Vulnerability factors for age-related cognitive decline

The Vulnerable Brain and Environmental Risks

Volume 3
Toxins in Air and Water

Edited by

Robert L. Isaacson
Binghamton University
Binghamton, New York

and

Karl F. Jensen
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina

Plenum Press • New York and London

Library of Congress Cataloging in Publication Data

(Revised for vol. 3)
The Vulnerable brain and environmental risks.
Includes bibliographical references and index.
Contents: v. 1. Malnutrition and hazard assessment—v. 2. Toxins in food—v. 3. Toxins in air and water.
1. Neurotoxicology. 2. Neurotoxicology—Environmental aspects. I. Isaacson, Robert L., 1928– . II. Jensen, Karl F. [DNLM: 1. Environmental Exposure. 2. Nervous System Diseases—chemically induces. 3. Neurotoxins. 4. Protein-Energy Malnutrition—complications. WL 100 V991]
RC347.5.V85 1992 616.8 92-49396
ISBN 0-306-44611-1

ISBN 0-306-44611-1

Chapter 2

Vulnerability Factors for Age-Related Cognitive Decline

Peter J. Houx and Jellemer Jolles

1. INTRODUCTION

It is quite firmly established that virtually all aspects of cognitive functioning deteriorate as age advances. The literature on age effects on cognition is expanding rapidly. Among others, Birren and Schaie (1985, 1990), Charness (1985), and Poon (1985) give excellent overviews. Normal aging people experience a range of cognitive impairments. The acquisition of new information is less efficient, an attrition that, coupled with a diminished retention of that information for later use, results in substantially poorer memory performance (Jolles, 1986). Also, planning of new activities, problem-solving, and complex decision-making, as well as flexibility, are noticeably diminished. Attentional processes appear to be invariably poorer in old subjects. In addition, there appears to be a general slowness, especially in the performance of tasks that have to be carried out either under time pressure or in demanding situations or both. At the root of this slowness, in turn, may be a general physiological slowing of the central nervous system (Botwinick, 1984).

However, from the fact that variability of performance in cognitive tests increases with age, we also know that not all individuals show decline at the same rate. Is general cognitive decline really something that all aging subjects are up against? In other words, is cognitive aging an inherent aspect of physiological aging, or are additional

Peter J. Houx and Jellemer Jolles • Department of Neuropsychology and Psychobiology, University of Limburg, 6200 MD Maastricht, The Netherlands.

The Vulnerable Brain and Environmental Risks, Volume 3: Toxins in Air and Water, edited by Robert L. Isaacson and Karl F. Jensen. Plenum Press, New York, 1994.

factors—i.e., biological or psychosocial factors or both—also responsible for cognitive aging? There is a shortage of data on individual patterns of cognitive aging (Rabbitt, 1990). This lack is especially evident in view of several studies showing that some of the elderly are not inferior in cognitive performance compared to normal young adults. This leaves us the question: What determines this successful cognitive aging or, conversely, what causes the majority of individual aging patterns to be less successful? What causes usual aging to be distinguishable from successful cognitive aging (Rowe and Kahn, 1987)?

The majority of the research performed in the realm of memory and aging has been based on the premise that the changes in memory with age are a corollary of the physiological aging process. Several terms have been proposed to define the condition in subjects who complain of deterioration of memory and memory-related functions. Crook *et al.* (1986) defined a condition named *age-associated memory impairment* (AAMI). They proposed diagnostic criteria that would also serve research purposes. A subject meeting these criteria would be characterized by—among other things—an absence of medical conditions involving the brain, which would imply that AAMI can be subsumed under normal aging. However, the fact that AAMI is by definition age-associated leaves room for the supposition that it is by no means inherent to age. This chapter aims at proving exactly that it is not.

1.1. Health-Related Factors in the Normal Population: Introduction to the Concept of Biological Life Events

It is only recently that some interest has arisen in health-related factors in relation to cognitive aging. Until a few years ago, there were no published reports on the possibility that subtle health-related factors might influence cognition and that these health effects might aggravate the age-related cognitive decline. Of course, cognitive dysfunctions in relation to well-established disease states such as moderate to severe brain trauma, depression, and chronic alcoholism are well documented. However, the issue we are especially interested in is whether conditions with unknown or ambiguous relation to brain and cognitive (dys)function—such as very mild closed head injury (CHI), social drinking, increased blood pressure, anesthesia, or diabetes mellitus—have some influence on cognitive functioning.

Recently, the term *biological life events* (BLEs) was proposed (Houx *et al.*, 1991a,b) to define

> those factors which are related to physical or mental health, experienced at any point in life and thought to be related to brain dysfunctioning, other than grossly impairing conditions like dementia and brain trauma.

Elias *et al.* (1990) found main effects of hypertension on performance on a neuropsychological test battery. Hartman (1988) reviews reports on the neuropsychological side effects of several anesthetics. Evidence that long-term performance decrements in aging subjects is attributable to anesthetics is inconclusive. Jones *et al.* (1990) found no significant effects at 3 months after operation. Their methods of testing, however, can be said to be rather insensitive. Regarding mild brain trauma, or CHI, an increasing number of reports are suggestive of mild interactions with cognitive func-

tioning (Binder, 1986). Little is known, however, about interactions with the effects of aging. A similar issue pertains to the effects of mild to moderate alcohol consumption, i.e., individuals who cannot be assumed to be alcoholic (e.g., Hartman, 1988). A wide variety of systemic diseases (e.g., see Knoefel and Albert, 1985) can lead to dementia. Medication constitutes another important area of possibly brain-damaging factors (Hartman, 1988). Many elderly subjects receive sleep medication as soon as they complain about insomnia, yet these factors are rarely considered in usual cognitive aging research. Finally, during their lives, individuals can be exposed to a whole array of neurotoxic agents, the core issue of this book. Table I summarizes the health-related factors that were proposed by Houx *et al.* (1991a).

From Table I, it can be concluded that not all BLEs are as discrete as the word "event" suggests. In fact, most BLEs can be thought of as being of wholly or partly continuous nature. We do not claim, therefore, any lasting validity for the term, and would welcome a more appropriate expression.

It can safely be said that subtle health-related factors are of great importance in cognitive aging. Presumably, these factors are not severe enough to cause any acute or perceivable trouble for the individual, but they still must have some impact on brain functioning. Health cannot be considered as some random error source in aging studies that can be expected to level out given large enough numbers of subjects. If health indeed plays a causative role in the concept of successful aging proposed by Rowe and Kahn (1987), it is inextricable from all aging research. In the vast majority of cognitive aging research, elderly individuals who volunteer for an experimental study are assumed to be "healthy and normal" subjects. Usually, the experimenters content themselves with asking their subjects whether they are healthy; occasionally, researchers let their volunteers rate their own health status. Accurate screening for health factors is thus very rare indeed.

In this chapter, we want to summarize a number of studies we presented on a large, cross-sectional study on the interactions between calendar and BLEs in their effect on cognitive aging (Houx *et al.*, 1991a,b, 1993; Houx and Jolles, 1993). In these studies, we discussed in detail age by BLE interaction effects on one single cognitive function, often examined with one single test. The remainder of this chapter will be

TABLE I. Factors Associated with Brain Dysfunctions or Cognitive Decline or Both: Biological Life Events (BLEs)[a]

1. Present or past treatment by a neurologist for transient ischemic attacks, epilepsy, migraine, meningitis, encephalitis, brain trauma, or other brain condition.
2. Present or past treatment for diseases with possible repercussions on the brain (e.g., renal dysfunction, diabetes mellitus, thyroid dysfunction), excluding hypertension.
3. More than three concussions, or one with a posttraumatic amnesia of more than 1 hr.
4. General anaesthesia more than three times or one time for more than 3 hr.
5. Use of medication that affects driving ability or consciousness;
6. Alcohol abuse (i.e., more than 35 glasses per week for men or 21 for women).
7. Other neurotoxic factors, such as exposure to organic solvents or substance abuse.
8. Present (or less than 5 years past) treatment by a psychiatrist.
9. Complications at birth or developmental problems in early childhood.

[a]Adapted from Houx *et al.* (1991b).

devoted to discussing these findings more generally, and beyond the single function–single test paradigm.

2. METHOD

2.1. Subjects

Volunteers who were normal and healthy and regarded themselves as such served as subjects. It appeared that most applicants were unaware of possible or real threats to the healthy functioning of their brains. More than a hundred applicants were excluded who, on being asked, reported major brain damage by trauma, stroke, disease, or poisoning, or who reported a major psychiatric illness known to be characterized by cognitive deficits; nonetheless, they judged themselves to be healthy and normal. Elderly people, especially those living in old people's homes, were over-represented in the group of subjects who had experienced BLEs. A total of 247 subjects were eventually preselected and tested. Prior to the actual examination, the subjects were once again screened for evidence of brain damage. Nine additional subjects did not pass this screening: six subjects were mildly demented, as assessed by the Mini Mental State Examination (MMSE) (Folstein *et al.*, 1975), with a score of less than 24; two subjects appeared to have had a major head injury resulting in persisting cognitive dysfunctions; and one subject had forgotten to mention a brain tumor. If doubt existed about the accuracy of the subjects' recollection of the events, their medical files could be consulted. Also, it was often possible to gather data provided by relatives to confirm the subject's statements. Thus, we had a large group of selected subjects (247) without any *a priori* likelihood of brain dysfunction or cognitive dysfunction attributable to a major neurological or psychiatric illness.

Care was taken to balance the level of education in each cohort. For this purpose, we used a scoring system originally developed for the Netherlands by Verhage (1964) and adapted in 1980: a 7-point scale, ranging from unfinished primary education (1) to master's degree (7).

Scoring and cutoff values are discussed in detail by Houx *et al.* (1991a). Subjects who were characterized by one or more BLEs were assigned to one of seven BLE groups with mean ages ranging from 20 to 80 years. Subjects without any BLEs were assigned to a corresponding optimally healthy age group. For the age groups of 70 and 80 years, the number of BLE-affected volunteers exceeded our testing capacity, so that we had to conduct an initial telephone interview about BLEs prior to the testing. About another 50 volunteers were excluded at this stage.

2.2. Recording Background Variables

In the age groups of ± 60, ± 70, and ± 80, a number of personal variables regarding daily activities were scored apart from the common demographic variables of age, gender, and education, and apart from the BLEs. These variables included: time

TABLE 2. Background Variables That Were Associated with Biological Life Events (BLEs): Frequencies

	Sports			Reading			Puzzles			Hobbies		
BLEs[a]	0	1	All	0	1	All	0	1	All	0	1	All
Time spent in activity[b]												
0 (None)	15	22	37	2	2	4	6	19	25	6	8	14
1 (Little)	10	16	26	10	21	31	8	9	17	5	14	19
2 (Average)	12	8	20	17	16	33	18	11	29	9	11	20
3 (Much)	29	6	35	37	13	50	45	19	64	33	12	45
All	66	52	118	66	52	118	77	58	135	53	45	98
X^2	17.2, $p < 0.001$			13.99, $p < 0.01$			16.86, $p < 0.001$			19.05, $p < 0.001$		

[a]BLEs: (0) BLEs absent; (1) BLEs present.

[b]Category: amount of time spent in activity (0 - none at all; 3 - much). See Section 3.2 for a more precise description of the category boundaries.

spent watching TV, reading, taking part in clubs or organizations, sports, "mental" games such as brain teasers, crosswords, chess, or bridge, and other hobbies, not including the activities already mentioned. This was done following a suggestion by Salthouse *et al.* (1988) regarding interactions between the effects of age and background variables on cognitive performance. They did not find many of these interactions, nor did they find interactions between age and health-related factors.

Salthouse and co-workers gave very precise measures of hours per week engaged in some activity. Unfortunately, no detailed information was provided as to how these measures were obtained; the subject completed a questionnaire. We found it virtually impossible to obtain reliable written self-estimated ratings about any subject variable. This obstacle was circumvented by providing the subject with some broader categories and letting him indicate which categories his activities belonged in. These six category ratings were used for subsequent analysis. To make the estimations easy for the subjects, they were asked to estimate how much time was spent per day (reading, TV, puzzles) or week (sports, club, hobbies). Ratings per day were multiplied by seven. The category boundaries were set arbitrarily (see Table 2) since, apart from anecdotal evidence, little is known about how older, community-dwelling people spend their time.

2.3. Neuropsychological Tests

A battery of neuropsychological tests was used. These tests included:

1. *Digit Span Test (DS).* As part of the most frequently used test for general intelligence (WAIS) (see Lezak, 1983, p. 268), DS aims at assessing primary or short-term memory.
2. *Memory Scanning Test (MST).* This test was designed to measure the speed at which search processes occur in primary memory (Houx *et al.*, 1991a). The MST consists of a number of subtests, involving the crossing out of one or more target letters, disregarding distractor letters. The time needed to complete a subtest is

recorded as a function of the number of letters that are to be memorized and crossed out.

3. *Visual Verbal Learning Test (VVLT).* This is a computerized, visual version of a test of secondary memory (Lezak, 1983, p. 424). In five consecutive trials, a list of 15 words is to be memorized and reproduced. Leaving out the often-administered distraction trials, the VVLT also involves delayed recall and recognition, thus enabling the measurement of memory storage as well as retrieval.
4. *Stroop Color-Word Test (SCWT).* The SCWT is a well-known test for the ease of shifting perceptual sets to conform to changing task requirements (Lezak, 1983, pp. 523–525). It is also often used to test attention. In one condition of the SCWT, 100 color names are printed on cardboard in incongruously colored ink. For instance, the word "green" is printed in red ink. The color of the ink is to be named, a process that is far less automatized than reading and therefore takes much longer to complete.
5. *Concept Shifting Test (CST).* This test is derived from the Trail Making Test, which has long been used to measure the ease of shifting between concepts in ongoing behavior (see Lezak, 1983, p. 557). There are three task conditions. In our version, the subject has to cross out in the proper order 16 circles with only digits (from 1 to 16), letters (from A to P), or both (1-A-2-B, etc.). In the latter subtest, one has to shift between the concepts "letters" and "digits." The percentage of extra time needed for this is taken to denote the relative slowing due to "shifting concepts."
6. *Tapping Test.* Finger-tapping is an often-assessed simple aspect of psychomotor performance (e.g., see Lezak, 1983, pp. 562–566). We used a computerized version, allowing the measurement of the decline of the tapping rate during 20 sec.
7. *Motor Choice Reaction Test (MCRT).* We recently presented the MCRT for clinical purposes to test the cognitive aspects of motor initiation and response preparation (Houx and Jolles, 1993). The slowing of motor reaction times in a cognitively complex condition is compared to that in a simple condition, as an expression of the cognitive effort involved in preparing a motor response.

3. RESULTS

In this section, we summarize some findings we have discussed in detail in other publications (Houx *et al.*, 1991a,b, 1993; Houx and Jolles, 1993). Findings in which test outcomes and background variables (see Section 2.2) are interrelated were published by Houx (1992).

3.1. Prevalence of Biological Life Events

Table 3 summarizes the outcomes of the screening for BLEs that preceded each examination. At first glance, Table 3 shows that no clear age trends were observed regarding any of the BLEs. Within the BLE group, there was no significant linear relationship between age and the number of BLEs a subject had experienced. There

TABLE 3. Numbers of Biological Life Events (BLEs) in the BLE-Affected Group[a]

BLE	Age group							
	20	30	40	50	60	70	80	All
1. Neurology	1	4	2	6	7	9	5	34
2. Systemic disease	2	1	2	5	7	5	2	24
3. Closed head injuries	0	1	3	3	6	0	3	16
4. Anesthesia	1	2	6	7	13	8	9	46
5. Medication	2	2	4	3	7	9	9	36
6. Alcohol	3	2	4	1	6	2	1	19
7. Neurotoxic factors	1	3	1	0	2	3	2	12
8. Psychiatry	2	2	5	4	5	5	4	27
9. Birth/developmental complications	3	4	3	4	4	1	3	22
Mean number of BLEs/subject	1.7	2.3	2.5	2.2	3.8	2.5	1.9	2.4
Number of subjects	31	29	34	35	35	42	41	247
Subjects with BLEs	9	9	12	15	15	17	20	97
Percentage of subjects with BLEs	29%	31%	35%	43%	43%	40%	49%	39%

[a]Subjects can be characterized by the presence of more than one BLE. See Sections 1.1 and Table 1 for further information about each BLE.

seems to be an increase in the age groups until ± 60 years of age, and a decrease in the groups aged 70 or 80. Possibly this is a "survivor effect": Older subjects, who have sustained many subtle health factors, may have died, or have become demented, or be less likely to volunteer for some other reason connected to the BLEs. This question cannot be answered by the present study.

The absence of any clear age differences also applies to the separate BLEs. Of those BLEs that could be quantified, three were significantly related to age: medication ($r = 0.31, p < 0.001$), alcohol ($r = -0.28, p < 0.001$), and CHI ($r = -0.167, p < 0.01$). The other quantitative measure (anesthesia) was not related. Although these correlations are significant, age has little predictive value for BLEs; only very small proportions of variance are explained by age. The trends for alcohol and CHI appeared to be negatively correlated with age, supporting the "survivor" hypothesis; conceivably, high alcohol consumption or many head injuries are associated with a reduced (healthy) life span. If this is indeed the case, it might affect the number of elderly volunteers affected by these BLEs.

Table 4 presents the mean values per age group of the quantifiable BLEs. For instance, the BLE-affected 20-year-old subjects took an average of 0.3 different medications on a regular base, whereas subjects aged 70 in the same group took as many as 3 different types of medication. It can be observed that the occurrence of no single BLE appeared to be linearly related to age.

In summary, then, analysis of the occurrence of BLEs in the present sample showed that the likelihood of having experienced at least one BLE increased markedly with age. However, there was no clear relationship between age and the number of BLEs experienced. Nevertheless, the usual implicit or explicit assumption that the health status of elderly volunteers is equal to that of young subjects was not confirmed by the present study. There was a relationship between the level of cognitive activity regularly engaged in and BLEs in elderly subjects: Those subjects who spent little time

TABLE 4. Mean Values of Quantifiable Biological Life Events (BLEs) in the BLE-Affected Group

	Age group						
BLE[a]	20	30	40	50	60	70	80
#Anesth	3.0	2.1	3.1	4.7	5.0	3.2	2.9
#CHI	0.2	0.9	1.0	1.1	1.9	0.2	0.7
#Alcohol	24.9	16.0	20.9	16.7	12.4	4.0	16.2
#Medic	0.3	0.6	0.7	0.5	0.9	3.0	2.2

[a](#Anesth) Weighted score of general anesthesia; (#CHI) weighted score of closed head injuries; (#Alcohol) score of weekly alcohol consumption; (#Medic) number of different medications taken regularly.

in cognitively demanding activities were significantly overrepresented in the BLE-affected subgroup.

3.2. Background Variables

No age differences were observed in this subgroup of subjects. They are therefore treated as a homogeneous group as for age. The BLE-affected subjects differed on some activities from their unaffected peers. This is shown in Table 5. BLE-affected subjects spent significantly less time in sports, reading, puzzles, and hobbies. The other two variables, participation in clubs or organizations and watching TV, showed no difference between the two groups.

At present, it cannot be stated whether there is any causal relationship between a lower level of activity and BLEs, or whether BLEs cause inactivity or the other way around. This may be determined only by a longitudinal follow-up of the present study. If subjects who at present spend little time in demanding activities are found to have deteriorated with respect to cognitive performance more than individuals who are still

TABLE 5. Background Variables

	Category[a]			
	0	1	2	3
Activity	Time spent (hr/wk)			
1. Reading (including newspapers)	—	<3.5	3.5–14	>14
2. Watching TV	—	<3.5	3.5–14	>14
3. Engaging in social activities: clubs or other types of organizations	—	<0.5	0.5–2	>2
4. Participating in sports, gymnastics, yoga, bicycling, or (for the very old) walking	—	<0.5	0.5–2	>2
5. Mental games (e.g., crosswords, brain teasers, chess, bridge)	—	<0.5	0.5–2	>2
6. Engaging in other hobbies, not including activities 1–5	—	<0.5	0.5–2	>2

[a]See Table 2, footnote *b*.

very active, then it can be said that these background variables indeed represent a protective factor.

3.3. Raw Test Scores

A very much condensed overview of test outcomes of healthy subjects who were either unaffected or affected by BLEs is given in Fig. 1. It can readily be seen that some test performances are more vulnerable to age and BLEs than others.

Primary memory span (DS) was least clearly related to age, but there was marked age–BLE interaction. With the MST, it was shown that not only perceptual processes and response preparation (intercept) but also the necessary primary memory search processes (slope) were affected by BLEs as well as age. This decrease in information processing may help explain why elderly and even middle-aged people who do not experience significant perceptual or intellectual deficits often do have difficulties with processing all information presented to them. These problems may well originate from a general reduction in the speed of information processing, already present in the fourth decade, but manifest only after the sixth or seventh decade.

Even though the total amount of reproduced words in the VVLT was somewhat reduced with advancing age, there was a remarkable exception to the rule that age affects memory. Maximum recall and recognition of memorized words was not affected at all in the group of subjects who had not experienced BLEs, showing that decline of certain aspects of memory functioning is related to factors other than mere calendar age. BLEs accounted for a large—if not the largest—part of the interindividual differences. Delayed recall in elderly BLE-affected subjects was very poor.

The Stroop test showed that the amount of language interference increased from some 70% in subjects aged 20 to 100% in 80-year-old BLE-unaffected elderly. This increment is small compared to the age effect observed in BLE-affected elderly subjects, some showing interference effects of well over 200%.

The interference effect of concept-shifting increased with age, as measured with the CST. Apparently, slowing of the kind of information processing that is involved in the planning of ongoing activity is already present at the age of 40, not dissimilar to the kind of slowing observed with the MST with respect to memory-search processes.

In the tapping test, young subjects started off at higher rates then the old, but their number of taps per second declined faster during the whole test, so that after 20 sec, elderly subjects tapped at a rate not much slower than younger ones. In BLE-affected subjects, however, the decline was parallel in all age groups.

The MCRT showed that simple reaction time need not be affected very much in healthy elderly subjects, but responses that are incompatible with the stimulus demand considerably longer latencies. This latency in BLE-affected elderly individuals dramatically increased in BLE-affected subjects, with reaction times of over 1 sec.

4. GENERAL DISCUSSION AND CONCLUDING REMARKS

We have described a cross-sectional study of several aspects of cognitive aging. A large sample of normal healthy subjects was studied. In each of seven age groups from

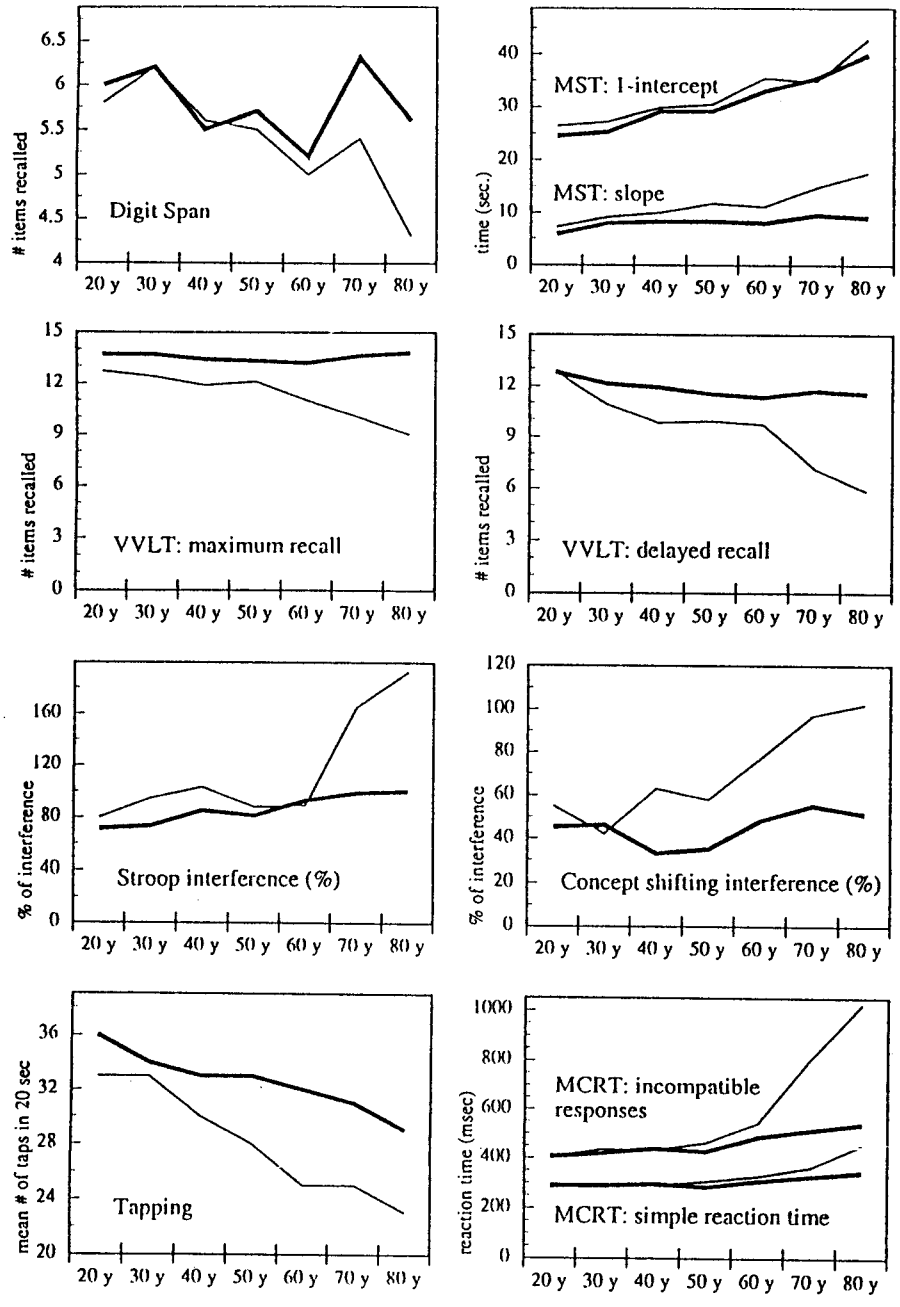

FIGURE 1. Summary of test outcomes. (MST) Memory Scanning Test; (VVLT) Visual Verbal Learning Test; (MCRT) Motor Choice Reaction Test. (———) BLE-affected subjects; (▬▬) BLE-unaffected subjects.

20 through 80 years, at least 10 males and 10 females were tested. Significant age-associated decline was observed in all aspects of cognitive functioning that have been studied. Of the four main areas of cognition that were identified, memory showed the least decline and cognitive speed the greatest. The same was true of the age-related increase in variability of test performance.

Taking biological life events (BLEs) into account much attenuated this decline, however. Subdivision of the total sample of subjects—all regarding themselves as normal and healthy—into BLE-free and BLE-affected showed large group differences. Compared to the overall averaged performance, age differences were much smaller when BLEs were absent and greatly enhanced when they were present. This confirms the data of Haxby *et al.* (1986) on differences between the visual memory of normal, healthy aging subjects and that of aging groups with health problems. Very few of the separate health-related factors that comprised these BLEs could account for a substantial part of the individual differences in test performance. Background variables, such as "hours spent on reading per day" and "hobbies," were associated with both BLEs and cognition. It appeared that those subjects who spent considerable time on reading, mind games, and sports were less likely to have experienced BLEs or to show extensive age-related cognitive deficits.

4.1. Implications for Health Care and Related Issues

As stated above, the danger of documenting *how* most people age, instead of how people can age *successfully,* is that processes that are not intrinsic to age are accepted as "natural" and in any case inevitable. Confusing the effects of age-extrinsic conditions with aging itself yields an overly pessimistic picture of aging. Not all the conditions can be prevented or cured, but some of them can, to a considerable extent. Conditions involving the brain that are thought to have disappeared or be cured completely when the patient no longer complains, or the CT scan no longer shows any anomalies, could form the substrate of the long-term effects of BLEs.

One very important area in which age-extrinsic factors could be circumvented is anesthetics. The number of operations under general anesthesia was the BLE that was most closely associated with age-related decline of several cognitive performances in the present study. If this finding can be reproduced, it should, in our view, have impact on the policy regarding anesthetics. Surgeons and patients should not routinely favor general anesthesia over local anesthesia. The issue of other somatic factors such as the physiological trauma associated with surgery is as yet unresolved, but every operation counts.

Another area of health care that can profit from findings like these is medication. If future research confirms the present finding of association between certain types of medication and behavior, clinicians should be more cautious in their prescription of medication, e.g., sleeping pills. The role of medications that can affect consciousness in cognition, their long-term effects, and the interaction of these effects with aging are insufficiently understood (Hartman, 1988). It is possible that old people are more vulnerable to the effects of benzodiazepines, and that their dosage should be adapted, or preferably, if possible, abolished completely. Every sleeping pill counts.

Repeated mild head injuries are yet another category of BLEs the frequency or severity of which could be reduced. It is now more or less agreed that head injury cannot be assumed to pass without any repercussion to brain functioning (Binder, 1986). Certain sports should be restrained by tighter safety measures and regulations. Boxing—or at least punches "above the collar"—should be abolished. Every knockout counts.

Exposure to neurotoxic agents in individuals' professions, for instance, is a factor that has fortunately gained the interest of many researchers (for an extensive survey of the issue, see Hartman, 1988). However, much remains to be done to increase safety for craftsmen such as roofers or carpet-layers who can—more often than not—be observed without any protection against inhalation of organic solvents or other toxic substances. Even for do-it-yourselfers, this matter can be important. Anyone who has ever varnished a parquet floor will have experienced some "lightheadedness" after having spent some hours above vaporizing solvents. Since this dizziness disappears after some time in the open air, and nothing is known about the impact of exposure of such short duration, little attention is paid to this phenomenon by the individual and researchers.

Much effort should be invested in the study of the impact of the various BLEs. As stated above, some BLEs are of discrete nature, whereas others are much less discrete, such as chronic exposure to neurotoxic agents or medication. Also, the mechanisms through which BLEs act on brain functioning may, and probably will, differ widely.

4.2. Implications for Research on Aging and Dementia

The present findings may have serious implications for virtually all cognitive aging research (Houx *et al.*, 1991a). In the vast majority of studies on cognitive aging, normal subjects are not explicitly screened for factors related to physical or mental health. It seems likely, therefore, that many of the effects of aging reported in the literature result from age-extrinsic factors, of which BLEs, as investigated in the present study, may be a good example. It is very probable that all aging studies will have included BLE subjects in their groups of nondiseased, usually aging subjects, when the subjects were not thoroughly screened for health as they were in the study of Haxby *et al.* (1986) or in the present study. In future research on aging and cognitive functions, a rigorous health screening of subjects for any factor that is known or likely to be associated with changes in brain functioning should be part of the experimental procedure. This is also the case for neuropsychological studies. After all, as brain–behavior relationships constitute the basis of neuropsychology, it is important to have information about the condition of the brain, the complex functions of which are being studied.

It might be argued that by discarding the secondarily aging subjects, no insight is gained into the actual distributions of the variables under investigation. Whether this argument applies depends on the research question. For most purposes, however, the implicit or explicit aim is to study primary, that is cognitive, aging, unaffected by any other factors. In those cases, the actual demographic distributions are irrelevant, since all BLE-affected subjects should be excluded. Whether the results of these studies are representative of the whole aging population is quite another matter.

The generalizability of such research to the whole aging population is probably low. However, research of this kind may constitute an important step in gaining knowledge about the nature of aging, especially when carried out on a prospective basis. Most of the BLEs are also accepted as risk factors for dementia, when they are more severe than in our definition. The work of Amaducci *et al.* (1986) is relevant in this respect. These authors found a significant relationship between clinically diagnosed Alzheimer's disease and a number of the factors that we identified as BLEs. If indeed BLEs are mild forms of conditions that can actually produce severe disorders of cognition, or even dementia, then it can be envisaged that the presence of one or more BLEs is a risk factor for pathological aging.

The question regarding determinants of age-related memory dysfunctions and possible determinants of further deterioration into dementia-like conditions is of great importance because of the complete lack of information on this topic and its implications for health care via early detection and early intervention.

BLEs might be thought of as bruises or marks on the brain. The effect on brain functioning of a single BLE may be minimal, as the bruises are too slight. Only severe single brain damage can have perceivable effects on cognitive functioning. However, if the number of bruises increases with age, so does their combined effect. If the effects of BLEs are indeed additive, then their impacts on cognition will become perceivable beyond some threshold value. Consistent with the notion of increased vulnerability (Rabbitt, 1990), this threshold probably declines with age, as an age-intrinsic process of primary aging. This would explain why the effect of BLEs on the average cognition scores was found to be larger in older subjects, and why in many cases the number of BLEs experienced could predict cognitive performance equally well as age *per se*.

4.3. Background Variables

It was found that poorly performing elderly subjects were overrepresented in those groups of individuals who did not spend any time (or not much time) in the following activities: reading, sports, and mind puzzles. No definite conclusions can be drawn from this finding, as the possibility of it being an artifact of the method of subject selection cannot be ruled out. At best, it can be regarded as circumstantial evidence for the notion that these variables do play some role in cognitive success in the elderly. It remains possible that elderly individuals who spend little or no time with cognitively demanding activities do not avoid such activities because of their inabilities. Most likely, both possibilities have some validity. Conceivably, engaging in such mental activities ("mind jogging") is the opposite of a risk factor—a "protective" factor against age-associated cognitive decline: "Use it or lose it." Much further research can and should be addressed to this topic.

4.4. Normality

The finding of large individual differences in a group of subjects who can be regarded as normal by any standard used in the experimental literature raises the issue

of normality. Recently, this matter has gained some interest. Rowe and Kahn (1987) published an influential review regarding normality in biological, psychological, and social aging. They stated that in a wide range of scientific disciplines, it is tacitly assumed that individuals who are not diseased are therefore normal and healthy. In their opinion, too little attention is being paid to the increase with age of the variability of the parameter of interest, not only in the area of cognition. Howe and colleagues (1990) edited a book on the subject of atypical aging. Atypical aging is the result of conditions that not all aging subjects experience, but are secondary rather than primary. Characteristics of aging that are essential to the aging process are regarded as primary (Salthouse *et al.*, 1990). Secondary conditions are all too often closely associated with aging, because their effects are greater in old age (due to increased vulnerability, longer exposure, or reduced resistance). Understanding secondary aging can eventually lead to understanding primary aging, i.e., those processes that are unavoidable concomitants of aging. Distinguishing secondary from primary processes can be of great importance, both to the individual and to society. Conceivably, a number of age-extrinsic conditions can be prevented, diminished, or even eliminated (Rabbitt, 1990).

What can be regarded as normal? Salthouse *et al.* (1990) employ an operational definition: Observations or entities can be regarded as typical if they fall within some fixed boundaries, for instance, inside the middle 90% of their distributions. Anything outside these boundaries would be irregular, out-of-the-ordinary. In fact, all terms like "usual," "regular," or "ordinary" imply some reference to a distribution of values. Of course, such an operational definition is only practical. It does not help us in theorizing about the nature of the processes to which such typicality or atypicality should be ascribed. Moreover, it could be an invitation to accept the actual distribution as normal.

Rowe and Kahn (1987) and, more recently, Stones *et al.* (1990) advocate a clear distinction between usual and successful aging. These are two types of primary aging, that is, disease-free aging. The notions of usual and unsuccessful resemble that of (a)typicality as advocated by Howe *et al.* (1990) and Salthouse *et al.* (1990), but with the important difference that the judgement of success depends on the parameter by which this success is being measured. According to Rowe and Kahn (1987) and Stones and colleagues (Stones *et al.*, 1990), merely distinguishing between nondiseased and diseased aging has serious limitations. Most importantly, the heterogeneity in the nondiseased elderly group is neglected. Furthermore, this notion of the normality of usual aging implies the harmlessness of several possibly health-threatening factors, such as BLEs. Finally, normality implies that what is usual is also natural, and cannot —or even should not—be modified. This notion of "normality" puts too great an emphasis on studying the level of functioning of most old individuals, instead of attempting to explain the increased heterogeneity. In the words of Rowe and Kahn (1987), "It tends to create a gerontology of the usual."

Stones's group (Stones *et al.*, 1990) identifies four different types of aging:

1. Primary (= successful) aging: functional changes that are intrinsic to age.
2. Usual aging: nonpathological deficiencies added to the age-intrinsic processes of successful aging.
3. Secondary aging: pathology-related decrements added to nonpathological aging.
4. Tertiary aging: pathological aging plus the effects of terminal illness. Tertiary

aging can thus be roughly equated to the "terminal drop" phenomenon as described by Riegel and Riegel (1972).

Usual aging is subsumed under primary aging by Rowe and Kahn (1987). With this model of multiple types of aging, it becomes understandable why age-associated decline can accelerate and why the variability increases with age, two trends often observed in aging research. The frequency of aging types 2–4 must increase with age, as these age-linked conditions and processes are irreversible in most cases, and any brain dysfunction that is caused by them is likely to be permanent. The onset of these age-extrinsic conditions can be assumed to vary among individuals. The aggregated deleterious effects of pathology or lifestyle on the average performance in a random sample of subjects is therefore expected to accumulate with age. Many an age-related decline observed in our test outcomes fits into this line of thinking. Conversely, processes that are age-intrinsic (primary aging) are more likely to cause a linear decline of cognition with age, if a given function is to decline at all as a result of primary aging. It is hypothesized here that BLEs constitute a biological substrate for nonpathological deficiencies that are associated with usual aging (type 2). Our difficulty in obtaining a sample of BLE-free subjects aged 80, and even 70, illustrates this point nicely: BLEs and pathology (type 3) were more frequent then their complete absence. Setting aside pathology and terminal drop, if aging as it is affected by BLEs or nonpathological deficiencies is the most frequent type, then it is regarded as the normative pattern in the operational definition of Salthouse *et al.* (1990). Aging types 1, 3 and 4 are then all to be regarded as atypical. Defining true age effects depends heavily on the extent to which deficiencies are still accepted as nonpathological.

Geffen and colleagues (Geffen *et al.*, 1990) stated that the age effects they found with the Auditory Verbal Learning Test were due to "*true age effects*" (emphasis theirs) because (1) cohort-specific factors such as education could be regarded as negligible, (2) subjects were matched for IQ, and (3) they were free of neurological symptoms (self-report). Few authors put it this explicitly, but this notion of aging is probably very common in cognitive gerontology. Geffen and colleagues did not take into consideration the nonpathological deficiencies associated with type 2 aging. Consistent with our thinking about the occurrence of BLEs as a predictor of less than successful aging, the average performance of their subjects lay between the means of the BLE-free and the BLE-affected groups in our sample and showed a larger variability than either of our two groups. We hypothesize, therefore, that subdivision of subjects based on BLEs equals the distinction between usual and successful aging, between aging types 1 and 2. This hypothesis should be further investigated in light of the fundamental issue about when age-associated changes can be regarded as age-intrinsic, that is, as physiological, and when the aging process is usual but nondiseased.

In conclusion, our notion of what is normal may be about to be radically changed —from what is average into what is optimal. As for aging, this means that we should vigorously seek for every conceivable age-extrinsic factor. Whatever the nature of aging research—be it biological or cognitive, be it cross-sectional or longitudinal— if these factors are not controlled for, true age effects will never be found. More important, however, there are many age-extrinsic factors we can do something about. Among these, toxins in air and water may constitute one of the more important ones.

REFERENCES

Amaducci, L.A., Fratiglioni, L., and Rocca, W.A., 1986, Risk factors for clinically diagnosed Alzheimer's disease: A case-control study of an Italian population, *Neurology* 36:922–931.

Binder, L.M., 1986, Persisting symptoms after mild head injury: A review of the postconcussive syndrome, *J. Clin. Exp. Neuropsychol.* 8:323–346.

Birren, J.E., and Schaie, K.W. (eds.), 1985, *Handbook of the Psychology of Aging*, 2nd ed., Van Nostrand Reinhold, New York.

Birren, J.E., and Schaie, K.W. (eds.), 1990, *Handbook of the Psychology of Aging*, 3rd ed., Van Nostrand Reinhold, New York.

Botwinick, J., 1984, *Aging and Behavior*, 3rd ed., Springer, New York.

Charness, N. (ed.), 1985, *Aging and Human Performance*, Wiley, Chichester, England.

Crook, T., Bartus, R.T., Ferris, S.H., Whitehouse, P., Cohen, G.D., and 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, *Dev. Neuropsychol.* 2:261–276.

Elias, M.F., Robbins, M.A., Schultz, N.R., and Pierce, T.W., 1990, Is blood pressure an important variable in research on aging and neuropsychological test performance?, *J. Gerontol.* 45:P128–135.

Folstein, M.F., Folstein, S.E., and McHugh, P.R., 1975, "Mini-Mental State," *J. Psychiatric Res.* 12:189–198.

Geffen, G., Moar, K.J., O'Hanlon, A., Clark, C., and Geffen, L., 1990, Performance measures of 16- to 80-year-old males and females on the auditory verbal learning test, *Clin. Neuropsychologist* 4:45–63.

Hartman, D.E., 1988, *Neuropsychological Toxicology: Identification and Assessment of Human Neurotoxic Syndromes*, Pergamon, New York.

Haxby, J.V., Grady, C.L., Duara, R., Robertson-Tchabo, E.A., Koziarz, B., Cutler, N.R., and Rapoport, S.I., 1986, Relations among age, visual memory, and resting cerebral metabolism in 40 healthy men, *Brain Cognition*, 5:412–427.

Houx, P.J., 1992, *Cognitive Aging and Health-Related Factors*, University of Limburg, Maastricht, The Netherlands.

Houx, P.J., and Jolles, J., 1993, Effects of age, brain, health, sex, and education, *Percept. Motor Skills* 76:195–211.

Houx, P.J., Vreeling, F.W., and Jolles, J., 1991a, Rigorous health screening reduces age effect on Memory Scanning Task, *Brain Cognition* 15:246–260.

Houx, P.J., Vreeling, F.W., and Jolles, J., 1991b, Age-associated cognitive decline is related to biological life events, in: *Alzheimer's Disease: Basic Mechanisms, Diagnosis and Therapeutic Strategies*, Wiley, Chichester, England, pp. 353–358.

Houx, P.J., Vreeling, F.W., and Jolles, J., 1993, Performance decline on the Stroop Color-Word Test: Effects of age and health screening, *Exp. Aging Res.* 19:209–224.

Howe, M.L., Stones, M.J., and Brainerd, C.J. (eds.), 1990, *Cognitive and Behavioral Performance Factors in Atypical Aging*, Springer, New York.

Jolles, J., 1986, Cognitive, emotional and behavioral dysfunctions in aging and dementia, in: *Progress in Brain Research*, Vol. 70 (D.F. Swaab, E. Fliers, M. Mirmirian, W.A. Van Gool, and F. Van Haaren, eds.), Elsevier, Amsterdam, pp. 15–39.

Jones, M.J.T., Piggott, S.E., Vaughan, R.S., Bayer, A.J., Newcombe, R.G., Twining, T.C., Pathy, J., and Rosen, M., 1990, Cognitive and functional competence after anaesthesia in patients aged over 60: Controlled trial of general and regional anaesthesia for elective hip or knee replacement, *Br. Med. J.* 300:1683–1687.

Knoefel, J.E., and Albert, M.L., 1985, Secondary demetias, in: *Handbook of Clinical Neurology*, Vol. 46, *Neurobehavioral Disorders* (J.A.M. Frederiks, ed.), Elsevier, Amsterdam, pp. 385–411.

Lezak, M.D., 1983, *Neuropsychological Assessment*, 2nd ed., Oxford University Press, New York.

Poon, L.W., 1985, Differences in human memory with aging: Nature, causes, and clinical problems, in: *Handbook of the Psychology of Aging*, 2nd ed. (J.E. Birren and K.W. Schaie, eds.), Van Nostrand Reinhold, New York, pp. 427–463.

Rabbitt, P.M.A., 1990, Applied cognitive gerontology: Some problems, methodologies and data, *Appl. Cognitive Psychol.* 4:225–246.

Riegel, K.F., and Riegel, R.M., 1972, Development, drop, and death, *Dev. Psychol.* 6:309–316.
Rowe, J.W., and Kahn, R.L., 1987, Human aging: Usual and successful, *Science* 237:143–149.
Salthouse, T.A., Kausler, D.H., and Saults, J.S., 1988, Investigation of student status, background variables, and the feasibility of standard tasks in cognitive aging research, *Psychol. Aging* 3:29–37.
Salthouse, T.A., Kausler, D.H., and Saults J.S., 1990, Age, self-assessed health status, and cognition, *J. Gerontol.* 45:P156–160.
Stones, M.J., Kozma, A., and Hannah, T.E., 1990, The measurement of individual differences in aging: The distinction between usual and successful aging, in: *Cognitive and Behavioral Performance Factors in Atypical Aging* (M.L. Howe, M.J. Stones, and C.J. Brainerd, eds.), Springer, New York, pp. 181–218.
Verhage, F, 1964, *Intelligentie en leefijd* [Intelligence and Age], Van Gorkum, Assen, The Netherlands.