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Validation of reaction time as a measure of cognitive function and quality of life in healthy subjects and patients

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ABSTRACT

Objective: Malnutrition is a common problem in hospitalized patients and is related to decreased cognitive function and impaired quality of life (QoL). We investigated the validity of reaction time as a simple bedside tool for measuring cognitive function in healthy subjects and patients, and additionally the relationships with QoL and malnutrition in patients.

Methods: Healthy subjects ($N = 130$) were assessed for simple and complex reaction time and cognitive function (Addenbrooke cognitive examination, ACE). Patients ($N = 70$) were assessed for simple and complex reaction time, cognitive function (ACE), and QoL (short-form health survey) ($N = 40$).

Results: Reaction time was related to cognitive function in both healthy subjects and patients. Reaction time was inversely related to the physical component summary of QoL in patients ($r = -0.42$, $P < 0.001$). Five of eight QoL scales and the mental component summary of QoL were significantly lower in malnourished patients. Reaction time and ACE were impaired in patients compared to healthy subjects, but not further impaired in malnourished patients.

Conclusion: Simple reaction time test is related to cognitive function in healthy subjects and patients and to QoL in patients. Complex reaction time test is related to more components of cognitive function. Thus, simple and complex reaction time tests could serve as bedside measurements reflecting, respectively, QoL or cognitive function.

Introduction

About 40% of hospitalized patients are malnourished [1,2] and this affects both morbidity and mortality [3]. Malnutrition is related to impaired quality of life (QoL) in patients with various diseases [4–9] and nutritional therapy improves both the physical and the mental scores of QoL, as determined by the short-form health survey (SF-36) [10,11]. One shortcoming of QoL questionnaires is the subjective recording of well-being. It would be useful with objective bedside tests reflecting the physical and mental scores of QoL, e.g., for assessment of nutritional status, for monitoring nutritional therapy and as outcome variables in controlled clinical trials.

We have previously validated handgrip strength as a simple bedside test by showing a positive correlation between handgrip strength and the physical and mental components of SF-36 in hospitalized patients [12]. We also showed that a physical performance test, Timed Up and Go, correlated with both handgrip strength and the physical and mental components of SF-36, which conceptually supported the association between QoL, physical performance, and the simple bedside test.

In this study, we examined the possibility that a continuous reaction time test more specifically may reflect the mental component of SF-36. We included a cognitive test, Addenbrooke Cognitive Examination [13], as a performance test, to examine the possible conceptual relationship between the simple bedside reaction time test and the mental component of SF-36.

Nutritional supplementation and/or adequate dietary intake has been shown to improve cognitive function (memory, attention, and verbal fluency [14–16]) or reaction time [14] in the elderly, but their relationship has not been examined and similar studies are not available in younger hospitalized patients. We also included an analysis of the possible relationship between the physical and mental tests by combining the data in this

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article with those in the previous article [12] and comparing the simple bedside tests (reaction time and handgrip strength), the performance tests (Addenbrooke cognitive examination and Timed Up and Go), and the physical and mental components of SF-36.

Subjects and methods

Study protocol

The study was conducted in three parts. Part I was carried out in healthy subjects and validated a simple auditory Continuous Reaction Time (CRT) test against cognitive function (Addenbrooke cognitive examination = ACE). Part II was conducted in healthy subjects and validated visual simple and complex reaction time tests from the test-battery for attentional performance (TAP) against cognitive function (ACE). Part III was carried out in hospitalized patients and validated a complex reaction time test from TAP against cognitive function (ACE). A subgroup ($N = 40$) of the patients in part III also performed the simple reaction time test (TAP) and answered the SF-36 questionnaire (overview of measurements in Table 1).

All measurements were performed in a standardized way during the daytime with the door closed, no disturbances, and in the postabsorptive phase.

Healthy subjects and patients

A total of 130 healthy subjects were studied, 56 (14 males, 42 females) and 74 (36 males, 38 females) subjects in parts I and II, respectively. These subjects were within an age range of 19-68 y and were recruited among students and employees from the Faculty of Life Sciences, by advertisement via an internal mail portal and posters at Faculty of Life Sciences, University of Copenhagen. Body mass index was calculated from reported body weight and height.

Seventy patients (32 males, 38 females) were included in part III and were recruited by daily visits to departments of surgery, gastroenterology, oncology, and internal medicine. All newly admitted patients were included if the nurse responsible for the patient considered the patient to be eligible.

Subjects and patients above 18 y were included. Subjects and patients with mental illness or a history of head trauma were excluded. Fifty-six of the healthy subjects and 40 of the patients were the same as those in Jakobsen et al. [12], now supplemented with 74 healthy subjects and 30 patients undergoing the TAP tests and ACE. Study design and selection of healthy subjects and patients were similar in the two studies. NRS-2002 [17] was used to determine if patients were at risk for nutrition-related complications. The study was approved by the local ethics committee. Healthy subjects and patients were recruited after obtaining verbal or written consent, respectively.

Reaction time

In part I, reaction time was assessed by a simple auditory CRT test, whereas in parts II and III reaction time was assessed by TAP, which included simple and complex visual reaction time tests. This change was based on a study by Fontani et al. [18], which showed that nutritional intervention with omega-3 fatty acids improved complex, but not simple, reaction time tests.

Simple continuous reaction time (CRT)

The CRT test was conducted using the EKHO system (Bitmatic, Aarhus, Denmark), which includes a set of earphones and a button connected to a computer. Subjects were exposed to a series of 150 auditory signals (500 Hz, 90 dB) at 2- to 5-s random intervals over 10 min. Participants were instructed to press the button with their thumb as fast as possible, as previously described by Elsass et al. [19]. The median reaction times for the CRT test were calculated using the EKHO system for Windows, Version 1.3.

Test battery for attentional performance (TAP)

The TAP tests consisted of three tests chosen from the tests available in TAP 2.1 (PsyTest, Herzoganrath, Germany), as in Fontani et al. [18]. The healthy subjects performed all three tests, whereas the patients performed only the Go/No-Go test (see below).

The tests were conducted according to [20]. The participant sat comfortably in front of a computer screen and responded to each stimulus by pressing a button connected to the computer with the forefinger of their dominant hand. Participants performed pretests for training and a 5-min rest was given between each test. The tests were performed in the following order:

1. Alertness: The subject was exposed twice to a series of 80 visual signals on the screen over 5 min, first without and then with a preceding auditory warning stimulus, designated intrinsic and phasic alertness, respectively [20]. It is a simple reaction time test and analyzes the subject's ability to react and maintain a high level of attention in anticipation of a stimulus. It does not require central analysis, but is rather a measure of pure reactivity [18], i.e., mainly speed of nerve conduction [21].
2. Go/No-Go: The participant is instructed to react only to two of five different figures, which appear consecutively one at a time with 60 stimuli over 3 min. The figures are square shaped patterns, which are rather similar in appearance. It is a complex, i.e., conditional, recognition reaction time test and analyzes the subject's ability to react to some stimuli and to withhold a response to others. It requires central analysis with suppression of undesired responses, i.e., a cognitive effort, in addition to reactivity [18].
3. Sustained Attention: The participant is instructed to react to figures of varying shapes, colors, fillings, and sizes, which appear consecutively one at a time, but only if the same shape appears twice in a row regardless of color, filling, and size. The test lasts for 15 min and includes 450 stimuli presented at regular intervals (i.e., every 2 s). This is also a conditional, recognition reaction time test and analyzes the subject's ability to maintain attention for a long period of time (endurance) in addition to central analysis with suppression of undesired responses, and reactivity.

Results were calculated using the TAP system for Windows Version 2.1. Errors, which happen if the subject responds prior to the stimuli and omissions, which happens if the subject neglects a stimulus, were registered by the TAP system. In this study, the sum of errors and omissions is presented as "Errors."

Addenbrooke cognitive examination (ACE)

The ACE test of cognitive function consists of six subtests assessing orientation, attention/concentration, verbal fluency, memory, language and visuospatial function [13]. ACE was developed from the mini-mental state examination (MMSE) to allow diagnosis of early Alzheimer's disease. It is reliable and sensitive for early dementia [13] and has also been shown to be applicable to other neurological diseases [22]. Mathuranath et al. observed a ceiling effect of the ACE test when measuring cognitive function in healthy subjects [13]. To avoid this, we modified the test by increasing the difficulty of the subtests assessing attention/concentration, verbal fluency, and memory (see English translation in Appendix 1). In the original test of attention/concentration, the participant is asked to continuously subtract 7 from 100 for a total of 5 subtractions, in which one point is given for each correct answer (93-65). In our modified version, the subject was asked to subtract 7 from 100 until the subject reached 2 (a total of 14 subtractions). We gave a maximum score of 5 if the complete test was performed correctly and one point

Table 1
Overview of measurements

	Healthy subjects ($N = 130$)		Patients ($N = 70$)
	Part I ($n = 56$)	Part II ($n = 74$)	Part III
Continuous reaction time (CRT)	X		
Test of attentional performance (TAP)		X	X
Addenbrooke cognitive examination (ACE)	X	X	X
Short form-36 (SF-36)			X (n = 40)

The study was conducted in three parts. Part I was carried out in healthy subjects and validated a simple auditory Continuous Reaction Time test against cognitive function (Addenbrooke Cognitive Examination). Part II was conducted in healthy subjects and validated visual simple and complex reaction time tests from the Test-battery for Attentional Performance (TAP) against cognitive function (ACE). Part III was carried out in hospitalized patients and validated a complex reaction time test from TAP against cognitive function (ACE). A subgroup ($N = 40$) of the patients in part III also performed the simple reaction time test (TAP) and answered the SF-36 questionnaire.

was subtracted for each incorrect answer. In the original test, verbal fluency is tested in two parts: 1) by asking the participant to name as many animals as possible and 2) by asking the participant to mention all words he could think of, starting with the letter P, except persons and places. Participants are given 60 s for each part in the original test and this was decreased to 45 s in our test. A maximum score of 8 was given if the subject could name more than 25 words. A score of 7 was given if the subject could name 21-25 words, etc. (see scores in Appendix 1). In the original test, memory is tested by the investigator's reading out loud a two-word name and a 5-word address of a fictive person and the participant is asked to repeat the complete name and address 4 times during the ACE test. In our modified version, a postal code was added to the address, resulting in a maximum score of 8 instead of 7 for each of the four trials.

Quality of life

QoL was assessed by SF-36v2 as described earlier [12], using the standard scoring algorithms described by Ware et al. [23] and summarized into two dimensions: physical component summary (PCS) and mental component summary (MCS).

Physical function

Handgrip strength was measured in the right hand with a Jamar 5030J1 Hydraulic Hand Dynamometer (Sammons Preston Rolyan, Bolingbrook, IL, USA), and mobility was measured by the Timed Up and Go test (TUG) as previously described by Jakobsen et al. [12].

Statistical analysis

Data were evaluated for Gaussian distribution and for clarity; all results are presented as means ± SD. To determine statistical significance of differences between groups, the Student's unpaired *t* test or the Mann-Whitney *U* test were used in accordance with the distribution of the variables (specified in the tables). For correlation analyses, Pearson's or Spearman's correlation coefficients were calculated depending on the distribution of the data (specified in the tables and figures).

Reaction time in patients was compared to that of healthy subjects by employing a general linear model (GLM), adjusting for age, gender, education, and body mass index and using patient (yes/no) as a categorical independent variable. GLM was also used to assess the association between the five individual components of NRS-2002 (i.e., BMI, weight loss, food intake the week before hospitalization, severity of disease, and age) and QoL ($N = 40$), ACE ($N = 70$), and reaction time ($N = 70$). The analysis of data of the present and the previous [12] studies, combining healthy subjects and patients, was also performed by GLM with patient (yes/no) as a categorical independent variable.

An acceptable level of statistical significance was established at $P < 0.05$. Statistical analysis was carried out using the software package SAS System for Windows Version 9.1 (SAS Institute Inc., Cary, NC, USA).

Results

Healthy subjects

Table 2 summarizes the characteristics of the healthy subjects and the results on the reaction time tests (CRT or TAP), and cognitive function (ACE). No subject scored the maximum points possible for ACE (max score = 89, cf. Appendix 1), indicating that our modifications eliminated the ceiling effect previously found [13].

Reaction time and cognitive function in healthy subjects

The CRT test was significantly inversely correlated to total ACE (Fig. 1) and to memory and verbal fluency (Table 3). The phasic alertness was related to language, and the Go/No-Go was significantly related to orientation, verbal fluency, and language (Table 3). Gender has been shown to affect various cognitive/mental functions [24], including reaction time tasks [25]. In our study, there was no difference in ACE, but males had a faster reaction time than females in intrinsic alertness ($P < 0.001$), phasic alertness ($P < 0.05$), Go/No-Go ($P < 0.001$), and sustained attention ($P < 0.01$). There were no gender differences regarding numbers of errors and omissions.

Table 2
Characteristics and cognitive function of 130 healthy subjects and 70 patients

	Healthy subjects ($N = 130$)	Patients ($N = 70$)
Gender (male/female)	50/80	32/38
Age (y)	29.3 ± 8.6	53.9 ± 14.2
Weight (kg)	69.1 ± 11.3	73.5 ± 18.0
Height (m)	1.75 ± 0.1	1.74 ± 0.08
Body mass index (kg/m^2)	22.5 ± 2.4	24.2 ± 5.4
Nutritional Risk Score ≥3	–	$N = 47$ (67.1 %)
Education: Primary school	4 (3%)	22 (31%)
Bachelor level	57 (43.8%)	27 (39%)
Master level	69 (53.1%)	7 (10%)
Missing	–	14
CRT (ms)	154 ± 23 ($N = 56$)	–
TAP intrinsic alertness (ms)	242 ± 31 ($N = 74$)	301 ± 55 ($N = 40$)†
TAP intrinsic alertness errors	0.0 ± 0.0 ($N = 74$)	0.0 ± 0.0 ($N = 40$)
TAP phasic alertness (ms)	243 ± 31 ($N = 74$)	291 ± 49 ($N = 40$)†
TAP phasic alertness errors	0.0 ± 0.2 ($N = 74$)	0.0 ± 0.2 ($N = 40$)
TAP Go/No-Go (ms)	481 ± 56 ($N = 74$)	620 ± 86†
TAP Go/No-Go errors	0.6 ± 0.8 ($N = 74$)	2.9 ± 5.1*
TAP sustained attention (ms)	461 ± 79 ($N = 74$)	–
TAP sustained attention errors	4.1 ± 4.6 ($N = 74$)	–
ACE total score	78.8 ± 5.8	66.6 ± 12.2†
Orientation	9.7 ± 0.6	9.3 ± 1.1
Attention/concentration	5.3 ± 1.4	4.2 ± 2.2
Memory	33.1 ± 4.1	26.8 ± 7.1
Verbal fluency	13.4 ± 1.7	10.8 ± 2.9
Language	12.7 ± 0.6	12.3 ± 1.0
Visuospatial abilities	4.7 ± 0.6	3.3 ± 0.9
Physical component summary ($N = 40$)	–	36.7 ± 10.7
Mental component summary ($N = 40$)	–	41.5 ± 14.7

Data are presented as mean ± SD.
ACE, Addenbrooke's Cognitive Examination; CRT, Continuous Reaction Time
Orientation, attention/concentration, memory, verbal fluency, language, and visuospatial abilities are components of ACE. Physical and mental component summaries are compounds of quality of life
Student's *t* test for unparied data was used for comparison (reaction time tests and cognitive function) between healthy subjects and patients.
* $P < 0.01$; † $P < 0.001$. These differences remained even after adjusting for differences in age, gender, education, and body mass index by GLM.

Difference between healthy subjects and patients

The 70 patients were distributed within the following diagnoses: 5 with cardiovascular disease, 1 with gastrointestinal disorders, 18 with infectious disease, 11 from rheumatology, 33 from oncology/haematology, and 2 from abdominal surgery.

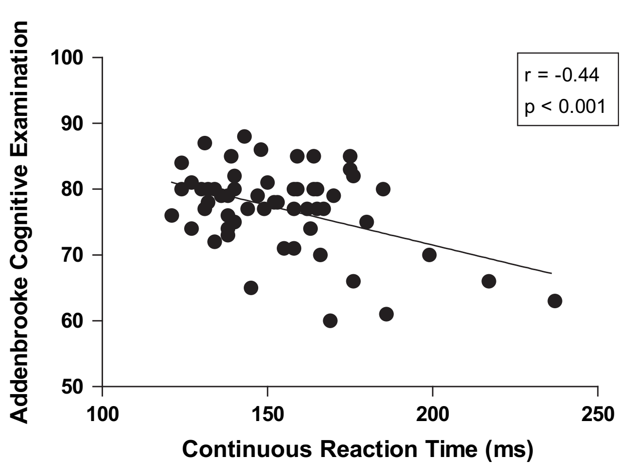

Fig. 1. Relationship between simple (CRT) reaction time and cognitive function (Addenbrooke Cognitive Examination) in 56 healthy subjects. Data were analyzed by Pearson correlation.

Table 3
Correlation coefficients (r) between reaction time and cognitive function in healthy subjects

Variable	ACE total	Orientation	Attention concentration	Memory	Verbal fluency	Language	Visuospatial abilities
CRT	$-0.44^{\ddagger}{}_{P}$	NS	NS	$-0.41^{\dagger}{}_{P}$	$-0.33^{*}{}_{P}$	NS	NS
Intrinsic alertness	NS	NS	NS	NS	NS	NS	NS
Phasic alertness	NS	NS	NS	NS	NS	$-0.25^{*}{}_{S}$	NS
Go/ No-Go	NS	$-0.25^{*}{}_{S}$	NS	NS	$-0.28^{*}{}_{P}$	$-0.27^{*}{}_{P}$	NS
Sustained attention	NS	NS	NS	NS	NS	NS	NS

The labels of the columns in the table present the ACE total score and ACE components. The rows present the reaction time tests. Numbers in the table are correlation coefficients (r) between reaction time and cognitive function performed by using either $_P$ = Pearson Correlation or $_S$ = Spearman Rank.
Results from part I and II are presented together.
ACE, Addenbrooke's cognitive examination; CRT, continuous reaction time; NS, not significant
Orientation, attention/concentration, memory, verbal fluency, language, and visuospatial abilities are components of ACE.
* $P < 005$.
† $P < 001$.
‡ $P < 0001$.

Characteristics, reaction time (TAP), cognitive function (ACE), and QoL of the patients are given in Table 2. After adjusting for differences in age, gender, education, and body mass index by GLM, the patients had longer reaction times in intrinsic alertness (24.0 ms), phasic alertness (22.9 ms), and Go/No-Go (66.0 ms) (all variables $P < 0.0001$), more errors in Go/No-Go (0.4; $P < 0.01$), and a lower score for ACE (−9.3; $P < 0.0001$) as compared to healthy subjects.

Reaction time and cognitive function in relation to quality of life in patients

Table 4 shows that phasic alertness was related to the ACE component orientation and that Go/No-Go was related to ACE total (Fig. 2) and the components attention/concentration, memory, verbal fluency, and language. Both intrinsic and phasic alertness were related to the PCS of QoL (Fig. 3). There were, however, no relationships between the complex reaction time tests or ACE with the PCS or MCS in QoL (Table 4).

Of the 40 patients given the SF-36 questionnaire, 16 were at-risk according to NRS-2002 [17]. The 16 patients were nutritionally at risk due to a combination of variables in the NRS-2002. Two patients had mildly impaired nutritional status, a mild severity of disease, and were ≥70 y. Eight patients had moderately impaired nutritional status and a mild severity of disease. Two patients had moderately impaired nutritional status, a mild severity of disease, and were ≥70 y. One patient had moderately impaired nutritional status and a moderate severity of disease. Four patients had severely impaired nutritional status and a mild severity of disease. Data are not shown. Both at-risk and not at-risk patients had impaired QoL in all scales when compared to normative values for the Danish adult population [23] (Fig. 4). The patients at risk had a significantly lower body mass index (23.2 ± 5.1 versus 26.5 ± 5.5, $P < 0.05$) and lower physical functioning, role physical, vitality, social functioning, role emotional, and MCS, as compared to patients not at risk (Fig. 4). There were no differences in TAP or ACE score between patients at risk and not at risk. However, when examined by GLM, the score for "food intake in the week before hospitalization" was positively associated with reaction time in $TAP_{Go/No\text{-}Go}$ ($P = 0.0116$), i.e., a low intake was associated with a prolonged reaction time.

Relationship between physical and cognitive/mental functions

Table 5 is a cross-analysis and a summary of the findings of the present and the previous article [12]. It shows that there was no relationship between the simple bedside tests (reaction time measured by CRT or TAP and handgrip strength). There was a significant relationship between the simple reaction time tests and the performance test Timed Up and Go. In addition, there was a significant relationship between the two performance tests (ACE versus Timed Up and Go). In patients, MCS was related to handgrip strength and Timed Up and Go and PCS was related to the simple reaction time tests, intrinsic and phasic alertness.

Discussion

Our results suggest that reaction time test may be a valid measure of cognitive function (ACE), or components of it, in both healthy subjects and patients. CRT correlated with the total ACE score and the ACE components: Memory and Verbal fluency in healthy subjects. The Go/No-Go test correlated with three components of ACE (Orientation, Verbal fluency, and Language)

Table 4
Correlation coefficients (r) between reaction time, cognitive function, and quality of life (SF-36) in patients

Variable	ACE total	Orientation	Attention/conc	Memory	Verbal fluency	Language	Visuospatial abilities	PCS	MCS
Intrinsic alertness	NS	NS	NS	NS	NS	NS	NS	$-0.42^{\dagger}{}_{P}$	NS
Phasic alertness	NS	$-0.31^{*}{}_{S}$	NS	NS	NS	NS	NS	$-0.38^{*}{}_{P}$	NS
Go/No-Go	$-0.43^{\ddagger}{}_{S}$	NS	$-0.26^{*}{}_{S}$	$-0.38^{\dagger}{}_{P}$	$-0.58^{\ddagger}{}_{S}$	$-0.37^{\dagger}{}_{S}$	NS	NS	NS
ACE total								NS	NS

The labels of the column in the table present the ACE total score, ACE components, and physical- and mental summary components (PSC and MSC) of quality of life. The rows present the reaction time tests and ACE total score. Numbers in the table are correlation coefficients (r) between reaction time, cognitive function, or PSC and MCS performed by using either $_P$ = Pearson Correlation or $_S$ = Spearman Rank.
ACE, Addenbrooke's cognitive examination. Orientation, attention/concentration, memory, verbal fluency, language, and visuospatial abilities are components of ACE.
MCS, mental component summary; NS, not significant; PCS, physical component summary Physical and mental component summaries are compounds of quality of life.
* $P < 0.05$.
† $P < 0.01$.
‡ $P < 0.001$.

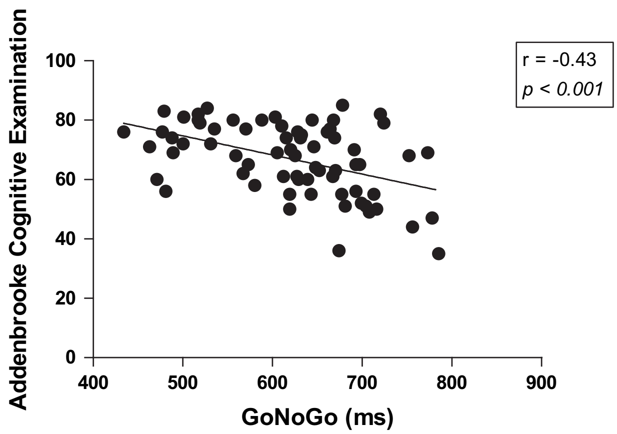

Fig. 2. Relationship between complex reaction time test (Go/No-Go) and cognitive function (Addenbrooke cognitive examination) in 40 patients. Data were analyzed by Spearman Rank.

in healthy subjects. We observed some corresponding correlations between measurements in healthy subjects and patients, i.e., correlations between Go/No-Go reaction time and the ACE components: Verbal fluency and Language.

Reaction time and cognitive function in healthy subjects

CRT and intrinsic alertness are similar in that they are both simple reaction time tests. Fontani et al. found that alertness was primarily a reflection of speed of nerve conduction, rather than speed of muscle contraction [21]. Intrinsic alertness was slower than CRT (Table 2), which can be explained by the different types of stimulus (i.e., visual reaction is slower than auditory reaction) [26], the electronic equipment involved, and/or the test conditions [27].

The CRT test correlated with ACE, whereas the intrinsic alertness did not. This may be explained by the fact that the CRT test lasts 10 min versus 5 min for the alertness test, and CRT may therefore be closer to the limit of continuous mental performance. Continuous mental performance may also be limiting for the tests of memory and verbal fluency, reflected in the total score of ACE.

The correlation between the 3-min Go/No-Go test and the components of ACE (orientation, verbal fluency, language) in healthy subjects may reflect that both tests require central analysis. Also in patients, the Go/No-Go test correlated with total score (Fig. 2) and components of ACE (attention/concentration, memory, verbal fluency, and language). The three components of ACE (orientation, verbal fluency, and language), which correlated with the Go/No-Go test in healthy subjects, are considered to be basic cognitive processes, which serve as building blocks for the development of higher intellectual abilities [28].

The 15-min sustained attention test also requires central analysis and, in addition, continuous mental performance. It was our impression, however, that the subjects developed their own system of mumbling-verbal recognition of the simple and easily discernible geometric shapes (circle, ellipse, square, and rectangle) during sustained attention. In contrast, the black and white patterns in the Go/No-Go test are more complex and not easily labeled or defined, and they are also more similar in appearance. This may require a higher degree of intensity in attention throughout the entire test, although it is of shorter duration. A less demanding analytical processing required in sustained attention may explain that reaction time was significantly shorter (mean $\pm$ SD: 19.7 $\pm$ 59.8 ms, $P < 0.006$) in sustained attention as compared to Go/No-Go (Table 2).

Difference between healthy subjects and patients

The patients had an 8% to 10% longer reaction time in all TAP tests, more errors and omissions, and 14% lower ACE scores compared to healthy subjects, after adjusting for differences in age, gender, education, and body mass index. To our knowledge, this is the first study reporting longer reaction times and reduced ACE in patients with somatic diseases. Longer reaction time has been found to be related to difficulties in maintaining attention, especially when being distracted, and having difficulties in organizing things, which can result in careless mistakes and forgetfulness [29]. Interindividual differences in reaction time performance have also been found to be related to differences in the physiological properties of white matter [30]. Cognitive function is modulated by a number of factors that are not considered to be cognitive functions themselves, such as “mental energy,” motivation, and mood [18]. In addition, physical discomfort can adversely influence cognition and all of these factors can reciprocally influence each other [24]. It is likely that all these factors are affected in patients admitted to hospital.

Reaction time and cognitive function in relation to quality of life in patients

As expected, QoL was impaired in the patients when compared to normative data from Denmark [23]. The intrinsic and phasic alertness tests were related to the PCS of QoL (Fig. 3 and Table 4). If these simple reaction time tests primarily

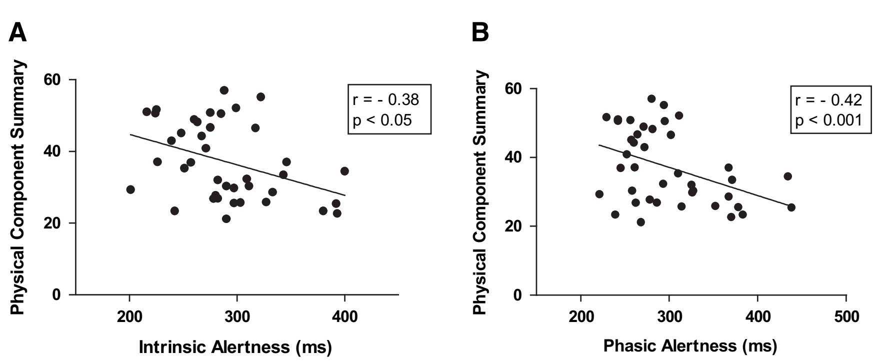

Fig. 3. Relationship between the simple reaction time tests: (A) intrinsic alertness and (B) phasic alertness and physical component summary of quality of life in patients ($N = 40$). Data were analyzed by Pearson correlation.

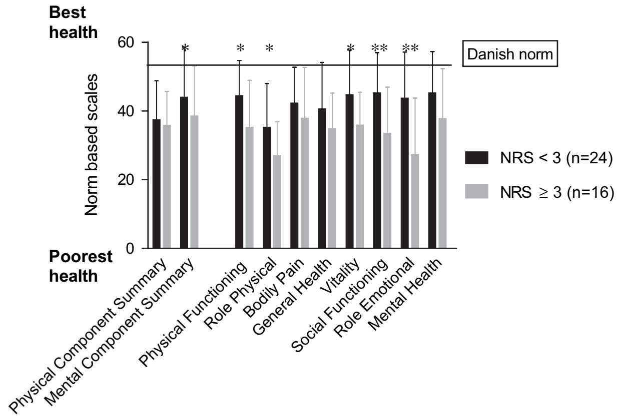

Fig. 4. Comparison of quality of life in patients not at risk versus patients at risk. All patients reported impaired quality of life in all scales when compared with norm values from the Danish adult population. Impaired quality of life was more pronounced in patients at risk. Data are presented as mean ± SD. The Mann-Whitney *U* test was used to determine the statistical significance of differences between groups. $^*P < 0.05$; $^{**}P < 0.001$.

reflect speed of nerve conduction [21] and physiological properties of white matter [30], this relationship may indicate that patients with short reaction times experience relatively few physiological limitations and therefore score a high PCS. The more complex Go/No-Go test, which was related to components in ACE, but not to PCS, reflects information processing rather than merely speed of nerve conduction [21] and therefore may not be tightly linked to physical function but still related to the more complex cognitive function.

There was no relationship between reaction time and MCS, or between ACE and MCS, indicating that neither test reflects the mental component of SF-36. We propose that this may be because cognitive function is not an important part of MCS of SF-36. MCS is in fact rather a measure of mood and social drive [31].

Effect of nutritional risk and gender

Patients at risk had significantly lower scores in five of eight scales in QoL, leading to a significant impairment of the MCS as compared to patients not at risk. This is similar to findings in other studies, which have observed an association between QoL and nutritional status [4–9]. Our study is the first to show an association between QoL and nutritional risk according to NRS-2002. In our previous article [12], the patients at risk had lower values for HGS and TUG, as compared to patients not at risk, but in the present article neither simple or complex reaction times (TAP) nor ACE was found to be affected by nutritional status. This suggests that reaction time (nervous reactivity, central analysis, endurance) and cognitive function are preserved functions during disease-related malnutrition, in contrast to muscle function. However, the association between inadequate intake of food in the week before hospitalization and a prolonged reaction time ($TAP_{Go/No\text{-}Go}$) suggests that a recent impairment of nutritional status affects reactivity and central processing. Still, this association needs to be confirmed in a larger study.

Concordantly with other studies [18,25,26], we observed that among healthy subjects, males performed better than females on the various reaction time tests, which have been ascribed to different attitudes and experiences [18,26].

Relationship between physical and cognitive/mental functions

Cognitive function seems to be related to physical fitness [32]. The cross-analysis of physical and cognitive/mental functions in Table 5 showed that the simple tests of reaction time were related to the performance test TUG and that the performance test ACE was related to the performance test TUG. The relationship between the performance tests (ACE and TUG) may be due to overlapping features of TUG requiring central cerebral processing during an inexperienced challenge, in addition to nerve and muscle function, and ACE requiring central analysis. The correlation between the simple tests of reaction time and the performance test TUG may reflect the nerve reactivity required for both exercises.

Simple reaction time was also related to PCS, suggesting that nerve reactivity required for the simple reaction time test is an important component of the scales summed up in the PCS of SF-36. HGS was related to MCS, and also to PCS [12]. Because the scales summed up in MCS mainly reflect mood and social drive, the relationship between HGS and MCS may reflect the motivation to employ a maximal force during the HGS test. MCS and

Table 5
Relationships between physical and cognitive/mental functions in healthy subjects and quality of life (SF-36) in patients

		Cognitive/mental functions		
		Simple tests (Reaction time)	Performance test (ACE total score)	MCS
Physical functions	Simple test (HGS)	CRT: NS (56 h, 0 p) IA, PA, Go: NS (0 h, 40 p)	NS (56 h, 40 p)	$r_s = 0.41^{\dagger}$ (0 h, 40 p)
	Performance test (TUG)	CRT: $r_p = 0.36^{\dagger}$ (56 h, 0 p) IA: $r_s = 0.52^{\dagger}$ (0 h, 40 p) PA: $r_s = 0.51^{\dagger}$ (0 h, 40 p) Go: NS (0 h, 40 p)	$r_{GLM} = -0.57^{\ddagger}$ (56 h, 40 p)	$r_s = 0.44^{*}$ (0 h, 40 p)
	PCS	IA: $-0.42^{\dagger}{}_P$ (0 h, 40 p) PA: $-0.38^{*}{}_P$ (0 h, 40 p) Go: NS (0 h, 40 p)	NS (0 h, 40 p)	NS (0 h, 40 p)

The labels of the column in the table presents the cognitive/mental functions including reaction time tests, ACE total score, and mental summary component of quality of life. The rows present physical functions including handgrip strength, timed up and go, and physical summary component of quality of life. Numbers in the table are correlation coefficients (*r*) between the above-mentioned variables performed by using either $_P$ = Pearson Correlation, $_S$ = Spearman Rank, or $_{GLM}$ = General Linear Model. Numbers in parentheses present the number of healthy subjects (h) and patients (p) in the analysis.
Reaction time tests include CRT (continuous reaction time), IA (intrinsic alertness), PA (phasic alertness), Go (Go/No-Go), and SA (sustained attention).
ACE, Addenbrooke's cognitive examination; GLM, a combined analysis of data of the present and the previous [12] study was performed with patient (yes/no) as a categorical independent variable, when data were obtained in both healthy subjects and patients; HGS, handgrip strength; NS = not significant; TUG, timed up and go
* $P < 0.05$.
† $P < 0.01$.
‡ $P < 0.001$.

PCS were not related to each other (Table 5). This confirms that PCS and MCS are independent components of QoL.

Limitations of the study

This study has certain limitations. The sample size was relatively small and we may have lacked the sensitivity to detect subtle associations. To generalize our results, a study with a larger number of subjects is essential. Patients receiving sedatives, morphine, which is known to influence reaction time, were included. If such patients had been excluded, the associations may have been different.

Conclusion

A simple reaction time test is valid as a measure of cognitive function in healthy subjects and patients and of QoL in patients. A complex reaction time test is related to more components of cognitive function, both in healthy subjects and in patients but not to QoL in patients. Cognitive function is not related to QoL in patients. Thus, simple and complex reaction time tests could serve as bedside measurements reflecting, respectively, QoL or cognitive function.

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References

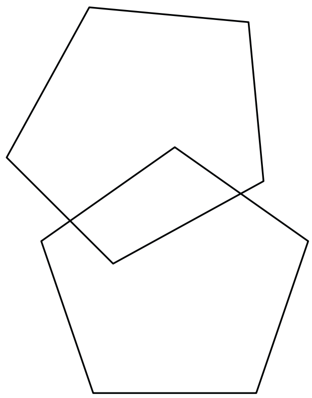
[1] Rasmussen HH, Kondrup J, Staun M, Ladefoged K, Kristensen H, Wengler A. Prevalence of patients at nutritional risk in Danish hospitals. Clin Nutr 2004;23:1009–15.
[2] Stratton RJ, Elia M. Deprivation linked to malnutrition risk and mortality in hospital. Br J Nutr 2006;96:870–6.
[3] Stratton RJ, Green CJ, Elia M. Disease-related malnutrition. an evidence-based approach to treatment. Wallingford: CABI; 2003.
[4] Gupta D, Lis CG, Granick J, Grutsch JF, Vashi PG, Lammersfeld CA. Malnutrition was associated with poor quality of life in colorectal cancer: a retrospective analysis. J Clin Epidemiol 2006;59:704–9.
[5] Kalantar-Zadeh K, Kopple JD, Block G, Humphreys MH. Association among SF36 quality of life measures and nutrition, hospitalization, and mortality in hemodialysis. J Am Soc Nephrol 2001;12:2797–806.
[6] Laws RA, Tapsell LC, Kelly J. Nutritional status and its relationship to quality of life in a sample of chronic hemodialysis patients. J Ren Nutr 2000;10:139–47.
[7] Norman K, Kirchner H, Lochs H, Pirlich M. Malnutrition affects quality of life in gastroenterology patients. World J Gastroenterol 2006;12:3380–5.
[8] Nourissat A, Bouteloup C, Vasson MP, Malhanche P, Goutte M, Barroux N, et al. Relationship between the nutritional state and quality of life in patients affected by cancer. Bull Cancer 2008;95:S42.
[9] Ravasco P, Monteiro-Grillo I, Vidal PM, Camilo ME. Cancer: disease and nutrition are key determinants of patients' quality of life. Support Care Cancer 2004;12:246–52.
[10] Beattie AH, Prach AT, Baxter JP, Pennington CR. A randomised controlled trial evaluating the use of enteral nutritional supplements postoperatively in malnourished surgical patients. Gut 2000;46:813–8.
[11] Norman K, Kirchner H, Freudenreich M, Ockenga J, Lochs H, Pirlich M. Three month intervention with protein and energy rich supplements improve muscle function and quality of life in malnourished patients with non-neoplastic gastrointestinal disease—A randomized controlled trial. Clin Nutr 2008;27:48–56.
[12] Jakobsen LH, Rask IK, Kondrup J. Validation of handgrip strength and endurance as a measure of physical function and quality of life in healthy subjects and patients. Nutrition 2010;26:542–50.
[13] Mathuranath PS, Nestor PJ, Berrios GE, Rakowicz W, Hodges JR. A brief cognitive test battery to differentiate Alzheimer's disease and fronto-temporal dementia. Neurology 2000;55:1613–20.
[14] Manders M, de Groot LCPG, van Staveren WA, Wouters-Wesseling W, Mulders AJMJ, Schols JMGA, et al. Effectiveness of nutritional supplements on cognitive functioning in elderly persons: A systematic review. J Gerontol A Biol Sci Med Sci 2004;59:1041–9.
[15] Velho S, Marques-Vidal P, Baptista F, Camilo ME. Dietary intake adequacy and cognitive function in free-living active elderly: a cross-sectional and short-term prospective study. Clin Nutr 2008;27:77–86.
[16] Wouters-Wesseling W, Wagenaar LW, Rozendaal M, Deijen JB, de Groot LC, Bindels JG, et al. Effect of an enriched drink on cognitive function in frail elderly persons. J Gerontol A Biol Sci Med Sci 2005;60:265–70.
[17] Kondrup J, Allison SP, Elia M, Vellas B, Plauth M. ESPEN guidelines for nutrition screening 2002. Clin Nutr 2003;22:415–21.
[18] Fontani G, Lodi L, Felici A, Corradeschi F, Lupo C. Attentional, emotional and hormonal data in subjects of different ages. Eur J Appl Physiol 2004;92:452–61.
[19] Elsass P, Christensen SE, Mortensen EL, Vilstrup H. Discrimination between organic and hepatic encephalopathy by means of continuous reaction times. Liver 1985;5:29–34.
[20] Zimmerman P, Fimm B. Test for Attentional Performance (TAP) Windows–-Version 2.1. psytest. Herzogenrath: Deutchland; 2007.
[21] Fontani G, Corradeschi F, Felici A, Alfatti F, Migliorini S, Lodi L. Cognitive and physiological effects of Omega-3 polyunsaturated fatty acid supplementation in healthy subjects. Eur J Clin Invest 2005;35:691–9.
[22] Bak TH, Rogers TT, Crawford LM, Hearn VC, Mathuranath PS, Hodges JR. Cognitive bedside assessment in atypical parkinsonian syndromes. J Neurol Neurosurg Psychiatry 2005;76:420–2.
[23] Ware JE, Gandek B, Kosinski M, Aaronson NK, Apolone G, Brazier J, et al. The equivalence of SF-36 summary health scores estimated using standard and country-specific algorithms in 10 countries: Results from the IQOLA Project. J Clin Epidemiol 1998;51:1167–70.
[24] Schmitt JA, Benton D, Kallus KW. General methodological considerations for the assessment of nutritional influences on human cognitive functions. Eur J Nutr 2005;44:459–64.
[25] Bezdjian S, Baker LA, Lozano DI, Raine A. Assessing inattention and impulsivity in children during the Go/NoGo task. Br J Dev Psychol 2009;27:365–83.
[26] Welford AT. Reaction times. London: Academic Press; 1980.
[27] Wetherell A. Performance tests. Environ Health Perspect 1996;104 (Suppl 2):247–73.
[28] Strub RL, Black FW. The mental status examination in neurology. 2nd ed. Philadelphia: F.A. Davis; 1985.
[29] Koschack J, Kunert HJ, Derichs G, Weniger G, Irle E. Impaired and enhanced attentional function in children with attention deficit/hyperactivity disorder. Psychol Med 2003;33:481–9.
[30] Tuch DS, Salat DH, Wisco JJ, Zaleta AK, Hevelone ND, Rosas HD. Choice reaction time performance correlates with diffusion anisotropy in white matter pathways supporting visuospatial attention. Proc Natl Acad Sci USA 2005;102:12212–7.
[31] Bjorner JB, Damsgaard MT, Watt T, Groenvold M. Tests of data quality, scaling assumptions, and reliability of the Danish SF-36. J Clin Epidemiol 1998;51:1001–11.
[32] Takata Y, Ansai T, Soh I, Kimura Y, Yoshitake Y, Sonoki K, et al. Physical fitness and cognitive function in an 85-year-old community-dwelling population. Gerontology 2008;54:354–60.

Appendix 1. Addenbrooke's Cognitive Examination modified for healthy subjects

Orientation What is the Year _______ Where are we Country __________ Season _______ State __________ Date _______ Town ___________ Day _______ Hospital/Building_________ Month _______ Floor/Level __________	**/10**
Language Say aloud: Brown, Conversation, Articulate. Ask the subject to repeat.	**/3**
Attention/Concentration Take away 7 from 100. Give 5 points for correct answer. Withdraw 1 point for each incorrect answer. Spell 'WORLD' backwards. 1 point for correct answer. 0 points for incorrect answer.	**/5** **/1**
Memory Ask the subject to recall the three words learned earlier.	**/3**
Language Naming: Show the subject a watch and a pen and ask the subject to name each of them. Repetition: Ask the subject to repeat this phrase: "The orchestra played and the audience applauded." Comprehension: Give the subject a piece of paper with a cross on it and tell him to: "take this paper in your left hand, fold it in half with the cross upwards. Then put the paper on the floor with the cross downwards." Score 1 point for each correctly performed step.	**/2** **/1** **/3**

Visuospatial abilities

Overlapping pentagons: Show the subject the following figure for 5 seconds. Cover the figure and ask the subject to copy this diagram. Score 1 point if copied correct.



/1

Anterograde memory

Tell the subject to repeat the name and address after you. Score 1 point for each element recalled correctly. Repeat the instruction twice in exactly the same way.

	1st trial	2nd trial	3rd trial	Delayed recall
Thomas Berg				
Vestre Skovvej 43				
3720 Aakirkeby				
Bornholm				
	/8	/8	/8	/8

/32

Retrograde memory

Score 1 point for each correct answer. Tell me the full name of

The prime minister

____

The last prime minister

____

The President of the United States of America **/4**

____

The leader of Germany during the 2nd World War___________________________________

Verbal fluency (45 seconds)

Category: Tell me the names of as many animals as you can. Animals:______ **/8**

(Score:>25 = 8, 21-25 = 7, 17-20 = 6, 14-16 = 5, 11-13 = 4, 9-10 = 3, 7-8 = 2, <7 = 1)

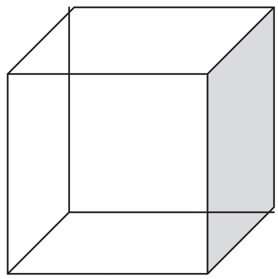
Letter: Tell me all the words you can think of, but not people and places, beginning with the letter P. P words:______ **/8**

(Score: >21 = 8, 17-21 = 7, 14-16 = 6, 11-13 = 5, 8-10 = 4, 6-7 = 3, 4-5 = 2, <4 = 1)

Language

Comprehension. Ask the subject to obey the following simple commands. **/2**

Point to the door. Point to the ceiling. Point to the ceiling and then to the door. Point to the door after touching the bed/desk. **/2**

<table>
<tr><td>Visuospatial abilities
Wire cube: Show the subject the following figure for 5 seconds. Cover the figure and ask the subject to copy this diagram. Score 1 point if copied correctly.
</td><td>/1</td></tr>
<tr><td>Clock: Ask the subject to draw a clock-face with numbers and the hands at five to two. Score one point each for correct circle, numbering of the clock-face, and position of the hands.</td><td>/3</td></tr>
<tr><td>Delayed recall of name and address</td><td></td></tr>
<tr><td>Total</td><td>/89</td></tr>
</table>