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COGNITIVE AGING: METHODOLOGICAL CONSIDERATIONS AND SOME THEORETICAL CONSEQUENCES

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The present paper reports and discusses three methodological considerations in research on cognitive aging that have theoretical consequences for the conclusions drawn in studies in the field and potentially for the development of future research in this area. The first issue is about cross-sectional data versus longitudinal data. It is argued that longitudinal data are to be preferred in studies of individual development and change. The second issue deals with the multidisciplinary nature of cognitive aging research. It is argued that such studies should involve behavioural data, brain imaging data and genetic data. For the third issue it is discussed that early cognitive data from childhood and genetic data might be regarded as a proxy for a hard-wired brain reserve that is interacting an experienced-based cognitive reserve that is developing and changing throughout adulthood and old age.

Life expectancy is reaching higher and higher in most countries around the world and the number of elderly persons is growing. Better health care is one crucial reason for this increase. Despite the improvement in medical care, the proportion of people suffering from dementia and other age-related diseases affecting the brain and the cognitive system remain much the same as it has been for many years. However, since the number of elderly is increasing, the number of persons with these diseases is also increasing. No medical treatment has yet been developed for dementia and the usual decline in cognitive function, as people grow older. The society has realised this and put in a lot of money for research on aging in general. Realising also that well functioning cognitive abilities is a prerequisite for a decent life in old age, a considerable amount of these grants has reached researchers in cognitive aging. This general state of affairs is reflected in the fact that cognitive aging is a rapidly growing research area. According to Web of Science, there were 6 papers published in this field in 1970, 14 papers in 1980, 83 in 1990, 1,797 papers in 2,000, and 5,381 papers in 2010. A major reason for this development is of

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course the realisation that there are many important issues to cover in this research. In this paper, I will touch upon three general issues that should be carefully considered by any researcher in this field. These issues are (1) cross-sectional versus longitudinal data, (2) the multidisciplinary nature of studies on cognitive aging, (3) possible advancement of knowledge on cognitive aging by means of life span data.

Cognitive aging is about individual development across the years from adulthood to old age and death. In essence, the research conducted on cognitive aging should seek to describe and explain the changes that the cognitive system undergoes as people become older. Ideally, the whole life span should be covered in this research, but for various reasons, this is seldom the case.

Given what is just said about cognitive aging as an area that should focus on how the individual develops and changes throughout adulthood and old age, it is interesting to see how cognitive aging has been studied during a very long time. A vast majority of the studies that have been carried out during many decades have used a cross-sectional design rather than a longitudinal design. The next section of this paper will discuss the consequences of this paradoxical state of affairs.

Cross-sectional versus longitudinal studies of cognitive aging

In cross-sectional studies of cognitive aging, the cognitive performance of one group of old people is compared with the cognitive performance of a young group of people. In a longitudinal study, the cognitive performance of one group of participants is measured at one baseline test occasion and is then followed up at subsequent test occasions. There are advantages and disadvantages with both approaches, but it is crystal clear that a longitudinal approach is the only possible design, when one wants to study how individuals develop and change, as they grow older.

One decisive advantage with a cross-sectional design is that only one test occasion is needed, which means, relatively speaking, that this type of research is inexpensive to conduct. An obvious disadvantage is that cohort effects are confounded with the effects of chronological age. It is self evident that a person who is 80 years old today grew up under quite different conditions than a person who is, say, 20 years today. Given that a person is affected cognitively by the conditions he or she is brought up in and lives in during many years, it follows that such cohort effects will account for a considerable amount of the variance in the data that is to be explained. An illustrative example of this is the research carried out within the context that is usually referred to as the Flynn effect. Considerable gains, referred to as time-lag gains, were demonstrated in several studies during the end of the 20th century (for reviews see Neisser, 1998; Rodgers, 1999) for measures of intelligence.

The effect is referred to as the Flynn effect, because of the seminal meta-analytic studies carried out by Flynn (1984; 1987) and later extensions (Flynn, 1990; 1994; 1998; 1999; 2000). These studies demonstrated at the population level that persons improved their intelligence across generations. A gain rate of at least 3 IQ points per decade was noted in many countries, on tests such as the WAIS and Ravens matrices (*cf* Owens, 1966; Schaie & Labouvie-Vief, 1974; Tuddenham, 1948). This estimate is equivalent to a mean-level increase of well over one standard deviation unit in the population. As an example from Rönnlund and Nilsson (2008), this means that an individual who was scoring above the 90th percentile 80 years ago and therefore was regarded as "very bright", would perform at an average level today. At the time when the Flynn effect was first discovered, the explanation was referred to as cohort effects.

In two recent studies from our own lab (Rönnlund & Nilsson, 2008; Rönnlund & Nilsson, 2009), we extended the Flynn effect to hold for various components of episodic memory (recall and recognition) and semantic memory (knowledge and fluency). Interestingly, we were able to demonstrate three factors that, taken together, could account for almost 100% of the variance in the memory data. These three factors are (1) cognitive and social influence from the society, (2) nutrition, and (3) family size. The proxies that we used for these three factors were number of years in formal education, body height, and sibship since, respectively. It is often agreed upon in the society that schooling has improved over the years, qualitatively and quantitatively. It is also generally well agreed upon that we eat healthier food now than we did some 80 years ago and therefore nutrition has improved in the society over the years. It is also well known that families are smaller now than they were during the early 1900s. On the basis of data from a longitudinal study, Holmgren, Molander, and Nilsson (2006; 2008) were able to show that participants in this Swedish study, who were born in the beginning of the 20th century on the average had many more siblings than participants who were born in the 1970s. It was not unusual, a century ago, that there were 15 or 16 children in a family and this is very rare now. On the basis of the Confluence and Resource Dilution Models (Blake, 1981; Downey, 1995; Downey, 2001; Zajonc, 1976), Holmgren et al. (2006; 2008) demonstrated that episodic and semantic memory performance was inversely related to sibship size.

The crucial advantage with a longitudinal approach when studying cognitive aging is that development and change for each individual can be examined as a function of increasing age. The longer the time frame is during which a sample of participants are followed, the better is the chance to discover reliable changes, but even a longitudinal study with only two measurement points is better than only one time of cognitive assessment as in cross-sectional studies. There are, however, potential problems also with a longitu-

dinal study. These problems are referred to as test-retest effects (sometimes referred to as practice effects) and attrition effects (Rönnlund, Lövdén, & Nilsson, 2008; Rönnlund & Nilsson, 2006; Rönnlund, Nyberg, Bäckman, & Nilsson, 2005). These effects can be controlled for if the study design is adequately composed. Schaie (1977) proposed such a design and Nilsson, Bäckman, Nyberg, Erngrund, Adolfsson, Bucht et al. (1997) started a longitudinal study in 1988 on the basis of Schaie's proposal.

This study is a longitudinal, prospective, cohort study. It will be briefly described here to illustrate the advantages and disadvantages with both cross-sectional and longitudinal data, and to illustrate how any of the problems mentioned can be avoided or at least how they can be controlled for.

This study, the Betula[1] Study (Nilsson, Adolfsson, Bäckman, de Frias, Molander, & Nyberg, 2004; Nilsson et al., 1997) was originally motivated by the wish to explore various aspects of the development of memory functioning and health in adulthood and late life in light of the fact that an increasingly larger portion of the population consists of elderly people. In addition to studying the development of memory and health in general, two more specific purposes were to explore early, pre-clinical signs and potential risk factors of dementia, and to obtain premorbid measures of memory and health in people who will be in accidents or acquire various other diseases during the course of the study. During the course of the study, two related purposes have been added to this list, namely to examine what the characteristics of successful aging are, and to determine the prerequisites for early diagnosis of neurodegenerative diseases.

The measures taken to accomplish these goals require an interdisciplinary approach involving scientists from several medical, social and psychological fields. Specifically, the aims of the study require the planning, conducting and analysing of data from medical examinations, blood sample testing, DNA extraction and genotyping, health status enquiries, explorations of daily living and leisure activities, critical life events, examination of social and economic factors, and an extensive examination of a wide variety of memory functions.

Several unique features of the Betula Study set the stage for considerable possibilities of new discoveries. These features include the design of the study, the large number of participants throughout the adult life span (35 to 100 years of age), a large number of health-related variables, a large number of social variables, and a large number of well-defined and theoretically motivated cognitive tests with a sharp focus on memory function.

1. The official title of the project in Swedish is Åldrande, Minne och Demens: En Prospektiv Undersökning. The project is colloquially often referred to as the Betula study. Betula [be'tula] is the Latin word for birch tree, which is the symbol for Umeå – a city in northern Sweden, where the study is being conducted.

The design employed for this study was modelled after Schaie (1965; 1977). Schaie proposed this design to be able to separate the effects of the three major sources of variation in developmental research: age, cohort, and time of measurement. The general design of the study, described in detail in Nilsson et al. (1997), is outlined in Table 1. Six samples of subjects participate (S1, S2, S3, S4, S5, and S6). Five waves of data collection have been completed (T1, T2, T3, T4, and T5), a sixth wave is planned.

Table 1

The Betula Design. Return rates are given in parentheses

T1 (1998-90)	S1					
T2 (1993-95)	S1 (86%)	S2	S3			
T3 (1998-00)	S1 (85%)	S2(83%)	S3(86%)	S4		
T4 (2003-05)	S1 (84%)		S3 (84%)		S5	
T5 (2008-10)	S1 (79%)		S3 (78%)			S6
T6 (2013-15)*	*S1*	*S2*	*S3*			*S6*

* Planned

It should be obvious that this design presents clear advantages when compared to traditional cross-sectional or even purely longitudinal designs, especially so when it is possible to make cross-sectional, cross-sequential, cohort-sequential, time-sequential, and longitudinal analyses with proper control for practice effects. To our knowledge, no previous study on memory and health has employed this type of extensive design.

At T1, S1 participants were 35, 40, 45, 50, 55, 60, 65, 70, 75, and 80 years of age. There were 100 persons in each of the 10 age cohorts. At T2, two new samples were added to the Betula Study. The participants of S2 were 35, 40, 45,…, 80 years of age in five-years intervals, whereas the participants of S3 were 40, 45, 50,…, 85 years of age. At T3, another new sample (S4) was included to be used as control for practice effects in S1-S3. A total of 600 persons were included in this sample, with 50 individuals in each of 12 different age cohorts (35, 40, 45,…, 90 years of age). A new sample (S5) was included to control for the size of the practice effects that will have emerged up to T3. It should be observed that the proportion of returnees is high and stable. Averaged across S1-S3, the reasons for no return were as follows: 7% died before T3, 4% refused further participation, and 4% had moved or were unavailable for other reasons.

Recruitment of each new sample of participants started by randomly obtaining names from the population registry in Umeå, Sweden, in each of the cohorts. The number of males and females selected for inclusion reflected the proportion of males and females in each age cohort of the Swedish population, for an overall ratio of 47/53 (males to females). As described in Nilsson

et al. (1997), participants and drop outs did not differ and participants did not differ from the Swedish population as a whole on a series of background variables, except for education and income, which was higher among participants.

In several recent studies (Nyberg, Salami, Andersson, Eriksson, Kalpouzos, Kauppi et al. 2010; Rönnlund et al., 2008; Rönnlund & Nilsson, 2006; Rönnlund et al., 2005) we have examined the results obtained by means of a cross-sectional design and a longitudinal design. Needless to say, the data from these two designs look quite different. An example of this on the basis of data from Rönnlund et al. (2005) is given in Figures 1 and 2.

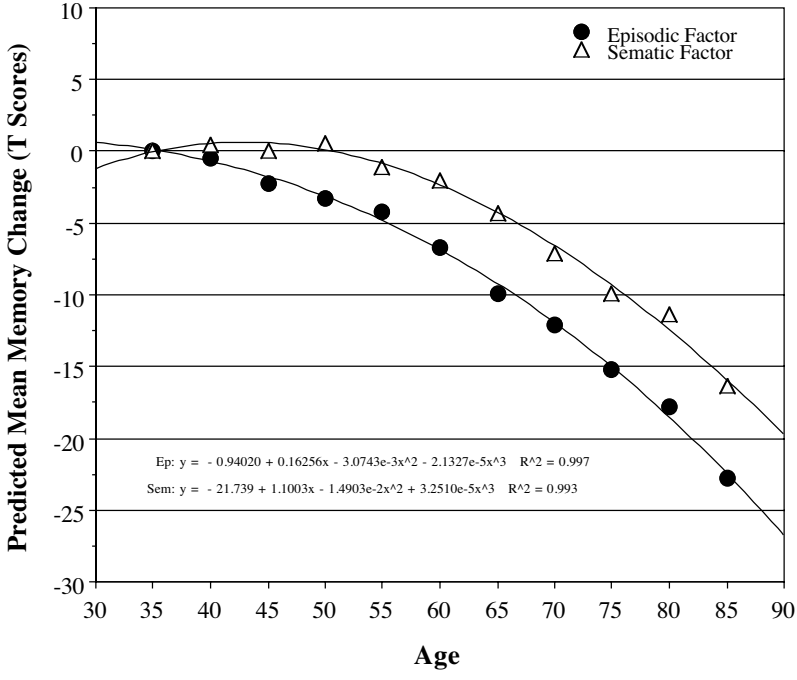

Figure 1

Estimated memory changes across age (T scores) for episodic and semantic memory on the basis of cross-sectional data. Reproduced with permission from Figure 1 in Rönnlund, Nyberg, Bäckman, and Nilsson (2005)

As can be seen from the cross-sectional data presented in Figure 1, the decrease in performance for episodic memory from the age of 35 years to the age of 85 years is approximately linear. This linear pattern has also been observed in several other cross-sectional studies (e.g., Schaie, 1994; see also

Park, Lautenschlager, Hedden, Davison, Smith, & Smith, 2002; Verhagen & Salthouse, 1997) and in some cases, the decrease in performance has been observed to start as early as at 20 years of age. Salthouse (2009) has argued that this gives a true picture of the development of episodic memory in adulthood and old age. Nilsson, Sternäng, Rönnlund, and Nyberg (2009) have argued that this cross-sectional pattern gives an overestimation of the age decrement in performance due to a confounding between maturational change and cohort-related influences. Raz and Lindenberger (2011) and Schaie (2009) have arrived at similar conclusions.

Based on the same participants in the Betula Study, longitudinal data for the same episodic memory tasks are presented in Figure 2. As can be seen, the data pattern is radically different as compared to the cross-sectional data presented in Figure 1. The longitudinal time frame of these data is 10 years measured at three points of measurement. In the longitudinal data presented in Figure 2, control has been made for attrition effects and test-retest effects by means of subtracting the gain in performance when participants are tested a second or a third time. The size of this gain can be estimated by comparing the performance when participants are tested the first time and when they are tested the second or the third time. For example, at T3 (see Table 1), participants in S4 are tested the first time, whereas participants in S2 and S3 are tested the second time, and participants in S1 are tested for the third time. Thus, when doing this type of control for longitudinal data, the decline in episodic memory performance is not observable in until much later than in cross-sectional data. Salthouse (1999) has argued that lack of power typically seen in longitudinal studies is a serious concern for such studies, but the time-related improvements seen in such studies when participants are tested a second or a third time are clearly difficult to reconcile with cross-sectional data (Rönnlund et al., 2005).

In summary, the data presented here show that cross-sectional results and longitudinal results are very different. When test-retest effects and attrition are controlled for, longitudinal data give a more valid picture of the development of cognitive function in adulthood and old age than cross-sectional data, which generally are contaminated by cohort effects.

Cognitive aging as a multidisciplinary research field

Some three or four decades ago, cognitive aging was considered to be a research field in cognitive psychology. Most studies were based solely on principles and methods developed within this discipline. Today, the picture is quite different. Most studies combine data from several disciplines. The traditional methods originating from cognitive psychology are often combined with data about structure and function of the brain, and data from genetics

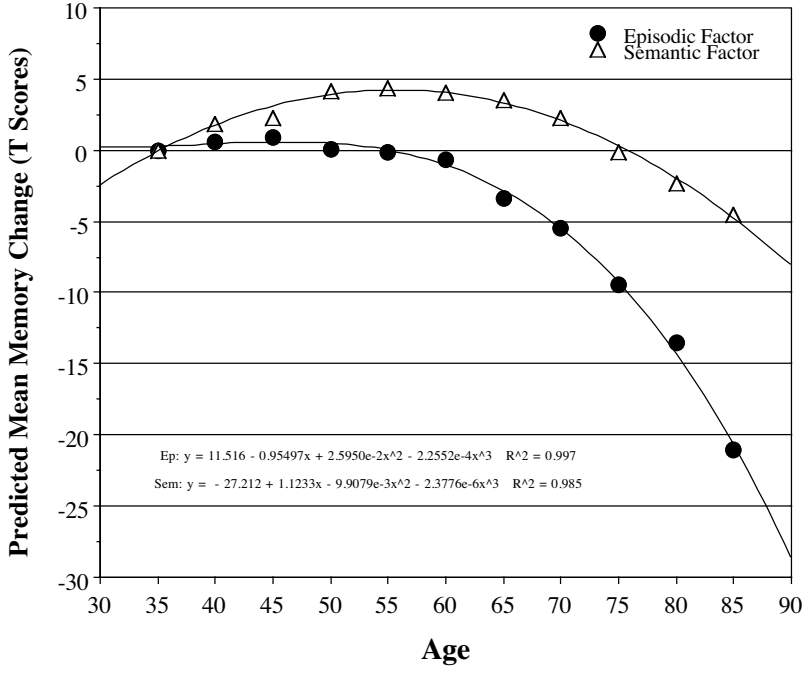

Figure 2

Estimated memory change across age (T scores) for the episodic and the semantic factors on the basis of practice-adjusted longitudinal data. Reproduced with permission from Figure 3 in Rönnlund et al. (2005)

obtained after DNA extraction and genotyping. Brain imaging studies have lead to new insights that can easily be combined with traditional cognitive data. One such recent study from our own research group (Nyberg et al., 2010) revealed an interesting parallel to the findings discussed in the previous section of differences in data pattern for cross-sectional and longitudinal data. Almost all previous brain imaging studies on cognitive function have been cross-sectional and a frequent finding has been that frontal lobe activity seems to increase with increasing age (Davis, Dennis, Daselaar, Fleck, & Cabeza, 2008; Rajah & D'Esposito, 2005). This result has been taken as evidence for a reorganisation of the brain when people grow older to make it possible to compensate for a natural decrease in cognitive ability. In Nyberg et al. (2010), we also found this result of a frontal lobe activity increase when analysing the data cross-sectionally. However, when analysing the brain imaging data longitudinally, we found that the frontal lobe activity was decreasing with advancing age. Moreover, when comparing cross-sectional

and longitudinal data this way, we discovered that the increase in frontal lobe activity we saw in cross-sectional data seemed to be due to cohort effects. The increase in frontal lobe activity was present only for high-performing participants with many years of formal education than other participants, who had fewer years in formal education. When inspecting the longitudinal data we found that the frontal lobe activity was decreasing also for these participants with many years of formal education.

The combination of classical cognitive data and genetic data will be illustrated by a relatively recent study in which we were interested in the role of ApolipoproteinE (*APOE*) on memory performance. This is a gene that is known as a risk factor for cardiovascular disease in middle age and a risk factor for Alzheimer's disease in old age (Corder, Saunders, Strittmatter, Schmwxhel, Gaskell, Small et al., 1993; Dupuy, Mas, Ritchie, Descomps, Badiou, Cristol et al., 2001; Poirier, Davignon, Bouthillier, Kogan, Bertrand, & Gauthier, 1993). *APOE* has three alleles, ε2, ε3, and ε4, and it is carriers of the ε4 allele who run a higher risk of getting cardiovascular problems in middle age and Alzheimer's disease in old age. Individuals who get one ε4 allele from the mother and one ε4 allele from the father, have the ε4ε4 genotype. These persons have 12 times higher risk of getting Alzheimer's disease as compared with those individuals, who do not have any ε4 allele. The relative frequency of the ε4ε4 genotype is fortunately relatively small in the population (2%). Individuals with the ε3ε3 genotype have a relative frequency of about 58% in the population and often serve as controls in studies of the role of *APOE* on cognition. The ε2ε2 genotype is regarded as a protective factor for Alzheimer's disease, but has a very low relative frequency in the population (1%). The relative frequencies of the heterozygotic combinations of the *APOE* alleles are as follows: the ε2ε3 genotype (12%), the ε2ε4 genotype (3%), and the ε3ε4 genotype (24%).

In a relatively recent study (Nilsson, Adolfsson, Bäckman, Cruts, Nyberg, Small et al., 2006), we examined the role of the ε3 and ε4 alleles on episodic memory and semantic memory performance in a healthy sample of the Betula study. More precisely, we compared the performance of those carriers who had one ε4 allele (ε3ε4), the double dose of this allele (i.e., the ε4ε4 genotype) with non-carriers of the ε4 allele (i.e., the ε3ε3 genotype), who served as controls. We regarded the participants in this study as relatively healthy, since we had excluded those participants in Betula who have had a heart infarct, those who had circulatory disorders or other heart diseases, those who had had stroke, and those who had been diagnosed as demented. Others who were excluded from this study were those who had diabetes and those who had a score of 24 or less on the Minimental State Examination test (Folstein, Folstein, & McHugh, 1975), which is a screening test for cognitive status and which is used all over the world in dementia examinations. This latter exclu-

sion was done to diminish the risk of including individuals who were in a state of incipient dementia. That is, individuals who had not yet been diagnosed as demented, but who might be in a very early stage of developing this disease and who perhaps were to be diagnosed as demented many years later. Despite exclusions of individuals with one or more of these many diseases, the study included a total of 1,550 participants.

The participants had been tested in several tests of episodic memory (recall and recognition) and semantic memory (knowledge and fluency). Composites of these four constructs of sub systems and the two main constructs were built. The results can be seen in Figures 3 and 4.

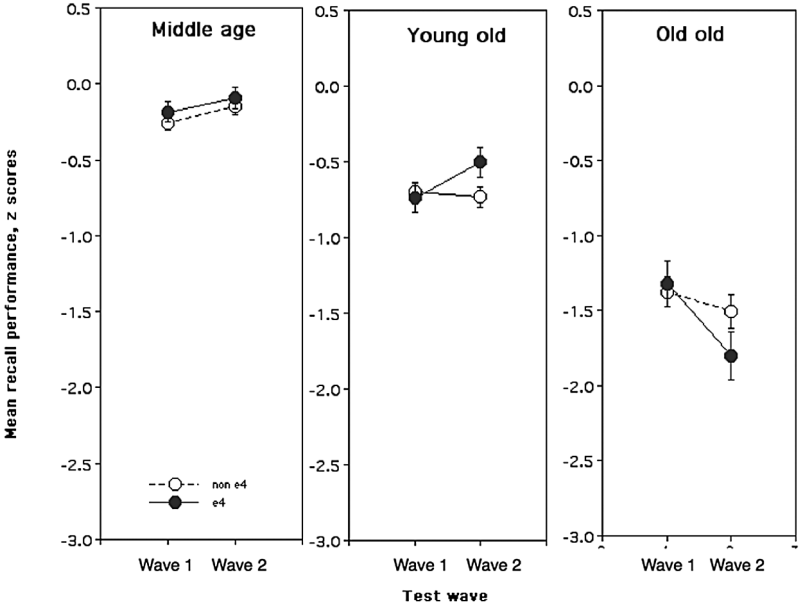

Figure 3

Mean recall performance z scores for middle-age (35-50 years), young-old (55-65 years), and old-old (70-85 years) carriers and noncarriers of the ?4 allele at Wave 1 and Wave 2. Reproduced with permission from Figure 4 in Nilsson, Adolfsson, Bäckman, Cruts, Nyberg, Small, and Van Broeckhoven (2006)

Figure 3 shows the significant interaction between age, *APOE*, and time of testing. Participants were divided into three age groups: middle-aged (35-45 years when first tested), young-old (50-60 years), and old-old (65-85 years). In the analyses of the data behind Figure 3, *APOE* was categorised in two levels, those with at least one ε4 allele (i.e., ε3ε4 and ε4ε4) as compared to none ε4 allele (i.e., the ε3ε3 genotype). Time of testing was categorised

into two levels, wave 1 and wave 2, respectively. Wave 1 was the first time S1 participants were tested, i.e., at T1 and the first time S2 and S3 participants were tested, i.e., at T2 (see Table 1). Wave 2 was T2 for S1 participants and T3 for S2 and S3 participants. The take-home message from this figure is that carriers of the ε4 allele in the old-old age group show a significant decline in performance when tested at Wave 2 and that it is a tendency for carriers of the ε4 allele in the middle-age group and in the young-old group to perform better than non-carriers of the ε4 allele.

We concluded from the first of these two observations that the ε4 allele has a direct negative effect on episodic memory in healthy group of old-old people, not mediated by any diseases for which the ε4 allele is a risk factor. The second observation described that the ε4 allele might have a positive effect at early stages of life. This suggested to us that the *APOE* allele might have different expressions across the life span, namely that the ε4 allele has a positive effect on episodic memory early in life and that this expression changes to be negative, when persons reach an old-old age as we defined in this study. Thus, a prediction is that the cognitive performance in younger age cohorts, say school children, should be higher for carriers of the ε4 allele than for non-carriers.

Figure 4 shows a dose-response effect of the ε4 allele in the old-old age group such that those participants with the double dose of the ε4 allele perform at the lowest level and the non-carriers of this allele perform at the highest level with those with one ε4 allele take a performance position in between. We concluded from these data that the dose-response effect was interesting and called for more research, but we also concluded that the mechanism underlying this effect is still missing. This issue will be discussed more below.

It should also be mentioned that *APOE* was not found to be a significant main effect in any of the analyses carried out in this study. Age was always found to have a moderating effect in the interactions with *APOE*. Another finding of general interest is that the effects reported were found for episodic memory but not for semantic memory. This dissociation between episodic memory and semantic memory provides support for the classical distinction between these two memory systems proposed by Tulving (1972) and evidenced by Nyberg and Tulving (1996) with respect to dissociations between episodic memory and semantic memory.

In three studies Lind and colleagues (Lind, Ingvar, Persson, Cruts, Van Broeckhoven, Adolfsson et al., 2006a; Lind, Larsson, Persson, Ingvar, Nilsson, Bäckman et al., 2006b; Lind, Persson, Ingvar, Larsson, Cruts, Van Broeckhoven et al., 2006c) combined classical cognitive data with brain imaging data and genetic data. In one of these studies, we (Lind et al., 2006c) we found results that provide support for the dose-response effect described

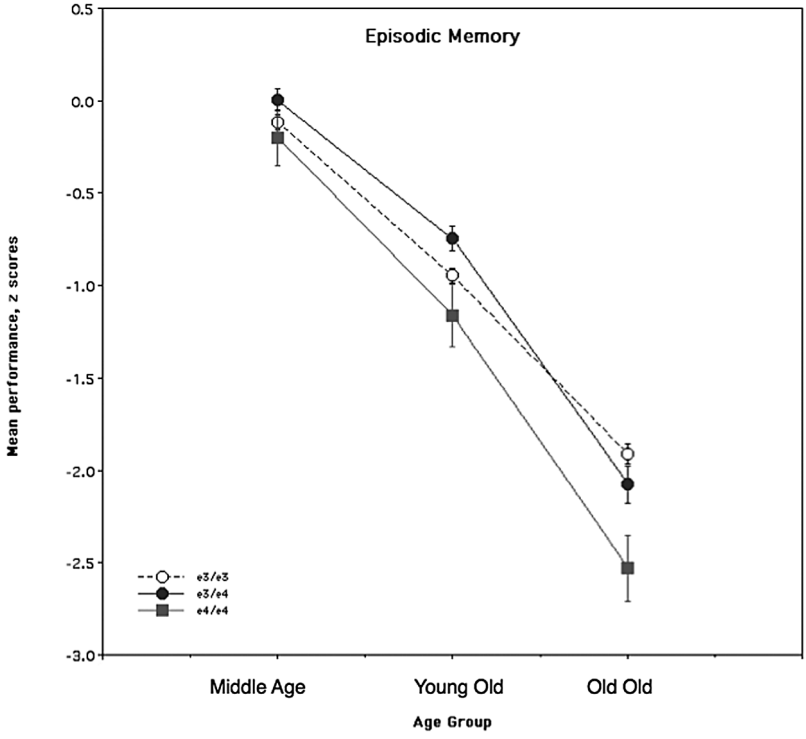

Figure 4

Mean performance z scores for middle-age (35-50 years), young-old (55-65 years), and old-old (70-85 years) carriers of two, one, and zero ε4 alleles. Reproduced with permission from Figure 3 in Nilsson et al. (2006)

in Nilsson et al. (2006) and that might be an explanatory mechanism for the behavioural data demonstrated by Nilsson et al. (2006).

In the study by Lind and colleagues (2006c), 60 participants were selected from the Betula Study. They were matched on age and sex and half of the participants had the ε3ε3 genotype (i.e., non-carriers of the ε4 allele), 20 participants were carriers of one ε4 allele (ε3ε4), and 10 participants were carriers of two ε4 alleles (i.e., the ε4ε4 genotype). The participants were placed in a 1.5 Tesla magnetic resonance machine and were asked to respond to a question for each word presented whether the word described an abstract or a concrete concept. The results demonstrated that a significantly higher degree of activity in the left parietal cortex for non-carriers of the ε4 allele (i.e., ε3ε3) than carriers of one ε4 allele (i.e., ε3ε4), who in turn showed a significantly higher activity in this brain region than carriers of the double ε4 dose (i.e., ε4ε4).

In Lind et al. (2006b), we demonstrated that carriers of the ε4 allele have a smaller hippocampal volume than non-carriers of this allele and they perform worse than non-carriers on a hippocampus-based protocol of recognition memory. This association might also give a hint of mechanism for the behavioural data discussed in the previous section in relation to the ε4 allele.

The take home message here is that pure analyses of cognitive performance is not enough for understanding cognitive aging. Other data should be involved. Here it has been suggested that brain imaging data and genetic data together provide a richer picture of what is happening to the individual development of cognitive function as people go through the years of adulthood and old age.

In saying this, a word of caution might be warranted. The claim here is not to say that there is necessarily a causal relationship between brain activity and genes, on the one hand, and cognitive performance, on the other. In most studies on cognitive neuroscience reported in the literature, the relationship is correlational, but sometimes claims are made that there is a causal implication. This is unfortunate, but the problem is hardly more common or serious in cognitive neuroscience than in any other field of research, as suggested by Salthouse (2011) that it would be. After all, as cleverly formulated by Rabbitt (2011) in exactly the same way as is intended in the present paper, "… inclusion, in analyses, of even gross measures of brain status such as loss of volume and white matter lesions can correct misinterpretations that occur when only behavioural data are examined" (Rabbitt, 2011, p. 758).

Lifespan development

I alluded to earlier in this paper that a lifespan approach might be valuable to employ when studying and exploring the true matter of cognitive aging. It was also stated that this seldom is done. The reason for this is practically impossible for a single researcher to do. If starting a project by the time the participants are children, say at early school years, and following the development of these participants until they have reached an age when cognitive decline have started or dementia is in full progress, the researcher himself or herself would have reached an age at which reliable and valid conclusions perhaps would not be possible. In this section of the paper, I will discuss the potential value of having very early cognitive data in studies of cognitive aging.

One reason why it would be interesting to take a lifespan approach in a project on cognitive aging is that it would be possible to take into account even the original prerequisites for an individual at birth. It is not far fetched to think that individuals vary considerably even at birth with respect to cognitive abilities. That is, variation in cognitive ability already at birth in abili-

ties that may play a basic role in cognitive ability and quality of life in old age. This way of thinking about cognitive aging can be conceptualised within the realm of the concept of reserve.

Brain reserve and cognitive reserve are two terms that have been discussed in this context. One attractive way to consider this issue as follows, I think, is to use the term brain reserve as a means to describe the starting point in a lifespan perspective. Viewed this way, brain reserve is a description of the hardware of the individual when starting an almost century-long lifespan. That is, the child is born with a certain genetic set up and certain anatomical and physiological prerequisites that will influence the functionality of this individual throughout life. However, these prerequisites requires maintenance at every stage of the development. If the environment provides good conditions the original prerequisites can be cultivated and improved. If the environmental conditions are not so good, the original prerequisites might be depleted in terms of functionality. This mechanism for influence of the original prerequisites might be an expression of what should be meant by the term cognitive reserve.

The term cognitive reserve was introduced to capture how education and schooling, demands on the individual in work life, social interactions, life style, engagements in relatives and friends, physical and intellectual ambitions etc. influence cognitive function in adulthood and old age. The cognitive reserve refers to the ability to make flexible use of the available brain reserve when performing cognitive tasks (Stern, 2002). Estimations of the cognitive reserve have been employed in a long series of different contexts: education (e.g., Stern, Alexander, Prohovnik, & Mayeux, 1992), literacy (e.g., Manly, Schupf, Tang, & Stern, 2005), occupational complexity (e.g., Staff, Murray, Deary, & Whalley, 2004), participation in leisure activities (e.g., Scarmeas, Levy, Tang, Manly, & Stern, 2001), cohesion of social networks (e.g., Fratiglioni, Wang, Ericsson, Maytan, & Winblad, 2000), and personality traits (e.g., Wilson, Schneider, Arnold, Bienias, & Bennett, 2007).

One of the most spectacular demonstrations of the influence of environmental factors on the cognitive reserve and the plasticity of the brain and the sensitivity of the brain to change in a positive way is generally known as the study of London cab drivers. This study (Maguire, Gadian, Johnsrude, Good, Ashburner, Frackowiak et al., 2000) showed that taxi drivers, who had learnt the streets of London to perfection and managed very well in finding their way around the city showed very good cognitive performance and also showed structural changes in the brain, namely an increased brain volume in comparison to controls who were not taxi drivers and who had not acquired the cognitive map of London. This was a cross-sectional study and it does not really say anything about the causal link between this map learning and the good cognitive performance or the structural changes of the hippocampus in

the brain, because those taxi drivers who managed well in tests might have had a larger hippocampus volume already from the beginning. However, Woollett and Maguire (2011) recently confirmed the findings in a longitudinal study showing that there is a causal link between cognitive training and structural changes of the brain. Similar associations between changes in brain structure after training has also been recently demonstrated by several other researchers and is nicely summarised by May (2011) and Simon, Yokomizo, and Bottino (2012).

The data just described were reported in this context to show that there is an impressive experience-dependent structural plasticity in the adult human brain. I turn next to the possibility of obtaining information about any variability in the brain structures already from the beginning, at birth or soon thereafter. Assumingly, this can be accomplished in at least two different ways.

One way to do this is to obtain early cognitive records of persons, who later are selected to be examined longitudinally and multidisciplinary in adulthood and old age. The so-called Nun Study is a wonderful example of this approach, although the baseline data were not obtained until when participants, who were going to be examined later in life, were teenagers. In a very well conducted and well cited study Snowdon, Kemper, Mortimer, Greiner, Wekstein, and Markesbery (1996) showed that linguistic ability is a strong predictor for dementia in old age. In this study, the researchers were able to demonstrate that those persons who developed dementia in old age were those, who, when they were teenagers, demonstrated a poor linguistic ability. The participants in this study were teenage girls who wanted to become nuns. When signing up for this type of future life, They had to write a story about their lives an to give reasons for why they wanted to become nuns. The years went by and soon they reached an age when cognitive decline began and some of them became demented. Many years passed by and some of these nuns developed dementia. Based on linguistic analyses it was discovered that those who became demented had written more poorly than others 60 years earlier. These data suggest that linguistic ability in young age might be a valid predictor of the development of dementia in old age.

To bring this a little bit further in this context, it might be possible to find cognitive markers very early, perhaps at the time when children get their first grades in school or even earlier, already at the time of infancy. There might be ethical issues against using such data to predict dementia in old age. But for the ambition to explore the interaction between brain reserve, as seen in these early markers, and cognitive reserve, as seen in identifiable indicators, as described above, in adulthood and old age, such early cognitive data would be valuable. Such data may exist as private enterprises in many countries and perhaps as public registers in some countries.

Another way to go about looking for early signs of cognitive function would be to find biological markers that are valid as predictors for cognitive ability from early years in life to adulthood and old age. The notion of successful aging as taken from the Betula Study may provide such a clue. Nilsson (2011) speculated recently that certain results might be an indication that the early prerequisites of the newborn can be a support for the notion of brain reserve. Nilsson based his reasoning on a recent follow up of a study carried out in the Betula Study (Nilsson et al., 1997; Nilsson et al., 2004) some years ago (Habib, Nyberg, & Nilsson, 2007). It was demonstrated in Habib et al. (2007) that successfully aged individuals showed some non-cognitive characteristics that were not characteristic of individuals who were not identified as successfully aged. According to Habib et al. (2007), the characteristic non-cognitive features of those Betula participants identified as successfully aged were high education, lack of disease, good health as indicated in subjective reports, number of siblings, number of rooms in housing, and having own teeth still at an advanced age. The classification by Habib et al. (2007) of Betula subjects in successfully aged and participants with usual or normal age was done on the basis of data collected in 1993 to 1995.

Nilsson (2011) used this classification to examine which of these participants had been diagnosed as demented a decade later (2005). Quite as a surprise Nilsson found that none of the participants who had been classified as successfully aged had been diagnosed as demented, whereas 26% of those participants in the same age range, who had not been diagnosed as successfully aged had been diagnosed as demented 10 years later. As previously stated in this paper the *APOE* gene is regarded as a strong predictor of Alzheimer's disease. Although there is a difference between those who were classified as successfully aged and those who were not in 1995 with respect to carry the risk allele for Alzheimer's disease, the ε4 allele, it is notable that none of those who were classified as successfully aged has become demented. Among those who had been classified as successfully aged 8% had this allele and among those who were not classified as successfully aged 15% had this allele. The fact that none of those who had been classified as successfully aged had become diagnosed as demented despite the fact that they were carriers of the risk allele is quite remarkable. It might be the case that those who had been classified as successfully aged in 1995 have some protective factor, biological or non-biological, to avoid the development of dementia. The search for such protective factors is presently underway in the Betula Study.

These data are very striking, especially so when evaluating the type of impact that the variables characterising successfully aged participants might have on the development of dementia (high education, good subjective health, number of siblings, number of rooms in housing, and own teeth). None of these variables are seriously regarded as protective factors for

dementia. Nilsson's (2011) speculation was that some other, yet unknown, factor should be responsible for the striking results obtained. Research in the Betula Study is, thus, presently underway to examine such possible factors.

There are other valuable reasons for bringing in life span studies in this context too. For example, Craik and Bialystok (2006) have remarked that cognitive abilities increase in efficiency from infancy to young adulthood, after which there is an interesting stability in performance to old age for some individuals or a decline, and in some cases a dramatic decline. As pointed out by Craik and Bialystok (2006), this pattern suggests corresponding continuities of mechanism and process. Despite this obvious relationship between the two research fields, the areas of cognitive development and cognitive aging have, as yet, made little contact. Much theoretical and methodological insights would be gained by a closer connection as argued by Craik and Bialystok (2006) and it is not difficult to agree.

The take-home message from this section is that lifespan analyses, from early childhood to old age, might be a new valuable avenue to future progress in the area of cognitive aging.

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