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Cognition in Preclinical Dementia: Current Knowledge and Future Prospects

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Abstract: In this article, I discuss the cognitive transition from normal aging to dementia -- a period often referred to as the preclinical phase of dementia. Research shows marked preclinical cognitive deficits several years before diagnosis in both Alzheimer´s disease and vascular dementia. The most pronounced prodromal impairment is observed for measures of episodic memory, speed, and executive functioning. The global nature of the impairment is consistent with neurobiological evidence that multiple lesions in limbic and neocortical regions. Despite large mean-level differences between cases and controls long before diagnosis, the performance distributions for the two groups overlap to a large degree. An important task for future research is to find means by which to decrease this overlap. This could be accomplished by combining cognitive and other (e.g., brain-based, genetic, clinical, social) markers into the prediction models. Other pressing issues for future research include (a) delineating the point at which precipitous decline normally occurs during the preclinical period; (b) asesssing individual differences in rate of change from preclinical to clinical dementia; and (c) determining how the strength of the association between a certain factor and subsequent dementia varies as a function of time to diagnosis.

Key words: aging; cognitive functions; episodic memory; preclinical dementia; Alzheimer´s disease; vascular dementia; dementia markers; dementia risk factors

Preclinical Cognitive Deficits in Alzheimer´s Disease

In the typical study addressing preclinical cognitive deficits in dementia, a group of older persons who are non-demented at baseline assessment is followed over a specified time interval (e.g., 4 years). If the study sample is old enough and large enough, a certain number of persons will, unfortunately, be diagnosed with dementia at follow-up assessment. The key issue is whether these incident dementia cases differed from those who remained non-demented at follow-up already at baseline assessment. The simple answer to that question is “yes.”

Preclinical cognitive deficits in AD have been documented several years before a clinical diagnosis of dementia may be rendered. Much of the interest in impaired cognition prior to the AD diagnosis has centered around episodic memory (Bäckman et al., 2004). This form of memory deals with the conscious retrieval of information acquired at a certain time in a certain place (e.g., recall of a list of words encountered in the laboratory; Tulving, 1983). A logical reason for the focus on episodic memory in prodromal AD is that there is evidence from histopathology (Braak & Braak, 1995; Van Hoesen et al., 1999), structural imaging (Fox et al., 1996; Visser et al., 1999), and functional imaging (e.g., Bäckman et al., 1999; Grady et al., 2001) that the hippocampus and neigboring regions (e.g., entorhinal cortex) are affected early on in the disease process. Evidence from lesion studies (e.g., Vargha-Khadem et al., 1997) and functional imaging research (e.g., Nyberg et al., 1996) strongly implicate the hippocampal complex in episodic remembering.

In agreement with these assertions, there is pervasive support for the view that episodic memory, whether assessed with recall (Bäckman, Small, & Fratiglioni, 2001; Rubin et al., 1998) or recognition (Chen et al., 2001; Howieson et al., 1997), is

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severely impaired many years before the AD diagnosis. At the same time, it is clear that preclinical deficits in AD are not restricted to episodic memory. Thus, impaired performance during the preclinical period has been observed for tasks assessing executive functioning (Blacker et al., 2007), perceptual speed (Fabrigoule et al., 1998), verbal ability (Jacobs et al., 1995), visuospatial skill (Small et al., 1997), and attention (Linn et al., 1995). Consistent with these patterns, preclinical deficits have been documented for composite measures of cognitive ability (Fabrigoule et al., 1998) as well as for global indicators of cognitive functioning such as the Mini-Mental State Examination (Small, Viitanen, & Bäckman, 1997).

Meta-Analytic Evidence

In a quantitative integration of this literature based on a total of 47 studies (1,207 preclinical AD cases and 9,097 controls), we examined potential differences across cognitive domains with regard to the size of the preclinical impairment (Bäckman et al., 2005). Here we also investigated differences in degree of impairment as a function of age of dementia onset, length of follow-up interval, sampling method (population-based vs. convenience sample), and whether or not subjects were classified with cognitive deficits (e.g., mild cognitive impairment) at baseline assessment. Finally, we were interested in whether task characteristics within the key domain of episodic memory (i.e., immediate vs. delayed testing; recall vs. recognition; verbal vs. non-verbal materials) had an impact on the degree of preclinical impairment.

Several aspects of the data from this study should be highlighted. First, the effect sizes (expressed in Cohen´s *d*, which is computed as the mean performance difference between cases and controls divided by the pooled standard deviation; Cohen, 1988) were remarkably large ($d > 1.0$) and virtually identical for the domains of episodic memory, executive functioning, and perceptual speed, as well as for global cognitive functioning. Somewhat smaller, albeit sizable, effect sizes ($d \approx 0.7$) were obtained for verbal ability, visuospatial skill, and attention, whereas no group differences were seen for measures of primary memory. The latter finding is expected in view of the fact that this form of memory is well preserved even among early clinical AD patients (Simon et al., 1995).

Thus, from these data it is clear that episodic memory does not have a unique status as an indicator of impending AD. Rather, the findings suggest that the preclinical phase is characterized by a rather generalized cognitive impairment. Given this pattern of findings, it is of interest to note that, although much of the neurobiological work in this area has targeted the medial-temporal lobe, evidence indicates that multiple brain structures and functions are affected long before the AD diagnosis. Specifically, preclinical AD is associated with reductions of grey-matter volume (Apostolova et al., 2006), decreased blood flow (Encinas et al., 2003), and reduced glucose metanolism (Jagust et al., 2006) in neocortical areas, including the frontal, parietal, and temporal cortices. Further, an increased amyloid burden (Rowe et al., 2007) as well as an increased number of neurofibrillary tangles (Markesbery et al., 2006) have been observed throughout the neocortex many years before diagnosis. Persons at risk for developing AD also exhibit reduced activation of specific parietal regions during semantic classification (Lind et al., 2006). Finally, general alterations of brain function in preclinical AD have been demonstrated, such as increases in white-matter hyperintensities (Wolf et al., 2000), and a reduction of whole-brain glucose utilization (Silverman et al., 2001). The obvious point, then, is that the generalized cognitive impairment in preclinical AD revealed in our meta-analysis (Bäckman et al., 2005) makes perfect sense in view of the multifaceted and widespread brain alterations in these individuals.

This analysis also showed that the magnitude of cognitive impairment was larger for earlier-onset (< 75 years) than for later-onset (75+ years) cases. This may reflect more severe brain lesions in earlier-onset cases (Mann, 1994), that the controls perform at lower levels in higher ages (Bäckman et al., 2000) restricting the room for further deterioration in preclinical AD, or a combination of the two. A more trivial observation was that the size of the preclinical impairment was greater for shorter (≈ 2 years before diagnosis) than for longer (≈ 5 years before diagnosis)

follow-up intervals. That said, quite sizable impairments ($d \approx 1.0$) were seen even in studies employing longer retest periods. Further, the degree of impairment generalized well across study samples (population-based, convenience) and participant status (non-classified, classified with cognitive impairment). Finally, within the episodic memory category, delayed testing revealed larger effect sizes than immediate testing and recall yielded larger effect sizes than recognition. In turn, these results may reflect the facts that (a) preclinical AD is associated with deficits memory consolidation, and (b) retrieval problems are present in preclinical AD, in addition to difficulties in encoding and consolidation.

Preclinical Cognitive Deficits in Vascular Dementia

Relatively little empirical attention has been directed at potential preclinical cognitive markers in VaD. This is an unfortunate lacuna, beacuse many vascular risk factors (e.g., hypertension) are amenable to treatment to a degree that is not true in AD. For several reasons, a preclinical phase with cognitive problems is to be expected also in VaD, and these problems may mimic those observed in preclinical AD. First, different forms of vascular alterations are known to affect cognition in the absence of dementia, including hypertension, atherosclerosis, diabetes, white-matter lesions, ”silent” strokes, and cardiovascular signs (Jonsson Laukka et al., 2009). Given that VaD develops through combined effects of different vascular mechanisms that influence cognitive performance, it is reasonable to expect cognitive deficits before the condition reaches its clinical threshold. Second, autopsy evidence suggests that a sizable proportion of patients diagnosed with AD or VaD exhibit brain pathology characteristic of the other disorder, and some degree of cerebrovascular pathology is present in almost all AD cases (de la Torre, 2002; Kalaria & Ballard, 1999). Third, given that early clinical AD and VaD patients show strikingly similar patterns of cognitive impairment (Almkvist et al., 1999; Fahlander et al., 2002; Hassing & Bäckman, 1997), similarities in preclinical manifestations might be expected as well.

Those studies that have addressed cognition before the VaD diagnosis demonstrate quite a consistent pattern, indicating preclinical deficits in VaD that resemble those observed in AD. Thus, for both global cognitive ability (Meyer et al., 2002a, 2002b) and episodic memory (Ingles et al., 2002; Sacuiu et al., 2005) clear deficits have been reported among those who will be diagnosed with VaD years before diagnosis, and the size of these deficits is similar to that reported for preclinical AD (Jonsson Laukka et al., 2009).

In several studies, we have systematically compared preclinical VaD and AD patients regarding the timing and extent of preclinical cognitive deficits. In two studies, we compared cognitive functioning in preclinical VaD, preclinical AD, and normal controls three years before the dementia diagnosis. The VaD diagnosis was mainly a diagnosis of post-stroke dementia (multi-infarct dementia or strategic single infarct). A key finding was that cognitive deficits were present three years before the diagnosis of VaD, both for a measure of global cognition (Jones et al., 2004) and for measures of episodic memory functioning (Laukka et al., 2004b). Further, the pattern of cognitive deficits in preclinical VaD was similar to that observed in preclinical AD, and there were no significant differences in cognitive performance between the two dementia groups.

In Laukka et al. (2004b), a comprehensive cognitive test battery was administered. The general pattern indicated poorer cognitive performance for both preclinical dementia groups compared to the controls. However, whereas the preclinical AD group performed worse than the controls on measures of episodic memory, verbal fluency, and visuospatial functioning, the preclinical VaD group showed deficits only on the episodic memory measures (word recall and recognition and face recognition). These results suggest a somewhat more pronounced cognitive deficit in preclinical AD. However, again there were no reliable differences between the two dementia groups in any task, and both groups showed the most pronounced impairment in episodic memory.

Further, similar levels of impairment in AD and VaD (Jonsson Laukka et al., 2004a; Small et al., 2000) were also demonstrated for a measure of global cognitive functioning six years before diagnosis. An exception to this pattern was observed in a study comparing the effect of preclinical dementia in two verbal fluency tasks. Although both preclinical dementia groups showed poorer performance on letter fluency, the preclinical VaD persons outperformed the preclinical AD persons on category fluency three years before diagnosis (Jones et al., 2006). The finding that the preclinical AD persons were disproportionally impaired in category fluency is in agreement with observations that the medial-temporal lobe is taxed in this task (Mungas et al., 2001; Pihlajamäki et al., 2000). A possible reason thereof is that the search process in a category fluency task (in this case supermarket fluency) invokes personal experiences and thus involves episodic memory retrieval. Given that the medial-temporal lobe is relatively more affected in preclinical AD compared to VaD (Braak & Braak, 1995; Fox et al., 1996), this might explain the larger category fluency impairment for the preclinical AD persons.

Two points should be made regarding the generally similar patterns of preclinical cognitive impairment in VaD and AD. First, the relevant research largely involves VaD patients of the post-stroke dementia type. The likelihood of observing differential patterns (e.g., larger episodic memory impairment in preclinical AD and larger executive impairment in preclinical VaD) may be greater in VaD of subcortical origin (Jonsson Laukka et al., 2009; Kramer et al., 2002). Second, the similar patterns observed in preclinical VaD and AD (e.g., large episodic memory problems) do not necessarily imply alterations in similar neural circuitries. Episodic remembering draws on a large distributed network, including prefrontal and medial-temporal regions (e.g., Cabeza & Nyberg 2000). Alterations at any one location in this network may cause episodic memory impairment. To illustrate this point, a study comparing AD and subcortical stroke patients observed a double dissociation between memory dysfunction and regional glucose metabolic activity: Whereas performance on an episodic memory task correlated with left-hippocampal and middle-temporal gyrus metabolism in AD patients, it correlated with prefrontal lobe metabolism in patients with subcortical stroke (Reed et al., 2000). Thus, the same cognitive deficit may have different neurological underpinnings depending on the etiology of the disorder.

Large Overlap Between Preclinical Cases and Controls

Although mean levels of cognitive performance differ markedly between preclinical dementia cases and controls many years before diagnosis, the performance distributions between these two groups overlap to a large degree. For example, in the meta-analysis on preclinical AD discussed above (Bäckman et al., 2005), effect sizes larger than 1.0 were documented for episodic memory, executive functioning, and speed. Nevertheless, nearly half of the samples (preclinical AD vs. controls) overlapped in performance for these task domains. Although this is bad news from a clinical perspective (e.g., regarding the possibility for early identification of specific individuals at risk), a pattern of overlapping distributions should be expected for at least two reasons. First, deficient cognitive functioning may have multiple origins in addition to being in a prodromal phase of dementia. These include demographic and social factors (e.g., low education and activity levels), but also psychiatric, metabolic, immunological, and hormonal disturbances (Bäckman et al., 2004). As a result, some persons who perform at low levels in cognitive tasks will be misclassified as at-risk individuals, despite the fact that they will not convert to clinical dementia during the follow-up period.

Conversely, persons who will be diagnosed with AD vary both in terms of onset of precipitous decline and rate of change during the preclinical period (Bäckman et al., 2003; Bäckman & Small, 2007; Rubin et al., 1998). In particular, incident AD cases who exhibit relatively normal cognitive performance until shortly before follow-up when decline occurs very rapidly will be difficult to catch (Palmer et al.,

2008). Consistent with these observations, several studies demonstrate that persons classified as cognitively impaired (e.g., mild cognitive impairment; cognitive impairment, no dementia) differ greatly with regard to future cognitive changes (Helkala et al., 1997; Hong et al., 2003; Palmer et al., 2002; Palmer et al., 2003) For example, Palmer et al. (2002) found that, although a sizable portion of their cognitively impaired sample progressed to dementia across a three-year period, an equally large portion remained stable or improved their cognitive performance over the same time frame. Obviously, such facts hamper the utility of cognitive tests in the early identification of persons at risk of developing dementia. Means by which to increase the clinical usefulness of cognitive and other markers of incipient dementia are discussed in a subsequent section.

The Trajectory of Preclinical Cognitive Decline

An important unresolved in the identification of at-risk individuals concerns the time period during which precipitous decline occurs among those who will develop dementia. Although there is consensus that incident AD persons show accelerated cognitive decline during the last 2-3 years before diagnosis (Bäckman et al., 2001; Chen et al., 2001; Small et al., 2000), evidence is mixed as to whether precipitous decline is observed longer before diagnosis. Stability of the magnitude of preclinical impairment from 6 to 3 years before diagnosis has been observed for measures of episodic memory (Bäckman et al., 2001) and global cognitive ability (Small et al., 2000; see also Small & Bäckman, 2007) in AD and more recently also in VaD (Jonsson Laukka et al., 2004a). Similarly, Amieva and colleagues (2005) reported differences between preclinical AD cases and controls on tests of memory and global cognitive ability 9 years prior to diagnosis, and that cognitive decline for the preclinical AD group began to accelerate around 3 years prior to diagnosis.

However, other evidence suggests that precipitous decline may occur in persons who will be diagnosed with AD longer before diagnosis. In two studies (Hall et al., 2000; Hall et al., 2001) accelerated decline in episodic memory was demonstrated more than 5 years before diagnosis, although speeded measures of performance IQ exhibited accelerated decline around 2 years before diagnosis (see also Jorm et al., 2005). Several factors may contribute to the equivocal findings, including the nature of the study sample. Conceivably, 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. Moreover, the number of measurement points during the preclinical period may affect the probability of observing a nonlinear change function. Amieva et al. (2005) evaluated persons annually over a 9-year period prior to diagnosis and applied sophisticated random-effects models to evaluate changes in functioning. This data-intensive design allows for a more detailed view into the nature of cognitive decline in preclinical AD. More information pertaining to this issue is critical in order to achieve a better understanding of the preclinical process in AD and VaD, and to improve early differentiation between cases and controls (Small et al., 2008).

Avenues for Future Research

In the following, I will highlight a number of research issues that are vital in furthering our theoretical understanding of the transition from normal aging to dementia, as well in increasing the clinical utility of such research. As noted, although mean cognitive scores of preclinical dementia cases and controls differ markedly years before diagnosis, the two groups still overlap to a considerable extent. That said, it should be noted that the meta-analytic evidence showing overlap scores around 50 % was based on individual cognitive domains (e.g., episodic memory). There is evidence that the identification of at-risk individuals increases greatly (with a concomitant decrease in overlap) when tasks assessing different cognitive domains (e.g., episodic memory, executive functioning, semantic memory) are incorporated into the same prediction model

(Chen et al., 2001; Small et al., 1997). Thus, the overlap scores reported by Bäckman et al. (2005) represent an underestimation of what could be achieved by intelligent selection of cognitive tasks.

Further, to minimize the overlap between cases and controls, future research should consider supplementing cognitive markers of incipient dementia with indicators from other domains that have been linked to dementia incidence. These include multiple measures of brain structure and function such as volumetric measures (Apostolova et al., 2006; van der Flier et al., 2002), glucose metabolism (Jagust et al., 2006; Silverman et al., 2001), blood flow (Encinas et al., 2003; Kogure et al., 2000), markers of amyloid deposition (Klunk, 1998; Rowe et al., 2007 and neurofibrillary tangles (Klunk, 1998; Markesbery et al., 2006), as well as white-matter alterations (Huang & Auchus, 2007; Yoshita et al., 2006). Markers for genetic predisposition such as presence of the APOE-ε4 allele (Farrer et al., 1997), subjective memory complaints (Palmer et al., 2003), family reports of cognitive impairment (Daly et al., 2000), depressive symptoms (Berger et al., 1999), as well factors such as social isolation (Fratiglioni et al., 2000) intellectual engagement (Crowe et al., 2003), physical activity levels (Rovio et al., 2005), and susceptibility to distress (Wilson et al., 2003) should also be considered in this context.

In applying such hybrid models in identifying persons at risk for developing dementia, the key issue is whether certain combinations of cognitive, biological, genetic, clinical, and social markers will increase prediction accuracy beyond what is achieved at the level of single categories of markers. Logically, improved differentiation will occur to the extent that the factors included contribute unique variance in group classification. Further, it will be of great interest to examine whether there are interactions between different classes of markers with regard to the probability of a future dementia diagnosis. For example, could it be that an unfavorable situation with regard to certain factors (e.g., carrying the APOE-ε4 allele, poor episodic memory) is offset by more favorable conditions for other factors (e.g., rich social network, low amyloid burden)? Relatedly, will several unfavorable characteristics lead to increased cognitive decline and risk of dementia to a degree that is not predicted from an individual evaluation of the factors?

We also need more data pertaining to the trajectory of decline during the transition from preclinical to clinical dementia (e.g., “Is the decline function linear over many years or does exacerbated loss occur only during the last few years preceding diagnosis”? An important issue related to this point concerns individual differences regarding rate of decline in preclinical dementia. Clinical observations suggest that some individuals show accelerated decline for only a short period of time before diagnosis, whereas others show gradual decline across a much longer time period. However, in investigating factors that are systematically related to rate of cognitive change in preclinical dementia, negative findings have been documented for a variety of factors, including age, sex, education, depression, APOE status, circulatory disease, vitamin B deficiency, and social network (Bäckman et al., 2003; Storandt et al., 2002; Wilson et al., 2000). Notably, many of these factors have been implicated as risk factors for AD, or been found to influence cognitive performance in normal aging. The negative findings may reflect the fact that the influence of individual-difference variables on cognitive performance is overshadowed by the emerging disease process itself. However, they could also be a function of the analytical methods employed (e.g., ANOVA or regression procedures). More recently developed analytical tools such as multilevel modeling may be more sensitive in identifying factors that share systematic relationships with rate of cognitive change in preclinical dementia. If such relationships were to be revealed, they would be extremely valuable in early identification of people destined to develop dementia.

The use of multilevel modeling will also permit addressing a fundamental issue regarding the development of AD and VaD; namely, whether a certain factor linked to the future occurrence of dementia (e.g., poor episodic memory, depressive symptoms, low social activity levels) should be characterized as a risk factor or as an early marker.

This constitutes a recurrent source of ambiguity in this field of research, for it is often difficult to differentiate between these possibilities. However, by using multi-wave longitudinal data, it should be possible to determine the extent to which certain variables remain stable, increase, or decrease in importance as a function of time to diagnosis, regarding their relationship to final dementia status. Thus, by systematically examining whether different markers change in the strength of the association to dementia outcome as a function of time to diagnosis, more precise knowledge regarding the nature of dementia-related correlates will be obtained.

In summary, outstanding issues in future research on preclinical dementia include (a) evaluating multifactorial prediction models of incidence; (b) delineating the point at which precipitous decline normally occurs during the preclinical period; (c) asesssing individual differences in rate of change from preclinical to clinical dementia; and (d) determining how the strength of the association between a certain factor and subsequent dementia varies as a function of time to diagnosis. For all these research problems, it will be of great interest to elucidate differences and similarities concerning patterns of outcome between AD and VaD.

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前临床期痴呆的认知特征：当前研究进展和未来研究展望

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摘 要 在这篇文章中，我将讨论从正常老化到痴呆，这一通常被称为痴呆前临床阶段的认知功能的转变。研究表明，阿尔茨海默症和血管性痴呆病人在临床确诊之前的几年中，会出现明显的认知损伤。早期最突出的损伤存在于情节记忆、加工速度以及执行功能。这些功能性损伤与神经生物学研究证实的边缘系统和新皮层区存在多重损伤是相一致的。虽然早在临床诊段之前，病人组和控制组的平均成绩存在巨大差异，但同时这两组测试成绩的分布在很大程度上是重叠的。寻求降低这种重叠度的方法是未来研究的一个重要任务。这有可能通过将认知的和其他指标(如基于脑的、基因的、临床的、社会的)相结合构建预测模型来实现。此外，在未来研究中以下三方面也是急需考虑问题：(a) 找出在前临床期间认知功能急速下降的时间点：(b) 评估从前临床到临床诊断变化速率中存在的个体差异；(c) 确定特定因素与随后发生的痴呆之间的关联强度是如何随时间向临床确诊推进而逐渐变化的。

关键词 老化；认知功能；情节记忆；痴呆前临床期；阿尔茨海默症；血管性痴呆；痴呆的标记物；痴呆的危险因素

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