The Maastricht Aging Study:

Determinants of cognitive aging

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1 MAAS: rationale and objectives

1.1 Introduction

The Maastricht Aging Study is a series of related projects in the realm of cognitive aging. It is carried out at the Maastricht University, the Netherlands. This paper is an adapted version of two other sources (Jolles et al., 1995; Van Boxtel, 1997) and describes the rationale, objectives, design and the methods used in MAAS and describes the scientific background and research infrastructure.
MAAS started in 1991 with research grants from NESTOR (a steering group of the Dutch Government - Departments of Education and Science and the former department of Welfare, Health and Cultural Affairs) and the Maastricht University. The core study is a longitudinal study into cognitive aging, where biomedical, psychological and sociodemographical factors are studied in relation to neurocognitive functioning. With respect to biomedical factors special attention is paid to prevalent 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 is devoted to a description of rationale and research questions (paragraph 1), design (paragraph 2), methods used in postal survey (paragraph 3), and methods used in medical and neuropsychological assessment (paragraph 4).

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 their relative impact. What makes memory function decline? Why do some individuals show a greater decline than others? Over the past years, a host of factors, including biological, medical, psychological and social factors, have been studied that may have an influence on this cognitive decline. The aim of MAAS is to relate these factors in an integrative study of cognitive aging. This can only be achieved by studying large numbers of normal healthy adults of all ages and by monitoring them for several years, which is the ambitious core of the MAAS project. Pathological forms of aging (e.g. dementia or depression) are studied in the longitudinal follow-up program. Some individuals who were normal and healthy at the first measurement point will eventually show abnormalities. For this reason, MAAS intends to perform case-finding studies of pathological aging involving subjects with

well-documented histories of premorbid functioning. The longitudinal phase of MAAS will open the possibility to search for prodromes of dementia (more specifically, dementia of the Alzheimer type or vascular dementia), and other forms of psychopathology, such as depression.
Different individuals age in different ways. The decline may be sudden or gradual, invalidating or mild, and may occur at different moments. 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 performance variance.
Additional information was obtained from nearly 4,000 subjects by the use of postal surveys and questionnaires. The demographic, biomedical, psychological, and social information are related to the results from extensive neuropsychological testing. Four consecutive panel studies were performed (referred to as A1 to A4), each involving 440 to 480 subjects, stratified for age in 12 discrete age groups.
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 have participated in the main study. Other projects require subject sampling independent of the main study, e.g. as part of PhD projects that are supported by grants from the Maastricht University and from third parties. All studies focus on questions which are related to the rationale of the main study.

1.3 MAAS research questions

MAAS was devised 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, 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 envisage. In addition, 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.

Question 1. The first and probably most basic question of MAAS 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: be it a physical event, such as an infective disease or head trauma, or a psycho-social 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 because the 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 amassed effects result in perceivable cognitive deficits. Terminal drop would then only occur as a result of some major abnormality. This latter possibility is clearly the more optimistic one, as it paves the way to better cognitive functioning in later years. As yet, it is not known which of either possibilities, or some combination, is applicable.

Unfortunately, the majority of experimental cognitive aging research performed up till now has focused on performance differences between young adults (most often students) and elderly subjects. Consequently, the information on cognitive deterioration in middle age is incomplete. Yet, it is essential to study the ages between 30 and 60 in order to gain insight into functional development during adulthood and to determine when functions start to decline.

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 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 increases as the age of the group increases, causing the average group performance to be poorer. Incidentally, this would also result in a higher variance 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. A second research question can thus be formulated: 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 cognitive functions? This is unlikely, as it is known that memory is not a unitary function and that 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 can have a great impact on general cognitive functions, but there need not be any direct or causal relationship with cognitive performance. Any loss of memory may well lag 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) showed that the terminal drop phenomenon mentioned above might be 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 define the underlying, more specific predictors of cognitive trajectories.

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? There is a great lack of information 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? There is no systematic information about determinants of healthy and pathological cognitive aging in the literature, which makes it important to acquire more information on individual cognitive aging trajectories and the factors that mediate them (Rabbitt, 1990). This is particularly relevant because several studies have shown that some elderly subjects perform cognitive tasks as good as young adults. This raises the question about what determines successful cognitive aging or, conversely, what causes the majority of individual aging patterns to be less successful? What causes usual aging to be different from successful cognitive aging (Rowe & Kahn, 1987)?
Are there particular biological or psychosocial determinants of pathological cognitive aging ('risk factors') in normal, healthy individuals? Do the so-called Biological Life Events (BLE) play a role in this respect? BLE are health-related factors possibly associated with brain functioning (Houx, Vreeling & Jolles, 1991). Examples of BLE are psychoactive medication, alcohol use, head injury, and general anaesthesia. Most individuals are exposed to one or more of these factors during their life. Usually, however, the impact of BLE goes unnoticed by the individual, which is why their importance is rarely acknowledged by medical doctors. Thus, MAAS aims to identify the determinants of successful or less-than-successful cognitive aging and to evaluate the validity of the BLE concept.

Question 4. What is the relationship between complaints about cognitive abilities (particularly memory) and cognitive test performance? Several studies did not 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 (especially metamemory) and psychosocial variables seem to be related to the existence and maintenance of complaints about cognitive functioning. However, it must be realized that several psychometric tests used in clinical and experimental settings are not standardized, and that many tests have been developed or modified in recent years. Often, far-reaching conclusions are drawn on the basis of a particular aspect of the test performance of a neuropsychological patient. For this reason case-control studies and other patient-related research involving cognitive testing can gain greatly from

well-designed normative studies. A related question has to do with possibilities which 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 use of information or information technology by the elderly.
The questions outlined above can only be addressed in a large-scale study involving different age groups where the subjects are monitored over a considerable period of time, i.e. a longitudinal aging study. Essentially, MAAS is such a study. Cross-sequentiality and a study population with a wide age range is needed to gain information about a substantial proportion of possible aging trajectories. In MAAS longitudinal and cross-sectional methodologies are combined, dealing with the shortcomings of both in the best possible way.
The societal relevance of MAAS 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 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 in the next few decades. 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.

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 at baseline. Data were collected in four consecutive panel studies. These panel studies were virtually identical with respect to structure and organization. In the first panel study A1 (1993) agroup of 2,000 subjects received an extensive postal questionnaire. Of these 2,000 subjects, 480 were actually tested at the behavioral laboratory. Three additional experiments (A2 to A4) were subsequently executed, in which some individual data were to be collected by means of postal questionnaire, and other data by in-depth neuropsychological and medical assessment, 440 to 480 subjects per panel study.
The next section describes the procedure, design and methods of MAAS. Briefly, MAAS consists of four panel studies A1 to A4, and an extended postal survey study that was part of A1. Each of these studies was age-stratified in 12 discrete age groups (n=40) between 24 and 81 years. Each age group was 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 Maastricht University. This project should provide answers to most of the scientific questions underlying the research program

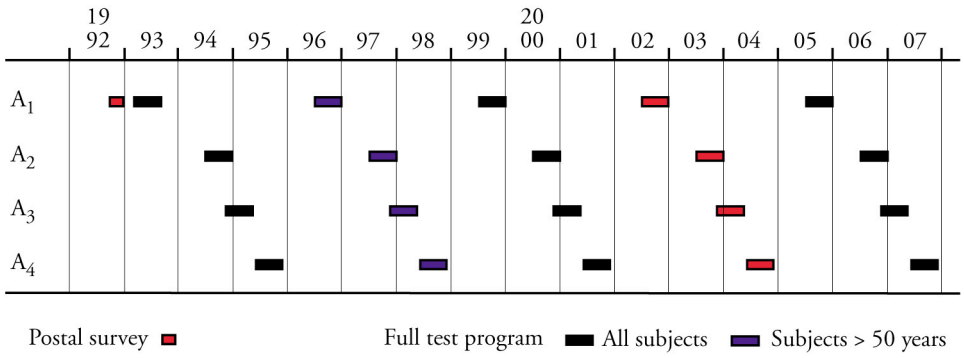
and in addition provide population norms for tests of memory and memory-related functions, for several medical tests, and prevalence estimates of risk factors and maintenance factors for (un-)healthy cognitive aging. A basic set of psychometric instruments and medical tests is used in all panel studies. The A-study was set up to meet the requirements for the longitudinal follow-up of all subjects participating in this project. The first 3-year follow-up of the A1 panel started in October 1996. The results from the A1 follow-up will help to define the necessary characteristics of the longitudinal phase of the study, which is planned to follow a cross-sequential design (see Figure 1 for a time schedule).

2 MAAS: study design

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 in the postal survey questionnaire and the test program can be found in the sections 3.3 and 3.4.
The cross-sectional phase of MAAS consists of four separate panel studies, A1 to A4. These studies share the same methodology with respect to sample frame, subject inclusion and 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 an equivalent of general ability (level of occupational activity, LOA; see section 2.5). The four panel studies have been executed between March 1993 and December 1995. The total number of subjects that proceeded to the follow-up phase was 1,823.
Follow-up assessments are made in the longitudinal phase. The frequency of follow-up depends on actual age, i.e. three years for subjects aged 50 years and older, and six years for younger subjects (baseline and first two follow-up waves). The third follow-up (9 years) consists of a full questionnaire survey. The total duration of the follow-up program is 12 years which will close with a full questionnaire survey and the final cognitive assessment in the laboratory. Figure 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 1. Timetable of the four MAAS panel studies and their successive follow-up measurements. Questionnaire (postal) surveys are always conducted in the full sample.



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 the 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. The subjects 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 is 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).

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. The request for participation in the study is made by an individual's general practitioner. This is expected to have a facilitative effect on compliance. In addition, it is possible to use RNH information to identify an eligible study sample beforehand. For instance, it is important to exclude subjects with morbidity that is known to interfere with cognitive function. Another advantage of RNH 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 dynamic RNH data base can facilitate case-finding in the longitudinal phase of MAAS.

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 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.

2.4 Procedure A1: Postal survey

MAAS study A1 consisted of two complementary projects: a postal survey which is described in the present section and that was followed by a cross-sectional test program described in the next section. This program involved extensive medical and neuropsychological screening of a subgroup that was recruited from the postal survey population. It is important to note here that the postal survey distinguishes panel A1 from other Ax panels. As discussed in section 3.1, in studies A2 to A4 the postal survey questionnaire was used only for subjects who participated 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 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 (2.3) as coded by the RNH reduced the group of eligible participants in the data base by 4 percent. This exclusion on medical grounds 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. For panel A1, all available subjects in the 85-year-age class were drawn from the RNH register.

Subjects were invited to participate in the study according to a standard RNH procedure. First, selected subjects were screened by the general practitioner for psychosocial reasons that precluded participation (e.g. experience of actual major life events); 5.0 percent (n=197) of the original selected population of 3,941 was excluded. Each general practitioner invited the selected patients in his or her practice to take part in the study personally. 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 percent) completed and returned the questionnaire in good order. Of this group, 61 percent (n=1,252) volunteered for the additional test program.

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, paragraph 3.3). The number of age classes was adjusted to 12 instead of 13 as only a very small percentage of subjects in the 85 year group was available and eligible for further examination. Stratification according to BLE status within each cell was performed in A1 only.

The subjects were assigned to two levels of occupational activity (LOA). LOA was based on a 7-point scale which estimates the highest level of professional activity (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 dichotomous classification of LOA was based on a median-split of the postal survey data (1-3 low, 4-7 high). The choice for LOA as an estimate of general ability (or 'intelligence'), instead of the more widely used educational level, is discussed in more detail in Jolles et al. (1995, pp. 69-71).

The subjects who agreed in the postal survey questionnaire to participate in further studies were contacted by telephone, who explained 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 (2.3). In particular, all RNH exclusion criteria used in the sampling procedure were checked again, this time in more detail, and the MMSE was administered. Finally, several tests were performed to screen for primitive reflexes (paragraph 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. Eighty-five subjects (12.5 percent) were excluded for medical reasons, particularly in the older age groups. 121 subjects (18.1 percent) 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 at this stage was the expected personal investment in time and effort.

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. Potential differences must be taken into consideration with respect to the external validity of findings in MAAS research. Particular variables of interest are age, sex, educational level, and general health status, operationalized as the total number of health problems.

To study the relation between background characteristics and participation in the A1 study, age was collapsed into 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, but 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 trend was observed, although the differences were less profound.

Participation was strongly influenced 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 (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 influence 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, reflecting somewhat more active problems in the not-selected group ($p < .01$, Mann-Whitney U-Test). However, 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 more elaborate discussion).

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

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 considered 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 useful estimation of the prevalence of BLE was not available until A1 had been completed. Despite ample subject sampling in A1 no satisfactory 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, the home visit prior to the test program was skipped in panels A2 to A4. Administration of the postal questionnaire in these panel studies was restricted to only those subjects who actually participated in the test program. Therefore, postal questionnaire and test program were merged into one functional unity from A2 onward.

Participants in the A2 to A4 test programs were again randomly recruited from the RNH data base (paragraph 2.2). They were stratified for age and sex, using the same procedure and medical exclusion criteria as described for A1 (paragraph 2.3 to 2.5). On the basis of compliance and exclusion rate data from A1 and later studies, an estimation 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 round 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 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 first two panel studies. The possibility to recruit subjects from other population samples (e.g. non-RNH general practices) was considered unsatisfactory for 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.

Compliance rate for the A1 postal survey was twice as high than the compliance rate for questionnaire and test program in A2-4 combined (59.2 percent and 30.2 percent, respectively). However, a much larger proportion of volunteers for the A1 test program withdrew after telephone contact (17.2 compared to 10.0 percent in other panel studies).

3 METHODS I: Postal survey

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 (paragraph 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 (see paragraph 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 (paragraphs 3.2 to 3.6, respectively). The questions that were used in the survey were mainly derived from existing and validated questionnaires. The quality of the questionnaire in terms of clarity and optimal length was evaluated in a pilot study with 80 older volunteers. The final version contained approximately 500 data fields in a 32-page booklet. The paragraphs 3.2 to 3.6 provide more information about each of the five main topics in the postal survey questionnaire.

3.2 Demographic variables

This section contains questions about subject parameters. 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 American and British scientific literature in this respect. 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.

Special attention was paid to the level of occupational activity (LOA) of the participants (see also paragraph 2.5). For this purpose, the type of occupation was given a 4-digit code, based on a functional description of the profession (CBS, 1985), which was transformed to a 7-point score (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 work. The LOA scale was originally developed as a guideline for employment and careers counselling (DGA, 1989).

3.3 Biological Life Events (BLE)

The concept of BLE and its relevance for MAAS was explained 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, use of psychoactive medication, alcohol or drug abuse, neurotoxic factors, treatment by a psychiatrist (within past five years), and perinatal or developmental complications (Jolles et al., 1995, pp. 40-41).

3.4 General health

Questions regarding past and present morbidity that might have relevance for cognitive functioning were derived from a medical screening questionnaire commonly used in general practice (LHV, 1981). Several items were included 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 its pharmacological characteristics and side-effects (custom classification, based on Dukes, 1988; Dukes & van Dijke, 1984).

The subjects were asked to rate their overall health on a 5-point scale; 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 VOEG-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 abilities, and health services consumption, including the use of alternative health care.

3.5 Lifestyle and psychological health

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

Several other psychosocial variables may play a mediating role in determining the presence or absence of complaints about cognitive functioning in later life, in addition to mood and health. The questionnaire covers the following psychosocial domains: daily activities (expressed as hours devoted to, e.g.

watching television, reading, and sports), experienced life-events in the past year, and quality of life / life-satisfaction.

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 when they were 25 years of age. The fact that subjects note a change in their cognitive functioning does not necessary 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 the way in which 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 ones 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).

3.7 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 about health-related life styles, health-related locus of control, and about ones expectations of medical services in case complaints about 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.

4 METHODS II: Test program; medical and neurocognitive assessment

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), used as a screening instrument 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 index 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 and auditory acuity).

Of course, the majority of the dependent variables in MAAS are 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 Ax-studies. The first of these is made up by those tests that are administered (at least once) in every parallel study. They constitute a leitmotiv of domains of cognitive functioning that are probed in MAAS and MAAS-related projects, but also 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. These tests are administered again at follow-up measurements (category 1 tests in Table 1). One typical example is the Verbal Learning Test, a ubiquitously 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 1).

The third category of tests (category 3 in Table 1) are under development and are administered only to a subsample of one or two Ax studies. Based 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).

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 A2 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 using the Landolt-C optotype chart, at a distance of five meters, under standard luminescence and with corrected vision.

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, using an automatic recording device (Critikon Dinamap 8100). In A2, 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).

Degree of hearing loss is assessed at four different frequencies that are important for adequate speech perception, using 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 tone detection thresholds. The rationale to assess perceptual acuity is the observation that hearing defects may cognitive outcome (Rabbitt, 1991; Van Rooij & Plomp, 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 between the prevalence of specific BLE (in particular general anesthesia and the use of psychotropic medication) (Vreeling et al., 1993).

4.3 Cognitive variables: description of core tests

Mini Mental State Examination (MMSE). As MAAS is a study into cognitive aging and dementia, and a large number of elderly subjects will be examined, it was considered important to use an internationally accepted dementia screening instrument. The Mini-Mental State Examination was chosen for this purpose (Folstein et al., 1975), 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

cognitive or psychometric qualities. Conclusions about the cognitive functions studied will therefore not be based upon items from this test, but on specific tests for the specific functions probed. 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), which is well-known in the Netherlands, is an adapted 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 recall as many words as possible. This procedure is repeated five times. After 20 minutes, delayed recall and recognition are tested. 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), also known as a coding task, is a modification of the procedurally identical Symbol-Digits Modalities Test (SDMT, see Lezak, 1983, pp. 554-555; Smith, 1968). In neuropsychological assessment, this test is an often used 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 can be 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 is to name as many four-letter words starting with a given letter ('M' and 'S') as possible.

Concept Shifting Test (CST). The well-known Trail Making Test (TMT) 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 circumvent several methodological problems with the TMT. On each test sheet, 16 small circles (diameter 15 mm) are grouped in a larger circle (diameter 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 to complete the tasks is recorded.

The **Stroop Color-Word Test** (SCWT) has often been used to test selective attention (e.g. Houx, Jolles & Vreeling, 1993). The test involves three cards which display a hundred stimuli each: color names, colored patches, and color names printed in incongruously colored ink (cards 1-3, respectively). The amount of time needed to read (card 1 and 3) or to name colors (card 2) is recorded. Performance on card 3 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), also 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 speed test, it is typically a 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, as they are, as a rule, not presented in the proper orientation. Although there is a time limit, this is not a speed test since most subjects do not need less than half the time allotted per item. Apart from mental rotation, this subtest also heavily draws upon constructive abilities.
- Analogies ['Woordmatrijzen'] (GIT4) can be regarded 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 more crystallized than fluid.

An overview of all cognitive tests that were used in MAAS panel studies A1 to A4 in one or more panel studies is given in Table 1. An more elaborate description of each test is given in Jolles et al. (1995).

Table 1. Neurocognitive test that were used in one or more Ax-studies.

Test	Abbrev.	Category	A1	A2	A3	A4
Aufmerksamkeits-Belastungstest	D22	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	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	LDTS	1	+	+	+	+
Letter-Digit Substitution Test - rotated	LDST-R	2	-	-	-	+
Lexical Decision Task	LDT	3*	-	-	-	+
(Hypersensitivity to) Light and Sound	HLS	2*	-	-	-	+
Line Bisection Test	LBT	2*	-	-	+	-
Logical Memory test	LM	2*	-	+	-	-
Memory Scanning Test	MST	1	+	+	+	+
Memory Scanning test Shadows and Cubes	MST S&C	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 Test	RMT	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	+	-	-	-

Notes. (a) Category: 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. (b) Exception: core test not included in all follow-up measurements.

4.4 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 subjective well-being (Pavot, Diener, Randall Colvin & Sandvik, 1991).

Positive and Negative Affect Schale (PANAS; A1). A 20-item mood scale that measures positive (10 items) and negative affect (10 items) (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.

The **RAND-36** is a general health questionnaire (A3-4). 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 (A2-4). 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 designed about 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 (A3-4). 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 (un-)happiness and of low scores on, for instance, the Satisfaction With Life Scale (SWLS).

4.5 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, Maastricht University), where all data are stored in a relational database (RCAD, Register of Cognitive Aging and Dementia). RCAD was implemented with RDB on a DEC-Alpha mini-computer, using a client-server concept. Data security is safeguarded by using username and password protection. Researchers who want to consult raw data from RCAD need to seek permission from the register team. After approval is obtained, the data blocks are delivered by the coordinator of the register as computer files that are ready-to-be-used in standard statistical packages. Data dictionaries can be consulted by researchers via the internet, or can be made available as a hard copy.

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

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