Aging Neuropsychology and Cognition
2004, Vol. 11, No. 2–3, pp. 212–244

Psychology Press
Taylor & Francis Group

Cognitive Functioning in Aging and Dementia: The Kungsholmen Project

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ABSTRACT

The Kungsholmen Project (KP) is a community-based longitudinal study of aging and dementia targeting the 75+ population. In this article, we review empirical studies with a cognitive focus from the KP. The main findings indicate that (a) there is an age-related decline for some cognitive domains (e.g., episodic memory, verbal fluency, visuoconstructive skill, psychomotor speed), but not for others (e.g., primary memory, visuoperceptive skill, motor-hand coordination), (b) multiple individual-difference variables within demographic (e.g., sex, education) life-style (e.g., activity levels), genetic (e.g., apolipoprotein E genotype), and health-related (e.g., vitamin B deficiency, depression, diabetes) domains are related to late-life cognitive functioning, (c) a potential for improving cognitive performance – a reserve capacity – is present also among very old adults, (d) the 2 most common dementia diseases, Alzheimer's disease (AD) and vascular dementia (VaD), affect cognition in a strikingly similar manner, (e) the role of individual-difference variables in cognitive functioning is markedly reduced in dementia – the pathogenesis itself may overshadow the influence of other variables, and (f) there is a long preclinical period in dementia during which cognitive deficits are detectable. As is true with the other projects represented in this issue, the KP portrays a rather diversified picture of cognitive aging, although systematic patterns are evident with regard to the variability of late-life cognitive functioning.

The Kungsholmen Project (KP) is a population-based longitudinal study involving individuals living in the Kungsholmen parish in Stockholm, Sweden, who were 75 years and older in 1987. The general aim of the KP is to provide new knowledge concerning the human aging process from medical, psychological, and social perspectives, with special focus on dementia disorders. A schematic overview of the study design is provided in Figure 1.

Figure 1 shows that the KP involves 5 times of assessment spanning a period of 13 years. A 2-phase study design was used at baseline, with an initial screening phase preceding a comprehensive clinical examination. The initial screening involved a nurse interview including administration of a test of global cognitive ability, the Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975). The screening was performed in order to identify possible

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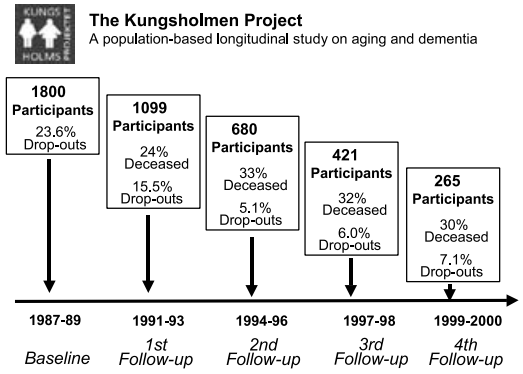

Fig. 1. Schematic overview of the Kungsholmen Project Study Design.

dementia cases, defined as persons with MMSE scores below 24. Possible dementia cases and age- and sex-matched controls underwent the comprehensive clinical examination. At the follow-up assessments, all participants received the clinical examination. A cohort of 90+ years old persons was added to the original study population from the first follow-up.

The clinical assessment comprised a variety of medical, social, and cognitive examinations. The medical examination included family history, personal clinical history (e.g., previous diseases, hospitalization, drug use), physical, neurological, and psychiatric examinations, and specific blood tests. Diagnosis of dementia, differential diagnosis of dementia (e.g., Alzheimer's disease vs. vascular dementia), and depression were made according to established criteria (i.e., DSM-III-R, DSM-IV) at each measurement occasion (for a detailed description of these procedures, see Fratiglioni et al., 1991, 1997; Fratiglioni, Grut, Forsell, Viitanen, & Winblad, 1992). From the blood analysis, we determined multiple cognitively relevant parameters (e.g., vitamin B_{12}, folic acid, thyroid stimulating hormone) as well as apolipoprotein E genotype. Assessment of social and environmental factors included basic demographic data, life-style habits, subjective judgment of health status, use of health and social services, living conditions, social network, activities of daily living (ADL), detailed occupational life history, and caregiver burden.

COGNITIVE ASSESSMENT

The cognitive battery in the KP includes multiple tests of episodic memory. Four recall tasks were administered: free recall of rapidly presented (2 s/word) unrelated words, free recall of slowly presented (5 s/word) unrelated words, free recall of organizable words, and category cued recall of organizable words. The selection of recall tasks was made in order to examine the influence of cognitive support on memory performance (Bäckman, 1985; Craik, 1983); the recall tasks may be viewed as instances along a continuum of cognitive support, where more study time, organizability, and retrieval cues are incrementally added to the memory task. For the two unrelated word lists, recognition performance was also assessed.

In addition, two tests of episodic face recognition were given involving faces of dated and contemporary famous characters. This task variation is also relevant to the issue of cognitive support in episodic memory. Older adults are known to possess more knowledge of public events and famous figures from the remote past compared to those from more recent decades (e.g., Kopelman, 1989; Lipinska, Bäckman, & Herlitz, 1992). Thus, successful utilization of cognitive support in the form of prior knowledge would be evidenced by higher recognition performance for dated than for contemporary faces among elderly persons. Although the specific episodic memory variables described above have been used in some studies, in others they were aggregated to form composite scores (e.g., free and cued recall of organizable words may be combined into an organized recall variable).

Further, short-term memory was assessed with Digit span (Wechsler, 1981), verbal fluency was assessed using tests of both category (supermarket) and letter (S and A) fluency, and visuospatial skill was measured with Block design (Wechsler, 1981), Popelreuter's figures (Christensen, 1984), as well as tests of clock drawing and clock reading (Christensen, 1984). Additional instruments included Trailmaking A and B (Reitan & Davidson, 1974) to assess attentional and executive skills and tests of the optic-spatial and

dynamic organization of the motor acts of the hands (Christensen, 1984).

STRUCTURE OF REVIEW

The general purpose of this article is to describe KP findings pertaining to cognitive functioning in aging and dementia. The review is organized into 3 broad domains: (a) normal aging, (b) dementia, and (c) the transition from normal aging to dementia. Our research on normal cognitive aging is further subdivided into sections addressing general trends versus the influence of various types of individual-difference variables on cognitive performance. As to the latter, a special focus in the KP concerns the role of health conditions in late-life cognitive functioning. A major line of research in our work on cognition in clinical dementia concerns whether the patterns of cognitive deficits are similar or different in the two most common dementia diseases, Alzheimer's disease (AD) and vascular dementia (VaD). In another series of studies, we examine the role of individual-difference variables for cognitive performance and progression rate in dementia. Finally, the chief objective in our work on the transition from normal aging to dementia is to delineate preclinical cognitive markers of an impending dementia disease.

NORMAL AGING

General Trends

In much of the work on normal cognitive aging in the KP, the study sample was divided into four age groups: 75–79, 80–84, 85–89, and 90–96 years of age. In these studies, participants were screened for dementia, psychiatric disease (i.e., major depression, dysthymia, psychosis, paranoia), auditory or visual handicap that interfered with the cognitive testing, neuroleptic and antidepressant medication, hypo- and hyperthyroidism, as determined by abnormal values on thyroid-stimulating hormone (TSH), and vitamin B deficiency. In addition, those who scored below 25 on the MMSE were eliminated to avoid including persons who may have been in an early clinical phase of dementia but missed in the diagnostic procedures (Sliwinski, Lipton, Buschke, & Stewart, 1996).

Episodic Memory

The cross-sectional research on episodic memory yields a very consistent pattern that can be summarized into 3 main points. First, there is a gradual decrease in performance across the age range examined. This pattern was obtained in face recognition (Wahlin et al., 1993), free recall and recognition of unrelated words (Wahlin, Bäckman, & Winblad, 1995), and free and cued recall of organizable words (Bäckman & Wahlin, 1995). Second, the size of the age-related episodic memory deficit was relatively small, with the age variable accounting for 10% or less of the performance variation. Conceivably, the latter finding reflects the relatively restricted age range as well as selective survival effects operating in the oldest cohorts (e.g., Perls, Morris, Ooi, & Lipsitz, 1993). These points were further illustrated in a study of healthy adults between 90 and 100 years of age (Hassing, Wahlin, & Bäckman, 1998), demonstrating no age-related performance differences in word recall and face recognition.

Finally, the ability to utilize cognitive support for improving episodic memory was unaffected by age. Specifically, cognitive support in the form of more study time (Wahlin et al., 1995), item organizability and retrieval cues (Bäckman & Wahlin, 1995), and task-relevant prior knowledge (Wahlin et al., 1993) facilitated episodic memory performance to a similar degree in persons from 75 through 96 years of age. As illustrated in Figure 2, when study time, organizability, and retrieval cues were added to the task, recall performance increased systematically across all age groups. These findings indicate that a potential for improving memory – a manifestation of cognitive reserve capacity (e.g., Baltes, 1987) – is a characteristic feature of episodic memory functioning in healthy very old individuals.

Several other aspects of the findings from these studies are worth noting. First, serial-position analysis of the free recall data (Wahlin et al., 1995) showed the characteristic U-shape with primacy and recency effects for all age groups. Further, when the free recall data were separated

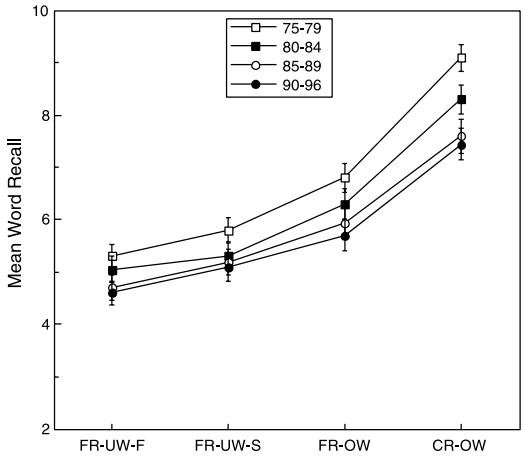

Fig. 2. Recall performance across age in 4 conditions: free recall of unrelated words presented at a fast rate (FR-UW-F), free recall of unrelated words presented at a slow rate (FR-UW-S), free recall of organizable words (FR-OW), and cued recall of organizable words (CR-OW). Bars represent standard errors around the means. (From Bäckman & Wahlin, 1995, copyright by Swets and Zeitlinger and Wahlin et al., 1995, copyright by Taylor and Francis).

into primary and secondary memory components (Tulving & Colotla, 1970), a gradual age-related deterioration was seen for secondary memory, although primary memory was unaffected by age. This suggests that transferring information from temporary storage to a more permanent memory representation became increasingly difficult with advancing age. By contrast, the ability to hold information in mind in a relatively untransformed fashion for a brief period of time was well preserved into very old age. The latter point was corroborated by the fact that no age-related differences in Digit span were observed in these studies.

Another interesting observation is that the size of the age-related deficit was attenuated, but not eliminated, in recognition relative to free recall of words (Wahlin et al., 1995). This pattern is consistent with most aging work comparing different retrieval conditions in episodic memory (e.g., Craik & McDowd, 1987; Nyberg et al., 2003). The result that age differences were attenuated but still existent in recognition suggests that problems at both encoding and retrieval may increase in late senescence. Additional evidence for this interpretation comes from qualitative analysis of the response protocols for free recall of organizable words (Bäckman & Wahlin, 1995). These recall data were partitioned into the number of categories represented in the protocols and the number of words recalled per category. Whereas the former variable is assumed to be determined by the person's retrieval plan, the latter is thought to reflect the extent to which information is organized at encoding (e.g., Tulving & Pearlstone, 1966). The notion that difficulties at both encoding and retrieval underlie the age-related deficits observed was supported by the fact that both variables that make up free recall of organizable words showed age-related decreases (Bäckman & Wahlin, 1995).

In both face (Wahlin et al., 1993) and word (Wahlin et al., 1995) recognition, we examined hits, false alarms, and response bias in addition to overall discrimination accuracy. Results indicated age-related deficits for both hits and false alarms. It has been suggested that decreases in hit rates may be attributed to deficits in performing a careful matching strategy during recognition, whereas increases in false alarms may reflect an increased reliance on perceived familiarity and a decrease of conscious recollection in making recognition judgments (e.g., Bartlett, Strater, & Fulton, 1991). To the extent that these assumptions are valid, our recognition data suggest age-related alterations in both these aspects of recognition memory. The recognition data further indicated a generally conservative response bias, with the degree of conservativeness increasing with increasing age. However, bias and discrimination were unrelated, making it unlikely that age-related differences in bias contributed to age-related differences in accuracy.

The general pattern of modest age-related deficits in episodic memory indicated by these cross-sectional data has been substantiated by longitudinal analyses. In a sample aged 75–96 years at the outset, Bäckman and Small (1998) found a slight performance decrease over a 3-year interval on measures of recall varying in the degree of cognitive support. However, the patterns pertaining to utilization of cognitive support were indistinguishable at baseline and

follow-up, with increasing levels of support being associated with higher recall performance. Thus, the size of the age-related decline and the effects of cognitive support on recall performance were congruent with the corresponding cross-sectional data reported by Bäckman and Wahlin (1995) and Wahlin et al. (1995). Relatedly, Small, Fratiglioni, Viitanen, Winblad, and Bäckman (2000) reported reliable 3-year decline on the delayed recall measure from the MMSE in a large sample of 75–96 year olds. However, in another sample from the same age range, Bäckman, Small, and Fratiglioni (2001) failed to document age-related changes across 3 years on measures of free recall and recognition of unrelated words. Recognition was superior to recall at both measurement occasions, again indicating successful utilization of retrieval support in very old age.

Finally, in a collaborative study involving the KP and the Victoria Longitudinal Study (VLS), Dixon et al. (in press) found very modest 3-year changes in free recall of organizable words in adults ranging from 54 to 94 years of age at baseline. This pattern was corroborated by findings that various qualitative indicators of recall performance (i.e., number of categories, number of words recalled per category, clustering) remained stable across time. However, the KP data revealed slight negative changes in a derived measure of secondary memory for both old-old and very old adults, although primary memory was unaffected by passage of time. In addition, there was a tendency of greater decline for more supported (i.e., cued recall and recognition) compared to less supported (i.e., free recall) tasks in both age groups. The latter finding may reflect subtle decreases in cognitive reserve capacity with advancing age, but also that substantial decline has already occurred in the less supported tasks, hence restricting the room for further deterioration.

In general, then, these findings are consistent with the contention that episodic memory functioning continues to deteriorate in very old age, although decline occurs so slowly that it may be difficult to detect in studies using short follow-up intervals (Bäckman, Small, & Wahlin, 2001; Zelinski & Burnight, 1997).

Other Cognitive Domains

As alluded to, no age-related differences in Digit span (forward or backward) have been observed in the KP, whether assessed cross-sectionally (Wahlin et al., 1993) or longitudinally (Bäckman, Small, & Fratiglioni, 2001). The lack of age-related differences in forward digit span is expected, considering that relatively passive short-term memory operations are well preserved also in AD and other conditions with severe effects on cognitive functioning (e.g., Morris, 1996). Thus, we should not expect such effects to occur across the normal aging process. The age invariance in backward digit span is somewhat more surprising, considering that this task require temporal reorganization of digits, and thus poses some demands on working memory.

Category (supermarket) and letter (initial S and A) fluency both yielded age-related deficits of moderate and similar size (Bäckman, Jonsson Laukka, Wahlin, Small, & Fratiglioni, 2002). Verbal fluency performance is thought to depend largely on two processes: clustering (i.e., producing words within a certain category) and switching (i.e., finding new categories). Thus, clustering is primarily contingent on the availability of items in semantic memory, whereas switching relies on effective search processes (Troyer, Moscovitch, & Winocur, 1997). It is conceivable that clustering is more critical to the category fluency task used in the KP, whereas switching is more critical to the letter fluency task. The fact that virtually identical age-related deficits were obtained in both fluency tasks indicates that the processes underlying fluency performance may be similarly affected in very old age.

Interestingly, the magnitude of the age-related deficit was quite similar in Trailmaking A and B (Robins Wahlin, Bäckman, Wahlin, & Winblad, 1996). The age-related differences observed in Trailmaking were localized to the speed with which the task could be completed; age was unrelated to accuracy. Of further note is that the age-related deficits occurred despite the fact that multiple tests of hand motor functions showed no age-related differences. Trailmaking is an omnibus test that requires multiple cognitive skills. Part A draws primarily on attentional skills and psychomotor speed. Although these abilities are

critical to performance in Part B as well, this part poses additional demands on executive functions (e.g., Lezak, 1983). The fact that the executive demands did not penalize the oldest participants disproportionally suggests that the age-related slowing observed in Trailmaking was largely attributable to deficits in visuomotor tracking.

The results from the visuospatial tasks revealed large age-related deficits in Block design, somewhat smaller deficits in Clock drawing, still smaller deficits in Clock reading (Robins Wahlin, Bäckman, Wahlin, & Winblad, 1993), and no age-related differences in Poppelreuter's figures (Bäckman et al., 2002). Block design and Clock drawing both require visuoconstructive abilities, although there are speed demands in Block design which are not present in Clock drawing. Clock drawing and reading involve a semantic-conceptual component (i.e., the understanding of time concepts); however, the constructional activity is essential in drawing but not reading of the clock, the latter rather tapping visuoperceptive ability. Finally, Poppelreuter's figures requires identifying objects that are superimposed on one another, and draws on visuoperceptive ability. Thus, the pattern of age-related differences observed in the visuospatial tasks was highly predictable from the demands on visuoconstructive skills and speed. Another point to be noted here is that the Block design task was administered with or without time limits. Across the entire age spectrum, Block design performance was higher when the time constraints were eliminated. As with the episodic memory data, then, these findings suggest that the potential for improving performance under more supportive conditions is present even among the oldest participants.

The general trends emerging from these cross-sectional and longitudinal findings are in good agreement with related research comparing younger and older adults (for overviews, see Craik & Salthouse, 1992, 1999) as well as with other studies targeting the older population (for an overview, see Bäckman, Small, Wahlin, & Larsson, 1999). Specifically, the KP data reviewed above indicate a clear age-related deterioration from the mid 70 s through the mid 90 s for tasks in which performance in contingent on new learning, speed, and flexible adjustments to new situational demands, By contrast, small or non-existent age-related differences were observed in tasks that draw on pre-experimental experience, have limited speed demands, and are highly automatized.

INDIVIDUAL DIFFERENCES

As reflected in the following, our research on individual differences in late-life cognitive functioning has focused largely on the influence of different health conditions on performance. However, we will begin this section by reviewing work on the relationship of demographic and lifestyle factors to cognitive performance.

Demographic Factors

Education

In terms of level of schooling, the KP sample ranged from 7 to 18 years, with a mean around 9 years. Thus, compared to similar large-scale studies in North-America, the KP participants, in general, have received relatively little formal education. We observed a positive relationship between education and performance in free recall of slowly and rapidly presented random words (Wahlin et al., 1995), free and cued recall of organizable words (Bäckman & Wahlin, 1995), and delayed (20 min) recall of words (Hassing et al., 1998). Interestingly, in organized free recall, education-related effects were seen for both the number of categories recalled and the number of words recalled per category (Hill, Bäckman, Wahlin, & Winblad, 1995). This suggests that education may influence both encoding and retrieval operations in episodic memory. A particularly noteworthy observation in the Hill, Wahlin, et al. study was that education was related to the magnitude of performance gains from cognitive support in the form of more study time and item organizability. These findings indicate that education plays a role not only in overall episodic memory functioning, but also influences cognitive reserve capacity in old age.

Positive education-related effects were also observed in Block design, Digit span, verbal fluency (Wahlin, Robins Wahlin, Small, &

Bäckman, 1998), and Clock test (Robins Wahlin et al., 1993) performance. By contrast, educational background was unrelated to performance in face (Hassing et al., 1998; Wahlin et al., 1993) and word (Wahlin et al., 1995) recognition and Trailmaking (Robins Wahlin et al., 1996) performance. The absence of education-related differences in episodic recognition along with clear effects of education in episodic recall suggests that education is most likely to affect memory performance in tasks with high strategic demands. Thus, with a few exceptions, the patterns of education-related influences on cognition in the KP resemble the corresponding patterns of age-related influences. An obvious point to note with regard to the education variable is that it is difficult to disentangle which aspects of this variable are most critical to the relationships observed. Specifically, the relative importance of events happening before (e.g., genetic and social selection), during (e.g., learning of cognitively relevant skills and strategies, dendritic growth), and after (e.g., cognitive stimulation during work, health behaviors) the educational experience remains unclear (Bäckman, Small, & Wahlin, 2001).

Sex

Given that the KP is a population-based study of very old adults, it follows that the sex distribution is rather uneven; in general, around 80% of the samples have comprised women, the proportion of women increasing with advancing age. The KP data portray a rather mixed picture concerning sex differences in cognitive performance. In Block design, which typically yields modest sex differences favoring men (e.g., Voyer, Voyer, & Bryden, 1995), we have found a male superiority in some samples (Wahlin et al., 1998), but not in others (Robins Wahlin et al., 1993). The pattern is equally mixed for episodic memory. In some studies, a female advantage was observed in face recognition (Hill, Grut, et al., 1995; Wahlin et al., 1993), verbal recall (Hill, Grut, et al., 1995), object recall (Hill, Stigsdotter Neely, & Bäckman, 1997), and a composite measure of non-verbal memory (Bäckman et al., 1998). However, other studies have documented sex invariance in free recall and recognition of random words (Wahlin et al., 1995), free and cued recall of organizable words (Bäckman & Wahlin, 1995), object recall (Hassing et al., 1998), spatial and activity recall (Hill, Grut, et al., 1995), immediate and delayed word recall (Hassing et al., 1998), and face recognition (Hassing et al., 1998). Finally, the only study examining potential sex differences in verbal fluency failed to demonstrate such differences (Wahlin et al., 1998).

The inconsistent findings regarding cognitive sex differences observed in the KP may be contrasted against the corresponding patterns from research with younger cohorts of adults. Of the task domains included in the KP battery, verbal fluency (e.g., Hyde & Lynn, 1988) and episodic memory (e.g., Herlitz, Nilsson, & Bäckman, 1997; Lewin, Wolgers, & Herlitz, 2001) typically yield a female superiority. A likely reason for the non-existent sex difference in verbal fluency and the mixed evidence regarding sex differences in episodic memory in our samples of very old adults is that selective survival effects favoring men are operating. That is, the men surviving into the 80 s and 90 s may have advantages (e.g., in terms of relevant genetic and biological factors) that counteract the female advantage in certain cognitive domains seen in younger cohorts. Relevant to this issue is also the fact that women have a higher incidence of dementia than men, especially after the age of 80 (Fratiglioni et al., 1997). Given that dementia may have a rather long preclinical period during which cognitive deficits are detectable (for an overview, see Bäckman, Small, & Fratiglioni, 2004), a greater proportion of preclinical female cases in the study samples will obviously lower average cognitive performance levels more so for women than for men.

Life-Style Factors

Our work on the role of life-style factors in cognitive functioning conducted hitherto is rather limited. However, Hill, Wahlin, et al. (1995) examined the role of social activity, exercise habits, and substance use on patterns of episodic memory performance. Several interesting findings were obtained. First, controlling for age and education, social activity levels were related to performance in free recall of slowly and rapidly

presented unrelated words as well as free and cued recall of organizable words. Second, exercise habits were related to performance in the 2 former, but not the 2 latter, tasks, whereas substance use showed no relationship to any episodic memory variable. Finally, social activity was also related to the magnitude of performance gains from the provision of retrieval cues, with gains increasing gradually as a function of increasing levels of activity.

In general, these findings are consistent with related research indicating a positive relationship between participation in social, cognitive, and physical activities and memory performance in old age (e.g., Hultsch, Hertzog, Dixon, & Small, 1998). As with the corresponding influence of education, the finding that social activity levels were associated with the size of improvement from cognitive support should be viewed in the context of the general relationship between individual-difference variables and the potential for memory improvement. Across many individual-difference variables (e.g., speed of processing, verbal ability, intelligence, depression, dementia), a consistent observation is that conditions that are negatively related to memory performance are also associated with a reduced reserve capacity in old age (Bäckman et al., 1999).

Health-Related Factors

The dimensions of health typically considered in cognitive aging research include subjective (or psychological) and medical (or physical) factors.

Subjective Health

Turning first to subjective health, in the KP this was assessed by asking the participants to rate their health as compared to their age peers. Although this type of health indicator is known to at least partially index medical status (e.g., Hoeymans, Feskens, Kromhout, & van den Bos, 1999), subjective health ratings are as likely to predict other outcomes independently of objective medical health status. Wahlin, Maitland, Bäckman, and Dixon (2004) combined data from the KP and the VLS to examine the association between 3-year changes in subjective health and episodic memory among persons aged 75–84 years at baseline. The key finding was that 3-year changes in subjective health were related to changes in episodic recall over the same time interval, although cross-sectional associations were non-significant. Interestingly, this data pattern generalized across studies despite sample differences in educational background, changes in physical health status, and subjectively experienced memory decline.

Typically, aging research on the relationship between health and cognitive performance has used self-reports on the presence or absence of various conditions. Although such self-reports may be related to both objective indicators of health (e.g., Elias, Elias, & Elias, 1990) and cognitive performance (e.g., Earles, Connor, Smith, & Park, 1997), research examining the relationship between objectively assessed conditions and cognitive performance should provide more exact information concerning the health-cognition link. The latter approach has been predominant in the KP. Investigating the influence of specific health conditions on cognition has been possible because of the availability of diagnostic information derived from physicians' examinations (i.e., psychiatry, neurology, geriatrics), health records from inpatient registries, as well as data on critical blood parameters.

Vitamin B Deficiency

In a series of studies, we have examined the relationship of serum vitamin B_{12} and folic acid status to cognitive performance (Hassing, Wahlin, Winblad, & Bäckman, 1999; Robins Wahlin, Wahlin, Winblad, & Bäckman, 2001; Wahlin, Hill, Winblad, & Bäckman, 1996). The general analytical strategy employed in this research involves comparing persons who have low levels on one or both of these vitamins with those having normal values, thus resulting in four vitamin groups based on established cut-offs for defining deficiency. Low B vitamin levels may be associated with impaired cognitive performance through several biologically plausible mechanisms. This includes effects on multiple CNS functions such as protein synthesis, phospholipids, myelin, nucleic acids, neurotransmitters, and reactions involving DNA, because of influence of vital methylation. In addition, vitamin deficiency results in overproduction of

homocysteine that could damage neurons and blood vessels (Calvaresi & Bryan, 2001).

Our research indicates that low levels of vitamin B_{12} and folic acid are associated with impaired performance in free recall of words (Hassing et al., 1999; Wahlin et al., 1996) and objects (Hassing et al., 1999). Vitamin-related deficits were found to be attenuated (Wahlin et al., 1996) or eliminated (Hassing et al., 1999) in tests of recognition memory. Moreover, vitamin-related deficits were observed in Block design, Trail Making-B, letter fluency, and backward digit span, but not in the Clock tests, Trail Making-A, forward digit span, or category fluency (Robins Wahlin et al., 2001). Thus, the picture that is emerging suggests that effects of low vitamin levels on cognitive performance are most likely to occur in tasks involving complex cognitive processing with demands on fluid intelligence and executive functions. By contrast, tasks that are less cognitively taxing and involve more familiar and structured materials appear to be less sensitive to variations in vitamin status. In this way, the cognitive influences of vitamin B deficiency (as with low education) appear to mimic those associated with normal aging.

Three other findings from this research should be highlighted. First, the combined effects of having low levels on both vitamins resulted in the largest performance decrement, likely reflecting biochemical interactions between the vitamins (e.g., Herbert, 1987). Second, the effects of low levels of folic acid were more pronounced than those of low B_{12} levels. This may be due to the fact that folic acid levels in blood reflect more accurately the availability of this vitamin in the brain than what is true with B_{12} (Botez, 1989). Third, although clear vitamin-related effects were observed using an extreme-groups approach, there were no linear relationships between vitamin status and cognitive performance. The latter observation suggests that vitamin status is not generally related to cognitive functioning in old age, but rather exerts its effects when a certain biologically relevant threshold is reached. Representative data illustrating the relationship between vitamin status and cognitive performance from the Hassing et al. (1999) study are shown in Figure 3. This figure portrays object recall performance as a function of vitamin group.

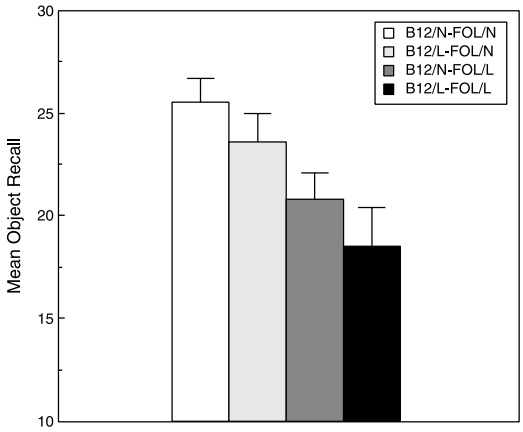

Fig. 3. Object recall performance across vitamin group. B_{12} = vitamin B_{12}; FOL = folic acid; N = normal; L = low. Bars represent standard errors around the means. (From Hassing et al., 1999, copyright by the Society of Biological Psychiatry).

Thyroid Disturbance

Another blood parameter with potential relevance to cognitive functioning is thyroid-stimulating hormone (TSH). Wahlin et al. (1998) investigated the effects of TSH on cognitive performance. It is important to note that only persons who had TSH values within normal ranges were included; thus, individuals suffering from hypo- or hyper-thyroidism were not part of the study. The key finding was that TSH was positively related to performance in all episodic memory tasks in the KP battery. By contrast, no TSH-related effects were seen in tasks assessing visuospatial skill, verbal fluency, short-term memory, or attentional and executive skills. There are several possible explanations for the TSH-episodic memory associations demonstrated in this study. Circulating TSH levels are known to modulate the effects of somatostatin, cortisol, and cytokines (Robbins, 1996). Further, thyroid hormones increase the response of the beta-adrenergic receptor to norephinedrine, which may serve as an adaptive mechanism in neuromodulation (Dratman & Gordon, 1996; Whybrow & Prange, 1981). Finally, low TSH levels are associated with

elevated steroid hormone levels within the hypothalamus-pituitary-adrenal axis (van Haasteren et al., 1996). Increased levels of cortisol, which is part of this circuitry, may result in hippocampal cell loss and impair episodic memory performance (Lupien et al., 1994).

Circulatory Disease

Circulatory disturbance is a major risk factor for cognitive impairment in old age, with pronounced deficits routinely observed in severe conditions such as stroke (Bowler, Hadar, & Wade, 1994) and VaD (Sulkava & Erkinjuntti, 1987). However, more subtle circulatory alterations may also have cognitive repercussions. In one study (Fahlander et al., 2000), we examined the effects of cardiovascular signs (CVS) on cognitive performance. Three specific CVS were targeted: systolic and/or diastolic murmur, dyspnea, and edema in the lower limbs. CVS-related effects were observed in all episodic memory tasks and Block design, but not for verbal fluency and short-term memory. CVS may reflect a generalized vascular disturbance with resulting effects on the CNS, but also indicate heart failure resulting in hypoperfusion in the brain (Meyer, Obara, Muramatsu, Mortel, & Shirai, 1995). In terms of their influence on cognitive functioning, the CVS assessed in this study may resemble "silent" cerebral infarctions (Price et al., 1997). As such, CVS may be located relatively close to one of the anchor points on a vascular risk factor continuum, with conditions such as stroke and VaD being located at the other end of the continuum.

Diabetes

Diabetes mellitus is a disease that is closely related to circulatory disturbance. In 2 recent studies on old age or Type II diabetes, we found that diabetes may be associated with cognitive deficits independently of different vascular conditions (e.g., prior stroke, transient ischemic attacks, coronary heart disease) and negative future events (i.e., impending death, incipient dementia). Nilsson, Fastbom, and Wahlin (2002) demonstrated a deficit among elderly diabetics on MMSE items with an episodic memory referent. In another study (Wahlin, Nilsson, & Fastbom, 2002), diabetic persons performed worse than controls on tests of episodic memory and verbal fluency, although the effects were less pronounced in tasks involving a higher level of semantic structure for both cognitive domains. Specifically, free recall and letter fluency resulted in larger diabetes-related deficits than cued recall and category fluency. In a series of follow-up analyses, we subdivided the sample based on forthcoming dementia or death within the next 3 years. As can be seen in Figure 4, these future events accounted for much of the observed diabetes-cognition associations. However, in letter fluency, the diabetes-related deficit remained after controlling for preclinical dementia and impending death.

Although the impact of diabetes on the CNS is well established, and the cognitive deficits commonly observed are likely to be caused by disruption of glucose metabolism (McCall, 1992), the evidence for diabetes-related focal brain damage is limited. Our results suggest, however, that the effects are moderated by level of cognitive support (i.e., the semantic structure inherent in the test materials) as well as by future events related to diabetes (i.e., dementia and death).

Depression

In another series of studies, we have examined the influence of depression on episodic memory functioning. Of interest here has been not only whether old age depression affects memory performance, but also the ability to utilize cognitive support for improving memory. Bäckman and Forsell (1994) found that individuals diagnosed with major depression (MD) performed at a generally lower level than controls in different episodic memory tasks. However, the most interesting finding was that MD patients, in contrast to controls, failed to utilize cognitive support in the form of more study time and item organizability. The MD patients showed memory facilitation only when organizability and encoding was combined with cues at retrieval.

In a follow-up study (Bäckman, Hill, & Forsell, 1996), we were interested in whether memory deficits could be demonstrated also in individuals who experienced some depressive symptoms, without fulfilling the diagnostic criteria for clinical depression. In this study, depressive symptoms were classified as either

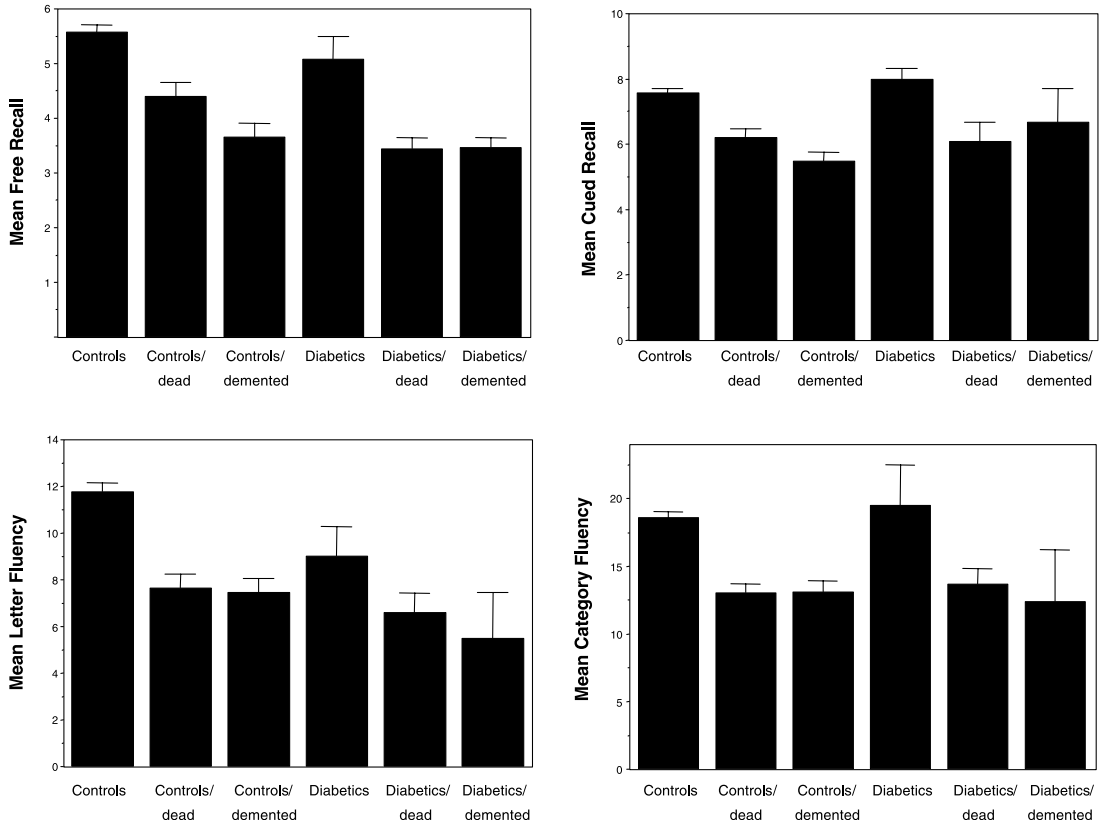

Fig. 4. Episodic recall and verbal fluency in diabetics and controls subdivided by impending death and preclinical dementia. Bars represent standard errors around the means. (From Wahlin et al., 2002, copyright by the American Psychological Association).

mood-related (e.g., dysphoria, feelings of guilt, suicidal thoughts) or motivation-related (e.g., lack of interest, concentration difficulties, loss of energy). Results indicated a relationship between the number of motivation-related symptoms and recall performance as well as the ability to utilize support for improving memory. To illustrate, Figure 5 shows recall performance across levels of cognitive support for three groups of subjects: the MD and control subjects from Bäckman and Forsell (1994) and those non-depressed individuals who had at least one motivation-related symptom from Bäckman, Hill, et al. (1996).

As can be seen in Figure 5, subjects with motivation-related symptoms occupy an intermediate position between the clinically depressed and the controls both with regard to overall performance levels and utilization of cognitive support: (a) the controls showed a gradual increase of performance with increasing levels of support, demonstrating cognitive reserve capacity in aging, (b) the MD patients exhibited performance gains only in the most supportive condition: cued recall of organizable words, and (c) the persons with some motivational symptoms failed to utilize more study time in free recall (like the MD patients, but unlike the controls), although they succeeded in making use of organizability (like the controls, but unlike the depressed). The pattern of results from these studies suggests a continuity view of the effects of depression on episodic memory in old age; as symptom severity increases to the point at which a clinical diagnosis could be made, there appears to be a gradual deterioration of episodic memory ability accompanied by a decrease in the potential

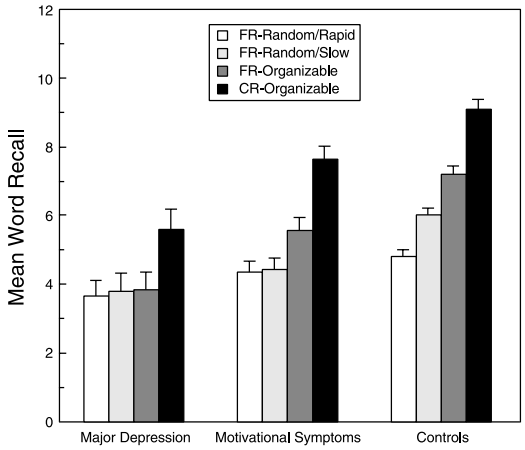

Fig. 5. Recall performance across increasing levels of cognitive support in persons with major depression, motivational symptoms of depression, and controls. FR = free recall; CR = cued recall. Bars represent standard errors around the means. (From Bäckman & Forsell, 1994 and Bäckman, Hill, et al., 1996, copyright by the American Psychological Association).

for improving memory. The influence of depression on memory found in this research should be viewed in light of the fact that this disease appears to be more chronic in nature in old age as compared to earlier parts of life. Specifically, Berger, Small, Forsell, Winblad, and Bäckman (1998) observed an elevation of depressive symptoms in individuals who were non-depressed at baseline assessment, but diagnosed with major depression at a 3-year follow-up.

We have also examined individuals with suspected delusional disorder, and found that individuals with mild symptoms of paranoia perform much like subjects with motivation-related symptoms of depression both with regard to overall performance levels and utilization of cognitive support in episodic memory (Herlitz & Forsell, 1996). This suggests some functional similarities between different psychiatric conditions in old age concerning their influence on episodic memory functioning.

Impending Death

Another focus of research in the KP has been on mortality-related effects on cognitive performance. It is known that individuals who will die within several years exhibit greater cross-sectional deficits, as well as more pronounced longitudinal changes (i.e., terminal decline) on measures of cognitive performance, as compared to individuals who will remain alive across the same ascertainment period (for reviews see Berg, 1996; Small & Bäckman, 1999). The KP is an excellent forum for these types of research questions, given the advanced age of the sample, as well as the population-based nature of sample ascertainment. With regard to the latter, the majority of longitudinal attrition from the KP can be attributed to death, as compared to self-selection which is typical of many longitudinal studies of aging (e.g., Hultsch et al., 1998; Schaie, 1996). As a result, we have been able to examine mortality-related effects with relatively large samples of individuals, as compared to past studies on this issue.

In this work, we have focused on several broad issues. These include the specificity of impairment, in terms of the breadth of cognitive ability measures that are impaired, the time course and magnitude of longitudinal changes associated with impending death, and whether cause of death exerts an impact on the presence or magnitude of mortality-related deficits. Each of these issues are discussed in turn.

We have demonstrated both cross-sectional (Hassing, Small, von Strauss, Fratiglioni, & Bäckman, 2002; Small & Bäckman, 1997) and longitudinal (Small, Fratiglioni, von Strauss, & Bäckman, 2003) deficits in cognitive performance associated with impending death. Furthermore, the impairments have been quite general, in terms of the breadth of cognitive abilities that have been affected. For example, cross-sectionally we have observed mortality-related deficits on multiple measures of episodic memory, verbal fluency, visuospatial functioning, and primary memory, as well as on a test of global cognitive functioning, the MMSE (Hassing et al., 2002; Small & Bäckman, 1997). Longitudinally, we have observed more precipitous decline among the terminal group, as compared to the survivors, on MMSE scores, as well as tests of backward digit span, category fluency, and a test of visuospatial functioning (Small et al., 2003). Thus, these

results suggest that mortality affects cognitive performance in a rather general manner.

We have also been able to derive information concerning the time course of mortality-related deficits. In Small et al. (2003), three groups of participants were examined: survivors, persons who would die within 3 years of the baseline assessment (*M* survival = 1.9 years), and persons who would die more than 3 years after baseline (*M* survival = 5.3 years). On tests of episodic memory, verbal fluency, and visuospatial functioning, individuals who would die within 3 years of baseline assessment performed significantly worse than persons who would die after the 3 years point, who were indistinguishable from the surviving group.

Finally, and perhaps most interestingly, we have examined the relationship between cause of death and baseline cross-sectional differences as well as longitudinal changes in cognitive functioning (Small et al., 2003). In this case, we partitioned individuals into whether they died from a cardio/cerebrovascular source (CVD; e.g., heart attack, stroke) or non-CVD disease (e.g., cancer, kidney disease). We chose CVD as the partitioning variable for two reasons. First, it allowed for roughly equivalent groups, in terms of sample size, to be created. Second, CVD has been consistently associated with impaired cognitive functioning, including reports from the KP (Fahlander et al., 2000).

Our analyses revealed that cause of death exerted no impact on the magnitude of cross-sectional mortality-related deficits, as well as longitudinal declines in cognitive performance associated with impending death. These results may help to provide information regarding the source of mortality-related cognitive deficits in very old age. Berg (1996) argued that terminal decline effects may have a source in specific disease pathologies, or be related to some form of biological vitality that decreases in close proximity to death. Our findings provide support for the latter contention, given that we observed comparable levels of cognitive impairment among persons with diverse causes of death. It is noteworthy that Rabbitt and colleagues (2002) recently reported that mortality-related deficits were not present in individuals who died from heart disease or malignancies, although such deficits were observed for individuals with other causes of death on a measure of episodic memory. Clearly, more evidence is required before definitive conclusions can be drawn regarding the influence of cause of death on mortality-related cognitive deficits.

General Implications

We would like to close the section on individual differences in late-life cognitive functioning by making some points of general interest. First, most of the factors discussed (demographic, lifestyle, or health-related) appear to affect cognitive functioning in a relatively similar fashion across adulthood and old age (Bäckman et al., 1999; Bäckman, Small, & Wahlin, 2001). Thus, knowledge of the relationships observed is not very useful in determining sources of age-related cognitive deficits, although it informs us of the multiple origins of cognitive variability in old age. At the same time, many of the health conditions investigated increase in prevalence in senescence. Thus, failure to screen for such conditions in cognitive aging research may result in an overestimation of normative age-related cognitive changes.

The latter point is illustrated by the fact that several studies from the KP in which we have used elite samples of optimally healthy persons reveal small or non-existent age-related differences (Hassing et al., 1998; Hill, Grut, et al., 1995) as well as 2-year changes (Bäckman et al., 1998; Hill, Stigsdotter Neely, & Bäckman, 1997) in cognitive performance. However, this should not be taken to mean that age-related cognitive changes reflect nothing but secondary aging processes. Evidence that many age-sensitive cognitive functions (e.g., episodic memory, perceptual speed), as well as cognitively relevant biological parameters (e.g., frontal volume, dopamine functions) may start declining in young adulthood or middle age (Bäckman et al., 2002), suggests that primary aging processes play an important role in cognitive functioning across adulthood.

DEMENTIA

The KP research on the cognitive effects of clinical dementia comprises two major lines of inquiry. First, we have compared patients suffering from the

two most common dementia diseases, AD and VaD, with regard to patterns of cognitive deficits. Second, we have investigated whether cognitive performance at a given point in time as well as rate of decline is modified by various individual-difference variables in dementia, as is true for non-demented older adults. Mildly to moderately demented patients have been included in these studies.

AD Versus VaD

AD and VaD are etiologically different. The pathological process of AD involves the formation of neurofibrillary tangles, neuropil threads, and senile plaques selectively destroying certain parts of the brain, whereas other regions remain intact until later stages of the disease. The cytoskeletal alterations are first found in the transentorhinal and entorhinal cortices. Further on the hippocampus is affected followed by neocortical regions. The disease process is insidious and progressive (e.g., Braak et al., 1999).

VaD encompasses multiple forms of brain damage caused by cerebrovascular disease (CVD), including large and small vessel dementia, hypoxic-ischemic/hypoperfusive dementia, and haemorrhagic dementia. Hence, the onset can be abrupt and stepwise in manner if caused by large infarcts or insidious if caused by small or incomplete infarcts, typically seen in the subcortical areas (e.g., Chui, 2000). In VaD, lesions in the frontostriatal circuitry are common early on in the disease.

Given the different etiologies, AD and VaD patients may be expected to manifest differential impairment of cognitive functioning. However, with few exceptions, we have failed to demonstrate differences in patterns of cognitive deficits between AD and VaD patients. Hassing and Bäckman (1997) examined AD patients, VaD patients, and controls in three episodic memory tasks: word recall, object recall, and face recognition. The word recall data were partitioned into primary and secondary memory, using Tulving and Colotla's (1970) lag method. Results showed clear dementia-related deficits across all memory variables, except for the primary memory score from the word recall task. This pattern is consistent with the view that dementia affects the ability to transfer information from consciousness to a more permanent representation, although the ability to maintain information in mind for a brief period of time remains unaffected (Morris, 1996; Simon, Leach, Winocur, & Moscovitch, 1995).

The two dementia groups were indistinguishable in object recall and face recognition. However, in the secondary memory component of word recall, there was a slight advantage for the VaD group over the AD group. At first glance, this finding would seem to be in agreement with the hypothesis that AD should affect episodic memory more than VaD, because of more severe lesions in memory-relevant regions in the medial temporal lobe (e.g., Cummings & Benson, 1992). However, note that the difference occurred in only one out of three episodic memory measures. Note also that the VaD advantage was seen in the most demanding memory task (free recall of words) rather than in the more supported tasks (object recall and face recognition). Investigators assuming more severe episodic memory problems in AD than in VaD have argued that these differences should show up more easily in recognition than in recall. This is so because the executive deficits associated with VaD are expected to result in poor free recall performance because of suboptimal strategies, although recognition performance should be less affected (e.g., Mega & Cummings, 1994; Tomlinson, 1992). This is contrasted against the more generalized episodic memory deficit associated with AD, as a result of medial temporal lobe lesions affecting initial encoding and consolidation of information (e.g., Braak & Braak, 1995; Zola-Morgan & Squire, 1993). Taken together, these observations suggest that the difference obtained between AD and VaD patients in word recall should be treated with caution.

In another study using new samples of AD patients, VaD patients, and controls, Almkvist, Fratiglioni, Agüero-Torres, Viitanen, and Bäckman (1999) examined whether the two dementia diseases have different effects on the ability to utilize cognitive support for improving memory. As expected, there were clear dementia-related deficits across all tasks. More interestingly, the control subjects were able to utilize more study time and organizability in free recall,

whereas both demented groups were not, indicating losses in reserve capacity in AD and VaD alike. However, both dementia groups exhibited performance gains when cues were provided in organized recall, although the size of the improvement was smaller than for controls. This finding is in agreement with the view that demented patients require cognitive support at both encoding (e.g., organizability) and retrieval (e.g., taxonomic cues) to demonstrate memory facilitation (see Bäckman & Herlitz, 1996). Analyses of free recall of organizable words revealed dementia-related deficits in both the number of categories recalled and the number of words recalled per category. These results suggest that AD and VaD patients may experience difficulties with regard to both encoding and retrieval processes (cf. Tulving & Pearlstone, 1966).

The most striking observation in the Almkvist et al. (1999) study, however, was that the AD and VaD patients showed similar gains from more study time as the controls when memory was tested with recognition rather than recall. This intriguing finding suggests that the demented patients may have encoded more information from the slowly compared with the rapidly presented word list. The effect may not have showed up in free recall because of the impoverished retrieval conditions. However, with the provision of copy cues in the recognition test, the memory traces could be activated more easily and facilitative effects from decreased task pacing were seen also in the dementia groups (see Fig. 6). This is a rather straightforward demonstration of the necessity of providing a dual cognitive support in order to demonstrate memory improvement in dementia.

The similar, if not identical, patterns of cognitive performance seen in AD and VaD are not confined to verbal episodic memory. Fahlander, Wahlin, Almkvist, and Bäckman (2002) found similar deficits in these groups of patients in face recognition, category and letter fluency, Block design, and Clock setting. The only difference observed was that the VaD patients were slightly more impaired than the AD patients in Clock reading. This may reflect more pronounced perceptual deficits in VaD compared with AD (Meier, 1995). Another observation made by

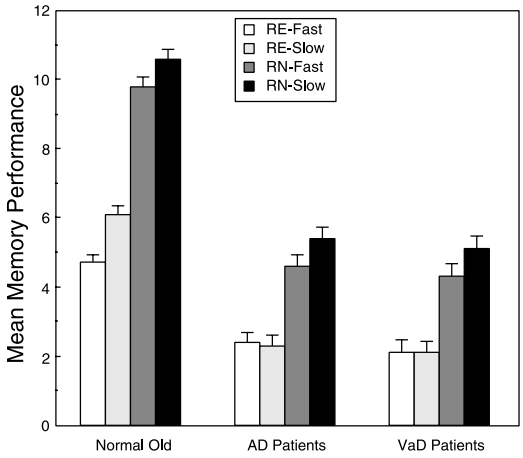

Fig. 6. Recall (RE) and Recognition (RN) performance for rapidly and slowly presented words in normal old adults and patients with Alzheimer's disease (AD) and vascular dementia (VaD). Bars represent standard errors around the means. (From Almkvist et al., 1999, copyright by Swets and Zeitlinger).

Fahlander et al. (2002) as well as Almkvist et al. (1999) was that the recognition memory impairment in AD and VaD applies to both hits and false alarms. This suggests that both dementia diseases may be associated with (a) failures in performing a careful matching between the test item and the underlying memory representation, and (b) an increased reliance on familiarity-based processes (as opposed to conscious recollective operations) in making recognition judgments (cf. Bartlett et al., 1991).

The strikingly similar patterns of cognitive impairment in AD and VaD observed in the KP may appear counterintuitive in view of the etiological differences between the two diseases. However, there are several reasons why functional similarities, rather than differences, in cognitive functioning may be expected. First, there is increasing evidence that vascular risk factors are implicated in AD and that neurodegenerative changes may occur also in VaD (Kalaria & Ballard, 1999). Second, the memory, verbal, and visuospatial tasks used in the KP draw on widespread networks in the brain (Cabeza & Nyberg, 2000). Failure at different sites of such neural networks may disrupt performance in a similar

manner. Thus, although AD and VaD affect the brain in different ways, the functional consequences may be indistinguishable at the behavioral level. Finally, the diagnosis of VaD in the KP emphasizes cerebral infarctions (e.g., multi-infarct dementia, strategic infarcts). It is possible that subcategories of VaD other than post-stroke dementia (e.g., subcortical ischemic vascular disease) may stand a greater chance of exhibiting patterns of cognitive impairment that deviate from those observed in AD (e.g., Yuspeh, Vanderploeg, Crowell, & Mullan, 2002).

Detection and Staging of Dementia

These studies along with those from several other groups (for an overview, see Morris, 1996) demonstrate a rather global cognitive impairment already early on in the dementia disease. However, this is not to say that all cognitive functions decline at the same time point and at the same rate in the pathogenesis. This issue was addressed by Herlitz, Hill, Fratiglioni, and Bäckman (1995). In this study, we sought to determine which cognitive variables were most effective in detecting (i.e., differentiating mildly demented patients from controls) and staging (i.e., differentiating mildly from moderately demented patients) dementia. Results showed that multiple measures of episodic memory (e.g., face recognition, cued recall of organizable words) and an indicator of executive functioning (i.e., Trailmaking B) distinguished controls from mild AD patients. By contrast, measures of visuospatial ability (i.e., Block design) and short-term memory (Digit span) differentiated mildly from moderately demented patients. These findings suggest that visuospatial ability and short-term memory may deteriorate later and/or at a slower rate than episodic memory and executive functions in the early stages of dementia.

Two other observations from this study are noteworthy. First, discrimination accuracy was greater in staging than in detecting dementia. Conceivably, this reflects the relatively old age of the sample: Normal age-related changes may have made it more difficult to distinguish the controls from the mildly demented persons. This hypothesis was supported by findings that the misclassified normal old were older than their correctly classified counterparts, whereas the reverse was true in the mildly demented group. Second, the pattern of results was nearly identical whether or not the analyses were confined to AD patients. Although this result is expected in view of the fact that AD constituted the largest diagnostic category, it provides further evidence that the pattern of cognitive deficits is similar in AD and VaD, the second largest diagnostic category.

Limited Effects of Individual-Difference Variables

As noted, the KP data concur with observations from numerous studies (e.g., Bäckman et al., 1999; Hultsch et al., 1998) that individual-difference variables within demographic, social, and health-related domains are related to cognitive functioning in normal aging. An important line of research within the KP has been to investigate whether those individual-difference variables implicated in normal cognitive aging influence performance also in dementia.

In two initial studies using cross-sectional data, we examined the role of demographic and biological variables for episodic memory (Bäckman, Hill, Herlitz, Fratiglioni, & Winblad, 1994) and visuospatial (Hill, Bäckman, Wahlin, & Winblad, 1995) functioning in AD and dementia. In Bäckman et al. (1994), composite measures of recall and recognition were used, whereas Block design, Clock setting, Clock reading, and Poppelreuter's figures comprised the outcome measures in Hill, Bäckman, Wahlin, et al. (1995). In addition to age, sex, and education, onset age and disease duration were included in the demographic block. The biological correlates included vitamin B_{12}, folic acid, and TSH, but also other cognitively relevant blood parameters (i.e., ferritin, albumin, and fructoseamine/albumin) as well as systolic and diastolic blood pressure. Of the numerous potential correlates examined, very few were related to cognitive performance once disease severity was controlled. Bäckman et al. found that higher age was related to lower recognition memory performance, whereas lower education was associated with lower Block design performance in the Hill, Bäckman, Wahlin, et al. study. Whether these relationships are replicable

and meaningful remains for future research to determine.

The general lack of relationships of the demographic and biological variables to memory and visuospatial performance contrasts sharply with the associations found among the non-demented persons in the KP, as reviewed above. One possibility is that the dementing process absorbs the influence of other individual-difference variables in cognitive functioning. However, a concern which has to be addressed before firm conclusions can be drawn with regard to this issue is that the size of the relationships of the demographics and the biomarkers to cognitive performance was relatively small, albeit reliable, also in the normal old.

One individual-difference variable which shows a pronounced effect on cognition in normal old adults is clinical depression (for reviews, see Burt, Zembar, & Niederehe, 1995; Kindermann & Brown, 1997), a finding that was substantiated in the KP (Bäckman & Forsell, 1994). The fact that the prevalence rate of depression is considerably higher in early AD than among non-demented older adults (e.g., Blazer, 1989; Migliorelli et al., 1995) underscores the importance of investigating the influence of comorbid AD and depression on cognitive functioning.

In three studies (Bäckman, Hassing, Forsell, & Viitanen, 1996; Berger, Fahlander, Wahlin, & Bäckman, 2002; Fahlander, Berger, Wahlin, & Bäckman, 1999), we have investigated whether the simultaneous occurrence of AD and depression exacerbates the cognitive problems associated with AD alone. Given that both dementia and depression result in marked cognitive problems, a person who suffers from both conditions may exhibit greater impairment than a non-depressed AD patient. On the other hand, to the extent that the neurodegenerative processes in AD has a strong overshadowing influence on other subject characteristics, no comorbidity effects may be expected. Data from the three studies addressing this issue unequivocally supported the latter notion. Specifically, those with AD and depression performed at the same levels as those with AD alone in tasks assessing word recall, object recall, and face recognition (Bäckman, Hassing, et al., 1996), free recall and recognition of slowly and rapidly presented words, and forward and backward digit span (Fahlander et al., 1999), and letter and category fluency as well as Block design and Clock drawing (Berger et al., 2002). Representative data on the similar levels of cognitive performance in AD patients with or without depression are shown in Figure 7. This figure depicts the results for letter and category fluency and Block design from the Berger et al. (2002) study.

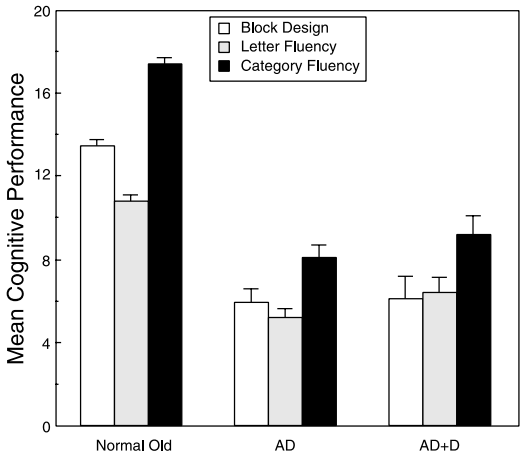

Fig. 7. Block design, letter fluency, and category fluency performance in normal old adults and patients with Alzheimer's disease (AD) with or without depression (D). Bars represent standard errors around the means. (From Berger et al., 2002, copyright by Karger).

Collectively, these findings indicate that depression does not aggravate the cognitive deficits associated with AD. One possibility for the absence of comorbidity effects is that those symptoms of depression that are most likely to cause cognitive problems (e.g., lack of interest, concentration difficulties, loss of energy; Bäckman, Hill, et al., 1996) are already part of the dementing syndrome. As a result, an additional diagnosis of depression will be redundant with regard to the cognitive status of the AD individual.

The weak or non-existent influence of individual-difference variables on cognitive functioning in dementia observed in these cross-sectional studies was corroborated in 2 longitudinal studies. Small, Viitanen, Winblad, and Bäckman (1997) observed marked decline in MMSE performance

across a 3-year period in a group of demented patients. However, using the same demographic and biological predictors as in the corresponding cross-sectional studies (Bäckman et al., 1994; Hill, Bäckman, Wahlin, et al., 1995), the investigators failed to demonstrate any significant relationships between the independent variables and rate of MMSE change. This was true despite that fact that substantial cognitive decline was observed over the follow-up period, with a mean annual MMSE loss of just below 2.5 points. In addition, rate of MMSE change was comparable in AD and VaD patients, corroborating the pattern of cognitive similarities between the two dementia diseases from the cross-sectional research.

These findings were extended to specific measures of episodic memory, visuospatial ability, and verbal fluency by Small and Bäckman (1998). As with the Small, Viitanen, Winblad, et al. (1997) study, none of the demographic or biological indices were related to rate of cognitive decline, and rate of decline was indistinguishable in AD and VaD. Thus, our cross-sectional and longitudinal work on the effects of individual-difference variables on cognitive performance and change in clinical dementia suggest that the pathogenetic process overshadows the influence of many variables that play a role in normal cognitive aging.

In a recent study, Bäckman, Jones, Small, Agüero-Torres, and Fratiglioni (2003) used a similar analytical strategy in examining predictors of rate of MMSE change from preclinical to clinical AD. Thus, the sample comprised persons who were all non-demented at baseline, but diagnosed with AD at a 3-year follow-up. We reasoned that the likelihood of obtaining reliable relationships between various subject characteristics and cognitive change should be greater in preclinical AD, because here the disease process may not have progressed to a point where other individual-difference variables are overshadowed by the pathogenesis. The predictor variables selected by Bäckman, Jones, et al. have all been implicated in normal cognitive aging or emerged as risk factors for dementia (i.e., age, sex, education, previous and recent disease, as determined from hospital records, depression, high blood pressure, vitamin deficiency, apolipoprotein E genotype, social network, substance use).

However, with a single exception, the Bäckman, Jones, et al. (2003) study failed to document any relationships between the predictor variables and 3-year changes on the MMSE. The exception concerned the finding that rate of cognitive decline increased as a function of the number of additional diseases (e.g., infectious disease, endocrine disease, blood disease, respiratory disease, digestive disease) requiring hospitalization between baseline and follow-up. In general, then, the findings from this study suggest that the limited role of individual-difference variables for cognitive functioning in AD generalizes to the preclinical period of the disease. Obviously, this observation provides strong evidence for the view that a dementing disease tends to make people more cognitively similar.

Of special note is the fact that many of the factors examined (e.g., higher age, lower education, female sex, apolipoprotein Eε4 allele, poor social network) have been associated with an increased risk of developing AD (for a review, see Fratiglioni & Rocca, 2001). Thus, although these factors seem to have limited effects on the progression once the disease process starts accelerating, they may be active in promoting the development of the degenerative process. In other words, these variables may play a role as risk factors, but not as precipitating or prognostic factors.

We would like to close this section by addressing the extent to which the cognitive deficits exhibited by demented patients in the laboratory relate to functional competence in natural settings. Hill, Bäckman, and Fratiglioni (1995) investigated the relationship between cognitive performance and everyday measures of basic (e.g., dressing, feeding) and instrumental (e.g., handling money, locating places in the person's environment) activities of daily living (ADL). Measures of episodic memory and visuospatial skill were related to both basic and instrumental ADL. However, when disease severity (as assessed with the MMSE) was statistically controlled, only Poppelreuter's figures (a simple measure of visuoperception) was associated with the ADL measures. This likely reflects colinearity

between the MMSE and the indicators of memory, but also highlight the importance of basic perceptual capabilities for functional competence in dementia.

THE TRANSITION FROM NORMAL AGING TO DEMENTIA

A major line of research in the KP during recent years has concerned the identification of so-called preclinical cognitive markers of an impending dementia disease. Evidence pertaining to this issue is relevant for both theoretical and clinical reasons. Theoretically, knowledge regarding the transition from normal aging to dementia is vital in furthering our understanding of how the disease evolves. From a clinical perspective, identifying individuals at risk for developing AD as early as possible would seem to be imperative to maximize treatment efficacy (e.g., Post, 1999).

Next, we review KP research addressing preclinical cognitive markers of dementia. Following a discussion of cognitive alterations observed in incident cases 3 years before clinical diagnosis, we describe recent data on the 6-year prediction of incipient dementia.

PRECLINICAL DEFICITS 3 YEARS BEFORE DIAGNOSIS

AD

Small, Viitanen, and Bäckman (1997) examined baseline and 3-year follow up performance on the MMSE in incident AD patients and controls. The incident cases exhibited a baseline deficit on the MMSE, indicating a preclinical cognitive impairment. However, this impairment was confined to two subscales of the MMSE, delayed recall and orientation to time. It is of note that both these items have an episodic memory referent. By contrast, at the 3-year follow-up the cases were impaired on all MMSE items. This pattern suggests that episodic memory impairment is an early harbinger of forthcoming AD, and that cognitive functioning declines in a rather global fashion during the transition from preclinical to clinical AD.

These findings were extended in a follow-up study focusing on the specific cognitive measures in the KP battery (Small, Herlitz, Fratiglioni, Almkvist, & Bäckman, 1997). In this study, we were interested in the relative importance of different cognitive markers for identifying at-risk individuals, but also in the extent to which the specific measures contribute to prediction accuracy over and above the MMSE. Those who were to develop AD showed deficits 3 years before diagnosis in all episodic memory tasks (recall of unrelated and organizable words; word and face recognition), all visuospatial tasks (Block design; Clock drawing and reading; Poppelreuter's figures), and letter and category fluency. The only exception to this pattern was Digit span; however, given that basic short-term memory operations are relatively well preserved in early clinical AD (e.g., Simon et al., 1995), preclinical deficits should, of course, not be expected in this task. Although the univariate analyses yielded preclinical deficits on nearly all cognitive tasks, a logistic regression analysis (controlling for colinearity) showed a dominance of tasks assessing episodic memory in separating incident cases from controls; organized recall, face recognition, and letter fluency emerged as reliable predictors of incident AD in the model. Another important finding was that specificity (i.e., the ability to classify the controls) was excellent, although sensitivity (i.e., the ability to classify the cases) was poor using only the MMSE. However, sensitivity increased with the addition of the episodic memory measures. This pattern of findings indicates that a combination of global and specific cognitive measures may optimize identification of individuals in a preclinical phase of AD.

Cognitive Support

Given that episodic memory is critically implicated before the AD diagnosis, it is of interest to investigate whether some episodic memory tasks are more sensitive than others in signaling AD development. This issue could be approached by considering the degree of cognitive support afforded by the memory task. If we analyze the effects of preclinical AD on episodic memory performance in terms of the provision of cognitive

support, three principal outcomes can be conceived. First, the size of the memory deficit in preclinical AD may be greater in more supported tasks (e.g., cued recall) than in less supported tasks (e.g., free recall). Such an outcome would indicate that a reduction in cognitive reserve capacity is a salient feature of preclinical AD, much like it is in early clinical AD. By contrast, the opposite result that persons in a preclinical phase of AD would show greater deficits in less supported tasks than in more supported tasks, would suggest that these individuals are particularly penalized under highly demanding task conditions. Finally, an outcome indicating that the magnitude of the episodic memory impairment in a preclinical AD is invariant across different levels of cognitive support, could be interpreted to mean that a general impairment of episodic memory precedes reductions of memory plasticity in the early pathogenesis of AD.

Bäckman and Small (1998) compared groups of incident AD cases and control subjects on four episodic memory tasks that vary with regard to the degree of cognitive support provided: free recall of rapidly presented random words, free recall of slowly presented random words, free recall of organizable words, and cued recall of organizable words. As noted, this task constellation represent a systematic variation in the degree of cognitive support provided.

The main findings from this study are portrayed in Figure 8. Several aspects of these data should be highlighted. First, although the normal old declined slightly across the 3-year retest interval, they showed proficient utilization of all three forms of cognitive support examined at both times of measurement, with performance increasing gradually with the addition of more study time, organizability, and retrieval cues. Second, the incident AD cases showed a clear performance deficit at baseline, which was further exacerbated at follow-up. The latter finding indicates that the time period just preceding the AD diagnosis is characterized by marked decline of episodic memory functioning. Third, and most interestingly, although they were impaired at baseline assessment, the incident AD cases still showed the same qualitative pattern as the controls, with performance gradually increasing

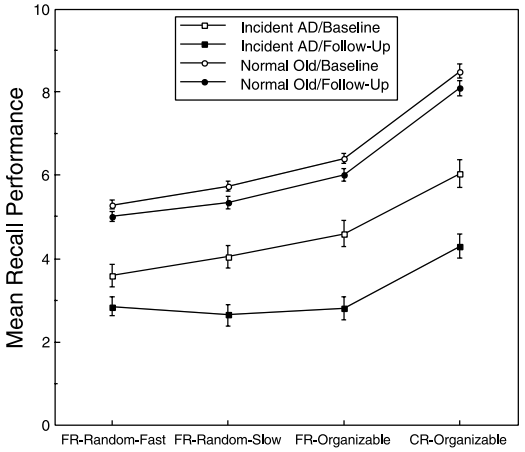

Fig. 8. Episodic memory performance in normal old adults and incident AD patients across level of cognitive support at baseline (3 years before diagnosis) and follow-up (diagnosis). Bars represent standard errors around the means. (From Bäckman & Small, 1998, copyright by the American Psychological Association).

across increasing levels of cognitive support. Finally, at the time of diagnosis, the incident AD cases failed to benefit from more study time and organizability in free recall; here, performance gains were observed only in the most supportive condition – when an organizational structure was combined with retrieval cues. The latter result was expected, as several studies have demonstrated that it may be necessary to provide support at both encoding and retrieval to show memory improvement in early clinical AD (for a review, see Bäckman & Herlitz, 1996).

The important point to be made from these results is that the size of the preclinical episodic memory impairment in AD does not seem to vary as a function of level of cognitive support. As shown in Figure 8, the deficit was highly generalizable across important dimensions of episodic memory, such as presentation time, organizability, and retrieval cues. The fact that the incident AD cases showed a normal pattern of utilization of cognitive support although they performed worse than the controls at baseline indicates that that losses in cognitive reserve capacity may occur somewhat later in the pathogenesis of AD than a general episodic memory impairment.

In the Bäckman and Small (1998) study, we also analyzed free recall of random words in terms of the relative contribution of primary and secondary memory. These analyses revealed that the preclinical deficit among the incident AD cases was confined to secondary memory. Corroborating the Digit span data described above, no group differences in primary memory were observed at baseline. The presence of clear secondary memory deficits along with preserved primary memory performance has been documented in early clinical AD (e.g., Simon et al., 1995). The Bäckman and Small data extend this pattern to the preclinical phase of the disease.

Depressive Symptoms

Preclinical alterations in AD are not restricted to cognitive tasks. Berger, Fratiglioni, Forsell, Winblad, and Bäckman (1999) reported an elevation of depressive symptoms 3 years before diagnosis. Interestingly, this elevation occurred for motivation-related (i.e., concentration difficulties, lack of interest) rather than for mood-related (e.g., dysphoria, feelings of guilt) symptoms of depression. The motivational symptoms of depression are cognitively loaded, and have been linked to the individual's basic processing resources, such as the ability to focus the attention on the task at hand, while closing out irrelevant information (Bäckman, Hassing, et al., 1996). As noted in a previous section, motivation-related, but not mood-related, symptoms of depression are related to cognitive performance in clinically non-depressed and non-demented older adults (Bäckman, Hill, et al., 1996). Given that the cognitive deficits in preclinical AD have been linked to changes in limbic and neocortical brain regions (e.g., Fox et al., 1996; Yamaguchi, Sugihara, Ogawa, Oshima, & Ihara, 2001), the observation that the incident AD patients showed elevated motivational symptoms of depression 3 years prior to diagnosis may reflect early changes in brain regions critical to the ability to allocate attentional energy.

Of further interest is that the increase of depressive symptoms in preclinical AD was unrelated to subjective memory complaints. This result suggests that the elevation of symptoms was not a mere reaction to self-perceived cognitive difficulties. The fact that the effects were not mediated by subjective memory problems is interesting in light of the observed dominance of motivation-related symptoms. Specifically, had there been an association between memory complaints and depressive symptoms, this association may have reflected insight into an emerging dementia disease and resulted in mood changes. Thus, the lack of relationship between memory complaints and depressive symptoms in preclinical AD is consistent with the view that mood-related symptoms are relatively uncommon in preclinical AD.

VaD

The work on cognition in preclinical dementia reviewed hitherto has focused on AD. In ongoing research, we are examining whether a preclinical phase with cognitive deficits can be documented also in VaD. There are several reasons why preclinical cognitive alterations may be expected in VaD as well. First, circulatory disturbances may cause gradual brain changes before the event of an actual stroke. Indeed, different forms of vascular alterations have been found to influence cognitive functioning in non-demented persons, including high blood pressure (e.g., Elias, Wolf, D'Agostino, Cobb, & White, 1993), atherosclerotic disease (e.g., Breteler, Claus, Grobbe, & Hofman, 1994), and cardiovascular signs (e.g., cardiac murmur, dyspnea; Fahlander et al., 2000). Second, there is increasing evidence of an overlap in pathology between VaD and AD, including the presence of vascular risk factors in AD and neurodegenerative processes in VaD (Kalaria & Ballard, 1999), Thus, given the well established preclinical period in AD, a prodromal phase may be expected also in VaD. Third, as reviewed above, early clinical VaD and AD patients exhibit similar patterns of cognitive performance across many task domains. This similarity may extend to the preclinical phase.

Indeed, preliminary evidence suggests the existence of preclinical cognitive deficits in VaD. Using the MMSE as the outcome measure, Jones, Jonsson Laukka, Small, Fratiglioni, and Bäckman (in press) found deficits in incipient VaD patients 3 years before diagnosis for the total score and for the delayed recall and orientation to time

subscales. However, from baseline to the 3-year follow-up, the VaD patients exhibited disproportionate decline across most MMSE items. In a parallel study using the KP cognitive battery, Jonsson Laukka, Jones, Small, Fratiglioni, and Bäckman (in press) observed baseline deficits among incident VaD cases in several measures of episodic memory (i.e., recall of unrelated words, word and face recognition). The pattern of preclinical cognitive deficits demonstrated by the VaD patients in these studies resembles closely that seen in AD. Thus, these data extend the findings of similar cognitive profiles in early clinical VaD and AD patients to the prodromal stages of the diseases. However, as is true in clinical AD and VaD, it is important to note that the VaD diagnosis in the KP focuses on multi-infarcts and strategic infarcts. Thus, whether the preclinical cognitive deficits observed in VaD and the apparent similarity to AD in this regard generalizes to other VaD etiologies (e.g., small vessel disease) remains unknown.

Sources of Misclassification

Despite the clear demonstrations of preclinical cognitive deficits in dementia, the KP research, as with related work from other groups (e.g., Albert, Moss, Tanzi, & Jones, 2001; Chen et al., 2001; Jacobs et al., 1995), indicates that group classification is far from perfect. To be sure, it may not be realistic to expect non-overlapping distributions of cognitive performance scores many years before diagnosis, given the large interindividual variability in preclinical AD (e.g., Fox et al., 1996; Rubin et al., 1998) as well among those who will remain non-demented (e.g., Korten et al., 1997; Lindenberger & Baltes, 1997).

In an attempt to determine sources of misclassification, persons who were classified as demented or not based on their cognitive performance at baseline were examined prospectively for development of dementia 3 years later (Herlitz, Small, et al., 1997). Among the incident dementia cases, those who were classified as demented by their cognitive performance but non-demented by the clinical diagnosis at baseline, performed at a lower level on most cognitive tasks, were older, had less education, and involved more women than the group who were diagnosed as demented and considered to be non-demented by the cognitive tests at the initial assessment. This intriguing pattern suggests that cognitive tests can detect many preclinical cases who may be missed in the clinical diagnostic procedure because of high age, low education, and female sex. At the same time, the cognitive tests may fail in identifying prevalent dementia cases due to insensitivity to the same demographic variables. Thus, these findings underscore the need of integrating clinical and cognitive data in the early detection of dementia.

Prospective Identification

Research on preclinical dementia which compares baseline cognitive performance in persons who have or have not developed dementia some time later may be termed retrospective, in that it works from diagnosis and backwards. Although such research may be informative from a theoretical point of view (e.g., in furthering our understanding of the cognitive pathogenesis of AD and VaD), its clinical utility is limited. In order to be clinically useful (e.g., regarding early treatment), research needs to identify individuals at risk prior to diagnosis and then follow these individuals prospectively to the time of diagnosis. Such prospective studies on the preclinical detection of dementia typically employ terms such as mild cognitive impairment (Petersen et al., 1999) or cognitive impairment, no dementia (CIND; Hogan & Ebly, 2000) in classifying at-risk individuals.

Palmer, Wang, Bäckman, Winblad, and Fratiglioni (2002) used baseline MMSE scores to define age- and education-specific norms for CIND. Not surprisingly, a sizable proportion (around 1/3) of those individuals classified with CIND were diagnosed with dementia 3 years later, and a similar proportion were dead by the follow-up assessment. However, the most intriguing finding from this study was that the remaining third of the CIND sample remained stable or even improved across the follow-up period. Moreover, the latter category had no increased risk of developing dementia a further 3 years ahead. This pattern of findings clearly indicates the heterogeneity of late-life cognitive impairment, and argues strongly against naive expectations

concerning the usefulness of cognitive tests in identifying persons for clinical trials and other applied purposes with a high degree of accuracy.

In a recent study (Palmer, Bäckman, Winblad, & Fratiglioni, 2003), we examined whether a combination of different markers would increase the prospective identification of incident dementia cases. Three sets of markers were considered: subjective memory complaints, CIND (as defined in the Palmer, Wang, et al., 2002 study), and domain-specific (i.e., episodic memory, verbal fluency, visuospatial skill) cognitive impairment. We reasoned that use of this constellation of indicators may mimic what might happen in everyday life. Specifically, an individual might first report memory problems to a general practitioner, then be assessed globally (e.g., with the MMSE) by a non-specialized physician, and finally have a more thorough cognitive examination in a specialized clinical setting. Using this strategy, we found that nearly all individuals who experienced memory problems, met the CIND criteria, and showed memory or verbal fluency impairment progressed to dementia within 3 years. It is notable that the high predictivity was achieved without sophisticated assessment tools such as neuroimaging. However, despite the excellent predicitivity, this procedure was able to identify only a small fraction of those who were to develop dementia, because of the low sensitivity of all measures. Thus, an important task for the future is to increase sensitivity at the first step. This may be accomplished by providing better information to the elderly population as to the importance of assessing cognitive functioning in the presence of self-perceived memory problems. In addition, combining preclinical markers from different cognitive and other (i.e., neural, genetic, subjective) domains may enhance identification of at-risk individuals (Bäckman, Small, et al., in press).

PRECLINICAL DEFICITS 6 YEARS BEFORE DIAGNOSIS

AD

Other KP research shows that preclinical cognitive deficits in dementia may be detected even longer before diagnosis. In one study (Bäckman, Small, & Fratiglioni, 2001), we assessed persons at three occasions over 6 years. At the last occasion, some individuals were diagnosed with AD, although the entire study sample was nondemented at the first 2 times of measurement. The key issue in this study was whether preclinical AD is characterized by accelerated memory decline relatively long before diagnosis. In addition, to obtain further evidence regarding the ability of different episodic memory tasks to identify persons at risk for developing AD, we administered tests of verbal free recall and recognition at both preclinical measurement occasions.

The results from this study are shown in Figure 9. Three aspects of the data in this figure should be highlighted. First, the normal old performed at about the same level at both measurement occasions. This is consistent with the results from several longitudinal studies, indicating that decline in episodic memory may not be observed in normal aging over relatively short follow-up periods (e.g., Hultsch, Hertzog, Small, McDonald-Miszczak, & Dixon, 1992; Zelinski & Burnight, 1997). Second, the incident AD cases showed clear deficits already 6 years before

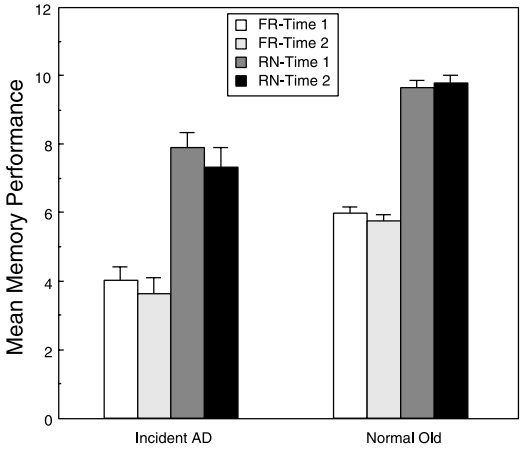

Fig. 9. Free recall (FR) and Recognition (RN) performance for normal old and incident AD persons 6 years (Time 1) and 3 years (Time 2) before the diagnosis of dementia. Bars represent standard errors around the means. (From Bäckman, Small, & Fratiglioni, 2001, copyright by Oxford University Press).

the time of diagnosis. Third, and most interestingly, although they exhibited episodic memory deficits already at the first time of measurement, the incident AD cases did not decline selectively between Time 1 and Time 2. Thus, the data suggest that the episodic memory deficit in preclinical AD is characterized by an early onset followed by relative stability, until a few years before a diagnosis may be rendered.

In addition, the impairment in preclinical AD generalized across the two episodic memory tests. In fact, the free recall and recognition tests were equally effective in discriminating between the two groups both 6 and 3 years before diagnosis. From a different perspective, the magnitude of performance gains from recall to recognition was similar in both groups. This finding is in agreement with the results of Bäckman and Small (1998), indicating that episodic memory functioning, in general, may be affected before losses in cognitive reserve capacity are observed in the development of AD.

Memory performance was not assessed at the time of diagnosis in the Bäckman, Small, and Fratiglioni (2001) study. In addition, the sample size in the incident AD group was relatively small, hence limiting the generalizability of the findings. To address these issues, we conducted a parallel study involving large samples of incident AD cases and control subjects, who were assessed 6 and 3 years before diagnosis, but also at the time of diagnosis (Small, Fratigioni et al., 2000). In this study, however, the assessment of cognitive performance was restricted to the MMSE.

At both preclinical measurement points, the incident AD cases showed deficits on one item only, namely delayed recall. This result provides additional support for the view that episodic memory impairment is an early harbinger of AD. However, from the 3-year interval to the time of diagnosis, the incident AD group exhibited disproportionate decline across most cognitive domains assessed in the MMSE. In addition, similar to the Bäckman, Small, and Fratiglioni (2001) study, the incident AD cases did not exhibit selective decline from 6 to 3 years before diagnosis in delayed recall, despite the fact that they performed at a considerably lower level than the non-demented persons at the initial measurement occasion. These results corroborate the notion that AD is associated with a long preclinical period during which memory deficits are detectable, although accelerated decline in performance may not be expected until the time period preceding diagnosis. A possible reason thereof is that the brain is capable of counteracting slowly occurring brain changes until a certain threshold is reached beyond which compensatory responses are no longer possible (Bäckman, Small, et al., in press; Small, Fratiglioni, & Bäckman, 2001).

LIMITED EFFECTS ON NORMAL AGE-RELATED COGNITIVE CHANGES

Given that (a) dementia has a long preclinical period during which cognitive deficits are detectable, and (b) the incidence of dementia increases dramatically with advancing age, it may be expected that some of the age-related variation observed in typical cognitive aging studies is attributable to a portion of the sample being in a prodromal phase of dementia (Sliwinski et al., 1996). Bäckman et al. (2002) addressed the influence of preclinical dementia and another cognitively relevant future event, impending death, on the size of cross-sectional age differences in tasks assessing episodic memory, verbal fluency, and visouspatial skill. As expected, preclinical dementia and forthcoming death were both associated with higher age and poorer cognitive performance. However, the key finding was that removal of those who were to be demented or die 3 years later affected only marginally the magnitude of the cognitive age differences at baseline. This suggests that other factors (e.g., primary aging processes, a combination of various subclinical health problems) are at play in determining age-related cognitive differences in the general population.

APOLIPOPROTEIN E GENOTYPE AND COGNITIVE PERFORMANCE

In this section, we present original data pertaining to the influence of genetic factors on cognitive

functioning in aging. Specifically, we focus on the relationship between apolipoprotein E (APOE) genotype and cognitive performance. APOE is a risk factor for AD with the $\varepsilon 4$ variant conveying an increased risk of developing the disease (e.g., Corder et al., 1993; Strittmatter et al., 1993). There has also been recent interest in the potential influence of the $\varepsilon 4$ allele on cognitive performance in normal aging. The available evidence portrays a rather mixed picture as to whether the presence of the $\varepsilon 4$ allele conveys a risk of cognitive impairment in normal aging. Some studies have reported evidence supporting this contention (Hofer et al., 2002; Wilson et al., 2002), whereas others have failed to observe any relationship between APOE status and cognitive functioning (Bondi, Salmon, Galasko, Thomas, & Thal, 1999; Small, Graves, et al., 2000).

In a previous paper, we examined cross-sectional differences and longitudinal changes in cognitive performance as a function of APOE genotype (Small, Basun, & Bäckman, 1998). In this study, there were no cross-sectional differences between groups of participants who either did or did not possess the $\varepsilon 4$ allele across a variety of global and specific measures of cognitive functioning. However, the $\varepsilon 4$ carriers did exhibit disproportionate decline on two measures of episodic memory (word and face recognition) across a 3-year follow-up period. At that time, we concluded that presence of the $\varepsilon 4$ allele was associated with greater longitudinal decline, but we also qualified our conclusions by the fact that another mechanism might be influencing rate of decline among the $\varepsilon 4$ carriers. Bondi et al. (1995, 1999) argued that in cases where $\varepsilon 4$ carriers exhibit cognitive deficits, this may be related to an overrepresentation of preclinical AD cases in that group. That is, because (a) $\varepsilon 4$ carriers are more likely to get AD, and (b) preclinical AD cases exhibit cognitive deficits, this may account for the apparent relationship between APOE genotype and cognitive impairment.

In the current context we are able to provide a direct test of this hypothesis with information from a subsequent wave of data collection that was not available at the time of the initial paper. Specifically, we will test whether the differential longitudinal change among the $\varepsilon 4$ carriers remains after preclinical AD cases are removed from the sample.

Participants for this comparison consist of 33 $\varepsilon 4$ carriers (3 $\varepsilon 2/\varepsilon 4$, 27 $\varepsilon 3/\varepsilon 4$, 3 $\varepsilon 4/\varepsilon 4$) and 82 non-$\varepsilon 4$ carriers (1 $\varepsilon 2/\varepsilon 2$, 13 $\varepsilon 2/\varepsilon 3$, 68 $\varepsilon 3/\varepsilon 3$) for whom cognitive data were available at the first two times of measurement and information about changes in diagnostic status was derived from the final measurement point (see Bäckman, Small, & Fratiglioni, 2001 for methodological issues associated with the identification of the preclinical AD cases). The two APOE groups were comparable in terms of age (80.8 years, 82.2 years, respectively; $p > .05$), years of education (9.5 years, 9.4 years, respectively; $p > .05$), and gender composition (% female: 81.8, 74.4, respectively; $p > .05$).

The main statistical analyses consisted of two repeated-measures multivariate analysis of variance computed on the four measures of episodic memory (free recall of unrelated words, cued recall of organizable words, word recognition, face recognition) from the first and second measurement points, with time as the within-subjects factor and APOE status ($\varepsilon 4$, non-$\varepsilon 4$) as the between-subjects factor. In the first analysis, all participants were included whereas individuals who would go on to develop dementia, the preclinical cases, were excluded from the second analysis.

A comparison of the $\varepsilon 4$ and non-$\varepsilon 4$ groups revealed no main effect of APOE genotype on cognitive functioning (Wilks $\lambda = .966$, $F(4, 110) = .94$, $p > .40$). A significant effect of Time was obtained (Wilks $\lambda = .747$, $F(4, 110) = 9.28$, $p < .001$), with reliable longitudinal decline in performance being observed for free recall of unrelated words, $F(1, 113) = 4.09$, $p < .05$, $\eta^2 = .04$, and face recognition, $F(1, 113) = 33.41$, $p < .001$, $\eta^2 = .23$. Most importantly, there was a statistically significant interaction between APOE status and Time (Wilks $\lambda = .901$, $F(4, 110) = 2.99$, $p < .03$). Follow-up repeated-measures analyses revealed that the $\varepsilon 4$ group experienced greater longitudinal decline than the non-$\varepsilon 4$ participants on word recall-unrelated, $F(1, 113) = 4.36$, $p = .039$, $\eta^2 = .04$, word recognition, $F(1, 113) = 7.00$, $p < .01$, $\eta^2 = .06$, and face recognition, $F(1, 113) = 4.49$, $p < .04$,

Table 1. Three-Year Changes in Memory Performance ($M \pm SE$) as a Function of APOE Genotype and Sample Composition.

	Entire sample		Restricted sample	
	Time 1 ($n = 82$)	Time 2 ($n = 33$)	Time 1 ($n = 78$)	Time 2 ($n = 30$)
Word Recall-Unrelated				
APOE-ε4	$5.77 \pm .31$	$5.15 \pm .32$	$5.95 \pm .32$	$5.35 \pm .31$
Non-APOE-ε4	$5.46 \pm .16$	$5.47 \pm .17$	$5.52 \pm .17$	$5.53 \pm .18$
Word Recall-Organizable				
APOE-ε4	$7.92 \pm .29$	$7.56 \pm .36$	$7.98 \pm .32$	$7.87 \pm .33$
Non-APOE-ε4	$7.96 \pm .22$	$7.56 \pm .26$	$8.06 \pm .21$	$7.73 \pm .23$
Word Recognition				
APOE-ε4	$2.90 \pm .15$	$2.76 \pm .15$	$2.97 \pm .16$	$2.85 \pm .15$
Non-APOE-ε4	$2.89 \pm .09$	$3.21 \pm .08$	$2.92 \pm .09$	$3.26 \pm .08$
Face Recognition				
APOE-ε4	$2.92 \pm .13$	$2.32 \pm .17$	$3.03 \pm .12$	$2.45 \pm .16$
Non-APOE-ε4	$2.82 \pm .09$	$2.54 \pm .10$	$2.86 \pm .09$	$2.57 \pm .10$

Note. Restricted sample excluded individuals who were in a preclinical phase of dementia.

$\eta^2 = .04$, although no differences were observed on word recall-organizable ($p > .20$). The longitudinal changes for the ε4 and non-ε4 carriers are shown in Table 1 for the four memory measures.

To further explore these findings, a second set of analyses was conducted where those who developed dementia at the final measurement point were eliminated. In the ε4 group, 3 persons were eliminated, whereas 5 participants were omitted from the non-ε4 group. Despite the fact that so few persons were eliminated, the pattern of results shifted slightly, in terms of whether differential effects were seen among the ε4 carriers. Specifically, although the overall interaction effect of APOE status $\times$ Time was still statistically significant ($p < .05$), the univariate effects for word recall-unrelated and face recognition were no longer statistically reliable ($p = .06$ and .07, respectively). However, the interaction effect for word recognition remained statistically significant ($p = .019$). The overall effect of APOE status was still not statistically significant ($p = .46$). The overall effect of Time remained statistically significant ($p < .05$), after the participants with preclinical AD were removed from the analyses. At the level of the individual tests, statistically significant declines in face recognition were present, $F(1, 105) = 30.59$, $p < .001$, $\eta^2 = .23$, but the effect for free recall of unrelated words no longer approached conventional significance, $F(1, 105) = 3.26$, $p = .07$, $\eta^2 = .03$.

These new analyses provide partial support for the contention that ε4-related cognitive impairment in non-demented persons may be influenced by the presence of cognitive deficits associated with preclinical AD. Our data are consistent with the work of Bondi et al. (1999), who reported that after partitioning out individuals who would go on to develop AD, as well as those who were lost at follow-up, the ε4/non-ε4 group differences in memory performance were no longer statistically reliable. Thus, the available evidence suggests that caution must be taken when ascribing group differences in cognitive performance to the presence or absence of APOE-ε4 alleles, especially among groups of individuals who are at risk of developing AD. For example, Wilson and colleagues (2002) reported that APOE-ε4 was associated with disproportionate decline across multiple domains of cognitive performance. However, they also noted that APOE-ε4 was associated with an increased risk of AD at the end of the follow-up period, although they failed to eliminate the preclinical AD cases from

their analysis of APOE and cognitive performance. As a result, it is likely that the cognitive deficits they observed in relation to APOE-ε4 reflect a combination of possible genetic influences and very strong influences of impending disease.

CONCLUSIONS

The KP research reviewed in this article may be summarized into the following main points:

1. The patterns of cognitive impairment observed in typical cognitive aging studies generalize to very old age: The age-related deficits observed in fluid tasks (e.g., free recall, Block design, Trailmaking) were attenuated or eliminated in tasks that are less cognitively taxing and involve more structured and familiar materials (e.g., Clock setting, Poppelreuter's figures, Digit span). Whenever observed, the age-related deterioration was relatively small, likely reflecting restriction of range as well as selective survival among the oldest cohorts. However, despite their small size, the age effects remained after controlling for impending dementia and death. This suggests that primary aging processes may affect cognitive functioning also in late senescence.
2. The ability to utilize supportive conditions in episodic memory and visuospatial tasks was well preserved across the age range examined. Thus, even in the 9th and 10th decades of life, individuals possess a cognitive reserve capacity – a potential for improving performance when cognitive support (e.g., retrieval cues, more time for task completion) is provided.
3. Many individual-difference variables within demographic (e.g., education, sex), social (e.g., activity levels), genetic (e.g., apolipoprotein E genotype), and health-related (e.g., circulatory factors, vitamin status, depressive symptoms) domains contribute to the variation of cognitive performance in very old age. Given that the prevalence of many unfavorable conditions (e.g., in terms of social or health-related factors) increase in late life, failure to account for such conditions may lead to an overestimation of normative age-related differences in cognitive functioning.
4. Cognitive deficits are substantial in magnitude and widespread across different domains of functioning already early on in the disease process in AD and VaD alike. The two major dementia diseases seem to affect many cognitive functions in a similar manner. A primary reason thereof may be that many higher cognitive functions (e.g., memory, verbal ability, visuospatial skill) draw on large distributed neural networks, in which changes at any of the multiple locations may impair performance. Thus, although AD and VaD patients may differ with regard to the degree of alteration at different sites in the networks, the functional outcomes are difficult to differentiate at the behavioral level.
5. Subject characteristics that are associated with cognitive functioning in normal aging tend to diminish in importance in dementia. This includes cognitively relevant demographic and biological parameters, but also conditions with severe cognitive repercussions in nondemented persons such as depression. This may reflect the fact that the influence of various individual-difference variables on cognition is overshadowed by the dementing process itself.
6. There is a long preclinical phase in AD during which cognitive deficits are detectable. Despite the length of the preclinical period, the level of impairment is remarkably stable until a few years prior to diagnosis when precipitous decline is observed. Recent findings indicate preclinical cognitive deficits in VaD as well, extending the observation of similar cognitive impairment in AD and VaD to the time period preceding clinical diagnosis. Despite the size of the preclinical cognitive impairment, group classification is far from perfect. In particular, the sensitivity of cognitive tasks in detecting future dementia cases is relatively low. Combining markers from different domains (e.g., cognitive, social, genetic, neural) may increase identification of at-risk individuals.

ACKNOWLEDGMENTS

We thank our colleagues in the Kungsholmen Project for data collection and management and for many productive discussions.

Preparation of this article was supported by grants from the Swedish Research Council and the Swedish Council for Working Life and Social Research.

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