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Physical health, vascular risk factors, and age-related cognitive decline

*Studies into physical determinants
of normal cognitive aging*

PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit Maastricht,
op gezag van de Rector Magnificus,
Prof. Mr. M. J. Cohen,
volgens het besluit van het College van Decanen,
in het openbaar te verdedigen op
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Paranimfen

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List of abbreviations

A ₁ , A ₁₋₄	Denotes one or more MAAS panel studies
AD	Alzheimer's Disease (or - Dementia)
ABPM	Ambulatory Blood Pressure Monitoring; technique to measure blood pressure repeatedly under normal living conditions
APAQ	Actual Physical Activity Questionnaire; proxy measure of caloric expenditure
BLE	Biological Life Event; health factors potentially related to cognitive decline, as identified in the Maastricht Memory Study (MMS)
BMI	Body Mass Index; body weight [kg]/ body length squared [m ²]; index of obesity
BRC	Brain Reserve Capacity; theoretical model to describe functional reserve and compensatory mechanisms in cognitive processes
CVA	Cerebrovascular Accident; irreversible neurological condition due to brain hemorrhage or infarction
CVE	Cardiovascular event; <i>here</i> : evidence of cardiovascular disease identified in the medical history
CST	Concept Shifting Task; task measuring simple and complex cognitive speed
DART	Dutch Adult Reading Test; measure of premorbid (verbal) intelligence
GIT	Groningen Intelligence Test; Dutch test of formal intelligence
GP	General Practitioner, or family doctor
ICPC	International Classification of Primary Care; coding system of health problems used in RNH
(N)IDDM	(Non-) Insulin-Dependent Diabetes Mellitus
ISH	Inventory of Subjective Health [<i>Vragenlijst Omtrent Ervaren Gezondheid, VOEG</i>]
LDST	Letter Digit Substitution Test; test of information processing speed
LOA	Level of Occupational Achievement; proxy measure of general ability, or <i>intelligence</i> , used in MAAS as stratification variable
MAAS	Maastricht Aging Study
MCRT	Motor Choice Reaction Test; test of simple and complex information processing speed
MEMIC	Center for Data and Information Management [formerly the <i>Medisch en Maatschappelijk Informatie Centrum</i>]; university service in charge of the RNH and RCAD data base
MMS	Maastricht Memory Study; preliminary study of MAAS performed between 1987-1990 that introduced the concept of Biological Life Events (BLE)
MMSE	Mini-Mental State Examination; screening test for cognitive impairment
MRI	Magnetic Resonance Imaging; a brain imaging technique
NESTOR	The Netherlands Program for Research on Aging [<i>Nederlandse Stuurgroep Ouderenonderzoek</i>]; primary sponsor of the cross-sectional phase of MAAS
PET	Positron Emission Tomography ; a brain imaging technique
RCAD	Register of Cognitive Aging and Dementia; the MAAS research data base
RNH	Registration Network Family Practices [<i>Registratienet Huisartspraktijken</i>]; sample frame of MAAS
SCSB	Short Cognitive Screening Battery; set of psychometric instruments covering a wide array of cognitive abilities
SPECT	Single Photon Emission Computed Tomography; a brain imaging technique
SCWT	Stroop Color-Word Test; test of cognitive interference, or <i>flexibility</i>
TIA	Transient Ischemic Attack; essentially reversible brain perfusion disorder
VO ₂ -max	Oxygen consumption of the body during maximal physical effort
WAIS	Wechsler Adult Intelligence Scale; the <i>golden standard</i> in IQ assessment
WHR	Waist-to-Hip Ratio; ratio of body circumferences as a measure of fat distribution
WLT	Word Learning Task; test of primary (or <i>immediate</i>) and secondary (or <i>delayed</i>) memory

CONTENTS

Chapter

1	General introduction	9
2	Physical health, vascular risk factors, and age-related cognitive decline: theoretical background	15
I	Physical health and cognitive aging	15
II	Vascular risk factors and cognitive aging	25
3	The Maastricht Aging Study (MAAS): rationale, objectives, design and methods	41
3.1	Rationale and objectives	41
3.2	MAAS study design	46
3.3	Methods I: Postal survey	53
3.4	Methods II: Medical and neurocognitive assessment	55
4	Self-reported physical activity, perceived health, and cognitive performance in older adults	65
	Abstract	65
	Introduction	65
	Methods	67
	Results	70
	Discussion	73
5	Aerobic capacity and cognitive performance in a cross-sectional aging study	77
	Abstract	77
	Introduction	77
	Methods	79
	Results	83
	Discussion	87
6	Repeated automatic versus ambulant blood pressure measurement: the effects of age and sex in a normal aging population	91
	Abstract	91
	Introduction	92
	Methods	93
	Results	95
	Discussion	103

7	Can blood pressure predict cognitive task performance in a healthy population sample?	109
	Abstract	109
	Introduction	109
	Methods	111
	Results	115
	Discussion	116
8	Is cognitive impairment related to a reduced nocturnal blood pressure drop?	123
	Abstract	123
	Introduction	124
	Methods	125
	Results	127
	Discussion	131
9	The relation between morbidity and cognitive performance in a normal aging population	137
	Abstract	137
	Introduction	137
	Methods	138
	Results	140
	Discussion	146
10	Concluding remarks	151
	Summary	161
	Samenvatting	165
	Curriculum vitae	171
	Dankwoord	173
	List of publications	174

Chapter 1

General introduction

Virtually all aspects of cognitive functioning in healthy individuals have been shown to deteriorate with increasing age (Birren & Schaie, 1990). In fact, the majority of elderly people complain about forgetfulness and decreased concentration, which in many cases compromise their quality-of-life to such an extent that professional help is sought (Jolles, Verhey, Riedel & Houx, 1996). Demographic projections indicate that the need for specialized health care facilities to deal with these health problems will rise dramatically, due to the increased life expectancy in Western societies (Fries, 1990).

One of the major problems in clinical practice is the differentiation of what may be regarded as an 'age-congruent' decline in cognitive capacities and the prodromal phase of a specific pathological syndrome, such as dementia. In prodromal stages of dementia the cognitive symptomatology may be similar to what may be considered the lowest extreme of normal cognitive function. Much research effort to date has therefore been devoted to delineate the *borderline* between normal cognitive aging and pathological conditions such as Alzheimer's disease (Jolles, 1996; Jolles et al., 1996), in order to force the notion of the continuity of adult cognitive development into the dichotomy of the medical model. In the past decades several attempts have been made to conceptualize the prodromal phase of cognitive pathology (chapter 2). In the most recent version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV, American Psychiatric Association, 1994) a new research category has been included as part of the class of cognitive disorders, called 'mild neurocognitive disorder'. Such widely accepted definitions are essential to clarify the natural history of cognitive disorders and may ultimately result in recommendations for the design of clinical drug trials and the planning and development of health care facilities.

What do we know about normal cognitive aging?

The knowledge we have about the normal aging of cognitive functions is far from complete and basic questions are as yet unanswered. For example, when in life do cognitive abilities start to deteriorate, is this decline universal for all cognitive abilities or are there differences in the rate of decline, and, most importantly, are there individual differences in cognitive aging trajectories, and finally, if so, which factors mediate these differences (Rabbitt, 1990)? These questions lie at the heart of modern cognitive gerontology and their answers may have major implications for diagnostic and therapeutic strategies for cognitive disorders (Bromley, 1990).

Rowe and Kahn (1987) have suggested in their theoretical review that even in normal, disease-free populations a substantial variation can be observed in virtually any functional parameter, such as memory function, and that this variation may increase with age. They suggested a distinction between *normal* (or usual) and *successful* aging in several functional

domains – such as cognition – and encouraged the scientific pursuit of the factors which can differentiate between these two aging categories. With respect to cognitive aging, health-related factors such as head trauma, prolonged psychotropic drug use or general anesthesia have in recent cross-sectional research been shown to moderate the relation between age and cognitive function (Houx & Jolles, 1993; Houx, Vreeling & Jolles, 1991; Jolles, Houx, Vreeling & Verhey, 1993). It has been hypothesized that these so-called *Biological Life Events* (BLE) constitute a biological substrate for the non-pathological cognitive deficiencies that are associated with normal aging. The importance of this notion was stressed quite recently in a multidisciplinary symposium devoted to diagnostic and therapeutic issues of cognitive impairment (Lancet Conference 1996, 'The challenge of the dementias', Edinburgh, UK). In their consensus statement in *The Lancet*, the Writing Committee concluded that the *challenge* that is referred to begins by characterizing normal brain aging in terms of neuropathology, neuroimaging, and neuropsychology, preferably within a longitudinal framework (Writing Committee Lancet Conference, 1996). Without this knowledge the borderline between normality and pathology cannot be determined in a satisfactory way. In particular, the role of vascular risk factors in normal and pathological cognitive dysfunctions was addressed during this meeting (Skoog, 1996). It is therefore essential to carry out large-scale studies into normal cognitive aging to account for the different aging patterns in cognitive abilities and to distinguish normal cognitive aging from pathological cognitive aging such as occurs in an early phase of dementia.

Longitudinal studies

Longitudinal studies that specifically address normal cognitive aging are relatively scarce as they require large human and financial resources (Deeg, 1989). The ongoing prospective population studies that include measures of cognitive function are less suitable for studying normal cognitive aging for a variety of reasons. Most importantly, some of these studies do not cover the complete adult life span, which seems imperative to gain insight into further functional development after brain maturation is reached in young adulthood (Selkoe, 1992). For example, in the French Paquid study (Barberger Gateau et al., 1992), only individuals aged 65 years or older were included at baseline. The Longitudinal Aging Study Amsterdam (LASA; Deeg et al., 1993) included young-old individuals (55 years and older) but only a limited set of cognitive instruments is being used because the primary focus of the study is on autonomy and well-being. A multi-stage assessment of cognitive function was made in the Rotterdam study, the aim of which is to identify factors related to chronic diseases, such as dementia, in a geographically well-defined population aged 55 years and older (Hofman, Grobbee, de Jong & van den Ouweland, 1991). Thus, specific cognitive domains were assessed in this study only when pathology was suspected. Studies that do cover the complete adult life span have other limitations. In the classical Baltimore Longitudinal Study of Aging (BLSA, Shock et al., 1984) cognitive tests were administered to the oldest participants only (60 years and older). The Betula study in Sweden shares with the Maastricht Aging Study (MAAS) the interest in health-related factors (Nillson, Winblad, Adolfsson, Bucht & Bäckman, 1992), but the dependent variables pertain primarily to memory function. Finally, in the Seattle studies

no systematic assessment was made of health status or morbidity (Schaie, Labouvie & Barrett, 1973).

MAAS started in 1991 with the aim of providing answers to the core questions of cognitive gerontology cited above by providing fundamental data on individual aging trajectories in different cognitive domains, which are studied as functions of contextual and biomedical characteristics (Jolles, Houx, van Boxtel & Ponds, 1995). The study covers the full adult life span and is characterized by a cross-sequential design and in-depth neurocognitive and biomedical evaluation of a group of initially healthy individuals. For this purpose, participants were randomly recruited from a patient data base of collaborating general practices in the Maastricht region (Registration Network of Family Practices – RNH). The core population of MAAS consists 1,900 individuals at baseline measurement. The population was stratified for age, sex, and general level of functioning (based on prior education and actual vocational achievement), the latter two as the most important and acknowledged confounding variables in cognitive aging research (Lezak, 1995). Thus, the design of MAAS may be characterized as quasi-experimental, to facilitate the study of relations between potential determinants of cognitive aging and relevant demographical background characteristics.

Outline of this thesis

This thesis deals with the results of the cross-sectional phase of MAAS and relates to normal cognitive aging and health-related variables, with special reference to vascular risk factors, as potential predictors of cognitive decline. Three other aspects of cognitive aging are dealt with in PhD theses issued by Neuropsych Publishers that are based on MAAS data: cognitive aging in relation to surgery under general anaesthesia (J. Dijkstra, April 1997), traumatic brain injury (M. Klein, April 1997), and metacognition (R. Ponds, expected in 1998).

The first part of **chapter 2** provides the theoretical background for the studies described in this thesis and provides a concise introduction to the issues at stake in today's research in cognitive gerontology. An overview is given of research findings within the triangle of health, aging, and cognitive function, and some basic concepts are outlined. The construct of *brain reserve capacity* is introduced as an explanatory model for the hypothesized effects of health-related factors on cognitive function that are explored more in depth in the subsequent chapters. In the second part of this chapter the evidence is reviewed for the role of cardiovascular and cerebrovascular risk factors in brain aging, several of which are evaluated in this thesis in relation to cognitive function.

Chapter 3 discusses the rationale and general outline of the MAAS study that provided the framework of the experimental studies described in the chapters 5 to 9. Background information is presented about the sample frame, participant characteristics, the study design and the type of measurements that are used. Basically, MAAS consists of four consecutive panel studies, referred to as A₁ to A₄, using independent subject samples of 440-480 each. Data presented in chapters 5 to 9 are derived from one such panel study (chapters 5, 6, and 8) or from pooling several of such studies (chapters 7 and 9), as indicated below.

Chapter 4 presents the first experimental data and deals with a complementary study in an independently recruited sample, to evaluate the use of a habitual activities questionnaire

(indexing daily caloric expenditure) in relation to cognitive function in 80 healthy individuals aged 55 years and over. It is hypothesized that the level of habitual physical activity and experienced health are related to higher levels of cognitive functioning.

In **chapter 5** the hypothesis of chapter 4 is extended to actual physical fitness as the outcome of habitual physical activity. A submaximal endurance protocol is used to estimate the aerobic capacity (VO_{2-max}) of 132 participants in the first MAAS panel A₁, aged between 24 and 76 years. Next, aerobic capacity is used to predict performance on several neurocognitive tests, in particular those that require large attentional resources.

In **chapter 6** the important methodological issue of blood pressure measurement in population studies is discussed. Blood pressure status is a target variable in chapters 7 and 8. Special attention was given to arrive at relatively unbiased estimate of blood pressure because only one measurement session was available for the evaluation of blood pressure. Particularly the potential bias of age, sex, and adaptation of blood pressure during the measurement session on the habitual blood pressure status is studied in this chapter. Data are presented that were obtained by repeated measurement of the blood pressure of 469 participants in MAAS panel study A₁. In addition, the habitual blood pressure measured in the laboratory was compared to that obtained by 24-hour ambulant blood pressure monitoring (ABPM) in a subgroup of 115 subjects to determine to what extent laboratory blood pressure is representative for blood pressure under daily living conditions.

Blood pressure status and other vascular risk factors (including smoking habits, alcohol consumption, body mass index, and regional fat distribution) are studied in relation to cognitive performance measures in **chapter 7**, based on data from MAAS panel studies A₁ and A₂ ($N = 936$).

Chapter 8 reports on analyses in the ABPM subgroup in the MAAS A₁ panel ($N = 115$), which are comparable to those in chapter 7, with respect to different indices of ambulant blood pressure. More specifically, the hypothesis is tested that the difference between day-time and night-time blood pressure (*dipping*) is inversely associated with brain dysfunction as measured with cognitive tests.

Chapter 9 presents the results obtained when data from the 1,360 participants of the MAAS panels A₁ to A₃ were pooled to analyze the impact of specific well-defined categories of morbidity, as recorded by the general practitioner, on cognitive function.

Finally, the experimental findings are assembled in **chapter 10**, in which the various vascular risk factors are evaluated as possible *mediators* in the age-cognition relationship. The limitations of a cross-sectional methodology are discussed with reference to research design and risk factor characteristics, and some final conclusions are drawn.

REFERENCES

- American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders: DSM-IV*. (4th ed.). Washington, DC: American Psychiatric Association.
- Barberger Gateau, P., Chaslerie, A., Dartigues, J. F., Commenges, D., Gagnon, M., & Salamon, R. (1992). Health measures correlates in a French elderly community population: The PAQUID study. *Journal of Gerontology*, 47, S88-95.
- Birren, J. E., & Schaie, K. W. E. (1990). *Handbook of the psychology of aging*. (3 ed.). San Diego: Academic Press.

- Bromley, D. B. (1990). *Behavioural Gerontology: Central issues in the psychology of ageing*. Chichester (UK): John Wiley & Sons.
- Deeg, D. J. H. (1989). *Experiences from longitudinal studies of aging*. (Vol. 3). Nijmegen, The Netherlands: Netherlands Institute of Gerontology.
- Deeg, D. J. H., Jonker, C., Launer, L. J., Schellevis, F. G., Smits, C. H. M., van Tilburg, T., Knipscheer, C. P. M., & van Tilburg, W. (1993). Change in autonomy and well-being: Background and preliminary proposal for the Longitudinal Aging Study Amsterdam. In D. J. H. Deeg, C. P. M. Knipscheer, & W. van Tilburg (Eds.), *Autonomy and well-being in the aging population: Concepts and design of the Longitudinal Aging Study Amsterdam*, (pp. 19-87). Bunnik: Netherlands Institute of Gerontology.
- Fries, J. F. (1990). Medical perspectives upon successful aging. In P. B. Baltes & M. M. Baltes (Eds.), *Successful aging: Perspectives from the behavioral sciences*, (pp. 35-49). Cambridge: Cambridge University Press.
- Hofman, A., Grobbee, D. E., de Jong, P. T. V. M., & van den Ouweland, F. A. (1991). Determinants of disease and disability in the elderly: The Rotterdam elderly study. *European Journal of Epidemiology*, 7, 403-422.
- Houx, P. J., & Jolles, J. (1993). Age-related decline of psychomotor speed: Effects of age, brain health, sex, and education. *Perceptual and Motor Skills*, 76, 195-211.
- Houx, P. J., Vreeling, F. W., & Jolles, J. (1991). Age-associated cognitive decline is related to biological life events. In K. Iqbal, D. R. C. McLachlin, B. Winblad, & H. M. Wisniewski (Eds.), *Alzheimer's disease: Basic mechanisms, diagnosis and therapeutic strategies*, (pp. 353-358). Chichester, UK: Wiley.
- Jolles, J. (1996). *Age-related cognitive decline and the borderland between normal ageing and dementia*. Paper presented at the Lancet Conference, 25-26 April 1996, Edinburgh, UK.
- Jolles, J., Houx, P. J., van Boxtel, M. P. J., & Ponds, R. W. H. M. (Eds.). (1995). *Maastricht Aging Study: Determinants of cognitive aging*. Maastricht: Neuropsych Publishers.
- Jolles, J., Houx, P. J., Vreeling, F. W., & Verhey, F. R. J. (1993). Cognitive aging, biological life events and primitive reflexes. *Neuroscience Research Communications*, 13(suppl. 1), S47-50.
- Jolles, J., Verhey, F. R. J., Riedel, W. J., & Houx, P. J. (1996). Cognitive impairment in elderly people: Predisposing factors and implications for experimental drug studies. *Drugs and Aging*, 7, 459-479.
- Lezak, M. D. (1995). *Neuropsychological Assessment*. (3rd ed.). New York: Oxford University Press.
- Nilsson, L.-G., Winblad, B., Adolfsson, R., Bucht, G., & Bäckman, L. (1992). Berula: En prospektiv undersökning om minnesfunktion och hälsa [Berula: a prospective study of memory function and health]. *Socialmedicinsk Tidskrift*, 69, 193-198.
- Rabbitt, P. (1990). Applied cognitive gerontology: Some problems, methodology and data. *Applied Cognitive Psychology*, 4, 143-149.
- Rowe, J. W., & Kahn, R. L. (1987). Human aging: Usual and successful. *Science*, 237, 143-149.
- Schaie, K. W., Labouvie, G. V., & Barrett, T. J. (1973). Selective attrition effects in a fourteen-year study of adult intelligence. *Journal of Gerontology*, 28, 328-334.
- Selkoe, D. J. (1992). Aging brain, aging mind. *Scientific American*, 267, 97-103.
- Shock, N. W., Greulich, R. C., Andres, R., Arenberg, D., Costa, P. T., Lakatta, E. G., & Tobin, J. D. (1984). *Normal human aging*. Washington DC: U.S. Government Printing Office.
- Skoog, I. (1996). *Clinical significance of cognitive impairment in non-demented elderly persons: Relation to dementia, vascular disorders and death*. Paper presented at the Lancet Conference, 25-26 April 1996, Edinburgh, UK.
- Writing Committee Lancet Conference. (1996). The challenge of the dementias. *Lancet*, 347, 1303-1307.

Chapter 2

Physical health, vascular risk factors, and age-related cognitive decline: theoretical background

INTRODUCTION

The preservation of cognitive skills at an adequate level is essential for the autonomy and independence of older individuals (Deeg et al., 1993). The rapidly growing proportion of elderly individuals in industrialized countries has given this notion high priority on the political and scientific agenda and has resulted in an increased research activity in the field of cognitive gerontology.

The negative association between different aspects of cognitive function – such as memory, attentional capacity and speed of information processing – and chronological age is one of the most consistent findings in the literature on the psychology of aging (e.g. Jolles, Houx, van Boxtel & Ponds, 1995; Poon, 1985; Salthouse, 1989; Birren & Birren, 1990). In addition, consistent evidence suggests that the general physical condition or specific disease entities may have repercussions for brain health and thereby for cognitive abilities (Elias, Elias & Elias, 1990a; Nolan & Blass, 1992), the effects of which may be difficult to distinguish from the intrinsic aging process. Both individual and environmental factors seem to be responsible to some extent for the increasing variation of cognitive function with age. Complex interrelations exist between aging, health or physical fitness, and cognitive performance, and we are only beginning to identify and understand the mechanisms underlying these interrelations.

Part I of this chapter presents an overview of the issues at stake in cognitive gerontology and provides a theoretical framework for the experimental chapters 4 to 9 of this thesis. The potential role of vascular risk factors as precursors of disease in the context of age-related cognitive decline is addressed more specifically in the remainder of the chapter.

I – PHYSICAL HEALTH AND COGNITIVE AGING

When discussing the concepts of age, health, and cognitive function and their interrelationships, it may be helpful to outline common definitions and underlying assumptions to clarify the object of our study. In succession, the concepts of age, health and cognitive function are discussed separately and in their mutual coherence. Above all, the discussion will be restricted to *normal* cognitive aging, although inevitably the borderland between normal and pathological cognitive aging, as in dementia, will be touched upon in the description of factors that are associated with an acceleration of the decline of cognitive abilities (for a review, see Jolles, Verhey, Riedel & Houx, 1996).

Concept definitions

Health – The definition of health as the absence of disease, an approach that originated from the medical model, has evolved in the last decades towards a more positive, multidimensional operationalization (König-Zahn, Furer & Tax, 1993; McDowell & Newell, 1987). For example, depending on one's disciplinary approach, health can be defined statistically in terms of a continuum between opposing extremes in physical functioning, biologically as an imbalance in physiological adaptation to environmental demands, sociologically as the optimal state to perform social roles, or psychologically as incorporating aspects of development, personality, or behavior. The term *disease* most commonly relates to the biomedical concept of intrinsic pathology in organ structures which may have functional consequences for the individual. Several schemes have been proposed to denote the chain of events leading from disease to *disability* (e.g. WHO, 1980; Verbrugge & Jette, 1994). The recent classification of the disablement process by Verbrugge and Jette (1994) discerns after disease or pathology an *impairment* (dysfunction and structural abnormality in a specific body system), which may be followed by *functional limitations* (restrictions in basic physical and mental actions), and *disability* as the final stage, which refers here to the difficulties experienced in any domain of life caused by a health problem, resulting from the gap between personal capability and environmental demands. *Risk factors* are thought to modulate this process in all its different stages. This classification illustrates that health is not solely an attribute of the individual, but also bears strong environmental and societal connotations. The validity of the health concept, its operationalization, and the choice for an instrument to measure it is therefore largely depending on the setting in which it is used (McDowell & Newell, 1987, p. 26). All the mentioned dimensions of health may be uniquely related to age and to cognitive processes, an issue that will be touched upon later in this chapter.

Cognition – The term cognition is generally used to address the intellectual process by which we learn from experience (Bromley, 1990, p. 191). Cognitive processes refer to the mental activity that controls behavior, in other words to the intervening variables that link the stimuli or experiences from the environment to the responses or behaviors that can be observed directly (Maddox et al., 1987, p. 121). However, for research purposes such definitions are too broad. Cognition from a neuropsychological perspective may be defined operationally (Colsher & Wallace, 1991) and incorporates distinct domains of function that can be labeled as intelligence, attention, language ability, learning and memory, visuospatial ability, and problem solving (LaRue, 1992). Special tests have been developed to probe the performance within these domains of function (Lezak, 1995).

Cognitive processes are primarily mediated by neocortical areas in the brain, which distinguish man from lower vertebrates. However, most other brain structures have a role in cognitive processes as well. Although no distinct brain substrate can be identified for specific cognitive domains, damage to certain brain structures may produce dramatic domain-specific changes. For example, damage to the hippocampal region (e.g. as the result of stroke or exposure to a toxic compound) may lead to an amnesic syndrome characterized by failure of long-term retention of novel information (Kolb & Whishaw, 1990, p. 539). Indeed, a large

part of our current knowledge on the relation between the brain and cognitive behavior is derived from studies with brain-damaged patients.

Age and aging – Aging can also be defined along different theoretical lines, and although most commonly it is understood in a biological sense, it has also psychological and social connotations. It was described comprehensively by Birren and Birren as “... the time-related transformation of the structures and functions of the organism with a resulting decline in self-regulating biological, social, and behavioral capacities ...” (Birren & Birren, 1990). Biological aging is characterized by a steady reduction of physiological reserve capacity after the age of 30, resulting in an increasing susceptibility to chronic disease and probability of death (Kirkwood, 1994). It is considered to be primarily intrinsic in nature, due to restrictions laid down in the genome, to immunological or neuroendocrine changes, or to insufficient mechanisms of cell repair, but environmental insults such as lifestyle variables or exposure to toxic agents also affect the rate of bodily change (Hayflick, 1985; Yates, 1993). From an evolutionary standpoint, the fact that the investment in somatic maintenance in humans is less than required for indefinite survival can be explained by the relatively high death rate due to environmental causes and the priority given to rapid and prolific maintenance (Kirkwood, 1994). However, in spite of many prevailing ‘aspect theories’, no comprehensive model of human aging is as yet available.

After briefly considering the single concepts of health, aging, and cognition, some pairwise interrelations between these concepts are now discussed – each covered by a distinct research area – before they are brought together in a final discussion.

Aging and health

As age increases there is a typical rise in the prevalence of diseases of virtually all organ systems (Figure 2.1). However, as stated earlier, a definition of health as the absence of clinically overt disease is limited in that it discards the subclinical change in organ systems with age.

Figure 2.1. Percentage of subjects with at least one active medical problem as recorded by the general practitioner in MAAS panels A1 to A3 ($N = 1,373$; see chapter 9).

There is a considerable overlap between the concepts of biological aging and health when the latter is understood as a continuum instead of the dichotomy of disease / no disease. For example, risk factors or a genetic make-up that are associated with morbidity in later life can be present in individuals who are clinically healthy. In many disease entities, such a predisposition is expressed as subclinical changes at a cellular or organ level. These degenerative changes may become clinically apparent as chronic diseases that accompany old age. The general loss of functional reserve capacity in organ systems with age eventually has a serious impact on behavior and in the resilience to cope with the demands of everyday life. However, there is a remarkable diversity in individual aging patterns and in the age-related loss of functional capacity. The interindividual variability in most bodily functions increases with age (Fozard, Metter, Brant, Pearson & Baker, 1993). To account for the heterogeneity in individual aging trajectories, several authors have suggested a hierarchy in subtypes of aging (Jolles et al., 1996; Rowe & Kahn, 1987; Stones, Kozma & Hannah, 1990; Table 2.1).

Table 2.1. Four types of aging patterns.

<i>Type</i>	<i>Function of</i>
1 Primary (or successful) aging	age-intrinsic changes
2 Usual aging	1 + nonpathological deficiencies
3 Secondary (or pathological) aging	2 + pathology-related functional decline
4 Tertiary aging	3 + effects of terminal illness

The successive aging subtypes are typical for the rate of functional decline in individuals at a certain point in time. Transition from one type to a subsequent type can take place during the life span. Thus, successful aging reflects the fortunate – but largely hypothetical – situation where only age-intrinsic factors contribute to a decline in physical (or mental) function when other risk factors for disease-related processes are eliminated or controlled for. Identification of the determinants of successful aging is one of the major challenges of contemporary gerontology (Fozard, Metter & Brant, 1990) and ways to limit the functional decline and manifestation of chronic diseases to the shortest possible interval before death is one of the challenges facing the medical sciences (Fries, 1990).

Aging and cognition

Parallel to the decline in physical reserve capacity there is a general trend towards a reduction in several basic cognitive abilities (Botwinick, 1981; Poon, 1985). The individual reduction in cognitive test performance at any point in life is however subtle when performance in young adulthood is taken as a reference, and proceeds only in some to a functional impairment, mostly at advanced ages. However, tasks that involve some form of processing of unfamiliar information, the use of long-term memory, some forms of abstract reasoning, visuospatial abilities, or complex attentional processes show an age-related decline which can be already detected in early adulthood (LaRue, 1992, pp. 47-77). These aspects of cognitive function that are particularly sensitive to age reflect maturational growth and are often referred to as

belonging to the domain of 'fluid intelligence' (Horn & Cattell, 1967). They are highly sensitive to a decay of neuronal structures (the cognitive 'hardware'). In contrast, *crystallized* abilities, consisting of the accumulated formal and informal experiences of life, which are mainly verbal in nature, remain relatively unaffected during the aging process (Botwinick, 1981; LaRue, 1992, pp. 47-77).

A general slowness of behavior is associated with age, especially when performance tasks are demanding or performance is measured under time constraints (Bromley, 1990, pp. 185-196). The most influential and comprehensive construct today that explains age-related cognitive decline is the resource limitation model in which cognitive processes are defined in terms of the energetic demands placed on the central information processing capacity, or *resources* (Salthouse, 1985; 1988; 1992). Salthouse hypothesizes that slowing of the rate of information processing (or, to use a computer metaphor again, a decreased 'cycle-time') may act as the causal determinant of a decline in all cognitive systems, with only relatively minor contributions of peripheral (sensory or motor) processes. The model predicts that effortful, controlled processes require more resources than overlearned, automatic processes (see also Hasher & Zacks, 1979). It is suggested that age is accompanied by a depletion of resources which constitutes the main reason why controlled processes are more strongly affected by age.

Several age-related changes in the central nervous system may underly this resource reduction, e.g. progressive loss of large neurons (that are in a post-mitotic phase from childhood onward), changes in dendritic branching and complexity, formation of degenerative plaques and tangles, deposition of amyloid, microvascular changes, and, on a functional level, depletion of neurotransmitter substances such as acetylcholine, dopamine, or catecholamines (LaRue, 1992, pp. 25-46; Selkoe, 1992). On a molecular level, processes which accompany old age, such as free-radical formation and oxidative stress, somatic mutation, increase in macromolecular errors, loss of unique genetic information, and molecular cross-linking, all may aggravate the decrease in brain integrity and functional loss (Calne, Eisen, McGeer & Spencer, 1986).

Health and cognition

As the brain has no metabolical buffer capacity, it depends on the integrity of multiple organ systems for the supply of energy (glucose and oxygen) and nutrients (Tarter, Edwards & van Thiel, 1988a). Effective brain function relies on a stable and intact internal environment. It can therefore be readily understood that factors related to physical health, which may disturb this delicate relation, have been associated with nonpathological decrements in cognitive function (Table 2.2). Some of these factors may also induce a dementia syndrome (LaRue, 1992, p. 53-156). Evidence comes for the largest part from epidemiological and case-control studies and has been reviewed extensively elsewhere (Birren & Schaie, 1990; Colsher & Wallace, 1991; LaRue, 1992; Nolan & Blass, 1992; Tarter, van Thiel & Edwards, 1988b, or more specifically in dedicated reviews referred to in Table 2.2). At least in theory, prevention or treatment of these conditions in individuals should limit (or even reverse) clinically significant cognitive decline when as yet no structural brain damage has developed (Nolan & Blass, 1992). Large scale evaluation of physical health status in cognitive aging studies is laborious and expensive.

Table 2.2. Health-related factors that have been associated with cognitive dysfunctions.

<i>Chronic diseases</i> (Colsher & Wallace, 1991; Tarter et al., 1988b)	
Hypertension	(Starr & Whalley, 1992; Waldstein, 1995)
Cardiovascular diseases	(Elias et al., 1990a; Herzog et al., 1978; Skoog, 1994)
Obstructive pulmonary disease	(Incalzi et al., 1993)
Diabetes	(U'ren, Riddle, Lezak & Bennington-Davis, 1990; Widom & Simonson, 1990)
Renal failure	(Moe & Sprague, 1994)
Liver failure	(Tarter et al., 1988a)
Cancer	(Berg, 1988)
Thyroid hypo-/hyperfunction	(Beckwith & Tucker, 1988)
Endocrine disorders	(Cushing's syndrome, Addison's disease, hypopituitarism)
<i>Medication use</i>	
Anxiolytic / hypnotic drugs	(Barbee, 1993)
Antidepressants	(Knegtering, Eijck & Huijsman, 1994)
Antipsychotic drugs	(Bilder, Turkel, Lipschutz Broch & Lieberman, 1992)
Antihypertensives	(Muldoon, Waldstein & Jennings, 1995b)
Anticonvulsants	(Dodrill, 1992)
Antiarrhythmic drugs	(Bowen & Larson, 1993)
Digitalis and related compounds	(Bowen & Larson, 1993)
Any drugs with anticholinergic activity	(e.g. scopolamine; Riedel & Van Praag, 1995)
Chemotherapeutic agents	(Bowen & Larson, 1993)
<i>Intoxications</i> (Hartman, 1988)	
Alcohol	(Molina et al., 1994)
Metals	(e.g. Pb, Mn, Al; Lewis, Worobey, Ramsay & McCormack, 1992)
Organic solvents	(Ganzevles & Geus, 1991)
Pesticides	(Mearns, Dunn & Lees Haley, 1994)
<i>Deficiencies</i>	
Vitamins	(e.g. B-series, E; Carney, 1990; Kleijnen & Knipschild, 1991)
Micronutrients	(e.g. zinc, cobalt; Sandstead, 1986)
<i>Other</i>	
Physical inactivity	(Chodzko-Zajko, 1991; Chodzko-Zajko & Moore, 1994)
Anesthesia / surgery	(Dekhuijzen & de Lange, 1993)
Head trauma	(Mortimer et al., 1991; Satz, 1993)

As an alternative, it has been suggested that subjective rating of physical health can be used as a proxy measure in the study of health and cognitive function as subjective health ratings are highly related to physicians health ratings (LaRue, Bank, Jarvik & Hetland, 1979). Several authors indeed report significant – though modest – relations between subjective health scales and objective cognitive test performance in relatively healthy adult population samples (e.g. Hultsch, Hammer & Small, 1993; Perlmutter & Nyquist, 1990) but others failed to do so (Salthouse, Kausler, & Sauls, 1990). It should be realized, however, that subjective health scales are relatively unspecific and often reflect the impact of disease on the individual (McDowell & Newell, 1987), or index satisfaction with life. Such scales may be systematically biased when they are used as general health measures, particularly in studies with a wide age range, as older subjects may rate their health differently than younger individuals (Hooker & Siegler, 1992; Salthouse et al., 1990; Siegler, 1990).

Aging, health, and cognitive function

There is a remarkable increase in the variability of scores for measures of cognitive performance within birth cohorts as a function of age, even though the pattern that emerges from cross-sectional studies of cognitive aging suggests that there is a *continuous decline* in performance. However, the rate of decline may differ between individuals of the same age cohort, or within individuals at different stages of the life span. To explain this, it has been suggested that the continuous decline in cognitive abilities can be regarded as an artifact that results from pooling the cognitive aging trajectories of different individuals (Rabbitt, 1990). Longitudinal data support this view as they show less outspoken trends towards lower performance with age (Rabbitt, 1993) and also demonstrate that in older individuals an abrupt decline in cognitive abilities can predict mortality ('terminal drop', see Deeg, Hofman & van Zonneveld, 1990; Riegel & Riegel, 1972). This sudden decrease in performance is particularly prominent for abilities that as a rule are only marginally affected in normal aging, such as vocabulary and other verbal skills (White & Cunningham, 1988).

Scattered but ample evidence supports the role of physical health as a mediating factor in the cognitive decline with age (LaRue, 1992). For example, Launer et al. investigated the relation between age, selected health conditions, and borderline to poor cognitive functioning as measured on the Mini-Mental State Examination (MMSE; Folstein, Folstein & McHugh, 1975) in a large population-based study of 3,974 individuals, aged between 65 and 84 years (Launer, Drinkgreve, Jonker, Hooijer & Lindeboom, 1993). In this study, Parkinson's disease, diabetes, and stroke, but not a history of heart attack, negatively affected the cognitive outcome, independent of age, education, and vision or hearing impairments. The odds-ratio's for cognitive impairment associated with age and education were attenuated up to 6.5% by these health conditions. The relevance of health-characteristics of a subject for cognitive decline with age was demonstrated by Houx and coworkers in a cross-sectional study (Maastricht Memory Study (MMS), Houx & Jolles, 1993; Houx & Jolles, 1994; Houx, Jolles & Vreeling, 1993a; Houx, Vreeling & Jolles, 1991a; Houx, Vreeling & Jolles, 1991b; Houx, Vreeling & Jolles, 1993b). A group of 247 apparently healthy subjects was stratified for age, sex, and educational background. Biological Life Events (BLE) were defined as those factors experienced in time that are related to physical or mental health that may induce a temporary decline in performance, but which have no serious after-effects. Examples are surgery under general anesthesia, mild head injury, long-term (but not actual) use of psychotropic drugs, or a substantial intake of alcohol (Houx et al., 1991b). Subjects with one or more BLE in their history performed consistently worse than other subjects did on tasks of memory storage and retrieval, sensorimotor speed, and information processing capacity. The differences in performance between BLE and non-BLE groups increased with age, suggesting that the impact of BLE is more pronounced in older individuals.

However, as the study population could have represented an elite group of older subjects, and in order to evaluate the contribution of specific BLE categories to the explained variance in performance, the Maastricht Aging Study (MAAS; see chapter 3 and Jolles et al., 1995) of the same research group set out to replicate the earlier findings and to explore them in greater detail in a larger population. In short, this ongoing cross-sequential study into determinants of

cognitive aging recruited subjects from a computerized patient register of collaborating general practices (Metsemakers, Höppener, Knottnerus, Kocken & Limonard, 1992). Four independent and virtually identical panel studies were performed with healthy subjects aged between 23 and 82, stratified for age, sex, and level of general ability. Medical exclusion criteria were defined as those active or inactive medical problems documented by the general practitioner that could interfere with actual cognitive function, such as cerebrovascular disease and other chronic neurological or psychiatric disorders. Preliminary results from the first panel study with 469 subjects on a selection of tests that were used also in the MMS, failed to corroborate the earlier findings with respect to BLE. Only minor effects of BLE on the immediate recall of words and on simple and incompatible movement time in a choice reaction time paradigm were observed, with no significant age by BLE interaction (Houx, van Boxtel & Jolles, 1995). Cohort differences in terms of health status or educational background (resulting from a different inclusion procedure) could be partly responsible for this discrepancy. This underscores the necessity for longitudinal follow-up of these studies to enable definite conclusions on the importance of BLE for cognitive aging.

Brain reserve capacity in normal and pathological cognitive aging

The implicit assumption in research on BLE and cognitive aging is that the impact of these health-related factors differs between individuals and will depend on the individual's vulnerability to specific challenges, which in turn tends to increase with age. There are few longitudinal studies which address this issue. With respect to psychotropic drug use, there is some empirical evidence that long-term users of benzodiazepines perform worse on memory and speeded performance tasks than benzodiazepine-free anxious patients and normal controls, who were matched for age, sex and education (Gorenstein, Bernik, Pompéia & Marcourakis, 1995). The between-group differences in this study were present at three weeks and ten months after cessation of benzodiazepine use and could not be explained by differences in anxiety or depressive symptomatology. A typical study that reported on long-term effects of brain trauma compared World War II veterans 30 years after they had sustained a penetrating head injury with controls who suffered from peripheral nerve injury, matched for age, education, and (premorbid) intelligence level (Corkin, Rosen, Sullivan & Clegg, 1989). The head injury group showed an accelerated decline on several cognitive tests (including arithmetic, vocabulary, and figure-ground discrimination) and this decline was greater in older patients. The authors suggested that the cumulative loss of 'redundancy in the CNS' may precipitate clinical cognitive defects.

The conclusion of Corkin et al. fully supports the concept of *brain reserve capacity* (BRC) – a hypothetical construct that was proposed to denote the amount of functional brain tissue (Mortimer, 1988) – which was recently redefined from a neuropsychological perspective as a theoretical model for cognitive defects after brain injury (Satz, 1993). However, BRC may also provide a helpful theoretical framework to understand the impact of other types of morbidity on cognition. It can be understood as the maximal cognitive energy that is available for central information processing, in which case a parallel can be drawn with the *resource* concept of Salthouse which also implies a central processing capacity (Salthouse, 1985). The

model of Satz presumes that protective factors or vulnerability to negative factors can extend or reduce the BRC. Satz cites evidence from autopsy and brain imaging studies that factors such as brain size, cortical surface area, and metabolic and neuronal efficiency are potential neurobiological correlates of BRC. Age reduces BRC, because aging affects virtually all these factors, which has a direct consequence for central nervous system efficiency. Furthermore, indirect measures, such as psychometric intelligence or educational level, can be regarded as proxies of BRC, as individuals at the lower end of the distribution are more at risk for the development of cognitive defects (Huppert, 1991; for a review, see Stern, Alexander, Prohovnik & Mayeux, 1991). Accumulation of brain-related morbidity can therefore result in a reduction in BRC that will become clinically apparent as dementia when a critical value or threshold is reached (Mortimer, 1994; Figure 2.2).

Figure 2.2. Hypothesized chain of events in age-related cognitive decline, with brain reserve capacity as the core construct (adapted from Satz, 1993).

The dementia syndrome is characterized by a progressive impairment of higher cortical functions, in particular memory, and eventually by loss of independence (McKhann et al., 1984). Alzheimer dementia (AD) causes over 70% of all dementia's, followed by dementia of a primary vascular origin and several other, more rare forms with a distinct clinical picture, like Pick's or Creutzfeldt-Jacob disease (Ott et al., 1995; Selkoe, 1992). AD afflicts 10% of the population aged 80 years, after which the prevalence rises steeply to 27% in individuals of 85 years and older (Ott et al., 1995). There may be a genetic (autosomal dominant) predisposition, and a history of hypothyroidism, brain trauma, depression, or a family history of parkinsonism or Down's syndrome all have been associated with an increased risk for AD (Breteler, Claus, van Duijn, Launer & Hofman, 1992; Kokmen, 1991).

Many neurobiological and cognitive-behavioral changes that are observed in normal aging are also found in dementia (Huppert & Brayne, 1994). In fact, dementia in an early stage is often difficult to distinguish from normal cognitive aging. This notion gave way in the past 30 years to multiple diagnostic labels for this 'borderland' between normal and pathological cognitive aging, such as *benign or malignant senescent forgetfulness* (Kral, 1962), *age-associated memory impairment* (AAMI; Crook et al., 1986), *aging-associated cognitive decline* (AACD; Levy, 1994), or *cognitive impairment no dementia* (CIND; Writing Committee Lancet Conference, 1996). However, the fact that no single marker for AD has yet been identified and because the population distributions of variables associated with this disease (e.g. neuritic plaques and neurofibrillary tangle formation) are essentially continuous made some researchers suggest that AD is the end stage of normal brain aging: any person who lives long enough will eventually develop dementia ('continuity hypothesis', Brayne & Calloway, 1988; Huppert & Brayne, 1994). It has been known for some time that degeneration of functionally related systems in the CNS may be selective and at different rates with increasing age, a process referred to as abiotrophy (Gowers, 1902). It has been hypothesized that in AD neuronal attrition in the medial basal forebrain remains subclinical for decades as the result of an impressive brain plasticity, on the analogy of the selective and progressive decay of dopaminergic neurons in the substantia nigra leading to Parkinson's disease (Calne et al., 1986). Thus, only when compensatory mechanisms fail – like neuronal sprouting or increase of transmitter substances in presynaptic neuron – and a critical *threshold* is reached, the functional decline becomes symptomatic (Satz, 1993). Extrapolation from prevalence figures of dementia would suggest in support of the continuity hypothesis that virtually everyone is afflicted by dementia if one lives to be a hundred (Huppert & Brayne, 1994).

Conclusions

The existence of age-sensitivity in BRC is analogous to the generally observed reduction in functional reserve capacity of other organ systems with age, like the heart (cardiac output) or the kidneys (glomerular filtration rate; Yates, 1993). The comprehensive model of BRC is attractive because it provides the conceptual link between normal and pathological cognitive aging, as many observations from neurobiological, clinical and behavioral studies on the aging of the brain fit elegantly within this framework (Satz, 1993). Research effort can be defined in terms of factors that may augment or reduce BRC in order to predict at what point in time an individual's threshold for pathologic cognitive function is reached. It was demonstrated that factors which are related to brain health (like BLE, or specific types of physical morbidity) potentially have a mediating role in cognitive decline with age. It remains unclear however to what extent a reduction of intellectual reserve is mediated directly by clinically observable morbidity, or if to some extent age-related disease and age-related cognitive decline are both linked to the same causative factor. The progressive change in structure and function of the systemic vasculature during adulthood paves the way for many chronic vascular diseases and may also have implications for cerebral functioning (Mortimer, 1994). In the next section the evidence is explored for a relationship between risk factors for vascular disease and impairment of intellectual function, in normal and pathological cognitive aging.

II – VASCULAR RISK FACTORS AND COGNITIVE AGING

Whereas the evidence for the continuity hypothesis in AD is as yet inconclusive, a stronger case can be made in this respect for dementia of vascular origin (Skoog, 1994; 1996). The cerebral vascular system changes slowly but progressively with age, and these changes, such as atherosclerosis of large and small vessels, hyperplasia of vascular smooth muscle, multiple microinfarctions, and altered cerebral blood flow, may lead to brain ischemia (Figure 2.3).

Figure 2.3. Proposed mechanism of cognitive decline as a function of exposure to vascular risk factors. (Adapted from Starr & Whalley, 1992; Swan, Carimelli & LaRue, 1996).

Regional cerebral blood flow studies (rCBF) and brain imaging studies using positron emission tomography (PET) demonstrate only small reductions in cerebral blood flow or brain metabolism in healthy older adults. However, the presence of clinical markers of vascular disease (e.g. hypertension, diabetes, or heart disease) has been associated in older adults with larger reductions in rCBF over a 3.5-year period (Meyer & Shaw, 1984). Vascular risk factors were found to be correlated with white matter abnormalities on magnetic resonance imaging (MRI; Breteler et al., 1994a), and white matter abnormalities were shown to be accompanied by a reduced speed of mental processing (Junqué et al., 1990; Schmidt et al., 1993). Comparable observations were made with electrophysiological methods that measure brain activity, such as electroencephalography (EEG) or event-related potentials (P300): age-related changes in healthy individuals are minor, but appear to be augmented by vascular risk factors or vascular disease and are reflected by slowing of the dominant alpha rhythm in EEG or increased P300 latency, which may be indicative of a reduced efficiency in neuronal processing (LaRue, 1992).

Given the strong association between cerebrovascular disease and neurobehavioral deficits (Bornstein & Kelly, 1991), it seems a logical step to study in greater depth the relevance of risk factors associated with vascular disease for age-related cognitive decline (Nolan & Blass, 1992). The relevance of indicators of vascular disease as predictors of cognitive dysfunction was illustrated recently by Breteler et al. (Breteler, Claus, Grobbee & Hofman, 1994b). They found in a large population study involving 4,971 subjects of 55 years and older negative associations between signs of peripheral artery disease (ankle/brachial blood pressure ratio and presence of atherosclerotic plaques in the internal carotid arteries) and an index of global cognitive function (Mini-Mental State Examination, or MMSE; Folstein, Folstein & McHugh,

1975). Clinically established primary risk factors such as hypercholesterolemia, hypertension, diabetes mellitus and cigarette smoking, alone or in combination, are related to vascular degeneration and thereby possibly also in producing mental dysfunctions (Table 2.3; Clowes, 1989; Gorelick, 1995; Skoog, 1994). The evidence for a role of each of these factors in cognitive decline will now be briefly reviewed. Although it may be argued that clinical signs of cardiovascular or cerebrovascular disease are risk factors in their own right (Gorelick, 1995), they also represent the outcome of pathological changes due to actual etiological factors. They can therefore at best be regarded as 'secondary' risk factors in that the chance of worsening of vascular disease is increased when the first clinical signs are evident. Therefore, the following discussion is restricted only to 'primary' risk factors.

Table 2.3. Risk factors for vascular disease: determinants of cognitive impairment?

Genetic factors	Obesity
Thrombogenic factors	Physical inactivity
Hypertension	History of smoking
Diabetes mellitus	Alcohol consumption
Hyperlipidemia	

Genetic factors – Late-onset AD has recently been associated with presence of the apolipoprotein-E4 (apo-E4) allele on chromosome 19 (Poirier et al., 1993; Saunders et al., 1993). Apo-E4 plays a role in the redistribution of lipids after deafferentation and neurodegeneration in the brain and is related to plaque and tangle formation and amyloid deposition in cerebral blood vessels. In 25 percent of the population one or both alleles on chromosome 19 are of the E4 subtype. The mean age of onset of AD decreases from 84 to 68 in direct proportion to the number of apo-E4 alleles (none, one, or two; Corder et al., 1993). Virtually all apo-E4 homozygotes in familial cases will develop AD by age 80 (Saunders et al., 1993). In a recent study with elderly men aged 70-89, the prevalence of cognitive impairment (MMSE score ≤ 25) was higher in apo-E4 carriers and the decline in MMSE score over a three year period was proportional to the number of apo-E4 alleles present (Feskens et al., 1994).

Variations of the apo-E genotype are linked to hyperlipidemia (Walden & Hegele, 1994) and to stroke (Couderc et al., 1993). Other genetic factors may be involved in the potentiation of specific vascular risk factor levels (e.g. hypertension, diabetes, fat metabolism, and thrombogenic factors).

Thrombogenic factors – The role of specific thrombogenic factors (in particular fibrinogen, De la Serna, 1994) in the etiology of cardiovascular disease is well established. Adequate anticoagulant therapy is effective in ischemic heart disease but also in the secondary prevention of cerebrovascular disorders such as transient ischemic attack (TIA) or stroke (Gorelick, 1995). In the Rotterdam study involving a group of 111 subjects (age 65-84 years) evidence was found for a relation between thrombogenic factors (VIIc, VIIIc, and fibrinogen) and white matter lesions on MRI on the one hand, and between white matter lesions and composite cognitive test score (CAMCOG) on the other, after control for age and education (Breteler et al., 1994a).

Hypertension – Hypertension is the most important risk factor for brain hemorrhage or infarction (population-attributable risk of 49 percent, Gorelick, 1995) and vascular dementia (Skoog, 1994), the respective risks being directly proportional to the mean blood pressure. Evidence suggests that subjects with essential hypertension have reduced cerebral blood flow (Rodriguez et al., 1987) and show more white matter lesions on MRI (Breteler et al., 1994a; Kawamoto et al., 1991; Van Swieten et al., 1991). In one study these lesions were accompanied by reduced performance on the MMSE and on several complex cognitive tasks compared to that of age- and sex-matched hypertensive controls with no lesions, and compared to normotensive subjects (Van Swieten et al., 1991). These findings were corroborated in a more recent study with 150 healthy elderly subjects with and without white matter hyperintensities on MRI (Schmidt et al., 1993). The same authors have demonstrated in a case-control study with hypertensives that the lower level of attentional and visuopractical skills in hypertensives was associated with more white matter hyperintensities and ventricular enlargement on MRI (Schmidt et al., 1995).

The general trend in a large corpus of case-control studies indicates that hypertension is associated with lower scores on tests of attention, mental flexibility, learning and memory, and abstract reasoning while scores on tests of other cognitive domains remain relatively unaffected (Waldstein, 1995). Results from the Framingham Heart Study have shown that in particular chronic exposure to elevated blood pressure predisposes stroke-free subjects to neuropsychological deficits (Elias, Wolf, D'Agostino, Cobb & White, 1993; Elias, D'Agostino, Elias & Wolf, 1995; Farmer et al., 1990). On a group level, the effects of hypertension seem subtle and deficits are never in the clinical range indicating brain injury. However, one cross-sectional study with 301 subjects aged 20 to 72 years produced some evidence that blood pressure in the normal to borderline range may even be predictive for a performance reduction that would otherwise be ascribed to primary aging (Elias, Robbins, Schultz & Pierce, 1990b).

It is noteworthy that performance on neuropsychological tests that are sensitive to the effects of hypertension for a large part relies on brain areas that are most afflicted by hypoperfusion and hypometabolism in hypertensive subjects (Waldstein, Manuck, Ryan & Muldoon, 1991). In fact, these deficits are commonly attributed to changes in brain perfusion and metabolism that are secondary to arteriosclerotic changes in the large and small cerebral blood vessels, or to multiple microinfarctions caused by microemboli that are released from more distal arteriosclerotic sources (e.g. the atrial wall or carotid arteries; Starr & Whalley, 1992). Individual differences in physiological reactions to stress have often been implicated in atherosclerotic diseases. Interestingly, it has recently been suggested that short-term hypertensive episodes caused by psychological stress may produce a transient increase in blood levels of factors that are associated with atherogenesis and thrombosis. Healthy young subjects who were exposed to a stressful and complex task (Stroop Color-Word test) showed increases in blood lipids, hemostatic factors, and blood viscosity, due to hemoconcentration (Muldoon et al., 1992; Muldoon et al., 1995a). However, other mechanisms may be involved in the etiology of hypertension related cognitive decline. For example, subjects with a parental history of hypertension, but no actual hypertension, have been shown to perform worse on memory search tasks than control subjects with no such history (Pierce & Elias, 1993). Some

studies indicate that specific conditions in association with hypertension can be used to identify subgroups with a higher risk for cognitive deficits, for instance hyperinsulinemia (Kuusisto et al., 1993) or plasma renin activity (Light, 1975).

Longitudinal data have demonstrated that elderly hypertensive subjects, in contrast to normotensive age-peers, show a gradual intellectual decline over a 10-year period (Wilkie & Eisdorfer, 1971). It was observed in this study that after the age of 60 the negative effect of high blood pressure on cognitive function increased. In young adult and middle-aged subjects the performance scores tended to be lower in young hypertensive subjects than in normotensive control subjects, but the differences between these categories were less striking in the middle-aged subjects (Elias et al., 1995). Taken together, these data suggest a U-shaped distribution of the correlation between hypertension and test performance across the life-span, but further evidence is needed to substantiate this (Waldstein, 1995).

In summary, chronically elevated blood pressure can promote structural brain damage which can ultimately be picked up by neuropsychological testing, but further pathophysiological and clinical evidence is needed to determine age- or risk factor-related high risk subgroups. The availability of techniques to measure blood pressure repeatedly under daily living conditions may enhance our knowledge of which aspects of blood pressure dynamics are relevant for cognition (Pickering, 1993). Indeed, studies with ambulant blood pressure monitoring have suggested that the classical 'casual' measurement in the doctors office do not always yield blood pressure values which are measured under daily living conditions (Pickering, 1993). For this discussion it may therefore be important first to address the methodological issue of how blood pressure measurement should be standardized in population-based studies to yield reliable estimates of habitual blood pressure (see chapter 6).

Diabetes – Diabetes mellitus is characterized by an inadequate control of blood glucose level, as the result of insufficient production of insulin, or a relative insensitivity of body tissues to insulin. The resulting hyperglycemia causes structural damage to organs, including the brain, as the result of metabolic disturbances, arteriosclerosis, and neovascularization. Diabetic patients have an increased risk for (ischemic) stroke that can be explained in part by the increased prevalence of cardiovascular disease in these individuals. Cerebral disorders associated with diabetes have been demonstrated at a neurochemical, electrophysiological, structural, and cognitive level (Biessels, Kappelle, Bravenboer, Erkelens & Gispen, 1994). Alterations in cerebral blood supply and metabolic changes may play a role, but the exact pathophysiology is as yet uncertain. Recurrent episodes of hypoglycemia and poor metabolic control may produce transient decreases in mental efficiency (Draeos et al., 1995) but are also related to permanent performance decrements, in particular when there is evidence of polyneuropathy (Ryan, Williams, Finegold & Orchard, 1993; Sachon et al., 1992). Diabetic subjects generally perform worse on tasks of learning and memory, psychomotor speed and problem solving than healthy control subjects, but the affected cognitive domains and the extent of performance deficit vary widely across studies. A strong association has been found between age of onset and general intelligence (Biessels et al., 1994) but elderly late-onset diabetic patients have repeatedly performed worse than control subjects on verbal and complex cognitive tasks (Reaven, Thompson, Nahum & Haskins, 1990; U'ren et al., 1990; Worrall, Moulton & Briffett, 1993). However, these deficiencies are usually mild. The evidence to date

suggests that therapeutic interventions aimed at blood glucose regulation within narrow limits will prevent most, but not all diabetic damage to the central nervous system (Biessels et al., 1994).

Hyperlipidemia – Cholesterol is a major constituent of cell membranes, hormones, bile salts, and vitamins and is largely of endogenous origin. More than 70% is distributed in low-density lipoproteins (LDL), and in this form cholesterol has been associated with ischemic heart disease. Smaller fractions are transported from peripheral tissues back to the liver as high-density lipoprotein (HDL): a low HDL-cholesterol level (in particular the HDL₂ subfraction) is also an independent risk factor for cardiovascular disease. Interestingly, as mentioned above, apo-E lipoprotein may differentially affect the total cholesterol level in the blood and thereby the vascular risk profile; apo-E2 lowers cholesterol while apo-E4 has the opposite effect (Walden & Hegele, 1994). There is some evidence that elevated cholesterol levels and low apo-E are more prevalent in older subjects with cerebrovascular disease (Couderc et al., 1993). A lower HDL-cholesterol level, in association with hypertension, was found in a group of older subjects with evidence of (neurologically asymptomatic) multiple lacunar infarctions on MRI (Kawamoto et al., 1991). These results were not replicated in the earlier mentioned Rotterdam study (Breteler et al., 1994a), although in this study total cholesterol was related to white matter lesions in the younger half of the study group (65-74 years).

Several studies have directly addressed the relation between blood lipids and cognitive function. Dementia has been described in relation to hyperlipidemia; the symptoms of dementia improved after pharmacological reduction of the blood lipid level (Heilman & Fisher, 1974). In an early study with 156 healthy men who were treated with cholesterol lowering agents for 12 months, subjects of 40 years and older who responded to treatment showed an improved performance on a battery of neurocognitive tests, while older non-responders and younger subjects showed no effect (Reitan & Shipley, 1963). Reversal of a global cognitive deficit in elderly patients with cerebrovascular disease and hypertriglyceridemia was possible with an antilipemic agent (gemfibrozil; Rogers, Meyer, Shaw & al., 1985). These changes were associated with an improvement in grey matter perfusion. Better performance on mental status testing was related to higher HDL-cholesterol levels in a geriatric population (mean age 87 years; Postiglione et al., 1989). In a study of 249 healthy elderly subjects (mean age 70.8 years), hypercholesterolemia increased the chance of a subject being in the group with poor memory performance by a factor of three, while performance on tasks for other domains (verbal functions, visuospatial abilities, attention) remained unaffected (Desmond, Tatemichi, Paik & Stern, 1993). However, conflicting evidence came from two other studies. An aging twin study (44 pairs, mean age 57 years) where discordance in performance changes on a complex task over a 5-year period (decline / no decline in digit-symbol substitution) was related to total cholesterol level: in decliners lower cholesterol levels were found than in the paired non-decliners (Swan, LaRue, Carmelli, Reed & Fabsitz, 1992). In a recent study of 89 nuns, aged 77-99 years, associations between a low total cholesterol level and mild cognitive impairment were found and a substantial decline of cognitive test performance over a 1-2 year period in participants with total cholesterol levels below the median at baseline measurement (Snowdon, Belcher, Tully & Greiner, 1996). The

results of the last two studies therefore make a straightforward role of blood lipids in cognitive decline less likely.

Obesity – Overweight is generally associated with an unhealthy life style and an unfavorable vascular risk profile. Obese individuals are less physically active, have lower HDL-cholesterol and higher total cholesterol levels, and are more often afflicted by diabetes or hypertension (Berns, 1995). A concentration of bodily fat in the abdominal region (measured in the waist-to-hip ratio) has proven to be an independent risk factor of cardiovascular disease (Désprés et al., 1990). In the above-mentioned Rotterdam study obesity was unrelated to white matter lesions in 111 subjects between 65 and 74 years of age (Breteler et al., 1994a). Studies on body composition in relation to cognitive function are scarce and inconclusive (see also Nolan & Blass, 1992). In a prospective study in 2,584 largely hypertensive individuals aged 65-74 years no association was found between body mass index and decline in performance on a cognitive test (Paired Associate Learning) within a 54 month period (Prince, Lewis, Bird, Blizard & Mann, 1996).

Physical inactivity – Physical activity during work or leisure time can promote physiological fitness and thereby increase general health (Bouchard, Shepard, Stephens, Sutton & McPherson, 1990). In contrast to body weight, physical activity attenuates the vascular risk profile by reducing obesity and insulin-insensitivity (in late-onset diabetes) and by improving the lipoprotein profile (LDL reduction and HDL increase), thereby slowing the process of atherosclerosis (Wood & Stefanick, 1990). Other factors related to activity may further improve the vascular risk profile. For example, physical activity is often linked to healthy life styles like a whole-food diet, non-smoking, and alcohol abstinence. Subjects with essential hypertension can lower their blood pressure up to 10% with endurance training (Hagberg, 1990). Regular aerobic training protects against cardiovascular diseases but no direct protective link has been demonstrated with cerebrovascular pathology. However, in a 4-year prospective cohort study of retired elderly subjects in the age of 62-70 years, the inactive group showed a gradual decline in regional cerebral blood flow and overall cognitive performance, while retirees who engaged in regular sporting activities maintained both cerebral perfusion and cognitive performance measures at approximately their baseline level (Rogers, Meyer & Mortel, 1990). It has been suggested that neuromuscular activity may alter cerebral circulation (*oxygen hypothesis*) or may directly enhance the efficiency of higher brain centers (*neurotrophic stimulation hypothesis*, Spirduso, 1980; Stones & Kozma, 1988). Ample support for either view can be found in the literature (for a review, Chodzko-Zajko & Moore, 1994).

Studies that compared fit and unfit elderly subjects generally report between-group differences in complex and attention demanding task paradigms but findings are less consistent on more simple, automatic tasks (Chodzko-Zajko, Schuler, Solomon, Heintz & Ellis, 1992). However, results of these studies can be confounded by differences in background characteristics between fit and unfit individuals, such as health habits (Spirduso, 1980) and psychological variables (anxiety or depression, Brown, 1990). Short-term exercise (up to four months) does not seem to improve cognitive processes, although the few studies on exercise and cognition are often flawed by a low statistical power (see Buchner, Beresford, Larson, LaCroix & Wagner, 1992, for a discussion). Long-term randomized intervention studies have demonstrated

increased differences in simple and choice reaction time between groups of sedentary and aerobic trained women of 57-85 years over a 3-year period in favor of the active group (Rikli & Edwards, 1991) and improvement on several simple and complex tasks after a 4-month aerobic training program in previously sedentary older subjects aged 55-70 years (Dustman et al., 1984), while others reported no effect of aerobic intervention (Blumenthal et al., 1991; Hill, 1989; Madden, Blumenthal, Allen & Emery, 1989). In summary, there may be some protective effect of physical activity on age-related cognitive processes if the exercise is strenuous enough to improve and maintain aerobic fitness at a high level for a prolonged period of time. This effect is probably mediated through several different pathways.

Smoking – A typical reason given by smokers to explain their habit is that smoking improves concentration and mental efficiency. This claim is indeed partly confirmed in empirical research. Acute administration of nicotine has been shown to have a small but significant effect on attention, memory, and sensorimotor function, or reverse experimentally induced cognitive decrements (with the anticholinergic compound scopolamine), while cessation of smoking may induce cognitive withdrawal effects (Sherwood, 1993). However, smoking produces carbon monoxide which has a high affinity for hemoglobin – the oxygen transporting protein in red blood cells. The resulting stable carboxyhemoglobin complex causes a prolonged state of mild hypoxemia in regular smokers which, at least theoretically, could impair performance. Chronic smoking produces a reduction in regional cerebral blood flow (Rogers, Meyer, Shaw & al., 1983), which could bring about intellectual changes in elderly subjects.

Interestingly, the mild agonist effect of nicotine on the cholinergic system has been suggested as an explanation for the protective effect of smoking on the development of AD (which is characterized by a central acetylcholine deficiency), by increasing the number of nicotinic receptors (Van Duijn & Hofman, 1991). However, the epidemiologic evidence for a protective effect of smoking in AD has not been confirmed in other studies (Fratiglioni, 1993) and may have been the result of confounding variables such as occupational background (Letenneur et al., 1994), or of selection bias when patients with mixed AD or vascular dementia were excluded (Mortimer, 1988).

The vascular risk profile is negatively affected by smoking in that smoking promotes hypertension and a reduction in blood levels of the protective HDL-cholesterol (Reitsma, 1995). Stroke risk increases with the number of cigarettes smoked daily (Gorelick, 1995), and there may be a role of smoking in the etiology of vascular dementia (Skoog, 1994). In a small prospective study of elderly patients with vascular dementia, cessation of smoking was related to improved cognitive scores after 3 to 48 months (Meyer, Judd, Tawakina, Rogers & Mortel, 1986). Normal aging studies have not yielded consistent evidence in favor of or against a mediating effect of smoking on cognitive function. Older smokers performed worse than non-smokers on speeded performance tasks, but not on a wide range of other measures (Hill, 1989). Current smoking habits were unrelated to changes in cognitive performance scores in a group of 1,201 individuals (aged 65 and older) over a 3-year period (Hebert et al., 1993), suggesting that smoking behavior does not accelerate normal cognitive aging.

Alcohol consumption – Epidemiological evidence reveals that 4.7% of all strokes are primarily the result of heavy drinking (Gorelick, 1995). No clear relation has been found between chronic alcohol intake and vascular dementia (Skoog, 1994) or AD (Graves et al., 1991). Alcohol exerts a direct toxic effect on the brain and other vital organs, leading to irreversible tissue damage, and may negatively affect cerebral blood flow (Rogers et al., 1985). In chronic alcohol abuse, the blood urea nitrogen may rise as the result of liver damage to a level that interferes with adequate brain function (Tarter, Arria & Van Thiel, 1991). In addition, chronic users may have a lower intake of vital nutrients such as B-vitamins (e.g. thiamine). This may result in specific neurocognitive disorders such as dementia or Wernicke-Korsakow encephalopathy, which is characterized by profound memory dysfunctions which is primarily caused by hippocampal damage (Butterworth, 1995).

The hippocampus seems particularly vulnerable to neurotoxic insults caused by alcohol or hypoxia (Stoltenburg-Didinger, 1994). Clinical studies report that 50-70% of chronic alcohol users show mild to moderate cognitive impairment, in particular in visuo-spatial abilities, abstract reasoning, learning, and memory (Molina et al., 1994). Results from normal population studies are more equivocal. In a 3-year longitudinal study of 1,201 subjects aged 65 and older, low-to-moderate alcohol intake did not predict change in memory function (Hebert et al., 1993). Mild to heavy alcohol intake was unrelated to different aspects of cognitive function in 249 stroke-free subjects (Desmond et al., 1993). However, in the Framingham study moderate alcohol intake was weakly associated with better overall performance in a stroke-free cohort of 1,702 subjects aged between 55-88 years (Elias et al., 1993). The long-term effects of chronic alcohol use on cognitive function seem therefore not to be large on a population level, but may be difficult to detect due to a curve-linear relation between intake and performance.

Conclusions

A combination of vascular risk factors will enhance the risk of morbidity more than would be expected on the basis of individual risk factors alone. Moreover, the prevalence of any combination of such risk factors rises markedly with age (and lower educational level), thereby putting elderly individuals in a particularly vulnerable position (Reitsma, 1995).

It has been shown that a broad range of health-related factors has been linked to a reduction in cognitive abilities. As a result, it has been recognized that cognitive aging studies should include adequate descriptions of the health status of the participants (Christensen, Moye, Armson & Kern, 1992; Houx et al., 1991b). However, rigorous health screening aimed at the identification of physical disturbances that could possibly be related to brain function will restrict the study population to the successful aging category and will inevitably result in quite unrepresentative older age groups. To gain insight into the predictors of normal aging, it is therefore necessary to include a representative cross-section of different birth cohorts that is described in terms of prevalent morbidity, but that is also screened for potentially relevant precursors of disease. Owing to the complexity of risk factor interactions, the most attractive way to elucidate vascular mechanisms in age-related cognitive decline would be to study prospectively as many different independent vascular risk factors as possible in large population samples, in combination with thorough medical and cognitive screening. It can be

readily conceived that such an approach requires a great amount of human and financial resources and raises many ethical issues. However, the evidence for a role of vascular risk factors in age-related cognitive dysfunctions is suggestive enough to justify further research on how these factors can differentiate (in the long run) between successful, normal, and pathological cognitive aging.

REFERENCES

- Barbee, J. G. (1993). Memory, benzodiazepines, and anxiety: Integration of theoretical and clinical perspectives. *Journal of Clinical Psychiatry*, 54(Suppl.), 86-97.
- Beckwith, B. E., & Tucker, D. M. (1988). Thyroid disorders. In R. E. Tarter, D. H. van Thiel, & K. L. Edwards (Eds.), *Medical Neuropsychology: The Impact of Disease on Behavior*, (pp. 197-218). New York: Plenum Press.
- Berg, R. A. (1988). Cancer. In R. E. Tarter, D. H. van Thiel, & K. L. Edwards (Eds.), *Medical Neuropsychology: The Impact of Disease on Behavior*, (pp. 265-290). New York: Plenum Press.
- Berns, M. P. H. (1995). *Over gewicht en hart- en vaatziekten [On body weight and cardiovascular disease]*. Den Haag: Nederlandse Hartstichting.
- Biessels, G. J., Kappelle, A. C., Bravenboer, B., Erkelens, D. W., & Gispen, W. H. (1994). Cerebral function in diabetes mellitus. *Diabetologia*, 37, 643-650.
- Bilder, R. M., Turkel, E., Lipschutz Broch, L., & Lieberman, J. A. (1992). Antipsychotic medication effects on neuropsychological functions. *Psychopharmacology Bulletin*, 28, 353-366.
- Birren, J. E., & Birren, J. A. (1990). The concepts, models and history of the psychology of aging. In J. E. Birren & K. W. Schaie (Eds.), *Handbook of the psychology of aging*, (3 ed., pp. 3-20). San Diego: Academic Press.
- Birren, J. E., & Schaie, K. W. E. (1990). *Handbook of the psychology of aging*, (3 ed.). San Diego: Academic Press.
- Blumenthal, J. A., Emery, C. F., Madden, D. J., Schniebol, S., Walsh-Riddle, M., George, L. K., McKee, D. C., Higginbotham, M. B., Cobb, F. R., & Coleman, R. E. (1991). Long-term effects of exercise on psychological functioning in older men and women. *Journal of Gerontology*, 46, P352-361.
- Bornstein, R. A., & Kelly, M. P. (1991). Risk factors for stroke and neuropsychological performance. In R. A. Bornstein & G. G. Brown (Eds.), *Neurobehavioural aspects of cerebrovascular disease*, (pp. 182-201). New York: Oxford University Press.
- Botwinick, J. (1981). Neuropsychology of aging. In S. B. Filskov (Ed.), *Handbook of Clinical Neuropsychology*, New York: John Wiley & Sons.
- Bouchard, C., Shepard, R. J., Stephens, T., Sutton, J. R., & McPherson, B. D. (1990). Exercise, fitness and health: The consensus statement. In C. Bouchard, R. J. Shepard, T. Stephens, J. R. Sutton, & B. D. McPherson (Eds.), *Exercise, fitness and health: A consensus of current knowledge*, (pp. 3-28). Champaign, Ill: Human Kinetics Books.
- Bowen, J. D., & Larson, E. B. (1993). Drug-induced cognitive impairment: Defining the problem and finding solutions. *Drugs and Aging*, 3, 349-357.
- Brayne, C., & Calloway, P. (1988). Normal ageing, impaired cognitive function, and senile dementia of the Alzheimer's type: A continuum? *Lancet*, 1(8597), 1265-1267.
- Breteler, M. B. B., van Swieten, J. C., Bots, M. L., Grobbee, D. E., Claus, J. J., van den Hout, J. H. W., van Harskamp, F., Tanghe, H. L. J., de Jong, P. T. V. M., van Gijn, J., & Hofman, A. (1994a). Cerebral white matter lesions, vascular risk factors, and cognitive function in a population-based study: The Rotterdam Study. *Neurology*, 44, 1246-1252.
- Breteler, M. M. B., Claus, J. J., Grobbee, D. E., & Hofman, A. (1994b). Cardiovascular disease and distribution of cognitive function in elderly people: The Rotterdam study. *British Medical Journal*, 308, 1604-1608.
- Breteler, M. M. B., Claus, J. J., van Duijn, C. M., Launer, L. J., & Hofman, A. (1992). Epidemiology of Alzheimer's disease. *Epidemiologic Reviews*, 14, 59-82.
- Bromley, D. B. (1990). *Behavioural Gerontology: Central issues in the psychology of ageing*. Chichester (UK): John Wiley.
- Brown, D. R. (1990). Exercise, fitness, and mental health. In C. Bouchard, R. J. Shepard, T. Stephens, J. R. Sutton, & B. D. McPherson (Eds.), *Exercise, fitness and health: A consensus of current knowledge*, (pp. 607-626). Champaign, Ill.: Human Kinetics Books.
- Buchner, D. M., Beresford, S. A. A., Larson, E. B., LaCroix, A. Z., & Wagner, E. H. (1992). Effects of physical activity on health status in older adults. II: Intervention studies. *Annual Review of Public Health*, 13, 469-488.
- Butterworth, R. F. (1995). Pathophysiology of alcoholic brain damage: synergistic effects of ethanol, thiamine deficiency and alcoholic liver disease. *Metabolic Brain Diseases*, 10, 1-8.

- Calne, D. B., Eisen, A., McGeer, E., & Spencer, P. (1986). Alzheimer's disease, Parkinson's disease, and mononuclear disease: Abiotropic interaction between aging and environment. *Lancet*, 2(8515), 1067-1070.
- Carney, M. W. (1990). Vitamin deficiency and mental symptoms. *British Journal of Psychiatry*, 156, 878-882.
- Chodzko-Zajko, W. J. (1991). Physical fitness, cognitive performance, and aging. *Medicine and Science in Sports and Exercise*, 23, 868-872.
- Chodzko-Zajko, W. J., & Moore, K. A. (1994). Physical fitness and cognitive functioning in aging. In J. O. Holloszy (Ed.), *Exercise and sport sciences reviews*, (Vol. 22, pp. 195-220). Baltimore: Williams & Wilkins.
- Chodzko-Zajko, W. J., Schuler, P., Solomon, J., Heisl, B., & Ellis, N. R. (1992). The influence of physical fitness on automatic and effortful memory changes in aging. *International Journal of Aging and Human Development*, 35, 265-85.
- Christensen, K. J., Moye, J., Armonson, R. R., & Kern, T. M. (1992). Health screening and random recruitment for cognitive aging research. *Psychology and Aging*, 7, 204-208.
- Clowes, A. W. (1989). Theories of atherosclerosis. In R. A. White (Ed.), *Atherosclerosis and arteriosclerosis: Human pathology and experimental animal methods and models*, (pp. 4-15). Boca Raton, Fla.: CRC Press.
- Colsher, P. L., & Wallace, R. B. (1991). Epidemiologic considerations in studies of cognitive function in the elderly: Methodology and nondementing acquired dysfunction. *Epidemiologic Reviews*, 13, 1-27.
- Corder, E. H., Saunders, A. M., Strittmatter, W. J., Schmechel, D. E., Gaskell, P. C., Small, G. W., Roses, A. D., Haines, J. L., & Pericak-Vance, M. A. (1993). Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science*, 261, 921-923.
- Corkin, S., Rosen, T. J., Sullivan, E. V., & Clegg, R. A. (1989). Penetrating head injury in young adulthood exacerbates cognitive decline in later years. *Journal of Neuroscience*, 9, 3876-3883.
- Couderc, R., Mahieux, F., Bailleul, S., Fenelon, G., Mary, R., & Fermanian, J. (1993). Prevalence of apolipoprotein E phenotypes in ischemic cerebrovascular disease: A case-control study. *Stroke*, 24, 661-664.
- Crook, T., Bartus, R. T., Ferris, S. H., Whitehouse, P., Cohen, G. D., & Gershon, S. (1986). Age-associated memory impairment: Proposed diagnostic criteria and measures of clinical change - report of a National Institute of Mental Health Work Group. *Developmental Neuropsychology*, 2, 261-276.
- De la Serna, G. (1994). Fibrinogen: a new major risk factor for cardiovascular disease: A review of the literature. *Journal of Family Practice*, 39, 468-477.
- Deeg, D. J., Hofman, A., & van Zonneveld, R. J. (1990). The association between change in cognitive function and longevity in Dutch elderly. *American Journal of Epidemiology*, 132, 973-82.
- Deeg, D. J. H., Jonker, C., Launer, L. J., Schellevis, F. G., Smits, C. H. M., van Tilburg, T., Knipscheer, C. P. M., & van Tilburg, W. (1993). Change in autonomy and well-being: Background and preliminary proposal for the Longitudinal Aging Study Amsterdam. In D. J. H. Deeg, C. P. M. Knipscheer, & W. van Tilburg (Eds.), *Autonomy and well-being in the aging population: Concepts and design of the Longitudinal Aging Study Amsterdam*, (pp. 19-87). Bunnik: Netherlands Institute of Gerontology.
- Dekhuijzen, L. S., & de Lange, J. J. (1993). De rol van algehele of regionale anesthesie bij het ontstaan van cognitieve stoornissen bij oudere mensen. Literatuuroverzicht [The role of general or regional anesthesia in the etiology of cognitive disorders in elderly subjects. Literature review]. *Tijdschrift voor Gerontologie en Geriatrie*, 24, 193-199.
- Desmond, D. W., Tatemichi, T. K., Paik, M., & Stern, Y. (1993). Risk factors for cerebrovascular disease as correlates of cognitive function in a stroke-free cohort. *Archives of Neurology*, 50, 162-166.
- Despres, J. P., Moorjani, S., Lupien, P. J., Tremblay, A., Nadeau, A., & Bouchard, C. (1990). Regional distribution of body fat, plasma lipoproteins, and cardiovascular disease. *Arteriosclerosis*, 10, 497-511.
- Dodrill, C. B. (1992). Neuropsychological aspects of epilepsy. *Psychiatric Clinics of North America*, 15, 383-394.
- Draeos, M. T., Jacobson, A. M., Weinger, K., Widom, B., Ryan, C. M., Finkelstein, D. M., & Simonson, D. C. (1995). Cognitive function in patients with insulin-dependent diabetes mellitus during hyperglycemia and hypoglycemia. *American Journal of Medicine*, 98, 135-144.
- Dustman, R. E., Ruhling, R. O., Russell, E. M., Shearer, D. E., Bonekat, H. W., Shigeoka, J. W., Wood, J. S., & Bradford, D. C. (1984). Aerobic exercise training and improved neuropsychological function of older individuals. *Neurobiology of Aging*, 5, 35-42.
- Elias, M. F., Elias, J. W., & Elias, P. K. (1990a). Biological and health influences on behaviour. In J. E. Birren & K. W. Schaie (Eds.), *Handbook of the psychology of aging*, (3 ed., pp. 79-102). San Diego: Academic Press.
- Elias, M. F., Robbins, M. A., Schultz, J. N. R., & Pierce, T. W. (1990b). Is blood pressure an important variable in research on aging and neuropsychological test performance? *Journal of Gerontology*, 45, P128-135.
- Elias, M. F., Wolf, P. A., D'Agostino, R. B., Cobb, J., & White, L. R. (1993). Untreated blood pressure level is inversely related to cognitive functioning: The Framingham Study. *American Journal of Epidemiology*, 138, 353-364.
- Elias, P. K., D'Agostino, R. B., Elias, M. F., & Wolf, P. A. (1995). Blood pressure, hypertension, and age as risk factors for poor cognitive performance. *Experimental Aging Research*, 21, 393-417.

- Farmer, M. E., Kittner, S. J., Abbott, R. D., Wolz, M. M., Wolf, P. A., & White, L. R. (1990). Longitudinally measured blood pressure, antihypertensive medication use, and cognitive performance: The Framingham Study. *Journal of Clinical Epidemiology*, 43, 475-480.
- Feskens, E. J. M., Havekes, L. M., Kalmijn, S., de Knijff, P., Launer, L. J., & Kromhout, D. (1994). Apolipoprotein e4 allele and cognitive decline in elderly men. *British Medical Journal*, 309, 1202-1206.
- Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini Mental State". *Journal of Psychiatric Research*, 12, 189-198.
- Fozard, J. L., Metter, E. J., & Brant, L. J. (1990). Next steps describing aging and disease in longitudinal studies. *Journal of Gerontology*, 45, P116-127.
- Fozard, J. L., Metter, E. J., Brant, L. J., Pearson, J. D., & Baker, G. T. (1993). Goals for the next generation of longitudinal studies. In J. J. F. Schroots (Ed.), *Aging, health and competence*, (pp. 35-52). Amsterdam: Elsevier.
- Fratiglioni, L. (1993). Epidemiology of Alzheimer's disease: Issues of etiology and validity. *Acta Neurologica Scandinavica*, 87, 3-70.
- Fries, J. F. (1990). Medical perspectives upon successful aging. In P. B. Baltes & M. M. Baltes (Eds.), *Successful aging: Perspectives from the behavioral sciences*, (pp. 35-49). Cambridge: Cambridge University Press.
- Ganzevles, P. G. J., & Geus, B. W. J. (1991). Clinical neuropsychological assessment of patients chronically exposed to organic solvents. *Archives of Toxicology Suppl.*, 15, 54-57.
- Gorelick, P. B. (1995). Stroke prevention. *Archives of Neurology*, 52, 347-355.
- Gorenstein, C., Bernik, M. A., Pompéia, S., & Marcourakis, T. (1995). Impairment of performance associated with long-term use of benzodiazepines. *Journal of Psychopharmacology*, 9, 313-318.
- Gowers, W. R. (1902). A lecture on abiotropy. *Lancet*, i, 1003-1007.
- Graves, A. B., van Duijn, C. M., Chandra, V., Fratiglioni, L., Heyman, A., Jorm, A. F., Kokmen, E., Kondo, K., Mortimer, J. A., Rocca, W. A., Shalat, S. L., Soininen, H., & Hofman, A. (1991). Alcohol and tobacco consumption as risk factors for Alzheimer's disease: A collaborative reanalysis of case-control studies. *International Journal of Epidemiology*, 20, S48-S57.
- Hagberg, J. M. (1990). Exercise, fitness, and hypertension. In C. Bouchard, R. J. Shepard, T. Stephens, J. R. Sutton, & B. D. McPherson (Eds.), *Exercise, fitness and health: A consensus of current knowledge*, (pp. 409-424). Champaign, Ill: Human Kinetics Books.
- Hartman, D. E. (1988). *Neuropsychological toxicology: Identification and assessment of human neurotoxic syndromes*. New York: Pergamon Press.
- Hasher, L., & Zacks, R. T. (1979). Automatic and effortful processes in memory. *Journal of Experimental Psychology: General*, 108, 356-388.
- Hayflick, L. (1985). The aging process: Current theories. *Drug Nutrient Interactions*, 4, 13-33.
- Hebert, L. E., Scherr, P. A., Beckett, L. A., Albert, M. S., Rosner, B., Taylor, J. O., & Evans, D. A. (1993). Relation of smoking and low-to-moderate alcohol consumption to change in cognitive function: A longitudinal study in a defined community of older persons. *American Journal of Epidemiology*, 137, 881-891.
- Heilmann, K., & Fisher, W. R. (1974). Hyperlipidemic dementia. *Archives of Neurology*, 31, 67-68.
- Herzog, C., Schaie, K. W., & Gribbin, K. (1978). Cardiovascular disease and changes in intellectual functioning from middle to old age. *Journal of Gerontology*, 33, 872-883.
- Hill, R. D. (1989). Residual effects of cigarette smoking on cognitive performance in normal aging. *Psychology and Aging*, 4, 251-254.
- Hooker, K., & Siegler, I. C. (1992). Separating apples from oranges in health ratings: Perceived health includes psychological well-being. *Behavior, Health and Aging*, 2, 81-92.
- Hörn, J. C., & Cartell, R. B. (1967). Age differences in fluid and crystallized intelligence. *Acta Psychiatrica Scandinavica*, 26, 107-129.
- Houx, P. J., & Jolles, J. (1993). Age-related decline of psychomotor speed: Effects of age, brain health, sex, and education. *Perceptual and Motor Skills*, 76, 195-211.
- Houx, P. J., & Jolles, J. (1994). Vulnerability factors for age-related cognitive decline. In R. L. Isaacson & K. F. Jensen (Eds.), *Toxins in air and water*, (pp. 25-41). New York: Plenum Press.
- Houx, P. J., Jolles, J., & Vreeling, F. W. (1993a). Stroop interference: Aging effects assessed with the Stroop Color-Word test. *Experimental Aging Research*, 19, 209-224.
- Houx, P. J., van Bostel, M. P. J., & Jolles, J. (1995). Cognitive performance, age, and health-related factors. In J. Jolles, P. J. Houx, M. P. J. van Bostel, & R. W. H. M. Ponds (Eds.), *The Maastricht Aging Study: Determinants of cognitive aging*, (pp. 95-103). Maastricht: Neuropsych Publishers.
- Houx, P. J., Vreeling, F. W., & Jolles, J. (1991a). Age-associated cognitive decline is related to biological life events. In K. Iqbal, D. R. C. McLachlin, B. Winblad, & H. M. Wisniewski (Eds.), *Alzheimer's disease: Basic mechanisms, diagnosis and therapeutic strategies*, (pp. 353-358). Chichester, UK: Wiley.
- Houx, P. J., Vreeling, F. W., & Jolles, J. (1991b). Rigorous health screening reduces age effect on memory scanning task. *Brain and Cognition*, 15, 246-260.

- Houx, P. J., Vreeling, F. W., & Jolles, J. (1993b). Decline of psychomotor performance: Calendar or health? In G. E. Stelmach & V. Hömberg (Eds.), *Sensorimotor impairment in the elderly*, (Vol. 75, pp. 31-39). Dordrecht: Kluwer.
- Hultsch, D. F., Hammer, D., & Small, B. J. (1993). Age differences in cognitive performance in later life: Relationships to self-reported health and activity life style. *Journal of Gerontology*, 48, P1-11.
- Huppert, F. A. (1991). Age-related changes in memory: Learning and remembering new information. In F. Boller & J. Grafman (Eds.), *Handbook of Neuropsychology*, (Vol. 5, pp. 123-147): Elsevier.
- Huppert, F. A., & Brayne, C. (1994). What is the relationship between dementia and normal aging? In F. A. Huppert, C. Brayne, & D. W. O'Connor (Eds.), *Dementia and normal aging*, (pp. 3-14). Cambridge: Cambridge University Press.
- Incalzi, R. A., Gemma, A., Maïra, C., Muzzolon, R., Capparella, O., & Carbonin, P. (1993). Chronic obstructive pulmonary disease: An original model of cognitive decline. *American Review of Respiratory Disease*, 148, 418-424.
- Jolles, J., Houx, P. J., van Boxtel, M. P. J., & Ponds, R. W. H. M. (Eds.). (1995). *Maastricht Aging Study: Determinants of cognitive aging*. Maastricht: Neuropsych Publishers.
- Jolles, J., Verhey, F. R. J., Riedel, W. J., & Houx, P. J. (1996). Cognitive impairment in elderly people: Predisposing factors and implications for experimental drug studies. *Drugs and Aging*, 7, 459-479.
- Junqué, C., Pujol, J., Vendrell, P., Bruna, O., Jódar, M., Ribas, J. C., Viñas, J., Capdevila, A., & Martí Vilalta, J. L. (1990). Leuko-araïosis on magnetic resonance imaging and speed of mental processing. *Archives of Neurology*, 47, 151-156.
- Kawamoto, A., Shimada, K., Matsubayashi, K., Nishinaga, M., Kimura, S., & Ozawa, T. (1991). Factors associated with silent multiple lacunar lesions on magnetic resonance imaging in asymptomatic elderly hypertensive patients. *Clinical and Experimental Pharmacology and Physiology*, 18, 605-610.
- Kirkwood, T. B. L. (1994). How do risk factors for dementia relate to current theories on mechanisms of aging? In F. A. Huppert, C. Brayne, & D. W. O'Connor (Eds.), *Dementia and normal aging*, (pp. 230-243). Cambridge: Cambridge University Press.
- Kleijnen, J., & Knipschild, P. (1991). Niacin and vitamin B6 in mental functioning: A review of controlled trials in humans. *Biological Psychiatry*, 29, 931-941.
- Knegtering, H., Eijck, M., & Huijsman, A. (1994). Effects of antidepressants on cognitive functioning of elderly patients: A review. *Drugs and Aging*, 5, 192-199.
- Kokmen, E. (1991). The Eurodem collaborative reanalysis of case-control studies of Alzheimer's disease: Implications for clinical research and practice. *International Journal of Epidemiology*, 20, S65-S67.
- Kolb, B., & Whishaw, I. Q. (1990). *Fundamentals of human neuropsychology*. (3rd ed.). New York: W. H. Freeman & Company.
- König-Zahn, C., Furer, J. W., & Tax, B. (1993). *Het meten van de gezondheidstoestand. Beschrijving en evaluatie van vragenlijsten. 1. Algemene gezondheid. [The assessment of health status. Description and evaluation of questionnaires. 1. General health]*. Assen: Van Gorcum.
- Kral, V. A. (1962). Senescent forgetfulness: Benign and malignant. *Canadian Medical Association Journal*, 86, 257-260.
- Kuusisto, J., Kiovisto, K., Mykkanen, L., Helkala, E., Vanhanen, M., Hänninen, T., Pyörälä, K., Riekinen, P., & Laakso, M. (1993). Essential hypertension and cognitive function: The role of hyperinsulinemia. *Hypertension*, 22, 771-779.
- LaRue, A. (1992). *Aging and neuropsychological assessment*. New York: Plenum Press.
- LaRue, A., Bank, L., Jarvik, L., & Hetland, M. (1979). Health in old age: How do physicians' ratings and self-ratings compare? *Journal of Gerontology*, 34, 687-691.
- Launer, L. J., Dinkgreve, M. A., Jonker, C., Hooijer, C., & Lindeboom, J. (1993). Are age and education independent correlates of the Mini-Mental State Exam performance of community-dwelling elderly? *Journal of Gerontology*, 48, P271-277.
- Letenneur, L., Dartigues, J. F., Commenges, D., Barberger Gateau, P., Tessier, J. F., & Orgogozo, J. M. (1994). Tobacco consumption and cognitive impairment in elderly people. A population-based study. *Annals of Epidemiology*, 4, 449-454.
- Levy, R. (1994). Aging-Associated Cognitive Decline: Working party of the International Psychogeriatric Association in collaboration with World Health Organization. *International Psychogeriatrics*, 6, 63-68.
- Lewis, M., Worobey, J., Ramsay, D. S., & McCormack, M. K. (1992). Prenatal exposure to heavy metals: Effect on childhood cognitive skills and health status. *Pediatrics*, 89, 1010-1015.
- Lezak, M. D. (1995). *Neuropsychological Assessment*. (3rd ed.). New York: Oxford University Press.
- Light, K. C. (1975). Slowing of response time in young and middle-aged hypertensive patients. *Experimental Aging Research*, 1, 209-227.
- Madden, D. J., Blumenthal, J. A., Allen, P. A., & Emery, C. F. (1989). Improving aerobic capacity in healthy older adults does not necessarily lead to improved cognitive performance. *Psychology and Aging*, 3, 307-320.

- Maddox, G. L., Archley, R. C., Poon, L. W., Roth, G. S., Siegler, I. C., & Steinberg, R. M. (Eds.) (1987). *The encyclopedia of aging*. New York: Springer.
- McDowell, I., & Newell, C. (1987). *Measuring health: A guide to rating scales and questionnaires*. New York: Oxford University Press.
- McKhann, G., Drachmann, D., Folstein, M., Katzman, R., Price, D., & Stadlan, E. (1984). Clinical diagnosis of Alzheimer's disease: Report of the NINCDS/ADRDA workgroup under the auspices of the department of Health and Human Services task force on Alzheimer's disease. *Neurology*, 34, 939-944.
- Mearns, J., Dunn, J., & Lees Haley, P. R. (1994). Psychological effects of organophosphate pesticides: A review and call for research by psychologists. *Journal of Clinical Psychology*, 50, 286-294.
- Metsemakers, J. F. M., Höppener, P., Knottnerus, J. A., Kocken, R. J. J., & Limonard, C. B. G. (1992). Computerized health information in the Netherlands: A registration network of family practices. *British Journal of General Practice*, 42, 102-106.
- Meyer, J. S., Judd, B. W., Tawakina, T., Rogers, R. L., & Mortel, K. F. (1986). Improved cognition after control of risk factor of multi-infarct dementia. *Journal of the American Medical Association*, 256, 2203-2209.
- Meyer, J. S., & Shaw, T. G. (1984). Cerebral blood flow in aging. In M. L. Albert (Ed.), *Clinical neurology of aging*, (pp. 178-196). New York: Oxford University Press.
- Moe, S. M., & Sprague, S. M. (1994). Uremic encephalopathy. *Clinical Nephrology*, 42, 251-256.
- Molina, J. A., Bermejo, F., del Ser, T., Jiménez-Jiménez, F. J., Herranz, A., Fernández Calle, P., Ortuño, B., Villanueva, C., & Sainz, M. J. (1994). Alcoholic cognitive deterioration and nutritional deficiencies. *Acta Neurologica Scandinavica*, 89, 384-390.
- Mortimer, J. A. (1988). Do psychosocial risk factors contribute to Alzheimer's disease? In A. S. Henderson & J. H. Henderson (Eds.), *Etiology of dementia of Alzheimer's type*, (pp. 39-52). Chichester: John Wiley & Sons.
- Mortimer, J. A. (1994). What are the risk factors for dementia? In F. A. Huppert, C. Brayne, & D. W. O'Connor (Eds.), *Dementia and normal aging*, (pp. 208-229). Cambridge: Cambridge University Press.
- Mortimer, J. A., van Duijn, C. M., Chandra, V., Fratiglioni, L., Graves, A. B., Heyman, A., Jorm, A. F., Kokmen, E., Kondo, K., Rocca, W. A., Shalat, S. L., Soininen, H., & Hofman, A. (1991). Head trauma as a risk for Alzheimer's disease: A collaborative reanalysis of case control studies. *International Journal of Epidemiology*, 20, S28-S35.
- Muldoon, M. F., Bachen, E. A., Manuck, S. B., Waldstein, S. R., Bricker, P. L., & Bennett, J. A. (1992). Acute cholesterol responses to mental stress and change in posture. *Archives of Internal Medicine*, 152, 775-780.
- Muldoon, M. F., Herbert, T. B., Patterson, S. M., Kameneva, M., Raible, R., & Manuck, S. B. (1995a). Effects of acute psychological stress on serum lipid levels, hemoconcentration, and blood viscosity. *Archives of Internal Medicine*, 155, 615-620.
- Muldoon, M. F., Waldstein, S. R., & Jennings, J. R. (1995b). Neuropsychological consequences of antihypertensive medication use. *Experimental Aging Research*, 21, 353-368.
- Nolan, K. A., & Blass, J. P. (1992). Preventing cognitive decline. *Clinics in Geriatric Medicine*, 8, 19-34.
- Ott, A., Breteler, M. M., van Harskamp, F., Claus, J. J., van der Cammen, T. J., Grobbee, D. E., & Hofman, A. (1995). Prevalence of Alzheimer's disease and vascular dementia: association with education. The Rotterdam study. *British Medical Journal*, 310, 970-973.
- Perlmutter, M., & Nyquist, L. (1990). Relationships between self-reported physical and mental health and intelligence performance across adulthood. *Journal of Gerontology*, 45, P145-155.
- Pickering, T. G. (1993). Clinical value of ambulatory blood pressure measurement in the elderly. *Cardiology in the Elderly*, 1, 490-493.
- Pierce, T. W., & Elias, M. F. (1993). Cognitive function and cardiovascular responsivity in subjects with a parental history of hypertension. *Journal of Behavioral Medicine*, 16, 277-294.
- Poirier, J., Davignon, J., Bouthillier, D., Kogan, S., Bertrand, P., & Gauthier, S. (1993). Apolipoprotein E polymorphism and Alzheimer's disease. *Lancet*, 342, 697-99.
- Poon, L. W. (1985). Differences in human memory with aging: Nature, causes and clinical implications. In J. E. Birren & K. W. Schaie (Eds.), *Handbook of the psychology of aging*. New York: Van Nostrand Reinhold.
- Postiglione, A., Cortese, C., Fischetti, A., Cicerano, U., Gnasso, A., Galotta, G., Grossi, D., & Mancini, M. (1989). Plasma lipids and geriatric assessment in a very aged population of South Italy. *Atherosclerosis*, 80, 63-68.
- Prince, M., Lewis, G., Bird, A., Blizard, R., & Mann, A. (1996). A longitudinal study of factors predicting change in cognitive test scores over time, in an older hypertensive population. *Psychological Medicine*, 26, 555-568.
- Rabbitt, P. (1990). Applied cognitive gerontology: Some problems, methodology and data. *Applied Cognitive Psychology*, 4, 143-149.
- Rabbitt, P. M. A. (1993). Methodological and theoretical lessons from the university of Manchester Longitudinal Studies of Cognitive Changes in Normal Old Age. In J. J. F. Schroots (Ed.), *Aging, health and competence*, (pp. 199-219). Amsterdam: Elsevier.
- Reaven, G. M., Thompson, L. W., Nahum, D., & Haskins, E. (1990). Relationship between hyperglycaemia and cognitive function in older NIDDM patients. *Diabetes Care*, 13, 16-21.

- Reitan, R. M., & Shipley, R. E. (1963). The relation of serum cholesterol changes to psychological abilities. *Journal of Gerontology*, 18, 350-357.
- Reitsma, J. B. (1995). *Hart- en vaatziekten in Nederland 1995: Cijfers over ziekte en sterfte [Cardiovascular diseases in the Netherlands: Figures on disease and mortality]*. Den Haag: Nederlandse Hartstichting.
- Riedel, W. J., & Van Praag, H. M. (1995). Avoiding and managing anticholinergic effects of antidepressants. *CNS Drugs*, 3, 245-259.
- Riegel, K. F., & Riegel, R. M. (1972). Development, drop, and death. *Developmental Psychology*, 6, 309-316.
- Rikli, R. E., & Edwards, D. J. (1991). Effects of a three-year exercise program on motor function and cognitive processing speed in older women. *Research Quarterly for Exercise and Sport*, 62, 61-67.
- Rodriguez, G., Arvigo, F., Marengo, S., Nobili, F., Sandini, G., & Rosandini, G. (1987). Regional blood flow in essential hypertension: Data evaluation by a mapping system. *Stroke*, 18, 13-20.
- Rogers, R. L., Meyer, J. S., & Mortel, K. F. (1990). After reaching retirement age physical activity sustains cerebral perfusion and cognition. *Journal of the American Geriatrics Society*, 38, 123-128.
- Rogers, R. L., Meyer, J. S., Shaw, T. G., & al., e. (1983). Cigarette smoking decreases cerebral blood flow suggesting increased risk for stroke. *Journal of the American Medical Association*, 250, 2796-2800.
- Rogers, R. L., Meyer, J. S., Shaw, T. G., & al., e. (1985). Reductions in cerebral blood flow associated with chronic alcohol consumption. *Journal of the American Geriatrics Society*, 31, 540-543.
- Rowe, J. W., & Kahn, R. L. (1987). Human aging: Usual and successful. *Science*, 237, 143-149.
- Ryan, C. M., Williams, T. M., Finegold, D. N., & Orchard, T. J. (1993). Cognitive dysfunction in adults with Type 1 (insulin-dependent) diabetes mellitus of long duration: Effects of recurrent hypoglycaemia and other chronic complications. *Diabetologia*, 36, 329-334.
- Sachon, C., Grimaldi, A., Digy, J. P., Pillon, B., Dubois, B., & Thervet, F. (1992). Cognitive function, insulin-dependent diabetes and hypoglycaemia. *Journal of Internal Medicine*, 231, 471-475.
- Salthouse, T. A. (1985). Speed of behavior and its implications for cognition. In J. E. Birren & K. W. Schaie (Eds.), *Handbook of the Psychology of Aging*, (pp. 400-427). New York: Van Nostrand Reinhold Co.
- Salthouse, T. A. (1988). Resource-reduction interpretations of cognitive aging. *Developmental Review*, 8, 238-272.
- Salthouse, T. A. (1989). Age-related changes in basic cognitive processes. In M. Storandt & G. R. Vandenbos (Eds.), *The adult years: Continuity and change*, (pp. 5-40). Washington: APA.
- Salthouse, T. A. (1992). *Mechanisms of age-cognition relations in adulthood*. Hillsdale, NJ: Lawrence Erlbaum.
- Salthouse, T. A., Kausler, D. H., & Scott Saults, J. (1990). Age, self-assessed health status, and cognition. *Journal of Gerontology*, 45, P156-160.
- Sandstead, H. H. (1986). A brief history of the influence of trace elements on brain function. *American Journal of Clinical Nutrition*, 43, 293-298.
- Satz, P. (1993). Brain reserve capacity on symptom onset after brain injury: A formulation and review of evidence for threshold theory. *Neuropsychology*, 7, 273-295.
- Saunders, A. M., Schmeider, K., Breitner, J. C. S., Benson, M. D., Brown, W. T., Goldfarb, L., Goldgaber, D., Manwaring, M. G., Szymanski, M. H., McCown, M., Dole, K. C., Schmeider, D. E., Strittmatter, W. J., Pericak-Vance, M. A., & Roses, A. D. (1993). Apolipoprotein E $\epsilon 4$ allele distributions in late-onset Alzheimer's disease and in other amyloid-forming diseases. *Lancet*, 342, 710-11.
- Schmidt, R., Fazekas, F., Offenbacher, H., Dusek, T., Zach, E., Reinhart, B., Grieshofer, P., Freidl, W., Eber, B., Schumacher, M., Koch, M., & Lechner, H. (1993). Neuropsychologic correlates of MRI white matter hyperintensities: A study of 150 normal volunteers. *Neurology*, 43, 2490-2494.
- Schmidt, R., Fazekas, F., Koch, M., Kapeller, P., Augustin, M., Offenbacher, H., Fazekas, G., & Lechner, H. (1995). Magnetic resonance imaging cerebral abnormalities and neuropsychologic test performance in elderly hypertensive subjects: a case-control study. *Archives of Neurology*, 52, 905-910.
- Selkoe, D. J. (1992). Aging brain, aging mind. *Scientific American*, 267, 97-103.
- Sherwood, N. (1993). Effects of nicotine on human psychomotor performance. *Human Psychopharmacology*, 8, 155-184.
- Siegler, I. C. (1990). Paradigms in developmental health psychology - From theory to application: Introduction to a special issue. *Journal of Gerontology*, 45, P113-115.
- Skoog, I. (1994). Risk factors for vascular dementia: A review. *Dementia*, 5, 137-144.
- Skoog, I. (1996). *Clinical significance of cognitive impairment in non-demented elderly persons: relation to dementia, vascular disorders and death*. Paper presented at the Lancet Conference, Edinburgh, UK.
- Snowdon, D. A., Belcher, J. D., Tully, C. L., & Greiner, L. H. (1996). *Plasma cholesterol and cognitive function in the elderly: Findings from the nun study*. Paper presented at the 6th Cognitive Aging Conference, 25-28 April 1996, Atlanta, GA.
- Spiriduso, W. W. (1980). Physical fitness, aging, and psychomotor speed: A review. *Journal of Gerontology*, 35, P850-865.
- Starr, J. M., & Whalley, L. J. (1992). Senile hypertension and cognitive impairment: An overview. *Journal of Hypertension (Suppl.)*, 10, S31-S42.

- Stern, Y., Alexander, G., Prohovnik, I., & Mayeux, R. (1991). Education provides a cognitive reserve against the clinical manifestations of Alzheimer's disease. *Society for Neuroscience Abstracts*, 17, 1258.
- Stoltenberg-Didinger, G. (1994). Neuropathology of the hippocampus and its susceptibility to neurotoxic insult. *Neurotoxicology*, 15, 445-450.
- Stones, M. J., & Kozma, A. (1988). Physical activity, age and cognitive/motor performance. In M. Howe & C. Brainard (Eds.), *Cognitive development in adulthood*, (pp. 273-322). New York: Springer.
- Stones, M. J., Kozma, A., & Hannah, T. E. (1990). The measurement of individual differences in aging: The distinction between usual and successful aging. In M. L. Howe, M. J. Stones, & C. J. Brainerd (Eds.), *Cognitive and behavioural performance factors in atypical aging*, (pp. 181-218). New York: Springer-Verlag.
- Swan, G. E., Carmelli, D., & LaRue, A. (1996). *CHD risk factors and neuropsychological performance in the elderly*. Paper presented at the Paper presented at the Annual Meeting of the International Neuropsychological Society, 16 February 1996, Chicago.
- Swan, G. E., LaRue, A., Carmelli, D., Reed, T. E., & Fabsitz, R. R. (1992). Decline in cognitive performance in aging twins: Heritability and biobehavioral predictors from the National Heart, Lung, and Blood Institute Twin Study. *Archives of Neurology*, 49, 476-481.
- Tarter, R. E., Arria, A. M., & Van Thiel, D. H. (1991). Hepatic encephalopathy coexistent with alcoholism. *Recent Developments in Alcoholism*, 9, 205-224.
- Tarter, R. E., Edwards, K. L., & van Thiel, D. H. (1988a). Perspective and rationale for neuropsychological assessment of medical disease. In R. E. Tarter, D. H. van Thiel, & K. L. Edwards (Eds.), *Medical Neuropsychology: The Impact of Disease on Behavior*, (pp. 1-10). New York: Plenum Press.
- Tarter, R. E., van Thiel, D. H., & Edwards, K. L. (1988b). *Medical Neuropsychology: The impact of disease on behavior*. New York: Plenum Press.
- U'ren, R. C., Riddle, M. C., Lezak, M. D., & Bennington-Davis, M. (1990). The mental efficiency of the elderly person with Type II diabetes mellitus. *Journal of the American Geriatrics Society*, 38, 505-510.
- Van Duijn, C. M., & Hofman, A. (1991). Relation between nicotine intake and Alzheimer's disease. *British Medical Journal*, 302, 1491-1494.
- Van Swieten, J. C., Geyskes, G. G., Derix, M. M. A., Peek, B. M., Ramos, L. M. P., van Latum, J. C., & van Gijn, J. (1991). Hypertension in the elderly is associated with white matter lesions and with cognitive decline. *Annals of Neurology*, 30, 825-830.
- Verbrugge, L. M., & Jette, A. M. (1994). The disablement process. *Social Science and Medicine*, 38, 1-14.
- Walden, C. C., & Hegele, R. A. (1994). Apolipoprotein E in hyperlipidemia. *Annals of Internal Medicine*, 120, 1026-1036.
- Waldstein, S. R. (1995). Hypertension and neuropsychological function: A lifetime perspective. *Experimental Aging Research*, 21, 321-352.
- Waldstein, S. R., Manuck, S. B., Ryan, C. M., & Muldoon, M. F. (1991). Neuropsychological correlates of hypertension: Review and methodological considerations. *Psychological Bulletin*, 110, 451-469.
- White, N., & Cunningham, W. R. (1988). Is terminal drop pervasive or specific? *Journal of Gerontology*, 43, P141-144.
- Widom, B., & Simonson, D. C. (1990). Glycemic control and neuropsychologic function during hypoglycemia in patients with insulin-dependent diabetes mellitus. *Annals of Internal Medicine*, 112, 904-912.
- Wilkie, F. L., & Eisdorfer, C. (1971). Intelligence and blood pressure in the aged. *Science*, 172, 959-962.
- Wood, P. D., & Stefanick, M. L. (1990). Exercise, fitness, and atherosclerosis. In C. Bouchard, R. J. Shepard, T. Stephens, J. R. Sutton, & B. D. McPherson (Eds.), *Exercise, fitness and health: A consensus of current knowledge*, (pp. 409-424). Champaign, Ill.: Human Kinetics Books.
- World Health Organisation. (1980). *International classification of impairments, disabilities, and handicaps*. Geneva: WHO.
- Worrall, G., Moulton, N., & Briffett, E. (1993). Effect of type II diabetes mellitus on cognitive function. *Journal of Family Practice*, 36, 639-643.
- Writing Committee Lancet Conference. (1996). The challenge of the dementias. *Lancet*, 347, 1303-1307.
- Yates, F. E. (1993). Biological perspectives on growing old. In J. J. F. Schroots (Ed.), *Aging, health and competence*, (pp. 55-63). Amsterdam: Elsevier.

Chapter 3

The Maastricht Aging Study (MAAS): Rationale, objectives, design, and methods¹

3.1 RATIONALE AND OBJECTIVES

3.1.1 *Introduction*

The research described in this thesis are part of a series of related projects in the realm of cognitive aging, called the Maastricht Aging Study (MAAS). This study is carried out at the University of Maastricht, the Netherlands. The present chapter describes the rationale, objectives, design and the methods used in MAAS and thus provides the scientific background and research infrastructure on which the research described in the experimental chapters of this thesis are based.

In 1991, MAAS started with research grants from the Dutch Government (Departments of Education and Science and the former department of Welfare, Health and Cultural Affairs) and the University of Maastricht. The core of the research program is a longitudinal study into cognitive aging, which investigates biomedical, psychological and sociodemographical factors in relation to neurocognitive functioning. With respect to biomedical factors, special attention is paid to experienced morbidity and to subclinical changes in physiological parameters. MAAS involves almost 2,000 healthy individuals aged 24 through 81 years at baseline. Data are collected by means of questionnaires, medical screening and neuropsychological investigation. This chapter describes the rationale and research questions (§3.1), design (§3.2), methods used in postal survey (§3.3), and methods used in medical and neuropsychological assessment (§3.4). It is an abridged version of the first four chapters of a recent book entitled *The Maastricht Aging Study: Determinants of Cognitive Aging*, by Jolles, Houx, van Boxtel and Ponds (1995). Descriptions of procedures and methodology, as well as results from ten research projects related to cognitive aging can be found in this book in more detail. The next paragraph gives an overview of the objectives and design of MAAS.

3.1.2 *MAAS objectives and design: an overview*

MAAS is largely devoted to the age-related decline of memory and memory-related functions in normal people and the search for determinants of both successful and pathological cognitive aging. A major objective is to find determinants of cognitive deterioration with age, and to estimate the relative impact of these factors. What makes memory function decline?

¹ Adapted from J. Jolles, P. J. Houx, M. P. J. van Boxtel, & R. W. H. M. Ponds (Eds.). (1995). *Maastricht Aging Study: Determinants of cognitive aging*. Maastricht: Neuropsych Publishers, Chapters 1-4.

Why do some individuals show a greater decline than others? Over the past few years, a host of factors, including biological, medical, psychological and social factors, have been studied in relation to cognitive decline. The aim of MAAS is to evaluate these factors in an integrative study of cognitive aging. This can only be achieved if large numbers of normal healthy adults of all ages are studied and if these subjects are monitored for some period of time. Pathological forms of aging (e.g. dementia or depression) are studied in the longitudinal follow-up program. It is expected that some subjects who were normal and healthy at the first measurement point will show abnormalities in the long run. For this reason, MAAS intends to perform case-finding studies of pathological aging involving subjects with well-documented histories of pre-morbid functioning. The longitudinal phase of MAAS will enable the search for prodromes of dementia (more specifically, dementia of the Alzheimer type or vascular dementia), and other forms of psychopathology (such as depression or anxiety disorder).

Different individuals may and do age in different ways. The decline may be sudden or gradual, invalidating or mild, and may occur at different points in time. The main study of MAAS involves the collection of information about individual patterns of cognitive aging. Much of the research that preceded MAAS was devoted to Biological Life Events (BLE, brain function-related health factors) as possible determinants of cognitive aging. Strong evidence from cross-sectional studies suggested that BLE accounted for much of the age-related decrease in cognitive performance and for the increase in the variance of performance.

In MAAS, additional information was obtained from nearly four thousand subjects by the use of postal surveys and questionnaires. The demographic, biomedical, psychological, and social information will be related to the results from extensive neuropsychological testing in almost half of this group. The test group is made up of the participants in four consecutive panel studies (referred to as A₁ to A₄). Each panel includes 440 to 480 subjects who are stratified for age in 12 discrete age groups. The chapters 5 to 9 of this thesis pertain to data derived from the first three panel studies (A₁ to A₃).

Several parallel studies are related to the *main study*. These involve dedicated experiments with smaller numbers of subjects. Some of these studies include subjects who took part in the main study and use parts of the basic data (so-called *adnex studies*). Other projects require subject sampling independent of the main study, e.g. as part of PhD projects that are supported by grants from the University of Maastricht or from third parties. Most of these studies focus on questions which are central to the research question of the main study.

3.1.3 MAAS research questions

MAAS intends to find answers to a number of questions about the normal (non-pathological) aging of cognitive functions, particularly memory. The emphasis on memory in MAAS is not because, as commonly thought, this function is affected most or even chiefly in the aging process, but because aging people invariably first complain about their memories. In fact, there is ample evidence that a number of other functions deteriorate earlier and to a greater extent than important aspects of memory. Psychomotor functions, attention, and reaction time have all been shown to deteriorate much earlier than the time when most individuals first experience a deterioration of memory. However, memory is one aspect of cognition that people can

directly relate to. Memory problems often constitute the first phase of the most important form of pathological aging, dementia. The main research questions of MAAS are then the *When*, *What*, and especially *Who*, of the decline of memory and memory-related functions associated with aging and will be discussed below.

Question 1 – The first and probably most basic question is: when in the course of a human lifetime do changes in memory and memory-related functions appear? Is there a distinct point in an individual's life when cognitive changes first emerge? Very little is known about when cognitive changes appear or how rapidly they progress. Does the decline start early in life and gradually go on or accelerate with age, or does it manifest itself abruptly? A sudden decline in cognitive performance, leading to death within a limited time interval (*terminal drop*), may occur after a major event. This can be a physical event, such as an infective disease or head trauma, or a psychosocial event, such as the death of a spouse. This sudden decline is of course more likely to occur in the second half of the life span, but since life expectancy has increased over the last century, this period can extend over the fourth to the ninth decades of life.

Another intuitively appealing possibility is that most individuals do indeed show a gradual decline in cognitive function with age, perhaps as a result of the accumulation of effects of minor brain dysfunction. At first, these minor abnormalities may have little impact, but as they accumulate, or as age advances, their combined effects result in cognitive deficits that can be perceived by the individual or clinically observed. Terminal drop would then only occur as a result of major abnormality. The latter possibility is clearly the more optimistic one, as it paves the way to better cognitive functioning in later years. As yet, we do not know which of the possibilities, or a combination of them, applies.

Unfortunately, the majority of experimental cognitive aging research performed up till now has focused on performance differences between young adults (mostly students) and elderly subjects, making the information on cognitive deterioration in middle age scarce. Yet, it seems essential to study the ages between 30 and 60 to gain insight into functional development during adulthood and to learn about which functions decline when.

Most studies on cognitive aging are cross-sectional, i.e. they study two or several age groups at one point in time. There is a distinct possibility that gradual cognitive decline in the reported studies is an artefact of so-called period effects (see chapter 10), or of the fact that older age groups merely contain more poorly performing subjects. This is because the number of elderly subjects in the period between the terminal drop and death within a given birth cohort increases as the age of the cohort increases. Consequently this would cause the average performance of an older group to be poorer and would result in a higher variance in performance within older age groups – a phenomenon often encountered in cross-sectional research. Individual age-performance trajectories, as Rabbitt (1990) put it, may differ widely, and yet result in a steadily declining average trajectory.

Question 2 – Do all functions deteriorate at the same rate or are specific aspects of cognitive functioning more affected than others? Does continuous decline or terminal drop exist to a comparable extent for the various domains of cognitive function? This is unlikely, because memory is not a unitary function and particular aspects of memory appear to remain relatively

intact until late in life. The decline in sensory function and physical performance that occurs with age may have some effect on the performance on cognitive function tests, but there need not be any direct or causal relationship with cognitive performance itself. Any loss of memory may well lag very much behind perceptual loss, or may not occur at all.

A well-known example of differential age trends in cognitive function is the dissociation between crystallized and fluid intelligence, as originally proposed by Cattell (1963). In this dichotomy, the former denotes those cognitive processes and skills that are more or less independent of age (such as retrieval of long-stored information), whereas the latter concerns processes that show age-related decline (such as attentional processes or spatial reasoning). White and Cunningham (1988) demonstrated that the terminal drop phenomenon mentioned above is probably limited to crystallized abilities. However, little is known about the fluidity of cognitive functions. Whatever the hypothetical underlying cause of the observed functional decline, it is important *not* to ascribe the observed decline blindly to age *per se*, but to determine the underlying, more specific factors that may trigger a decline in cognitive abilities.

Question 3 – The third main research question is closely related to the first two. Do individuals differ with respect to the age of onset and the rate of progression of cognitive aging? Information is lacking about whether all aging people experience a general deterioration of their cognitive functions. In other words, is cognitive aging an inherent aspect of physiological aging or are additional factors, such as biological or psychosocial factors, also responsible for cognitive aging? No systematic information is available in the literature about determinants of healthy and pathological cognitive aging. This makes it important to acquire more information on individual cognitive aging trajectories and the factors that mediate them (Rabbitt, 1990). Several studies have shown that some elderly subjects perform cognitive tasks just as well as young adults do, which raises the question about what determines *successful* cognitive aging, or, conversely, what causes the majority of individual aging patterns to be less successful (Rowe & Kahn, 1987).

Are there particular biological or psychosocial determinants, or *risk factors*, of pathological cognitive aging in normal, healthy individuals? Do so-called Biological Life Events (BLE) play a role in this respect? BLE are health-related factors that are possibly associated with brain functioning (Houx, Vreeling & Jolles, 1991). Examples of BLE are the use of psychoactive medication, use of alcohol, closed head injury, and general anaesthesia. Most individuals are exposed to one or more of these factors during their lifetime. Usually, however, the impact of BLE goes unnoticed by the individual, which is why their importance is rarely acknowledged by physicians. The MAAS study aims to identify the determinants of successful or less-than-successful cognitive aging and to evaluate the BLE concept.

Question 4 – What is the relationship between complaints about cognitive abilities (particularly memory) and cognitive test performance? Several studies have failed to find a clear relationship between complaints about memory function and performance memory tests. Older subjects who complain about memory may perform well on memory tests, and vice versa. Psychological and psychosocial variables (e.g. *metamemory*) seem to be related to the existence

and maintenance of complaints about cognitive functioning. However, it should be realized that several psychometric tests that are used in clinical and experimental settings are not standardized, and that many tests have been developed or modified in recent years. Far-reaching conclusions are often drawn on the basis of a particular aspect of the test performance of a neuropsychological patient. For this reason one may expect that case-control studies and other patient-related research involving cognitive testing can gain greatly from well-designed normative studies.

A related question involves the possibilities that patients with memory complaints or dysfunctions may have to compensate for deteriorating functions and what can be done to overcome the handicap many elderly experience in acquiring, retrieving, and applying information in daily-life situations. This question pertains to the need for educational facilities for the elderly and the necessity to improve the use of information or information technology by the elderly.

The questions outlined above can only be addressed in a large-scale study such as MAAS that involves different age groups and that monitors the subjects for a considerable period of time. A cross-sequential design and a study population with a wide age range is essential to collect the necessary information about a substantial part of different aging trajectories. This approach appears to be the optimal combination of longitudinal and cross-sectional methodology, dealing with the shortcomings of both in the best possible way (Williams & Klug, 1996).

The relevance of MAAS to society is found in the difficulties that many individuals experience in the course of the aging process, difficulties which adversely affect their quality-of-life because of decreased mental abilities and increased forgetfulness. Furthermore, the memory problems of aging individuals have a large impact on society because of the *double aging* caused by the rapidly growing number of elderly individuals. The impact is also reflected by the sharply increasing financial and organizational costs of health promotion and health care for the middle-aged and older population.

3.1.4 General approach: the cross-sectional phase of MAAS

The basis of MAAS (the so-called *A*-study) is founded by a cross-sectional study involving several thousands of healthy subjects aged 24 to 86 years. Data were collected in four consecutive *panel studies* that were identical in structure and organization. In the first study A_1 which took place in 1993, some 2,000 subjects received an extensive postal questionnaire. Of these 2,000 subjects, 480 were actually screened in the test laboratory. Based on the experience with the A_1 three additional experiments (A_{2-4}) were scheduled, in which some individual data were to be collected by means of postal questionnaire, and other data by in-depth neuropsychological and medical examinations of 1,450 additional subjects, 440 to 480 subjects in each panel.

The next section describes the procedure, design and methods of MAAS. Briefly, MAAS now consists of four panel studies A_{1-4} and an extended postal survey study that was part of A_1 . Each panel study was age-stratified in 12 or 11 discrete age groups ($n = 40$) between 24 and 81 years. All age groups were subdivided into four subgroups ($n = 10$) by the factor sex and the

level of occupational activity (LOA, two levels). The subjects were recruited from the Registration Network Family Practices (*Registratienet Huisartspraktijken*, RNH), a data base managed by the Department of General Practice of the University of Maastricht. This project should provide answers to most of the scientific questions underlying the research program. It should provide population norms for tests of memory and memory-related functions, for several medical tests, and for the prevalence of risk factors and maintenance factors for (un-)healthy cognitive aging. A basic battery of psychometric instruments and medical tests was used for all subjects. Additional information was obtained with questionnaires.

The A-study was set up to meet the requirements for longitudinal follow-up. The results from the A₁ follow-up will be used to define the necessary characteristics of the longitudinal phase of the study, which is planned to follow a cross-sequential design.

3.2 MAAS STUDY DESIGN

3.2.1 Introduction

This paragraph describes the logistic implementation of MAAS, its study design, time schedule, and subject inclusion procedure. A description of the methods used (postal survey questionnaire and test program) can be found in the sections 3.3 and 3.4.

The cross-sectional panel studies of MAAS share the same methodology with respect to sample frame, subject inclusion, stratification criteria, and basic measurement protocol. Each A-study includes an independent population sample and a set of specific variables in addition to the set of variables that is constant for all A-studies. Each subject panel is stratified for age, sex, and a proxy measure of *general ability* (section 3.2.5). Four cross-sectional panel studies were executed between March 1993 through December 1995 of which the total number of subjects that will proceed to the follow-up phase was 1,823. The frequency of follow-up assessment depends on actual age at baseline, i.e., three years for subjects aged 54 years and older, and six years for subjects younger than 52. The total duration of the follow-up program is at least 12 years, but may last longer if supplemental funding can be acquired. The first 3-year follow-up of panel A₁ was conducted from October 1996 to January 1997. Figure 3.1 displays a schematic time schedule for the complete MAAS project. In the following sections, a description is given of the sample frame, inclusion and exclusion criteria, and procedure.

Figure 3.1. Timetable of the four MAAS panel studies and their successive follow-up measurements.

3.2.2 *Sample frame: Registration Network Family Practices (RNH)*

MAAS closely collaborates with the Registration Network Family Practices (*Registratienet Huisartspraktijken*, RNH). This register intends to serve as a sample frame for research in primary care and related scientific fields (Metsemakers, Höppener, Knottnerus, Kocken & Limonard, 1992). The RNH will eventually contain a set of demographic and health characteristics of 80,000 patients from 15 general practices and 42 practitioners in the province of Limburg, the Netherlands. This information is updated and stored every three months in a central data base. Patients included in the RNH register are considered to be representative for the Limburg and Dutch populations with respect to demographic characteristics (age, gender, educational level, and type of health insurance). The register contains background information such as socioeconomic status, level of formal education, and marital status. All relevant health problems are coded in a problem list. A health problem can be defined as '*anything that has required, does or may require health-care management and has affected or could significantly affect a person's physical or emotional well-being*'. Problems are identified and recorded according to the International Classification of Health Problems in Primary Care (ICPC; Lamberts and Wood, 1987). They are only recorded by the general practitioner if they are permanent (no recovery expected), chronic (duration longer than six months) or recurrent (more than three recurrences within six months). An overview of the most common problems is given in chapter 9.

The use of RNH as a sample frame for MAAS subject panels has several advantages over sampling procedures in the general population, e.g. the use of census registers. For example, the invitation to participate in the study is sent by the personal family doctor, which is expected to promote the compliance. Furthermore, a preselection of subjects based on the medical and demographical RNH information can be made beforehand. Subjects with known morbidity which may have severe consequences for cognitive ability are considered ineligible to participate. A major advantage is that the effect of pre-inclusion attrition can be evaluated in the successive phases of each panel study by comparing the general characteristics of each subsample to those of the original sample. Finally, the continuously updated RNH data base can facilitate case-finding in the longitudinal phase of MAAS.

3.2.3 *Medical exclusion criteria*

Medical exclusion criteria for the subject sampling procedure at baseline were defined as those active or inactive medical conditions in the RNH problem list that may seriously interfere with normal cognitive function. This definition included the following problems: coma (only active), cerebrovascular pathology, all tumors of the nervous system, congenital malformations of the nervous system, multiple sclerosis, parkinsonism, epilepsy (all types), dementia, organic psychosis (other than dementia), schizophrenia, affective psychosis, and mental retardation. In addition, before participation in the test program all participants were screened in a semi-structured interview to update RNH exclusion criteria and to check for the following exclusion criteria that were not coded in the RNH data base: history of transient ischemic attacks (TIA), brain surgery, hemodialysis for renal failure, electroconvulsive therapy, and

regular use of psychotropic drugs. Transient conditions, such as intercurrent illness or hospitalization, was a reason to postpone participation. Finally, a score below 24 on the MMSE (Mini-Mental State Examination, Folstein, Folstein & McHugh, 1975), a cognitive screening test for dementia, led to exclusion from the study.

3.2.4 Procedure A₁: Postal survey

MAAS study A₁ consisted of two complementary projects: a postal survey, described in the present section, that was followed by a test program described in section 3.2.5. This program involved extensive medical and neuropsychological screening of a subgroup that was recruited from the postal survey population. It should be noted that the postal survey distinguishes A₁ from other A-studies. As discussed in section 3.1, the postal survey questionnaire was administered in studies A₂ to A₄ only to participants in the test program.

Subject inclusion in the postal survey A₁ was as follows: all subject panels of MAAS A-studies were stratified for age (13 discontinuous classes ranging from 25 ± 1 years to 85 ± 1 years), and sex. As no information on compliance rates was available at the start of the program, the number of subjects drawn per cell was fixed.

Screening for medical exclusion criteria (§3.2.3) as coded by the RNH reduced the group of eligible participants in the data base with 4%. Exclusion for medical reasons was age-dependent: for four aggregated age categories (25-35, 40-50, 55-65, and 70-85 years) the exclusion percentages were 2.3, 3.3, 4.4, and 8.9, respectively. From the resulting population, approximately 310 subjects were randomly selected for each discontinuous age class, balanced for sex. To meet the requirements for A₁, all subjects in the 85-year-age class present were drawn from the RNH register.

Subjects were invited to participate in the study according to a standard RNH procedure. First, the selected subjects were screened by the general practitioner for psychosocial reasons to participate (e.g. actual major life events). Five percent ($n = 197$) of the original selected population of 3,941 was excluded for this reason. Each general practitioner personally invited the selected patients in his or her practice to take part in the study. A short introductory letter with an enclosed return postcard was sent to all subjects. Of this group, 62 percent ($n = 2,340$) agreed to take part in the postal survey. After four weeks a reminder was sent to all nonresponders. In total 2,043 subjects (54%) completed and returned the questionnaire in good order. Of this group, 61 percent ($n = 1,252$) volunteered for the additional test program.

3.2.5 Procedure A₁: Test program

Subjects for the A₁ test program were randomly drawn from the pool of 1,252 individuals who volunteered for the test program in the postal survey. The participants were stratified for age class, sex, level of occupational activity (LOA, 2 levels; see below), and health status (*Biological Life Events*, BLE, §3.3.3). The number of age classes was limited to 12, because only a very small percentage of subjects in the 85 year group was both available and eligible for further assessment. Stratification according to BLE status within each age by sex by LOA cell was performed in A₁ only.

The subjects were assigned to two levels of occupational activity (LOA). LOA was based on a split-half (1-3 *low*, 4-7 *high*) of scores on a 7-point scale which estimates the highest level of professional achievement (DGA, 1989). This scale ranges from the lowest extreme of unskilled, very simple labor to highly specialized labor at academic level. Classification was based on the reported occupation and a description of the professional labor. When the information was insufficient to classify LOA, subjects were contacted by telephone for further inquiry. Participants with no history of professional activity were assigned to the class of their professionally active partner. The choice for LOA as an estimate of general ability (or intelligence), instead of the more widely used level of education is discussed in more detail in Jolles et al. (1995, pp. 69-71).

Subjects who agreed in the postal survey questionnaire to participate in further studies were contacted by telephone, to inform them about the purpose of the program, session length (approximately three hours), and test schedule. An appointment was made to visit the subject at home within two weeks before the actual test session.

During the home visit the subjects were screened once more for specific medical conditions that may be associated with impaired cognitive performance (§3.2.3). In particular, all RNH exclusion criteria used in the sampling procedure were checked again in more detail and the MMSE was administered. Finally, several tests were performed to screen for primitive reflexes (§3.4.2).

In total 211 of 679 subjects who were contacted by telephone or who were visited at home eventually did not take part in the test program (Table 3.1). Eighty-five subjects (12.5%) were excluded for medical reasons, particularly in the older age groups. A substantial group of 121 subjects (18.1%) withdrew after being told about the study program in greater detail or after an appointment for the test program was made. The most reported reason for withdrawal was the expected personal investment in time and effort.

Written information about two different additional (*adnex*) studies was handed out at the end of the home visit. Participation in the MAAS test program was in no way made contingent on participation in an *adnex* study. The subjects in the age classes 30, 40, 50, 60, 70, and 80 (± 1) years were asked to take part in a collaborative study with the Department of Internal Medicine (24-hour ambulant blood pressure monitoring, see chapters 6 and 8 of this thesis). Intervening age groups in the age between 25 and 75 (± 1) years were encouraged to volunteer for additional physical fitness assessment at the Department of Movement Sciences (chapter 5). The additional studies took place within four weeks after the A₁ test program.

3.2.6 *Effect of inclusion procedure on subject characteristics in A₁*

It is important to identify systematic differences in potentially relevant background variables of the compliance and noncompliance groups that were formed on the basis of the data from the postal survey. It is known that cognitive impairment can be associated with a higher risk of morbidity and mortality and also with refusal of cognitive testing (Colsher & Wallace, 1989). Between-group differences should be taken into account with respect to the external validity of

findings in MAAS research. Particular variables of interest in this respect are age, sex, educational level, and general health status, which was operationalized as the total number of recorded health problems.

To study the relation between background characteristics and participation in the A₁ study, age level was reduced to four groups: young 25-35 years, young middle-aged 40-50 years, old middle-aged 55-65 years, and old 70-85 years. Each group consisted of approximately the same number of people. With respect to the effect of age on subject compliance, there was an increase in compliance with age in the first three age groups. A sharp decrease in the percentage of compliance was observed in the oldest age group compared to the other three groups (Jolles et al., 1995, pp. 32-35).

Participation rate was also influenced by sex, albeit only in the youngest and the oldest age group. In the youngest age group a significantly higher percentage of women were willing to participate. In the oldest age group the opposite was observed, although the difference was smaller.

The RNH educational level discerns three levels of education: *low, medium, or high*. Participation was strongly affected by educational level. Subjects in all four age groups with a lower education were less willing to participate than other subjects. No clear differences in compliance rate were found between subjects with a medium or high level of education.

With respect to the mean numbers of recorded health problems for compliance and noncompliance groups, a small but significant difference was found in the oldest aged group (mean $\pm$ SD was 6.5 ± 3.8 in the compliance group, versus 6.0 ± 3.6 in the noncompliance group, $p < .05$, Mann-Whitney *U*-Test). Thus, assuming that the number of health problems is a valid proxy for general health status, it can be concluded that health status did not seem to have an important effect on compliance rate.

Health status of the participants of the A₁ test program was compared to that of the remainder of the group that was originally selected from the RNH data base. The inclusion procedure did not affect the total number of health problems. A small but significant overall selection effect was found on the total number of active problems, i.e. slightly more active problems were present in the not-selected group ($p < .01$, Mann-Whitney *U*-Test). However, in age-stratified analyses this difference could not be attributed to one of the four age groups. This finding is in accordance with our expectations, as some volunteering subjects were excluded on medical grounds (see Jolles et al. (1995) for a more elaborate discussion on this subject).

In general, selection did not have a substantial effect on health status, based on aggregated RNH morbidity.

3.2.7 Procedure of subject enrolment in A₂, A₃ and A₄

There were some procedural differences between A₁ and other panel studies. On the basis of logistic experience and preliminary data from the A₁ study, it was deemed necessary to adjust the subject inclusion procedure in some respects. The sample number of 3,941 subjects drawn from the register in A₁ was needed to get a sufficient number of subjects with and without specific BLE in each of the 48 age by sex by LOA strata. However, a valid estimation of the

prevalence of BLE was not available until the end of A₁. Despite ample subject sampling, no adequate stratification of subjects on the basis of BLE status was possible in the youngest and oldest age cohorts. Subjects free of BLE were over-represented in the younger age categories, whereas the opposite was true for the older age categories. BLE status was therefore not maintained as a stratification criterion in A₂ to A₄. Next, as no additional advantage was expected, no home visits were performed prior to testing in A₂ to A₄. The administration of the postal questionnaire in these panel studies was restricted to only those subjects who participated in the test program, as screening of a much larger population sample was no longer necessary. Therefore, postal questionnaire and test program were merged into one functional unity from A₂ onward.

Participants in the A₂₋₄ test programs were again randomly recruited from the RNH data base (§3.2.2). They were stratified for age and sex, using the same procedure and medical exclusion criteria as described for A₁ (§3.2.3 to 3.2.5). On the basis of the compliance and exclusion rate data from A₁ and later studies, an estimate was made of the number of subjects needed to meet the age class by sex by LOA stratification criteria for each successive panel study. Generally, older subjects were oversampled, particularly older females. When for some strata the required number was not reached at finalization of one study, additional subjects were drawn in the sampling procedure for the next study. Redundant subjects in one study who were willing to participate and were still eligible with respect to age requirements were invited to take part in the next study. Interim analysis of the subjects available for A₃ and A₄ in the RNH data base revealed that specific age by sex strata had become prematurely exhausted as a result of the ample oversampling in these categories to meet the requirements for studies A₁ and A₂. At the start of MAAS, age and sex related non-compliance could not be estimated. After two studies it was concluded that non-compliance in the older age groups was a major concern. As expected, older subjects are excluded for medical reasons more often than young or middle-aged subjects. As a result, more than eightfold oversampling rates appeared necessary to meet the required number of individuals for certain strata. The 80 ± 1 year age class was omitted from A₃ and A₄, as this category was exhausted by the time the first two panel studies were completed. The option of subject recruitment from other population samples (e.g. non-RNH general practices) was considered unsatisfactory for both methodological and logistic reasons. Therefore, additional measures were taken in A₃ and A₄ to accommodate the specific needs of subjects aged 69 years and older, such as transportation to and from the test laboratory and (general) feedback of test results.

The subjects were informed about each study in a letter that was signed by the general practitioner. Willingness to participate in the test program could be indicated on a return postcard.

The response status and lost-to-follow-up status immediately after the completion of the panel studies A₁₋₄ are summarized in Table 3.1. Results for A₁ are displayed separately from other panel studies, because of the postal survey phase that preceded A₁ and the resulting two-stage sampling procedure for the test program. It can be readily observed that the compliance rate for the A₁ postal survey was twice as high compared to the compliance rate for questionnaire and test program in A₂₋₄ combined (59.2% and 30.2%, respectively). However, a much larger proportion of volunteers for the A₁ test program withdrew after telephone

Table 3.1. Response status and lost-to-follow-up status for each panel. One should note that the response status for panel A₁ pertains to the postal survey. Row totals are given separately for A₂₋₄ and A₁₋₄, because of the procedural differences between A₁ and the later three panel studies with respect to the inclusion procedure.

	Panel study					Row totals				
	A ₁		A ₂	A ₃	A ₄	A ₂₋₄		A ₁₋₄		
	N	%	N	N	N	N	%	N	%	
<i>Response status (= sample drawn from RNH)</i>										
Noncompliers ('No')	679	17.2	862	1,224	766	2,852	40.6	3,531	32.2	
Compliers ('Yes') ^a	2,362	59.2	676	703	749	2,128	30.2	4,490	40.9	
Nonresponders (no answer received)	703	17.9	509	622	541	1,672	23.8	2,375	21.7	
Removed by the GP from selection	197	5.0	89	201	89	379	5.4	576	5.2	
Column total	3,941		2,136	2,750	2,145	7,031		10,972		
<i>^a Compliers</i>										
Total tested ^b	471	69.4	498	459	446	1,403	65.9	1,874	66.8	
Exclusion after telephone contact ^c	85	12.5	70	67	79	216	10.1	301	10.7	
Exclusion due to exceeding the age limit	0	.0	28	70	117	215	10.1	215	7.7	
Not interested after telephone contact	117	17.2	63	71	78	212	10.0	329	11.7	
Did not show up for test program	6	.9	17	36	29	82	3.9	88	3.1	
Column total	679 ^d		676	703	749	2,128		2,807		
<i>^b Lost-to-follow-up status (= total tested)</i>										
Complete and reliable	468	99.4	475	446	434	1,355	96.9	1,823	97.4	
Exclusion: MMSE < 24	0	.0	13	5	9	27	1.9	27	1.4	
Unreliable test results	1	.2	7	8	1	16	1.1	17	.9	
Exclusion: other	2	.4	2	0	1	3	.1	5	.3	
Column total	471		497	459	445	1,401		1,872		
<i>^c Exclusion after telephone contact</i>										
Daily use of psychoactive medication	18	21.2	35	22	28	85	39.4	103	34.2	
Status incompatible with testing	27	31.7	12	18	10	40	18.5	67	22.3	
Cerebrovascular disease (TIA / CVA)	8	9.4	8	10	11	29	13.4	37	12.3	
Dutch not native language	0	.0	4	4	13	21	9.7	21	7.0	
Extremely poor visual / auditory function	11	13.0	2	7	5	14	6.5	25	8.3	
Other neurological conditions	9	10.6	9	1	4	14	6.5	23	7.6	
Other /undocumented	12	14.1	0	5	8	13	6.0	25	8.3	
Column total	85		70	67	79	216		301		

Note. Reference date for status assessment was the day after completion of the panel study. GP = general practitioner; MMSE = Mini-Mental State Examination; TIA = transient ischemic attack; CVA = cerebrovascular accident. ^d Number of subjects who volunteered for the A₁ test program in the postal survey that were contacted by telephone.

contact (17.2% compared to 10.0% in other panel studies). Loss of subjects as the result of exceeding the age limit did not take place in A₁ where a relative large pool of potential participants was available.

3.3 METHODS I: Postal survey

3.3.1 *Introduction*

In the first phase of the A₁ study, an extensive postal questionnaire was sent to approximately 2,350 subjects aged between 24 and 86 years. A postal survey was considered necessary for two reasons. Firstly, there was no information about the prevalence of BLE in a normal healthy population. This information was necessary for the stratification of participants in the A₁ test program (§3.2.5). Secondly, epidemiological data were needed on memory complaints or experienced change in memory and memory related functions in relation to age, psychosocial functioning, mood, and health, with reference to research question 4 (§3.1.3). The main topics of interest can be clustered as follows: demographic variables, BLE, physical health, psychological health, and subjective complaints about, or experienced changes in memory and memory-related functions, described in sections 3.3.2 to 3.3.6, respectively). The questions used were derived mainly from existing and validated questionnaires. The quality of the questionnaire in terms of comprehensibility and length was evaluated in a pilot study with 80 subjects. The final version contained approximately 500 data fields in a 32-page booklet. The following section provides more information about the five main topics in the postal survey questionnaire.

3.3.2 *Demographic variables*

Level of education was measured on an 8-point scale, ranging from primary education to higher vocational training and university (De Bie, 1987). In addition, the number of years of full-time education was recorded, to comply with the American and British scientific literature. Information was collected about marital status, socioeconomic status (working position and responsibilities, living conditions, and housing, De Bie, 1987), and the social network of the respondents.

To arrive at the level of occupational activity (LOA) of the participants (see also §3.2.5), the full description of occupational activities was given a 4-digit code (CBS, 1985). This score was then transformed to the 7-point LOA score, based on a functional classification (Van den Brand et al., 1990). The LOA score incorporates the degree of complexity of professional work, and the associated knowledge and experience required, ranging from low skilled to scientific labor. The LOA scale was originally developed as a guideline for employment and career counselling (DGA, 1989).

3.3.3 *Biological Life Events (BLE)*

The concept of BLE and its relevance for MAAS was discussed earlier. In short, BLE can be regarded as health-related factors that are associated with brain dysfunction. Nine types of BLE could be identified on the basis of information from the questionnaire: treatment by a neurologist, systemic disease, brain trauma, general anaesthesia, psychoactive medication use, alcohol and drug abuse, neurotoxic factors, treatment by a psychiatrist (within the past five years), and perinatal or developmental complications (for a further description see Jolles et al., 1995, pp. 40-41).

3.3.4 *General health*

Questions regarding past and present morbidity that may have relevance for cognitive functioning were derived from a medical screening questionnaire commonly used in general practice (LHV, 1981). Several items were added about the type of medical consultation resulting from health complaints or illnesses. Medication use (including over-the-counter drugs) was recorded and coded according to a custom classification, based on the pharmacological characteristics and side-effects of drugs (Dukes, 1988; Dukes & van Dijke, 1984).

The subjects were asked to rate their overall health on a 5-point scale in three ways: in general, compared to that of age mates, and compared to their overall health one year ago (ranging from *very bad* to *very good*). The VOG-21 (inventory of subjective health) was included as an index of subjective health (Dirken, 1967) which probes health complaints of a somatic and psychosomatic nature. It was included because of the expected relationship between subjective measures of memory and memory-related functions, and subjective health. More specific questions cover the instrumental activities of daily living (IADL), functional status, and consumption of health services, including the use of alternative health care.

3.3.5 *Lifestyle and psychological health*

Detailed information was collected about alcohol, coffee, and tea consumption, and smoking habits. Because of the expected relationship between mood and memory complaints, three subscales of the Symptom Check List (SCL-90) were included (depression, anxiety, and sleep). The SCL-90 is a widely used multidimensional checklist for psychopathological complaints (Arrindell & Ettema, 1986).

In addition to mood and health, several other psychosocial variables may play a mediating role in determining the presence or absence of complaints about cognitive functioning in later life. For this reason the questionnaire covered the following psychosocial domains: daily activities (expressed as *hours devoted to*, for example, watching television, reading, and practicing sports), experienced life-events in the past year, the quality of life, and the life-satisfaction.

3.3.6 Subjective complaints about memory and memory-related functions

Most research on age-related (subjective) changes in cognitive functioning has focused solely on memory. To what extent age-related changes occur in other cognitive domains, e.g. attentional functions, mental speed, and planning, is largely unknown. Therefore, the subjects were asked to rate their present cognitive functioning in three ways: by comparing it to that of people of their own age, by comparing it to their own level of cognitive functioning 5-10 years ago, and, finally, by comparing their present level of cognitive functioning with their functioning at the age of 25 years. The fact that subjects notice a change in their cognitive functioning does not necessarily imply that they have complaints about cognitive functioning. Therefore, specific questions were included about memory complaints and perceived hindrance in other cognitive domains (e.g. attention, reading, motor performance) and about how people dealt with this.

Detailed information about subjective memory functioning is obtained with the Metamemory in Adulthood Questionnaire (Dixon, Hultsch & Herzog, 1988). One is asked to rate, on a 5-point Likert scale, 108 statements describing one's memory functioning and the knowledge of general memory processes. The MIA is a multidimensional questionnaire consisting of seven dimensions, or subscales. Three of these scales (*change, capacity and anxiety*) can be combined to form one higher-order dimension of *memory self-efficacy*, reflecting the beliefs about one's capacity to use memory efficiently in different situations (for further details, see Jolles et al., 1995, pp. 85-94).

3.3.7 The MAAS-questionnaire in A₂₋₄

The contents of the questionnaire remained largely unmodified after the analysis of the A₁ postal survey data. The extensive MIA questionnaire was reduced to about half the length of the original questionnaire (Ponds & Jolles, 1996). Furthermore, additional questions were included regarding health-related life styles, health-related locus of control, and about one's expectations of medical services when complaints with respect to cognitive functioning were reported. The final version of the questionnaire was used in the A₂, A₃ and A₄ panel studies and now serves as the basic questionnaire for many other research projects.

3.4 METHODS II: medical and neurocognitive assessment

3.4.1 Introduction

This section describes the medical and neurocognitive measurements that were used in the A₁-A₄ studies.

Not all cognitive tests that are used in MAAS serve as dependent measures. Tests may be applied as screening instruments or even serve as exclusion criterion (e.g. the Mini-Mental State Examination (MMSE), as a screening test for possible dementia) and some are used as independent subject variables (e.g. hand preference). The outcome of several subtests from the Groningen Intelligence Test (GIT; Luteijn & van der Ploeg, 1983) are combined to make an

reliable estimation of formal IQ. Finally, variables derived from medical tests can be used as indicators of sensory function and health status and may serve as covariates in statistical analyses (e.g. visual acuity).

The majority of the dependent variables in MAAS are of course cognitive, as MAAS is essentially a cognitive gerontological project. The cognitive tests can be divided into three categories, based on the frequency of their use in the A-studies. The first is made up by those tests that are given at least once in every parallel study. They constitute a *leitmotiv* of domains of cognitive functioning probed in MAAS and, indeed, in clinical assessment. For each of these aspects of cognition, one or more variables are defined as being central to the domain. After statistical validation, these variables are used to arrive at standardized compound scores indexing specific cognitive domains (see §3.4.4). These tests are re-administered at all follow-up measurements (category 1 tests in Table 3.2). One typical example is the Verbal Learning Test, a widely used test of secondary memory.

A second category of tests is administered to subjects within several but not all A-studies. These tests are used to study specific research questions that are not central to the MAAS project, as a whole. They are administered to a sufficiently large sample population to arrive at age norms which are essentially needed if a test is to be used in a clinical setting (category 2, Table 3.2).

The third category of tests (number 3 in Table 3.2) are under development and are administered only to a subsample of one or two A_x studies. Based on the experience gained in the study, the test can be modified, or provisional norms can be drawn up. This procedure has the additional advantage that more tests can be studied (see Jolles et al., 1995).

3.4.2. Medical variables

The *anthropometric parameters* length, weight, waist, and hip circumference, are determined to calculate the Body Mass Index (BMI), and waist-to-hip ratio. Both indices are used as independent risk factors for vascular damage (Egger, 1992; Mueller et al., 1991) and can therefore be directly or indirectly associated with cognitive function. From A_2 onward, head circumference was measured as an index of cranial volume that may be used as estimate of brain reserve capacity (Graves et al., 1996).

Binocular *visual acuity* is determined by means of the Landolt-C optotype chart, at a distance of five meters, under standard luminance and with corrected vision.

Hearing acuity is assessed at four different frequencies that are important for adequate speech perception, with the aid of pure tone audiometry. Each ear is tested separately at frequencies of .5, 1.0, 2.0, and 4.0 kHz in steps of 10 dB to determine pure tone detection thresholds. The rationale to assess sensory loss is the observation that hearing defects may moderate cognitive outcome measures (Rabbitt, 1991; Van Rooij & Plomp, 1991).

Blood pressure is a well-recognized risk factor for vascular pathology. During each test session, blood pressure and pulse are measured five times in 20 minutes at fixed intervals, on the left arm and with the subject, seated, by means of an automatic recording device (Critikon Dinamap® 8100). In A_2 , two additional blood pressure measurements were performed with

the subject standing upright after 20 minutes to detect an orthostatic hypotensive reaction. Several studies have suggested that blood pressure status may be related to cognitive measures (e.g. Elias, Robbins, Schultz & Pierce, 1990; Elias, Wolf, D'Agostino, Cobb & White, 1993; Scherr, Hebert, Smith & Evans, 1991).

In A₁ only, a set of nine *primitive reflexes* were scored for amplitude and persistence according to the standard protocol of Vreeling, Jolles, Verhey and Houx (1993). For example, the existence of the grasp reflex, palmomental reflex, and pollicomental reflex was determined on both sides of the body. The prevalence of primitive reflexes increases with age and a relationship with the presence of specific BLE (e.g. general anesthesia and the use of psychotropic medication) was demonstrated earlier (Vreeling et al., 1993).

3.4.3 Cognitive variables: description of core tests

Mini Mental State Examination (MMSE). As MAAS is a study into cognitive aging, and a large number of elderly people are included, it was considered necessary to use an internationally accepted screening instrument for dementia: the Mini-Mental State Examination (Folstein et al., 1975). The MMSE is a test which broadly assesses several domains of cognitive functioning. It should be noted that the MMSE was included in MAAS because of its widespread use, *not* because of its psychometric qualities. Conclusions about the cognitive functions studied will therefore not be based upon items from this test, but on more extensive, domain-specific tests. The instrument consists of the subscales orientation, registration, recall, attention, language, and construction.

Verbal Learning Test (VLT). The *Groningen Fifteen Words Test* (Brand & Jolles, 1985; Deelman, Brouwer, van Zomeren & Saan, 1980) is an improved version of a test originally devised by Rey (1964). Fifteen words are successively presented, separated by short time intervals. Next, the subject is asked to reproduce as many words as possible. This procedure is repeated five times. After 20 minutes, delayed recall and recognition are assessed. In its present form, the VLT makes it possible to assess separately learning capacity, memory storage and memory retrieval of newly learned verbal material.

The *Letter-Digit Substitution Test (LDST)* is a modification of the procedurally identical Symbol-Digits Modalities Test (SDMT, see Lezak, 1983, pp. 554-555; Smith, 1968). In neuropsychological assessment, this coding task yields a measure of the speed of processing of general information, i.e., the test is supposed to draw upon several (cognitive) processes simultaneously, without the intention of making inferences about specific processes, such as visual scanning and perception, visual memory, visuoconstruction, or motor functions.

The *Memory Scanning Test - paper and pencil version (P&P-MST)* is designed to study the speed of memory processes (Brand & Jolles, 1987). The underlying principle is that the additional time needed to complete a test in which there is a stepwise increase in the amount of information to be kept in memory, reflects the ease at which information is processed in working memory (Sternberg, 1975).

The *Motor Choice Reaction Test (MCRT)* is a computerized test, in which reaction times are studied as a function of the complexity of task requirements (Houx, Vreeling & Jolles, 1993). In addition, the speed and accuracy of arm movements over short trajectories are also studied.

Fluency is defined here as the ability to produce as many words as possible in a given category, within a fixed time span. It is regarded as a measure for the adequate, strategy-driven retrieval of information from semantic memory. If, for instance, the subject is requested to name as many animals as possible within one minute, performance is greatly enhanced when a limited number of categories (such as farm animals or aquarium fish) are systematically searched. The naming of animals and professions / trades for one minute each is a subtest of the GIT (see below). Another fluency task that is used is to name as many four-letter words starting with a given letter (*M* and *S*) as possible.

Concept Shifting Test (CST). This is an adapted version of the Trail Making Test (TMT) that is used to measure visual conceptual and visuomotor tracking. The TMT has been used for clinical diagnostic purposes, especially as part of the Halstead-Reitan Battery (Reitan, 1958). The CST was designed to avoid several methodological problems with the TMT. On each test sheet, 16 small circles ($\varnothing$ 15 mm) are grouped in a larger circle ($\varnothing$ 8 cm). In the smaller circles, the test items (numbers (A), letters (B), or both (C)) appear in a fixed random order. Subjects are requested to cross out the items in the right order. The time needed to complete the tasks is recorded.

The *Stroop Color-Word Test (SCWT)* is often used to test selective attention (e.g. Houx, Jolles & Vreeling, 1993). It involves three cards which display a hundred stimuli each: color names, colored patches, and color names printed in incongruously colored ink (cards I-III, respectively). The amount of time needed to read (card I and III) or to name colors (card II) is recorded. Performance on card III is determined for a large part by the time needed to discard irrelevant but very salient information (verbal), in favor of a less obvious aspect (color naming), a process known as cognitive *interference*.

Four subtasks of the *Groningen Intelligence Test* (GIT, Luteijn & van der Ploeg, 1983) are administered to arrive at an estimation of the intelligence quotient, or IQ. The GIT tends to rely less on verbal abilities and is therefore deemed better suited than the also broadly used Wechsler Adult Intelligence Scale (WAIS, Wechsler, 1981) which is more performance-based. These subtasks are:

Doing sums [in Dutch: 'Cijferen'] (GIT1) involves the correct completion of as many sums (addition) as possible in one minute. As this is a timed task, it can be considered a typical performance test, involving *fluid* abilities.

Vocabulary ['Woordenlijst'] (GIT2) is a multiple-choice test for perhaps the most *crystallized* ability of all. The subject is asked to indicate which of five alternative words is exactly synonymous with a given word.

Mental rotation ['Legkaart'] (GIT3) requires the subject to indicate which two-dimensional shapes from a larger set are needed to exactly fill up a given space on the test page. Subjects have to mentally rotate each of the shapes that are, as a rule, not presented in the proper orientation. Although there are time constraints, it is not a speed test since the time allotted

per item is seldom exceeded. Apart from mental rotation, this subtest also draws heavily upon constructional abilities.

Analogies ['Woordmatrijzen'] (GIT4) can be considered as a multiple choice version of the well-known *Similarities* subtest of the WAIS. The task is to indicate which of five alternatives is related in the same way to a given word as words in an example are related. This test calls upon verbal reasoning capacity, which is thought to be primarily a crystallized ability.

An overview of all cognitive tests that were used in MAAS-A₁₋₄ in one or more panel studies is given in Table 3.2: an elaborate description of each test is given in Jolles et al. (1995).

3.4.4 *Compound scores of cognitive performance measures*

The ample cognitive data base of MAAS forces the individual researcher to make strategic choices with respect to the set of outcome measures of interest, depending on the question under study. For this purpose the use of composite cognitive scores is recommended in which raw test scores measuring performance in the same cognitive domain are combined to yield a more robust estimate of function within such domain. Three different domains are generally distinguished, *memory*, *sensorimotor* or *basic speed*, and *cognitive* or *complex speed*. The distinction in two discrete speed measures is based primarily on the assumption that some cognitive measures more closely reflect direct stimulus-response connections and only a low level of central processing (e.g. word reading or digit cancellation) while other tests draw heavily on resources and more closely reflect the time needed for higher order information processing (e.g. concept shifting, color-word interference; see Larue, 1992). This approach is employed in the chapters 4, and 7 to 9 and is discussed in more detail in chapter 10.

3.4.5 *Additional questionnaires*

Several questionnaires were added to the test battery in the course of the program.

Effort scales (A₁₋₄). Visual analogue scales are used to assess subjective effort to complete the cognitive tests. These measures are taken to study the potential discrepancy between performance and the amount of effort needed to complete a task, as is often observed in neuropsychological practice (Zijlstra & Meijman, 1989).

Satisfaction with Life Scale (SWLS; A₁₋₄). A five-item questionnaire developed as a measure of overall subjective well-being (Pavot, Diener, Randall Colvin & Sandvik, 1991).

Positive and Negative Affect Schedule (PANAS; A₁). A 20-item mood scale that measures positive and negative affect (Watson, Clark & Tellegen, 1988).

Maastricht questionnaire (A₂). This 23-item questionnaire is sensitive to psychological prodromes of cardiovascular morbidity (Appels, Höppener & Mulder, 1987) and was administered in one panel study to arrive at normative values for a non-clinical population.

Neuro-vegetative questionnaire (A₂₋₄). The questionnaire consists of a list of 28 neuro-vegetative symptoms that can be reduced to a single score. The outcome correlates with persisting complaints after mild head injury (Bohnen, Twijnstra & Jolles, 1992). Reference values for this questionnaire are obtained from three different MAAS panels.

Table 3.2. Neurocognitive test that were used in one or more A-studies.

	Category ^a	Panel study			
		A ₁	A ₂	A ₃	A ₄
Aufmerksamkeits-Belastungstest (D2)	2*		•		
Benton Visual Retention test (BVRT)	2	•			
Benton Revised Visual Retention Test (BVRT-R)	2*			•	
Boston Naming Test (BNT)	2*				•
Bicycle Drawing Test (BDT)	2	•			
Cattell Culture Fair (CCF)	2*		•		
Concept Shifting Test (CST)	1	•	•	•	•
Continuous Tapping (TAP)	2	•			
Design Fluency (DF)	3*				•
Discursive Arithmetic (DA)	3*				•
Dutch Adult Reading Test (NLV)	2	•			
Dutch Adult Reading Test: contextual version (NLV-C)	3*				•
Edinburgh Handedness Inventory (EHI) ^b	1	•	•	•	•
Episodic Memory (EM)	2	•			
Four Choice Spatial Reaction Time Task (FCSRT)	2				•
Groningen Arithmetic Memory Scanning Task (GAMST)	2*				•
Groningen Category Task (GCT)	2*				•
Groningen Intelligence Test – abbreviated (GIT) ^b	1	•	•	•	•
Letter-Digit Substitution Test (LDST)	1	•	•	•	•
Letter-Digit Substitution Test – rotated (LDST-R)	2				•
Lexical Decision Task (LDT)	3*				•
(Hypersensitivity to) Light and Sound	2*				•
Line Bisection Test (LBT)	2*			•	
Logical Memory (LM)	2*		•		
Memory Scanning Test (P&P-MST)	1	•	•	•	•
Memory Scanning test Shadows and Cubes (S&C P&P-MST)	2*			•	
Mini Mental State Examination (MMSE)	1	•	•	•	•
Motor Choice Reaction Test (MCRT)	1	•	•	•	•
Prospective Memory (PM)	3		•		
RAKIT Hidden Figures (RAK-HF)	2*				•
Raven's Standard Progressive Matrices (RSPM)	2	•			
Recognition Memory (RM)	2*		•		
Self-Paced Auditory Serial Addition Test (SPASAT)	2*		•		
Signal Detection Test (SDT)	2	•	•	•	
Stroop Color-Word Test (SCWT)	1	•	•	•	•
Stroop Color-Word Test Plus (SCWT+)	2		•		
Tower of London Test (TOL)	2	•			
Verbal Learning Test (VLT)	1	•	•	•	•
Verbal Learning Test: ISI manipulation (VLT-E)	3			•	
Verbal Learning Test: with interference (VLT-I)	3*				•
Warrington's Facial Recognition Test (WFRT)	2*		•		
Word Span Test (WST)	2	•			

Note. ^aCategory: 1 = core test included in all follow-up measurements; 2 = included for normative or validation purposes; 3 = tests under development; * = administered to a subgroup of a panel study.

^bException: core test *not* included in all follow-up measurements.

The *RAND-36* is a general health questionnaire (A_{3.4}). This scale has recently been adapted for the Dutch language and is identical to the American MOS SF-36 (Van der Zee & Sanderman, 1993). The scale defines health in terms of functional capacity and includes subscales for physical function, social function, role limitations induced by physical problems, mental health, energy, pain, and general health perception.

COOP / WONCA functional health assessment charts (A_{2.4}). The original charts probe seven aspects of functional status, physical condition, emotional condition, daily activities, social activities, overall health, change in health and pain (Nelson, Wasson, Kirk & al., 1987; Scholten & Weel, 1992). An additional chart was added regarding the cognitive status (memory and concentration). The eight charts contain simple pictograms to help respondents choose the appropriate answer. Chart scores can be used as potential predictors of cognitive outcome and to define reference values in a non-clinical population.

Loneliness questionnaire (A_{3.4}). The scale is used as a correlate of subjective outcome measures in MAAS (De Jong-Gierveld & Kamphuis, 1986). Perceived loneliness may well be a strong determinant of happiness or unhappiness and of low scores on, for instance, the Satisfaction With Life Scale (SWLS).

3.4.6 Data management

All MAAS questionnaires and test forms were structured in such a way that all data could be stored readily in numerical fields. Final versions of data files were transferred to MEMIC (Center for Data and Information Management, University of Maastricht), where all data are stored in a relational database (Register of Cognitive Aging and Dementia, RCAD). RCAD is implemented on a DEC-Alpha mini-computer, using a client-server concept. Data security is safeguarded by the use of username and password protection. Researchers who want to consult data in RCAD require permission from the register team. After approval is obtained, the data blocks are delivered by the coordinator of the register as computer files that can be readily used in standard statistical packages (e.g. SPSS). Data dictionaries can be consulted by researchers via the internet, or are made available as hard copy.

Data from the RNH register can be linked to data in RCAD for specific purposes. For example, information about past and actual morbidity can be coupled to test performance data. The key code for matching procedures is kept by MEMIC, the university service that also manages RNH. Personal identification codes are stripped from files that contain matched RNH and RCAD data by MEMIC before delivery to the requesting research department to guarantee confidentiality. RCAD complies to governmental regulations regarding registration of personal data (Wet Persoonsregistraties, 1988).

MAAS can be visited on the internet (WWW) at: <http://np0011.rulimburg.nl/MAAS/>

REFERENCES

- Appels, A., Höppener, P., & Mulder, P. A. (1987). A questionnaire to assess premonitory symptoms of myocardial infarction. *International Journal of Cardiology*, 17, 15-24.
- Arrindell, W. A., & Ettema, J. H. M. (1986). *SCL-90. Een multidimensionele psychopathologie indicator (SCL-90. A multidimensional indicator of psychopathology)*. Lisse, the Netherlands: Swets & Zeitlinger.
- Bohnen, N., Twijnstra, A., & Jolles, J. (1992). Post-traumatic and emotional symptoms in different subgroups of patients with mild head injury. *Brain Injury*, 6, 481-487.
- Brand, N., & Jolles, J. (1985). Learning and retrieval rate of words presented auditory and visually. *Journal of General Psychology*, 112, 201-210.
- Brand, N., & Jolles, J. (1987). Information processing in depression and anxiety. *Psychological Medicine*, 17, 145-153.
- Cattell, R. B. (1963). Theory of fluid and crystallized intelligence: A critical experiment. *Journal of Educational Psychology*, 54, 1-22.
- Centraal Bureau voor de Statistiek. (1985). *Beroepenclassificatie 1984 [Classification of Occupations 1984]*. Voorburg: CBS.
- Colsher, P. L., & Wallace, R. B. (1989). Data quality and age: Health and psychobehavioural correlates of item nonresponse and inconsistent responses. *Journal of Gerontology*, 44, P45-52.
- De Bie, S. E. (1987). *Standaardvragen 1987: Voorstellen voor uniformering van vraagstellingen naar achtergrondkenmerken en interviews [Standard questions 1987: Proposal for uniformization of questions regarding background variables and interviews]*. (2nd ed.). Leiden: Leiden University Press.
- De Jong-Gierveld, J., & Kamphuis, F. H. (1986). The development of a Rasch-type Loneliness scale. *Applied Psychological Measurement*, 9, 289-299.
- Deelman, B. G., Brouwer, W. H., van Zomeren, A. H., & Saan, R. J. (1980). Functiestoornissen na trauma capitis [functional disorders after brain trauma]. In A. Jennekens-Schinkel, J. J. Diamant, H. F. A. Diesfeldt, & R. Haaxma (Eds.), *Neuropsychologie in Nederland*. Deventer, The Netherlands: Van Loghum Slaterus.
- Directoraat-Generaal voor de Arbeidsvoorziening (DGA) (1989). *Handleiding voor de functie-analyse [Manual functional analysis]*. Den Haag: SDU Uitgeverij.
- Dirken, J. M. (1967). *Het meten van 'stress' in industriële situaties [Measurement of 'stress' in industrial situations]*. Groningen: Wolters.
- Dixon, R. A., Hultsch, D. F., & Herzog, C. (1988). The Metamemory in Adulthood (MIA) questionnaire. *Psychopharmacology Bulletin*, 24, 671-688.
- Dukes, M. N. G. (1988). *Meyler's side effects of drugs: An encyclopedia of adverse reactions and interactions*. (11 ed.). Amsterdam: Elsevier.
- Dukes, M. N. G., & van Dijke, C. P. H. (1984). *Bijwerkingen van geneesmiddelen [Side-effects of drugs]*. (1st ed.). Amsterdam: Elsevier.
- Egger, G. (1992). The case for using waist-to-hip ratio measurements in routine medical checks. *The Medical Journal of Australia*, 156, 280-285.
- Elias, M. F., Robbins, M. A., Schultz, J. N. R., & Pierce, T. W. (1990). Is blood pressure an important variable in research on aging and neuropsychological test performance? *Journal of Gerontology*, 45, P128-135.
- Elias, M. F., Wolf, P. A., D'Agostino, R. B., Cobb, J., & White, L. R. (1993). Untreated blood pressure level is inversely related to cognitive functioning: The Framingham Study. *American Journal of Epidemiology*, 138, 353-364.
- Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). 'Mini Mental State'. *Journal of Psychiatric Research*, 12, 189-198.
- Graves, A. B., Mortimer, J. A., Larson, E. B., Wenzlow, A., Bowen, J. D., & McCormick, W. C. (1996). Head circumference as a measure of cognitive reserve: Association with severity of impairment in Alzheimer's disease. *British Journal of Psychiatry*, 169, 86-92.
- Houx, P. J., Jolles, J., & Vreeling, F. W. (1993). Stroop interference: Aging effects assessed with the Stroop Color-Word test. *Experimental Aging Research*, 19, 209-224.
- Houx, P. J., Vreeling, F. W., & Jolles, J. (1991). Age-associated cognitive decline is related to biological life events. In K. Iqbal, D. R. C. McLachlin, B. Winblad, & H. M. Wisniewski (Eds.), *Alzheimer's disease: Basic mechanisms, diagnosis and therapeutic strategies*, (pp. 353-358). Chichester, UK: Wiley.
- Houx, P. J., Vreeling, F. W., & Jolles, J. (1993). Decline of psychomotor performance: Calendar or health? In G. E. Stelmach & V. Hömberg (Eds.), *Sensorimotor impairment in the elderly*, (Vol. 75, pp. 31-39). Dordrecht: Kluwer.
- Jolles, J., Houx, P. J., van Boxtel, M. P. J., & Ponds, R. W. H. M. (Eds.). (1995). *Maastricht Aging Study: Determinants of cognitive aging*. Maastricht: Neuropsych Publishers.
- LaRue, A. (1992). *Aging and neuropsychological assessment*. New York: Plenum Press.
- Lezak, M. D. (1983). *Neuropsychological Assessment*. (2nd ed.). New York/Oxford: Oxford University Press.

- Landelijke Huisarts Vereniging (LHV) (1981). *Vragenlijst basiskeuring [Questionnaire basic medical examination]*. Amsterdam: LHV.
- Luteijn, F., & van der Ploeg, F. A. E. (1983). *Handleiding Groninger Intelligentietest (GIT) [Manual Groningen Intelligence Test]*. Lisse, the Netherlands: Swets and Zeitlinger.
- Metsemakers, J. F. M., Höppener, P., Knottnerus, J. A., Kocken, R. J. J., & Limonard, C. B. G. (1992). Computerized health information in the Netherlands: A registration network of family practices. *British Journal of General Practice*, 42, 102-106.
- Mueller, W. H., Wear, M. L., Hanis, C. L., Emerson, J. B., Barton, S. A., Hewett-Emmett, D., & Schull, W. J. (1991). Which measure of body fat distribution is best for epidemiologic research? *American Journal of Epidemiology*, 133, 858-886.
- Nelson, E. C., Wasson, J., Kirk, J., et al. (1987). Assessment of function in routine clinical practice. Description of the COOP chart method and preliminary findings. *Journal of Chronic Diseases*, 40(Suppl. 1), 55S-64S.
- Pavor, W., Diener, E., Randall Colvin, C. R., & Sandvik, E. (1991). Further validation of the Satisfaction With Life Scale: Evidence for the cross-method convergence of well-being measures. *Journal of Personality Assessment*, 57, 149-161.
- Ponds, R. W. H. M., & Jolles, J. (1996). The abridged Dutch Metamemory in Adulthood (MIA) Questionnaire: Structure and effects of age, sex, and education. *Psychology and Aging*, 11, 324-332.
- Rabbitt, P. (1990). Applied cognitive gerontology: Some problems, methodology and data. *Applied Cognitive Psychology*, 4, 143-149.
- Rabbitt, P. (1991). Mild hearing loss can cause apparent memory failures which increase with age and reduce with IQ. *Acta Otolaryngologica Stockholm*, 476 (Suppl.), 167-176.
- Reitan, R. M. (1958). Validity of the Trail Making Test as an indication of organic brain damage. *Perceptual and Motor Skills*, 8, 271-276.
- Rey, A. (1964). *L'examen psychologique dans les cas d'encéphalopathie traumatique [Psychological assessment in cases of traumatic brain injury]*. Paris, France: Presses Universitaires de France.
- Rowe, J. W., & Kahn, R. L. (1987). Human aging: Usual and successful. *Science*, 237, 143-149.
- Scherr, P. A., Hebert, L. E., Smith, L. A., & Evans, D. A. (1991). Relation of blood pressure to cognitive function in the elderly. *American Journal of Epidemiology*, 134, 1303-1315.
- Scholten, J. H. G., & Weel, C. v. (1992). *Functional status assessment in family practice: The Dartmore COOP functional health assessment charts /WONCA*. Lelystad: Meditekst.
- Smith, A. (1968). The Symbol Digit Modalities Test: A neuropsychological test for economic screening of learning and other cerebral disorders. *Learning Disorders*, 36, 83-91.
- Sternberg, S. (1975). Memory scanning: New findings and current controversies. *Quarterly Journal of Experimental Psychology*, 27, 1-32.
- Van den Brand, P. A., Goldbohm, R. A., van 't Veer, P., Volovics, A., Hermus, R. J. J., & Sturmans, F. (1990). A large-scale prospective cohort study on diet and cancer in the Netherlands. *Journal of Clinical Epidemiology*, 43, 285-295.
- Van der Zee, K. I., & Sanderman, R. (1993). *Het meten van de algemene gezondheidstoestand met de RAND-36: Een handleiding [Measurement of general health with the RAND-36: A manual]*. (1st ed.) Groningen: Noordelijk Centrum voor Gezondheidsvraagstukken.
- Van Rooij, J. C. G. M., & Plomp, R. (1991). Auditive and cognitive factors in speech perception by elderly listeners. *Acta Otolaryngologica Stockholm*, 476, 177-181.
- Vreeling, F. W., Jolles, J., Verhey, F. R. J., & Houx, P. J. (1993). Primitive reflexes in healthy, adult volunteers and neurological patients: Methodological issues. *Journal of Neurology*, 240, 495-504.
- Watson, D., Clark, L. A., & Tellegen, A. (1988). Development and validation of brief measures of positive and negative affect: The PANAS scales. *Journal of Personality and Social Psychology*, 54, 1063-1070.
- Wechsler, D. (1981). *Manual of the Wechsler Adult Intelligence Scale-Revised*. New York: Psychological Corporation.
- White, N., & Cunningham, W. R. (1988). Is terminal drop pervasive or specific? *Journal of Gerontology*, 43, P141-144.
- Williams, J. D., & Klug, M. G. (1996). Aging and cognition: Methodological differences in outcome. *Experimental Aging Research*, 22, 219-244.
- Zijlstra, F., & Meijman, T. (1989). Het meten van mentale inspanning met behulp van een subjectieve methode [Measurement of mental effort using a subjective method]. In T. Meijman (Ed.), *Mentale belasting en werkstress*, (pp. 42-61). Assen/Maastricht: Van Gorcum.

Chapter 4

Self-reported physical activity, subjective health, and cognitive performance in older adults²

ABSTRACT

The literature to date suggests a positive relationship between physiological indicators of physical fitness (such as aerobic capacity) and indices of cognitive performance. However, the complexity and cost of methods to measure physical fitness prohibits their use in large population studies in cognitive aging research. In this study a questionnaire measuring habitual physical activity was used as an indirect estimate of physical fitness, to predict performance in several cognitive domains in an age and sex stratified sample of 80 healthy older adults (55 years and over). Age effects were found on several measures of cognitive speed and fluency, but not on memory performance. Women were slower in sensorimotor speed than men but scored higher on memory tasks. No main effects of activity on cognitive measures were found, but two measures which assess cognitive speed were sensitive to the age by activity interaction term. Subjective health also appeared to contribute to the explained variance in the same two indices of cognitive speed. Limitations of the use of activity questionnaires in cognitive aging research are discussed.

INTRODUCTION

Evidence from population studies suggests that several basic cognitive abilities are affected by chronological age (Poon, 1985). In particular, tasks that involve some form of fluid intelligence, secondary memory, abstract reasoning or visuospatial abilities show an age-related decline (for a comprehensive review, see LaRue, 1992). Recently, it was demonstrated that factors which could potentially influence brain functioning may have a substantial effect on the cognitive performance of healthy elderly subjects (Houx & Jolles, 1993; Houx, Vreeling & Jolles, 1991). Habitual physical activity has received much attention in this respect as a potential protective factor for neurocognitive functioning (Chodzko-Zajko, 1991).

Physical activity may improve the aerobic capacity, defined as the maximal oxygen consumption of the body, and may be positively related to brain function in several ways. Improvement of cerebral blood flow through physical activity can play an important role in the maintenance of adequate brain function in old age (Rogers, Meyer & Mortel, 1990). Physical exercise may increase the oxidative capacity of the brain and is presumed to exert a trophic effect on brain centers involved in sensorimotor function (Spirduso, 1980).

² M. P. J. van Boxtel, K. Langerak, P. J. Houx, and J. Jolles (1996). *Experimental Aging Research*, 22, 363-379.

Several cross-sectional studies suggest a positive relationship in older adults between aerobic capacity or aerobic exercise level and, e.g., reaction time, working memory, abstract reasoning (Clarkson-Smith & Hartley, 1989; Clarkson-Smith & Hartley, 1990), psychomotor speed (Baylor & Spirduso, 1988; Spirduso, 1975), symbol-digit substitution (Stones & Kozma, 1989), and visuospatial processing (Shay & Roth, 1992). However, longitudinal studies that have directly manipulated aerobic capacity in an exercise intervention program have yielded mixed results. Elsayed, Ismail and Young (1980) found that a 4-month aerobic training program improved the performance of a relatively young sample (24-68 year) on subtests of fluid intelligence, but not on crystallized intelligence. In another study, a 55-70 year old group was investigated before and after a 4-month exercise program (Dustman et al., 1984). The performance in this group showed an exercise related improvement of simple reaction time, digit-symbol substitution and Stroop interference, but not of nonverbal reasoning or choice reaction time. In another sample of older adults (60-83 year) no exercise-mediated improvement was found on reaction time tests of attention and memory retrieval after 16 weeks of aerobic exercise training (Madden, Blumenthal, Allen & Emery, 1989). Blumenthal and Madden (1988) found that the memory search performance of middle-aged subjects (30-58 years) was positively related to aerobic capacity only at the start of a 12-week fitness program but was unrelated to the increased fitness achieved in this period. Finally, in another study no improvement on a broad range of cognitive performance measures was found after a 1-year training program in sedentary older subjects between 60 and 73 years of age (Hill, Storandt & Malley, 1993). In summary, older subjects with an active lifestyle often perform better than their sedentary contemporaries on performance tasks that are typically sensitive to the effects of age. The effects of short-term exercise intervention programs on performance are, however, equivocal (Hawkins, Kramer & Capaldi, 1992).

Population-based research aimed at the complex relationship between physical activity and cognitive function is frustrated by a lack of practical and valid instruments to estimate the level of physical activity. In general, there is a strong need for comprehensive methods to measure energy expenditure directly or indirectly (LaPorte, Montoye & Caspersen, 1985). The most valid and reliable methods to date are based on physiological monitoring, e.g. by determining the maximal oxygen consumption ($\text{VO}_2\text{-max}$). Such techniques are laborious, expensive, and may even interfere with the actual behavior under study. In addition, performance-based measures may be unsuitable for older individuals or may imply a serious health hazard. Survey methods using questionnaires are practical in larger studies but must be validated for specific usage (Montoye & Taylor, 1984; Washburn & Montoye, 1986).

In the present study, the level of habitual physical activity was measured by using a questionnaire that has recently become available for use in gerontological populations to assess activity-based caloric expenditure (Voorrips, Ravelli, Dongelmans, Deurenberg & van Staveren, 1991). On the assumption that energy expenditure can be estimated indirectly by using a questionnaire that measures habitual physical activity, this study evaluates the predictive value of habitual activity on cognitive performance, as measured by objective tests. It is hypothesized that speeded tasks that require effortful processing of new information are most sensitive to the level of physical activity (Chodzko-Zajko, 1991). In addition, a measure of subjective health was used as copredictor of cognitive performance in view of the fact that

physical activity and health status are related phenomena, especially in older study groups (Clarkson-Smith & Hartley, 1990). Moreover, self-reported physical health has been related to performance in tests for crystallized and fluid intelligence (Perlmutter & Nyquist, 1990).

METHODS

Subjects

Eighty subjects were included in the study, stratified for sex and age in five continuous age classes (55-59 years, 60-64 years, 65-69 years, 70-74 years, and 75 years and older). To reach this number, healthy community dwelling subjects were recruited through newspaper advertisements and direct mailing of organizations for older people in the region of Maastricht, the Netherlands. To assure participation of sufficiently physically active subjects, local organizations which provide aerobic sports for older adults were included in the mailing. A total of 228 subjects volunteered for the study, of whom 107 were screened by telephone for exclusion criteria to yield sufficient subjects in each stratum, i.e. actual medical conditions with a possible impact on brain function; a history of cerebrovascular disease (stroke, transient ischemic attacks), epilepsy, parkinsonism, neurosurgery, other chronic neurological states, psychiatric disorders or actual daily use of psychotropic drugs. Twenty-seven subjects in this group did not meet the health criteria, the use of sedatives or hypnotics being the most prominent reason for exclusion. All 80 participants were professionally inactive, which is a prerequisite for the use of the actual physical activity questionnaire (APAQ; see next section). Table 4.1 presents demographic information about the study population.

Procedure

All participants completed a postal questionnaire that served as the basis for the interview within two weeks after the health screen by telephone. A semi-structured interview of 1.5 hours was conducted by two trained senior medical students. It consisted of a check of the postal questionnaire for completeness and administration of the Mini-Mental State Examination (MMSE), physical activity questionnaire and a cognitive test battery that lasted 45 minutes. Subjects were paid Hfl. 20.= for their participation.

Measurements

Demographic variables and health status. Socioeconomic background and detailed medical information were obtained with the postal questionnaire. The questionnaire consists of standard rating scales to assess level of education, ranging from primary education to higher vocational training and university on an 8-point scale (De Bie, 1987), demographic parameters, medical history, and subjective health. The latter is expressed as the total of affirmative answers on a 21-item health complaint rating scale (inventory of subjective health, ISH, Dirken, 1967). The Mini-Mental State Examination (MMSE, Folstein, Folstein & McHugh, 1975) was used to

screen for dementia. It was decided to exclude individuals with a MMSE score below 24, but all screened subjects scored well above this limit (Table 4.1).

Actual Physical Activity Questionnaire (APAQ). This semi-structured questionnaire probes three domains of physical activity in the preceding year that are relevant for older people: household work, sport, and leisure-time physical activity. The caloric work load of household activities was scored as total outcome on ten rating scales. Sport and leisure-time activity scores were the sums of the products of estimated caloric intensity (expressed in an intensity code with no unit, derived from estimated energy costs) and reported frequency, for each sport or activity. The overall index of the daily caloric expenditure is expressed as the total of scores in the three activity domains. The APAQ score correlates reasonably well with pedometer data and measures of dietary caloric intake (Spearman's r of .72 and .78, respectively, Voorrips et al., 1991) but has to date not been validated with direct measures of caloric expenditure, such as $\text{VO}_2\text{-max}$.

Short Cognitive Screening Battery (SCSB). A set of standard neuropsychological tests was used to assess different aspects of cognitive function (SCSB, Jolles, Houx, van Boxtel & Ponds, 1995). The test battery includes tasks to assess the neuropsychological core constructs immediate and delayed recall, attentional capacity, planning, verbal intelligence, and sensorimotor speed (Jolles, 1985). A short description of each test is given below.

Word Learning Task (WLT). This test is based upon the Auditory Verbal Learning Test (Brand & Jolles, 1985) and evaluates the ability to acquire and retain new verbal information. Fifteen frequently used monosyllabic words are presented, in three trials, on cards at a rate of one every two seconds. The subject is instructed to memorize the words. Each trial ends with a free recall of the words. This procedure is repeated two times, using the same word set in fixed order. After 20 minutes the subject is asked to reproduce the set of words. The total number of correctly reproduced words on the three immediate recall trials is recorded, together with the maximum score in three trials and the number of correctly reproduced words after 20 minutes (Houx et al., 1991).

Concept Shifting Task (CST). Based on the trail making task of the Army Individual Test Battery, this test evaluates behavioral planning and evaluation (Houx et al., 1991). The subject's ability to alternate two psychological concepts during task performance is measured, i.e., number and letter cancellation in correct order. A test sheet contains 16 small diameter circles ($\varnothing$ 15 mm) arranged in a larger circle ($\varnothing$ 16 cm). Two *null* versions (part 0) contain no symbols in the circles, the number version (part A) presents figures 1 to 16 in random order in the circles, a letter version (part B) depicts random letters, and finally a number / letter version (part C) alternates the numbers 1 to 8 and letters A to H. The subject is instructed to cross out the circles in correct order, as fast as possible without making errors. The time required to complete each task is recorded.

Letter Digit Substitution Test (LDST). This paper-and-pencil test is a modified version of the Symbol Digit Modalities Test (SDMT, Smith, 1968) and measures fundamental information processing speed. The subject is requested to copy numbers in cells that are indexed by a letter. The letter refers to nine letter / number combinations at the top of the form. The total number of correctly copied corresponding numbers in 60 seconds is recorded as test outcome.

Stroop Color-Word Test (SCWT). The abbreviated version of this perceptual interference test consists of three subtasks. Each subtask consists of a test sheet containing four rows of ten columns of color names or colored spots. The test examines the speed at which color names are read (subtask I) and the speed at which color spots are named (subtask II). Subtask III involves color names again but the printing ink is different from the color name. The speed at which the color of the printing ink of the words is named is recorded. This test shows robust effects of chronological age (Houx, Jolles & Vreeling, 1993).

Word Fluency. The total number of animal names correctly reproduced in 60 seconds is recorded (Luteijn & van der Ploeg, 1983). The test reflects the level of organization among clusters of meaningful related words.

Dutch Adult Reading Test (DART). This is the Dutch version of the National Adult Reading Test, NART (Nelson, 1982). A series of 50 words with an irregular pronunciation has to be reproduced correctly by the subject. The DART score is calculated from the number of words pronounced correctly multiplied by two, raised with the number of doubtfully correctly reproduced words. Scores can be converted to WAIS-IQ (Schmand, Lindeboom & van Harskamp, 1992) but we preferred to use the more elementary raw score. In patients suffering from brain damage this test reflects the premorbid level of verbal intelligence (Schmand, Bakker, Saan & Louman, 1991). The DART score was used in this study to control for intelligence level as a known predictor of cognitive performance.

Continuous tapping (TAP). Though not part of the SCSB, this test was included to assess peripheral motor speed more specifically (Houx, 1991). The subject is required to press the button of an electronic counting device with the index finger at maximum frequency for 20 seconds. Dominant and non dominant hands are tested alternately twice. The average number of taps over these four trials is recorded.

Data reduction and analysis

Selected raw test scores for specific performance tasks were clustered in the three domains *memory*, *cognitive flexibility*, and *sensorimotor speed*, to yield compound cognitive performance indices. This was done to reduce the number of dependent variables while improving the robustness of the underlying cognitive construct. Raw test scores were transformed to Z-scores in the total population. Next, the average was calculated of the Z-transformed scores that were included in a compound performance index. Thus a *memory* score was derived from the Z-transformed total, maximal and delayed recall scores of the WLT. The *cognitive flexibility* score included the C version of the CST and subtask III of the SCWT (LaRue, 1992, pp. 114-115) and *sensorimotor speed* was calculated from the 0, A and B versions of the CST, the continuous tapping score, and subtask I of the SCWT. In formula:

$$\text{Memory (MEMORY)} = (Z_{\text{WLTOT}} + Z_{\text{WLTMAX}} + Z_{\text{WLTDEL}}) / 3$$

$$\text{Cognitive flexibility (FLEX)} = - (Z_{\text{CST-C}} + Z_{\text{SCWT-III}}) / 2$$

$$\text{Sensorimotor speed (SPEED-S)} = - (Z_{\text{CST-0}} + Z_{\text{CST-A}} + Z_{\text{CST-B}} - Z_{\text{TAP}} + Z_{\text{SCWT-I}}) / 5$$

The sign of the speed and flexibility score was inverted to make them reflect above average performance when positive and below average performance when negative. LDST and fluency test outcomes were treated as separate variables as performance in these tests draws on virtually every aspect of cognitive function.

In the first step of data analysis, multivariate analysis of variance (MANOVA) and separate univariate ANOVA's were performed on subjective health (ISH), physical activity level (APAQ), and cognitive scores to detect effects of age and sex. Next, hierarchical regression analysis was performed on five cognitive performance scores with age, sex, DART intelligence, APAQ, and ISH as potential predictors of cognitive test outcome. In addition, the APAQ by age and the ISH by age interaction terms were entered in the model to study the possibility that age moderates the effects of APAQ and ISH. Residual scores were screened for systematic trends, but were not identified in the five final models. Error probabilities of .05 or less were considered as statistically significant. All analyses were performed with the SPSS statistical software series.

RESULTS

Physical activity level, subjective health, and cognitive test outcome by age class and sex are listed in Table 4.1. The average score on education (3.5) was equivalent to secondary level education (De Bie, 1987). A multivariate analysis of variance test revealed a significant age (Wilks $F(32,234) = 2.19, p < .001$), sex ($F(8,63) = 2.51, p < .05$), but no age by sex interaction effect ($F(32,234) = 1.06, n.s.$) for a combination of main independent and dependent variables that were included in the regression models. In separate univariate ANOVA's (Table 4.2) no main or interaction effect of age and sex was found on measures of intelligence, activity level, or subjective health, suggesting a homogeneous distribution of these predictor variables in the study population. However, the compound speed and flexibility measures, LDST and fluency, showed strong age effects that indicated lower scores with increasing age. No age effect was found on the memory score. A sex difference was found on compound scores for memory and sensorimotor speed: women were slower than men but had higher scores for memory. Sex did not moderate the age effects on cognitive performance: no significant age by sex interaction effects were demonstrated.

In Table 4.3 the zero-order correlations are shown between predictor variables and dependent variables. Apart from a weak but significant negative correlation between APAQ and ISH scores ($r = -.28; p \leq .05$, two-tailed), no significant relationship between predictor variables appeared to exist in the study population. All five cognitive outcome measures were highly correlated ($r = .33$ to $.77$), with age as an intermediate variable that was also strongly predictive for all these cognitive measures ($r = -.29$ to $-.66$). The negative correlation between the memory score and age was significant ($r = -.29, p < .01$), in contrast to the absence of an age effect on memory in the univariate ANOVA.

A series of hierarchical regression analyses were performed to predict cognitive measures from the background variables age, sex, and intelligence (DART) and the experimental variables physical activity level (APAQ), subjective health (ISH), and the interaction terms of

Table 4.1. Mean ($\pm$ SD) levels of background characteristics, physical activity, subjective health, and cognitive performance measures by age class and sex.

	Age class (years)					Sex	
	55-59	60-64	65-69	70-74	≥ 75	Male	Female
<i>n</i>	16	16	16	16	16	40	40
Age	57.4 (1.5)	61.8 (1.2)	67.0 (1.5)	71.2 (1.1)	78.3 (3.0)	67.5 (7.9)	66.8 (7.3)
Education	4.4 (1.6)	4.3 (1.7)	2.8 (2.1)	2.9 (2.0)	2.9 (2.2)	3.6 (2.3)	3.4 (1.9)
MMSE	29.6 (.7)	29.3 (1.0)	29.1 (1.4)	29.2 (.8)	28.9 (1.2)	29.2 (1.1)	29.2 (1.1)
DART ^a	85.5 (16.3)	82.8 (20.5)	80.6 (18.5)	81.8 (15.8)	75.8 (17.3)	81.8 (15.0)	80.8 (20.1)
APAQ	10.8 (4.9)	7.6 (3.7)	9.0 (3.6)	9.3 (4.6)	7.4 (4.2)	9.2 (4.5)	8.4 (4.2)
ISH	3.8 (3.8)	4.7 (3.6)	3.2 (2.4)	4.4 (4.8)	4.9 (3.7)	4.0 (3.7)	4.5 (3.7)
MEMORY ^b	.52 (.81)	-.06 (.73)	.00 (.92)	-.2 (.86)	-.30 (1.13)	-.25 (.99)	.25 (.79)
SPEED-S ^b	.57 (.37)	.24 (.53)	.09 (.54)	-.29 (.47)	-.62 (1.04)	.15 (.80)	-.15 (.66)
FLEX ^b	.61 (.46)	.42 (.54)	.21 (.56)	-.24 (.57)	-.99 (1.16)	.05 (.98)	-.05 (.81)
LDST	35.1 (5.3)	30.3 (5.3)	31.1 (6.2)	25.5 (4.6)	23.1 (6.6)	28.8 (7.0)	29.3 (7.0)
Fluency	28.1 (5.1)	25.1 (5.0)	23.0 (6.1)	22.3 (6.1)	20.7 (6.9)	24.3 (6.5)	23.3 (6.1)

Note. MMSE = Mini-Mental State Examination score, DART = Dutch Adult Reading Test score, APAQ = actual physical activity questionnaire score, ISH = inventory of subjective health score, MEMORY = compound memory score, SPEED-S = compound sensorimotor speed score, FLEX = compound cognitive flexibility score, LDST = Letter Digit Substitution Test score.

^aMean DART scores for men and women are equivalent to WAIS-IQ scores of 102 and 103, respectively (Schmand et al., 1992). ^bPopulation-based Z-scores.

age with each of the latter two variables. In the first step of the analysis the background variables were entered in the equation (Table 4.4). In separate steps thereafter, APAQ, APAQ by age, ISH, and ISH by age were entered.

The background variables age, sex, and intelligence explained the largest amount of variance in cognitive measures. The proportion of explained variance in cognitive measure ranged from .17 for memory and fluency scores to .54 for the cognitive flexibility score. Beta coefficients that range from -.24 (MEMORY) to -.57 (LDST) indicate the predominant load of

Table 4.2. Effects of age and sex and their interaction in univariate ANOVA's on DART intelligence, physical activity, subjective health and cognitive performance.

	Age <i>F</i> (4,70)	Sex <i>F</i> (1,70)	Age x Sex <i>F</i> (4,70)
DART	<1	<1	1.04
APAQ	1.77	<1	1.17
ISH	<1	<1	<1
MEMORY	2.20	6.49*	<1
SPEED-S	9.05***	4.75*	1.15
FLEX	12.54***	<1	<1
LDST	11.14***	<1	<1
Fluency	3.68**	<1	<1

Note. DART = Dutch Adult Reading Test score, APAQ = actual physical activity questionnaire score, ISH = inventory of subjective health score, MEMORY = memory score, SPEED-S = sensorimotor speed score, FLEX = cognitive flexibility score, LDST = Letter Digit Substitution Test score.

* $p \leq .05$, ** $p \leq .01$, *** $p \leq .001$.

Table 4.3. Zero-order correlations between predictor variables ($N = 80$ for all coefficients).

	1	2	3	4	5	6	7	8	9
1. Age	.								
2. Sex	-.05	.							
3. DART	-.17	-.03	.						
4. APAQ	-.15	-.09	.02	.					
5. ISH	.08	.07	-.07	-.28*	.				
6. MEMORY	-.29**	.27*	.18	.05	-.07	.			
7. SPEED-S	-.58**	-.20	.23*	.16	-.24*	.38**	.		
8. FLEX	-.66**	-.06	.42**	.15	-.24*	.36**	.77**	.	
9. LDST	-.61**	.03	.26*	.10	-.25*	.47**	.71**	.72**	.
10. Fluency	-.39**	-.08	.20	.17	-.24*	.33**	.44**	.51**	.43**

Note. DART = Dutch Adult Reading Test score, APAQ = actual physical activity questionnaire score, ISH = inventory of subjective health score, MEMORY = memory score, SPEED-S = sensorimotor speed score, FLEX = cognitive flexibility score, LDST = Letter Digit Substitution Test score.

* $p \leq .05$, ** $p \leq .01$.

chronological age on all cognitive measures. The habitual physical activity score did not add significantly to the explained variance in step two: R^2 remained virtually unchanged after step two in all five models. Cognitive flexibility and LDST, however, were positively correlated with the APAQ by age interaction term in step three. This may be interpreted as higher performance scores, when a high APAQ is associated with a relatively old age, or vice versa. In step four subjective health increased the explanatory power of two of the models further, again for cognitive flexibility (2%) and LDST (4%). In step five the ISH by age interaction term did not alter one of the models significantly, thus indicating no differential effect of subjective health with age on performance. In addition, as APAQ score and subjective health score were significantly correlated ($r = -.28$), it was investigated post hoc if the effect of health on cognitive variables was moderated by the activity level: no activity by health interaction effects could be demonstrated when the APAQ by ISH interaction term was added to the models after step 5 (results not shown).

Table 4.4. Hierarchical regression analysis on cognitive measures: standardized regression coefficients (*Beta*) in the final model, *R*² and significance of *R*² change after each step.

Predictors	MEMORY		SPEED-S		FLEX		LDST		Fluency	
	<i>Beta</i>	<i>R</i> ²	<i>Beta</i>	<i>R</i> ²	<i>Beta</i>	<i>R</i> ²	<i>Beta</i>	<i>R</i> ²	<i>Beta</i>	<i>R</i> ²
1. Age	-.22	.17**	-.57	.41***	-.62	.54***	-.57	.39***	-.35	.17*
Sex ^a	.28		-.22		-.08		.01		-.08	
DART	.14		.11		.30		.15		.12	
2. APAQ	.03	.17	.01	.41	.01	.55	-.03	.39	.07	.19
3. APAQ x Age	-.04	.17	.14	.43	.23	.59**	.20	.44*	.17	.22
4. ISH	-.04	.17	-.17	.46	-.17	.61*	-.21	.48*	-.18	.25
5. ISH x Age	-.21	.21	.05	.46	.11	.62	-.04	.48	-.03	.25

Note. DART = Dutch Adult Reading Test score, APAQ = actual physical activity questionnaire score, ISH = inventory of subjective health score, MEMORY = memory score, SPEED-S = sensorimotor speed score, FLEX = cognitive flexibility score, LDST = Letter Digit Substitution Test score.

^aSex: 1 = male, 2 = female

* $p \leq .05$, ** $p \leq .01$, *** $p \leq .001$.

Finally, to test the possibility that age was masking the effects of variables introduced after step one, age was also entered last instead of in the first step. This procedure yielded essentially the same pattern of effects and the results are therefore not presented here.

DISCUSSION

In this study the predictive value of a habitual activity questionnaire score for cognitive performance was tested in a population of healthy older adults. Strong effects of age were found on several measures of cognitive flexibility and fluency, but not on memory. Women performed worse on sensorimotor tasks but better on memory-related tasks than men. The activity score measured with the physical activity questionnaire (APAQ) did not appear to contribute significantly to explaining variance in the three cognitive domains of memory, sensorimotor and cognitive flexibility, or the word fluency or LDST performance, when the effects of chronological age, sex and intelligence were controlled for. However, the small but significant contribution of the age by activity interaction term on cognitive flexibility and LDST performance may indicate a differential effect of activity with age on basic information processing speed. These findings are in agreement with other recent studies showing age by activity interaction effects on complex cognitive tasks, although these studies used less specific activity measures (Christensen & Mackinnon, 1993; Hultsch, Hammer & Small, 1993). Still, the absence of a main effect of activity on performance does raise several questions that have to be dealt with.

Activity

Given that the APAQ score and cognitive performance do not seem to be related, it can be argued that the distribution of APAQ scores in the present study is not representative for an

active older population, in part due to self-selection of participants. However, mean APAQ scores in the study of Voorrips et al. (1991), who used a comparable subject inclusion procedure and population age range (63–80 year), were comparable to the present results ($M = 11.0$ ($SD\ 4.6$), vs. $M = 8.8$ ($SD\ 4.3$) in this study). Still, it is remarkable that the APAQ scores were independent of age in the present study, in contrast to earlier findings that the habitual activity level tends to be lower in older age groups (e.g. Kannel & Sorlie, 1979). This might be because relatively active older adults were recruited as the result of the inclusion procedure, to achieve an adequate representation of active subjects in the older age classes. Random recruitment from the general population, irrespective of activity level, would have been an alternative inclusion strategy, but for a population based study larger samples are needed to attain adequate variance of activity level in all age groups.

It seems inevitable that some degree of inaccuracy remains when daily caloric expenditure is estimated from an activity questionnaire. Subjects may, whether or not deliberately, be inaccurate in their report of daily activities, thereby affecting the validity of the questionnaire. A particular problem with the use of activity scales in aging research based on self report is that the outcome largely relies upon the ability of subjects to recall recent experiences, a cognitive skill that is known to decline with age (Poon, 1985). The free recall capability may have a particular impact on the APAQ cluster 'leisure-time activities', where the meticulous reporting of relatively minor activities may add up to a substantial cluster score. In addition, it is not clear if the intensity of these relatively low aerobic activities is substantial enough to contribute to the overall aerobic capacity. This suggests the need for further validation of the APAQ score with other physiologically based indices of caloric expenditure, particularly the maximal oxygen uptake ($VO_{2\text{-max}}$).

The present findings and the discussion above raise another important issue. It has been suggested that the physical activity history should be taken into account when the relationship between aerobic capacity and cognitive function is studied (Paas, Adam, Janssen, Vrencken & Bovens, 1994). If the assumption holds that the maintenance of an adequate level of physical activity throughout life provides a cognitive reserve capacity in old age – equivalent to a reduced risk of osteoporosis – then the actual level may grossly under- or overestimate the lifetime effect of physical activity. This notion accentuates the need of a valid instrument to estimate lifetime physical activity. Several attempts have been made to measure this construct (Kriska et al., 1988; Voorrips, et al., 1992), but the methodological difficulties are obvious.

Taken together, the present findings suggest that the more widespread use of a questionnaire-based index of habitual physical activity as a predictor of cognitive performance cannot be advocated until the relationship between habitual physical activity and physiological indices of physical fitness is further elucidated. It may, however, still be of some interest to test the external validity of our conclusions and to replicate the above results in a larger, population based study, as in this study active elderly are potentially over-represented.

Health

Subject selection based on health criteria was deemed necessary to control for the potential modification of the effect of activity on cognitive performance (Christensen, Moye, Armson &

Kern, 1992). It cannot be ruled out, however, that a more rigorous health screening procedure would have attenuated several of the effects found in this study, in particular that of age on speeded performance tasks. The issue of adequate subject selection is difficult to resolve, as rigorous health screening will inevitably result in study groups that are no longer representative for age-matched population samples, as they may differ in more respects than the factor health alone, such as personality characteristics or nutritional factors (Spirduso & MacRae, 1990).

In our study, subjective health was positively related to cognitive flexibility and LDST but, in contrast to activity, no interactions with age were observed. This would be in partial agreement with recent findings that older subjects who are regarded as healthy according to gerontological criteria can be divided into two groups on the basis of the absence or presence of mild health-related factors (Houx, 1991; Houx & Jolles, 1993). Houx et al. (1991) found that very old subjects (80 years) without these factors and who judged their subjective health as 'good' were not characterized by the usual age-related cognitive decline. Health as a construct obviously includes more than health perception alone, and although some authors suggest a close relationship between subjective health and more objective health assessments (e.g. physician rated health, LaRue, Bank, Jarvik & Hetland, 1979) it is preferable to define health as a multidimensional characteristic of subjects (and to measure it accordingly). In doing this, one may arrive at more specific conclusions about which aspect of health is relevant for cognitive function throughout life.

REFERENCES

- Baylor, A. M., & Spirduso, W. W. (1988). Systematic aerobic exercise and components of reaction time in older women. *Journal of Gerontology*, 43, P121-126.
- Blumenthal, J. A., & Madden, D. J. (1988). Effects of aerobic exercise training, age, and physical fitness on memory-search performance. *Psychology and Aging*, 3, 280-285.
- Brand, N., & Jolles, J. (1985). Learning and retrieval rate of words presented auditory and visually. *Journal of General Psychology*, 112, 201-210.
- Chodzko-Zajko, W. J. (1991). Physical fitness, cognitive performance, and aging. *Medicine and Science in Sports and Exercise*, 23, 868-872.
- Christensen, H., & Mackinnon, A. (1993). The association between mental, social and physical activity and cognitive performance in young and old subjects. *Age and Ageing*, 22, 175-182.
- Christensen, K. J., Moye, J., Armson, R. R., & Kern, T. M. (1992). Health screening and random recruitment for cognitive aging research. *Psychology and Aging*, 7, 204-208.
- Clarkson-Smith, L., & Hartley, A. A. (1989). Relationships between physical exercise and cognitive abilities in older adults. *Psychology and Aging*, 4, 183-189.
- Clarkson-Smith, L., & Hartley, A. A. (1990). Structural equation models of relationships between exercise and cognitive abilities. *Psychology and Aging*, 5, 437-446.
- De Bie, S. E. (1987). *Standard questions 1987: Proposal for uniformization of questions regarding background variables and interviews*. (2nd ed.). Leiden: Leiden University Press.
- Dirken, J. M. (1967). *Measurement of 'stress' in industrial situations*. Groningen: Wolters.
- Dustman, R. E., Ruhling, R. O., Russell, E. M., Shearer, D. E., Bonekat, H. W., Shigeoka, J. W., Wood, J. S., & Bradford, D. C. (1984). Aerobic exercise training and improved neuropsychological function of older individuals. *Neurobiology of Aging*, 5, 35-42.
- Elsayed, M., Ismail, A. H., & Young, R. J. (1980). Intellectual differences of adult men related to age and physical fitness before and after an exercise program. *Journal of Gerontology*, 35, 383-387.
- Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini Mental State". *Journal of Psychiatric Research*, 12, 189-198.
- Hawkins, H.L., Kramer, H.F., & Capaldi, D. (1992). Aging, exercise and attention. *Psychology and Aging*, 7, 643-653.
- Hill, R. D., Storandt, M., & Malley, M. (1993). The impact of long-term exercise training on psychological function in older adults. *Journal of Gerontology*, 48, P12-17.
- Houx, P. J. (1991). *Cognitive aging and health related factors*. Doctoral Thesis, University of Maastricht.

- Houx, P. J., & Jolles, J. (1993). Age-related decline of psychomotor speed: Effects of age, brain health, sex, and education. *Perceptual and Motor Skills*, 76, 195-211.
- Houx, P. J., Jolles, J., & Vreeling, F. W. (1993). Stroop interference: aging effects assessed with the Stroop Color-Word test. *Experimental Aging Research*, 19, 209-224.
- Houx, P. J., Vreeling, F. W., & Jolles, J. (1991). Age-associated cognitive decline is related to biological life events. In K. Iqbal, D. R. C. McLachlin, B. Winblad, & H. M. Wisniewski (Eds.), *Alzheimer's disease: Basic mechanisms, diagnosis and therapeutic strategies*, (pp. 353-358). Chichester, UK: Wiley.
- Hultsch, D. F., Hammer, D., & Small, B. J. (1993). Age differences in cognitive performance in later life: Relationships to self-reported health and activity life style. *Journal of Gerontology*, 48, P1-11.
- Jolles, J. (1985). Early diagnosis of dementia: possible contributions from neuropsychology. In W. H. Gispen & J. Traber (Eds.), *Aging of the brain*, (pp. 84-100). Berlin: Springer.
- Jolles, J., Houx, P. J., van Boxtel, M. P. J., & Ponds, R. W. H. M. (Eds.). (1995). *Maastricht Aging Study: determinants of cognitive aging*. Maastricht: Neuropsych Publishers.
- Kannel, W. B., & Sorlie, P. (1979). Some health benefits of physical activity: The Framingham study. *Archives of Internal Medicine*, 139, 857-861.
- Kriska, A. M., Sandler, R. B., Cauley, J. A., LaPorte, R. E., Hom, D. L., & Pambianco, G. (1988). The assessment of historical physical activity and its relation to adult bone parameters. *American Journal of Epidemiology*, 127, 1053-1063.
- LaPorte, R. E., Montoye, H. J., & Caspersen, C. J. (1985). Assessment of physical activity in epidemiologic research: Problems and prospects. *Public Health Reports*, 100, 131-146.
- LaRue, A. (1992). *Aging and neuropsychological assessment*. New York: Plenum Press.
- LaRue, A., Bank, L., Jarvik, L., & Hetland, M. (1979). Health in old age: How do physician's ratings and self-ratings compare? *Journal of Gerontology*, 34, 687-691.
- Luteijn, F., & van der Ploeg, F. A. E. (1983). *Handleiding Groninger Intelligentietest (GIT) [Manual Groningen Intelligence Test]*. Lisse, the Netherlands: Swets & Zeitlinger.
- Madden, D. J., Blumenthal, J. A., Allen, P. A., & Emery, C. F. (1989). Improving aerobic capacity in healthy older adults does not necessarily lead to improved cognitive performance. *Psychology and Aging*, 3, 307-320.
- Montoye, H. J., & Taylor, H. L. (1984). Measurement of physical activity in population studies: A review. *Human Biology*, 56, 195-216.
- Nelson, H. E. (1982). *National Adult Reading Test Manual*. London: National Hospital.
- Paas, F. G. W. C., Adam, J. J., Janssen, G. M. E., Vrencken, J. G. P. M., & Bovens, A. M. P. M. (1994). Effects of a 10-month endurance-training program on performance of speeded perceptual-motor tasks. *Perceptual and Motor Skills*, 78, 1267-1273.
- Perlmutter, M., & Nyquist, L. (1990). Relationships between self-reported physical and mental health and intelligence performance across adulthood. *Journal of Gerontology*, 45, P145-155.
- Poon, L. W. (1985). Differences in human memory with aging: nature, causes and clinical implications. In J. E. Birren & K. W. Schaie (Eds.), *Handbook of the psychology of aging*. New York: Van Nostrand Reinhold.
- Rogers, R. L., Meyer, J. S., & Mortel, K. F. (1990). After reaching retirement age physical activity sustains cerebral perfusion and cognition. *Journal of the American Geriatrics Society*, 38, 123-128.
- Schmand, B., Bakker, D., Saan, R., & Louman, J. (1991). The Dutch Adult Reading Test: A measure of premorbid intelligence. *Tijdschrift voor Gerontologie en Geriatrie*, 22, 15-19.
- Schmand, B., Lindeboom, J., & van Harskamp, F. (1992). *Manual Dutch Adult Reading Test*. Lisse, The Netherlands: Swets & Zeitlinger.
- Shay, K. A., & Roth, D. L. (1992). Association between aerobic fitness and visuospatial performance in healthy older adults. *Psychology and Aging*, 7, 15-24.
- Smith, A. (1968). The Symbol Digit Modalities Test: A neuropsychological test for economic screening of learning and other cerebral disorders. *Learning Disorders*, 36, 83-91.
- Spiriduso, W. W. (1975). Reaction and movement time as a function of age and physical activity level. *Journal of Gerontology*, 30, 435-440.
- Spiriduso, W. W. (1980). Physical fitness, aging, and psychomotor speed. *Journal of Gerontology*, 35, 850-865.
- Spiriduso, W. W., & MacRae, P. G. (1990). Motor performance and aging. In J. E. Birren & K. W. Schaie (Eds.), *Handbook of the psychology of aging*, (3 ed., pp. 183-200). San Diego: Academic Press.
- Stones, M. J., & Kozma, A. (1989). Age, exercise, and coding performance. *Psychology and Aging*, 4, 190-194.
- Voorrips, L. A., Meijers, J. H. H., Sol, P., Seidell, J. C., & van Staveren, W. A. (1992). History of body weight and physical activity of elderly women differing in current physical activity. *International Journal of Obesity*, 16, 199-205.
- Voorrips, L. E., Ravelli, A. C. J., Dongelmans, P. C. A., Deurenberg, P., & van Staveren, W. A. (1991). A physical activity questionnaire for the elderly. *Medicine and Science in Sports and Exercise*, 23, 974-979.
- Washburn, R. A., & Montoye, H. J. (1986). The assessment of physical activity by questionnaire. *American Journal of Epidemiology*, 123, 563-576.

Chapter 5

Aerobic capacity and cognitive performance in a cross-sectional aging study³

ABSTRACT

In a population unselected for aerobic fitness status, the aerobic fitness and its interaction with age were used to predict performance on several cognitive outcome measures that are known to be sensitive to effects of chronological age. It was hypothesized that in particular cognitively demanding tasks would be sensitive to aerobic capacity, as measured in a submaximal bicycle ergometer protocol. Healthy subjects between 24 and 76 years of age were recruited from a larger cognitive aging study ($N = 132$). The participants were more hours per week engaged in aerobic sports and felt healthier than non-participants of the same age. No group differences were found on anxiety and depression symptomatology, or basic anthropometrical variables. Two out of four subtasks that reflect complex cognitive speed (Stroop interference and Concept Shifting Test) showed main and interaction effects with age of aerobic capacity in a hierarchical regression analysis, accounting for up to 5% of variance in parameter score, after correction for age, sex, and intelligence main effects. These findings add to the notion that aerobic fitness may selectively and age-dependently act on cognitive processes, in particular those that require relatively large attentional resources.

INTRODUCTION

It becomes increasingly clear that the aging process is accompanied by deterioration of cognitive functions such as memory, attention, reaction time, and the speed of information processing (e.g. Jolles, Houx, van Boxtel & Ponds, 1995; Poon, 1985; Salthouse, 1989). Also, differences in cognitive performance within groups of individuals of the same age tend to increase as a function of calendar age (Morse, 1993). It is recognized that age-extrinsic factors that are related to physical health may play a role in explaining the increase with age in variability of cognitive performance within birth cohorts (Houx & Jolles, 1993; Houx & Jolles, 1994; Nolan & Blass, 1992).

Physical fitness is one of the potential intervening factors that may be responsible for the larger variance in cognitive performance measures with increasing age. The most important functional aspect of physical fitness is the cardiorespiratory component, known as the aerobic capacity (VO_{2-max}), which can be defined as the oxygen uptake capacity of the body during

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maximal physical exercise (LaPorte, Montoye & Caspersen, 1985). Although conclusive evidence is still lacking, there are two basic mechanisms which have been suggested to explain the effect of aerobic fitness on cognitive processes; the *cerebral circulation hypothesis* (induction regional cerebral blood flow, also known as the *oxygen hypothesis*; Rogers, Meyer & Mortel, 1990) and the *neurotrophic stimulation hypothesis* which predicts a beneficial effect of neuromuscular activity on higher brain centers (Spirduso, 1980), or a combination of both (*neural efficiency hypothesis*). Experimental evidence in support of either mechanism in humans is however largely circumstantial (Chodzko-Zajko & Moore, 1994).

The positive relation between physical fitness and cognitive performance has not been consistent for specific cognitive domains (Chodzko-Zajko, 1991), with the exception of performance in timed task paradigms, where differences between high and low fit elderly subjects have been demonstrated repeatedly (Spirduso & MacRae, 1990). Intervention studies that employed exercise programs to improve aerobic capacity, in order to test the effect of this manipulation on cognitive performance, have shown mixed results (Buchner, Beresford, Larson, LaCroix & Wagner, 1992). Dustman et al. (1984) found improvement in a group of 55-70 year old sedentary subjects after an aerobic training program of four months on the critical flicker fusion threshold (CFF), digit symbol substitution test (DSST), simple reaction time, and Stroop interference, but did not employ a non-exercise control group. Other controlled longitudinal community studies of middle-aged subjects (Blumenthal & Madden, 1988), and healthy elderly (Emery & Gatz, 1990; Madden, Blumenthal, Allen & Emery, 1989; Panton, Graves, Pollock, Hagberg & Chen, 1990) found no beneficial effect of aerobic training. A recent study using a twelve month aerobic intervention program in a group of 87 sedentary older adults found no improvement in cognitive task performance associated with the increase in $\text{VO}_{2\text{-max}}$, compared to a non-exercising control group (Hill, Storandt & Malley, 1993). In contrast, Rikkli and Edwards (1991) reported a decrease in reaction time in older women between 57 and 85 year of age after a three year exercise program, compared to inactive controls. They suggest that duration of the intervention may be a critical factor in establishing a beneficial effect of aerobic training on brain function.

A common design in cross-sectional studies to test the effect of physical fitness on cognitive processes is to randomise discrete age cohorts in different subgroups on the basis of self-reported physical activity level (e.g. Clarkson-Smith & Hartley, 1989; Rikli & Busch, 1986; Sparrow & Wright, 1993), based on the notion that aerobic capacity is in part determined by regular engagement in vigorous physical activity (LaPorte et al., 1985). However, relations between self-reports of physical activity and measures of cardiorespiratory fitness are weak, as many factors (such as genetic constitution or inaccuracy of recall) may contribute to the error variance (LaPorte et al., 1985). Next, apart from the potential subjective bias in activity classification based on self-report one can argue that selection of highly active or fit subjects neglects other personal background characteristics that may confound the effect of activity on cognition, like mood, life style, motivational drive, or educational level (Spirduso, 1975; Stones & Kozma, 1988).

No clear conclusion can be drawn from earlier studies about what can be expected from the cognitive effect of aerobic fitness in a normal aging population. We therefore studied aerobic capacity as a potential predictor of performance in different cognitive task paradigms. A

healthy population sample, aged between 24 and 76 years was recruited from a larger group of participants in a cognitive aging study, *independent* of the aerobic capacity status. This procedure enabled a comparison between the participating and non-participating groups on several background characteristics and thereby some evaluation is possible of the effect of the inclusion procedure on study outcome. It was hypothesized that after removal of effects of age, sex and intelligence level some additional variance in cognitive performance could be explained by aerobic capacity or the age by aerobic capacity interaction term. The latter effect would express the age-dependency of the relation between aerobic capacity and cognition. These effects were expected to be most prominent in tasks that require some form of effortful processing, as performance tasks in this category have shown the largest degree in consistency in demonstrating activity or aerobic capacity effects (Chodzko-Zajko & Moore, 1994).

METHODS

Subjects

The study program was part of a larger cross-sequential study into the determinants of cognitive aging (Maastricht Memory Study, MAAS, Jolles et al., 1995). Subjects in MAAS were randomly drawn – stratified for age and sex – from a register of family practices in the region of the city of Maastricht, the Netherlands (Metsemakers, Höppener, Knottnerus, Kocken & Limonard, 1992). The sample register contains all relevant past and present health problems of all subscribed patients. Eligible subjects from the register were excluded for the MAAS study when specific morbidity was present that can be related to brain health (Houx & Jolles, 1994): cerebrovascular disease, chronic neurological pathology (such as dementia, epilepsy and parkinsonism), mental retardation, or psychotropic drug use. Participants in the MAAS study took part in an extensive neuropsychological test program of three hours. All 245 subjects in the six discrete age groups of 25 ± 1 year, 35 ± 1 year, ..., 75 ± 1 year were invited to take part in an additional fitness test session. Of this group, 55 subjects did not want to participate on beforehand. In the remaining group there was evidence in 30 subjects of some degree of cardiovascular morbidity (e.g. angina pectoris, prior myocardial infarction, cardiac insufficiency, or arrhythmias) and in 22 subjects of other medical conditions (in particular pulmonary and musculoskeletal morbidity) that resulted in exclusion. Finally, strict criteria were used to control for homogenous distribution of IQ within age group: six subjects with extreme IQ scores (five below 90 and one above 140) were not included in the study group, resulting in a total group of 132 subjects. Sociodemographic and anthropometric descriptors of the study sample are presented in Table 5.1.

Test procedure

The additional fitness protocol was administered within three weeks after the neuropsychological test session. On this occasion additional anthropometric measurements were performed and $\text{VO}_{2\text{-max}}$ was determined in a submaximal ergometer protocol. All tests

were administered under medical surveillance and informed consent in writing was obtained from all participants. As part of MAAS, all participants filled out an extensive questionnaire pertaining sociodemographic characteristics and physical and mental health. The Symptom Check List (Arrindell & Ettema, 1986) was used to measure symptomatology related to anxiety and depression and subjects were asked to rate their general health on a five point scale (1: *very bad*, to 5: *very good*). Finally, one was asked to rate in hours the average weekly engagement in aerobic sports, such as jogging, swimming, or racket sports.

Physical fitness measurements

Anthropometry. Body height and weight was measured to the nearest cm and kg in all MAAS subjects. The method of Durnin and Womersley (Durnin & Womersley, 1974) was employed to calculate the fat-free body mass from body weight and the biceps and triceps skinfold thickness on the left arm in the participants of the fitness study.

Submaximal cycle ergometer test. Maximal aerobic capacity ($\text{VO}_{2\text{-max}}$) was estimated in a submaximal endurance protocol (Siconolfi, Cullinane, Carleton & Thompson, 1982), to maximize compliance to the study while keeping health hazards in some untrained individuals in the sample while at an acceptable level. Subject were instructed to maintain a constant cycling rate of 50 rotations per minute on a cycle ergometer (Erich Jaeger ER800). Heart rate (HR) was monitored using a standard chest lead connected to a digital pulse transmitter (Polar Sporttester PE3000). A wristwatch-type receiver on the arm of the subject displayed the on-line HR. For each subject the HR at 70% of maximal aerobic capacity was estimated using the formula: $\text{HR}_{70\%} = .7 \times (220 - \text{age} [\text{years}])$, in beats-per-minute (BPM). The initial work load of the cycle test was set off at 25 W. Work load was increased every two minutes in 25 W steps until HR was at or above the target $\text{HR}_{70\%}$. The subject was to maintain this final work load (W_{ss}) for at least another two minutes to reach a steady-state HR (HR_{ss}). For male subjects under 35 years the protocol was different. Initial work load was set at 50 W and increase in 50 W steps every two minutes, until HR was between 60 and 70% of the estimated maximal HR. Next, work load was increased after every two minutes in 25 W steps until the 70% limit was reached. Again, HR_{ss} was recorded after at least two minutes cycling. The average duration of the endurance protocol was eight minutes.

$\text{VO}_{2\text{-max}}$ was calculated for males and females differently, using the following regression equations (age in years, HR in BPM, $\text{VO}_{2\text{-max}}$ in $\text{l} \cdot \text{min}^{-1}$; Åstrand & Ryhming, 1954; Siconolfi et al., 1982):

$$\text{Males: } \text{VO}_{2\text{-max}} = 0.348 * X - 0.035 * \text{age} + 3.011 \text{ [where } X = (174.2 * \text{W}_{ss} + 4,020) / (103.2 * \text{HR}_{ss}) - 6,299 \text{]}$$

$$\text{Females: } \text{VO}_{2\text{-max}} = 0.302 * X - 0.019 * \text{age} + 1.593 \text{ [where } X = (163.8 * \text{W}_{ss} + 3,780) / (104.4 * \text{HR}_{ss}) - 7,514 \text{]}$$

Validation of the endurance protocol was done in a healthy population sample in the age between 20 and 70 years. The outcome can be considered as a safe and reliable measure of cardiovascular fitness that correlated .94 with direct measurements of $\text{VO}_{2\text{-max}}$ (Siconolfi et al., 1982). To compensate for the systematic decrease in fat free mass with age (Jackson et al.,

1990), and because body fat must be regarded as metabolic relatively inert tissue, $\text{VO}_{2\text{-max}}$ was corrected for weight and percentage body fat using the fat free mass (ffm). This procedure yielded a $\text{VO}_{2\text{-max}}$ in $\text{ml}\cdot\text{min}^{-1}\cdot\text{kg}\cdot\text{ffm}^{-1}$.

Cognitive assessment

A set of neuropsychological tests was used to tap the cognitive domains of memory and memory related functions, simple psychomotor speed and information processing speed. These tests were selected for their robustness in detecting aging effects in normal aging populations (Jolles et al., 1995). A short description of each test is given below.

General intelligence

Groningen Intelligence Test (GIT). The GIT is the commonly used Dutch estimate of formal IQ which was used in its abbreviated form (Luteijn & van der Ploeg, 1983).

Memory

Visual verbal learning test (VVLT). This test evaluates the ability to acquire and retrieve new verbal information (Brand & Jolles, 1985). A fixed sequence of fifteen frequently used monosyllabic words were presented on a computer screen. Subjects were asked to reproduce the words after each of five subsequent trials. The total of correctly reproduced words in five trials was recorded (immediate recall), together with the number of correctly reproduced words 20 minutes after the last trial (delayed recall).

Verbal fluency (VF). Outcome of this test reflects the level of organization in memory between clusters of meaningful related words. The number of animal names correctly produced in 60 seconds was recorded (Luteijn & van der Ploeg, 1983).

Simple psychomotor speed

Continuous tapping (CT). The continuous tapping task required the subject to press the button of an electronic counting device at maximum frequency during 30 seconds, using the index finger of the dominant hand. The total tap count was recorded as index of peripheral motor speed (Lezak, 1995, pp. 672-673).

Information processing speed

Concept Shifting Test (CST). This test evaluates behavioral planning and evaluation (Houx, Vreeling & Jolles, 1991). The subject's ability to alternate two psychological concepts during task performance is measured, i.e., number and letter cancellation in correct order. A test sheet contains 16 small diameter circles ($\varnothing$ 15 mm) arranged in a larger circle ($\varnothing$ 16 cm). The digit version (Part A) presents figures 1 to 16 in random order in the circles, a letter version (Part B) depicts random letters, and finally a digit / letter version (Part C) alternates the numbers 1 to 8 and letters A to H. The subject is instructed to cross out the circles in correct order, as fast as possible without making errors. Outcome is the time required to complete each separate task.

Motor Choice Reaction Test (MCRT). A computer test was used that evaluates reaction times as a function of the complexity of task requirements (Houx & Jolles, 1993). It consists of a simple and a complex choice reaction subtask. In the simple task the subject is required to push a central button on a switch panel with the index finger of the dominant hand. When a white button 5 cm above the central button lights up, one is instructed to push this button and then to return the finger on the central button. The complex task introduces a decision component: one of three adjacent white buttons, positioned on a 90 degree arc 5 cm above the central red button, may light up in a random order, again requiring the subject to push the button that is lit as fast as possible. Target parameters are median initiation time (decision making and motor preparation) and actual movement time, calculated after 30 trials for both subtasks.

Letter Digit Substitution Test (LDST). This paper-and-pencil test is a modification of the Symbol Digit Modalities Test and intends to measure fundamental processing speed (Smith, 1968). Subjects were instructed to copy numbers in cells indexed by a letter. The letter refers to nine letter / number combinations at the top of the form. The number of correctly copied corresponding numbers in 90 seconds is recorded.

Stroop Color Word Test (SCWT). This perceptual interference test consists of three subtasks. Each subtask consists of a test sheet containing four rows of ten columns of color names or colored spots. The test measures the speed at which color names are read (subtask I) and the speed at which color spots are named (subtask II). Subtask III involves color names again but the printing ink is different from the color name. The speed at which the color of the printing ink of the words is named is recorded. The time to complete this subtask reflects the ability to inhibit overlearned responses and has shown robust effects of chronological age (Houx, Jolles & Vreeling, 1993).

In particular, the complex subtask of the MCRT, the letter / digit version (Part C) of the CST and Stroop subtask III can be regarded as being on the effortful extreme of the effortful versus automatic cognitive processing demand continuum (Chodzko-Zajko & Moore, 1994).

Statistical analysis

Differences between participating and non-participating groups on several measures of mood and physical activity were studied using analysis of covariance (ANCOVA), with age and sex as covariates. All cognitive outcome measures were tested for age, sex and age by sex interaction effects with ANCOVA, after correction for differences in general intelligence. The effects of aerobic capacity (VO_{2-max}) and VO_{2-max} by age interaction on cognitive performance were tested in several multiple hierarchical regression models, where age, sex and IQ were entered together in the first step of the analysis. In effect, this means that the effects were tested of aerobic capacity on residual scores of the cognitive parameters. 'Goodness-of-fit' of the model was described in terms of variance explained by the variables in the equation, expressed as (adjusted) R^2 . Increase of explained variance by the model was tested for significance after each step. Residual scores were screened for systematic trends, but these were not identified in the fitted models.

RESULTS

When participating and non-participating groups were compared it was found that included subjects were more engaged in aerobic sport activities (2.0 vs. .9 hours / week, $F(1,241) = 7.77$, $p = .006$) and rated themselves higher on the general health dimension (4.0 vs. 3.6, $F(1,239) = 7.94$, $p = .005$). No group differences were observed on years of formal education (11.0 vs. 11.3 years for non-participants and participants, respectively, $F(1,241) = 1.81$), general intelligence (GIT-IQ 113.2 vs. 112.0, $F(1,241) < 1$) or the mood subscales depression and anxiety of the SCL questionnaire (SCL depression 21.7 vs. 20.3, $F(1,224) < 1$; SCL anxiety 12.9 vs. 12.3, $F(1,224) < 1$). Furthermore, the anthropometric measures body height (1.68 vs.

Table 5.1. Mean ($\pm$ SD) anthropometric measures in the participant group by age and sex ($N = 132$).

	Age Class (years)						Sex	
	25 $\pm$ 1	35 $\pm$ 1	45 $\pm$ 1	55 $\pm$ 1	65 $\pm$ 1	75 $\pm$ 1	M	F
<i>n</i>	23	24	28	25	21	11	77	55
M / F ratio	15/8	16/8	13/15	15/10	13/8	5/6		
Body height (cm)	173.2 (8.0)	176.2 (8.3)	172.8 (7.1)	170.9 (8.2)	167.4 (7.2)	163.0 (8.8)	176.3 (6.1)	165.0 (6.8)
Body weight (kg)	70.3 (11.3)	78.5 (14.8)	75.2 (10.2)	76.9 (9.5)	73.5 (10.1)	69.8 (12.2)	79.7 (10.0)	67.5 (9.5)
Body Mass Index (kg·m ⁻²)	23.4 (3.3)	25.2 (3.9)	25.2 (3.2)	26.3 (2.9)	26.2 (3.2)	26.1 (2.7)	25.6 (2.9)	24.9 (3.9)
% Body fat	23.8 (9.0)	28.4 (6.0)	34.0 (7.4)	38.4 (7.9)	34.7 (7.5)	35.7 (4.4)	28.0 (7.9)	38.2 (6.3)
Fat-free weight (kg)	53.5 (10.2)	56.2 (11.3)	49.5 (8.0)	47.5 (9.1)	47.9 (8.0)	44.9 (9.1)	57.0 (6.9)	41.4 (4.7)
VO ₂ -max (ml·min ⁻¹ ·kg ⁻¹)	41.1 (9.3)	33.0 (7.0)	27.7 (7.3)	25.3 (6.0)	23.5 (7.1)	14.5 (3.2)	33.7 (9.5)	22.3 (6.6)
VO ₂ -max -ffm (ml·min ⁻¹ ·kg ⁻¹)	53.5 (7.6)	45.7 (7.1)	41.6 (8.1)	41.0 (9.0)	35.6 (8.9)	22.5 (4.2)	46.3 (10.6)	35.8 (8.7)

Note. VO₂-max = estimated maximal aerobic capacity; VO₂-max -ffm = maximal aerobic capacity, corrected for body fat.

1.71 m), weight (72.9 vs. 74.4 kg), or body mass index (BMI; 25.6 vs. 25.3 kg·m⁻²) were not distributed differently in participant and nonparticipant groups ($F(1,238) < 1$). Table 5.1 displays the mean scores of anthropometric variables by levels of age class and sex in the participants group. Descriptives of the cognitive dependent parameters used are presented in Table 5.2.

Aerobic capacity, both corrected and uncorrected for body composition, showed lower values for women and older age groups (Table 5.3). An age by sex interaction effect was found

Table 5.2. Mean ($\pm$ SD) cognitive outcome measures, by levels of age and sex ($N = 132$).

	Age class (years)						Sex	
	25 $\pm$ 1	35 $\pm$ 1	45 $\pm$ 1	55 $\pm$ 1	65 $\pm$ 1	75 $\pm$ 1	M	F
IQ	110.0 (11.0)	117.3 (10.2)	115.3 (13.1)	113.4 (13.2)	113.3 (10.1)	119.5 (13.2)	116.3 (12.4)	111.7 (10.8)
VVLT: recall total	47.3 (10.3)	49.4 (6.4)	44.3 (6.8)	45.0 (8.4)	37.5 (9.9)	34.9 (10.5)	42.2 (10.3)	46.5 (7.9)
VVLT: delayed recall	10.4 (2.7)	10.2 (2.9)	9.5 (2.4)	9.8 (2.4)	7.7 (3.0)	7.9 (4.0)	8.9 (3.0)	10.3 (2.5)
SRT: initiation (ms)	316.9 (48.3)	311.0 (34.0)	326.4 (57.6)	341.5 (55.5)	367.1 (72.1)	376.3 (84.9)	332.5 (61.8)	339.5 (59.4)
SRT: movement (ms)	104.2 (22.5)	114.1 (32.8)	121.8 (27.0)	134.1 (36.8)	150.0 (36.0)	154.5 (36.3)	116.1 (29.2)	142.0 (38.1)
CRT: initiation (ms)	349.3 (38.2)	357.4 (37.4)	350.7 (27.2)	367.2 (50.6)	398.0 (43.4)	391.8 (72.6)	363.9 (50.1)	368.3 (40.6)
CRT: movement (ms)	110.4 (23.8)	120.7 (27.4)	123.6 (24.7)	137.0 (36.0)	147.4 (30.8)	168.6 (46.3)	119.8 (27.3)	146.4 (37.1)
Stroop I: words (s)	41.6 (6.3)	43.6 (6.7)	45.5 (6.2)	47.3 (6.5)	49.9 (9.3)	50.4 (7.5)	44.6 (7.4)	47.8 (7.4)
Stroop II: colors (s)	55.3 (8.2)	55.4 (8.4)	55.2 (8.0)	60.8 (7.8)	62.2 (11.8)	64.0 (16.0)	57.6 (10.2)	58.9 (9.8)
Stroop III: color / words (s)	83.1 (14.3)	81.6 (12.6)	88.0 (18.9)	103.5 (16.1)	104.3 (21.5)	127.5 (37.1)	94.0 (23.1)	96.0 (23.8)
CST: digits (s)	15.8 (3.6)	18.3 (4.3)	18.4 (4.1)	21.2 (3.7)	23.9 (5.2)	24.6 (7.2)	19.7 (5.1)	19.9 (5.6)
CST: letters (s)	21.7 (8.1)	23.2 (6.3)	22.5 (6.1)	27.7 (7.6)	29.4 (7.9)	29.2 (6.1)	25.8 (8.5)	24.2 (6.2)
CST: digit / letters (s)	25.4 (6.2)	27.9 (6.6)	29.9 (9.6)	34.1 (6.2)	39.2 (8.9)	50.6 (19.2)	32.9 (10.3)	32.3 (12.5)
LDST	65.5 (10.3)	61.4 (8.5)	61.5 (10.0)	54.4 (9.4)	52.3 (8.9)	48.0 (12.9)	58.4 (10.7)	58.0 (11.6)
Tapping	203.6 (19.1)	193.6 (22.1)	188.7 (15.8)	176.0 (27.3)	171.6 (17.5)	146.4 (30.2)	191.8 (21.9)	172.1 (27.9)
Fluency	25.4 (6.6)	24.3 (6.2)	23.1 (4.8)	21.9 (5.5)	22.9 (7.1)	19.6 (5.0)	22.9 (6.1)	23.5 (6.0)

Note. IQ = Groningen Intelligence Test (GIT) - IQ; VVLT = Visual Verbal Learning Test; SRT = simple reaction time; CRT = complex reaction time; CST = Concept Shifting Test; LDST = Letter Digit Substitution Test.

only for aerobic capacity, uncorrected for body fat, indicating lower values of $\text{VO}_{2\text{-max}}$ with increasing age in men, when compared to women. No effect of age was observed on the general ability measure GIT-IQ, indicating a homogeneous distribution of IQ – after the exclusion of six subjects with extreme values. Female IQ scores tended to be somewhat lower. All

Table 5.3. Results of analysis of covariance (ANCOVA) on aerobic capacity and cognitive outcome measures; tests for main and interaction effects of age and sex, with IQ as covariate ($N = 132$).

	Age $F(5,119) =$	Sex $F(1,119) =$	Age x Sex $F(5,119) =$	IQ $F(1,119) =$
VO _{2-max} (ml·min ⁻¹ ·kg ⁻¹)	47.99***	113.89***	3.03*	1.49
VO _{2-max} (ml·min ⁻¹ ·kg·ffm ⁻¹)	34.41***	50.14***	1.79	1.25
GIT-IQ ^a	1.69	6.18*	<1	—
VVLT: recall total	9.77***	17.60***	1.11	4.20*
VVLT: delayed recall	5.09***	16.23***	<1	4.36*
SRT: initiation time	5.38***	<1	<1	23.55***
SRT: movement time	8.63***	16.79***	<1	5.72*
CRT: initiation time	5.74***	<1	<1	12.94***
CRT: movement time	9.21***	19.88***	1.74	5.11*
Stroop I: word naming	5.93***	2.20	1.01	14.73***
Stroop II: color naming	4.06**	<1	1.14	13.73***
Stroop III: color/words	18.51***	1.70	<1	28.69***
CST: digit cancellation	13.80***	<1	2.38*	7.40**
CST: letter cancellation	6.81***	7.32**	<1	19.51**
CST: digit / letter cancellation	23.07***	5.08*	2.14	21.60***
LDST	10.72***	1.00	<1	12.32***
Tapping	18.98***	19.77***	2.23	13.31***
Fluency	2.72*	2.68	1.46	5.16*

Note. VO_{2-max} = maximal aerobic capacity (in ml·min⁻¹·kg⁻¹); VO_{2-max}·ffm = maximal aerobic capacity - corrected for body fat (in ml·min⁻¹·kg⁻¹ fat free mass); IQ = Groningen Intelligence Test - IQ; VVLT = Visual Verbal Learning Test; SRT = simple reaction time; CRT = complex reaction time; CST = Concept Shifting Test; LDST = Letter Digit Substitution Test.

^a Result of ANOVA with only age and sex as independent variables.

* $p \leq .05$, ** $p \leq .01$, *** $p \leq .001$

cognitive outcome measures were more or less strongly age and IQ sensitive, showing lower average performance values for older age groups and lower IQ scores. Men outperformed women on movement times of the simple and choice reaction time tasks (SRT and CRT, respectively), on the concept shifting test (CST) subtasks letter and digit / letter cancellation, and on finger tapping speed. However, the opposite was true for the immediate and delayed recall of learned words (VVLT) where women scored higher. Age interacted with sex on CST digit cancellation, where the time required to complete the task tended to increase more with age in women, when compared to men.

Before the regression models were fitted, zero-order correlations were computed between independent and dependent variables as used in the subsequent analysis (Table 5.4). All cognitive measures (except CRT movement time) were correlated with chronological age and intelligence level in the expected direction, lower performance being associated with lower IQ levels or higher age. VO_{2-max} was strongly correlated with cognitive measures, except in word

fluency. This may be in part due to the intermediate factor age which is associated with both cognitive and physical performance measures. Higher levels of the age by aerobic capacity interaction term were associated with higher total VVLT recall scores and faster CRT initiation, Stroop III performance, and CST digit / letter cancellation, indicating that the effect of aerobic capacity was age-dependent.

In the final phase of the analysis, hierarchical regression models were fitted for all cognitive outcome measures, in order to test the predictive value of $VO_{2\text{-max}}$ (in step 2) and of the $VO_{2\text{-max}}$ by age interaction term (in step 3), after linear correction for main effects of age, sex and IQ in step 1 (Table 5.5). By far the largest proportion of R^2 increase was observed in step 1 in all cognitive measures, which confirms the effects already present in the ANCOVA's. When $VO_{2\text{-max}}$ was entered there was an increase in R^2 of 1% and 2%, for the interference version (III) of the Stroop and concept shifting – digit / letter cancellation – respectively. Again, R^2 increased significantly for both tests on introduction of the interaction term age by $VO_{2\text{-max}}$ in step 3, with 2% and 5%, respectively. In addition, R^2 of the choice reaction time task – movement time – increased with 2% in step 3. All other outcome measures remained unaffected by the aerobic capacity measures in the final two steps of the analysis.

Table 5.4. Correlations between predictors chronological age, sex, IQ, $VO_{2\text{-max}}$, age x $VO_{2\text{-max}}$ and cognitive dependent variables (Pearson's r).

	Age	Sex	GIT-IQ	$VO_{2\text{-max}}$	Age x $VO_{2\text{-max}}$
Age	–				
Sex	.07	–			
GIT-IQ	.07	-.17	–		
$VO_{2\text{-max}}$	-.67**	-.47**	.05	–	
Age x $VO_{2\text{-max}}$	-.12	.07	-.06	.17	–
VVLT: recall total	-.42**	.22*	.23**	.25**	.17*
VVLT: delayed recall	-.30**	.24**	.23**	.18*	.12
SRT: initiation time	.34**	.06	-.35**	-.32**	-.11
SRT: movement time	.47**	.36**	-.17*	-.49**	-.10
CRT: initiation time	.34**	.05	-.28**	-.32**	-.11
CRT: movement time	.46**	.38**	-.15	-.49**	-.19*
Stroop I: word naming	.39**	.21*	-.31**	-.40**	-.09
Stroop II: color naming	.30**	.07	-.33**	-.24**	-.07
Stroop III: color / word	.53**	.04	-.37**	-.46**	-.24**
CST: digit cancellation	.54**	.02	-.23**	-.35**	-.16
CST: letter cancellation	.38**	-.11	-.35**	-.27**	-.14
CST: digit / letter	.58**	-.03	-.33**	-.47**	-.31**
LDST	-.48**	-.02	.29**	.35**	.15
Tapping	-.56**	-.37**	.24**	.56**	.16
Fluency	-.23**	.06	.43**	.10	.06

Note. GIT-IQ = Groningen Intelligence Test - IQ; $VO_{2\text{-max}}$ = maximal aerobic capacity - corrected for body fat (in $\text{ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ fat free mass); VVLT = Visual Verbal Learning Test; SRT = simple reaction time; CRT = complex reaction time; CST = Concept Shifting Test; LDST = Letter Digit Substitution Test.

* $p \leq .05$, ** $p \leq .01$ (two-tailed)

Table 5.5. Results of multiple hierarchical regression analysis; age, sex and GIT-IQ were entered in step 1 of the analysis, $VO_{2\text{-max}}$ and age x $VO_{2\text{-max}}$ interaction in step 2 and 3, respectively. Displayed are standardized regression coefficients (*Beta*) in the final model, R^2 (equivalent to the proportion of explained variance) and significance of R^2 change after each step.

	<i>Beta</i>					R^2 after step		
	Age	Sex	IQ	VO_{2m}	Age x VO_{2m}	1	2	3
VVLT: recall total	-.37	.37	.26	.14	.09	.29***	.29	.30
VVLT: delayed recall	-.22	.42	.26	.19	.03	.21***	.22	.22
SRT: initiation time	.25	-.09	-.41	-.15	-.06	.23***	.23	.23
SRT: movement time	.42	.25	-.17	-.08	-.07	.33***	.33	.33
CRT: initiation time	.23	-.08	-.31	-.17	-.06	.17***	.17	.17
CRT: movement time	.44	.29	-.17	-.03	-.16	.33***	.33	.35*
Stroop I: word naming	.30	.07	-.31	-.14	-.05	.24***	.24	.24
Stroop II: color naming	.26	-.07	-.37	-.05	-.01	.17***	.16	.16
Stroop III: color/word	.46	-.08	-.42	-.15	-.18	.42***	.43*	.46**
CST: digit cancellation	.61	-.04	-.28	.06	-.10	.35***	.35	.35
CST: letter cancellation	.33	-.28	-.41	-.13	-.07	.29***	.30	.29
CST: digit / letter	.48	-.18	-.37	-.18	-.23	.44***	.46*	.51***
LDST	-.47	.08	.34	.02	.10	.28***	.28	.28
Tapping	-.52	-.27	.25	.05	.11	.45***	.44	.45
Fluency	-.31	.06	.24	-.09	.05	.08**	.07	.07

Note. IQ = Groningen Intelligence Test - IQ; $VO_{2\text{-max}}$ = estimated maximal aerobic capacity - corrected for body fat (in $\text{ml}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$ fat free mass); VVLT = Visual Verbal Learning Test; SRT = simple reaction time; CRT = complex reaction time; CST = Concept Shifting Test; LDST = Letter Digit Substitution Test.

* $p \leq .05$, ** $p \leq .01$, *** $p \leq .001$

DISCUSSION

Our chief aim in this study was to assess the relationship between aerobic capacity ($VO_{2\text{-max}}$) and cognitive test performance, in a healthy, normal aging population, in particular without a priori stratification on physical fitness parameters. After evaluation and control for relevant background characteristics, a positive association was found between $VO_{2\text{-max}}$ and the age by $VO_{2\text{-max}}$ interaction on the one hand, and two measures of information processing speed (Stroop III and CST - digit / letter cancellation) on the other. Test outcome related to memory and simple psychomotor speed was relatively unaffected by aerobic capacity measures, except for an isolated association between CRT-movement time and the age by $VO_{2\text{-max}}$ interaction term. We have to evaluate these findings in the light of earlier research.

Study population characteristics

No clear effect of the inclusion procedure was present on mood parameters, years of formal education or general intelligence. However, differences in hours per week spent in aerobic

activities and perceived general health between participant and nonparticipant groups suggest that some selection bias may have been present, in part due to the health exclusion criteria that were employed. The reason for our strict scrutiny with respect to health status was to forestall any potential bias due to cardiopulmonary pathology on study outcome (see Herzog, Schaie & Gribbin, 1978) and to prevent any health hazard for participants due to the fitness protocol. It cannot be ruled out entirely that because levels of aerobic activity and functional health may be directly related to actual aerobic capacity (Dehn & Bruce, 1972; LaPorte et al., 1985) this bias may have resulted in a *restriction of range* of VO_{2-max} in the study group, thereby attenuating the effects of VO_{2-max} on cognitive outcome. This is a well-known methodological problem in developmental research where the ultimate goal is to obtain unbiased estimates of change (Hayslip & Panek, 1989). Furthermore, although differences in overall IQ between participant and non-participant groups were absent (112.0 vs. 113.2, respectively) it is obvious that the averages are in the high-normal range (Luteijn & van der Ploeg, 1983). A higher level of IQ has been shown to protect against age-related memory performance deficits (Huppert, 1991). As all measures of cognitive test performance in this study were positively related to IQ, it cannot be ruled out that the study population is less inclined to benefit from higher aerobic capacity levels. Higher IQ and restriction of range may therefore have attenuated the observed effects of aerobic capacity.

The values for VO_{2-max} , uncorrected for body fat, that were obtained in this study are somewhat higher compared those in the Siconolfi et al. (1982) validation study, who employed a comparable inclusion procedure and used approximately the same age groups that were balanced for sex. Their averages ranged from $37.2 \text{ ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ body weight ($SD = 7.9$) in the 20-29 year group to 20.6 ($SD = 6.1$) in subjects between 60 and 70 years. The difference may be attributable to a relative underrepresentation of women in this study.

Speed of information processing and aging

It has been suggested that cognitively demanding tasks are most sensitive to aspects of physical fitness, in particular tasks where processing speed is the target variable, and tasks of high complexity and low S-R compatibility (Chodzko-Zajko, 1991; Chodzko-Zajko & Moore, 1994). Both the Stroop task III (interference) and the complex concept shifting task which showed effects of aerobic capacity in this study can be classified as tasks that require effortful cognitive processing. Both task variables combined in a compound score were sensitive to habitual physical activity measured by questionnaire in a healthy group of older adults (Van Boxtel, Langerak, Houx & Jolles, 1996). Furthermore, the age by fitness interactions that were found fit in with the *moderator model* proposed by Stones and Kozma (Stones & Kozma, 1988). This model predicts an augmentation of fitness effects with age, as the result of a decrease in attentional resources. Within a theoretical framework that defines cognitive aging in terms of resource limitation, it can indeed be understood that tasks that draw heavily on the central information processing capacity generally have shown the largest effects of calendar age (Salthouse, 1988). Additional support for this notion has been found in several studies that demonstrated an association between complex reaction time (CRT) and physical activity level (Spiriduso, 1980) or CRT and improvement in VO_{2-max} after an aerobic training intervention

(Rikli & Edwards, 1991). Our results, however, indicated that CRT initiation time – which is known to represent the time needed for stimulus evaluation and response formation – did not covary with aerobic capacity or its interaction with age. Of course, this may in part be the result of procedural differences in the employed task compared to earlier studies. Absence of aerobic fitness effect on digit copying (LDST) is more readily understood, as the central processing contribution to the outcome of this task is to some extent confounded by basic sensorimotor speed.

In summary, small proportions of variance explained by aerobic capacity and the aerobic capacity by age interaction term could be demonstrated in two out of four tasks that measure speed of information processing. These findings add to the notion that aerobic capacity, measured as a continuous variable in a healthy adult population sample, may act selectively in task paradigms that require cognitive effort. Our findings suggest that aerobic fitness per se is a factor of moderate importance in cognitive aging research. However, the authors feel that any evidence for the existence of a factor that may prevent or postpone age-related cognitive decline and that is amenable to intervention should be fully explored and justifies further research that uncovers the underlying mechanism of action in more detail.

REFERENCES

- Arrindell, W. A., & Ettema, J. H. M. (1986). *SCL-90. Een multidimensionele psychopathologie indicator (SCL-90. A multidimensional indicator of psychopathology)*. Lisse, the Netherlands: Swets & Zeitlinger.
- Åstrand, P. O., & Ryhming, I. (1954). A nomogram for calculation of aerobic capacity (physical fitness) from pulse rate during submaximal work. *Journal of Applied Physiology*, 7, 218-221.
- Blumenthal, J. A., & Madden, D. J. (1988). Effects of aerobic exercise training, age, and physical fitness on memory-search performance. *Psychology and Aging*, 3, 280-285.
- Brand, N., & Jolles, J. (1985). Learning and retrieval rate of words presented auditory and visually. *Journal of General Psychology*, 112, 201-210.
- Buchner, D. M., Beresford, S. A. A., Larson, E. B., LaCroix, A. Z., & Wagner, E. H. (1992). Effects of physical activity on health status in older adults II: Intervention studies. *Annual Review of Public Health*, 13, 469-488.
- Chodzko-Zajko, W. J. (1991). Physical fitness, cognitive performance, and aging. *Medicine and Science in Sports and Exercise*, 23, 868-872.
- Chodzko-Zajko, W. J., & Moore, K. A. (1994). Physical fitness and cognitive functioning in aging. In J. O. Holloszy (Ed.), *Exercise and sport sciences reviews*, (Vol. 22, pp. 195-220). Baltimore: Williams & Wilkins.
- Clarkson-Smith, L., & Hartley, A. A. (1989). Relationships between physical exercise and cognitive abilities in older adults. *Psychology and Aging*, 4, 183-189.
- Dehn, M. M., & Bruce, R. A. (1972). Longitudinal variations in maximal oxygen intake with age and activity. *Journal of applied Physiology*, 33, 805-807.
- Durnin, J. V. G. A., & Womersley, J. (1974). Body fat assessed from total body density and its estimation from skinfold thickness: Measurements on 481 men and women aged from 16 to 72 years. *British Journal of Nutrition*, 32, 77-97.
- Dustman, R. E., Ruhling, R. O., Russell, E. M., Shearer, D. E., Bonekat, H. W., Shigeoka, J. W., Wood, J. S., & Bradford, D. C. (1984). Aerobic exercise training and improved neuropsychological function of older individuals. *Neurobiology of Aging*, 5, 35-42.
- Emery, C. F., & Gatz, M. (1990). Psychological and cognitive effects of an exercise program for community-residing older adults. *Gerontologist*, 30, 184-188.
- Hayslip, B., & Panek, P. E. (1989). *Adult development and aging*. New York: Harper & Row.
- Herzog, C., Schaie, K. W., & Gribbin, K. (1978). Cardiovascular disease and changes in intellectual functioning from middle to old age. *Journal of Gerontology*, 33, 872-883.
- Hill, R. D., Storandt, M., & Malley, M. (1993). The impact of long-term exercise training on psychological function in older adults. *Journal of Gerontology*, 48, P12-17.
- Houx, P. J., & Jolles, J. (1993). Age-related decline of psychomotor speed: Effects of age, brain health, sex, and education. *Perceptual and Motor Skills*, 76, 195-211.

- Houx, P. J., & Jolles, J. (1994). Vulnerability factors for age-related cognitive decline. In R. L. Isaacson & K. F. Jensen (Eds.), *Toxins in air and water*, (Vol. 3, pp. 25-41). New York: Plenum Press.
- Houx, P. J., Jolles, J., & Vreeling, F. W. (1993). Stroop interference: Aging effects assessed with the Stroop Color-Word test. *Experimental Aging Research*, 19, 209-224.
- Houx, P. J., Vreeling, F. W., & Jolles, J. (1991). Age-associated cognitive decline is related to biological life events. In K. Iqbal, D. R. C. McLachlin, B. Winblad, & H. M. Wisniewski (Eds.), *Alzheimer's disease: Basic mechanisms, diagnosis and therapeutic strategies*, (pp. 353-358). Chichester, UK: Wiley.
- Huppert, F. A. (1991). Age-related changes in memory: Learning and remembering new information. In F. Boller & J. Grafman (Eds.), *Handbook of Neuropsychology*, (Vol. 5, pp. 123-147). Amsterdam: Elsevier.
- Jackson, A. S., Blair, S. N., Mahar, M. T., Wier, L. T., Ross, R. M., & Stuterville, J. E. (1990). Prediction of functional aerobic capacity without exercise testing. *Medicine and Science in Sports and Exercise*, 22, 863-870.
- Jolles, J., Houx, P. J., van Boxtel, M. P. J., & Ponds, R. W. H. M. (Eds.). (1995). *Maastricht Aging Study: Determinants of cognitive aging*. Maastricht: Neuropsych Publishers.
- LaPorte, R. E., Montoye, H. J., & Caspersen, C. J. (1985). Assessment of physical activity in epidemiologic research: Problems and prospects. *Public Health Reports*, 100, 131-146.
- Lezak, M. D. (1995). *Neuropsychological Assessment*, (3rd ed.). New York: Oxford University Press.
- Luteijn, F., & van der Ploeg, F. A. E. (1983). *Handleiding Groninger Intelligentietest (GIT) [Manual Groningen Intelligence Test]*. Lisse, the Netherlands: Swets and Zeitlinger.
- Madden, D. J., Blumenthal, J. A., Allen, P. A., & Emery, C. E. (1989). Improving aerobic capacity in healthy older adults does not necessarily lead to improved cognitive performance. *Psychology and Aging*, 3, 307-320.
- Metsemakers, J. F. M., Höppener, P., Knottnerus, J. A., Kocken, R. J. J., & Limonard, C. B. G. (1992). Computerized health information in the Netherlands: A registration network of family practices. *British Journal of General Practice*, 42, 102-106.
- Morse, C. K. (1993). Does variability increase with age? An archival study of cognitive measures. *Psychology and Aging*, 8, 156-164.
- Nolan, K. A., & Blass, J. P. (1992). Preventing cognitive decline. *Clinics in Geriatric Medicine*, 8, 19-34.
- Panton, L. B., Graves, J. E., Pollock, M. L., Hagberg, J. M., & Chen, W. (1990). Effect of aerobic and resistance training on fractionated reaction time and speed of movement. *Journal of Gerontology*, 45, M26-31.
- Poon, L. W. (1985). Differences in human memory with aging: Nature, causes and clinical implications. In J. E. Birren & K. W. Schaie (Eds.), *Handbook of the psychology of aging*. New York: Van Nostrand Reinhold.
- Rikli, R., & Busch, S. (1986). Motor performance of women as a function of age and physical activity level. *Journal of Gerontology*, 41, 645-649.
- Rikli, R. E., & Edwards, D. J. (1991). Effects of a three-year exercise program on motor function and cognitive processing speed in older women. *Research Quarterly for Exercise and Sport*, 62, 61-67.
- Rogers, R. L., Meyer, J. S., & Mortel, K. F. (1990). After reaching retirement age physical activity sustains cerebral perfusion and cognition. *Journal of the American Geriatrics Society*, 38, 123-128.
- Salthouse, T. A. (1988). Resource-reduction interpretations of cognitive aging. *Developmental Review*, 8, 238-272.
- Salthouse, T. A. (1989). Age-related changes in basic cognitive processes. In M. Storandt & G. R. Vandenbos (Eds.), *The adult years: Continuity and change*, (pp. 5-40). Washington: American Psychological Association.
- Siconolfi, S. F., Cullinane, E. M., Carleton, R. A., & Thompson, P. D. (1982). Assessing VO₂-max in epidemiologic studies: Modification of the Astrand-Ryhmung test. *Medicine and Science in Sports and Exercise*, 14, 335-338.
- Smith, A. (1968). The Symbol Digit Modalities Test: A neuropsychological test for economic screening of learning and other cerebral disorders. *Learning Disorders*, 36, 83-91.
- Sparrow, W. A., & Wright, B. J. (1993). Effect of physical exercise on the performance of cognitive tasks. *Perceptual and Motor Skills*, 77, 675-679.
- Spiriduso, W. W. (1975). Reaction and movement time as a function of age and physical activity level. *Journal of Gerontology*, 30, 435-440.
- Spiriduso, W. W. (1980). Physical fitness, aging, and psychomotor speed: A review. *Journal of Gerontology*, 35, P850-865.
- Spiriduso, W. W., & MacRae, P. G. (1990). Motor performance and aging. In J. E. Birren & K. W. Schaie (Eds.), *Handbook of the psychology of aging*, (3 ed., pp. 183-200). San Diego: Academic Press.
- Stones, M. J., & Kozma, A. (1988). Physical activity, age and cognitive / motor performance. In M. Howe & C. Brainard (Eds.), *Cognitive development in adulthood*, (pp. 273-322). New York: Springer.
- Van Boxtel, M. P. J., Langerak, K., Houx, P. J., & Jolles, J. (1996). Self-reported physical activity, perceived health, and cognitive performance in older adults. *Experimental Aging Research*, 22, 363-379.

Repeated automatic versus ambulatory blood pressure measurement: the effects of age and sex in a normal aging population⁴

ABSTRACT

Blood pressure adaptation was studied in relation to age and sex in 469 healthy volunteers, aged between 23 and 82 years, who were stratified for age, sex and educational level. In a subsample, laboratory blood pressure measurements were compared with ambulatory day-time blood pressure measurements to determine the degree of agreement between both methods. The night-time blood pressure reduction was analyzed as a function of blood pressure status, age, and sex. These preliminary analyses were performed prior to several studies on the relationship between blood pressure and cognitive performance.

Laboratory blood pressure was measured automatically five times during a 20 min recording session (Dinamap® 8100). Cardiovascular events in the medical history were identified in order to analyse the cardiovascular event-free group separately. Within three weeks after laboratory blood pressure measurement, ambulatory blood pressure was monitored for 24 hours in 135 volunteers from the main study.

Both diastolic and systolic blood pressure changed markedly in a single measurement session as a function of age, independent of mean pressure level. No further lowering of blood pressure was observed after 15 minutes. Based on the average of the final two blood pressure measurements, 18.8% of the subjects were in the hypertensive range (WHO / ISH guidelines). Ambulatory blood pressure measurements were in accord with earlier findings and correlated .74 and .73 with laboratory diastolic and systolic blood pressure, respectively, albeit weighted *Kappa* values indicated only moderate agreement (.42 and .51). Women showed a more profound reduction in night-time blood pressure than did men.

In conclusion, there is a substantial change in blood pressure during a single measurement session which is greater in older age groups. The moderate agreement between both methods of blood pressure measurement indicates that blood pressure measured in a single session has only limited generalizability to the average day-time level in a population sample and that the outcome of both measurements should be treated as separate entities.

⁴ M. P. J. van Boxtel, C. Gaillard, P. N. van Es, J. Jolles, and P. W. de Leeuw (1996). *Journal of Hypertension*, 14, 31-40.

INTRODUCTION

Hypertension has an important role in the pathogenesis of cardiovascular and cerebrovascular disease. Although it is recognized that repeated blood pressure measurements on separate occasions are necessary to reach a definite diagnosis of hypertension (WHO/ISH, 1993), this may not always be achieved in large population-based studies. It is common practice in epidemiological studies to define blood pressure status based on measurements taken during a single visit. This procedure may produce a less accurate estimate of the average habitual blood pressure as a result of uncontrolled environmental conditions, in addition to the normal physiological variability in blood pressure (Llabre et al., 1988). In particular, the *alerting reaction* to blood pressure measurement, resulting in a transient pressor response, is a well-described clinical phenomenon which is for a large part determined by the presence of a medical professional (Mancia, Casadei, Groppelli, Parati & Zanchetti, 1991; Mancia et al., 1987). Besides the average blood pressure level, short-term changes in blood pressure and diurnal variation are potential factors that may mediate the detrimental effects of hypertension (Pickering, 1994). The variability of circadian blood pressure is known to increase with age (Pickering, 1991) and the extent to which this may interfere with blood pressure adaptation during a measurement session is not clear.

The main focus of this study was to determine age- and sex-related changes in blood pressure measured in a laboratory setting, on the basis of repeated oscillometric measurements during a single session. These analyses were performed in order to define an optimal estimate of the habitual blood pressure after adaptation. In addition, laboratory blood pressure values were compared with day-time averages, obtained by 24 h ambulatory blood pressure monitoring, for a subgroup of subjects. Because the extent to which single session blood pressure measurements in a non-clinical population can be generalized to average blood pressure on the basis of repeated measurements over a longer period of time is not clear, we further analyzed the agreement between single session blood pressure and average blood pressure during normal daily activities. Finally, the effects of age and sex on the circadian blood pressure rhythm were evaluated.

In this study, which is a part of the Maastricht Aging Study (MAAS; Jolles, Houx, van Boxtel & Ponds, 1995), blood pressure was measured in a healthy population sample aged between 23 and 82 years. The panel was stratified for age and sex, and thus the data allow the analysis of the effect of these variables on blood pressure and its variability. The rationale for introducing blood pressure into the MAAS study and to perform these preliminary analyses is the accumulating evidence that hypertension may play a role in age-related cognitive decline (for a review, see Waldstein, Manuck, Ryan & Muldoon, 1991). In this respect, there is special interest in ambulatory blood pressure monitoring because the blood pressure measurements obtained with this technique are superior to single blood pressure measurements in predicting latent cerebrovascular disease in elderly subjects (Shimada, Kawamoto, Matsubayashi & Ozawa, 1990).

The specific questions addressed in this study can be summarized as follows: how is age related to the adaptation of blood pressure in a laboratory setting and what are the effects of age, sex, and cardiovascular status on diastolic and systolic pressure? How is blood pressure

measured in the laboratory related to comparable ambulant measures in terms of averages and variability, and, finally, what effect do chronological age and sex have on the differences in day-time and night-time blood pressure?

METHODS

Subjects

A total of 469 community-dwelling subjects were recruited from a register of family practices (Metsemakers et al., 1992). Exclusion criteria were previous or current medical conditions with known impact on cognitive function, namely overt cerebrovascular disease (including stroke), chronic neurological pathology (e.g. dementia, epilepsy, and Parkinson's disease), mental retardation, or chronic psychotropic drug use. The sample was stratified for age (12 classes, ranging from 25 ± 1 , 30 ± 1 , 35 ± 1 , ..., 80 ± 1 years, mean age 51.4 (*SD* 16.8) years), sex and two levels of occupational activity, to control for the effect of relevant cognitive performance predictors. For the purpose of data presentation in this study two successive pairs of age groups were combined to form new age classes (25–30, 35–40, to 75–80 years).

Procedure

All of the 469 subjects completed a postal questionnaire and were visited at home by a research nurse who took a semistructured medical interview. Detailed information about the medical history and use of medication was obtained during this session. Next, all of the participants were tested within two weeks after the home visit in a neuropsychological test laboratory. A broad range of cognitive tests was administered in two test clusters of one hour each, during a morning (09.00–12.00 h) or afternoon session (13.30–16.30 h). During a 25 min intermission blood pressure was measured five times at the left arm, with the subject in seated position, using an oscillometric technique. A Dinamap® 8100 monitor (Critikon, Tampa FL, USA) with the appropriate cuff size (*small*, *medium*, or *large adult*) was programmed for automatic blood pressure measurement at 5 min intervals. During the measurement interval the subject was left unattended and was instructed to refrain from smoking, to relax, and to remain seated until the research assistant returned. A subgroup of 135 subjects in the six age classes 30, 40, 50, 60, 70, and 80 (± 1) years agreed to participate in 24 h ambulatory blood pressure monitoring, scheduled 1–4 weeks later at a convenient moment for the subject. The subjects visited the hypertension laboratory of the university hospital between 08.00 and 09.00 h where an ambulatory blood pressure monitor (Spacelabs® 90207, Spacelabs Inc., Redmond WA, USA) was applied. The apparatus was programmed to measure blood pressure four times every hour during the day (07.00–22.59 h) and twice every hour at night (23.00–06.59 h). All participants were asked to refrain from unusual physical activities and to adhere to their regular sleeping hours.

The prevalence of cardiovascular morbidity was expressed as the presence of one of the following disorders or events reported in the medical interview: angina pectoris, cardiac

arrhythmia, myocardial infarction, cardiac insufficiency, valvular lesions, heart surgery, peripheral atherosclerosis or cardiac reanimation. A subjective report of hypertension or the use of antihypertensive medication was recorded separately. On the basis of this information the subjects were divided into a group with and without cardiovascular events in their history. The cardiovascular event group was defined by the reported occurrence of current or past cardiovascular disorders or events – hypertension excluded – or the current use of antihypertensive drugs, or both. The subjective report of a diagnosis of hypertension was not considered sufficient unless the subject was also receiving antihypertensive drugs. These medical population characteristics are summarized in Table 6.1. There was no clinical evidence for renal or renovascular abnormalities in the study group.

All of the subjects were classified into two categories of blood pressure status, based on the average of the fourth and fifth blood pressure measurements, namely *normal blood pressure* when systolic blood pressure was < 140 mmHg and diastolic blood pressure was < 90 mmHg, and *hypertension* when systolic blood pressure was ≥ 140 mmHg or diastolic blood pressure was ≥ 90 mmHg. Isolated systolic hypertension (ISH) was defined as a systolic blood pressure of 140 mmHg or higher with diastolic pressure remaining below 90 mmHg. These criteria are currently being proposed by the WHO for classification of hypertension based on standard office readings on repeated occasions (WHO/ISH, 1993).

Ambulatory blood pressure values were classified using the regression equations that described in this study the relation between mean laboratory blood pressure and mean day-time ambulatory blood pressure. The WHO/ISH cut-off points for normotension (140/90 mmHg) were entered into these equations for systolic and diastolic blood pressure separately to compute the corresponding ambulatory blood pressure monitoring values; day-time mean blood pressure above 135.2/88.6 mmHg was considered to be in the hypertensive range. This procedure was employed as no definite reference values for ambulatory blood pressure monitoring are as yet available for clinical purposes.

Statistical analysis

Diastolic and systolic blood pressure were treated separately in all subsequent analyses. Linear and non-linear effects of age on blood pressure change within 20 min were tested in a one-way analysis of variance procedure. For this analysis the difference between blood pressure at the first and last measurement was expressed as the absolute difference and as a percentage of the average blood pressure over five measurements. This average was corrected for the effect of mean absolute blood pressure level on blood pressure variability (Pickering, 1991), using the formula:

$$(M_1 - M_5) \cdot 100 / [(M_1 + M_2 + M_3 + M_4 + M_5) / 5]$$

where M_1 indicates blood pressure at the time of first measurement, and so forth. The end of blood pressure adaptation was defined as the absence of a significant decrease in systolic and diastolic blood pressure between two consecutive measurements, using paired t -tests with an adjusted $p = .01$ (Bonferroni correction for multiple comparisons). Multiple hierarchical regression analysis was used to test the independent variables cardiovascular event-group

membership, age, sex and the age by sex interaction term on laboratory blood pressure outcome, and to evaluate the effect of blood pressure status, age, sex, and age by sex interaction on day-night blood pressure differences, in terms of the overall proportion of variance explained in the outcome measure. In case of a significant contribution of a variable to the explained overall variance, its associated partial regression coefficient (B) and the 95% confidence interval (CI) was presented. Comparisons between estimates of mean and variability in blood pressure based on laboratory measurement or ambulatory blood pressure monitoring were presented as Pearson's r and as weighed *Kappa* (K_w). K_w is commonly used as a measure of agreement (*concordance*) because it expresses the degree of interchangeability between two measurements that are intended to assess the same concept, whereas r is only an index of general relatedness, or *trend* (Kramer & Feinstein, 1981). For this purpose all ambulant day-time parameters were ranked in quartiles. Next, laboratory parameters were ranked according to the same ambulatory day-time classification criteria. From the resulting 4 x 4 cross-tabulation table K_w was computed.

Deviation from normality of day-night blood pressure differences was tested using the Kolmogorov-Smirnov test statistic ($K-S$). $P < .05$ was considered statistically significant. All analyses were performed with the SPSS program series (Norusis, 1990).

RESULTS

Relation between age and blood pressure adaptation during repeated laboratory measurement

The average systolic and diastolic pressures during the laboratory session were calculated for every consecutive measurement (M_x) and age class (Figure 6.1). A steady overall increase in systolic pressure was observed with age. The increase in diastolic pressure was less outspoken and diastolic pressure remained relatively constant after 45–50 years of age. Furthermore, a gradual mean decrease in systolic and (again less extreme) diastolic blood pressures over consecutive measurements was apparent.

A linear increase in diastolic and systolic blood pressure difference with age was found, for both the absolute blood pressure differences and the differences in terms of percentage (one-way analysis of variance, $F(1,456) = 14.8$ and 15.2 (both $p < .001$), respectively, for diastolic blood pressure; $F(1,456) = 26.4$ and 16.0 (both $p < .001$), for systolic blood pressure). The mean absolute difference between the first and the last diastolic blood pressure measurements ranged from 0 in the youngest to 5 mmHg in the oldest group. For systolic pressure these values were 6 and 12 mmHg, respectively. The same pattern was observed when the subjects of the cardiovascular event group were excluded from the analysis. No evidence was found for a significant non-linear trend in pressure differences with age. Thus, the decrease in diastolic and systolic blood pressure during the measurement interval was more profound with increasing age, even after correction for the mean pressure level.

In the next step it was determined when this decrease in blood pressure was completed. Differences in blood pressure of four successive pairs of measurements (1–2, 2–3, 3–4 and 4–5, respectively) computed for the total group were 1.3 ($t = 2.9$, $p < .01$), 1.1 ($t = 3.0$, $p < .01$),

Figure 6.1. Mean systolic and diastolic blood pressures (BP) on five consecutive measurements within 20 min. Separate plots are shown for different age classes. Error bars indicate the standard error of the mean; total group, $n = 469$.

Figure 6.2. Average laboratory systolic and diastolic pressures by age class (1, 25-30 years, to 6, 75-80 years) and sex, for the total group ($n = 469$) and for the group free of cardiovascular events ($n = 349$), separately. Error bars indicate the standard error of the mean.

Table 6.1. Presence of reported hypertension, use of antihypertensive medication, and cardiovascular morbidity by age class and sex.

	Age class (years)												Total	
	25-30		35-40		45-50		55-60		65-70		75-80			
Sex	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Hypertension (reported)	4	—	6	2	12	4	7	12	9	18	5	13	45	49
Antihypertensive drug use	1	—	1	—	5	5	7	8	11	14	15	11	40	38
Cardiovascular events	1	1	1	—	6	6	9	11	22	16	24	13	63	47
<i>n</i>	41	40	40	41	40	41	40	41	41	40	35	29	237	232

Note. Cardiovascular events included angina pectoris, cardiac arrhythmia, myocardial infarction, cardiac insufficiency, valvular lesions, heart surgery, peripheral atherosclerosis, reanimation, or antihypertensive drug use.

.7 ($t = 2.6$, $p < .05$), and -7 mmHg ($t = -2.3$, n.s) for diastolic blood pressure, and 6.5 ($t = 15.0$, $p < .001$), 2.4 ($t = 5.9$, $p < .001$), 1.0 ($t = 3.0$, $p < .01$), and $.3$ mmHg ($t = .8$, n.s) for systolic blood pressure (all analyses $df = 461$). This indicates that, at least on a group level, no major adaptation of blood pressure is to be expected after measurement 4. On the basis of these results it was chosen to average the diastolic and systolic pressure level of measurement 4 and 5 as the optimal estimates of habitual blood pressure after adaptation. These averages were used in further analyses.

Table 6.2. Percentage of hypertensive subjects (WHO/ISH criteria) and percentage of subjects with isolated systolic hypertension in different subgroups.

	<i>n</i>	Age class (years)						All
		25-30	35-40	45-50	55-60	65-70	75-80	
<i>Hypertension (%)</i>								
Men	237	4.9	17.5	15.0	15.0	26.8	40.8	19.4
Women	232	.0	.0	7.3	22.0	42.5	44.8	18.1
All	469	2.5	8.6	11.1	18.5	34.6	42.2	18.8
CVE-free group	359	1.3	7.5	10.1	16.4	20.9	48.1	12.8
<i>Isolated systolic hypertension (%)</i>								
Men	237	2.4	7.5	5.0	12.5	19.5	34.3	13.1
Women	232	.0	.0	7.3	14.6	32.5	31.0	13.4
All	469	1.2	3.7	6.2	13.6	25.9	32.8	13.2
CVE-free group	359	.0	3.8	7.2	13.1	14.0	40.7	9.2

Note. CVE = Cardiovascular event.

Effects of age, sex, and cardiovascular status on adapted diastolic and systolic pressure

Figure 6.2 illustrates the relation between age class and diastolic or systolic pressure, for male and female participants separately. Additional plots are shown for the group with no reported cardiovascular events in their medical history.

The effects of membership of the cardiovascular event-group, calendar age, sex, and age by sex interaction on diastolic and systolic pressures were analyzed in two hierarchical multiple regression analyses. In both regression models, cardiovascular event membership (coded as 0/1 for no/yes) was entered in the first step, and sex (coded as 1/2 for male/female), chronological age and the age by sex interaction term in the second step. The overall proportion of the variance explained in the final models by these variables was .09 and .27, for diastolic and systolic blood pressure respectively, both $p < .001$. The presence of cardiovascular events was associated with higher diastolic blood pressure (partial regression coefficient $B = 2.7$, 95% confidence interval (CI) for $B = .2$ to 5.3 ; $p < .05$) and systolic blood pressure ($B = 5.3$, 95% $CI = 1.5$ to 9.2 ; $p < .01$). Women showed lower mean diastolic blood pressure levels ($B = -4.6$, 95% $CI = -6.5$ to -2.7 ; $p < .001$) but the same trend in systolic blood pressure was not significant. Only in systolic blood pressure a substantial age by sex interaction was found ($B = 3.7$, 95% $CI = 2.3$ to 5.1 ; $p < .001$), indicating a more prominent increase in mean systolic blood pressure with age in women than in men (Figure 6.2). Chronological age was associated with higher diastolic blood pressure ($B = .1$, 95% $CI = .0$ to $.1$; $p < .05$) and systolic blood pressure ($B = .4$, 95% $CI = .3$ to $.5$; $p < .001$).

Table 6.2 summarizes the hypertensive status for each age class, based on the WHO/ISH classification criteria. The prevalence of hypertension gradually increased with age (both uncorrected and corrected for cardiovascular event status) but was lower in the cardiovascular event-free group, except for the 75–80 year old subjects (48.1% versus 42.2%). The proportional contribution of ISH rose with age, from .48 and .00 in the 25 to 30 year group, up to .78 and .85 in the 75–80 year group, for the cardiovascular event uncorrected and corrected groups, respectively.

Laboratory blood pressure and its variability in relation to ambulant blood pressure

Of 135 subjects who participated in the additional 24 h blood pressure measurements within 4 weeks of the laboratory tests, 28 reported one or more cardiovascular events in their medical history, or used antihypertensive medication. In addition, eight ambulant recordings yielded incomplete data during the night-time period because some subjects felt uncomfortable wearing the arm cuff while sleeping, leaving 99 subjects for the 24 h ambulant blood pressure data presented in Table 6.3. No subjects reported unusual sleeping episodes or abnormal events during the night.

Several aspects of laboratory and ambulant day-time measurements were analyzed for all 135 subjects. The averages of the laboratory diastolic and systolic pressures at measurements 4 and 5 were used as the mean habitual blood pressure. The standard deviation of five repeated measurements and differences in diastolic and systolic pressures at measurements 1 and 5 were analysed as estimates of pressure variability. These parameters of laboratory blood pressure

Table 6.3. The 24 h ambulatory blood pressure for each age class and sex. Only subjects with no cardiovascular events in the medical history and with complete 24 h blood pressure readings are included ($n = 99$).

	Age class (years)						Sex		All
	30	40	50	60	70	80	M	F	
Total n	16	18	25	18	14	8	55	44	99
M/F ratio	10/6	7/11	14/11	11/7	7/7	6/2			
<i>Laboratory mean</i>									
Systolic	121(11)	116(11)	124(14)	125(11)	134(11)	135(23)	129(13)	119(14)	125(14)
Diastolic	70(7)	70(11)	75(12)	76(8)	69(12)	70(13)	76(10)	67(10)	72(11)
<i>Ambulatory day-time mean</i>									
Systolic	124(9)	123(10)	127(9)	125(9)	130(14)	133(16)	129(10)	124(11)	126(11)
Diastolic	76(5)	79(9)	83(7)	80(7)	78(8)	77(10)	81(8)	77(8)	79(8)
<i>Ambulatory night-time mean</i>									
Systolic	110(8)	107(10)	113(11)	111(10)	116(15)	120(20)	115(11)	109(13)	112(12)
Diastolic	61(4)	64(10)	69(8)	67(9)	63(10)	64(12)	68(9)	62(8)	65(9)
<i>Ambulatory 24 h mean</i>									
Systolic	121(9)	120(11)	124(9)	121(9)	127(14)	130(17)	126(10)	120(11)	123(11)
Diastolic	72(5)	76(9)	80(7)	77(7)	75(8)	73(10)	78(8)	74(7)	76(8)

Note. Values are expressed as means ($\pm$ SD). M = male, F = female.

Table 6.4. Relation between mean blood pressure and estimates of variability [difference in highest and lowest recording (DHL) and the standard deviation (SD)] of laboratory and ambulatory day-time blood pressure measurement.

	Total group ($n = 135$)		Cardiovascular event-free group ($n = 106$)	
	r	K_w	r	K_w
Diastolic blood pressure	.74**	.42	.74**	.56
Mean arterial pressure	.71**	.49	.69**	.55
Systolic blood pressure	.73**	.51	.73**	.56
DHL diastolic	.13	.00	.10	.00
DHL mean arterial	.23**	.01	.17	.07
DHL systolic	.23**	.02	.25**	.00
SD diastolic	.24**	.06	.21*	.07
SD mean arterial	.36**	.15	.24*	.13
SD systolic	.28**	.11	.32**	.08

Note. The relationship is expressed in terms of correlation (Pearson's r) and agreement (weighed $Kappa$, K_w), the latter based on classification of ambulatory day-time values in quartiles. The total group and cardiovascular event-free group are described separately. Strength of agreement measured by K_w : < .20 is poor; .21 to .40 is fair; .41 to .60 is moderate; .61 to .80 is good; > .80 is very good (Altman, 1991).

* $p \leq .05$, ** $p \leq .01$.

were compared with the mean diastolic and systolic ambulant day-time pressure. Variability in ambulant day-time pressure was defined as the difference between the highest and the lowest diastolic or systolic day-time pressure and as the day-time standard deviation of these pressures. Correlations (Pearson's r) were computed between continuous scaled laboratory and ambulant parameters as indices of general relatedness. In addition, weighted Kappa's (K_w) were computed to test the agreement (*concordance*) between these measures. Analyses were performed for the total group and for the cardiovascular event-free group separately (Table 6.4). For both groups there was a moderate correlation and concordance for mean pressure parameters but low correlations and extremely poor concordance for estimates of variability.

The relation between ambulant day-time blood pressure and laboratory blood pressure was studied in more detail. Using the scatterplots for diastolic and systolic pressures presented in Figure 6.3, the regression equations were determined that predicted day-time blood pressure from laboratory means for all subjects. These were $40.9 + .53x$ ($r = .74$, $p < .01$) and $59.6 + .54x$ ($r = .73$, $p < .01$) for diastolic and systolic pressures, respectively. Laboratory measurement clearly underestimates mean day-time pressures in the lower pressure range but overestimates in the high pressure range (regression line and *line of identity* intersect at 130 and 87 mmHg for systolic and diastolic pressure, respectively). This can be illustrated even more clearly when the differences between laboratory and ambulant day-time means for diastolic and systolic blood pressures are plotted against their means (Figure 6.4). This method is commonly used to compare two clinical assessments when systematic measurement bias is suspected (Bland & Altman, 1986). Diastolic pressure measured in the laboratory tended to be systematically lower than ambulant day-time diastolic pressure, but the difference became smaller and eventually disappeared with higher levels of diastolic blood pressure. In approximately 95% of the present subjects the difference ranged between 6.9 and -21.6 mmHg. The difference in systolic pressures tended to change from a negative to a positive value with increasing mean pressure. Furthermore, a slight increase in variability was observed with increasing mean pressure, suggesting an increase in error bias. For systolic pressure the 95% limits of agreement ranged from -22.1 to 19.3.

In order to put the relationship between the two methods of measurement in a more clinical perspective, we classified the blood pressure status of all ambulatory blood pressure monitoring participants based on both their laboratory value (using the WHO/ISH criteria) and of their mean day-time blood pressure, according to the predicted ambulatory blood pressure monitoring values (135.2 / 88.6 mmHg) that were calculated by entering the WHO/ISH cut-off points (140 / 90 mmHg) in the regression equations presented above. A total of 19 out of 39 subjects in the ambulatory blood pressure monitoring group who were classified as hypertensive on the basis of either ambulatory or of laboratory measurement, were classified as hypertensive using *both* methods, four subjects were in the hypertensive range in the laboratory only, and 16 subjects were hypertensive based on ambulatory blood pressure monitoring values only. These results indicate that the agreement between both methods is poor when clinical criteria for grouping are used.

Figure 6.3. Scatter plots of diastolic and systolic blood pressures measured in the test laboratory and with day-time ambulatory recording (upper plots, total group $n = 135$) and night-time ambulatory recording (lower plots, total group $n = 127$). The line of identity and regression line are also displayed.

Age- and sex-related effects on day-time and night-time blood pressure differences

Ninety-nine antihypertensive drug-free subjects with no cardiovascular event in their medical history were included in the analysis. Twelve subjects in this group could be classified as *non-dippers*, showing overall night-time reductions in systolic and diastolic blood pressure of less than 10%, compared with day-time values (Verdecchia, Schillaci & Porcellati, 1991).

Both differences in day-night diastolic and systolic blood pressure were normally distributed: tests to detect deviation from normality (Kolmogorov-Smirnov) were not significant for the distribution of both pressure differences ($K-S = .04$ and $.07$ ($df = 99$), for diastolic and systolic blood pressure, respectively). This clearly demonstrates that the night-time reduction in blood pressure (*dipping*) is a gradual phenomenon that follows a unimodal distribution. As a consequence, any classification rule for *dipper* status may be considered largely arbitrary.

Finally, the extent to which day-night differences in blood pressure could be explained by the factors hypertensive status, age, sex, and the age by sex interaction term, was analysed in two separate hierarchical multiple regression models for diastolic and systolic blood pressure. Hypertensive status, based on the day-time average blood pressure and predicted WHO/ISH cut-off points, was entered as the first variable in the model, all other variables were entered in step 2. Day-night blood pressure differences were not influenced by hypertensive status, age or the age by sex interaction term. Only sex contributed significantly to explained variance in diastolic day-night blood pressure difference: the night-time decrease in diastolic blood pressure was predicted to be 3.0 mmHg greater for women than for men when all other variables were controlled for ($B = 3.0$, 95% $CI = .9-5.0$; $p < .01$). The final models predicted 12% ($p < .05$) and 2% (n.s.) of the variance in day-night differences of diastolic and systolic blood pressure, respectively.

Figure 6.4. Bland-Altman plots for diastolic and systolic blood pressures (BP); differences in pressure (laboratory minus mean day-time values) are plotted against the average of the two measures. Thin dotted lines indicate the mean difference and the distance of 2 SD from the mean; 95% of cases tend to fall within these limits (95% limits of agreement), skewed lines indicate regression lines.

DISCUSSION

Blood pressure adaptation and age

One of the main features of our study is that the reduction in systolic and diastolic blood pressure, measured automatically over a 20 min period, increased with age. This effect was still present when blood pressure differences over time were corrected for mean blood pressure levels. Using a different approach, Mancia et al. (1987) found no direct relation between age and adaptation to an intra-arterial measured blood pressure response that was induced by the presence of a medical professional. However, they studied a smaller ($N = 46$) and younger group (age range 16–64 year) of hospitalized inpatients of mixed hypertensive status in an less standardized measurement environment. It may even be argued that the observed effects of age on blood pressure adaptation will be even greater in a clinical setting, in particular in hypertensive patients. For instance, all our measurements were performed in the absence of an observer, thereby minimizing a possible pressor response (*white coat effect*, Høegholm, Kristensen, Madsen & Svendsen, 1992) and measurement bias. Furthermore, the pressure response in our experimental setting may be less extreme because the individuals were less stressed because the blood pressure measurement had no direct implications for medical intervention (Mancia et al., 1991). Finally, blood pressure variability is greater in hypertensive subjects (Mancia et al., 1983). Until these studies are repeated in a clinical setting it seems reasonable not to underestimate the effect of age on blood pressure adaptation during a measurement session.

The trend analysis of five consecutive measurements in 20 min indicated that adaptation of blood pressure took place within 10–15 min on the average, and, furthermore, that the blood pressure measured after this episode reflects the basal blood pressure more accurately than the average of all five measurements taken together. Although risk estimates for blood pressure in the pathogenesis of vascular disease are based on unavoidably biased casual measurements in a doctor's office, we adhere to the use of an approximated *basal* blood pressure because there is evidence that blood-pressure-mediated target organ damage is more closely related to 24 h ambulatory blood pressure than to office values (Devereux & Pickering, 1991; Omboni, Frattola, Parati, Ravogli & Mancia, 1992). We chose to use an adaptation period of 15 min before basal blood pressure recordings were made. Fifteen min of adaptation is in any case longer than the 'several minutes' advised by the WHO/ISH guidelines for office measurement (WHO/ISH, 1993). However, some authors have shown that increasing the number of blood pressure measurements by means of (semi-) automatic devices may enhance the reproducibility of blood pressure estimates, expressed as the reciprocal value of the standard deviation of the differences between measurements ($1/SD$; Mancia, Ulian, Parati & Trazzi, 1994; Trazzi et al., 1991). Although these observations were made in hypertensive subjects in whom, as mentioned above, blood pressure variability is known to be higher (in contrast to our largely normotensive population) it can not be ruled out that prolongation of the laboratory measurement interval or increasing the number of measurements after 15 min might have improved the prediction of day-time blood pressure in this study.

Blood pressure status and age

Laboratory blood pressure measurements showed a general increase in systolic and diastolic blood pressure with age, the former increase being more extreme in women than in men. These results are in accord with earlier findings of large population surveys in which classical sphygmomanometric measurements were made (e.g. the National Health and Nutrition Examination Survey 1976–1980 (NHANES II), see Kaplan, 1990). The same patterns for age and sex were found in the prevalence of hypertension when criteria proposed for office readings were used. It must be taken into account, however, that prevalence of hypertension in this study may be slightly underestimated by the generally lower blood pressure values obtained by automatic measurement when compared to office blood pressure readings. In contrast, the fact that blood pressure was measured on only one occasion may have produced the opposite effect, because in clinical settings blood pressure tends to decrease on repeated visits. The percentage of men with blood pressure in the hypertensive range gradually increased from 4.9% in the 25–30 year group to 40.8% in the group aged 75–80 years. Women with hypertension were first found in the group aged 45–50 years (7.3%), after which the percentage rose steeply towards 44.8% in the 75–80 year group. Even in the cardiovascular event-free group, the prevalence of untreated hypertension was substantial (12.8%). It is not clear whether this indicates a selective undertreatment in this group. The prevalence of isolated systolic hypertension in our population is in accord with earlier findings that isolated systolic hypertension is largely restricted to the older age groups (Amery, Fagard, Guo, Staessen & Lutgarde, 1991).

Comparison between parameters of laboratory and ambulatory blood pressure measurement

The mean values for 24 h ambulatory blood pressure measurements were similar to earlier published reference data (O'Brien et al., 1990; Staessen et al., 1991). Day-time and night-time values for women were slightly higher in this study than the values reported by O'Brien et al. (124/77 mmHg day-time and 109/62 mmHg night-time in our study, versus 118/75 mmHg and 102/58 mmHg in their study).

The blood pressure measured in the doctor's office is systematically higher than values derived from ambulatory measurements (O'Brien et al., 1990). Our laboratory diastolic pressure levels were lower than the ambulatory day-time values whereas systolic pressures did not differ (7.2 mmHg, $p < .001$, versus 1.2 mmHg, n.s., respectively). We expect this to be, at least partly, to be a result of a lower pressor response (or *white coat* effect) in our study.

Correlations between laboratory blood pressure and ambulatory day-time blood pressure values for systolic and diastolic measurements were .73 and .74, respectively, and are comparable to those of other studies. Enström (1991) found correlations of .81 systolic and .61 diastolic between ambulatory day-time blood pressure and blood pressure measured repeatedly in a doctor's office in a group of 48 middle-aged normotensive men, and lower correlations between the same measures in 81 borderline hypertensive middle-aged men (.62 and .54 for systolic and diastolic pressure, respectively). Staessen et al. (1991) found correlations of .72 and .60 for systolic and diastolic pressures between blood pressure measured repeatedly by a trained observer at home and mean ambulatory day-time blood pressure, in a

population sample aged 20–81 years ($N = 328$). Correlations between measures of variability in this study were significant, but low. However, the extremely poor agreement between the measures of variability indicates that the blood pressure variability of repeated measurements on a single occasion is not comparable in magnitude to the spontaneous fluctuation of ambulatory day-time blood pressure. This may not be surprising because the circumstances under which variability was assessed were essentially different for both measurements. The laboratory indicators of variance (SD and highest/lowest blood pressure difference) are more related to standardized blood pressure adaptation in a resting position, whereas SD in ambulatory day-time recordings is more determined by less controllable environmental factors like physical activity or posture.

Notwithstanding the reasonable correlations between day-time mean and laboratory pressures, the difference between both pressures varied with the average diastolic and systolic blood pressure level in an almost linear fashion. The systematic discrepancies between both measurement procedures are reflected in only moderate weighted *Kappa* values when the values measured by both methods for systolic, mean arterial and diastolic pressure are classified uniformly. In addition, classification of hypertensive status may lead to different results depending on the chosen type of measurement. If the laboratory blood pressure measurements were to be used to predict ambulatory day-time values a linear transformation of the data would seem to be appropriate. However, the fit of such a model may be rendered poor by an increase in error bias with increasing mean blood pressure level, as can be observed for systolic pressure in Figure 6.4b. One has to realize therefore that estimation of habitual day-time blood pressure from laboratory blood pressure levels during a single session is more error-prone with increasing blood pressure level.

Another factor that may have attenuated the accuracy of prediction in ambulatory blood pressure values is that the time of laboratory session within the day was not fixed. Di Rienzo et al. (1985) have shown that differences between mean 24 h blood pressure and subsequent 30 min intervals of such recordings shows considerable diurnal variation. It can be argued that fixed day-time measurement intervals will reduce this type of inaccuracy.

Day-night blood pressure difference

Gender was the only factor that contributed significantly to the variance in day-night diastolic blood pressure difference, with women tending to have a larger blood pressure difference than had men. Age and hypertensive status did not have a significant effect. The classification according to *dipper* status (Verdecchia et al., 1991) may suggest a bimodal distribution of pressure level difference, where a sharp distinction can be made between *dippers* and *non-dippers* according to a dichotomous criterion. Our data clearly demonstrate the continuous, normal distribution of day-night blood pressure differences and that any classification for *dipper* status is essentially arbitrary in this largely normotensive population sample. It needs to be confirmed in future research whether the day-night difference in blood pressure shows a normal distribution in hypertensive groups also, but at this point we prefer to include the absolute decrease in day-night blood pressure instead of *dipper* status in any risk analysis that pertains to the relation between day-night blood pressure differences and target organ damage.

Conclusion

In summary, these findings demonstrate that the importance of an adequate adaptation phase for single blood pressure measurement increases with age. We chose to average blood pressure measurements after 15 and 20 min of relaxation because no further decrease in blood pressure was observed after 15 min on a group level. Furthermore, it was confirmed that, at least for day-time ambulatory blood pressure, a clear linear relation with laboratory blood pressure can be demonstrated in this largely normotensive population sample. However, defining the hypertensive status on the basis of both measurements separately may lead to unequivocal conclusions, because the error bias in predicting ambulatory systolic pressure from laboratory measurements of systolic pressure is likely to increase as the absolute pressure level increases. As stated earlier, parameters of ambulatory blood pressure may reflect the blood pressure load that leads to target organ damage more accurately than do pressure levels derived from single measurements alone. Current knowledge about the relation between blood pressure and target organ disease is largely based on studies where repeated casual blood pressure measurements are made and there is still much debate about the use of parameters related to ambulatory blood pressure as more sophisticated risk factors for vascular morbidity and mortality (White, 1991). We therefore suggest that vascular risk estimates based on ambulatory blood pressure and repeated single measurements should be treated as different entities until the relation between blood pressure, measured with combined techniques, and vascular damage has been elucidated in more detail.

REFERENCES

- Altman, D. G. (1991). *Practical statistics for medical research*. (1st ed.). London: Chapman & Hall.
- Amery, A., Fagard, F., Guo, C., Staessen, J., & Lutgarde, T. (1991). Isolated Systolic Hypertension in the elderly: an epidemiological review. *American Journal of Medicine*, 90 (suppl 3A), 64S-70S.
- Bland, J. M., & Altman, D. G. (1986). Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet*, i, Feb 8, 307-310.
- Devereux, R. B., & Pickering, T. G. (1991). Relationship between the level, pattern and variability of ambulant blood pressure and target organ damage in hypertension. *Journal of Hypertension*, 9, S34-S38.
- Di Rienzo, M., Parati, G., Pomidossi, G., Veniani, M., Pedotti, A., & Mancia, G. (1985). Blood pressure monitoring over short day and night times cannot predict 24-hour average blood pressure. *Journal of Hypertension*, 3, 343-349.
- Enström, L., Thulin, T., & Lönndholm, L. (1991). How good are standardized blood pressure recordings for diagnosing hypertension? A comparison between office and ambulatory blood pressure. *Journal of Hypertension*, 9, 561-566.
- Höegholm, A., Kristensen, K. S., Madsen, N. H., & Svendsen, T. L. (1992). White coat hypertension diagnosed by 24-h ambulatory monitoring: Examination of 159 newly diagnosed hypertensive patients. *American Journal of Hypertension*, 5, 64-70.
- Jolles, J., Houx, P. J., van Boxtel, M. P. J., & Ponds, R. W. H. M. (Eds.). (1995). *Maastricht Aging Study: Determinants of cognitive aging*. Maastricht: Neuropsych Publishers.
- Kaplan, N. M. (1990). *Clinical Hypertension*. (5 ed.). Baltimore: Williams & Wilkins.
- Kramer, M. S., & Feinstein, A. R. (1981). Clinical biostatistics. LIV. The biostatistics of concordance. *Clinical Pharmacology and Therapeutics*, 29, 111-123.
- Llabre, M. M., Ironson, G. H., Spitzer, S. B., Gellman, M. D., Weidler, D. J., & Schneidermann, N. (1988). How many blood pressure measurements are enough? An application of generalisability theory to the study of blood pressure reliability. *Psychophysiology*, 25, 97-105.
- Mancia, G., Casadei, R., Groppelli, A., Parati, G., & Zanchetti, A. (1991). Effect of stress on diagnosis of hypertension. *Hypertension*, 17 (Suppl III), 56-62.

- Mancia, G., Ferrari, A., Gregorini, L., Parati, G., Pomidossi, G., Bertinieri, G., Grassi, G., Rienzo, M. d., Pedotti, A., & Zanchetti, A. (1983). Blood pressure and heart rate variabilities in normotensive and hypertensive human beings. *Circulation Research*, 53, 96-104.
- Mancia, G., Parati, G., Pomidossi, G., Grassi, G., Casadei, R., & Zanchetti, A. (1987). Alerting reaction and rise in blood pressure during measurement by physician and nurse. *Hypertension*, 9, 209-215.
- Mancia, G., Ulian, L., Parati, G., & Trazzi, S. (1994). Increase in blood pressure reproducibility by repeated semi-automatic blood pressure measurements in the clinic environment. *Journal of Hypertension*, 12, 469-473.
- Metsmakers, J. F. M., Höppener, P., Knottnerus, J. A., Kocken, R. J. J., & Limonard, C. B. G. (1992). Computerized health information in the Netherlands: A registration network of family practices. *British Journal of General Practice*, 42, 102-106.
- Norusis, M. J. (1990). *SPSS/PC+ Advanced Statistics 4.0*. Chicago: SPSS Inc.
- O'Brien, E., Murphy, J., Tyndall, A., Atkins, N., Mee, F., McCarthy, G., Staessen, J., Cox, J., & O'Malley, K. (1990). Twenty-four-hour ambulatory blood pressure in men and women aged 17 to 80 years: The Allied Irish Bank Study. *Journal of Hypertension*, 9, 355-360.
- Omboni, S., Frattola, A., Parati, G., Ravogli, A., & Mancia, G. (1992). Clinical value of blood pressure measurements: Focus on ambulatory blood pressures. *American Journal of Cardiology*, 70, 4D-8D.
- Pickering, T. G. (1991). *Ambulatory monitoring and blood pressure variability*. London: Science Press.
- Pickering, T. G. (1994). Blood pressure measurement and detection of hypertension. *Lancet*, 344, 31-35.
- Shimada, K., Kawamoto, A., Matsubayashi, K., & Ozawa, T. (1990). Silent cerebrovascular disease in the elderly: Correlation with ambulant pressure. *Hypertension*, 16, 692-699.
- Staessen, J., Bulpitt, C. J., Fagard, R., Mancia, G., O'Brien, E. T., Thijs, L., Vyncke, G., & Amery, A. (1991). Reference values for the ambulatory blood pressure and the blood pressure measured at home: A population study. *Journal of Human Hypertension*, 5, 355-361.
- Trazzi, S., Mutti, E., Frattola, A., Imholz, B., Parati, G., & Mancia, G. (1991). Reproducibility of non-invasive and intra-arterial blood pressure monitoring: Implications for studies on antihypertensive treatment. *Journal of Hypertension*, 9, 115-119.
- Verdecchia, P., Schillaci, G., & Porcelatti, C. (1991). Dippers versus non-dippers. *Journal of Hypertension*, 9 (Suppl 8), S42-S44.
- Waldstein, S. R., Manuck, S. B., Ryan, C. M., & Muldoon, M. F. (1991). Neuropsychological correlates of hypertension: Review and methodological considerations. *Psychological Bulletin*, 110, 451-469.
- White, W. B. (1991). Blood pressure load and target organ effects in patients with essential hypertension. *Journal of Hypertension*, 9, S39-S41.
- WHO/ISH. (1993). 1993 Guidelines for the management of mild hypertension: memorandum from a World Health Organization/International Society of Hypertension meeting. *Journal of Hypertension*, 7, 689-693.

Can blood pressure predict cognitive task performance in a healthy population sample?⁵

ABSTRACT

Hypertension increases the risk of cerebrovascular disease and has been consistently associated with reduced performance on cognitive tasks. It remains unclear to what extent blood pressure status contributes to age-related cognitive decline in the population. We studied the relation of blood pressure and other vascular risk factors (smoking, alcohol, body mass index, body fat distribution) with five measures of cognitive ability, including verbal memory and speed of information processing. A group of 936 healthy adults was recruited from a register of family practices, stratified for age (24-81 years), sex, and occupational level, and took part in a medical and neurocognitive test program. Blood pressure was measured five times using an automatic recording technique (Dynamap® 8100). After adjustment for age, sex and educational level in a hierarchical regression analysis, no straightforward association was found between mean systolic and diastolic blood pressure (or other vascular risk factors) and cognitive test performance in the total group, nor in the subgroup of subjects free of antihypertensive medication or cardiovascular events in their medical history. Stratified analysis within four age levels did not reveal any age-specific associations between blood pressure and cognitive function. Subjects whose blood pressure was in the hypertensive range did not perform worse than matched controls. We conclude therefore that in a community sample in which there is a high standard of hypertension treatment the relation between blood pressure status and cognitive performance is not of clinical importance.

INTRODUCTION

The integrity of cognitive abilities is vital to maintain independence in the aged, and any potential risk factor for cognitive decline that is open to intervention warrants careful evaluation. In recent years it has been a matter of debate whether blood pressure status contributes independently to the impairment of cognitive function that comes with age. Hypertension has been associated with atherosclerotic changes in large and small cerebral blood vessels and a reduced autoregulation of cerebral blood flow (Launer, Masaki, Petrovitch, Foley & Havlik, 1995; Starr & Whalley, 1992) and is a major risk factor for stroke and vascular dementia. Clinically *silent* white matter lesions in hypertensive subjects have been observed on neuroimaging and may in turn be associated with decrements in cognitive functioning (Breteler

⁵ M. P. J. van Boxtel, C. Gaillard, P. J. Houx, F. Buntinx, P. W. de Leeuw, and J. Jolles (*Subm.*)

et al., 1994; Van Swieten et al., 1991). The majority of case-control studies have reported a functional impairment of the central nervous system in hypertensive subjects, as assessed with neuropsychological tests (Battersby et al., 1993; Boller, Vrtunski, Mack & Kim, 1977; Goldman, Kleinman, Snow, Bidus & Korol, 1974; Herzog, Schaie & Gribbin, 1978; Madden & Blumenthal, 1989; Shapiro, Miller, King, Ginchereau & Fitzgibbon, 1982; Spieth, 1964; Waldstein, Manuck, Ryan & Muldoon, 1991; Wilkie & Eisdorfer, 1971), but several studies did not demonstrate different cognitive profiles between hypertensives and normotensive control subjects (e.g. Light, 1975; Perez Stable, Coates, Halliday, Gardiner & Hauck, 1992). The deficiencies that were most consistently associated with hypertension were found in memory function, attentional capacity, abstract reasoning, and response speed (King & Miller, 1990; Waldstein, 1995; Waldstein et al., 1991). Longitudinal data suggest that cognitive decline over time is more outspoken in hypertensives compared to normotensive control subjects (Wilkie & Eisdorfer, 1971), although other investigators did not find a differential rate of change in cognitive scores related to hypertensive status (Elias, Schultz, Robbins & Elias, 1989; Schultz Jr, Elias, Robbins, Streeten & Blakeman, 1989). However, from a clinical perspective the between-group differences are small and not very specific.

Population based studies on this issue have shown mixed results. In the Framingham Heart Study, 2,123 subjects between 55 and 89 years were tested with a short cognitive screening battery (Farmer et al., 1987). After adjustment for the effects of age, sex, education, vascular risk factors (smoking, alcohol intake), and antihypertensive medication use, no relation was found between diastolic or systolic blood pressure (measured once or twice) and cognitive performance scores. However, when information from the past biennial control visits on blood pressure status and antihypertensive medication use was taken into consideration, an inverse relation was found between the cognitive compound score on the one hand, and the proportion of blood pressure measurements in the hypertensive range and overall mean systolic and diastolic blood pressure on the other in subjects who had not been treated with antihypertensive medication (Farmer et al., 1990). Re-analysis of these data revealed an inverse relation between historical mean blood pressure levels and overall cognitive performance (Elias, Wolf, D'Agostino, Cobb & White, 1993). Finally, in the 4,678 surviving male members of the Honolulu-Asia Aging Study (mean age 78 years), the level of midlife systolic blood pressure – but not diastolic BP – was negatively related to the score on a cognitive screening instrument 25 years later, independent of age, education, cardiovascular disease, or subclinical atherosclerosis (Launer et al., 1995).

The issue becomes more complex when the factor age is taken into account. It was suggested that blood pressure may account for variance in measures of cognitive performance that otherwise would be ascribed to primary or 'intrinsic' aging (Elias, Robbins, Schultz & Pierce, 1990). The prevalence of both hypertension and cognitive impairment rises with age. Conversely, cerebral blood flow is known to decline markedly with age and the structural changes in the brain associated with hypertension may induce cerebral ischemia (Starr & Whalley, 1992), a process that indirectly may aggravate the age-related cognitive decline (Boller et al., 1977; Van Swieten et al., 1991). Remarkably, some evidence from cross-sectional studies suggests that elevated blood pressure may exactly be beneficial for the cognitive status in older subjects by promoting cerebral blood flow (Elias et al., 1990; Farmer

et al., 1987; Launer, Drinkgreve, Jonker, Hooijer & Lindeboom, 1993; Launer et al., 1995). Thus, as the prevalence of vascular risk factors (including blood pressure in the hypertensive range) and the development of vascular pathology and end organ damage are intricately related with age and sex, it is important to control these variables the relation is studied between vascular risk factors and cognitive function. This study intends to examine the relation between repeatedly measured blood pressure and performance on tests of global and specific cognitive functioning in a large adult population sample, with rigorous adjustment for factors age, sex, and general ability. Other vascular risk factors (smoking behavior, alcohol intake, body mass index, and fat distribution) were included in the analysis as potentially confounding variables (Swan, Carmelli & LaRue, 1996).

METHODS

Subjects

The study population consisted of the first panel of 936 participants in the Maastricht Aging Study (MAAS; Jolles, Houx, van Boxtel & Ponds, 1995). This community-dwelling adult cohort was randomly drawn from a register of family practices in the region of Maastricht (Metsemakers, Höppener, Knottnerus, Kocken & Limonard, 1992). Inclusion was stratified for age (12 classes, ranging from 25 ± 1 years, 30 ± 1 years, up to 80 ± 1 years), sex, and two levels of occupational achievement, the latter to control beforehand for the factor general ability (Jolles et al., 1995). The subjects were invited to take part in the study in an introductory letter from their general practitioners. The overall compliance rate was 32%. Participating and non-participating groups did not differ on the number of medical problems or on the presence of a number of specific chronic diseases, as recorded by their general practitioners. Non-complying subjects were more often in the youngest or oldest age classes, were less well educated, and were more often female (Jolles et al., 1995).

Subjects with past or present morbidity generally associated with brain dysfunction, namely, overt cerebrovascular disease (including stroke), chronic neurological diseases (such as dementia, epilepsy, and Parkinson's disease), mental retardation, or psychotropic drug use, were not included. Subject characteristics are summarized in Table 7.1.

The study protocol was approved by the local ethics committee and all participants gave their informed consent.

Measurements

Background characteristics

A postal questionnaire filled in by all participants covered background characteristics, including education (8-point scale, ranging from primary education to university degree (De Bie, 1987) and an extensive health history. A structured medical interview was administered to all participants prior to the actual tests, to check eligibility for inclusion and to screen all

information in the questionnaire for completeness. Tobacco use and alcohol intake were scored as dichotomous variables: present or past smoking yes / no, alcohol intake of less / more than 21 standard consumptions per week for females, or 35 for males (WHO, 1980). Subjects with medically confirmed previous or actual cardiovascular morbidity (cardiovascular event, or CVE, including angina pectoris, cardiac arrhythmia, myocardial infarction, cardiac insufficiency, valvular lesions, heart surgery, cardiac reanimation, or evidence of peripheral atherosclerosis) and subjects currently on antihypertensive medication were identified, to enable separate analyses to be done on data from subjects without these factors. The prevalence of these characteristics is displayed in Table 7.1. Subjects were then thoroughly screened in a medical and neuropsychological test battery, to obtain objective information about their physical and cognitive status.

Physical measurements

Body height and weight were measured to calculate the body mass index (BMI, in $\text{kg}\cdot\text{m}^{-2}$). In addition, waist and hip circumference was measured, the waist-to-hip ratio being used as an independent vascular risk factor (Despres et al., 1990). Blood pressure was automatically recorded five times, with fixed intervals of five minutes, during the 30-minute intermission between two test blocks. Measurements were made at the left arm with a Critikon Dinamap® 8100 monitor (Critikon, Tampa FL, USA) that was equipped with the appropriately sized arm cuff. During blood pressure measurements the subjects were seated, did not smoke or drink caffeine containing beverages and were left unattended by the researcher after they had been given careful instructions. The five consecutive measurements were averaged to yield mean systolic and diastolic blood pressure values.

Cognitive assessment

Standard neuropsychological tests were used to assess the cognitive domains general intelligence, memory, sensorimotor speed, and information processing speed / cognitive flexibility (Jolles et al., 1995), which are described briefly here.

Four subtests of the *Groningen Intelligence Test* (GIT) were used to arrive at a measure of formal IQ (Luteijn & van der Ploeg, 1983).

The *Word Learning Task* (WLT) is based upon the Auditory Verbal Learning Test (Brand & Jolles, 1985) and evaluates the ability to acquire and retain new verbal information. A set of fifteen frequently used monosyllabic words is presented in fixed order at a rate of one every two seconds in each of five trials. After every trial the subject is asked to reproduce the memorized words (immediate recall). Twenty minutes after the last trial the subject is asked again to reproduce the set of words (delayed recall). The total of correctly reproduced words on five trials, the maximum score in five trials, and the number of correctly reproduced words after 20 minutes are recorded.

The *Concept Shifting Task* (CST) is a test of behavioral planning and is analogous to the Trail-Making-Test of the Army Individual Test Battery (Houx, Vreeling & Jolles, 1991). The subject's ability to alternate two psychological concepts during task performance is measured, i.e., number and letter cancellation in correct order. A test sheet contains 16 small diameter circles ($\varnothing$ 15 mm) arranged in a larger circle ($\varnothing$ 16 cm). Two *null* versions (part 0)

Table 7.1. Mean (*SD*) levels of main independent and dependent variables used in this study, by levels of age (regrouped in six classes) and sex. Note that the cognitive outcome measures presented here are population based, *Z*-transformed scores (population mean = 0; *SD* = 1).

	Age class						Sex	
	25/30	35/40	45/50	55/60	65/70	75/80	M	F
Total <i>n</i>	161	162	162	159	162	130	475	461
Men / women ratio	81/80	81/81	80/82	81/78	81/81	71/59	—	—
Diastolic blood pressure (mmHg)	67 (8)	71 (10)	75 (10)	76 (11)	76 (11)	76 (12)	76 (10)	71 (11)
Systolic blood pressure (mmHg)	119 (11)	120 (11)	126 (14)	133 (17)	142 (19)	147 (21)	133 (17)	128 (20)
Hypertension ^{a b}	5	11	23	39	67	62	118	89
Waist-to-hip ratio	.81 (.08)	.84 (.09)	.86 (.10)	.88 (.08)	.90 (.08)	.90 (.07)	.91 (.07)	.81 (.08)
Body Mass Index (kg.m ²)	24.8 (3.9)	25.6 (3.8)	27.0 (5.5)	27.1 (3.6)	27.9 (4.1)	27.6 (3.5)	26.7 (4.0)	26.5 (4.6)
Smokers (past/actual) ^b	87	124	123	102	98	88	365	257
High alcohol intake (actual) ^b	3	7	9	8	1	4	14	18
Antihypertensive drug use ^b	1	1	16	26	51	59	76	78
Cardiovascular event (CVE) ^b	1	6	7	25	48	57	92	52
CVE / antihypertensive drug use ^b	2	7	18	39	74	76	119	97
Memory	.56 (.76)	.47 (.76)	.10 (.78)	.01 (.84)	-.40 (.91)	-.91 (.87)	-.26 (.95)	.27 (.87)
Sensorimotor speed	.65 (.43)	.47 (.45)	.25 (.54)	-.08 (.64)	-.47 (.69)	-1.00 (.81)	-.01 (.79)	.03 (.82)
Cognitive flexibility	.67 (.45)	.51 (.53)	.28 (.65)	-.09 (.67)	-.49 (.76)	-1.13 (.89)	-.04 (.87)	.07 (.89)
Letter / Digit Substitution Test	.90 (.70)	.56 (.74)	.25 (.78)	-.19 (.71)	-.63 (.78)	-1.12 (.72)	-.08 (.96)	.08 (1.03)
Word fluency	.42 (.94)	.31 (.94)	.18 (.97)	-.15 (.97)	-.31 (.97)	-.57 (.82)	-.03 (1.01)	.03 (.99)

Note. ^a Diastolic blood pressure ≥ 90 mmHg or systolic blood pressure ≥ 140 mmHg (WHO/ISH, 1993).

^b Displayed are cell counts.

contain no symbols in the circles, the number version (part A) presents figures 1 to 16 in random order in the circles, a letter version (part B) depicts randomly the letters A to P, and finally a number/letter version (part C) alternates the numbers 1 to 8 and letters A to H. The subject is instructed to cross out the circles in correct order, as fast as possible without making errors. Outcome is the time needed to complete each task.

Susceptibility to perceptual interference was measured in the *Stroop Color Word Test* (SCWT), consisting of three subtasks; color word naming (I), color naming (II) and naming of

color words printed in a different color (interference task III). This test shows robust effects of chronological age (Houx, Jolles & Vreeling, 1993).

The *Letter Digit Substitution Test* (LDST) is a modified version of the paper-and-pencil Symbol Digit Modalities Test (Smith, 1968) and measures basic information processing speed. The subject is requested to copy numbers in cells that are indexed by a letter. The letter refers to nine letter / number pairs in a key at the top of the form. The total number of corresponding numbers correctly copied in 90 seconds is recorded.

Finally, *Word Fluency* was scored as the total number of animal names correctly reproduced in 60 seconds (Luteijn & van der Ploeg, 1983). The test reflects the organizational level among clusters of meaningful related words.

Data reduction and analysis

To limit the number of dependent variables and to improve the robustness of the underlying cognitive construct (Houx & Jolles, 1994; Van Boxtel, Langerak, Houx & Jolles, 1996), the relevant raw test scores were clustered in three compound performance indices, labelled *memory*, *cognitive flexibility*, and *sensorimotor speed*. Raw scores were transformed to standardized *Z*-scores for the total group ($z = [x - \bar{x}] / SD$). Next, the average was taken of *Z*-scores from tests that were included in the compound performance index: the memory score was derived from the total, maximal and delayed recall scores of the WLT; the cognitive flexibility score included the C version of the CST and subtask III of the SCWT (LaRue, 1992); sensorimotor speed was calculated from the 0, A, and B versions of the CST, and subtask I of the SCWT. Thus, in formula: Memory = $(Z_{WLTOT} + Z_{WLTMAX} + Z_{WLTDEL}) / 3$, cognitive flexibility = $-(Z_{CST-C} + Z_{SCWT-III}) / 2$, and sensorimotor speed = $-(Z_{CST-0} + Z_{CST-A} + Z_{CST-B} + Z_{SCWT-I}) / 4$. Signs of the speed and flexibility scores were inverted to make them reflect above average performance when positive and below average performance when negative. LDST and fluency test outcomes were also transformed to *Z*-scores but not included in compound scores as the performance on these tests is less domain specific.

Performance on cognitive outcome variables was predicted using multiple hierarchical regression analysis, where chronological age, sex, and education were entered in the first step. Then all vascular risk factors and their interaction with age were tested pairwise in separate steps to detect an association with cognitive outcome measures. Predictor variables under study were systolic and diastolic blood pressure, BMI, WHR, alcohol intake, smoking behavior, antihypertensive drug use, and presence of cardiovascular events (CVE) in the medical history. Separate models were fitted for all subjects and for subjects free of CVE and antihypertensive medication use ($n = 720$).

Next, subjects were classified according to clinical criteria as hypertensive when the diastolic blood pressure was ≥ 90 mmHg, or systolic blood pressure was ≥ 140 mmHg (WHO/ISH, 1993). All hypertensive subjects were matched, for age in years, sex, and educational level, with normotensive controls, and between-group differences were tested with paired *t*-tests. *P*-values of .01 or lower were considered statistically significant, unless indicated otherwise.

RESULTS

Table 7.1 summarizes mean levels (or prevalence) of predictor variables and cognitive outcome measures by age class and sex.

Zero-order correlations between predictor variables and cognitive outcome measures are presented in Table 7.2. All cognitive parameters were highly negatively correlated with age (-.34 up to -.68), and, to a lesser extent, with educational level (.35-.48) and general intelligence (.11-.36). Relatively high correlations of cognitive parameters with educational level may in part be explained by the -.39 correlation between age and education. Systolic blood pressure, diastolic blood pressure, BMI, WHR, antihypertensive medication use, and cardiovascular events in the medical history were also negatively correlated with cognitive outcome scores, but again a large part of the common variance was shared with age.

Table 7.2. Zero-order correlations between age, sex, educational level, vascular risk factors and cognitive parameters.

	Age	Sex ^b	IQ ^a	Educ.	Memory	SS ^a	CF ^a	LDST ^a	Fluency
Age	—	—	—	—	-.50*	-.67*	-.65*	-.68*	-.34*
Sex	-.02	—	—	—	.28*	.03	.06	.08	.03
IQ	.12*	-.21*	—	—	.11*	.24*	.27*	.27*	.36*
Education	-.39*	-.07	.48*	—	.35*	.46*	.47*	.48*	.36*
Diastolic BP	.26*	-.25*	.07	-.10*	-.17*	-.17*	-.16*	-.21*	-.11*
Systolic BP	.55*	-.13*	.07	-.24*	-.30*	-.40*	-.38*	-.41*	-.21*
Pulse Pressure	.51*	.02	.05	-.21*	-.26*	-.38*	-.37*	-.37*	-.18*
Body Mass Index	.24*	-.03	-.05	-.20*	-.17*	-.16*	-.18*	-.18*	-.10*
Waist-to-hip Ratio	.36*	-.55*	.10*	-.18*	-.35*	-.26*	-.27*	-.30*	-.18*
Alcohol intake ^c	-.01	.03	.04	.04	.03	.02	.03	.03	.04
Smoking behavior ^c	.01	-.22*	.10*	-.02	-.09*	.03	.01	.01	.05
Antihyp. medication ^c	.41*	.01	.03	-.14*	-.22*	-.28*	-.27*	-.30*	-.17*
Cardiovascular events ^c	.40*	-.11*	.11*	-.10*	-.26*	-.23*	-.25*	-.26*	-.10*

Note. ^a Abbreviations: IQ = Intelligence Quotient; SS = Sensorimotor Speed; CF = Cognitive Flexibility; LDST = Letter Digit Substitution Test.

^b 0 = male, 1 = female; ^c 0 = no, 1 = yes.

* $p \leq .01$ (two-tailed test)

The associations between vascular risk factors, the risk factor by age interaction, and the five cognitive scores (memory, sensorimotor speed, cognitive flexibility, letter digit copying, and fluency) were tested in separate multiple hierarchical regression analyses, after adjusting for age, sex, and educational level. No contribution to the prediction of cognitive outcome measures was observed when the variables BMI, WHR, smoking, alcohol intake, antihypertensive medication use, cardiovascular events (CVE), and their respective interaction with age, were entered in pairs in the regression models (p associated with R^2 increase $> .05$). These variables were not included as control variables in the final models in which blood pressure and the blood pressure by age product term were tested as predictors of cognitive outcome, in order to minimize the number of redundant variables.

Separate models that were fitted for diastolic and systolic blood pressure showed that predictors in step 1 explained between 17% (word fluency) and 50% (letter / digit copying) of the variance in cognitive scores, which was for the largest part due to the factor age. No main effect of blood pressure on any cognitive parameter was observed in step 2. However, for systolic blood pressure the age by blood pressure interaction term was negatively associated with two speed indices, sensorimotor speed and cognitive flexibility. There was no noticeable change in the size or direction of the observed effects when the entry of blocks was reversed and age was entered in the last block of variables, or when the analyses were iterated on the subgroup with no history of cardiovascular events or antihypertensive drug use. Table 7.3 summarizes the regression results for systolic blood pressure on the total group and on the group free of cardiovascular events (CVE) and antihypertensive drug use ($n = 720$). Results for diastolic blood pressure are not shown, but were virtually identical up to step 1.

In terms of explained variance, the contribution of blood pressure to the models was small (up to 1.0% in the cognitive flexibility score for systolic blood pressure in the unmedicated and CVE-free group). However, the observed age by systolic blood pressure interactions suggested that the blood pressure / cognitive performance relation was age-dependent. Identical regression analyses were therefore performed post-hoc on the data, in four age strata: 25-35 years, 40-50 years, 55-65 years, and 70-80 years. No association between systolic blood pressure and any of five cognitive variables was observed within any age stratum at the $p = .05$ level, or lower, using the same adjustments for background variables as in earlier analyses. Moreover, no systematic trend was observed in the *Beta* weights over the four age classes, to account for the significant interaction effects in the overall analyses.

In an attempt to replicate earlier findings of cognitive deficits in patient groups with clinical hypertension, subjects whose blood pressure was in the hypertensive range, based on the mean of laboratory values, were matched with normotensive controls with respect to age (± 1 year), sex, and educational level. Of 207 thus identified hypertensive subjects (diastolic blood pressure ≥ 90 mmHg or systolic blood pressure ≥ 140 mmHg), 195 could be matched in this way. The raw cognitive scores of this subgroup were again transformed to individual *Z*-scores and compound scores, using the above described formulae. Both groups are contrasted in Table 7.4. Paired *t*-tests revealed a higher mean BMI in the hypertensive group, but the groups did not differ on cognitive outcome measures.

DISCUSSION

In this study the relation between vascular risk factors – in particular blood pressure status – and several aspects of cognitive performance was evaluated in an adult population that was stratified for age, sex, and general ability. This was done in an attempt to discriminate the effects on cognitive processes of factors related to cerebrovascular pathology, and of primary aging. Apart from the weak inverse associations between the age by systolic blood pressure interaction term and two measures of information processing speed (sensorimotor speed and cognitive flexibility), it was found that blood pressure status nor any other vascular risk factor did have a main effect on cognitive performance, after the variance explained by age, sex, and educational level was accounted for. The same conclusion was reached when the sample was

Table 7.3. Results of multiple hierarchical regression analyses of cognitive outcome variables. Shown are standardized regression coefficients (*Beta*) and the significance level of the unstandardized regression coefficient (*B*) in the final model, and R^2 (proportion of explained variance) and significance of R^2 change after each step. Separate models were fitted for all subjects ($N = 936$), and for subjects free of cardiovascular events or antihypertensive drug use ($n = 720$).

	Step 1			Step 2		R^2 after step	
	Age	Sex	Education	SBP ^a	Age x SBP	1	2
<i>All subjects</i>							
Memory	-.40**	.30**	.21**	.05	-.08	.331**	.336
Sensorimotor speed	-.57**	.05	.24**	.03	-.11**	.478**	.487**
Cognitive flexibility	-.54**	.10**	.28**	.03	-.10**	.485**	.493**
Letter / digit copying	-.55**	.09**	.26**	-.01	-.02	.498**	.499
Word fluency	-.22**	.06	.28**	.00	-.03	.173**	.174
<i>CVE- and medication-free subjects^b</i>							
Memory	-.35**	.29**	.25**	.02	-.07	.302**	.306
Sensorimotor speed	-.54**	.05	.25**	.00	-.11**	.456**	.467**
Cognitive flexibility	-.51**	.11**	.31**	-.02	-.10**	.489**	.499**
Letter / digit copying	-.50**	.09*	.26**	-.05	-.03	.466**	.469
Word fluency	-.21**	.08*	.28**	.03	-.02	.157**	.158

Note. ^a SBP = Systolic blood pressure; ^b CVE = Cardiovascular event.

* $p \leq .01$; ** $p \leq .001$

Table 7.4. Characteristics of subjects whose blood pressure was in the hypertensive range (diastolic blood pressure ≥ 90 mmHg or systolic blood pressure ≥ 140 mmHg (WHO/ISH, 1993); $N = 195$) compared to normotensive controls from this sample, matched for age, sex, and educational level. In both groups 80 subjects were female.

	Control group		Hypertensive group	
	<i>M</i>	(<i>SD</i>)	<i>M</i>	(<i>SD</i>)
Age (years)	63.3	(12.5)	63.3	(12.5)
Education	2.8	(1.6)	2.8	(1.6)
IQ ^a	114.1	(13.1)	114.0	(13.0)
Body Mass Index (kg·m ⁻²)	27.3	(3.7)	28.2	(3.9)*
Waist-to-hip ratio	.90	(.08)	.90	(.07)
Diastolic blood pressure (mmHg)	69.4	(9.5)	83.9	(10.1)***
Systolic blood pressure (mmHg)	125.3	(8.3)	154.1	(14.8)***
Memory	.01	(.89)	-.02	(1.00)
Sensorimotor speed	.07	(.78)	-.03	(.78)
Cognitive flexibility	.09	(.85)	.03	(.86)
Letter / Digit substitution	.06	(1.02)	-.06	(.98)
Word fluency	.04	(.91)	-.04	(1.08)

Note. ^a IQ = intelligence quotient.

* $p \leq .05$, ** $p \leq .01$, *** $p \leq .001$

broken down into four, equally sized age strata that were balanced for sex and general ability: again blood pressure status failed to explain unique variance, which indicates that there was no age-specific interrelation between blood pressure and performance. Finally, subjects in this sample who were identified as being hypertensive had similar performance scores than age-, sex-, and education-matched normotensive control subjects.

Several methodological issues need to be addressed before a final conclusion can be drawn. Blood pressure was measured under standardized conditions because it was measured on one occasion only and because blood pressure can be temporarily affected by factors such as posture, speech, and physical or mental activity (Pickering, 1991). Furthermore, blood pressure was measured in the absence of an observer to minimize the pressure response in some individuals, as the result of an alerting reaction (Mancia, Casadei, Groppelli, Parati & Zanchetti, 1991). In this respect, single or duplicate blood pressure measurement with classical sphygmomanometry is particularly error-prone, because an observer is present to record blood pressure. Nevertheless, classical single or duplicate measurement of blood pressure has been used in most studies that were reviewed here (e.g. Breteler et al., 1994; Elias et al., 1993; Farmer et al., 1987; Starr, Whalley, Inch & Shering, 1993) – with one exception in which repeated measurements were made using an oscillometric technique (Elias et al., 1990) – which may have resulted in somewhat biased estimates of habitual blood pressure.

Our findings do not corroborate those of Elias et al. (Elias et al., 1990). From a study in 301 healthy subjects, aged 20 to 72 years, they reported negative correlations between systolic and diastolic blood pressure (in the normal to hypertensive range) and performance on relatively complex cognitive tests, after the effects of age, sex, and educational level were controlled for. The number of subjects in their study was much smaller and, more importantly, more hypertensive participants were included who were encouraged by their physician to take part in the cognitive test program. This inclusion procedure may have biased their sample in that a priori knowledge of the study participants with respect to their blood pressure status was unavoidable and inclusion of a larger proportion of hypertensive patients may have resulted in a higher prevalence of vascular morbidity in this sample.

A potential – but as yet speculative – mechanism that could explain the negative association between blood pressure and cognition found in some studies is that the same factors which induce an alerting reaction and an increase in blood pressure may also induce a temporary lapse in performance on some cognitive tasks. Indeed, in a subgroup of this sample we also found a tendency towards lower blood pressure at the end of the 20-minute measurement session that was more pronounced in the older age groups (Van Boxtel, Gaillard, van Es, Jolles & de Leeuw, 1996). This may indicate that some adaptation of blood pressure had taken place during the measurement interval. It was therefore decided to perform additional post hoc analyses, using the averages of the first two and of the last two systolic and diastolic blood pressure measurements as predictors of performance, intending to reflect blood pressure before and after adaptation, respectively. The resulting regression models were however not substantially different from those that were fitted using the average of all five measurements.

It can be argued that the cross-sectional nature of this study may threaten in some respects the external validity of our negative findings with respect to the blood pressure / cognition relationship. Blood pressure status was based on repeated blood pressure measurement during a

single session. Reliable information about the subjects' blood pressure status in the past, to reconstruct the systemic blood pressure *load* over time, was not available. The importance of such additional data was supported by two large population studies in which blood pressure over time was demonstrated to predict cognitive decline (Framingham study, Elias et al., 1993; Honolulu-Asia study, see Launer et al., 1995). In addition, bias due to cohort effects may in part counteract potential negative associations between blood pressure status and performance, such as selective survival of individuals whose vascular system is less compromised and who may therefore be at lower risk for cognitive impairment. Apart from overt cerebrovascular disease, which was reason for exclusion, our population was unselected with respect to vascular health status. Self-selection bias can, however, not be ruled out entirely, even though participants did not differ in morbidity (as recorded by the family physician) when compared to non-compliers (Jolles et al., 1995). Limitations of this kind, however, pertain to any cross-sectional study on this subject and to any other predictor of age related cognitive dysfunctions. They can only be circumvented by follow-up measurements in the same cohort.

Even though antihypertensive medication use or experienced CVE covers a heterogeneous cluster of different drugs and types of morbidity, it is clear that excluding subjects from the analysis who had one or more of these characteristics reduces the prevalence of vascular pathology in the remaining group, including subclinical cerebrovascular damage. The presence of cardiovascular disease has earlier been associated with cognitive deficits (e.g. Herzog et al., 1978; Spieth, 1964). However, neither antihypertensive medication use nor CVE was associated with performance in this study. The most convincing population-based studies to date that demonstrated hypertension-related cognitive impairment used a blood pressure exposure index within a time frame when no effective drug therapy was available on a large scale (Elias et al., 1993; Launer et al., 1995). It is likely that any population study in Western societies will be confounded by the widespread use – and heterogeneity – of drug treatment, which may partially cover up the true extent of subclinical brain damage caused by high blood pressure. It can therefore not be concluded from these data that chronically elevated blood pressure in susceptible individuals does not contribute to cognitive decline with age, but our findings do suggest that in a community-dwelling healthy population where there is a high standard of antihypertensive drug treatment, the relation between blood pressure status and cognitive function is at least too weak to be of clinical importance.

REFERENCES

- Battersby, C., Hartley, K., Fletcher, A. E., Markowe, H. J. L., Brown, R. G., Styles, W., Carnes, S., Jamieson, T., Koppel, I., Fraser, S., Sapper, H., & Bulpitt, C. J. (1993). Cognitive function in hypertension: A community based study. *Journal of Human Hypertension*, 7, 117-123.
- Boller, F., Vrtunski, P. B., Mack, J. L., & Kim, Y. (1977). Neuropsychological correlates of hypertension. *Archives of Neurology*, 34, 701-705.
- Brand, N., & Jolles, J. (1985). Learning and retrieval rate of words presented auditory and visually. *Journal of General Psychology*, 112, 201-210.
- Breteler, M. B. B., van Swieten, J. C., Bots, M. L., Grobbee, D. E., Claus, J. J., Van den Hout, J. H. W., Van Harskamp, F., Tanghe, H. L. J., de Jong, P. T. V. M., van Gijn, J., & Hofman, A. (1994). Cerebral white matter lesions, vascular risk factors, and cognitive function in a population-based study: The Rotterdam Study. *Neurology*, 44, 1246-1252.

- De Bic, S. E. (1987). *Standaardvragen 1987: Voorstellen voor uniformering van vraagstellingen naar achtergrondkenmerken en interviews [Standard questions 1987: Proposal for uniformization of questions regarding background variables and interviews]*. (2nd ed.). Leiden: Leiden University Press.
- Despres, J. P., Moorjani, S., Lupien, P. J., Tremblay, A., Nadeau, A., & Bouchard, C. (1990). Regional distribution of body fat, plasma lipoproteins, and cardiovascular disease. *Arteriosclerosis*, 10, 497-511.
- Elias, M. F., Robbins, M. A., Schultz, J. N. R., & Pierce, T. W. (1990). Is blood pressure an important variable in research on aging and neuropsychological test performance? *Journal of Gerontology*, 45, P128-135.
- Elias, M. F., Schultz, J. N. R., Robbins, M. A., & Elias, P. K. (1989). A longitudinal study of neuropsychological performance by hypertensives and normotensives: a third measurement point. *Journal of Gerontology*, 44, P25-28.
- Elias, M. F., Wolf, P. A., D'Agostino, R. B., Cobb, J., & White, L. R. (1993). Untreated blood pressure level is inversely related to cognitive functioning: The Framingham Study. *American Journal of Epidemiology*, 138, 353-364.
- Farmer, M. E., Kittner, S. J., Abbott, R. D., Wolz, M. M., Wolf, P. A., & White, L. R. (1990). Longitudinally measured blood pressure, antihypertensive medication use, and cognitive performance: The Framingham Study. *Journal of Clinical Epidemiology*, 43, 475-480.
- Farmer, M. E., White, L. R., Abbott, R. D., Kittner, S. J., Kaplan, E., Wolz, M. M., Brody, J. A., & Wolf, P. A. (1987). Blood pressure and cognitive performance: The Framingham study. *American Journal of Epidemiology*, 126, 1103-1114.
- Goldman, H., Kleinman, K. M., Snow, M. Y., Bidus, D. R., & Korol, B. (1974). Correlation of diastolic blood pressure and signs of cognitive dysfunction in essential hypertension. *Diseases of the Nervous System*, 35, 571-572.
- Herzog, C., Schaie, K. W., & Gribbin, K. (1978). Cardiovascular disease and changes in intellectual functioning from middle to old age. *Journal of Gerontology*, 33, 872-883.
- Houx, P. J., & Jolles, J. (1994). Vulnerability factors for age-related cognitive decline. In R. L. Isaacson & K. F. Jensen (Eds.), *Toxins in air and water*, (Vol. 3, pp. 25-41). New York: Plenum Press.
- Houx, P. J., Jolles, J., & Vreeling, F. W. (1993). Stroop interference: Aging effects assessed with the Stroop Color-Word test. *Experimental Aging Research*, 19, 209-224.
- Houx, P. J., Vreeling, F. W., & Jolles, J. (1991). Age-associated cognitive decline is related to biological life events. In K. Iqbal, D. R. C. McLachlin, B. Winblad, & H. M. Wisniewski (Eds.), *Alzheimer's disease: Basic mechanisms, diagnosis and therapeutic strategies*, (pp. 353-358). Chichester, UK: Wiley.
- Jolles, J., Houx, P. J., van Boxtel, M. P. J., & Ponds, R. W. H. M. (Eds.). (1995). *Maastricht Aging Study: Determinants of cognitive aging*. Maastricht: Neuropsych Publishers.
- King, H. E., & Miller, R. E. (1990). Hypertension: cognitive and behavioral considerations. *Neuropsychology Review*, 1, 31-73.
- LaRue, A. (1992). *Aging and neuropsychological assessment*. New York: Plenum Press.
- Launer, L. J., Dinkgreve, M. A., Jonker, C., Hooijer, C., & Lindeboom, J. (1993). Are age and education independent correlates of the Mini-Mental State Exam performance of community-dwelling elderly? *Journal of Gerontology*, 48, P271-277.
- Launer, L. J., Masaki, K., Petrovitch, H., Foley, D., & Havlik, R. J. (1995). The association between midlife blood pressure levels and late-life cognitive function: the Honolulu-Asia Aging Study. *Journal of the American Medical Association*, 274, 1846-1851.
- Light, K. C. (1975). Slowing of response time in young and middle-aged hypertensive patients. *Experimental Aging Research*, 1, 209-227.
- Luteijn, F., & van der Ploeg, F. A. E. (1983). *Handleiding Groninger Intelligentietest (GIT) [Manual Groningen Intelligence Test]*. Lisse, the Netherlands: Swets and Zeitlinger.
- Madden, D. J., & Blumenthal, J. A. (1989). Slowing of memory-search performance in men with mild hypertension. *Health Psychology*, 8, 131-142.
- Mancia, G., Casadei, R., Groppelli, A., Parati, G., & Zanchetti, A. (1991). Effect of stress on diagnosis of hypertension. *Hypertension*, 17 (Suppl III), 56-62.
- Metsemakers, J. F. M., Höppener, P., Knotterus, J. A., Kocken, R. J. J., & Limonard, C. B. G. (1992). Computerized health information in the Netherlands: A registration network of family practices. *British Journal of General Practice*, 42, 102-106.
- Perez Stable, E. J., Coates, T. J., Halliday, R., Gardiner, P. S., & Hauck, W. W. (1992). The effects of mild diastolic hypertension on the results of tests of cognitive function in adults 22 to 59 years of age. *Journal of General Internal Medicine*, 7, 19-25.
- Pickering, T. G. (1991). *Ambulatory monitoring and blood pressure variability*. London: Science Press.
- Schultz Jr, N. R., Elias, M. F., Robbins, M. A., Streeten, D. H. P., & Blakeman, N. (1989). A longitudinal study of the performance of hypertensive and normotensive subjects on the Wechsler Adult Intelligence Scale. *Psychology and Aging*, 4, 496-499.

- Shapiro, A. P., Miller, R. E., King, H. E., Ginchereau, E. H., & Fitzgibbon, K. (1982). Behavioral consequences of mild hypertension. *Hypertension*, 4, 355-360.
- Smith, A. (1968). The Symbol Digit Modalities Test: A neuropsychological test for economic screening of learning and other cerebral disorders. *Learning Disorders*, 36, 83-91.
- Spiehl, W. (1964). Cardiovascular health status, age, and psychological performance. *Journal of Gerontology*, 19, 277-284.
- Starr, J. M., & Whalley, L. J. (1992). Senile hypertension and cognitive impairment: An overview. *Journal of Hypertension (Suppl.)*, 10, S31-S42.
- Starr, J. M., Whalley, L. J., Inch, S., & Shering, P. A. (1993). Blood pressure and cognitive function in healthy old people. *Journal of the American Geriatrics Society*, 41, 753-756.
- Swan, G. E., Carmelli, D., & LaRue, A. (1996, February). *CHD risk factors and neuropsychological performance in the elderly*. Paper presented at the Annual Meeting of the International Neuropsychological Society, Chicago, Ill.
- Van Boxtel, M. P. J., Gaillard, C., van Es, P. N., Jolles, J., & de Leeuw, P. W. (1996). Repeated automatic versus ambulatory blood pressure measurement: The effects of age and sex in a normal ageing population. *Journal of Hypertension*, 14, 31-40.
- Van Boxtel, M. P. J., Langerak, K., Houx, P. J., & Jolles, J. (1996). Self-reported physical activity, perceived health, and cognitive performance in older adults. *Experimental Aging Research*, 22, 363-379.
- Van Swieten, J. C., Geyskes, G. G., Derix, M. M. A., Peek, B. M., Ramos, L. M. P., van Latum, J. C., & van Gijn, J. (1991). Hypertension in the elderly is associated with white matter lesions and with cognitive decline. *Annals of Neurology*, 30, 825-830.
- Waldstein, S. R. (1995). Hypertension and neuropsychological function: A lifetime perspective. *Experimental Aging Research*, 21, 321-352.
- Waldstein, S. R., Manuck, S. B., Ryan, C. M., & Muldoon, M. F. (1991). Neuropsychological correlates of hypertension: review and methodological considerations. *Psychological Bulletin*, 110, 451-469.
- WHO. (1980). *Problems related to alcohol consumption: Report of a WHO expert committee*. Geneva: World Health Organisation.
- WHO/ISH. (1993). 1993 Guidelines for the management of mild hypertension: memorandum from a World Health Organization/International Society of Hypertension meeting. *Journal of Hypertension*, 7, 689-693.
- Wilkie, F. L., & Eisdorfer, C. (1971). Intelligence and blood pressure in the aged. *Science*, 172, 959-962.

Chapter 8

Is cognitive impairment related to a reduced nocturnal blood pressure drop?⁶

ABSTRACT

The outcome of 24-hour ambulatory blood pressure monitoring was used to predict cognitive performance, in order to evaluate the potential relevance of blood pressure status for cognitive function in healthy individuals. Furthermore, the hypothesis was tested that a reduction in the physiological blood pressure drop during sleep (*dipping*) is associated with a cognitive performance deficit, in line with studies in hypertensives that suggest associations between non-dipping and target organ damage.

For this purpose, a group of 115 largely normotensive community residents in the age between 28 and 82 years were recruited from a larger study on cognitive aging. All participants were screened for past or present cardiovascular events and medication use and underwent standard 24-hour blood pressure monitoring within three weeks after the administration of a cognitive battery of tests, including verbal memory, attention, simple speed, and information processing speed. Raw test scores were *Z*-transformed and combined in compound measures of memory performance, sensorimotor speed and cognitive flexibility.

Mean levels of systolic or diastolic blood pressure during the day or the night were not predictive for cognitive outcome, after control for age, sex and educational level. However, the absolute and relative difference between mean day-time and night-time blood pressure was positively associated with performance on verbal memory (8-9% of additional variance explained), but not with speed-related cognitive measures. The relation found for memory was independent of both antihypertensive medication use and evidence of cardiovascular events in the medical history. *Non-dippers* ($n = 15$) showed lower levels of both the memory and sensorimotor speed scores compared to *dippers* ($n = 100$).

In conclusion, mean ambulatory blood pressure was not predictive for cognitive performance. However, blunting or absence of the nocturnal blood pressure drop may be associated with quite specific cognitive deficits. The underlying mechanism remains as yet unclear.

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INTRODUCTION

Blood pressure is considered to be a key factor in the development of cerebrovascular disease, in particular stroke and vascular dementia (Gorelick, 1995; Skoog, 1994). Hypertension may cause a reduction in regional cerebral blood flow (Rodriguez et al., 1987) and subclinical brain damage on structural imaging, such as white matter hypodensities (Breteler et al., 1994; Shimada, Kawamoto, Matsubayashi & Ozawa, 1990; Van Swieten et al., 1991) or signs of local brain atrophy (Salerno et al., 1992). Elevated blood pressure levels contribute to functional cerebral impairment in susceptible individuals, in particular when other vascular risk factors leading to cerebral ischemia are present (Starr & Whalley, 1992). Individuals diagnosed as being hypertensive consistently perform worse on cognitive performance tasks of learning and memory, attention and information processing speed when compared to normotensive controls (King & Miller, 1990; Waldstein, 1995; Waldstein, Manuck, Ryan & Muldoon, 1991). Population studies on the relation between blood pressure and cognitive status have shown mixed results. Results from the Framingham Heart Study indicated that longitudinally measured untreated blood pressure in the hypertensive range is negatively associated with cognitive performance, in particular in the domains of memory and attention (Elias, Wolf, D'Agostino, Cobb & White, 1993; Farmer et al., 1990). In a large cohort of older Asian men (mean age 78 years) the systolic blood pressure, but not diastolic blood pressure, was inversely related to performance on a broad cognitive screening test that was administered approximately 25 years later (Launer, Masaki, Petrovitch, Foley & Havlik, 1995). A study in 301 largely normotensive to borderline hypertensive adult subjects showed inverse associations between systolic and diastolic blood pressure status and speeded performance tasks, suggesting that even small blood pressure elevations may result in functional decline (Elias, Robbins, Schultz & Pierce, 1990). However, a recent large age-stratified study in 936 subjects of mixed blood pressure status did not corroborate the findings of Elias et al. (Van Boxtel, Gaillard, Houx, de Leeuw & Jolles, 1996).

An important methodological pitfall in studies on the blood pressure / cognition relationship is the measurement of blood pressure itself. Blood pressure can be highly variable over time due to endogenous or exogenous stimuli. Furthermore, a substantial proportion of individuals is prone to a alerting reaction during blood pressure measurement that persists over successive measurements (*white coat effect*, Mancia et al., 1987). This may result in higher blood pressure readings in a medical than values obtained under daily living conditions. The measurement bias in studies that use on only a small number of blood pressure readings may thereby reduce the chance of picking up an association between blood pressure status and functional cerebral decline, if such association exists.

Non-invasive ambulatory blood pressure monitoring (ABPM) enables one to obtain repeated measurements of blood pressure under normal living conditions, thereby providing a more reliable estimation of blood pressure status and potentially a more valid prediction of hypertension-related complications (Pickering, 1994). Although prognostic studies to substantiate this notion are as yet not available, there is some support that ABPM is superior to casual blood pressure (assessed with classical auscultatory measurement) in predicting hypertension-related target organ damage, such as retinopathy or left ventricular hypertrophy

(Devereux & Pickering, 1991). As evidenced by a study of 73 healthy elderly subjects of mixed blood pressure status, clinically silent cerebral lesions on magnetic resonance imaging can be predicted by ambulant blood pressure, but not by the blood pressure level measured in the doctor's office (Shimada et al., 1990). Moreover, the circadian blood pressure rhythm provides additional information on the condition of the vascular system, as blunting of the physiological blood pressure reduction during the night (*non-dipping*) is suggested to be linked with more cardiovascular complications of essential hypertension (Verdecchia, Schillaci & Porcellati, 1991). Comparable observations have been made with respect to cerebrovascular pathology as the incidence of stroke may be higher in non-dippers (O'Brien, Sheridan & O'Malley, 1988). In a recent case-control study that contrasted patients with vascular dementia of the Binswanger type with non-demented age-matched controls, the day-night differences in ambulant blood pressure were smaller in the patient group (Toghi, Chiba & Kimura, 1991). Finally, a study in elderly hypertensives reported a higher prevalence of cerebrovascular damage on magnetic resonance imaging in subjects with a reduced nocturnal blood pressure fall (Shimada et al., 1992).

In this study the potential was tested of parameters derived from 24-hour ambulatory blood pressure monitoring in predicting cognitive test performance, thereby ruling out measurement bias that would have resulted from fewer blood pressure readings. Moreover, the hypothesis was investigated that a reduction in the circadian variation in blood pressure is associated with a cognitive performance decrement.

METHODS

Subjects

Participants in this study were recruited from a larger subject sample that took part in a cross-sectional cognitive aging study (Maastricht Aging Study, Jolles, Houx, van Boxtel & Ponds, 1995). Subjects for this cross-sectional study were randomly drawn from a register of general practices (Registration Network Family Practices, Metsemakers, Höppener, Knottnerus, Kocken & Limonard, 1992). Clinical evidence of past or present morbidity or drug use that could compromise brain function rendered a subject not eligible for the study: cerebrovascular disease, chronic neurological pathology – including dementia, epilepsy, and parkinsonism – and mental retardation or psychotropic medication use. Subjects were stratified for age (12 discontinuous groups; 25 ± 1 year, 30 ± 1 year, 35 ± 1 year, ..., 80 ± 1 year), sex, and two levels of occupational activity, used here as a proxy measure of general ability. In total 126 subjects in six age groups (30 ± 1 year, 40 ± 1 year, up to 80 ± 1 years) with complete cognitive data were invited and agreed to participate in additional ABPM, within 3–4 weeks after completion of a comprehensive neuropsychological test battery. Eleven subjects were dropped from the analysis because of incomplete ABPM recordings, defined as a proportion of valid measurements during the 24-hour measurement interval of less than two-thirds of the maximal number of readings. Thus, data from 115 subjects were available.

The study protocol was approved by the local ethics committee and informed consent in writing was obtained from all participants.

Measurements

All subjects filled in a questionnaire pertaining socioeconomic background variables and medical history. Educational level was measured on an 8-point scale, ranging from primary school to higher vocational training and university degree (De Bie, 1987). In addition, a more specific medical interview was taken to screen for past or present cardiovascular morbidity: angina pectoris, myocardial infarction, cardiac insufficiency, cardiac arrhythmia, heart valve defects, heart surgery or peripheral atherosclerosis, and the use of antihypertensive medication. Reported evidence of past or present hypertension was recorded separately.

Cognitive assessment

All participants were screened on several aspects of cognitive function, including memory, attention, simple speed and cognitive processing speed, of which the procedure is described in detail elsewhere (Jolles et al., 1995). The tests that were used are describe here in short.

The *Word Learning Task* (WLT) is based upon the Auditory Verbal Learning Test (Brand & Jolles, 1985) and evaluates the ability to acquire and retain new verbal information. A set of fifteen frequently used monosyllabic words is presented in fixed order at a rate of one every two seconds in each of five trials. After every trial the subject is asked to reproduce the memorized words (immediate recall). Twenty minutes after the last trial the subject is asked again to reproduce the set of words (delayed recall). The total number of correctly reproduced words on five trials is recorded, in addition to the maximum score in five trials and the number of correctly reproduced words after 20 minutes.

The *Concept Shifting Task* (CST) evaluates behavioral planning and evaluation (Houx, Vreeling & Jolles, 1991). The subject's ability to alternate two psychological concepts during task performance is measured, here number and letter cancellation in correct order. The test sheet contains 16 small diameter circles ($\varnothing$ 15 mm) arranged in a larger circle ($\varnothing$ 16 cm). Two *null* versions (part 0) contain no symbols in the circles, the number version (part A) presents figures 1 to 16 in random order in the circles, a letter version (part B) depicts random letters, and finally a number / letter version (part C) alternates the numbers 1 to 8 and letters A to H. The subject is instructed to cross out the circles as fast as possible in correct order. Outcome is the time required to complete each task.

Susceptibility to language interference was measured in the *Stroop Color Word Test* (SCWT), consisting of three subtasks; color word naming (I), color naming (II) and naming of color words printed in a different color (interference task III). The SCWT task III is often considered a test of selective attention and shows robust effects of chronological age (Houx, Jolles & Vreeling, 1993).

Ambulant blood pressure monitoring

ABPM was scheduled to start in the morning between 08.00–09.00 h with a total duration of 24 h. A Spacelabs® 90207 monitor (Spacelabs Inc., Redmond WA, USA) was attached to the

non-dominant arm of the subject at the hypertension laboratory of the University Hospital. It was programmed to measure blood pressure at 15 min intervals during the day (07.00–22.59 h) and every 30 min during the night (23.00–06.59 h). Subjects were instructed to adhere to normal daily activities and regular sleeping hours and to report any unusual event during the recording interval. No evidence of sleep disturbance during the night was reported by the participants.

Data reduction and analysis

Three domains of cognitive performance were defined: *memory*, *sensorimotor speed*, and *cognitive flexibility*. Compound domain scores were computed for each individual, based on *Z*-transformed raw scores in the total sample, where $z = (x - \bar{x}) / SD$. In this way, a reduction of performance outcome parameters can be achieved while the robustness of the underlying cognitive construct is improved (Salthouse, 1992). Next, the average was taken of *Z*-scores from tests that were included in the compound performance index: the *memory* score was derived from the total, maximal and delayed recall scores of the WLT, the *cognitive flexibility* score included the C version of the CST and subtask III of the SCWT (LaRue, 1992, pp. 114–115), and *sensorimotor speed* was calculated from the 0, A and B versions of the CST, and subtask I of the SCWT. In formula: $\text{memory} = (Z_{WLT-TOT} + Z_{WLT-MAX} + Z_{WLT-DEL}) / 3$, $\text{cognitive flexibility} = -(Z_{CST-C} + Z_{SCWT-III}) / 2$, and $\text{sensorimotor speed} = -(Z_{CST-0} + Z_{CST-A} + Z_{CST-B} + Z_{SCWT-I}) / 4$. Signs of the speed and flexibility scores were inverted to make them reflect performance better than average when positive and performance below average, when negative.

Separate day-time and night-time averages of blood pressure and heart rate were calculated using the custom software provided by the manufacturer of the ABPM recorder. From these averages the absolute and relative differences were computed (expressed as a percentage of the day-time average) between day-time and night-time blood pressure. Subjects were classified as *non-dippers* when the nocturnal lowering of both systolic and diastolic blood pressure was less than 10% of the mean day-time level (Verdecchia et al., 1991). In all other cases participants were assigned to the *dipper* category.

Associations between ABPM-related variables and cognitive outcome measures were analyzed with multiple hierarchical regression analysis, using adjustments for chronological age, sex, and educational level. Separate models were fitted for the total group, and the group of subjects free of cardiovascular events (CVE) or antihypertensive medication use. Finally, dippers and non-dippers were contrasted on background variables, ABPM parameters and cognitive measures using a Student's *t*-test for groups, or a *Chi*²-test in case of 2 x 2 tables.

RESULTS

No differences in age, education, day-time mean blood pressure or cognitive performance were apparent between the group that was excluded for missing ABPM data ($n = 11$) and the final sample of 115 (*t*-test for groups, all $p > .05$). Table 8.1 displays the number of participants, mean IQ, educational level, and cognitive outcome scores, by levels of age and sex.

Table 8.1. Mean ($\pm SD$) levels of background characteristics and cognitive dependent variables, by levels of age class and sex ($N = 115$).

	Age class						Sex	
	30 $\pm$ 1	40 $\pm$ 1	50 $\pm$ 1	60 $\pm$ 1	70 $\pm$ 1	80 $\pm$ 1	M	F
Total n per cel	16	15	33	22	20	9	68	47
M/F ratio	9/7	5/10	17/16	14/8	15/5	8/1	—	—
Educational level	4.3 (1.5)	3.5 (1.9)	3.7 (1.6)	3.5 (1.6)	2.7 (1.7)	2.9 (2.5)	3.6 (1.9)	3.4 (1.5)
Memory	.56 (.64)	.47 (.68)	.19 (.83)	-.02 (.63)	-.21 (.96)	-1.26 (.92)	-.16 (.92)	.36 (.78)
Sensorimotor speed	.73 (.35)	.46 (.37)	.22 (.58)	.02 (.66)	-.53 (.42)	-.55 (.57)	-.01 (.67)	.24 (.64)
Cognitive flexibility	.57 (.33)	.33 (.60)	.33 (.60)	.13 (.59)	-.58 (.77)	-1.25 (.87)	-.05 (.80)	.18 (.80)

Note. Presented cognitive outcome measures are population based, Z-transformed scores (population mean = 0, SD = 1).

Table 8.2 summarizes for the same strata the mean values of ABPM parameters and the prevalence of antihypertensive medication use, presence of cardiovascular events (CVE) in the medical history, and the distribution of *non-dipper* status. In total, 26 subjects (23%) took antihypertensive medication or reported evidence of CVE. Fifteen subjects (13%) were classified as non-dipper.

Lower values for heart rate are expected during normal, uninterrupted sleep, irrespective of dipper status (Pickering, 1991, p. 5.9). No differences were found in day-time or night-time mean heart rate between dipper and non-dipper groups that could have been caused by between-group differences in sleeping pattern (day-time HR = 77 ± 10 BPM and 78 ± 11 BPM ($p > .05$), night-time HR = 64 ± 9 BPM and 67 ± 12 BPM, for dippers and non-dippers, respectively, for both differences $p > .05$).

Next, age, sex and educational level were entered first in regression models that were intended to predict the three cognitive outcome scores (Table 8.3). The standardized regression coefficients (*Beta*) indicate that age was by far the strongest predictor of performance, followed by educational level: older age and lower education were consistently predictive for lower test outcome. Being of the female sex was associated with higher scores on the memory tests. Together these variables explained 29%, 45% and 44% of the variance in memory performance, sensorimotor speed, and cognitive flexibility, respectively.

To test the predictive value of mean blood pressure levels and day-time / night-time blood pressure differences we entered the ABPM variables separately in step 2. In a comparable fashion it was checked if a relation was present between performance and antihypertensive drug use or CVE in the medical history. Table 8.3 displays the *Beta*'s for these variables in the respective models. Mean day-time or night-time averages of diastolic or systolic blood

Table 8.2. Mean ($\pm$ SD) levels of diastolic and systolic ambulatory blood pressure, day / night blood pressure differences and prevalence of antihypertensive medication use, cardiovascular events and dipper status, by levels of age and sex ($N = 115$).

	Age class						Sex	
	30 $\pm$ 1	40 $\pm$ 1	50 $\pm$ 1	60 $\pm$ 1	70 $\pm$ 1	80 $\pm$ 1	M	F
DBP day (mmHg)	76 (5)	79 (9)	83 (7)	81 (8)	78 (6)	83 (9)	81 (8)	78 (7)
DBP night (mmHg)	61 (4)	63 (10)	69 (7)	68 (9)	63 (9)	72 (10)	68 (9)	63 (8)
DBP 24-hour (mmHg)	72 (5)	76 (10)	80 (7)	78 (8)	74 (6)	80 (9)	78 (8)	75 (7)
SBP day (mmHg)	123 (9)	123 (10)	128 (10)	127 (11)	129 (10)	141 (18)	130 (12)	124 (10)
SBP night (mmHg)	110 (8)	106 (10)	113 (11)	114 (11)	114 (14)	129 (20)	116 (13)	109 (12)
SBP 24-hour (mmHg)	120 (8)	119 (10)	124 (10)	124 (11)	125 (10)	139 (18)	127 (11)	120 (10)
DBP day-night (mmHg)	15 (3)	16 (5)	15 (7)	13 (5)	15 (9)	11 (5)	13 (6)	16 (6)
SBP day-night (mmHg)	13 (5)	17 (5)	15 (9)	13 (7)	15 (11)	12 (10)	14 (9)	15 (7)
Dippers ^a (#)	0	1	6	4	2	2	8	7
Antihypertensive drug use (#)	0	0	6	3	4	2	11	4
CVE (#)	1	0	3	4	7	4	15	4
CVE or antihypert. drug use (#)	1	0	8	5	8	4	18	8
Total n	16	15	33	22	20	9	65	47

Note. DBP = Diastolic blood pressure; SBP = Systolic blood pressure; CVE = prevalence of cardiovascular events. ^a Classified according to the criteria of Verdecchia et al. (1991).

pressure were not related to cognitive performance measures when the effects of background variables were controlled for. However, both the absolute and relative difference in day-time / night-time systolic or diastolic blood pressure were positively correlated to memory performance, albeit no such association was found for the two compound speed measures. In terms of additional explained variance these variables increased the prediction of memory performance with 8 to 9% (R^2 -change, equivalent to partial r -squared). When the nocturnal blood pressure drop was defined as dipper status according to Verdecchia et al. (1991) the prediction of memory performance was improved with 3%. Interestingly, dipper status now additionally explained 5% in the sensorimotor speed score, which had remained unaffected by the day-time / night-time differences. In statistical terms the effect of dipper status was comparable with being 22.4 years older with respect to memory performance, and with being 14.7 years older regarding sensorimotor speed performance. This estimation was computed as

Table 8.3. Regression of age, sex, educational level, and ABPM parameters on cognitive performance outcome: displayed are standardized regression coefficients (*Beta*) and partial correlation coefficients (*r_p*), adjusting for age, sex and educational level in step 1. The variables entered in step 1 explained 29%, 45% and 44% of the variance in memory performance, sensorimotor speed, and cognitive flexibility, respectively. Note that *beta*'s for drug use, CVE and ABPM parameters represent the values when the respective variables are entered *separately* in the model in step 2.

	Memory		Sensorimotor speed		Cognitive flexibility	
	<i>Beta</i>	<i>r_p</i>	<i>Beta</i>	<i>r_p</i>	<i>Beta</i>	<i>r_p</i>
Age (years)	-.37***	—	-.55***	—	-.49***	—
Sex ^a	.21*	—	.06	—	.04	—
Educational level	.20*	—	.25***	—	.32***	—
Antihypertensive drug use ^b	-.03	-.02	.02	.04	.05	.08
CVE ²	-.04	-.06	-.08	-.10	.10	.10
DBP daytime (mmHg)	.15	.14	.11	.14	.10	.13
SBP daytime (mmHg)	.05	.04	.02	.03	.00	.02
DBP nighttime (mmHg)	-.07	-.08	.02	.03	.07	.10
SBP nighttime (mmHg)	-.14	-.14	-.05	-.05	-.05	-.03
DBP dip (mmHg)	.29***	.30***	.12	.14	.03	.02
DBP dip (%)	.24**	.28***	.09	.10	.00	-.01
SBP dip (mmHg)	.28***	.28***	.09	.11	.06	.08
SBP dip (%)	.26**	.29***	.09	.12	.07	.09
Dipper status ^c	.17*	.17*	.18*	.22**	-.01	-.04

Note. CVE = Cardiovascular events; DBP = diastolic blood pressure; SBP = systolic blood pressure.

^a Sex: 0 = male, 1 = female; ^b Antihypertensive drug use / CVE: 0 = no, 1 = yes; ^c Dipper status: 0 = non-dipper, 1 = dipper.

* $p \leq .05$; ** $p \leq .01$; *** $p \leq .001$.

$B_{\text{dipperstatus}} / B_{\text{age (years)}}$, or .448 / -.020 and .354 / -.024, respectively). The observed associations were age-independent, as separate models fitted for age by ABPM parameter interactions indicated no significant contributions of these factors to the compound cognitive scores (results not shown).

Although no relations of CVE or antihypertensive drug use with cognitive variables were observed, the analyses were repeated on the group of 89 CVE-free and unmedicated subjects. A small attenuation was found of the strength of observed relations (results not presented here), but the pattern of effects remained essentially unchanged.

The background variables (Table 8.4) and cognitive scores (Figure 8.1) of non-dippers were contrasted with those of subjects who showed a normal circadian blood pressure pattern. No between group differences were found with respect to age, educational level, sex, prevalence of cardiovascular events or antihypertensive drug use. The difference in reported evidence of hypertension (12% in non-dippers, versus 27% in the dipper group) did not reach statistical

Table 8.4. Background characteristics and mean ambulant blood pressure values of dippers and non-dippers: displayed are means ($\pm$ SD) or counts (%) and the significance level of groupwise comparison.

	Dippers (<i>N</i> = 100)	Non-dippers (<i>N</i> = 15)
Age (years)	52.9 (15.0)	58.7 (11.8)
Educational level	3.6 (1.8)	2.9 (1.4)
IQ	117.3 (12.9)	113.1 (11.0)
Females (#)	40 (40%)	7 (47%)
History of hypertension (#)	12 (12%)	4 (27%)
Antihypertensive drug use (#)	13 (13%)	2 (13%)
CVE (#)	15 (15%)	4 (27%)
Antihypertensive drug use / CVE (#)	21 (21%)	5 (33%)
DBP daytime (mmHg)	80 (8)	83 (8)
SBP daytime (mmHg)	127 (11)	132 (14)
DBP nighttime (mmHg)	64 (8)	78 (8)***
SBP nighttime (mmHg)	111 (10)	129 (18)**
DBP dip (mmHg)	15 (5)	6 (4)***
DBP dip (%)	19 (6)	7 (5)***
SBP dip (mmHg)	16 (7)	4 (7)***
SBP dip (%)	13 (5)	3 (5)***

Note. 2 x 2 Tables were tested using the χ^2 statistic, with continuity correction (Yates); means were compared with Student's *t*-test for groups. CVE = cardiovascular event.

* $p \leq .05$; ** $p \leq .01$; *** $p \leq .001$.

significance. The differences in blood pressure levels were limited to the night-time values and, obviously, the nocturnal blood pressure drop. Non-dippers performed worse on memory and on sensorimotor speed. No difference was observed on cognitive flexibility.

DISCUSSION

In this study, blood pressure estimates from 24-hour ambulant monitoring were used to arrive at a more accurate description of blood pressure related factors that may add to – or mediate – the age-related decline in cognitive function. After adjustment for effects of age, sex and educational level, it was found that mean day-time and night-time blood pressure levels were unrelated to the composite cognitive scores, with or without control for antihypertensive drug use or cardiovascular events in the medical history. These observations comply with our earlier findings regarding the effect of habitual blood pressure status on comparable cognitive measures in a larger population ($N = 936$; Van Boxtel et al., 1996). However, attenuation or absence of the physiological lowering of blood pressure at night, a phenomenon that repeatedly

Figure 8.1. Mean cognitive performance scores (+SEM) as a function of dipper status (* $p \leq .05$; ** $p \leq .01$).

Figure 8.2. 24-Hour systolic and diastolic blood pressure in dippers ($n = 100$) and non-dippers ($n = 15$).

has been associated with evidence of cardiovascular and cerebrovascular damage in hypertensives, was related to a substantial lower performance on verbal memory. When dipper status was classified according to the criteria commonly used in clinical practice, additional evidence was found for lower sensorimotor speed in non-dippers.

Apart from a small but significant association between dipper status and sensorimotor speed, there were no relations of nocturnal blood pressure reduction and speeded cognitive performance. Global cognitive decline associated with aging generally shows a pattern in which speed-related cognitive parameters are more affected by chronological age than non-speeded tasks, like word learning (Salthouse, 1989). This pattern can also be observed in our data, where *Beta* levels associated with age are much higher for both speed related compound scores (-.55 and -.49) than for the memory score (-.37). The association between nocturnal blood pressure reduction – a variable that was relatively unaffected by age in this sample (Van Boxtel et al., 1996) – and cognitive performance is indeed largely restricted to the domain of learning and memory, which may suggest a selective decline in brain function. Multiple brain systems are involved in human memory processes (Markowitsch, 1995), but some, in particular older brain structures like specific areas in the hippocampus, are exceptionally vulnerable to hypoxia (Cervós-Navarro & Diemer, 1991). If non-dipping is indeed related to focal damage to specific brain structures it may be identified with brain-imaging techniques in future research.

To date, associations between absence of nocturnal dipping and target organ damage have only been described in hypertensive populations, as ABPM is seldom used in healthy population studies. It seems, however, that absence of the nocturnal blood pressure drop is not restricted to hypertensive individuals, as the mean day-time blood pressure of subjects in the dipper category was not different from mean day-time blood pressure in non-dippers. Typically it was the mean night-time blood pressure that differed in both groups (Figure 8.2). Although no such evidence came forward from our subjects, a reason for non-dipping may have been a shallow or interrupted sleep due to the measurement of blood pressure itself (Pickering, 1991). The apparatus that was used is generally well tolerated by patients and performs virtually noiseless (O'Brien, Mee, Atkins & O'Malley, 1991). In addition, no differences were found in day-time or night-time mean heart rate between dipper and non-dipper groups. It seems therefore unlikely that an abnormal sleeping pattern is responsible for the observed relations.

The mechanism of nocturnal dipping of blood pressure is still largely unknown, but reduced sympathetic nervous activity during the night probably plays a role (Pickering, 1991). A blunted reduction of blood pressure during the night may have an adaptive function in maintaining the night-time blood flow in vital organs at acceptable levels – including the blood supply to the brain – in advanced stages of vascular insufficiency, especially when autoregulatory function fails (Imai & Abe, 1993). Furthermore, in contrast to the blood flow in other organs, cerebral blood flow increases during the night as a result of an increased oxygen demand (Townsend & Prinz, 1973). Although it is unlikely that substantial cerebrovascular insufficiency was present in our largely normotensive subjects it still may be possible that brain hypoxia at night is related to the observed functional decline in memory performance.

Causal inferences from correlational studies such as these must be made with caution. The present findings need to be replicated in an independent sample before definite conclusions can

be drawn. If the relation between night-time reduction in blood pressure and memory related function proves to be robust, the next step is to relate these findings to the morphological and functional characteristics of brain structures that are engaged in memory function, using brain imaging techniques, such as MRI and SPECT.

REFERENCES

- Brand, N., & Jolles, J. (1985). Learning and retrieval rate of words presented auditory and visually. *Journal of General Psychology*, 112, 201-210.
- Breteler, M. B. B., van Swieten, J. C., Bots, M. L., Grobbee, D. E., Claus, J. J., Van den Hout, J. H. W., Van Harskamp, F., Tanghe, H. L. J., de Jong, P. T. V. M., van Gijn, J., & Hofman, A. (1994). Cerebral white matter lesions, vascular risk factors, and cognitive function in a population-based study: The Rotterdam Study. *Neurology*, 44, 1246-1252.
- Cervós-Navarro, J., & Diemer, N. H. (1991). Selective vulnerability in brain hypoxia. *Critical Reviews in Neurobiology*, 6, 149-182.
- De Bie, S. E. (1987). *Standaardvragen 1987: Voorstellen voor uniformering van vraagstellingen naar achtergrondkenmerken en interviews [Standard questions 1987: Proposal for uniformization of questions regarding background variables and interviews]*. (2nd ed.). Leiden: Leiden University Press.
- Devereux, R. B., & Pickering, T. G. (1991). Relationship between the level, pattern and variability of ambulant blood pressure and target organ damage in hypertension. *Journal of Hypertension (Suppl.)*, 9, S34-S38.
- Elias, M. F., Robbins, M. A., Schultz, J. N. R., & Pierce, T. W. (1990). Is blood pressure an important variable in research on aging and neuropsychological test performance? *Journal of Gerontology*, 45, P128-135.
- Elias, M. F., Wolf, P. A., D'Agostino, R. B., Cobb, J., & White, L. R. (1993). Untreated blood pressure level is inversely related to cognitive functioning: The Framingham Study. *American Journal of Epidemiology*, 138, 353-364.
- Farmer, M. E., Kittner, S. J., Abbott, R. D., Wolz, M. M., Wolf, P. A., & White, L. R. (1990). Longitudinally measured blood pressure, antihypertensive medication use, and cognitive performance: The Framingham Study. *Journal of Clinical Epidemiology*, 43, 475-480.
- Gorelick, P. B. (1995). Stroke prevention. *Archives of Neurology*, 52, 347-355.
- Houx, P. J., Jolles, J., & Vreeling, F. W. (1993). Stroop interference: Aging effects assessed with the Stroop Color-Word test. *Experimental Aging Research*, 19, 209-224.
- Houx, P. J., Vreeling, F. W., & Jolles, J. (1991). Age-associated cognitive decline is related to biological life events. In K. Iqbal, D. R. C. McLachlin, B. Winblad, & H. M. Wisniewski (Eds.), *Alzheimer's disease: Basic mechanisms, diagnosis and therapeutic strategies*, (pp. 353-358). Chichester, UK: Wiley.
- Imai, Y., & Abe, K. (1993). Clinical significance of nocturnal blood pressure in the elderly. *Cardiology in the Elderly*, 1, 483-489.
- Jolles, J., Houx, P. J., van Boxtel, M. P. J., & Ponds, R. W. H. M. (Eds.). (1995). *Maastricht Aging Study: Determinants of cognitive aging*. Maastricht: Neuropsych Publishers.
- King, H. E., & Miller, R. E. (1990). Hypertension: cognitive and behavioral considerations. *Neuropsychology Review*, 1, 31-73.
- LaRue, A. (1992). *Aging and neuropsychological assessment*. New York: Plenum Press.
- Launer, L. J., Masaki, K., Petrovitch, H., Foley, D., & Havlik, R. J. (1995). The association between midlife blood pressure levels and late-life cognitive function: The Honolulu-Asia Aging Study. *Journal of the American Medical Association*, 274, 1846-1851.
- Mancia, G., Parati, G., Pomidossi, G., Grassi, G., Casadei, R., & Zanchetti, A. (1987). Alerting reaction and rise in blood pressure during measurement by physician and nurse. *Hypertension*, 9, 209-215.
- Markowitsch, H. J. (1995). Anatomical basis of memory disorders. In M. S. Gazzaniga (Ed.), *The cognitive neurosciences*, (pp. 765-779). Cambridge Massachusetts: MIT Press.
- Metsemakers, J. F. M., Höppener, P., Knottnerus, J. A., Kocken, R. J. J., & Limonard, C. B. G. (1992). Computerized health information in the Netherlands: A registration network of family practices. *British Journal of General Practice*, 42, 102-106.
- O'Brien, E., Mee, F., Atkins, N., & O'Malley, K. (1991). Accuracy of the Spacelabs 90207 determined by the British Hypertension Society Protocol. *Journal of Hypertension*, 9, 573-574.
- O'Brien, E., Sheridan, J., & O'Malley, K. (1988). Dippers and non-dippers [letter to the editor]. *Lancet*, 2(8607), 397.
- Pickering, T. G. (1991). *Ambulatory monitoring and blood pressure variability*. London: Science Press.
- Pickering, T. G. (1994). Blood pressure measurement and detection of hypertension. *Lancet*, 344, 31-35.

- Rodriguez, G., Arvigo, F., Marengo, S., Nobili, F., Sandini, G., & Rosandini, G. (1987). Regional blood flow in essential hypertension: Data evaluation by a mapping system. *Stroke*, 18, 13-20.
- Salerno, J. A., Murphy, D. G. M., Horwitz, B., DeCarli, C., Haxby, J. V., Rapoport, S. I., & Schapiro, M. B. (1992). Brain atrophy in hypertension: A volumetric magnetic resonance imaging study. *Hypertension*, 20, 340-348.
- Salthouse, T. A. (1989). Age-related changes in basic cognitive processes. In M. Storandt & G. R. Vandenbos (Eds.), *The adult years: Continuity and change*, (pp. 5-40). Washington: American Psychological Association.
- Salthouse, T. A. (1992). *Mechanisms of age-cognition relations in adulthood*. Hillsdale, NJ: Lawrence Erlbaum Associates.
- Shimada, K., Kawamoto, A., Matsubayashi, K., Nishinaga, M., Kimura, S., & Ozawa, T. (1992). Diurnal blood pressure variations and silent cerebrovascular damage in elderly patients with hypertension. *Journal of Hypertension*, 10, 875-878.
- Shimada, K., Kawamoto, A., Matsubayashi, K., & Ozawa, T. (1990). Silent cerebrovascular disease in the elderly: Correlation with ambulant pressure. *Hypertension*, 16, 692-699.
- Skoog, I. (1994). Risk factors for vascular dementia: A review. *Dementia*, 5, 137-144.
- Starr, J. M., & Whalley, L. J. (1992). Senile hypertension and cognitive impairment: An overview. *Journal of Hypertension (Suppl.)*, 10, S31-S42.
- Toghi, H., Chiba, K., & Kimura, M. (1991). Twenty-four hour variation of blood pressure in vascular dementia of the Binswanger type. *Stroke*, 22, 603-608.
- Townsend, R. E., & Prinz, P. N. (1973). Human cerebral blood flow during sleep and waking. *Journal of Applied Physiology*, 35, 620-625.
- Van Boxtel, M. P. J., Gaillard, C., Houx, P. J., de Leeuw, P. W., & Jolles, J. (Submitted). Can blood pressure predict cognitive task performance in a healthy population sample?
- Van Boxtel, M. P. J., Gaillard, C., van Es, P. N., Jolles, J., & de Leeuw, P. W. (1996). Repeated automatic versus ambulatory blood pressure measurement: The effects of age and sex in a normal ageing population. *Journal of Hypertension*, 14, 31-40.
- Van Swieten, J. C., Geyskes, G. G., Derix, M. M. A., Peck, B. M., Ramos, L. M. P., van Latum, J. C., & van Gijn, J. (1991). Hypertension in the elderly is associated with white matter lesions and with cognitive decline. *Annals of Neurology*, 30, 825-830.
- Verdecchia, P., Schillaci, G., & Porcellati, C. (1991). Dippers versus non-dippers. *Journal of Hypertension*, 9 (Suppl 8), S42-S44.
- Waldstein, S. R. (1995). Hypertension and neuropsychological function: A lifetime perspective. *Experimental Aging Research*, 21, 321-352.
- Waldstein, S. R., Manuck, S. B., Ryan, C. M., & Muldoon, M. F. (1991). Neuropsychological correlates of hypertension: review and methodological considerations. *Psychological Bulletin*, 110, 451-469.

Chapter 9

The relation between morbidity and cognitive performance in a normal aging population⁷

ABSTRACT

Factors related to physical health have been proposed to account for both the normal and the pathological aging of cognitive abilities. To substantiate this notion, we studied existing morbidity, as diagnosed by the general practitioner, as a potential predictor of cognitive test performance in a cross-sectional study. A population of 1,360 individuals living in the community, aged 24 to 81 years, was stratified for age, sex, and level of general ability. Active and total morbidity were classified according to the International Classification of Primary Care (ICPC). Neurocognitive tests were used to probe the domains of verbal memory, sensorimotor speed, and cognitive flexibility. Multiple regression analyses with adjustment for age, sex and educational level showed both insulin-dependent and non-insulin dependent diabetes to be negatively associated with all cognitive measures. More selective effects were found for chronic bronchitis (on performance speed) and presbycusis (on memory). Notably, single or aggregated cardiovascular morbidity clusters (including hypertension) were unrelated to test performance. It is concluded that the total sum of existing morbidity contributes only modestly (up to 3.5%) to the total variance in cognitive outcome measures. However, some specific, relatively common diseases in older individuals, such as diabetes and chronic bronchitis, may aggravate the age-related decline in cognitive ability.

INTRODUCTION

On a population level, most cognitive abilities such as memory function, information processing speed and attentional capacity tend to decline with advancing age (Poon, 1985; Salthouse, 1989). Adequate preservation of cognitive abilities is of primary importance to older people, as cognitive decline in the aged can result in a loss of independence and autonomy (McSweeney, Grant, Heaton, Prigatano & Adams, 1985). Interindividual differences exist, however, in the rate of decline of specific cognitive functions that can, at least in part, be mediated by individual differences in physical health (Elias, Elias & Elias, 1990; Salthouse, 1992). Several studies have suggested that health-related factors, such as closed head injuries, general anesthesia, and chronic psychotropic medication use (e.g. Houx & Jolles, 1993; Houx & Jolles, 1994) may be involved in the enhanced cognitive decline seen with increasing age. In addition, several disease entities have been associated with a reduced cognitive capacity in

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epidemiological surveys and clinical case-control studies (Colsher & Wallace, 1991). For example, disorders such as thyroid disease, renal or hepatic failure, cardiac insufficiency, or chronic obstructive pulmonary disease may be accompanied by relatively non-specific neuropsychological deficits (Tarter, van Thiel & Edwards, 1988), and may aggravate a dementia syndrome in geriatric populations (Nolan & Blass, 1992).

Mild cognitive impairment with no frank dementia (CIND) has recently been recognized as a relevant clinical entity which must be identified in an early stage of its development (Writing Committee Lancet Conference, 1996). The family physician may play a crucial role in recognizing patients who are at risk of cognitive deterioration that is mediated by physical disease or disability, as he is pre-eminently confronted with early stages of disease. It is unclear, however, if the findings on cognition-related morbidity in clinical populations can be readily transposed to the general practice setting. Clinical studies most often refer to advanced stages of disease and are therefore inclined to overestimate the potential effect of specific morbidity categories on cognitive function in earlier stages. A cross-sectional design was used in this study to ascertain the potential relevance of well-described morbidity categories as possible determinants of cognitive function in a large sample of community living adult individuals, using established classification criteria for existing morbidity in general practice. More specifically, it was hypothesized that existing morbidity related to the vascular system is particularly prone to produce deficits in cognitive function.

METHODS

Sample frame

The study was part of a larger research program on determinants of normal cognitive aging, the Maastricht Aging Study (MAAS, Jolles, Houx, van Boxtel & Ponds, 1995). Participants were recruited from the Registration Network Family Practices (RNH, Metsemakers, Höppener, Knottnerus, Kocken & Limonard, 1992). The Registration Network was once established as a sample frame for research in primary care. It consists of the background characteristics and health problems of 60,000 patients in 15 general practices that are updated on a continuous basis via a computerized system. Health problems are classified according to the International Classification of Primary Care (ICPC, Lamberts & Wood, 1987), along with the dates of becoming active and – for some problems – of becoming inactive. A health problem is diagnosed when it affects the functional status of the individual at present or in the future. Therefore, as a rule, only permanent, chronic or recurrent problems are included (Metsemakers et al., 1992). The randomly drawn individuals were personally invited by their family doctor to take part in the cognitive test program.

The a priori knowledge on the medical status of patients in the register enabled exclusion of individuals with evidence of stroke, chronic neurological pathology (e.g. dementia, epilepsy, parkinsonism and malignancies related to the nervous system), mental retardation or chronic psychotropic drug use.

Participants were stratified for age (12 age classes, ranging from 25 ± 1 year, 30 ± 1 year, to

80 $\pm$ 1 year), sex, and level of general ability (two levels, based on the achievement in professional life, Van Berkel & Tax, 1990), to control these background variables that in itself may affect cognitive performance (Jolles et al., 1995). The study populations of the first three MAAS panel studies, executed between april 1993 and december 1995, were combined in the current population of 1,373 participants. Of this group, thirteen individuals were not included in the present analysis due to one or more missing values in the cognitive dataset.

Measurements

All participants filled in a questionnaire pertaining to socioeconomic background and medical history. Educational level was measured on an 8-point scale, ranging from primary school to higher vocational training and university degree (Jolles et al., 1995).

Cognitive assessment

Standard neuropsychological tests were used to assess the cognitive domains of memory, sensorimotor speed and information processing speed / cognitive flexibility (see Jolles et al., 1995, for a full description).

The *Word Learning Task* (WLT) evaluates the ability to acquire and retain new verbal information: A set of fifteen frequently used monosyllabic words is presented in fixed order at a rate of one every two seconds in each of five trials. After every trial the participant is to reproduce the memorized words (immediate recall). Twenty minutes after the last trial the participant is asked again to reproduce the set of words (delayed recall). Recorded are the total of correctly reproduced words on five trials, the maximum score in five trials and the number of correctly reproduced words after 20 minutes.

The *Concept Shifting Task* (CST) evaluates behavioral planning and evaluation. It measures one's ability to alternate two psychological concepts during task performance, i.e., number, letter, and number / letter cancellation in correct order. Outcome is the time required to complete each task.

Selective attention and susceptibility to perceptual interference was measured in the *Stroop Color Word Test* (SCWT), consisting of three subtasks; color word naming (I), color naming (II) and naming of color words printed in a different color (interference task III).

The *Letter Digit Substitution Test* (LDST) is a paper-and-pencil task, measuring basic information processing speed.

Word Fluency was scored as the total number of unique animal names correctly reproduced in 60 seconds. The test reflects the organizational level among clusters of meaningful related words.

Morbidity status

The active and total morbidity status of all participants at the time of cognitive testing was retrieved from the Registration Network database. ICPC morbidity categories with a sample prevalence of 13 (= 1%) or more were determined to be used in the analyses, including several

with potential direct or indirect impact on brain functioning: cardiovascular diseases, obstructive pulmonary disease, atherosclerotic disease, hypertension, endocrine disorders (such as diabetes and thyroid disease), malignancies, hepatic or renal disease, neurological disturbances, and hearing loss (Colsher & Wallace, 1991; Tarter et al., 1988). The same procedure was used for total (active + inactive) morbidity, in order to test the potential effect of relevant health events that in the ICPC coding system may only temporarily be coded as an active problem, e.g. acute myocardial infarction, or brain concussion. The list of all codes that were retained for further analysis is presented in Table 9.1.

Data reduction

To limit the number of dependent variables and to improve the robustness of the underlying cognitive construct, most of the raw test scores were clustered in three compound performance indices, labeled *memory*, *cognitive flexibility*, and *sensorimotor speed*. For all participants the raw scores were transformed to standardized *Z*-scores ($z = [x - \bar{x}] / SD$). *Z*-scores from tests that were included in each compound performance index were averaged. Thus, the memory score was derived from the total, maximal and delayed recall scores of the WLT, the cognitive flexibility score included the C-version of the CST and subtask III of the SCWT, and sensorimotor speed was calculated from the O, A and B versions of the CST, and subtask I of the SCWT. Signs of the speed and flexibility scores were inverted to make them reflect above average performance when positive and below average performance when negative. LDST and fluency test outcomes were not included in compound scores as the performance on these tests is far less dependent on the integrity of one specific cognitive domain.

Several single morbidity codes were uniquely combined in more broad morbidity clusters, including chronic diseases and malignancies (according to Knottnerus, Metsemakers, Höppener & Limonard, 1992), hearing loss, cardiovascular diseases, cardiac rhythm disturbances, and obstructive pulmonary disease (see *aggregated codes* in Table 9.1).

Statistical analysis

Separate linear regression models were fitted for cognitive parameters, adjusting for age, sex and educational level, using active or total ICPC morbidity codes that were present in at least 1% of all participants, using a backward elimination procedure. This procedure was followed for both the active and total aggregated morbidity clusters. All analyses were performed with the SPSS statistical program series. *P*-values of .01 or less were considered to be statistically significant unless indicated otherwise.

RESULTS

Table 9.1 shows the single and aggregated morbidity categories with an associated prevalence of .01 or higher. It can be readily concluded from these data that discrepancies between active and total morbidity status depend for a large part on the impact of the disease or complaint on

Table 9.1. Number of single *active* (and *total*) health problems, by levels of age and sex (total $N = 1,360$). Only those *total* morbidity categories are shown that were present in at least 1% of this population and that were used in the regression analyses. Categories of *active* morbidity used in the regression analyses (with an associated $n \geq 13$) are marked with an asterisk (*). Aggregated morbidity categories are displayed in the second half of the table. Letter / digit codes refer to the respective category in the ICPC.

	Age class (years)						Sex		All
	25-30	35-40	45-50	55-60	65-70	75-80	M	F	
Total n per cell	236	240	239	238	241	166	688	672	1,360
<i>Single codes</i>									
D85 Duodenal ulcer	0 (0)	1 (1)	2 (5)	3 (8)	3 (15)	1 (9)	9 (33)	1 (5)	10 (38)
D86 Other peptic ulcer	0 (0)	0 (0)	0 (2)	5 (10)	1 (4)	2 (7)	7 (14)	1 (9)	8 (23)
D93 Irritable bowel syndrome*	3 (4)	0 (0)	3 (5)	4 (6)	5 (9)	1 (4)	2 (7)	14 (21)	16 (28)
D98 Cholecystitis /cholelithiasis*	1 (1)	1 (6)	1 (6)	2 (16)	5 (20)	4 (23)	2 (15)	12 (57)	14 (72)
H84 Presbycusis*	0 (0)	0 (0)	1 (1)	1 (1)	14 (14)	15 (15)	22 (22)	9 (9)	31 (31)
H85 Acoustic trauma /noise-related deafness*	0 (0)	2 (2)	0 (0)	6 (6)	4 (4)	1 (1)	12 (12)	1 (1)	13 (13)
H86 Deafness or hearing loss n.c.e. **	2 (2)	2 (3)	11 (11)	7 (7)	12 (13)	9 (10)	23 (26)	20 (20)	43 (46)
K00 Family history of vascular disease*	4 (4)	4 (4)	4 (4)	10 (10)	4 (4)	2 (2)	16 (16)	12 (12)	28 (28)
K74 Angina pectoris*	0 (0)	0 (0)	4 (5)	7 (7)	11 (16)	17 (20)	26 (33)	13 (15)	39 (48)
K75 Acute myocardial infarction*	0 (0)	0 (0)	1 (3)	3 (6)	4 (16)	8 (24)	14 (42)	2 (7)	16 (49)
K76 Ischemic heart disease, other and chronic*	0 (0)	0 (0)	2 (2)	2 (3)	12 (14)	12 (18)	23 (29)	5 (8)	28 (37)
K77 Heart failure	0 (0)	0 (0)	0 (0)	1 (2)	3 (5)	8 (10)	7 (10)	5 (7)	12 (17)
K78 Atrial fibrillation /-flutter*	0 (0)	0 (0)	0 (0)	3 (3)	5 (7)	9 (15)	12 (15)	5 (10)	17 (25)
K80 Ectopic heart rhythm, all types	0 (0)	1 (1)	1 (2)	4 (5)	2 (4)	2 (2)	5 (7)	5 (7)	10 (14)
K84 Other heart disease	0 (0)	0 (0)	1 (2)	7 (7)	2 (3)	2 (3)	8 (9)	4 (6)	12 (15)
K85 Increased blood pressure /no hypertension*	0 (0)	1 (2)	2 (3)	7 (8)	5 (6)	2 (2)	11 (14)	6 (7)	17 (21)
K86 Hypertension /no organ damage*	5 (5)	2 (2)	19 (20)	29 (30)	51 (53)	30 (34)	58 (59)	78 (85)	136 (144)
K87 Hypertension /organ damage*	0 (0)	0 (0)	1 (1)	1 (1)	4 (4)	7 (7)	7 (7)	6 (6)	13 (13)
K91 Atherosclerosis, not. in heart /brain*	0 (0)	0 (0)	1 (1)	6 (6)	6 (7)	3 (6)	13 (16)	3 (4)	16 (20)
K92 Other peripheral arterial diseases*	0 (0)	1 (1)	1 (1)	7 (7)	7 (9)	6 (11)	19 (24)	3 (5)	22 (29)
L01 Cervical symptoms /complaints [not. N01]	1 (3)	2 (4)	0 (0)	4 (4)	1 (1)	1 (2)	2 (4)	7 (10)	9 (14)
L02 Back symptoms /complaints*	1 (3)	8 (13)	6 (7)	10 (12)	3 (4)	4 (5)	20 (23)	12 (21)	32 (44)
L03 Low back pain /no radiation [not. L86]*	4 (6)	20 (22)	12 (16)	17 (20)	3 (6)	3 (3)	32 (37)	27 (36)	59 (73)
L83 Cervical syndromes; other*	1 (1)	2 (4)	6 (8)	11 (15)	16 (19)	10 (14)	21 (29)	25 (32)	46 (61)
L84 Spinal arthrosis*	1 (1)	2 (2)	1 (2)	14 (14)	11 (13)	19 (19)	26 (27)	22 (24)	48 (51)
L86 Degenerated intervertebral disk + radiation*	4 (7)	2 (6)	15 (24)	13 (22)	19 (37)	8 (17)	31 (61)	30 (52)	61 (113)
L88 Rheumatoid arthritis /ankylosing spondylitis*	3 (4)	0 (0)	24 (3)	4 (7)	2 (7)	9 (5)	6 (15)	15 (11)	24 (26)

Note. This table is continued on the next page.

Table 9.1. (Continued)

	Age class (years)						Sex		All
	25-30	35-40	45-50	55-60	65-70	75-80	M	F	
N01 Headache [not. R09/N89/N02/N03]	2 (4)	2 (3)	0 (2)	1 (2)	1 (4)	2 (2)	4 (9)	4 (8)	8 (17)
N02 Tension headache*	5 (5)	6 (8)	4 (7)	5 (5)	2 (3)	1 (2)	12 (15)	11 (15)	23 (30)
N79 Concussion	0 (5)	0 (4)	0 (2)	0 (3)	0 (4)	0 (1)	0 (9)	0 (10)	0 (19)
N89 Migraine*	5 (5)	8 (10)	6 (6)	3 (3)	4 (6)	4 (4)	11 (11)	19 (23)	30 (34)
P01 Anxious feelings /nervousness*	1 (5)	9 (10)	4 (9)	8 (10)	9 (11)	3 (4)	16 (23)	18 (26)	34 (49)
P03 Depressive feelings	1 (1)	1 (5)	1 (2)	2 (4)	3 (5)	2 (3)	0 (5)	10 (15)	10 (20)
P15 Chronic alcohol abuse	0 (0)	3 (3)	1 (5)	1 (4)	0 (0)	1 (4)	6 (10)	0 (6)	6 (16)
P76 Depressive neurosis*	1 (3)	4 (8)	2 (9)	4 (12)	1 (6)	1 (4)	4 (19)	9 (23)	13 (42)
R70 Pulmonary tuberculosis	0 (0)	0 (0)	0 (1)	1 (8)	1 (7)	1 (8)	3 (20)	0 (4)	3 (24)
R91 Chronic bronchitis /bronchiectasis*	4 (5)	3 (7)	1 (2)	7 (7)	8 (8)	12 (12)	25 (27)	10 (14)	35 (41)
R95 Emphysema*	0 (0)	1 (1)	2 (2)	2 (2)	6 (6)	13 (13)	18 (18)	6 (6)	24 (24)
R96 Asthma*	11 (12)	9 (10)	6 (8)	10 (10)	8 (10)	4 (4)	33 (38)	15 (16)	48 (54)
T83 Obesity*	6 (7)	3 (3)	5 (6)	9 (9)	9 (9)	8 (8)	18 (20)	22 (22)	40 (42)
T85 Hyperthyroidism	1 (1)	1 (2)	1 (2)	2 (5)	1 (3)	0 (2)	1 (2)	5 (13)	6 (15)
T90 Diabetes mellitus*	1 (1)	2 (4)	3 (6)	11 (12)	12 (12)	21 (23)	27 (27)	23 (31)	50 (58)
T93 Disorder of lipid metabolism*	0 (0)	2 (2)	12 (12)	22 (24)	12 (12)	8 (9)	28 (28)	28 (31)	56 (59)
<i>Aggregated codes</i>									
Anaemia [B78/B80/B81/B82]	2 (3)	2 (2)	0 (1)	2 (3)	1 (3)	3 (5)	5 (5)	5 (12)	10 (17)
Peptic ulcers [D85/D86]	0 (0)	1 (1)	2 (7)	8 (16)	4 (19)	3 (16)	16 (45)	2 (14)	18 (59)
Hearing loss [H83/H84/H85/H86]	2 (2)	4 (5)	14 (14)	15 (15)	30 (32)	26 (27)	57 (60)	34 (35)	91 (95)
Cardiac insufficiency [K77/K82]	0 (0)	0 (0)	0 (0)	1 (2)	3 (5)	8 (10)	7 (10)	5 (7)	12 (17)
Cardiac rhythm disturbances [K78/K79/K80]	0 (0)	1 (2)	1 (2)	8 (10)	9 (12)	12 (19)	18 (22)	13 (23)	31 (45)
Cervical syndromes [L01/L83/L84]	3 (5)	6 (10)	7 (10)	28 (32)	27 (32)	29 (32)	47 (56)	53 (65)	100 (121)
Lumbar syndromes/lumbar hernia [L02/L03/L86]	8 (14)	30 (39)	32 (45)	38 (51)	25 (46)	15 (24)	83 (117)	65 (102)	148 (219)
Chronic disease ^b	52 (66)	59 (77)	80 (99)	117 (133)	142 (157)	133 (143)	310 (351)	273 (324)	583 (675)
Malignant disease ^b	0 (0)	5 (6)	2 (3)	5 (8)	12 (18)	27 (33)	30 (40)	21 (28)	51 (68)
Cardiovascular disease ^c	5 (5)	5 (6)	25 (31)	55 (58)	86 (95)	78 (88)	145 (159)	109 (124)	254 (283)
COPD ^d [R91/R95/R96]	14 (16)	13 (18)	8 (12)	19 (19)	21 (26)	26 (28)	70 (81)	31 (38)	101 (119)

Note. ^a n.c.e. = not coded elsewhere. ^b See for full description (Knottnerus et al., 1992). ^c Aggregated codes K28, K71, K74 to K80, K82 to K84, K86 to K89, and K91. ^d COPD = chronic obstructive pulmonary disease.

current health and physical functioning. For example, prevalence of active and total presbycusis (H84) is exactly the same, presumably as the impact of age-associated hearing loss for daily functioning is permanent, but consequences of a disease such as angina pectoris (K74) may in fact disappear after initiation of proper treatment.

All single codes in Table 9.1 ($n = 43$) were entered in the analyses for total morbidity and the codes marked with an asterisk ($n = 31$) were used in the analysis of active morbidity. Table 9.2 displays the results of regression analysis of age, sex, educational level, and specific ICPC-morbidity codes on cognitive outcome variables. The regression coefficients in the first column demonstrate that age and education are highly associated with all cognitive parameters and that women outperform men on memory, cognitive flexibility and letter / digit copying. Together the variance in performance explained by age, sex, and educational level ranged between 17% for fluency and 48% for sensorimotor speed. To illustrate the strong age-dependency of the cognitive variables more closely, the differences in standardized cognitive performance scores were calculated for each age category, compared to young adults as a reference group (Figure 9.1). This picture indicates, firstly, that the rate of age-related decline varies over cognitive measures. Thus, performance on self-paced tasks such as fluency and verbal word learning shows a more gradual course as a function of age than performance on the other tasks where speed of performance is the critical factor (cf. the regression coefficients for age in Table 9.2).

Final regression models that include significantly contributing morbidity codes are displayed in Table 9.2, for active (column 2) and total morbidity codes (column 3). All morbidity codes that remained in the models were negatively associated with the performance scores. Most consistently diabetes (T90) was associated with lower performance scores on all cognitive parameters, the effect ranging from $-.36$ times SD in memory score to $-.52$ times SD in cognitive flexibility score (Table 9.2, column 2: active morbidity), adjusted for all other factors in the model. Other associations between morbidity codes and cognitive were more sporadic, but consistent in the analyses for both active and total morbidity. Chronic bronchitis (R91) remained in the models for sensorimotor speed and cognitive flexibility. Presbycusis (H84) was present in the model that was fitted for memory, while cholecystitis (D98) accounted for variance in the cognitive flexibility score only when coded as *total* (column 3). Two other morbidity categories coded as *total* were present in the model fitted for verbal fluency only: hyperthyroidism (T85) and disturbances in atrial rhythm (K78).

Similar analyses were repeated with the aggregated morbidity codes, as displayed in Table 9.2, for active and total morbidity separately. No single significant relation was found between these new variables and cognitive performance levels.

Given the strong association between diabetes and cognitive test performance, additional post hoc tests were performed with diabetes as independent variable (coded *active*), firstly to evaluate a potential age by diabetes interaction, and secondly, to differentiate between associations with cognitive function for insulin- and non-insulin dependent diabetes mellitus (IDDM and NIDDM, respectively). When diabetes and the age by diabetes interaction term were entered in the regression models, no significant interaction was present on any cognitive parameter on a $p \leq .05$ level. This indicates that the association between diabetes and cognitive function is not dependent on age. Then the analysis was repeated after dividing the diabetes

group in insulin users and non-insulin users ($n = 15$ and $n = 35$, mean ages 59.6 (SD 14.9) and 69.9 (SD 10.1), respectively, $p < .05$), based on reported information about medication use by the participant (Table 9.3). Except for verbal fluency in the NIDDM group, all remaining cognitive outcome measures were negatively associated with both types of diabetes. Regression coefficients for both types of diabetes were quite comparable in size in all models.

Table 9.2. Results of regression analyses of demographic variables (after step 1) and active or total morbidity (final models) on cognitive performance measures. Shown are the regression coefficients B and its standard error, the associated p -value and the total proportion of variance explained (R^2).

	Step 1: <i>demographic variables</i>				Final model: <i>active morbidity</i>				Final model: <i>total morbidity</i>			
	B	(SE)	p	R^2	B	(SE)	p	R^2	B	(SE)	p	R^2
<i>Memory</i>												
Age ^a	-.024	(.001)	.00		-.022	(.001)	.00		-.022	(.001)	.00	
Sex ^b	.481	(.043)	.00		.472	(.042)	.00		.477	(.042)	.00	
Education	.102	(.012)	.00		.101	(.012)	.00		.101	(.012)	.00	
T90–Diabetes ^c					-.462	(.113)	.00		-.439	(.105)	.00	
H84–Presbycusis					-.374	(.143)	.01		-.377	(.144)	.01	
				.327				.339				.339
<i>Sensorimotor speed</i>												
Age	-.027	(.001)	.00		-.025	(.001)	.00		-.026	(.009)	.00	
Sex	.054	(.032)	.09		.045	(.032)	.16		.051	(.032)	.11	
Education	.120	(.009)	.00		.118	(.009)	.00		.118	(.009)	.00	
T90 – Diabetes					-.369	(.085)	.00		-.301	(.080)	.00	
R91 – Chronic bronchitis					-.338	(.100)	.00		-.281	(.093)	.00	
				.476				.487				.485
<i>Cognitive flexibility</i>												
Age	-.029	(.001)	.00		-.027	(.001)	.00		-.027	(.001)	.00	
Sex	.103	(.036)	.00		.092	(.036)	.01		.114	(.036)	.00	
Education	.139	(.010)	.00		.137	(.010)	.00		.136	(.010)	.00	
T90 – Diabetes					-.523	(.096)	.00		-.410	(.090)	.00	
R91 – Chronic bronchitis					-.369	(.113)	.00		-.328	(.105)	.00	
D98 – Cholecystitis									-.235	(.082)	.00	
				.458				.474				.474
<i>Letter Digit Substitution Test</i>												
Age	-.033	(.001)	.00		-.033	(.001)	.00		-.033	(.001)	.00	
Sex	.135	(.039)	.00		.134	(.039)	.00		.137	(.039)	.00	
Education	.141	(.011)	.00		.142	(.011)	.00		.142	(.011)	.00	
T90 – Diabetes					-.364	(.104)	.00		-.283	(.097)	.00	
				.491				.495				.493
<i>Fluency</i>												
Age	-.013	(.002)	.00		-.012	(.014)	.00		-.011	(.002)	.00	
Sex	.042	(.050)	.39		.041	(.050)	.41		.052	(.050)	.29	
Education	.150	(.014)	.00		.150	(.014)	.00		.149	(.014)	.00	
T90 – Diabetes					-.414	(.133)	.00		-.321	(.124)	.01	
T85 – Hyperthyroidism									-.618	(.236)	.01	
K78 – Atrial fibrillation/-flutter									-.491	(.186)	.01	
				.168				.174				.181

Note. ^a Age is chronological age; ^b Sex: 0 = men, 1 = women; ^c Morbidity codes: 0 = absent, 1 = present.

Figure 9.1. Differences in average standardized cognitive performance scores (+SEM) between the youngest age class (25-30 years) and each subsequent age class. Speed-G: sensorimotor speed; Speed-C: cognitive flexibility; LDST: Letter Digit Substitution Test.

Table 9.3. Regression of active insulin- and non-insulin dependent diabetes ($n = 15$ and $n = 35$, respectively) on cognitive outcome measures: displayed are regression coefficients (B , and SE of B) and proportion of explained variance (R^2) after each step.

	Entered on step 1					Entered on step 2				
	Age ^a		Sex ^b		Education	<i>R</i> ²	IDDM ^c		NIDDM	
	<i>B</i>	(<i>SE</i>)	<i>B</i>	(<i>SE</i>)			<i>B</i>	(<i>SE</i>)	<i>B</i>	(<i>SE</i>)
Memory	-.023 (.001)***	.479 (.042)***	.102 (.012)***	.327	-.505 (.202)*	-.449 (.135)***	.336			
Sens. speed	-.026 (.001)***	.052 (.032)	.119 (.009)***	.476	-.304 (.152)*	-.396 (.102)***	.483			
Cogn. flexibility	-.027 (.001)***	.101 (.036)**	.139 (.010)***	.458	-.576 (.171)***	-.498 (.114)***	.470			
LDST ^d	-.033 (.001)***	.134 (.039)***	.142 (.011)***	.491	-.442 (.184)*	-.330 (.123)**	.495			
Fluency	-.012 (.002)***	.043 (.050)	.151 (.014)***	.168	-.771 (.236)**	-.258 (.158)	.176			

Note. ^a Age is chronological age; ^b Sex was coded 0 for men, 1 for women; ^c (N)IDDM: (Non-) Insulin Dependent Diabetes Mellitus; ^d LDST: Letter Digit Substitution Test.

* $p \leq .05$; ** $p \leq .01$; *** $p \leq .001$.

DISCUSSION

Associations between active and total ICPC morbidity, and objective neurocognitive test performance were investigated in a healthy adult population sample. Significant negative associations were found between diabetes and all studied cognitive domains, and, more sporadically, between presbycusis and memory performance, and also between chronic bronchitis and performance speed (psychomotor speed and cognitive flexibility). Other single associations were only related to codes of total morbidity, including cholecystitis, hyperthyroidism, and disturbances of atrial rhythm. However, related morbidity codes that were aggregated in newly formed clusters did not add to the proportion of explained variance in cognitive measures. Several issues need to be discussed before conclusions can be drawn from these data.

Study participants were stratified for age, sex, and general ability which are recognized confounding variables in cognitive research. Although demographically this group is not a representative sample of the general population, possible sampling bias due to the stratification procedure was adjusted for by controlling these variables in the regression analyses.

Several specific disease entities that are theoretically important with respect to brain function (e.g. hepatic cirrhosis) were not included in the present analyses as their prevalence did not reach the 1% level criterion. Potential significant relations of relatively rare diseases with measures of mental efficiency are unlikely to be picked up, because the standard error – and thus the significance – of regression coefficients strongly depends on the number of prevalent cases in the study population. This problem was partially bypassed by combining related morbidity categories in larger clusters, but this procedure inevitably leads to loss of disease specificity.

Two factors which, at least theoretically, can moderate morbidity / cognition relations were not included in our models because they could not be reliably assessed: *disease duration* and (the success of) *intervention*. Firstly, although it seems fair to expect that the impact of disease on cognitive processes is mediated by the duration of exposure to the disease, it was considered that in most cases the available 'date of diagnosis' by the general practitioner as an inexact indicator of disease duration. In general practice, the date of diagnosis is for a large part dependent on patient and physician related characteristics, that are not associated with the actual onset of a disease process: unless identified as a health problem by one or both parties a disease may therefore remain undetected. Secondly, adequacy or success of therapeutic intervention is disease-specific and may not be defined in a straightforward sense for purposes such as in this study.

It has been suggested that problems with information processing in patients with a chronic disease are related to restrictions in functional health (McSweeney et al., 1985). However, not all participants with a chronic disease in this study experience functional limitations in daily life. An explanation for the absence of a relationship in our data between chronic diseases and cognitive function may be found in selective participation of relatively fit and healthy participants in this study. This possibility cannot be ruled out entirely, but earlier analyses have shown that participants in MAAS did not differ with the original Registration Network sample with respect to the number of active or total number of morbidity codes (Jolles et

al., 1995). This observation makes a strong health selection bias due to the inclusion procedure less likely.

The observed associations between ICPC morbidity and cognitive function in part corroborate earlier findings. Diabetic patients have been found to perform worse on tasks of memory and learning, psychomotor speed and problem solving when compared to healthy controls, possibly due to cerebral changes in blood supply and metabolism, but the affected cognitive domains and the extent of performance deficit vary widely across studies (Biessels, Kappelle, Bravenboer, Erkelens & Gispen, 1994). Elderly NIDDM patients have repeatedly performed worse than controls on verbal and complex cognitive tasks (Reaven, Thompson, Nahum & Haskins, 1990; U'ren, Riddle, Lezak & Bennington-Davis, 1990; Worrall, Moulton & Briffett, 1993). In this study the domains of verbal memory and information processing speed were also negatively related to diabetes, irrespective of age and insulin-dependency. More importantly, comparison of the regression coefficients for IDDM and NIDDM in Table 9.3 suggests that the strength of association was not substantially different in both types of diabetes. At first this observation may seem remarkable when disease duration is considered. As was mentioned earlier, reliable information on the duration of disease was not available in this group. Generally, however, IDDM is of the early onset type which would suggest a longer exposure time and consequently more structural organ damage in afflicted subjects, resulting in more cognitive impairment in IDDM than in NIDDM. One possibility is that progression of cognitive functional loss is limited in the early phase of IDDM in young adulthood to middle-age, when the brain has more reserve capacity to compensate for the loss of functional integrity than the brain in older patients with NIDDM (Satz, 1993), but this explanation remains largely speculative.

Lowered auditory thresholds have been implicated in reduced performance on verbal memory when stimuli are presented acoustically (Rabbitt, 1991). In this study target words were presented visually, to minimize the negative effect of hearing disorders on performance. Still, if older individuals experienced more difficulty in understanding the verbal instruction to a task, the observed negative association between presbycusis and memory performance may reflect a procedural artefact that needs further consideration.

Interestingly, we did not find relations between single or aggregated cardiovascular morbidity codes and cognitive performance, apart from an isolated single association between word fluency and atrial rhythm disturbances. Other studies have suggested that cardiovascular disease and its risk factors, such as hypertension, may be particularly involved in cognitive decline and dementia (Skoog, 1994; Waldstein, 1995). However, cross-sectional studies with a wide age range such as ours may be biased towards underestimating such associations, as vascular disease is the most important cause of death in middle-aged groups, thereby yielding older groups with different vascular risk profiles.

As this study was performed in participants with no overt signs of a cognitive disorder such as dementia it can be difficult to interpret the clinical relevance of the found associations between several health problems and performance. One way to describe the predictive value of one type of morbidity for cognitive performance – in the absence of age by morbidity interactions – is to express its impact in terms of another predictor in the statistical model, in this case chronological age. For example, one can calculate the average number of years that

specific groups of patients are *cognitively older*, by taking the ratio between the regression coefficients associated with the morbidity code and with age – in years. Thus, active diabetes in our model adds $-.462 / -.022 = 21$ years to the cognitive age with respect to memory function, and $-.523 / -.027 = 19$ years in the case of cognitive flexibility. Even though no direct inferences can be made regarding causality, this may seem a rather dramatic notion.

On a more general level, it can be argued that prevalent morbidity does not explain a large proportion of individual differences in cognitive abilities. For example, additional variance explained after entry of all active morbidity codes ranged from 1.5% (not significant) to 3.5% ($p < .001$), for digit copying and word fluency, respectively. This observation may cast some doubt on the contention that physical health is an important determinant of cognitive aging (Albert, 1993; Elias et al., 1990; Houx & Jolles, 1994; Houx, Vreeling & Jolles, 1991; Nolan & Blass, 1992). The prevalence of many health problems correlates strongly with chronological age (Table 9.1), albeit age itself still remains the most powerful predictor of cognitive abilities. Other as yet covert individual characteristics related to age need to be identified to account for this age-associated pool of variance.

In conclusion, the strong negative association between both IDDM and NIDDM and a broad spectrum of cognitive abilities may warrant careful follow-up of these functions by the physician in attendance from the time of diagnosis onwards, and should be considered as a possible mediating factor when cognitive dysfunction is found.

REFERENCES

- Albert, M. (1993). Neuropsychological and neurophysiological changes in healthy adult humans across the age range. *Neurobiology of Aging*, 14, 623-625.
- Biessels, G. J., Kappelle, A. C., Bravenboer, B., Erkelens, D. W., & Gispen, W. H. (1994). Cerebral function in diabetes mellitus. *Diabetologia*, 37, 643-650.
- Colsher, P. L., & Wallace, R. B. (1991). Epidemiologic considerations in studies of cognitive function in the elderly: Methodology and nondementing acquired dysfunction. *Epidemiologic Reviews*, 13, 1-27.
- Elias, M. F., Elias, J. W., & Elias, P. K. (1990). Biological and health influences on behaviour. In J. E. Birren & K. W. Schaie (Eds.), *Handbook of the psychology of aging*. (3 ed., pp. 79-102). San Diego: Academic Press.
- Houx, P. J., & Jolles, J. (1993). Age-related decline of psychomotor speed: Effects of age, brain health, sex, and education. *Perceptual and Motor Skills*, 76, 195-211.
- Houx, P. J., & Jolles, J. (1994). Vulnerability factors for age-related cognitive decline. In R. L. Isaacson & K. F. Jensen (Eds.), *Toxins in air and water*, (pp. 25-41). New York: Plenum Press.
- Houx, P. J., Vreeling, F. W., & Jolles, J. (1991). Age-associated cognitive decline is related to biological life events. In K. Iqbal, D. R. C. McLachlin, B. Winblad, & H. M. Wisniewski (Eds.), *Alzheimer's disease: Basic mechanisms, diagnosis and therapeutic strategies*, (pp. 353-358). Chichester, UK: Wiley.
- Jolles, J., Houx, P. J., van Bortel, M. P. J., & Ponds, R. W. H. M. (Eds.). (1995). *Maastricht Aging Study: Determinants of cognitive aging*. Maastricht: Neuropsych Publishers.
- Knottnerus, J. A., Metsemakers, J., Höppener, P., & Limonard, C. (1992). Chronic illness in the community and the concept of 'social prevalence'. *Family Practice*, 9, 15-21.
- Lamberts, H., & Wood, M. (1987). *ICPC. International classification of primary care*. Oxford: Oxford University Press.
- McSweeney, A. J., Grant, I., Heaton, R. K., Prigatano, G. P., & Adams, K. M. (1985). Relationship of neuropsychological status to everyday functioning in healthy and chronically ill persons. *Journal of Clinical and Experimental Neuropsychology*, 7, 281-291.
- Metsemakers, J. F. M., Höppener, P., Knottnerus, J. A., Kocken, R. J. J., & Limonard, C. B. G. (1992). Computerized health information in the Netherlands: A registration network of family practices. *British Journal of General Practice*, 42, 102-106.
- Nolan, K. A., & Blass, J. P. (1992). Preventing cognitive decline. *Clinics in Geriatric Medicine*, 8, 19-34.

- Poon, L. W. (1985). Differences in human memory with aging: Nature, causes and clinical implications. In J. E. Birren & K. W. Schaie (Eds.), *Handbook of the psychology of aging*. New York: Van Nostrand Reinhold.
- Rabbitt, P. (1991). Mild hearing loss can cause apparent memory failures which increase with age and reduce with IQ. *Acta Otolaryngol Suppl Stockh*, 476, 167-176.
- Reaven, G. M., Thompson, L. W., Nahum, D., & Haskins, E. (1990). Relationship between hyperglycaemia and cognitive function in older NIDDM patients. *Diabetes Care*, 13, 16-21.
- Salthouse, T. A. (1989). Age-related changes in basic cognitive processes. In M. Storandt & G. R. Vandenbos (Eds.), *The adult years: Continuity and change*, (pp. 5-40). Washington: American Psychological Association.
- Salthouse, T. A. (1992). *Mechanisms of age-cognition relations in adulthood*. Hillsdale, NJ: Lawrence Erlbaum Associates.
- Satz, P. (1993). Brain reserve capacity on symptom onset after brain injury: A formulation and review of evidence for threshold theory. *Neuropsychology*, 7, 273-295.
- Skoog, I. (1994). Risk factors for vascular dementia: A review. *Dementia*, 5, 137-144.
- Tarter, R. E., van Thiel, D. H., & Edwards, K. L. (1988). *Medical Neuropsychology: The impact of disease on behavior*. New York: Plenum Press.
- U'ren, R. C., Riddle, M. C., Lezak, M. D., & Bennington-Davis, M. (1990). The mental efficiency of the elderly person with Type II diabetes mellitus. *Journal of the American Geriatrics Society*, 38, 505-510.
- Van Berkel, A. B., & Tax, B. (1990). *Naar een standaardoperationalisatie van sociaal-economische status voor epidemiologisch en sociaal-medisch onderzoek [Towards a standard operationalization of socio-economical status for epidemiological and socio-economical research]*. Den Haag: Ministerie van Welzijn, Volksgezondheid en Cultuur.
- Waldstein, S. R. (1995). Hypertension and neuropsychological function: A lifetime perspective. *Experimental Aging Research*, 21, 321-352.
- Worrall, G., Moulton, N., & Briffett, E. (1993). Effect of type II diabetes mellitus on cognitive function. *Journal of Family Practice*, 36, 639-643.
- Writing Committee Lancet Conference. (1996). The challenge of the dementias. *Lancet*, 347, 1303-1307.

Chapter 10

Concluding remarks

In the experimental chapters of this thesis the relationship was assessed between several distinct health-related factors, such as vascular risk factors, self-reported physical health, prevalent morbidity, and cognitive outcome measures. Some general points should be made before the final conclusions of this research are presented.

Measurement of cognitive function

The outcome measures used in this thesis are derived largely from objective tests of cognitive performance that are also common in neuropsychological assessment. Tests were selected for their sensitivity to chronological age and their established capability to measure subtle group differences or individual changes in performance due to cerebral damage (Jolles, 1985; Jolles, Houx, van Boxtel & Ponds, 1995). These tests probe a wide range of cognitive abilities but may differ in domain-specificity in that the outcome of a test may express the cumulative efficiency of several different cognitive subsystems. For example, the Stroop Color-Word Test can be used to measure a subject's susceptibility to perceptual interference (Lezak, 1995, pp. 373-376) and can best be regarded as a test of both simple and complex information processing speed (Houx, Jolles & Vreeling, 1993). However, the time required to complete the complex condition (naming of the ink color of a color word) is also affected to some extent by elementary sensorimotor processes, such as stimulus encoding, response selection, and motor response. As another example, word recall requires some form of attention or concentration to enable adequate encoding, storage, and retrieval of the target words. Thus, it is difficult to make a strict classification of test parameters based on the cognitive domain that is intended to be measured. For most studies described in this thesis, the large set of available cognitive outcome measures were reduced to yet a few, distinct parameters that provide unique information about different aspects of cognitive function. Compound measures for *sensorimotor* and *complex speed* were distinguished on the basis of the underlying neuropsychological constructs of each test (LaRue, 1992; Salthouse, 1992, pp. 3-35), as has been applied in related research areas (e.g. Houx, 1991; Elias et al., 1993). Analogous strategies for data-reduction are established in psychometrics, for example in intelligence measurement and clinical indices of impairment, such as the Halstead-Reitan Impairment Index (Lezak, 1995, pp. 709-713). However, it cannot be concluded at this point that the method that was used for the reduction of raw data in the present studies is the optimal solution and that other combinations of raw test scores are less valid. For this reason, a confirmatory analysis must be performed, using the total data set of MAAS, in order to determine the discriminant validity of the structure of the compound measures, in accordance with suggestions from the statistical literature (e.g. Walsh & Betz, 1990, p. 69).

Limitations of a cross-sectional methodology

In this cross-sectional phase of the MAAS study, cognitive aging was studied under the assumption that the variation in cognitive abilities in successive birth cohorts represent actual cognitive aging trajectories. However, this may well be an oversimplification of the actual aging process, as we deal with age group differences and not with changes occurring over time within a specific age group (Bromley, 1990, p. 337). The differences found between successive age groups not only reflect the aging process but also incorporate the effect of cohort membership, in other words: age and cohort are confounded (Williams & Klug, 1996). Examples of such *cohort effects* are secular trends in accessibility of health care or educational facilities, or lifetime exposure to environmental hazards, which all may have repercussions on the integrity of brain function (Satz, 1993). It has been argued that, as the result of this confounding, cross-sectional studies tend to overestimate to some extent the true effect of age on cognition (Schaie, 1988). The scarce longitudinal studies devoted to aging patterns in cognitive function have in fact suggested non-linear relationships between chronological age and cognitive abilities: in these studies most cognitive abilities remain stable or even demonstrate a subtle gain from young adulthood to middle age (Schaie, 1994). Undoubtedly, only longitudinal studies enable examination of the processes of aging as they interact (Schroots & Birren, 1993), but when such a design is chosen one has to deal with other sources of bias, such as confounding of age with period effects, or selective attrition (Hayslip & Panek, 1989). Although the limitations of cross-sectional research are well-known, the bulk of our knowledge in the field of cognitive gerontology is based on cross-sectional studies (Bromley, 1990). The strength of the design lies in its potential to generate, within a relatively short time frame, hypotheses about causal relationships which can be tested in a longitudinal study or in subsequent dedicated studies, thereby safeguarding a steady progress in this research domain.

Nature and stability of risk factors

The studies presented in this thesis are in fact *experiments of nature* in that one cannot manipulate the individual risk factor level and one has to rely therefore on data from relatively large samples from the population. The hypothesized predictors of cognitive dysfunction that were addressed are *proximal* in nature, in that they reflect a health-related quality of the individual which is at best valid at the time of the assessment, but which may be less indicative for the historical (or *distal*) risk factor profile. For example, generalizability of the habitual physical activity at one point in life to lifetime activity habits is limited, as many influences in the course of a lifetime may affect the activity lifestyle. Theoretically, time may be a critical factor in that not only the actual level of a risk factor but also the duration of exposure to the risk factor should be incorporated in an explanatory model of age-related cognitive decline. Conversely, it seems obvious that reliable information on risk factor status in the past is extremely difficult or even impossible to obtain. One valid way to circumvent this problem is to collect information on risk factor status and cognitive function prospectively and to construct indices of risk factor exposure, for example by calculating the area below the risk factor status by time curve (or *integral*).

Another relevant issue when studying predictors of age-related functions is that little is known about the stability of risk factors over time (Fozard, Metter, Brant, Pearson & Baker, 1993). Thus, risk factors that are present during middle age may have different associations with indices of functional status or disease than those that are present in old age. In some experiments in the present thesis this problem could be partially resolved by performing age-stratified analyses. It seems that, ultimately, only a better understanding of the basic neurobiological mechanism of cognitive aging can refine our research design. Given the current state of our rather patchy knowledge it is not unlikely that risk factors for cognitive decline represent a proxy measure of yet another, basic neurobiological factor that is more directly involved in the pathogenesis of disturbances in brain function. Furthermore, when the relation between health-related variables and cognitive function is studied in a cross-sectional fashion, participation in such a study will depend to some extent on the individual risk factor profile. This may result in cohorts containing relatively large proportions of successfully aging older adults.

An issue related to risk factor stability over time is brought up by recent evidence that vascular risk factor profiles may be different for men and women, particularly post-menopausal women. In a quite recent study by Prince, Lewis, Bird, Blizard and Mann (1996) evidence was found that in a hypertensive sample of 2,584 individuals in the age between 65 and 74 years, who were followed up for 54 months, the decline in performance over time on a test of semantic memory (Paired Associated Learning Test) was more prominent in women than men. If accelerated atherosclerosis after the menopause is the basic reason behind a sex-related differential decline of function this finding may call for sex-stratified analysis when studying cognitive aging patterns in older individuals.

With respect to the present data, the methodological difficulties outlined above cannot be resolved satisfactorily at present. Ultimately, longitudinal data will come available in the MAAS study when the cross-sectional measurements in the same population are repeated after distinct time intervals (chapter 3). This procedure permits the separate assessment of effects related to age, cohort membership and interactions between age and cohort (cf. Nolan & Blass, 1992). Until that time prudence is called for when inferences are made about patterns of cognitive aging on the basis of cross-sectional data only.

Cognitive aging: a statistical model

The outcome of cognitive test performance may vary as a function of age and educational level – or vocational achievement – and this is why age- and education-graded norms were made available for most accepted neuropsychological tests (Lezak, 1995, pp. 99-101). In addition, even though no overall differences in intellectual ability exist between the sexes, there may be differences in the patterns of ability between men and women (Kimura, 1992). For these reasons it is necessary to control these background variables (or covariates) when studying associations between potential risk factors and cognitive function. This may be achieved by restrictive selection of the study sample, but only at the risk of reducing the external validity of the study outcome (Altman, 1991). Another approach is to use statistical control procedures, as employed in the present studies. A linear multiple regression approach was adopted for

population samples that were stratified for age, sex, and general ability, in order to assess the unique association of specific independent variables with cognitive outcome measures after the effects of age, sex, and education were accounted for. Thus correlational techniques, such as regression analyses, may be quite informative even if they do not permit inferences about causality. Indeed, it has been argued that linear models are applicable to normal cognitive aging (Salthouse, 1992, p. 12); provided that the study population is free of dementia (Jorm, 1994). In some cases the correlation between predictor and cognitive outcome measure may vary as a function of the level of yet another variable, such as age. For example, as a rule, the impact of disease on functional status can be much more dramatic in older individuals when compensatory mechanisms fail. Under such circumstances one could speak of moderation of the age-cognition relationship by a third variable, in this case health (Baron & Kenny, 1986) and age-stratified analysis would be the preferred analytic approach. However, when the distribution of a predictor variable is not approximately the same in the different strata – which is true in most of the studies described here – interaction terms can be typically introduced in the regression model to improve the ‘goodness-of-fit’.

A slightly different approach is used when one aims at explaining effects of age on cognitive function in terms of intermediate variables, or mediators (Baron & Kenny, 1986). The central issue of such an approach was rather eloquently stated by Bromley (1991):

“Chronological age is no more than a convenient time marker in terms of which the complex biopsychological causal pathways involved in human ageing can be compared and related. (...) It is obvious then that what produces the ageing effects we are interested in must be the various biomedical, psychological, social and environmental processes and sequences that occupy time and produce effects that accumulate and interact over time”. (Bromley, 1990, p. 318).

Or, as P. Houx (personal communication, March 9, 1996) put it more boldly: “...age is time, and time is nothing...”: the generally observed age effect on cognitive outcome measures is an accumulation of effects of covert (age-related) variables that in fact need to be identified. In essence, this notion indicates that in studies of cognitive aging, the proportion of variance in test performance associated with age is not relevant *as it is*. Rather, the variance should be split up into smaller proportions of variance that each can be uniquely attributed to more specific individual characteristics that are related to the cognitive domain under study and that also show age-dependence (Salthouse, 1992). This would imply that the generally observed relation between chronological age and cognitive function is *mediated* by age-related factors that are linked in a more meaningful way than age itself to the chain of neurobiological events that eventually lead to cognitive decline. Figure 10.1 represents the theoretical relationships between age, a mediator variable, and cognitive performance. Venn diagrams depict the total proportion of variance in each variable, which may be shared to some extent with the other variables in the model. Here, the mediator is defined as a variable that is placed between age and cognition and that in part can explain the relation between these variables (represented by the shared area marked 1 in the figure). In addition, there may be a mediator-independent relation between age and cognition (area 2) or an age-independent relation between the mediator variable and the cognitive parameter (area 3). Analysis of these relations by using a regression approach implies that, after introduction of a potential predictor (or mediator)

Figure 10.1. Schematic representations of possible relationships between age, mediator variable, and measures of cognitive function: on the left the pathways of action by which age-related processes may exert their effect on cognition, on the right the representation of the variance in the three variables with their potential overlap, or shared variance (see text for the interpretation of the numbered areas; adapted from Salthouse, 1992).

one should not only inspect the potential increase in variance explained by the regression model – which can be low when the shared variance with chronological age is large – but should also contrast the relevance of the predictor variable with that of age itself, for example by evaluating the (standardized) regression weights. The experimental data presented in the chapters 4 to 9 were therefore analyzed along these lines and are discussed together in the following section.

Towards a synthesis: did we study 'mediators of age-related cognitive decline'?

It may be illustrative to express the outcome of the studies presented in this thesis in terms of a mediator model of cognitive aging. A mediator of age-related cognitive decline was defined above as a variable placed between age and cognitive function with shared variance in both (Fig. 10.1). According to the definition of Salthouse (1992), in order to be a *true* mediator a variable must firstly at least correlate with both age and the cognitive outcome measure. Secondly, the importance of the mediator is reflected in the reduction of the shared variance between age and cognitive function when the mediator is controlled for, which may be expressed as the percentage of mediator-related variance, or %MRV). Table 10.1 summarizes information derived from the different studies presented here about the relations between chronological age and cognitive outcome measures, with and without controlling for the health-related variables under study. Here, these variables are treated as potential mediators of the age / cognition relationship. To this end, the associations between cognitive parameter and educational level or sex were kept constant.

These data may seem a bit puzzling at first sight, but several interesting inferences can be made from them. Firstly, the correlations between age and mediator variables are in the expected direction, i.e. lower activity level, lower aerobic capacity, higher blood pressure, lower night-time reduction in systolic blood pressure, and presence of diabetes all are associated with older age. Systolic blood pressure and $\text{VO}_{2\text{-max}}$ are highly correlated with age, but this relation is virtually absent for the night-time 'dipping' of blood pressure (shared

Table 10.1. Correlation between mediator and age (r_{MA}), between mediator and cognitive outcome measure^a (r_{MC}), and the percentage of shared variance ($r^2 \times 100\%$) between age and cognitive outcome measure, with and without control of the mediator level. The percentage of mediator-related variance (%MRV) expresses the amount of shared variance between age and cognitive parameter accounted for by the mediator.

Mediator	Chapter	Total N	Age range (years)	r_{MA}	r_{MC}	r^2_{AC} (%)	$r^2_{AC MC}$ (%)	%MRV ^b
APAQ	4	80	55-85	-.15	.19	34	33	4
VO _{2-max}	5	132	24-76	-.66	.47	30	13	57
SBP	7	936	24-81	.50	-.28	27	21	23
Δ day / night SBP	8	115	29-81	-.05	.27	12	12	0
Diabetes ^c	9	1,360	24-81	.18	-.21	26	24	7

Notes. APAQ = actual physical activity questionnaire; VO_{2-max} = maximal aerobic capacity, corrected for body fat; SBP = systolic blood pressure.

^a Outcome measure is *cognitive flexibility*, except for day / night difference in systolic blood pressure, where *memory* was used as being the primary affected measure. All cognitive parameters were adjusted for their association with sex and educational level.

^b %MRV (% mediator-related variance) is calculated as $100 \times (r^2_{AC} - r^2_{AC|MC}) / r^2_{AC}$, where r^2_{AC} is the squared zero-order correlation between age and the cognitive variable and $r^2_{AC|MC}$ the squared partial correlation between age and cognitive variable, with the level of predictor controlled for (Hair, Anderson & Tatham, 1987, pp. 46-47). This is equivalent to $100 \times (\text{area 1}) / (\text{area 1} + 2)$ in Fig. 10.1 (Salthouse, 1992).

^c Diabetes coded as 0 = absent, 1 = present.

variance is .0025%). Secondly, all mediator variables are associated with the cognitive outcome measure in the opposite way compared to age, with shared variance ranging from 4% (APAQ) to 22% (VO_{2-max}): higher values for these variables are associated with poorer performance. Thus, all variables comply to some extent with the basic conditions for being a mediator between age and cognition. When the common variance between age and cognitive measure is inspected, and it becomes clear that this relation is attenuated by controlling for the level of the mediator variable, it can be readily concluded that systolic blood pressure and VO_{2-max} are by far the most important mediators, with associated mediator-related variances of 23 and 57%, respectively. It seems however counterintuitive to regard these two variables as important mediators of age-related cognitive decline as we have demonstrated that no variance in performance is *independently* explained by blood pressure (not even in an age-stratified analysis, cf. chapter 7) and only a small amount is explained by VO_{2-max} (chapter 5). Absence of an age-independent association between cognitive function and a mediator with a large mediator-related variance can only imply that *all* its shared variance with cognitive performance will coincide with that of age and cognition. In fact, *any* variable which varies systematically with age, such as hair grayness or skin elasticity (correlation (r) with age is .82 and .64, respectively, Anstey, Lord & Smith, 1996), will to some extent share variance with measures of cognitive function. One important difference between other age-related physiological variables and blood pressure or VO_{2-max} is, however, that indirect evidence points to the existence of a causal link between these variables and the integrity of cognitive function, even if this evidence is far from conclusive. True mediation seems less convincing in the absence of independent predictive power of these variables, such as was found for night-time 'dipping' of blood pressure and prevalent diabetes. In our opinion, diabetes has the largest

potential for being a true mediator because this condition is directly related to both age and cognitive function and additionally shows an age-independent relation with cognitive function.

Conversely, night-time dipping of blood pressure was unrelated to age. This seems odd when a blunted night-time dip is considered to be the result of a pathophysiological process. Two explanations are conceivable. First, non-dipping reflects a genetic predisposition, of which the clinical expression is relatively independent of other aspects of physiological aging. Even in the virtual absence of longitudinal research on blood pressure dipping, this possibility seems, however, rather unlikely, because non-dipping is associated with a number of systemic disorders in which it seems at least partially reversible after appropriate treatment (e.g. pheochromocytoma or Cushing's syndrome, Pickering, 1991, pp. 5.9-5.10). The second possibility is that non-dippers make up a distinct risk category of individuals who may develop disease relatively early in life, which reduces their ability or eligibility to take part in a cross-sectional aging study like MAAS, thus causing selection bias. For now the latter explanation seems the most plausible, because this type of bias is the major source of error variance in any developmental study using a cross-sectional design (Hayslip & Panek, 1989).

The issue of mediation of age effects on cognitive function by means of factors related to vascular disease cannot be resolved satisfactorily using a cross-sectional study design. For our purpose a longitudinal approach will bypass several sources of bias, including the confounding of age and cohort, but only then if other typical sources of bias such as selective attrition and confounding of age with period effects can be adequately accounted for. It may be expected that only repeated measurement of cognitive function in association with assessment of the risk factor profile in the same population can ultimately demonstrate true causal mechanisms at work in mediator (or moderator) models of cognitive aging.

Implications of current findings for health care and future research

As mentioned earlier, the cross-sectional nature of the present data does not permit straightforward inferences about cause-and-effect relationships. With respect to an intermediary role of the studied risk factors in the age-cognition relationship, it can be concluded that cross-sectional data may at best *suggest* true mediation. Longitudinal follow-up of this population and, in particular, a more basic knowledge about the neurobiological mechanisms of associations between risk factor and integrity of brain function, is essential to substantiate these notions. The associations found between health-related factors and cognitive outcome measures will particularly direct the focus of research in the longitudinal phase of the MAAS project, when the predictors of actual performance today may prove to be the true mediators of decline in performance at follow-up.

Evidence was found that aerobic fitness is positively related to the speed of information processing in healthy adults. This indicates that older individuals may benefit from training programs that aim at improving the level of aerobic fitness by expanding their functional *brain reserve capacity*. It seems unlikely that the definite study to underpin this assertion will ever be performed, due to the high costs, large effort and procedural difficulties associated with a large-scale and long-term intervention program. However, a larger cognitive decline at follow-up in the less active or aerobically less fit individuals, compared to an attenuated

pattern of decline in their fit age peers, will be in line with our prediction. Until then, we believe that the advocacy of training programs to improve aerobic fitness in older individuals for the sole reason to slow down cognitive decline is not sufficiently grounded. The importance of such measures which are intended to ameliorate the quality-of-life is probably much larger in other functional domains, such as those related to the locomotor and cardiovascular system – provided that they are implemented under expert supervision to minimize the risk of health hazards.

It was shown that the within-subject variability of blood pressure varies considerably as a function of age. This finding has practical implications for the clinical assessment of blood pressure status. As a rule, the blood pressure level in older subjects will be overestimated when the relatively strong adaptation of blood pressure over time in these individuals is not taken into account, and one relies on a limited number of measurements during a patient contact. Overdiagnosing hypertension will lead to unnecessary drug therapy in older individuals, which in turn could enhance iatrogenic disorders in this relatively vulnerable group, such as episodes of hypotension, or falls. We suggest to rely therefore not only on repeated measurements of blood pressure but also to consider the measurements taken after a 10-15 minute interval as the only reliable estimates of the habitual blood pressure. In general practice, where patient contacts are of relatively short duration, this guideline may be impractical to implement for screening purposes. We therefore advocate a more widespread use of reliable automatic recording devices in this particular setting, which has the additional advantage that the probability of erroneously high readings due to a pressor response in some individuals is substantially reduced.

Associations between blood pressure or other vascular risk factors (body mass index, waist-to-hip ratio, smoking) and cognitive performance were absent, which casts doubt on the role of these factors in the normal cognitive decline seen with increasing age. Still, repeated assessment of the vascular risk factor profile at follow-up will provide important information about the evolution of risk factor status in relation to cognitive functioning. For example, it has been demonstrated that prolonged exposure to vascular risk factors such as hypertension may well be associated with lower performance levels, even when they are in the non-pathological range of cognitive functioning (chapter 7). This makes it worthwhile to continue the assessment of the risk factor profile at the follow-up measurements in MAAS.

It was demonstrated that attenuation of the physiological 'dipping' of blood pressure – an established risk factor for target organ damage in hypertensive patients – was quite specifically related to lower performance on memory tests. As mentioned earlier, this finding should be reassessed in an independent sample, but may point at a specific category of individuals who are at risk of accelerated decline. The independence of the day-time / night-time blood pressure difference of mean average day-time blood pressure needs to be examined more closely. More specifically, a case-control study in hypertensive and normotensive individuals that includes neurocognitive assessment, 24-hour ambulatory blood pressure monitoring and brain-imaging (MRI) can provide essential information in this respect. A study of this kind is projected in the course of 1997, in collaboration with the Department of Internal Medicine of the University of Maastricht.

Both insulin- and non-insulin-dependent diabetes were negatively associated with indicators of cognitive function, while other existing morbidity in the participants was not. It has been suggested that the negative effects of diabetes on higher cortical processes are primarily of vascular origin. It remains unclear which aspects of the disease are most relevant in the etiology of cognitive dysfunction. To this end, a prospective study is needed in diabetes patients and age-matched controls that incorporate comprehensive assessment of both neurocognitive function and disease evolution, such as disease control, target organ damage, and therapy adherence. Such a study is currently prepared for the near future as a sidearm project of MAAS.

REFERENCES

- Altman, D. G. (1991). *Practical statistics for medical research*. (1st ed.). London: Chapman & Hall.
- Anstey, K. J., Lord, S. R., & Smith, G. A. (1996). Measuring human functional age: A review of empirical findings. *Experimental Aging Research*, 22, 245-266.
- Baron, R. M., & Kenny, D. A. (1986). The moderator-mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. *Journal of Personality and Social Psychology*, 51, 1173-1182.
- Bromley, D. B. (1990). *Behavioural Gerontology: Central issues in the psychology of ageing*. Chichester (UK): John Wiley & Sons.
- Elias, M. F., Wolf, P. A., D'Agostino, R. B., Cobb, J., & White, L. R. (1993). Untreated blood pressure level is inversely related to cognitive functioning: The Framingham Study. *American Journal of Epidemiology*, 138, 353-364.
- Fozard, J. L., Metter, E. J., Brant, L. J., Pearson, J. D., & Baker, G. T. (1993). Goals for the next generation of longitudinal studies. In J. J. F. Schroots (Ed.), *Ageing, health and competence*, (pp. 35-52). Amsterdam: Elsevier.
- Hair, J. E., Anderson, R. E., & Tatham, R. L. (1987). *Multivariate data analysis*. New York: Macmillan.
- Hayslip, B., & Panek, P. E. (1989). *Adult development and aging*. New York: Harper & Row.
- Houx, P. J. (1991). *Cognitive aging and health related factors*. Doctoral Thesis, University of Maastricht.
- Houx, P. J., Jolles, J., & Vreeling, F. W. (1993). Stroop interference: Aging effects assessed with the Stroop Color-Word test. *Experimental Aging Research*, 19, 209-224.
- Jolles, J. (1985). Early diagnosis of dementia: possible contributions from neuropsychology. In W. H. Gispen & J. Traber (Eds.), *Ageing of the brain*, (pp. 84-100). Berlin: Springer.
- Jolles, J., Houx, P. J., van Boxtel, M. P. J., & Ponds, R. W. H. M. (Eds.). (1995). *Maastricht Aging Study: Determinants of cognitive aging*. Maastricht: Neuropsych Publishers.
- Jorm, A. F. (1994). A method for measuring dementia as a continuum in community surveys. In F. A. Huppert, C. Brayne, & D. W. O'Connor (Eds.), *Dementia and normal aging*, (pp. 244-253). Cambridge: Cambridge University Press.
- Kimura, D. (1992). Sex differences in the brain. *Scientific American*, 267, 81-87.
- LaRue, A. (1992). *Ageing and neuropsychological assessment*. New York: Plenum Press.
- Lezak, M. D. (1995). *Neuropsychological Assessment*. (3rd ed.). New York: Oxford University Press.
- Nolan, K. A., & Blass, J. P. (1992). Preventing cognitive decline. *Clinics in Geriatric Medicine*, 8, 19-34.
- Pickering, T. G. (1991). *Ambulatory monitoring and blood pressure variability*. London: Science Press.
- Prince, M., Lewis, G., Bird, A., Blizard, R., & Mann, A. (1996). A longitudinal study of factors predicting change in cognitive test scores over time, in an older hypertensive population. *Psychological Medicine*, 26, 555-568.
- Salthouse, T. A. (1992). *Mechanisms of age-cognition relations in adulthood*. Hillsdale, NJ: Lawrence Erlbaum.
- Satz, P. (1993). Brain reserve capacity on symptom onset after brain injury: A formulation and review of evidence for threshold theory. *Neuropsychology*, 7, 273-295.
- Schaie, K. W. (1988). Internal validity threats in studies of adult cognitive development. In M. L. Lowe & C. J. Brainerd (Eds.), *Cognitive development in adulthood*. New York: Springer Verlag.
- Schaie, K. W. (1994). The course of adult intellectual development. *American Psychologist*, 49, 304-313.
- Schroots, J. J. F., & Birren, J. E. (1993). Theoretical issues and basic questions in the planning of longitudinal studies of health and aging. In J. J. F. Schroots (Ed.), *Ageing, health and competence*, (pp. 3-34). Amsterdam: Elsevier.
- Walsh, W. B., & Betz, N. E. (1990). *Tests and assessment*. (2nd ed.). Englewood Cliffs, NJ: Prentice-Hall.
- Williams, J. D., & Klug, M. G. (1996). Aging and cognition: Methodological differences in outcome. *Experimental Aging Research*, 22, 219-244.

Summary

A decline in cognitive abilities, such as memory or speed of information processing, is usually considered to be an inevitable aspect of the aging process. Recent research has shown that risk factors or protective factors can be identified in so-called pathological cognitive decline – e.g. dementia – that could mediate the onset of cognitive symptomatology. However, little is known about the normal or *usual* decline of cognitive function with age: which functions deteriorate, is the rate of decline the same for different functions, and which differences exist between individuals that could explain differential aging patterns?

This thesis deals with individual differences in cognitive ability that are either directly or indirectly related to the health status. It is investigated if these differences can explain the variance in cognitive functioning that can be observed in the general population and that tends to increase with age. Particular emphasis is put on factors which are generally related to the condition of the vascular system.

Chapter 1 – This introductory chapter provides the rationale of the research described in this thesis and outlines the contents of the different subjects at stake.

Chapter 2 – The concepts of *age*, *health*, and *cognition* are defined and the relation between these concepts is reviewed on the basis of previous research. Different, as yet hypothetical, forms of cognitive aging are described: *primary* or *successful* aging, characterized primarily by age-intrinsic factors laid down in the genome; *usual* aging, in which pathological deficiencies exist in addition to intrinsic factors; *secondary* or *pathological* aging, where aging effects are enhanced by physical disease; and finally *tertiary* aging, which is characterized by superimposed functional loss as the result of terminal illness. The borderline between usual and pathological aging is explored: from a medical perspective a sharp distinction is often made between an age-congruent decline of cognitive functions and pathological states, such as in dementia. The theoretical model of *brain reserve capacity* (BRC) rather assumes a maximal cognitive processing capacity that is determined primarily by genetic and environmental factors. According to this model, cognitive aging can be understood as a gradual transition of normal cognitive function, in which functional compensation of structural damage to the substrate (the brain) is still possible, towards pathological function when the point is reached that compensatory mechanisms fail.

The second part of chapter 2 reviews the available literature on the potential role of vascular risk factors in cognitive aging. Elevated blood pressure, or hypertension, and physical fitness, or aerobic activity / capacity, have in particular been tested with varying success for a relationship with cognitive variables in normal aging populations. However, the methodological differences and deficiencies in these studies do not permit a clear judgement of the detrimental or protective effects of these factors for brain function.

Chapter 3 – The Maastricht Aging Study (MAAS) provides the scientific framework for all studies described in this thesis. Rationale and methodology of MAAS are presented in chapter 3. The core program of MAAS is made up by a cross-sequential study in nearly 2,000

individuals aged between 24 and 81 years. These subjects were recruited from a patient register of collaborating general practitioners in the Maastricht region (Registration Network Family Practices, or RNHF, in Dutch). The study population was stratified for age (12 discontinuous age classes between 23 and 82 years at baseline), sex, and level of occupational achievement as an index of premorbid functioning. MAAS intends to followup all participants for 12 years, at 3 or 6 year intervals depending on age. The most important goal of this research program is to find an explanation for differences between the individual trajectories of cognitive aging. More specifically, it addresses the relationship between health-related factors, psychosocial factors, and cognitive outcome measures. On finalization of this thesis, the data collection and analysis of three-quarters of the first, cross-sectional measurement had been completed.

Chapter 4 – In previous studies a relationship was observed between the degree of habitual physical activity and the performance on primarily speeded cognitive tasks. The supposed mechanism behind this relationship is an increase in cerebral oxygen supply, or a direct stimulation of brain areas related to sensorimotor function, as the direct result of physical training. Chapter 4 describes the results of a study in 80 healthy individuals aged 55 years and older dealing with the relationship between habitual physical activity and cognitive functioning. For this purpose, an activity questionnaire was used that was designed for use in older populations and which reflects the habitual activity level (including sports) in terms of daily caloric expenditure. In addition, a questionnaire was used to probe the experienced health of all participants. Aging effects were found on measures of cognitive speed, but not on verbal memory. Women performed worse on an index of simple sensorimotor speed than men, but were better on memory. No direct relation was found between physical activity and cognitive test performance. However, activity did interact with age on both measures indexing cognitive speed, and the level of experienced health was positively related to the same speed measures. The latter observation confirms the relevance of general health for cognitive function. The absence of a uniform relationship between activity and cognition may be the result of a relatively small variance of activity level and the above-average mean level of activity in this sample. Other possible causes for not finding a relationship are discussed.

Chapter 5 – A more direct measurement of physical fitness is the determination of the maximum aerobic capacity (VO_{2-max}). In the first MAAS panel study, VO_{2-max} was determined in 132 participants in the age between 24 and 76 years. Participation in this additional protocol was on a voluntary basis, but to limit the health hazard, individuals with significant cardiovascular or musculoskeletal complaints or disorders were not admitted. Participants were engaged more hours per week in sporting activities and judged their general health better than non-participants. After correction for age, sex, and the level of general intelligence, a small increase in explained variance in performance was observed when VO_{2-max} – corrected for fat-free mass – was introduced in the regression models. This was observed for both speed measures that, when combined, constitute the cognitive flexibility score (letter / digit version of the Concept Shifting Test, and color / word interference of the Stroop test). No relationship was found between memory performance and VO_{2-max} . The relation between measures of information processing speed and aerobic capacity may implicate a protective

effect of physical fitness on cognitive function, even though the observed associations were modest.

Chapter 6 – High blood pressure is an important risk factor for cardiovascular and cerebrovascular disease. Determination of the habitual blood pressure level is often hampered by several methodological pitfalls. The outcome of casual (sphygmomanometric) blood pressure measurement varies considerably within individuals and between observers. The cardiovascular orienting response that is observed on blood pressure measurement does not seem to habituate in some individuals, a phenomenon sometimes referred to as *white coat effect* because the presence of an observer generally is the causative factor. As a preparatory step in advance to the studies described in chapters 7 and 8 in which the relevance of blood pressure status for cognitive function is the key issue, this chapter describes which demographical variables may affect habituation of repeatedly measured blood pressure under standard laboratory conditions and what should be regarded as the optimal estimate of the habitual blood pressure level. For this purpose, blood pressure was measured 5 times within 20 minutes in all 469 participants of the first panel study, in the absence of an observer. Habituation of both systolic and diastolic blood pressure within the 20 minute period was clearly more outspoken in the older age groups. On a group level no further decrease of blood pressure was observed after 15 minutes. From these findings it can be concluded that the importance of an adequate rest period (and possibly also habituation to the measurement itself) preceding the blood pressure measurement in older individuals should not be underestimated. In addition, the outcome of automatic blood pressure measurement was compared with average day-time and night-time blood pressure levels in a subgroup of 135 participants. The relatively low concordance between these parameters (weighed *Kappa* 0.42–0.51) indicates that, in spite of standardization of measurement, the outcome of laboratory measurement gives only a limited indication of the average blood pressure level in daily life.

Chapter 7 – In the first two panel studies ($N = 936$), the habitual blood pressure and other vascular risk factors (smoking habits, alcohol consumption, body mass index, and waist-to-hip ratio) were related to cognitive outcome measures. Blood pressure and other risk factors did not explain additional variance in cognitive performance, after control for age, sex, and educational level, both in the total group and in the group without cardiovascular diseases or antihypertensive medication usage ($n = 720$). Stratified analyses within four age classes (25–35, 40–50, 55–65, and 70–80 years) did not reveal an association between blood pressure and cognitive function. It is concluded that in this population in which in general the treatment of hypertension is pursued with great vigor, the relation between blood pressure status and cognitive function is of no true clinical relevance.

Chapter 8 – In this chapter the focus is on cognitive outcome as a function of ambulant blood pressure level (mean day-time and night-time pressure, and the day/night pressure difference) in participants of the 24-hour blood pressure measurement protocol. The absence of the physiological nocturnal decrease in blood pressure was considered to be an additional risk factor in this respect. It has been demonstrated repeatedly in patients with hypertension that

non-dippers show more frequent and more extensive end organ damage – including the brain. Day-time and night-time mean blood pressure levels were unrelated to cognitive parameters, in line with earlier findings with respect to laboratory blood pressure (chapter 7). However, the difference between day-time and night-time blood pressure was highly predictive for verbal memory function (8–9% of unique variance explained in memory performance): *non-dippers* performed clearly worse than *dippers*, even after control of vascular morbidity and medication usage. This finding may implicate that an attenuated or absent nocturnal blood pressure decrease is related to a quite specific cognitive deficit. However, the mechanism underlying this relationship remains as yet uncertain and replication of this finding in an independent sample is necessary.

Chapter 9 – Prevalent diseases as recorded by the general practitioner are related with the cognitive outcome measures. Of all participants in the first three panel studies ($N = 1,360$), the information on existing health problems, which were identified in the patient record according to a strict classification system, were anonymously linked to the test data. Morbidity that was present in at least 1% of the population as active or inactive health problem, was tested in separate regression analyses for an association with cognitive function, after correction for demographical background characteristics. Both insulin dependent and non-insulin dependent diabetes mellitus was strongly predictive for lower performance within all investigated cognitive domains: the strength of the association was in some models comparable to adding 20 years to the chronological age. Furthermore, chronic bronchitis was negatively associated with simple and complex cognitive speed, and presbycusis was related to lower memory performance. Remarkably, apart from diabetes no vascular disorders such as hypertension or coronary heart disease contributed to the explanation of variance in the different regression models.

Chapter 10 – Several basic methodological assumptions that are at the basis of these studies are discussed in more detail. It is argued that age *as such* cannot explain age-related deterioration of cognitive decline, but instead it is important to identify those factors, or *mediators*, which can explain, at least partly, the strong relation between age and cognitive function. When the findings from the different studies described in this thesis are brought together, it becomes clear that a relationship between age and vascular risk factor on the one hand and between cognitive performance and risk factor on the other does not always imply that such factor mediates the relationship between age and cognition. Indeed, it is argued that a potential mediator should always explain variance in cognitive performance *independent* of age itself.

All findings from MAAS are to date cross-sectional in nature. The issue of causality can only be addressed in the longitudinal phase of this research program.

Samenvatting

Doorgaans wordt de achteruitgang van cognitieve vaardigheden, zoals geheugenfunctie en de snelheid waarmee complexe informatie wordt verwerkt door het brein, beschouwd als een onvermijdelijk gevolg van het verouderingsproces. Wanneer gekeken wordt naar pathologische cognitieve achteruitgang, zoals bij het dementiesyndroom, wordt het steeds duidelijker dat er risicofactoren of juist beschermende factoren in het spel kunnen zijn die de kans op het vroeg ontstaan van een dergelijke stoornis kunnen beïnvloeden. Over de gangbare achteruitgang van cognitieve functies is echter relatief weinig bekend: om welke functies gaat het precies, gaan deze allemaal achteruit met het ouder worden, en zijn er verschillen tussen individuen die kunnen verklaren dat sommige mensen nauwelijks achteruitgang ondervinden terwijl anderen juist al vroeg *cognitief oud* lijken te worden. Dit proefschrift handelt over individuele verschillen in cognitief functioneren welke direct of indirect te maken kunnen hebben met verschillen in de gezondheidstoestand. Onderzocht wordt of deze verschillen een verklaring kunnen bieden voor de spreiding in cognitief functioneren die in de populatie wordt gevonden en die lijkt toe te nemen met het ouder worden. In het bijzonder wordt onderzocht de rol van factoren die samenhangen met de toestand van het vasculaire systeem, zoals lichamelijke fitheid, bloeddrukstatus, en suikerziekte.

Hoofdstuk 1 – In dit inleidende hoofdstuk wordt de rationale van het beschreven onderzoek uiteengezet en wordt een overzicht gegeven van de verschillende onderwerpen die in dit proefschrift aan de orde komen.

Hoofdstuk 2 – In het eerste deel wordt een overzicht gegeven van wat doorgaans onder de begrippen *leeftijd*, *gezondheid*, en *cognitie* verstaan wordt en wordt geprobeert de verbanden hiertussen te inventariseren aan de hand van eerder onderzoek. Verschillende, vooralsnog hypothetische, vormen van cognitieve veroudering worden beschreven: *primaire* of *succesvolle* veroudering, die voornamelijk wordt bepaald door leeftijds-intrinsieke factoren zoals vastgelegd in het genoom, de *gangbare* veroudering, waarbij bovenop de intrinsieke factoren niet-pathologische deficiënties kunnen bestaan, *secundaire* of *pathologische* veroudering, waar verouderingseffecten versterkt worden door lichamelijke aandoeningen, en *tertiaire* veroudering tenslotte, waarbij er sprake is van gesuperponeerd functieverlies als gevolg van terminale ziekte. Het grijze overgangsgebied tussen de gangbare en pathologische veroudering wordt verkend: het medisch model maakt doorgaans een scherp onderscheid tussen leeftijd-congruente achteruitgang van cognitieve functies en pathologische vormen zoals in dementie. Het theoretische model van hersenreservcapaciteit (*brain reserve capacity*, of BRC) veronderstelt dat er veeleer sprake is van een door genetische factoren en omgevingsfactoren bepaalde maximale cognitieve verwerkingscapaciteit. Volgens dit model is cognitieve veroudering een graduele overgang van normale cognitieve functie, waarin compensatie van structurele schade aan het substraat, i.c. de hersenen, nog mogelijk is, naar pathologische functie wanneer het punt wordt bereikt dat compensatiemechanismen ontoereikend worden.

Het tweede deel van dit hoofdstuk behandelt de beschikbare literatuur aan de hand waarvan de mogelijke rol van vasculaire risicofactoren in cognitieve veroudering verduidelijkt wordt. In

het verleden zijn met name een verhoogde bloeddruk (hypertensie) en lichamelijke fitheid (gemeten als aërobe activiteit, c.q. capaciteit) met wisselend resultaat onderzocht op een samenhang met cognitieve variabelen in normaal verouderende populaties. De methodologische verschillen tussen en onvolkomenheden in deze studies laten echter niet altijd een duidelijke uitspraak toe over de schadelijke, dan wel beschermende effecten van deze factoren voor de hersenfunctie.

Hoofdstuk 3 – De Maastricht Aging Study (MAAS) vormt het kader waarbinnen het onderzoek zoals beschreven in deze thesis is uitgevoerd. De rationale en methodologie van MAAS wordt in dit hoofdstuk beschreven. Het basisprogramma van MAAS wordt gevormd door een cross-sequentiële studie in bijna 2.000 personen in de leeftijd tussen 24 en 81 jaar. Deze personen werden gerecruteerd uit een patiëntenregister van samenwerkende geacademiseerde huisartspraktijken in de regio Maastricht (Registratienet Huisartspraktijken, of RNH). De onderzoekspopulatie werd gestratificeerd naar leeftijd (12 discontinue leeftijdsklassen tussen 23 en 82 jaar bij aanvang van het onderzoek), sexe en het niveau van beroepsmatig functioneren, als index voor het premorbide functioneren. Het ligt in de bedoeling deze populatie gedurende 12 jaar in de tijd te volgen met follow-up intervallen die afhankelijk zijn van de leeftijd bij aanvang; iedere drie jaar voor personen van 49 jaar en ouder, iedere zes jaar bij personen jonger dan 49 jaar. De belangrijkste vraag in dit onderzoeksprogramma is welke factoren verantwoordelijk kunnen zijn voor de waargenomen verschillen in de wijze waarop en de mate waarin men cognitief veroudert. In het bijzonder is het onderzoek gericht op de samenhang tussen gezondheids-gerelateerde factoren, psychosociale factoren en cognitieve prestatie-maten. In dit proefschrift wordt gerapporteerd over de resultaten uit de eerste drie van in totaal vier panelstudies waaruit MAAS bestaat.

Hoofdstuk 4 – In eerder onderzoek is een verband gelegd tussen de mate waarin men lichamelijk actief is en de prestatie op cognitieve tests, vooral wanneer deze op snelheid gebaseerd zijn. Het veronderstelde mechanisme hierbij is dat als gevolg van de lichamelijke training de cerebrale zuurstofvoorziening verbetert, dan wel dat training een direct stimulerend effect heeft op hersendelen die betrokken zijn bij de sensomotoriek. Dit hoofdstuk beschrijft de resultaten van een studie naar de relatie tussen habituele lichamelijke activiteit en cognitief functioneren in 80 gezonde personen van 55 jaar en ouder. Hiertoe werd gebruik gemaakt van een speciaal voor ouderen ontwikkelde vragenlijst, waarmee de totale lichamelijke activiteit van alledag – waaronder sport – kan worden omgerekend naar een index van het calorische verbruik als gevolg van deze activiteit. Tevens werd een vragenlijst afgenomen naar het subjectieve gezondheidswelbevinden van de deelnemers. Leeftijdseffecten werden gevonden op de cognitieve snelheidsmaten, maar niet op het verbaal geheugen. Vrouwen scoorden lager op de index voor simpele snelheid dan mannen, maar hoger op verbaal geheugen. Er werd geen direct verband gevonden tussen lichamelijke activiteit en cognitieve testprestatie. Wel bleek activiteit te interacteren met leeftijd op de twee cognitieve snelheidsmaten, en was de mate waarin men zichzelf als gezond beschouwde positief gecorreleerd aan dezelfde snelheidsmaten. Met deze laatste observatie lijkt het belang van gezondheid voor cognitieve functie opnieuw bevestigd. Het ontbreken van een verband tussen activiteit en cognitie kan samenhangen met de

relatief geringe spreiding in deze parameter en het hoge gemiddelde niveau van activiteit in deze groep. Andere mogelijke oorzaken voor het niet vinden van een verband worden besproken.

Hoofdstuk 5 – Een meer directe meting van de lichamelijke fitheid is het vaststellen van de maximale aërobe capaciteit (VO_{2-max}). Deze werd bepaald in een submaximaal fietsergo-meterprotocol bij 132 deelnemers aan de eerste panelstudie van MAAS, in de leeftijd tussen 24 en 76 jaar. Men nam vrijwillig deel aan dit aanvullende onderzoek, waaraan overigens ter beperking van het gezondheidsrisico alleen personen mochten meedoen zonder significante cardiovasculaire klachten of aandoeningen, of problemen met het bewegings-apparaat. Deelnemers besteedden in vergelijking met niet-deelnemers gemiddeld meer uren per week aan sportbeoefening en bleken de eigen gezondheid als beter te beoordelen. Na correctie voor de effecten van leeftijd, sexe en algemeen intelligentieniveau werd een toename van verklaarde variantie gevonden na introductie van VO_{2-max} in het regressiemodel, voor de twee snelheidsmaten die samen de cognitieve flexibiliteitsscore vormen (letter / cijfer versie van de Concept Shifting Test, en de kleur / woord interferentie kaart III van de Stroop-test). Geen verband werd aangetoond tussen geheugen en VO_{2-max} . De gevonden samenhang tussen de maten voor informatie-verwerkingssnelheid en aërobe capaciteit kan wijzen op een beschermend effect van lichamelijke fitheid op cognitie, al waren de gevonden relaties in omvang bescheiden.

Hoofdstuk 6 – Hoge bloeddruk is een belangrijke cardiovasculaire en cerebrovasculaire risicofactor. Het vaststellen van de habituele bloeddruk kent echter verschillende methodologische problemen. De uitkomst van een handmatige bloeddrukmeting met auscultatie varieert sterk binnen individuen en tussen beoordelaars. Er kan sprake zijn van een oriëntatiereactie die na herhaalde metingen niet verdwijnt en aanleiding geeft tot verhoogde meetwaarden, wat een gevolg kan zijn ofwel van de meting zelf ofwel van de aanwezigheid van een observator (*witte-jas-effect*). Als voorbereiding op de hoofdstukken 7 en 8, waarin het belang van de bloeddrukstatus voor cognitieve functies centraal staat, wordt in dit hoofdstuk nagegaan welke demografische factoren een invloed hebben op de habituatie van herhaald gemeten bloeddruk en wat onder gestandaardiseerde testcondities de optimale schatter is van de habituele bloeddruk. Hiertoe werd de bloeddruk bij alle 469 deelnemers aan de eerste panelstudie gedurende 20 minuten 5 maal automatisch gemeten met een oscillometrische techniek (DinamapTM), in afwezigheid van de proefleider. Habituatie van zowel de systolische als diastolische bloeddruk over 20 minuten was beduidend sterker bij oudere leeftijdsgroepen. Op groepsniveau vond geen significante daling van de bloeddruk meer plaats na 15 minuten. Hieruit kan worden afgeleid dat juist bij ouderen het belang van een rustperiode, en mogelijk ook de gewinning aan de meting zelf, voor een betrouwbare bloeddrukmeting niet moet worden onderschat. Verder werden de uitkomsten van de automatische meting vergeleken met de gemiddelde dag- en nachtbloeddruk, verkregen uit 24-uurs ambulante bloeddrukmeting bij een deelgroep van 135 personen. De relatief lage concordanties die tussen deze parameters werden gevonden (gewogen *Kappa* 0,42–0,51) wijzen erop dat ondanks standaardisatie de uitkomsten van de laboratoriummeting slechts beperkt generaliseerbaar zijn naar de gemiddelde bloeddruk-waarden in het dagelijkse leven.

Hoofdstuk 7 – In de eerste twee panelstudies ($N = 936$) werd de relatie onderzocht van habituele bloeddruk en andere vasculaire risicofactoren rookgedrag, alcoholgebruik, Queteletindex, en taille / heup-ratio, met de verschillende cognitieve uitkomstmaten. Bloeddrukstatus en de overige risicofactoren verklaarde geen additionele variantie in cognitieve prestatie, na controle voor leeftijd, geslacht en opleidingsniveau. Dit goldt zowel voor de totale groep als voor de groep opgeschoond voor personen met cardiovasculaire aandoeningen of gebruikers van antihypertensieve medicatie ($n = 720$). Gestratificeerde analyses in 4 leeftijdsgroepen (25–35, 40–50, 55–65 en 70–80 jaar) lieten eveneens geen relaties tussen bloeddruk en cognitieve functie zien. Geconcludeerd wordt dat in deze groep personen, die in geval bestaande hypertensie doorgaans adequaat medicamenteus behandeld worden, de relatie tussen de bloeddrukstatus en cognitieve functie niet van klinische relevantie is.

Hoofdstuk 8 – Dit hoofdstuk richt zich op de relatie tussen ambulante bloeddrukwaarden (gemiddelde bloeddruk overdag en 's nachts, en het verschil hiertussen) en de drie samengestelde cognitieve uitkomstmaten in de groep personen die meededen aan de 24-uurs registratie van de bloeddruk. Het uitblijven van de fysiologische bloeddrukdaling gedurende de nacht werd hierbij als additionele vasculaire risicofactor beschouwd. Uit onderzoek bij hypertensiepatiënten is bij herhaling naar voren gekomen dat deze zogenaamde *non-dippers* vaker en meer uitgebreide eindorgaanschade te zien geven, inclusief in het brein. Zoals reeds voor de laboratoriumbloeddruk werd vastgesteld kon ook voor de ambulante gemiddelde bloeddrukwaarden geen unieke relatie met cognitieve functie worden aangetoond. Het verschil tussen zowel systolische als diastolische dag- en nachtdruk bleek echter sterk voorspellend voor de verbale geheugenfunctie, overeenkomend met 8–9% uniek verklaarde variantie in de geheugenscore: *non-dippers* presteerden duidelijk slechter dan *dippers*, ook wanneer werd gecontroleerd voor vasculaire morbiditeit en medicijngebruik. Dit kan betekenen dat afvlakking of afwezigheid van de nachtelijke bloeddrukdaling verband houdt met vrij specifieke cognitieve afwijkingen, al blijft het onderliggend mechanisme vooralsnog onopgehelderd en is replicatie van deze bevinding in een onafhankelijk cohort noodzakelijk.

Hoofdstuk 9 – Informatie over het bestaan van specifieke ziekten, zoals gediagnostiseerd door de huisarts, wordt in dit hoofdstuk in verband gebracht met de cognitieve testprestatie. Van alle deelnemers aan de eerste drie MAAS-panelstudies ($N = 1.360$) werden de gezondheidsproblemen zoals volgens strikte criteria gecodeerd op de patiëntenkaart van de huisarts op anonieme wijze gekoppeld aan de testgegevens. Het bestaan van morbiditeit welke bij minimaal 1% van de deelnemers als totaal of actief probleem bekend was, werd in verschillende regressieanalyses onderzocht op een samenhang met cognitieve functie, waarbij werd gecontroleerd voor leeftijd, sexe en het opleidingsniveau. Zowel insulineafhankelijke als niet-insulineafhankelijke diabetes mellitus was sterk voorspellend voor een lagere prestatie op alle onderzochte cognitieve deelfuncties: de sterkte van dit verband was in sommige modellen vergelijkbaar met het behoren tot een 20 jaar oudere leeftijdsgroep. Verder hing chronische bronchitis negatief samen met simpele en complexe cognitieve snelheid, en kon ouderdoms-slechthorendheid in verband worden gebracht met een slechtere geheugen-prestatie. Opmerke-

lijk was dat behalve diabetes de overige vasculaire aandoeningen zoals hypertensie en coronairlijden geen bijdrage leverden aan de verschillende regressiemodellen.

Hoofdstuk 10 – In dit hoofdstuk worden een aantal methodologische uitgangspunten van de beschreven studies nader toegelicht. Betoogd wordt dat leeftijd *op zichzelf* geen verklaring kan bieden voor leeftijd-gerelateerde cognitieve achteruitgang. Veeleer moet worden gezocht naar factoren (*mediatoren*) die een deel van de samenhang tussen leeftijd en cognitieve functie kunnen verklaren. Wanneer de afzonderlijke bevindingen uit de verschillende beschreven studies worden samengebracht blijkt dat een verband tussen leeftijd en vasculaire factor enerzijds, en tussen cognitieve prestatie en vasculaire factor anderzijds niet zonder meer betekent dat de betreffende factor een mediërende rol speelt in de relatie tussen leeftijd en cognitie. Er wordt geconcludeerd dat een potentiële mediator altijd ook variantie in cognitieve prestatie moet kunnen verklaren, onafhankelijk van de factor leeftijd.

Er wordt ingegaan op het belang van deze studies voor verder onderzoek. Voorlopig zijn alle resultaten uit MAAS van cross-sectionele aard. De vraag naar causaliteit zal in de longitudinale fase van MAAS aan de orde komen.

Curriculum vitae

Martin van Boxtel werd in 1959 geboren te Tilburg. Hij doorliep daar het gymnasium B aan het Theresialyceum waarvan in 1978 het diploma werd behaald. Vervolgens was hij twee jaar werkzaam in de detailhandel als in-/verkoopmedewerker van een bedrijf in consumenten-electronica. In 1981 behaalde hij het propedeutisch diploma in de psychologie aan de Katholieke Universiteit Brabant (voorheen Katholieke Hogeschool Tilburg), als opmaat voor de studie geneeskunde in Maastricht. Deze werd in 1988 afgerond met het behalen van het basisartsgetuigschrift.

Van 1988 tot 1992 werkte hij als medisch supervisor en projectleider aan het Instituut voor Geneesmiddelen, Veiligheid en Gedrag (IGVG, tegenwoordig het *Institute for Human Psychopharmacology*, IHP). Vanaf 1992 is hij verbonden aan de vakgroep Psychiatrie en Neuropsychologie, sectie Neuropsychologie en Psychobiologie, aanvankelijk als toegevoegd onderzoeker en vanaf november 1995 als universitair docent. Hier geeft hij mede leiding aan de Maastricht Aging Study, een longitudinaal onderzoeksprogramma naar determinanten van cognitieve veroudering.

Martin van Boxtel is getrouwd met vertaalster Paulien Copper en heeft twee kinderen, Lotte (1991) en Simon (1994).

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List of publications

Articles

- Adam, J. J., Teeken, J. C., Paas, F. G. W. C., van Boxtel, M. P. J., Houx, P. J., & Jolles, J. Effects of age and gender on performance in a spatial precuing task. Submitted for publication.
- Algera, M., Nijhuis, F., van Boxtel, M., & Jolles, J. Unemployed workers: have they a poorer experienced health? Submitted for publication.
- Buntinx, F., Knottnerus, J. A., Jolles, J., van Boxtel, M. P. J., Muris, J. W. M., Schouten, H. J. A., & Höppener, P. (1994). Dementia in general practice: incidence, prevalence, social prevalence and co-morbidity. *Archives of Public Health*, 52, 475-487.
- Martens, M. F. J., Nijhuis, F. J. N., van Boxtel, M. P. J., & Knottnerus, J. A. (1995). Flexibele arbeidsomstandigheden en gezondheidsklachten. *Gedrag en Organisatie*, 1, 50-59.
- Martens, M. F. J., Nijhuis, F. J. N., van Boxtel, M. P. J., & Knottnerus, J. A. Flexible working conditions and mental and physical health. Submitted for publication.
- Riedel, W. J., Peters, M. L. A., van Boxtel, M. P. J., & O'Hanlon, J. F. The influence of piracetam on actual driving behaviour and postural stability of elderly subjects. Submitted for publication.
- Teeken, J. C., Adam, J. J., Paas, F. G. W. C., van Boxtel, M. P. J., Houx, P. J., & Jolles, J. (1996). Effects of age and gender on discrete and reciprocal aiming movements. *Psychology and Aging*, 11, 195-198.
- Van Boxtel, M. P. J. (1997). Book review 'Behavioural gerontology' by D. B. Bromley. *Journal of Chemical Neuroanatomy*, 12, in press.
- Van Boxtel, M. P. J., Buntinx, F., Houx, P. J., Metsemakers, J., & Jolles, J. The relation between morbidity and cognitive performance in a normal aging population. Submitted for publication.
- Van Boxtel, M. P. J., Gaillard, C., Houx, P. J., Buntinx, F., de Leeuw, P. W., & Jolles, J. Can blood pressure predict cognitive task performance in a healthy population sample? Submitted for publication.
- Van Boxtel, M. P. J., Gaillard, C., Houx, P. J., Buntinx, F., de Leeuw, P. W., & Jolles, J. Is cognitive impairment related to a reduced nocturnal blood pressure drop? Submitted for publication.
- Van Boxtel, M. P. J., Gaillard, C., van Es, P. N., Jolles, J., & de Leeuw, P. W. (1996). Repeated automatic versus ambulatory blood pressure measurement: The effects of age and sex in a normal ageing population. *Journal of Hypertension*, 14, 31-40.
- Van Boxtel, M. P. J., Langerak, K., Houx, P. J., & Jolles, J. (1996). Self-reported physical activity, subjective health, and cognitive performance in older adults. *Experimental Aging Research*, 22, 363-379.
- Van Boxtel, M. P. J., Paas, F. G. W. C., Houx, P. J., Adam, J. J., Teeken, J. C., & Jolles, J. (1997). Aerobic capacity and cognitive performance in a cross-sectional aging study. *Medicine and Science in Sports and Exercise*, in press.

Book sections

- Buntinx, F., Knottnerus, J. A., Metsemakers, J., van Boxtel, M. P. J., & Jolles, J. (1995). The Registration Network of Family Practices and cognitive aging research. In J. Jolles, P. J. Houx, M. P. J. van Boxtel, & R. W. H. M. Ponds (Eds.), *The Maastricht Aging Study: Determinants of cognitive aging*, (pp. 171-176). Maastricht: Neuropsych Publishers.
- Dijkstra, J. B., Houx, P. J., van Boxtel, M. P. J., & Jolles, J. (1997). An operation under general anaesthesia as a risk factor for age-related cognitive decline: Results from a large cross-sectional population study. In J. B. Dijkstra (Ed.), *An operation under general anaesthesia and cognitive ageing [Doctoral Thesis]*, (pp. 115-125). Maastricht: Neuropsych Publishers.
- Hogervorst, E., Riedel, W. J., Rozendaal, N., van Boxtel, M. P. J., & Jolles, J. (1995). Smoking and cognitive complaints. In J. Jolles, P. J. Houx, M. P. J. van Boxtel, & R. W. H. M. Ponds (Eds.), *The Maastricht Aging Study: Determinants of cognitive aging*, (pp. 105-110). Maastricht: Neuropsych Publishers.
- Houx, P. J., van Boxtel, M. P. J., & Jolles, J. (1995). Cognitive performance, age, and health-related factors. In J. Jolles, P. J. Houx, M. P. J. van Boxtel, & R. W. H. M. Ponds (Eds.), *The Maastricht Aging Study: Determinants of cognitive aging*, (pp. 95-103). Maastricht: Neuropsych Publishers.
- Jolles, J., Houx, P. J., van Boxtel, M. P. J., & Ponds, R. W. H. M. (Eds.). (1995). *Maastricht Aging Study: Determinants of cognitive aging*. Maastricht: Neuropsych Publishers.
- Jolles, J., van Boxtel, M. P. J., Ponds, R. W. H. M., & Houx, P. J. (1996). Veroudering van hersenfuncties en geheugen. In M. Santvoort & M. Spanjer (Eds.), *Ouder worden, gezond en wel*, (Vol. II, pp. 87-95). Utrecht: NIG.
- Paas, F. G. W. C., Adam, J. J., Teeken, J. C., Verstappen, F., van Boxtel, M. P. J., Houx, P. J., & Jolles, J. (1995). Vitality and cognitive aging. In J. Jolles, P. J. Houx, M. P. J. van Boxtel, & R. W. H. M. Ponds (Eds.), *The Maastricht Aging Study: Determinants of cognitive aging*, (pp. 127-132). Maastricht: Neuropsych Publishers.

Van Boxtel, M. P. J., Gaillard, C., de Leeuw, P. W., & Jolles, J. (1995). Habitual blood pressure and cognitive performance. In J. Jolles, P. J. Houx, M. P. J. van Boxtel, & R. W. H. M. Ponds (Eds.), *The Maastricht Aging Study: Determinants of cognitive aging*, (pp. 119-125). Maastricht: Neuropsych Publishers.

Abstracts

- Adam, J. J., Teeken, J. C., Paas, F. G. W., van Boxtel, M. P. J., Houx, P. J., & Jolles, J. (1994). Aging-effects in a spatial precuing task. *Journal of Sport and Exercise Psychology*, 16, S25.
- Adam, J. J., Teeken, J. C., Paas, F. G. W. C., Bostel, M. P. J. v., Houx, P. J., & Jolles, J. (1994). Effect of age on speeded performance in a 4-choice reaction time task: The bowed serial position effect. *Journal of Sport and Exercise Psychology*, 17, S19.
- Hogervorst, E., Riedel, W., van Boxtel, M., Visser, P., Hameleers, P., Sey, S., & Jolles, J. (1996). Hypoxia and hyperventilation as models for cognitive deficiencies. *European Neuropsychopharmacology*, 6 (Suppl 3), 145.
- Houx, P. J., Ponds, R. W. H. M., van Boxtel, M. P. J., & Jolles, J. (1996, 25-28 April). *Maastricht Aging Study (MAAS): Five-years follow-up of the first cross-sectional study*. Poster presented at the Cognitive Aging Conference, Atlanta, GA. Abstractno. II-36.
- Jolles, J., Houx, P. J., & van Boxtel, M. P. J. (1995, 23 March). *Determinanten van geheugenstoornissen bij ouderen*. Paper presented at the symposium 'Ouderen, wetenschap en beleid', Utrecht.
- Jolles, J., Houx, P. J., & van Boxtel, M. P. J. (1995, 30 August-2 September). *Individual patterns in cognitive aging: Results from a large cross-sectional population study*. Paper presented at the IIIrd European Congress of Gerontology, Amsterdam, Abstractno. 062-1111.
- Jolles, J., van Boxtel, M. P. J., & Houx, P. J. (1995, 30 August-2 September). *Health and cognition: Results from cognitive aging studies*. Paper presented at the Submitted Symposium on the IIIrd European Congress of Gerontology, Amsterdam.
- Teeken, J. C., Paas, F. G. W. C., Adam, J. J., van Boxtel, M. P. J., Houx, P. J., & Jolles, J. (1994). Effects of aging on movement time in discrete and reciprocal aiming tasks. *Journal of Sport and Exercise Psychology*, 16, S114.
- Van Boxtel, M. P. J. (1993, 1-2 April). *Somatische factoren en cognitieve veroudering*. Paper presented at 'De Geriatrische Reuzen', Retraite NWO dwarsverband Gerontologie en Geriatrie / NESTOR, Amersfoort.
- Van Boxtel, M. P. J. (1994, 23 June). *NMAP: het Maastrichtse verouderingsproject*. Paper presented at the Werkgroep Huisartsgeneeskundig Klinisch Epidemiologisch Onderzoek - Hakleon, KUL, Leuven (Belgium).
- Van Boxtel, M. P. J. (1996, 23 March). *Het brein en de gezondheid: bestaat er een recept voor 'succesvol' cognitief ouder worden?* Paper presented at the symposium 'Wat heet oud?', UBV, Utrecht.
- Van Boxtel, M. P. J., Houx, P. J., & Jolles, J. (1995, 30 August-2 September). *Health-related factors and cognitive aging*. Paper presented at the IIIrd European Congress of Gerontology, Amsterdam. Abstractno. 022-0311.
- Van Boxtel, M. P. J., & Jolles, J. (1994, 15 December). *Subjectieve gezondheid; de VOG-21 in NMAP*. Paper presented at the NESTOR Workshop 'Subjectieve Gezondheidsmeting', Utrecht.
- Van Boxtel, M. P. J., Langerak, K., Houx, P. J., & Jolles, J. (1994, 5-8 June). *Value of self-reported physical activity and perceived health as predictors of cognitive performance in healthy elderly*. Paper presented at the International workshop on the borderland between normal and pathological mental aging, International Psychogeriatric Association - IPA, Amsterdam.
- Van Boxtel, M. P. J., Gaillard, C., Houx, P. J., de Leeuw, P. W., & Jolles, J. (1996, 25-28 April). *The relation between habitual blood pressure status, 24-hour ambulant blood pressure and cognitive test performance in healthy adults*. Poster presented at the Cognitive Aging Conference, Atlanta, GA. Abstractno. III-49.

Registered research reports

- Ramaekers, J. G., van Boxtel, M. P. J., & O'Hanlon, J. F. (1992). *A study to compare acrivastine's and terfenadine's effects on several aspects of driving performance as a function of dose and time after dosing* (92-25). Maastricht: Institute of Human Psychopharmacology.
- Van Boxtel, M. P. J., De Silva de Freitas, C., & O'Hanlon, J. F. (1992). *The effect of diazepam on electrophysiological measures in an experimental model of human anxiety: A randomized, double blind, cross-over, placebo-controlled study* (92-08). Maastricht: Institute of Human Psychopharmacology.
- Van Boxtel, M. P. J., Robbe, H. W. J., Westerink, B. H. C., & O'Hanlon, J. F. (1990). *The effects of eltopazine and diazepam on aggressive and anxious arousal in healthy volunteers* (90-14). Maastricht: Institute of Human Psychopharmacology.