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ORIGINAL CONTRIBUTION

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General methodological considerations for the assessment of nutritional influences on human cognitive functions

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Summary The premise that cognitive functioning can be influenced through dietary means has gained widespread interest. The assessment of cognitive functioning is a key method to scientifically substantiate such nutritional effects on cognition. The current paper provides a basic overview of the main concepts, issues and pitfalls of human cognitive research. General methods of cognitive assessment, selection of appropriate tests, factors that may mediate task performance and issues pertaining to the interpretation of the results are discussed.

Key words cognition – mood – nutrition – behavioural-assessment methodology – human

Introduction

The measurement of mental states and cognitive abilities is a widely used procedure in numerous clinical, diagnostic and experimental settings, ranging from the evaluation of the behavioural sequelae of brain injuries, illnesses and aging, to the determination of (side-)effects of medicinal and illicit drugs and investigations of fundamental processes of human cognition and neurobiology. As a result of the fast growing interest in potential functional properties of nutrients for mental performance, and the associated need to scientifically substantiate such effects, the area of cognitive psychology has also become relevant for nutritionists, food scientists, food regulatory officials, and government and food industry representatives.

Recently, the European Committee consorted action PASSCLAIM taskforce (Process for the Assessment of Scientific Support for Claims on Foods) evaluated the existing scientific methodology for the investigation and substantiation of nutritional influences on mental state and performance [1]. In its report, the taskforce concluded that claims on the nutritional enhancement of specific mental functions can be scientifically demonstrated through behavioural assessments. The PASSCLAIM report provides an extensive selection of validated tests and methods, as well as guidelines for scientific substantiation of mental claims.

The current paper discusses the methodological aspects of assessing human cognitive functions from a more practical point of view. The main aim is to provide those individuals who lack a background in experimental cognitive science with a basic overview of the main concepts, issues and pitfalls of human cognitive research. Such knowledge is instrumental in the design of human trials on nutrition and cognition and a critical evaluation of study proposals, reports and articles in this field. In this introductory overview, the area of cognitive psychology and human cognitive assessment can only be addressed in relatively broad terms. For a more detailed discussion of the various concepts and examples of assessment methods the reader is initially referred to the aforementioned PASSCLAIM publication

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[1] and to the accompanying papers by Benton et al. and Kallus et al. in this issue.

Cognitive functions: basic concepts

"Cognitive functions" is a term that is used to describe a great variety of different brain-mediated functions and processes. These brain functions allow us to perceive, evaluate, store, manipulate, and use information from external sources (i.e. our environment) and internal sources (experience, memory, concepts, thoughts), and to respond to this information.

Cognitive functions can be clustered into six main domains: executive functions, memory functions, attention functions, perceptual functions, psychomotor functions and language skills (Fig. 1). Each of the cognitive domains can be further divided in a number of more specified functions. Memory functions, for example, include short-term and long-term memory encoding, storage and retrieval functions and working memory. Further differentiation is made with regard to the type of information that is processed, e.g. auditory, visual, verbal, spatial, abstract, procedures. Attention can be subdivided in selective, divided and sustained attention functions, whereas executive functions encompass more complex processes such as reasoning, planning, concept formation, evaluation and strategic thinking. It is important to note that despite their classification in separate cognitive functions, these various processes are often very much interlinked. Efficient functioning of one cognitive process is often dependent on the integrity of various other cognitive processes. For example, efficient storage of new information in the long-term memory cannot occur without proper attention for the relevant information, adequate perceptual processing, and the use of executive learning strategies. By evaluating cognitive performance over a wide area of cognitive domains it is often possible to gain insight in the relative contribution of the separate cognitive sub-functions.

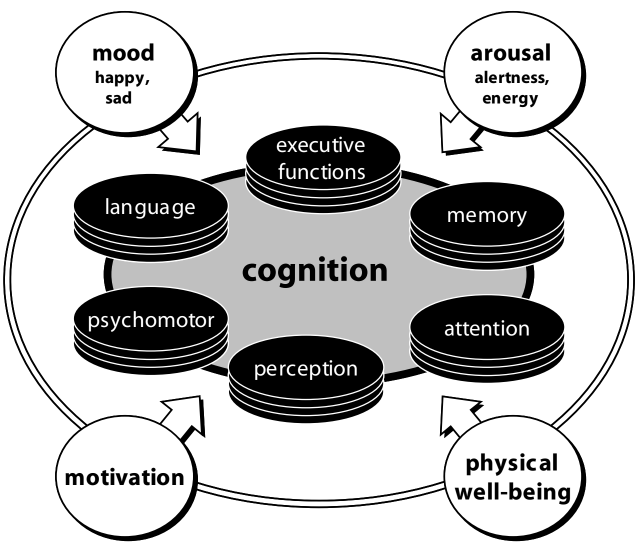

Fig. 1 Schematic representation of the interaction between the cognitive functions (in black) and the factors that may modulate the efficiency of cognitive processing (in white). See text for a more detailed discussion

Cognitive functioning can be modulated by a number of other factors, which are not considered to be cognitive functions themselves (Fig. 1). A key modulator is the level of central arousal, which can be roughly described as the level of "mental energy" or "energetic resources" that are available for cognitive processes [2]. Arousal is not necessarily linked to biological energy, such as ATP availability, but should be seen as a psychological concept that is used to describe performance changes due to mental fatigue or activation, sedation or stimulation. It is thought that the relationship between the level of arousal and task performance follows an inverted U-curve: performance decrements can occur due to under- and over-arousal [3]. The optimal level of arousal level is thought to be inversely related to task complexity (see [4]). Mood state is also known to modulate cognitive function [5], as well as motivation [6]. In addition, physical discomfort can adversely influence cognition. Again, these factors can reciprocally influence each other.

Measurement of cognitive functions

Cognitive functioning can be objectively assessed by a large variety of neuropsychological performance tests (see e.g. [1, 7, 8]). These tests may be designed to primarily target a cognitive function with a certain degree of specificity but may also measure the final outcome of a complex of various cognitive functions. Computerized tests have the advantage of a standardized presentation and accurate and detailed response capture. With appropriate adaptations, they can be used in nearly all populations, including children and cognitively impaired elderly. Alternatively, there is also a great assortment of 'paper and pencil' tests (which often formed the basis for the computerized versions), providing greater mobility and a more personal approach.

The level of performance on a test is usually measured in terms of speed and accuracy of responding, although the emphasis may vary. In certain memory tasks, such as free recall of information, accuracy (the amount of correct information that is retrieved) is the most important or even the only performance indicator. Other tests use speed as the primary outcome measure, for example simple reaction time tests where no errors can be made, or tests in which the error levels are typically very low, for example the Memory Scanning test [9] and Stroop Color Word test [7].

Additional insight in the location and efficacy of a number of cognitive processes can be obtained using electrophysiological measurements, such as electroencephalograms (EEG) with event-related potentials (ERP), whereas functional magnetic resonance imaging (fMRI), positron emission tomography (PET) and magnetoencephalography (MEG) provide insight into the activation of the brain areas that are associated with a specific cognitive task. Whether measures of neural activation can offer independent, valid insights into cognitive processes, i. e. in the absence of overt behavioural changes, is very much a matter of debate [10, 11]. Both behavioural assessments [11] and neural activation measures [12] are subject to shortcomings and the complex relationship between neuronal activity, brain topography and functional ability is presently poorly understood [13]. Any conclusions regarding functional cognitive benefits of nutritional manipulations that are based solely on changes in brain activity should therefore be made with extreme caution.

Several peripheral markers have been correlated with central arousal, such as heart rate, blood pressure, galvanic skin conductance, and peripheral cortisol excretion. Determination of the frequency at which flickering light is perceived as a steady light source (Critical Flicker Fusion threshold, CFF) is also used as a marker of central arousal [14]. Changes in central arousal can also be inferred from more general changes in neuropsychological test performance over a wide area of cognitive domains or in sustained attention tasks that are particularly sensitive to arousal changes [15].

Mood state and physical well-being are assessed using validated self-rating scales (visual analogue scales and questionnaires). Currently, no established objective mood assessment methods are available, but changes in responses to stimuli with emotional valence in neuropsychological tests can provide an indication of mood changes [5].

Several compound measures that provide information on overall cognitive ability are also available. These typically consist of a selection of neuropsychological tests and/or questionnaires yielding a single, composite outcome measure. A well-known example of this type of measure is IQ (intelligence quotient). Another example is the MMSE (Mini Mental State Examination) for dementia. These measures are often designed and validated as tools for comparative studies, individual assessments or clinical diagnosis of a specific cognitive disorder, and although they are sometimes used in an experimental setting, their sensitivity to relatively subtle changes due to short-term nutritional interventions is limited.

Selecting the appropriate outcome measures

The abundance of potential cognitive outcome measures leaves the cognitive researcher with both the opportunity and the necessity to tailor the test battery to the specific requirements of the study. It is clear that the primary cognitive outcome variables should be those that are most likely to be affected by the manipulation. If possible, the selection of these measures should be based on existing experimental data obtained with similar manipulations or with the presumed active ingredient(s) of a new manipulation. In addition, specific performance deficits that have been associated with deficient nutrient intake can be valuable to select cognitive measures for experimental trials with that particular nutrient, but the applicability may be limited for populations without such a deficiency. Sometimes anecdotic reports of perceived beneficial effects of nutrients or herbal substances may also offer helpful clues. If no relevant behavioural results are available, a (probable) mechanism of action together with neurobiological and neuropsychological data may provide an indication of the most plausible cognitive effects. Finally, in the absence of an adequate rationale, a 'shot-gun' approach may be employed, aimed at exploring the effects of a nutritional manipulation over a wide range of cognitive functions.

An additional consideration for test selection is test sensitivity in relation to the expected effect. Tests measuring the appropriate function but with low sensitivity are less suitable to demonstrate relatively subtle effects of nutritional interventions. Sensitivity is strongly associated test-retest variability, i. e. the unexplained fluctuation of performance on the test, and increased variability hinders the detection of significant results. Furthermore, floor and ceiling effects in test performance reduce the sensitivity to detect improvements and impairments, respectively, and should therefore be avoided by adjusting task difficulty to the appropriate level for the study population (e. g. children, college students, elderly, patients). Inappropriate task difficulty may also lead to frustration and loss of motivation. Finally, when using a repeated measures design, the use of different but parallel versions of the cognitive tests at each testing session is essential to avoid variance in performance due to learning effects.

Although a cognitive test battery may consist primarily of measures of the most susceptible cognitive functions, the incorporation of a set of other measures is necessary to correctly interpret the findings. First, the assessment of a variety of cognitive functions provides insight into the specificity of the effect. For example, performance changes over a wide range of cognitive domains suggest that the effect may be mediated by non-specific mechanisms, such as sedation or activation, mood changes or motivation. Also, as discussed earlier, the efficacy of many cognitive functions may depend on the quality of a number of other functions. Additional assessments can provide information on these functional interactions and hence help identify the primary source of performance changes. For example, if test performance is measured in terms of response speed, the assessment of simple reaction times is required to determine the contribution of changes in basic psychomotor speed. The benefits of using a multitude of assessments should be weighed against the potential disadvantages of an (over-)extended test battery. A lengthy task battery induces fatigue and may diminish motivation, leading to possible performance decrements towards the end of the test battery (time-on-test battery effect) and the risk of the order of the test administration becoming an effect modifier. When assessing acute, transient nutritional effects the length of the test battery should be compatible with the duration of the psychopharmacological effect of the manipulation.

Managing performance variability

As is the case with any experimental study, in order to specifically attribute changes in cognitive function to a (nutritional) manipulation, the influence of other potential mediating factors needs to be excluded as much as possible. Furthermore, as the level of cognitive performance is subject to great variability, both between subjects and within one individual, the sources of this variance should be methodologically controlled for as much as possible in order to maximize trial sensitivity.

Using well-defined inclusion and exclusion criteria for the study population is a useful method to limit between-subject variability. Demographical characteristics such as age [16], gender [17], socio-economic background and level of education have been shown to affect various cognitive functions. Health status, both in the present and the past, as well as life events [18] (e.g. exposure to neurotoxins, prolonged stress or physical trauma) may also be strongly associated with the level of cognitive functioning. The use of a selected homogenous study population has clear methodological advantages, but may hamper the generalizability of the findings to a broader population.

The performance level of an individual may fluctuate quite rapidly due to the presence of fatigue, hunger, and physical discomfort, changes in mood and motivation, and the effects of psychoactive compounds, including caffeine and nicotine. Environmental factors, such as noise, ambient temperature and lighting may also influence performance levels. Special care should be taken to exclude or at least standardize these factors as much as possible, hereby limiting within-subjects variability. Often "living instructions" are imposed on the volunteers during or prior to the test days, including dietary rules, restriction of alcohol and drug intake, and guidelines for sleep and exercise. Protocols for food intake and activities during the test days help standardize the conditions under which subjects are tested. The use of secluded, sound insulated rooms to avoid distraction will also reduce variability. To avoid possible circadian influences in performance [19], testing should ideally be scheduled at similar times of the day on each occasion. Confounding factors that cannot readily be controlled or excluded, for example mood changes or adverse effects that may occur as a consequence of the nutritional manipulation, should be measured to assess their potential contribution to any cognitive changes and subsequently taken in account when interpreting the results.

It is well known that cognitive test performance may improve with repeated assessments [20], a phenomenon referred to as procedural learning or practice effects. Unfamiliarity with the study procedures, experimenters and assessment methods may be perceived as stressful and may consequently lead to underperformance, particularly at the initial test session(s). In addition, with repeated testing the subject often learns to employ certain strategies to optimize task performance. The incorporation of one or more separate training sessions in the study design to familiarize the subjects with the tests and study procedures is often used to minimize procedural learning effects. Training sessions have the added benefit of providing an opportunity to verify the subjects' understanding of the test instructions, requirements and objectives prior to actual data collection. To avoid warm-up effects (transient poor performance at the beginning of testing [21]) on the actual test days, a test may start with a series of responses to "dummy" stimuli, which are not included in the analyses.

Interpreting the results

Because of the aforementioned interactions between the various cognitive functions and associated mood and physical states, the interpretation of the findings needs to take into account the overall pattern of results, rather than a function or measurement orientated approach. A main initial question is whether the observed effects can be attributed to one or more primary causes. For example, is there an indication of non-specific cognitive changes due to changes in arousal, mood or physical discomfort? Is such a mechanism supported by any additional subjective or physiological measures? Can changes in for example perception, attention or psychomotor functions underlie effects on other tasks? The identification or exclusion of potential functional interactions greatly enhances the insight in the underlying cognitive mechanisms of performance changes.

Secondly, evaluation of performance level on any particular task generally requires that both speed and accuracy measures are inspected in conjunction to avoid misleading conclusions. This is particularly true when speed and accuracy measures change in opposite directions. This pattern is indicative of speed/accuracy tradeoff, i. e. subjects have sacrificed speed for accuracy or vice versa. For example, it is clear that increased speed of responding accompanied by an increased error rate does not signify improved function. Instead such findings may be suggestive of increased impulsiveness or risk taking behaviour, which is an interesting observation in itself. Since speed of incorrect responses has no relevance to the function that is measured, reaction times for correct responses are the most appropriate primary speed measure. It should always be kept in mind that the significance of any speed changes should be viewed in context of the function that was assessed. In other words, a change in speed in, for example, a working memory task tells us something about working memory; a change in speed in a selective attention task tells us something about selective attention (in absence of general psychomotor changes). As obvious as this may seem, the notion of speed as a function in itself is a common misconception and potentially leads to misinterpretation of behavioural test results.

Furthermore, it is noteworthy that the level of cognition performance is not a passive entity. Normally, an individual is capable of regulating his or her level of performance to a significant extent in order to meet the cognitive demands by temporarily recruiting additional energetic resources for task performance, a mechanism referred to as compensatory effort [22, 23]. Increases in compensatory effort can temporally counteract decrements in specific cognitive functions. This means that relatively subtle changes in cognitive abilities may not produce any overt changes in task performance, particularly when tasks are of short duration. This is particularly true in the typical setting of cognitive research, where the awareness of being monitored generally motivates subjects to perform well. Although not commonly applied, it is clear that considering 'costs' of performance in addition to overt performance levels may provide a more genuine picture of changes in cognitive abilities following (nutritional) manipulations. Such costs may become noticeable as increased fatigue after testing sessions, in subjective ratings of task difficulty or by changes in secondary performance measures in complex tasks where only the primary component is usually protected [24].

Finally, an important and valid question is how results that are obtained in neuropsychological studies relate to real life situations. There is an ongoing debate whether the experimental setting, the nature of the test stimuli and the required responses are representative of the world outside the psychological laboratory [25]. Neuropsychological test results have been shown to be correlated with the ability to perform activities of daily living, employability, job performance and driving competence in individuals with various conditions [7, 26, 27], but data pertaining to healthy subjects are very limited [27]. The use of performance tests that resemble real life activities, for example actual car driving on public roads [28], improves the ecological validity of the test method, but due to difficulties in defining an objective overall measure of complex behaviour, ultimately the level of performance remains often expressed based on (a limited number of) measurable sub-functions. Nevertheless, it is clear that separate cognitive (sub-)functions are the building blocks of more complex cognitive behaviours that are common in real life. Although changes in individual functions are therefore likely to influence cognitive behaviour in daily life, the actual impact remains difficult to predict and varies depending on the magnitude and nature of the effects, the individual requirements in professional and leisure activities, and use of compensatory strategies (see [27] for a detailed discussion).

Concluding remarks

Food components can affect brain cell structure and integrity, neurotransmission and signal transduction, brain energy supply and metabolism. There is no doubt that nutrition has the potential to influence brain function. The challenge for future research is to identify, specify and characterize the interaction between food constituents and mental state and performance. Epidemiological associations, animal data and in vitro studies can provide valuable clues to this end. However, intervention studies in humans are essential to verify the actual functional benefits of particular nutrients or diets. It has been pointed out that the data on cognitive enhancing drugs obtained in animal models generally have poor predictive value for humans [29]. With nutritional interventions, where toxicology is often not an issue, it may therefore be most efficient, in both scientific and financial terms, to immediately test the behavioural effects in humans.

With the appropriate study design and procedures, behavioural assessment is the key method to gain objective insight into human cognitive abilities and the changes herein due to the effects of psychoactive compounds, including nutrients. Although some general strategies in order to maximize trial sensitivity and obtain valid, interpretable data can be identified, the operationalization of each study calls for a customized approach taking in account the specific study aims (what needs to be substantiated?), product characteristics (seems prudent to measure?) and target population (what is feasible to measure?). It is clear that considerations from a behavioural science perspective on the study's outcome component should be complemented by expertise from nutrition sciences and human biology on the specifics of the nutritional manipulation. Such an interdisciplinary approach is vital for a fruitful exploration of dietary effects on behaviour.

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