deficits are observed both in studies that employ population-based sampling and those that use convenience samples recruited via memory clinics, newspaper advertisements and the like. However, for both global cognitive ability [7, 21, 25, 27, 29, 41, 66] and episodic memory [4–6, 27, 40, 58, 59, 67], the size of the impairment appears to be somewhat larger in population-based samples. Conceivably, this reflects the fact that memory and other cognitive problems are common amongst people who actively seek participation in studies on aging and cognition, irrespective of whether or not they are in a preclinical phase of dementia. Consequently, cognitive performance would be expected to be lower also for the controls in these types of studies, resulting in smaller group differences.

A key difference between studies in this area, and one that is of particular relevance to the current collection of papers, concerns whether participants have been classified as cognitively impaired already at baseline assessment, using categories such as MCI or CIND. On the one hand, it may appear reasonable

that studies that follow a group of preclassified persons prospectively should yield larger effect sizes than those that work retrospectively from diagnosis to baseline. On the other hand, recent evidence indicates that categories like MCI are rather heterogeneous. For example, it has been shown that, although a large portion of cognitively impaired older adults go on to develop AD within a few years, a sizable portion remain stable or even improve across the same time period [68, 69]. Obviously, the latter fact speaks against prospective studies resulting in larger effect sizes.

For global cognitive ability, the evidence suggests that MCI-type studies and retrospective studies yield quite similar differences between incident AD cases and controls [8, 60–62, 64, 70–72]. By contrast, for episodic memory, the size of the impairment appears to be larger in studies that preclassify subjects on the basis of cognitive impairment at baseline assessment [2, 20, 23, 24, 26, 48, 50]. The latter finding may be expected, given that episodic memory impairment constitutes a cardinal criterion for inclusion in the MCI category [73].

Task variation in episodic memory

Within the domain of episodic memory, the size of the preclinical deficit varies in a rather orderly fashion. First, it is clear that the deficit is exacerbated in studies that employ delayed testing [3, 19, 23, 57] as opposed to those in which memory is tested immediately after study [3, 6, 19, 21, 25]. Provided that delayed testing taxes consolidation processes to a greater extent than immediate testing [74, 75], this result is consistent with the view that failure in transferring information from temporary storage to a more permanent memory representation is a characteristic feature of the episodic memory impairment in preclinical AD [35]. Secondly, it is equally clear that larger group differences are obtained when memory is tested with recall [4, 7, 26, 50, 67] compared with recognition [2, 5, 19, 25, 48]. Given that the retrieval demands are considerably greater in recall than in recognition [76, 77], these data suggest that retrieval problems, in addition to difficulties in encoding and consolidation, may be characteristic of preclinical AD. Finally, verbal episodic memory tasks [2, 5, 19, 25] appear to yield somewhat larger group differences than nonverbal episodic memory tasks [3, 6, 24, 25, 31]. This may reflect the fact that verbal materials (e.g. words, paired-associates) are typically poorer in terms of the features available at encoding compared with nonverbal materials (e.g. faces, pictures). As a result, the requirement of self-initiated elaborative encoding operations are generally greater for verbal materials [78], which may be particularly handicapping for preclinical AD cases. The patterns of data described above indicate that the episodic memory deficit in preclinical AD is exacerbated with increasing cognitive demands.

Albeit these influences of study and task characteristics, it is important to note that large group differences are manifest across the board for global cognitive ability and episodic memory. Thus, the differences observed should not conceal the fact that preclinical cognitive deficits in AD generalize across (i) several key domains of cognitive functioning; (ii) major characteristics of research studies; and (iii) multiple aspects of episodic memory.

Caveats

Although the present analysis of cognitive markers in preclinical AD provides a comprehensive account of the current state of knowledge in this domain of research, there are limitations to note. First, few of the available studies provide information on all, or even most, of the cognitive ability domains targeted. Thus, the discussion pertaining to the influence of sample characteristics was restricted to global cognitive ability and episodic memory. As a result, it is not possible to examine whether differences between preclinical AD cases and controls vary across cognitive domain depending on the time between assessment and diagnosis. For example, advocates of the view that episodic memory is the earliest cognitive marker of incipient AD could still argue their case; the present analysis is not informative regarding the onset of decline for different cognitive functions. However, for studies that employ long follow-up periods, differences between incipient AD cases and controls appear to be larger for measures of global cognitive ability [27, 41, 60, 64, 66, 72] than for episodic memory measures [2, 6, 27, 48, 50]. Note also that those studies using assessment periods spanning several decades have found clear preclinical impairment in domains other than episodic memory such as linguistic skill [11] and general intelligence [12].

Another consequence of the limited database is that it is not possible to examine the influence of different study characteristics simultaneously. In some cases, study characteristics may be confounded. For example, studies in which participants are preselected based on their cognitive performance may primarily use convenience sampling rather than population-based sampling. Disentangling the influence of these and other variables would require considerably more studies than what is available in the current literature. Thirdly, the available studies vary quite markedly with regard to the length of the follow-up interval. Future longitudinal studies should address this issue in order to provide more definite information as to the specific time at which precipitous cognitive decline normally occurs in preclinical AD.

Conclusions

With the above caveats in mind, the current overview clearly suggests that impairment in multiple cognitive domains several years before clinical diagnosis is characteristic of AD. The generality of the cognitive impairment observed is highly consistent with recent observations that numerous brain structures and functions are affected prior to the diagnosis of AD. We would also like to highlight the finding that the magnitude of the preclinical cognitive impairment seems to be only marginally affected by various study and task characteristics.

Issues to consider in future research

Although cognitive performance scores obtained several years before diagnosis can discriminate quite well between incident AD cases and controls at the group level, it is clear that the distributions of scores for the two groups overlap to a considerable degree. This fact hampers optimism regarding the utility of cognitive markers in identifying persons eligible for pharmacological intervention and other clinical purposes. The large cognitive overlap between cases and controls deserves several comments. First, it is well known that a vast number of factors, in addition to being in a prodromal phase of dementia, may affect cognitive functioning in aging. These include, but are not limited to, demographic factors (e.g. education), social and life-style factors (e.g. activity patterns), genetic factors [e.g. apoliporotein E (APOE) status], as well as a variety of health-related factors [e.g. vitamin and thyroid deficiency, circulatory disturbance, depression; 79, 80]. Analogously, there is interindividual variability amongst persons who will develop AD both with regard to performance at a given point in time (e.g. 4 years before diagnosis) and in rate of decline during the preclinical period [26, 81]. These two facts make it unlikely that cognitive performance scores alone would yield a clear separation between incident AD cases and controls.

Extending the pool of preclinical markers

In the current overview, however, different cognitive domains were examined separately. There is evidence that the ability to identify persons at risk for developing AD increases substantially when tasks assessing different cognitive domains (e.g. episodic memory, executive functioning, verbal ability) are combined into the same prediction model [3, 5, 19]. In addition, the cognitive variables used in this research may be broadened from traditional cognitive performance scores (e.g. number of words recalled, lexical decision time) to alternate measures such as those dealing with within-person performance variability. Evidence suggests that increased variability across trials in RT tasks may be associated with several factors known to be related to brain functioning [e.g. impending death, clinical dementia, head injury, physical health; 82, 83]. Importantly, this association remains strong even after partialing out mean performance levels. Thus, including measures of within-person variability may increase prediction accuracy.

Further, indicators of other domains of functioning may be useful in identifying at-risk individuals. This includes multiple measures of brain structure and function such as volumetric measures [37, 38], glucose metabolism [41, 45], blood flow [17, 40], amyloid deposits [42, 43] and white matter hyperintensities [44]. It also includes markers for genetic predisposition such as presence of the APOE $\epsilon 4$ allele [84] as well as subjective memory complaints [85], family reports of cognitive impairment [20] and depressive symptoms [86]. The identification of precipitating factors may provide further help in differentiating between preclinical AD and cognitive impairment of other origins. Possible precipitating factors include medical

events such as unrecognized hypertension [87], head trauma [88] and stroke [89] as well as social factors such as isolation [90].

Given this state of affairs, an important avenue for future research would be to combine predictors from different behavioural and biological domains. Such an approach may not only increase overall prediction accuracy; it also enables examining possible interactive effects amongst various preclinical markers (e.g. poor episodic memory, unrecognized hypertension, depressive symptoms). Although it is conceivable that such a multivariate approach may decrease the overlap between preclinical cases and controls, very large samples will be required to fully utilize its potential. Moreover, improved classification will, of course, occur only to the extent that the predictor variables included contribute unique variance.

Onset of precipitous decline

Another unresolved issue of importance to the correct identification of at-risk individuals has to do with the time at which precipitous decline occurs amongst those who will develop AD. Although there is consensus that persons who will develop AD show precipitous cognitive decline during the last 2–3 years before diagnosis [8, 19, 26], evidence is mixed regarding whether accelerated decline is observed longer before diagnosis. Using data from a population-based study of individuals aged 75 years and older at the outset, we observed stability of the magnitude of preclinical impairment from 6 to 3 years before diagnosis for measures of episodic memory [2] and global cognitive ability [63]. Coupled with other evidence that preclinical impairment may be seen decades before diagnosis [10–12], this pattern could be interpreted to mean that accelerated cognitive decline may not be expected until various biological events (e.g. the accumulation of amyloid and neurofibrillary tangles, inflammation, oxidative stress, loss of synapses, death of neurones) have reached a certain threshold [91, 92]. This notion rests on the assumption that the brain is capable of counteracting AD-related neural changes to a point at which compensatory responses are no longer possible. Indeed, there is evidence from cognitive psychology [93], neuroimaging [94], histopathology [95] and neurochemistry [96] that the aging brain possesses compensatory capabilities.

However, other evidence suggests that precipitous decline may occur in persons who will be diagnosed with AD longer before diagnosis. In two studies [49, 97] accelerated decline in measures of episodic memory was demonstrated more than 5 years before diagnosis, although speeded measures of performance IQ exhibited accelerated decline around 2 years before diagnosis. Several factors are likely to contribute to the equivocal findings, including the nature of the study sample. For example, it is conceivable that accelerated cognitive decline longer before diagnosis is more likely to be observed when strict selection criteria (e.g. removal of persons with other conditions that affect cognitive functioning) are employed. Obviously, more information pertaining to this issue is vital in order to achieve a better understanding of the preclinical process in AD, and to improve differentiation between cases and controls.

Individual differences in onset and rate of change

An important factor in this context has to do with whether there are individual differences with regard to onset and rate of change in preclinical AD. Indeed, clinical observations suggest that some individuals may show accelerated decline for only a short period of time before diagnosis, whereas others show gradual decline across a much longer time period. However, delineating factors that are systematically related to rate of cognitive change in preclinical AD has proved difficult. Negative findings have been documented for a variety of factors, including age, sex, education, depression, APOE status, family history of dementia, circulatory disease, vitamin B deficiency, social network and substance use [81, 98–99]. Note that most of these factors have been implicated as risk factors for AD, or been found to influence cognitive performance in normal aging.

One possibility is that the negative findings reflect the fact that the influence of individual difference variables is overshadowed by the emerging pathogenetic process [81]. However, they could also, in part, be a function of the analytical methods employed (e.g. ANOVA or regression procedures with listwise deletion). More recently developed analytical tools such as multilevel modelling may be more sensitive in identifying factors that share systematic relationships with rate of cognitive change in preclinical AD. Specifically, these procedures allow

for differences in baseline functioning, as well as differences in longitudinal rate of change, to be incorporated into the statistical models, which is directly relevant to the longitudinal trajectories in preclinical AD seen previously [2, 19]. If systematic relationships between specific individual difference variables and rate of change were to be revealed, they would be informative in identifying people destined to develop AD at the earliest possible time.

Conflict of interest statement

No conflict of interest declared.

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