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ORIGINAL CONTRIBUTION

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How should we measure nutrition-induced improvements in memory?

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Summary There is a basic distinction between declarative memories, which can be stated verbally, and non-declarative memory, such as how to ride a bicycle, which cannot be expressed in words. With age it is the performance of declarative memory, particularly episodic memory that requires recall of events placed in time, that declines. As memory is not a unitary phenomenon, it should be ideally monitored using a range of tests that reflect theoretical conceptions of the topic. If circumstances demand the use of a single test then a measure of episodic memory is suggested. When it proves only possible to use a rating scale it should be ensured that memory is distinguished from other aspects of cognition and that different types of memory are not confused. The tests used, and the form in which they are used, need to be chosen to be of appropriate difficulty for the sample studied. A major conclusion is that the selection of the measure of memory used in the study of a dietary intervention should never be routine. It is inevitable that the form of the test used will need to be chosen carefully for the population being studied.

Key words aging – dementia – phosphatidylserine – memory – vitamin E

Introduction

Can memory in young adults be improved by diet? Can the decline in memory that occurs with age be slowed or even prevented by appropriate nutrition? Although particular nutrients have been studied in this context, and on occasions even marketed with the claim that a beneficial response is to be expected, it is an area characterized by data limited both in quantity and methodological quality. One aspect of the methodology, the measurement of memory, is considered and ways that future studies might approach the topic are suggested.

The many, varied and complex ways in which psychologists conceive memory contrast starkly with the often limited conceptions of such phenomena in many nutritionally inspired studies. Initially the most common ways that memory is viewed and measured by psychologists are outlined and then related to the study of memory in nutritional studies. As a way of directing attention to potentially more informative tests, changes in those aspects of memory that typify the aging process are identified. Those aspects of memory that predict at an early stage the probable development of dementia are also considered, leading to recommendations of the types of memory tests that should be used in dietary studies.

The conception of memory

There are a number of stages at which diet may potentially influence memory and only a battery of carefully chosen tests will allow different mechanisms to be distinguished. A common distinction is made between encoding – putting information into memory; storage –

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maintaining the memory; retrieval – recovering the memory from store. Memory can fail at each of these stages. A second distinction is between the type of information that is stored, is it a fact or a skill, is it verbal or non-verbal. A third distinction is between short- and long-term storage. A great deal of the information we take in never gets beyond short-term stores; some information we retain for only seconds whereas other information is stored for decades. A wide range of tests would be required to reflect the many permutations of these dimensions.

The term working memory is used increasingly, implying that short-term memory is used as mental working space while performing a task; it is conceived as the area where information is manipulated and partial solutions are stored during problem solving. The working memory mechanism is said to consist of three parts [1]. A central executive of limited capacity is aided by the articulatory loop and visuospatial sketchpad that are viewed as relatively passive slave systems responsible, respectively, for the temporary storage of verbal and visual information. The articulatory loop contains a small amount of speech-based information and allows the rehearsal of verbal material. The visuospatial sketchpad stores visual images that can be manipulated, it is the "inner eye", a rehearsal system for visual input. More recently a so-called episodic buffer has been added to the model of working memory. It provides temporary storage of information from different modalities and from long-term memory and combines it into a unitary representation [2].

From the study of those with brain damage, and other evidence, it has been established that there are various types of long-term memory (Fig. 1). A basic distinction is between declarative or explicit memory (knowing that) and non-declarative, procedural or implicit memory (knowing how). Declarative memories can be stated verbally – they can be declared. A procedural memory, such as how to ride a bicycle, cannot be expressed in words; the memory is implicit. The ability to reflect consciously on prior experience, which is required for declarative memory, is different from the more automatic procedural memory, which does not require conscious attention. A feature of implicit memory is that there is no awareness of remembering at the time of retrieval. People who suffer with amnesia have a profound inability to acquire new factual information although implicit memory, for example as demonstrated by the ability to speak, appears normal. Not all types of memory are disrupted. With amnesia new perceptual and motor skills may be learnt readily and old ones are used without a problem. The distinction between declarative and non-declarative memory seems well founded.

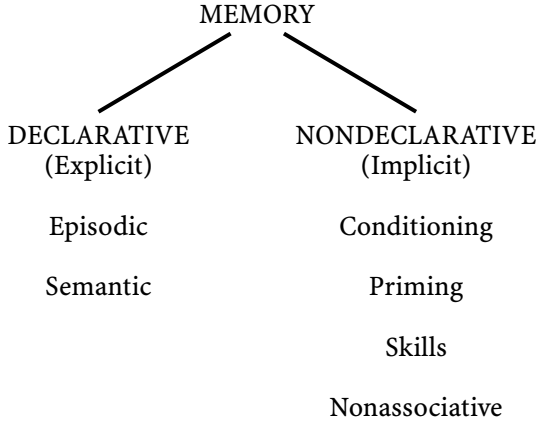

Fig. 1 The basic structure of memory

There are two types of declarative memory, semantic and episodic. Semantic memory reflects general knowledge about the world that is not unique to us and is not recalled in the context of a particular time. Examples would include knowing that the capital of France is Paris or that a young dog is called a puppy; these are facts that you know but you are unlikely to recall where and when you learnt them. Such memories lack context, they are remembered simply as known facts. In contrast episodic memory reflects personally experienced events, for example your wedding or what you ate for breakfast. Such memories are based in time and place, although details may not be as easy to recall as the event.

Both the use of imaging techniques and the study of those with brain damage suggest that different circuits in the brain are responsible for different aspects of memory. For example during encoding the left hemisphere of the brain is particularly active, whereas during retrieval it is the right hemisphere [3]. Patients with medial-temporal-lobe amnesia have severe impairment of long-term memory but normal short-term functioning. Semantic memory induced the activation of the left lateral frontal lobe, left middle temporal lobe and left inferior temporoparietal cortex; whereas episodic memory induced activity in the left hippocampus, frontopolar cortex and superior temporal gyrus [4]. Our growing knowledge that different brain circuits modulate different aspects of memory suggests that a particular dietary intervention may have the potential to influence one but not another aspect of memory. As such, the impact of a nutritional intervention will only be apparent from the use of a range of tests. It is misguided to use a single test to measure the impact of nutrition on memory. Memory is not a unitary phenomenon; it cannot be represented as a single number.

Memory and healthy aging

Although it is well established that memory declines with age it has become apparent that different aspects of memory are differentially impaired. Age differences in

primary memory, the ability to hold information for short periods, are slight [5]. Tests such as digit span measure this ability. However, if the material has to be manipulated decrements in performance occur with age, an example would be mental arithmetic [6].

In the short-term the ability to recall episodic memories is similar in younger and older adults, but the elderly have greater problems with long-term recall. There is evidence that retrieval is a cause of major problems. The ability to freely recall information is poorer in the elderly, but the problem is less with cued-recall and there are few difficulties with recognition tasks. The evidence is that the encoding of information may also be compromised with aging, although the retention of stored information is not [6]. Prospective memory involves remembering to do something in the future, for example to call into a shop on the way home. As such tasks require self-initiated retrieval it is not surprising that they are particularly disrupted [7]. It proves more difficult for the elderly to remember to do something that is time-based, for example to do something next week, rather than event-based, for example to ask Kathy something when you meet.

A very common complaint in the elderly is the tip-of-the-tongue phenomenon, the inability to bring to mind a particular word or the name of a person that you are certain you know. There appears to be a difficulty in retrieving the relevant phonological code. The number of tip-of-the-tongue responses increases with age [8], although when given time there is a chance of subsequent retrieval, demonstrating that the information was safely stored although access was compromised.

The majority of both cross-sectional and longitudinal studies of aging have found deficits of measures of verbal episodic learning. In contrast studies tend to report, at this early stage, a sparing of semantic memory [9]. When Nilsson [10] reviewed the topic he concluded that episodic memory decreased with age, although there was a relatively stable performance level up to middle age, followed by a sharp decline. In contrast studies of semantic memory, short-term memory, perceptual representation system, and procedural memory show a relatively constant performance level across the adult life span. It was concluded that episodic memory is unique in showing an age deficit.

Individual differences in memory

Although there is general agreement that with age there is a decline in various measures of cognitive functioning, the question arises as to what extent an average decline reflects in a minority the development of dementia, whereas with others performance is relatively unchanged. Where studies have excluded those with dementia there are still on average declines in measures of cognition, although on a smaller scale [11]. With increasing age the rate of cognitive decline increases, particularly in those over 85 years of age. Average scores, however, hide individual differences, with consistent reports that there are some whose functioning remains constant, whereas in others it declines. Over a 28 month period in 15 % of participants there was no cognitive decline, whereas 28 % had improved scores on retesting, leaving 57 % where performance was poorer [12]. Similarly in an American sample the performance of only 68 % of the sample declined over a period of 11 years [13]. It is possible that nutritional interventions will be particularly beneficial in those selected as being likely to suffer with future memory problems.

Mild cognitive impairment

Thus age-related changes in memory are variable. There is growing evidence of a long pre-clinical stage, of up to seven years, before the symptoms of Alzheimer's disease (AD) manifest themselves. However, groups with particular cognitive problems, which do not lead to dementia, have been distinguished. An ability to identify an 'at risk' group will be of considerable interest to those developing functional foods as they represent an important market. In addition if pre-clinical neuro-psychological changes can be established these will suggest means of monitoring the success of nutritional interventions.

The term Mild Cognitive Impairment (MCI) is used increasingly as a generic term for age-associated changes in cognition. The history of a series of related constructs has been reviewed [14]. With most of these constructs the nature of the cognitive tests has not been prescribed but rather is left to the investigator to choose. Although there have been a number of attempts to produce a satisfactory definition of MCI it has been suggested [14] that no construct was totally satisfactory. In fact it may be that it is too heterogeneous to allow clearly defined criteria.

There is, however, general agreement that there is a higher subsequent risk of developing dementia in those complaining of memory problems. MCI is not necessarily a precursor of disease, rather it has been associated with the development of dementia at a rate of 10–15 % a year, compared with controls who developed dementia at 1–2 % a year [15]. The profile of cognitive deficits with MCI is similar to the early stages of AD although less severe, typically semantic memory is spared during the early phases of cognitive decline [16]. Collie and Maruff [9] reviewed the topic and concluded that performance on tests of episodic memory predicted AD, although they are better predictors of those who will not, rather than will, develop dementia.

Memory and dementia

Although at one time dementia was believed to reflect global intellectual deterioration, more recently it has been established that, at least in the early stages, there are distinct patterns of impairment. AD accounts for about two thirds of all cases of dementia. By far the commonest symptoms in the early stages are complaints about failures of memory. Not all aspects of memory are similarly adversely affected and by far the most common major problems in the early stages are associated with anterograde episodic memory; there is a decreased ability to remember new information, in particular a deficit in encoding information. Problems of episodic memory can precede other symptoms by several years but eventually problems develop with working, semantic and remote memory, language, attention and executive abilities [17]. The overwhelming message is, however, that tests of episodic memory are likely to be most sensitive at an early stage.

Summary

- There is general agreement that memory performance declines with age although the decline is greater in some tasks than others.
- There is only a slight decline in non-declarative and working memory tasks.
- There is a relatively large decline in prospective memory and tasks requiring free recall, in particular there is a decline in verbal episodic memory that requires the retrieval of information.
- Verbal episodic memory is most compromised in those with MCI risk factors.
- In the early stages of AD anterograde episodic memory is the most common problem.

Tests of memory

When having to select a single, or a limited range of tests, it makes sense to choose those that are known to be sensitive to the aging process in the general population. The message from both the study of normal aging and dementia is that problems with verbal episodic memory occur earlier than problems with other aspects of memory. As such it is reasonable to suggest that tests that tap episodic memory should be the first to be used, certainly if time dictates the use of only one test. However, the need for individual testing by a researcher may in large scale epidemiological studies prevent this approach. Instead the only practical approach may be to use rating scales or self-report questionnaires.

Rating scales

Although many rating scales have been developed to monitor dementia [18], the area will be illustrated and evaluated by focusing attention on some of the more commonly used examples. Initially it is important to recognize that a fundamental reason to develop rating scales was to allow the rapid screening for dementia in a primary care setting, rather than to offer sensitive research tools. In the primary care environment the time taken to perform the assessment is critical. A typical example is the General Practitioner Assessment of Cognition [19] that asks the patient six questions such as the date, to recall something in the news, and to recall a name and address given by the doctor. In addition an informant is asked five questions dealing with the existence of memory problems and the ability to deal with day-to-day matters such as paying bills and taking medicine. In addition to cognition, some questionnaires also consider interpersonal relationships, social and more global functioning.

Perhaps the most commonly used measure, at least in clinical trials, is the Mini-Mental State Examination (MMSE) [20], which was the most frequent instrument of choice with phosphatidylserine (see Table 1). An assessment is made under five headings: Orientation – what is the date and where are we; Memory – repeat the names of three objects; Attention and calculation – spell WORLD backwards or count backwards by removing seven from a starting number; recall – remember the three objects previously learnt; Language – repeat a tongue-twister; perform a three-stage instruction. A maximum score of 30 points can be generated. Although those with Alzheimer's disease typically score less than 24 points, it is not a test of the disease as low scores can result for many reasons, including depression, confusion and schizophrenia. The MMSE concentrates on cognitive functioning, to a large extent on aspects of semantic, episodic and working memory, although attention and the use of language are also examined. The production of a single score, however, prevents a consideration of different aspects of memory and cognitive functioning and includes some measures that are less likely to be influenced during healthy aging.

Sub-tests of the MMSE have been related to scores obtained using more extensive neuro-psychological tests [21]. They found that the memory, attention-concentration and constructional items correlated significantly with other cognitive tests. In contrast four out of five language items had a low sensitivity and three out of five failed to correlate with other neuro-psychological measures. To increase sensitivity, while decreasing the time needed for administration, there have been various attempts to identify the sub-tests that best predict dementia. For example four items were found to detect the disorder as well as the full MMSE [22]; they were know-

ing the date, day of the week, your address and the name of the current prime minister. The study found that the MMSE correctly distinguished those with dementia on 65 % of occasions but concluded that it had limited use for diagnosing dementia in general practice, although it could represent one aspect of a more general picture. Although those suffering with dementia will perform such tests poorly they are unable to reliably identify early changes or subtle improvements.

Most memory researchers acknowledge the limitations of the MMSE and see it at the most as the means of grading established dementia. It lacks the sensitivity to detect the early stages of dementia, never mind the more subtle changes associated with normal aging or nutritional interventions.

However, in large scale surveys there may be no alternative to collecting information by questionnaire. In this instance there is a need to use instruments that selectively measure memory and do not confound different aspects of memory. An instrument that can be recommended as offering a relatively pure measure of a particular aspect of memory is the Pfeiffer mental status questionnaire [23]. Twice this questionnaire has been related to vitamin E status [56, 63]. Of the ten questions nine ask for retrieval of well-consolidated memories; "Where were you born?" "What is your mother's maiden name?" "What is your phone number?" The tenth question can be criticized as it considers a different phenomenon; it requires a considerable element of working memory; "Can you count backwards from 20 by 3's?" It would be better considered separately. Depending on the number of errors, memory is considered to be normal, mildly, moderately or severely impaired. The consistency of the nature of the majority of questions is likely to produce a relatively reliable measure of semantic memory. Thus the criticism of the MMSE that it adds disparate measures, to produce a single score of uncertain nature, is avoided. However, given the evidence that semantic memory is not disrupted in the early stages of either healthy aging or disease, it would be better when a single questionnaire is used that it concentrates on episodic memory.

A more recently developed questionnaire has not been used to study nutrition but it can be recommended as it considers those specific aspects of memory that are disrupted in healthy aging. The Prospective and Retrospective Memory Questionnaire (PRMQ) [24] has sixteen questions that ask about prospective or retrospective memory; whether the memory is short- or long-term; whether the subject has to cue themselves or is cued by the environment. For example the question "Do you decide to do something in a few minutes' time and then forget to do it?" considers short-term prospective memory that is self-cued. Whereas the question "Do you repeat the same story to the same person on different occasions?" considers long-term retrospective memory that is environmentally cued. Normative data for a sample of the general population are available [24].

Memory battery

The Wechsler Memory Scale is the most commonly used memory test battery that in its original form was used to produce a memory quotient. The approach fell out of favour as it became widely accepted that memory had many facets and could not be reduced to a single number. It was criticized in its original form for being predominantly verbal in nature. More modern revisions [26] acknowledge these problems and give separate short-term and long-term retention scores and differentiate between verbal and non-verbal elements of memory. Its usefulness is limited by taking over two hours to administer although its various sub-tests are often used alone.

Episodic memory

Word lists

The most commonly used tests of episodic memory involve the recall of lists of words or short stories. Where the experimental design requires a number of word lists it is important that they are of similar difficulty and the lists should be matched for the frequency that the words occur in English, whether they are concrete or abstract and hence the extent to which visual images can be formed. The basis on which the words are chosen should be reported. The length of the list will vary with the population being studied to ensure appropriate difficulty. A problem with the use of word lists is that the performance can be enhanced greatly by the use of memory strategies, for example the combining of words into a story. A solution would be to remove subjects from the study when baseline memory scores are noticeably higher than the normal range.

The Auditory-Verbal Learning Test [27] presents a list of 15 words that the subject recalls. The list is presented a second time and again words are recalled. The procedure is repeated five times with the original list. A second list is then read and recalled after which the subject is asked again to recall the first list. The resulting responses are used to measure a learning curve and obtain other evidence of the strategy used.

With the selective reminding test as many words as possible are recalled from a list that has just been heard. All words that have been omitted are then read out and the subjects again try to recall the list. The procedure continues until the entire list is correctly recalled [28, 29]. From the resulting data information concerning the storage, retention and retrieval of information can be gained.

Story recall

An alternative to word lists is to read a paragraph and to count the number of elements that are recalled. There are several standard paragraphs that have been used in different tests. Perhaps that most frequently used is the so-called Logical memory sub-test of the Wechsler Memory Scale [26] that offers two stories of similar difficulty. It has suggested [30] that the difference between the immediate and delayed recall of a paragraph is a measure of episodic memory: this measure has been suggested to be more sensitive to the defects of amnesic patients than simple immediate recall. With a young and intelligent population, such as students, a ceiling effect may occur. Although not a standard procedure, in practice it may be necessary to use a story with a greater than standard length. Alternatively the test may be made more difficult by only giving credit when precise terms are recalled rather than allowing synonyms or general ideas.

Word association/paired associates

Another approach to the measurement of episodic memory is to consider the learning of pairs of words. A familiar example is the Associative Learning Subtest of the Wechsler Memory Scale [55]. Ten pairs of words are presented that differ in their degree of association, for example the pair cabbage/pen has no ready relationship. The list is read three times and the subject responds to the prompt of the first word by saying the second.

Remote memory

The ability to access long established information is termed remote memory. Given the well-described association between the 'tip-of-the-tongue' phenomenon and aging it is a topic of interest. An inability to recall something 'you know you know' increases with age. The problem is that as everybody's experience is different you can never be completely sure whether an inability to recall a distant event reflects a problem of retrieving the memory rather than never knowing the fact in the first place. Asking subjects to record their 'feeling of knowing' of a fact can indicate whether the information was at one time familiar. As those with a greater 'feeling of knowing' are more likely to be subsequently able to recall information, this rating is an indication that the information is in fact known.

One approach is to ask the names of the photographs of people so famous that virtually everybody could be expected to have known them; politicians, film stars or sportsmen [31]. Depending on the age of the subjects the examples can be chosen to represent a succession of decades. In such tests the choice of stimuli is critical and systematic preliminary studies may be needed to get responses that not everybody gets right or virtually nobody remembers. The stimuli for this type of test may generalize poorly from one group to another and may date quickly.

Appropriate test difficulty

It is essential that the difficulty of the test is appropriate for the sample being studied. If too difficult there will be a floor effect; that is there will be small distribution of very low marks. Motivation will be lost quickly so that little attempt may be made to perform the task. Giving a very difficult test may confirm the worries about memory experienced by somebody with dementia: this is cruel and provides no meaningful data. On the other hand if the task is too easy then a ceiling effect occurs: a large proportion of the sample will achieve a small range of high scores. The data will not be normal, the mean will be artificially lowered, the standard deviation will be truncated and both reliability and validity will suffer.

Uttl [32] noted that many widely used memory tests were afflicted with severe ceiling effects, particularly when used with young healthy adults: these include the Verbal Paired Associates and Word Lists tests from the Wechsler Memory Scales and the Rey Auditory Verbal Learning Test. If a test is too easy the full variability amongst individuals will not be apparent and improvements in performance may not register. For example, although there are claims that event-cued prospective memory is spared by aging this finding is reported only when performance approaches maximal scores for the test; the probability of supporting that observation declines as a test is used that does not allow performance to approach a ceiling value [33]. The supposed lack of a decline in performance is an artifact of poor methodology.

It follows that a test must be tailored to the sample being studied and will vary with age, intelligence, education and the state of the progress of dementia, if any. It is suggested that if the mean score of a sample is within one standard deviation of the maximum score of the test then performance of 25% of the sample will be influenced by ceiling effects. If the difference is one and a half standard deviations then fewer than 10% of the sample will be affected by ceiling effects [32]. The solution may be no more difficult than choosing an appropriate length of test: with young adults the ceiling effects associated with the learning of word lists were apparent with lists of 9, 12 and 15 words although with 24 words only a few participants achieved maximum scores [32].

Judging the quality of a test

There are three basic elements to be considered when judging the quality of a psychological test; reliability, validity, and the existence of normative data.

A useful test must be reliable, that is it must produce consistent scores. All questions on a test should measure the same thing; they should correlate with each other. If the test is taken on two occasions and the scores are correlated a reliability coefficient of 0.8 is often the accepted minimum, with many psychometric tests having reliability in excess of 0.9, when the maximum is 1.00. There are two basic approaches. Firstly the same test is given twice to the same group of people. If they exist, another approach is to administer two different, but equivalent, forms of the same test.

Reliability is increased by administering and scoring a test in a highly standardized manner. When considering nutrition it is often necessary to measure memory before and after dietary intervention. There are inevitably practice effects, gains in scores that occur when a person is retested, which reflects the experience of having taken the test rather than an improvement in basic functioning. Such improvements occur irrespective of whether feedback on test items is provided. When the Logical Memory Test was given on four occasions large increases in scores were reported [34]. It follows that demonstrating a change in scores when taking a test a second time is not evidence of a reaction to a change in diet. The critical distinction is between an improvement following dietary intervention and the improvement following a control intervention that is equally plausible, but does not offer the nutritional advantage under consideration. Both groups are likely to produce higher scores when tested again, but is the nutrient in question associated with a greater gain?

When the General Memory Index consisting of Logical Memory and two similar tests was derived on two occasions from the Wechsler Memory Scale, a correlation of 0.96 resulted [35]. With parallel forms of the Auditory Verbal Learning Test correlations for the learning trials varied from 0.61 to 0.86 and for the recall trials from 0.51 to 0.72 [36].

Validity refers to whether a test measures what it is supposed to measure and is traditionally considered under various headings. Content or face validity asks whether the test includes relevant content. Are the items appropriate? For example if the measure is of episodic memory there is no point in considering tasks involving working memory. A related question is whether the test is suitable for the participants; the question of appropriate difficulty is considered above. Criterion validity involves relating scores on the test to another measure of what the test claims to measure. For example a test of memory might be expected to produce lower scores in those with a diagnosis of dementia and to decline with age.

Although there may be methodological advantages to working under highly controlled laboratory conditions the resulting measure must predict the 'real-world.' Typically the correlations between test scores and measures of the outside world are much lower than those obtained when considering reliability, a reflection of the multitude of factors that impact on human behaviour. However, scores on the Logical Memory Subtest of the Wechsler Memory Scale decline with age [26] and the test has been associated to vitamin E status [37].

Having administered a test a score is produced; yet does this reflect a poor or above average performance? Without appropriate norms the results of a test convey little meaning. Therefore a score for an individual is interpreted by comparing it with the scores obtained from a large group of people. When using norms it is very important to determine how the normative group was selected. For example memory will vary with age and intelligence so that a false impression will be gained if a score is related to an inappropriate population. In particular the Wechsler Memory Scale provides extensive norms [26]. Separate norms are offered for those aged 16–17, 18–19, 20–24, 25–29, 30–34, 35–44, 45–54, 55–64, 65–69, 70–74, 75–79, 80–84 and 85–89 years. Based on census data the normative sample was selected to be representative of the population, paying attention to variables such as educational attainment, socio-economic status and race/ethnicity. Similarly Rey [38] produced norms for the Auditory-Verbal Learning Test for children, adolescents and adults according to age and socio-economic status. A convenient collection of norms for these and other tests is available [39].

Phosphatidylserine

Having above discussed various aspects of memory, for illustrative purposes the impact of two nutrients on tests of memory will be outlined to show the implication of the choice of test for the generality of any conclusions. The first example is phosphatidylserine (PS) as substantial sales are generated by advertising copy such as:

> "Clinical studies over a period of 20 years have shown that regular supplementation with phosphatidylserine restores and maintains adequate nerve cell function in a variety of ways which leads to improvements in long term memory…"
>
> "The premier brain nutrient for lifelong cognitive enhancement … Clinical studies show that phosphatidylserine helps improve cognitive functions that decline with age…"

As PS does not occur abundantly in food the amount supplied by the diet is limited. However, by using a complex series of reactions, the body can make it, albeit with a substantial investment of energy. When taken by

mouth PS is absorbed rapidly and crosses the blood-brain barrier where it is believed to influence the structure of cell membranes. The membranes of neurones have a particularly high PS content so it is associated with the conduction of the nerve impulse and also the storage and release of neurotransmitters. The membrane plays a critical role as the cell boundary influences the transport of nutrients, ions, messengers and waste products. Although membrane-based ion pumps, transport molecules and enzymes are proteins, they depend on the phospholipid membrane matrix for their functional capacity. The amino head group of PS tends to associate with ATPases, kinases and other membrane proteins that may be the key to the effects of PS on the brain [40].

PS has been shown to influence the aging of rats and various parameters of neural functioning. A full discussion of these topics is beyond the remit of this paper; however in elderly rats that had been given PS the number of nerve cells, their number, size and capacity, were nearer those of young animals [41]. In demented humans given PS imaging techniques have shown improved brain metabolism [42].

Table 1 lists double-blind studies that have considered the influence of PS on memory.

In those with mild to moderate dementia on no occasion did PS improve tests of non-declarative memory. With tests of declarative memory a significant improvement was found in three out of the five studies reported. There was, however, inconsistency, with studies both reporting and failing to report an improvement in digit span and the selective reminding task. The picture is that declarative rather than non-declarative memory is most likely to be influenced, although the findings are inconsistent. The nature of the test chosen will determine whether significant changes result.

Several studies used a rating scale as a dependent variable and in four out of six cases found an improvement. It is interesting that positive results have been most commonly found with rating scales. Their nature is discussed above; typically they do not only measure memory and fail to distinguish one aspect of memory from another. As such they preclude an unequivocal statement about memory as such, as it is possible that more general changes have resulted.

Serious interest in the MCI topic began with the construct of Age Associated Memory Impairment (AAMI), which was defined as secondary memory one standard deviation below the mean, in those over 50 years who complain of memory problems, although other aspects of intellectual functioning were adequate [54]. Although AAMI has attracted criticism, it offers an example of the study of those selected for memory problems; PS selectively helped a group of those who satisfied the criteria [51]. However, the *post hoc* selection of a sub-group of those with poor memory questions the faith that can be placed on the finding. The *a priori* selection of AAMI subjects and the demonstration that they responded to PS would represent much more convincing data. Schreider [55] in an open trial, reported that fifteen out of 18 subjects with AAMI, who took PS for 3 months, improved significantly over time. However, without a placebo and a double-blind design it is unclear whether the changes are more than a reflection of a familiarity with the tests on re-testing. The security of the basic finding was called into question by the only other double-blind study of AAMI. Jorissen [52] in 120 elderly subjects, who *a priori* fulfilled the criteria for AAMI, did not find that PS improved memory.

As most of the advertising of PS is directed to those displaying normal aging, its use in such samples is of interest. There is little evidence that PS will help those with normal memory. Crook et al. [51] found that PS produced no general improvement in memory in an unselected group of those over 50 years. Benton and Donohoe [53] gave PS to healthy individuals over the age of 55 years and although they found that memory as measured by the recall of a story decreased with age, supplementation did not lead to an improvement.

In summary, there is only limited evidence that PS improves the memory of a healthy aging population although the possibility exists that the taking of PS over a period longer than three months may be beneficial has not been explored.

Vitamin E

Given the major theory that free radical damage may play an important role in the aging process the intake of anti-oxidants has attracted attention. In particular vitamin E is of interest as it is fat soluble and hence crosses the blood-brain barrier. Compared with PS vitamin E has been considered over longer time periods, in larger samples, using a range of approaches. Table 2 summarizes the findings of 13 studies that have estimated vitamin E intake from food intake, measured its level in serum or have considered the use of supplements either freely taken or under double-blind conditions.

In eight out of the thirteen studies positive associations were reported. In these studies the dependent variables were variously psychological tests of memory, questionnaire measures or clinical diagnoses. Naturally the monitoring of populations to await the development of AD requires studies that take place over many years. Although the distinguishing of AD from other types of dementia is difficult without post-mortem examination, it can be safely assumed that problems of memory will be obvious. The approach, however, ignores the normal problems of age-related memory decline that are not the early stages of disease. Also such gross measures are likely to hide more subtle aspects of memory whose de-

Table 1 The influence of phosphatidylserine on memory

Study	Subjects	Sample size	Age	Declarative memory	Ratings	Other memory tests	Comments
Delwaide et al. [43]	Mild to moderate AD	35	65–91		Rating of everyday functioning PS > Placebo		Scale included memory but biased to other features
Palmieri et al. [44]	Moderate cognitive deterioration	87	55–80	Word list recall PS < Placebo Digit span n.s.			
Villardita et al. [45]	Cognitive deterioration MMSE 14–23	170	55–80	Word list recall PS < Placebo Digit span PS < Placebo Semantic verbal memory PS < Placebo		Visual memory n.s.	
Engel et al. [46]	Mild Dementia MMSE 15–27	33	55–75	Associate learning n.s. Paragraph recall n.s.	Clinical global impression PS > Placebo	Benton visual retention test n.s.	Rating scale not exclusively of memory
Crook et al. [47]	AD MMSE 12–23	51	55–85		Global improvement scale Psychiatric rating scale		
Cenacchi et al. [48]	Moderate to severe decline MMSE	494	> 65	Buschke selective reminding test PS > Placebo	Geriatric rating scale		Memory improved 23–24 % S.D.
Heiss et al. [49]	AD MMSE 13–26	35	48–79	Verbal selective reminding test n.s. Verbal fluency n.s.	MMSE PS > Placebo	Pictorial selective reminding test n.s. Corsi tapping test n.s.	Response defined as 3 point increase in MMSE – PS 50 % Control 11 %
				Non-demented subjects			
Maggioni et al. [50]	Depressed elderly	10	70–81	Buschke selective reminding test PS > Placebo	Nurse observation scale PS > Placebo		Memory improved 1 S.D.
Crook et al. [51]	AAMI IQ = 130	149	50–75	Name-face recognition PS > Placebo Facial recognition PS > Placebo Telephone number recall PS > Placebo			IQ 2 S.D. above mean Memory 1 S.D. below mean
Jorissen et al. [52]	AAMI MMSE > 24 Mean IQ 115–120	120	> 57	Visual verbal learning test n.s. Verbal fluency test n.s. Memory scanning test n.s.			IQ 1 S.D. above mean Memory 1 S.D. above mean
Benton & Donohoe [53]	Healthy Subjects IQ = 112	239	> 55	Recall of story n.s. Verbal fluency n.s. Recall of capital cities n.s.			Subjects not selected for memory problems

AD Alzheimer's disease; *AAMI* Age associated memory impairment; *MMSE* Mini mental state examination; *PS* Phosphatidylserine

Table 2 The influence of vitamin E on memory

Study	Subjects	Sample size	Age	Declarative memory	Ratings/clinical status	Other memory tests	Comments
Dietary intake							
Ortega et al. [56]	Living in community	260	65–90 y mean 71 y		MMSE n.s.		7 day weighted intake
					PMSQ $p < 0.05$		Higher vit E intake better PMSQ
La Rue et al. [20]	Living in community	137	66–90 y mean 77 y	Story recall $p < 0.01$		Design reproduction $p < 0.01$	3 day diary record Vit E intake 6y previous predicted performance
Engelhart et al. [57]	Living in community	5395	> 55 y mean 68 y		Clincal diagnosis AD		FFQ Higher intake vit E lower risk AD
Morris et al. [58]	Living in community	2889	65–102 y mean 74 y	Story recall n.s.	MMSE n.s.		FFQ
				Summated cognitive measures $p < 0.05$			In highest vit E quintile less cognitive decline
Morris et al. [59]	Living in community	815	mean 73 y		Clinical diagnosis AD $p < 0.04$		FFQ Likelihood of AD decreases with vit E intake
Luchsinger et al. [60]	Living in community	980	mean 75 y		Clinical diagnosis AD n.s.		FFQ Both dietary source and supplements n.s.
Serum							
Perrig et al. [61]	Random sample	442	> 65 y	Semantic memory n.s.		Priming, recognition pictures n.s.	Vit E did not predict memory.
				Free recall n.s. Working memory n.s.			β-carotene and vit C both predicted semantic memory
Perkins et al. [62]	NHANES III	4809	> 60y	Story/word recall $p < 0.02$			Higher serum vit E but not vit C or β-carotene associated with better memory
Ortega et al. [63]	Living in community	120	65–91 y		PMSQ $p < 0.05$		Higher serum vit E better PMSQ
Supplements							
Sram et al. [64]	In homes for elderly	96	60–90 y	Story $p < 0.001$ in females Digit span $p < 0.001$	Crichton geriatric rating scale $p < 0.01$	Figure drawing $p < 0.001$	Vit C 1000 g + vit E 300 mg for 1 y in open trial. Verbal memory responded more than short-term memory
Sano et al. [65]	Moderate AD	169	Mean 73 y		MMSE n.s. Death $p < 0.05$ AD assessment scale n.s.		Double blind 2000 IU vit E for 2 y.
Smith et al. [66]	Living in community	205	60–80 y	Recall word list n.s. Delayed recognition n.s.			Double blind 400 mg vit E, 500 mg vit C, 12 mg β-carotene for 1y
Masaki et al. [67]	Living in community	3496	71–93 y		Cognitive abilities screening instrument Better with vit E		Freely taken supplements Scores also better with vit C

AD Alzheimer's disease; *MMSE* Mini mental state examination; *PMSQ* Pfeiffer Mental Status Questionnaire; *FFQ* Food frequency questionnaire

cline may be gradual and only apparent with the use of sensitive tests.

The use of questionnaires allows some quantification of early memory loss in large scale epidemiological studies, although, as discussed above, they often confuse different aspects of memory and combine memory with other cognitive, behavioural and social phenomena. Although more time consuming, a better approach is the use of psychological tests that tap specific aspects of memory. In fact about half of the studies in Table 2 used at least one such test, although in the majority of studies it is unclear on what basis the tests were selected.

Rarely, if ever, will it prove possible to give a battery of psychological tests that will fully reflect the varied nature of human memory. The choice of test needs to be made on some theoretical basis [5–7, 10] that will increase the likelihood of meaningful and useful findings. The above consideration of the nature of normal age-related cognitive decline offers a way of homing in on the tests that are likely to prove most informative.

Discussion

A major conclusion is that the selection of the measure of memory used in the study of a dietary intervention should never be routine. This conflicts with the view [19] that there was a need for an "international gold-standard neuropsychological test battery which can be used ... in the investigation and treatment of cognitive problems in the elderly." Although such a test battery would be extremely valuable, if it was a realistic expectation, what this request ignores is that the tests used need to be appropriate for the sample that is being considered. The tests need to be appropriate in terms of the background and abilities of the population, and in terms of those aspects of memory that are being considered. Often there is a narrow band of difficulty that is appropriate for a particular sample, to avoid either ceiling or floor effects. The best that can be expected is that the particular aspects of memory to be considered will be specified in general terms, although the nature and the appropriate difficulty of the test will differ with age and the progression of disease.

How should memory be measured? Ideally a series of tests should be administered that reflect a range of measures indicated in Fig. 1. The study of Perrig [61] can be singled out as an example of good practice. Clearly they had in mind the nature of memory as outlined in Fig. 1. They had measures of episodic memory (recall of series of pictures), semantic memory (definition of words), implicit memory (effect of priming on recognition of pictures) and working memory (speed of response to dual tasks). Although serum levels of vitamin E did not predict any aspect of memory both the levels of β-carotene and vitamin C predicted semantic memory. That semantic memory was selectively influenced illustrates the need to consider a number of aspects of memory and that the findings with one test should not be generalized to other aspects of memory.

If practical considerations allow the administration of only one test the evidence is that measures of episodic memory offer the best chances of significant findings both in the early stages of dementia and with healthy populations. However, the use of a single memory test will limited interpretation: nutrition theoretically has the potential to influence many aspects of memory depending on its biochemical influence.

When considering global improvements in large-scale studies it is inevitable that rating scales are used. You should, however, ensure that when a rating scale considers memory it does not confound its assessment with measures of more global functioning. However, even when questions are asked about memory, in practice it will be difficult to distinguish different aspects of memory, and memory from other aspects of cognition. Although with large-scale studies carried out over long periods it is inevitable that rating scales will be often used this can never be the optimal solution. In a situation where the aging process is causing problems over a period of years, even many decades, cognitive testing is likely to prove more sensitive with short-term interventions. With subjects without dementia, or who are in its early stages, rating scales cannot offer the necessary sensitivity and are unlikely to pick up minor diet-induced improvements.

Grady and Craik [5] noted that there are similarities between the age-related declines in vision, hearing and memory and that balance, gait and grip strength correlate with intellectual functioning. The implication is that at least some of the memory problems experienced by the elderly reflect problems with sight and hearing. As such there is a need to exclude range of factors before concluding that memory as such is influenced. It is generally accepted that depression is associated with poorer memory to the extent that some older people suffering from depression have been misdiagnosed with AD. Certainly antidepressants have been reported to have a positive impact on learning and memory. It is thus good practice to ensure that when attempting to improve memory those with disturbed mood are excluded from the sample. Considerable effort must be taken to ensure that a full picture is obtained of the populations examined to ensure that changes in memory performance do not reflect other factors.

Problems of memory are amongst the most obvious signs of aging and are of concern to large sections of the population. If you could demonstrate that the progression of such problems could be slowed by nutritional means, it would have a significant implication for health as well as offering a substantial marketing opportunity. Aspects of nutrition that have been suggested to im-

prove memory include phosphatidylserine (Table 1), acetyl-carnitine, lecithin, choline, poly-unsaturated fatty acids, vitamin B_6, vitamin B_{12}, folate and anti-oxidant substances such as vitamin A, vitamin C, vitamin E (Table 2), beta-carotene and selenium. Although a number of aspects of nutrition have been suggested to be helpful, the data are limited and to date preclude an unequivocal positive recommendation. For example studies of PS (Table 1) have in the main considered only those with mild to moderate dementia. To the extent that an improvement with rating scales has been reported this can be viewed as evidence of an important beneficial response. You would, however, expect that if memory as such had been influenced, the findings would be paralleled by improvements in more sensitive and specific tests of memory. It is important that in the few studies of PS that considered a healthy population, memory did not improve. The case of PS illustrates the need for evidence from a series of well-designed studies before marketing nutritional remedies.

There are, however, plausible hypotheses that suggest an association between nutrition and the aging process; the free-radical theory; homocysteine as a risk factor for AD; the role of acetylcholine in the modulation of memory. A major problem is the slow nature of the aging process: small and slow changes are most likely to be demonstrated with sensitive tests chosen for sound theoretical reasons. At an early stage there may be no way to predict on which aspects of memory nutrition will impact. However, when making a preliminary investigation of a possible role for nutrition, the use of a range of tests, based on the theoretical conception of memory, which precisely as possible monitor particular aspects of memory, will facilitate progress.

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