Mechanisms of Ageing and Development 181 (2019) 42–46

Contents lists available at ScienceDirect

Mechanisms of Ageing and Development

journal homepage: www.elsevier.com/locate/mechagedev

Role of frailty in the assessment of cognitive functioning

Marco Canevelli[a,b], Matteo Cesari[c,d,*], Riccardo Raganato[a], Federica Trentin[a], Martina Valletta[a], Emanuela Salati[a], Giuseppe Bruno[a]

[a] Department of Human Neuroscience, Sapienza University, Rome, Italy
[b] National Center for Disease Prevention and Health Promotion, National Institute of Health, Rome, Italy
[c] Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy
[d] Geriatric Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

ARTICLE INFO

Keywords:
Aging
Geriatrics
Neurology
Neuropsychological tests
Cognitive assessment
Health
Cognition
Frailty Index

ABSTRACT

Neuropsychological tests, besides reflecting the cognitive reserves and deficits of the tested individual, might also be differently affected by his/her underlying biological asset. In this context, the construct of frailty may offer an opportunity for better weighting the results of traditional tests. We evaluated the relationships between a set neuropsychological measures and a 35-item Frailty Index (FI). The role played by the FI in the relationship between neuropsychological tests and global cognition was also explored.

Data from the first neurological and neuropsychological assessments of 79 subjects attending our university memory clinic because complaining cognitive disturbances were considered for the present analysis.

A statistically significant correlation between FI and Trail Making Test-B was observed (Spearman's rho 0.33; $p = 0.02$). The relationship between the performance at the Rey Complex Figure and global cognition (as measured by the Mini Mental State Examination) was influenced by the FI. In fact, participants with higher FI levels had a weakened association linking constructional/visual memory abilities and general cognitive functioning.

The interpretation of the neuropsychological assessment can be biased by the frailty status of the tested individual. It can be hypothesized the need of developing new models of correction, that may better reflect the person's biology and complexity.

1. Introduction

The neuropsychological assessment constitutes a cornerstone of the clinical approach to cognitive disturbances (Lezak et al., 2004). It allows the objective and standardized measurement of the individual's cognitive abilities and deficits, thus indirectly yielding information about the structural and functional integrity of the brain regions and networks. In other words, it plays a major role in the diagnostic definition of dementia and other cognitive disorders (e.g., mild cognitive impairment), also supporting the discrimination of the different etiologies, the longitudinal tracking of the condition, as well as orienting clinical and therapeutic choices (Sorbi et al., 2012).

Tests included in the traditional neuropsychological assessment are usually aimed at examining (alone or in combination) independent cognitive domains that are thought to be sub-served by distinct neuroanatomical structures (Rascovsky, 2016). Nevertheless, the relationship between neuropsychological test and the pertaining cognitive tasks (and, consequently, the underlying neural substrates) may not be as "pure" as theoretically described. For instance, numerous socio-demographic determinants (i.e., age, education, or -to a lower extent- ethnicity and gender) are important predictors of the individual's performance for most neuropsychological tests (Ganguli et al., 2010). Therefore, in order to properly interpret the findings of the neuropsychological examination, raw scores are frequently converted into standardized scores by correcting for these potential confounders. Along the same lines, it can be hypothesized that biological factors may similarly and independently affect the relationship between neuropsychological tests and the examined cognitive functions. In fact, the performance at a given test may not unequivocally reflect the cognitive reserves and deficits of the individual, but also include (at least part of) his/her biological asset.

In this context, the construct of frailty (i.e., the age-related exhaustion of homeostatic reserves, determining a state of increased vulnerability to stressors) may offer an opportunity for better weighting

* Corresponding author at: Geriatric Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore, Policlinico, Via Pace 9, 20122 Milan, Italy.
E-mail address: macesari@gmail.com (M. Cesari).
@macesari (M. Cesari)

https://doi.org/10.1016/j.mad.2019.111122
Received 2 January 2019; Received in revised form 31 May 2019; Accepted 2 June 2019
Available online 03 June 2019
0047-6374/

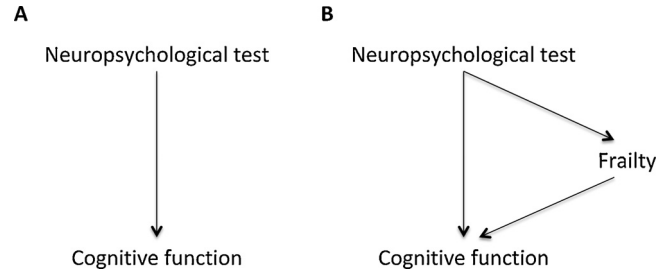

Fig. 1. Model for including frailty in the evaluation of cognitive functions. The traditional approach (panel A) is based on the assumption that each neuropsychological test measures a specific cognitive function. The model here proposed (panel B) sees frailty as a potential mediator or confounder of the association. As such, the assessment of the biological complexity of the individual is crucial for discriminating the etiological nature of the eventual cognitive disorder.

the results of traditional tests. In fact, by measuring a surrogate of biological aging, frailty may nest a comprehensive evaluation of the organism's status in the profiling of the individual. In particular, the frailty model proposed by Rockwood and Mitnitski based on the age-related accumulation of deficits (Mitnitski et al., 2001), seems specially suitable for this use because *ad hoc designed* for capturing the biological complexity of the person in a single, comprehensive variable (the so-called Frailty Index [FI]).

In the present study, it is hypothesized that neuropsychological tests are differently affected by the underlying biological status of the tested individual. As such, there might be instruments that more than others may require a careful contextualization of their results with the person's biological status (Fig. 1, first hypothesis). In parallel, frailty could act as a moderator in the relationship between specific neuropsychological domains and the overall cognitive functioning of the individual. That is, the biological complexity of the subject could influence his/her global cognitive performance in relation to the impairment in specific neurocognitive functions and measures (Fig. 1, second hypothesis). To address these two hypotheses, the relationships between a wide set of routinely adopted neuropsychological measures and a FI are evaluated in a sample of subjects referred to a memory clinic. The influence of the FI in the relationship between neuropsychological tests and global cognition is explored.

2. Methods

All participants included in the present analyses had been referred to the Memory Clinic of the Department of Human Neuroscience, "Sapienza" University of Rome (Rome, Italy) because complaining cognitive disturbances. Data from the neurological and neuropsychological assessments conducted at their first evaluation (occurred between January 2018 and April 2018) were considered for the present analysis. Patients and caregivers (or legal guardians when necessary) provided written informed consent for allowing the utilization of the collected data for research purposes (as required by the local Ethics Committee).

Detailed medical history, neurological evaluation, and physical examination were conducted. The participants' global cognitive performance and functional independence were assessed by the means of the Mini Mental State Examination (MMSE)(Folstein et al., 1975), and the Activities of Daily Living (ADL)(Katz et al., 1963) and Instrumental ADL (IADL)(Lawton and Brody, 1969) scales, respectively. Subjects also underwent a comprehensive neuropsychological assessment consisting of the following standardized tests: Rey Auditory Verbal Learning Test (RAVLT; measuring verbal memory and learning); Rey Complex Figure (RCF; evaluating the constructional ability and visual memory); Trail Making Test A and B (TMT-A, TMT-B; exploring the conceptual tracking and shifting abilities); Colored Progressive Matrices (CPM; focused on abstract thinking); FAS test and Animal Naming (assessing the phonemic and semantic verbal fluency). Raw scores were adjusted for demographic variables (i.e., age and education). The normal ranges of the adjusted scores were provided by applying the cut-points based on the normative data for the Italian population (Carlesimo et al., 2002 1996; Giovagnoli et al., 1996; Zarino et al., 2014).

The participant's frailty status was measured by means of a 35-item FI, computed according to the standard procedure proposed by Searle and colleagues (Searle et al., 2008). More in details, the index was generated as the ratio between the deficits presented by the individual and 35, that is the total number of age-related, multidimensional health deficits (i.e., chronic diseases, symptoms, signs, and disabilities) considered for its computation (Annex 1 in Supplementary data). Since the aim of the study was to explore the relationship between frailty and cognitive performance, no neurological/cognitive variable was included in the FI. Each item included in the FI was coded as 0 (absence of the deficit) or 1 (presence of the deficit). Therefore, the FI ranged between 0 (no deficit is present) and 1 (all the 35 items are present).

Means (and standard deviations, SD) and percentages are provided for describing the studied sample. The strength and direction of the relationships between the FI and the neuropsychological test scores are provided as correlation coefficients derived from Spearman's statistical models (being the variables not normally distributed). Linear regression models are used to evaluate the relationship between neuropsychological measures (independent variables) and global cognitive performance as measured by the MMSE (dependent variable). These models are also used to test the significance of interaction terms with the aim of exploring the role played by the FI in the studied associations.

3. Results

A total of 79 subjects (mean age 71.5, SD 6.3; women 55.7%) underwent the neurocognitive and clinical assessment. Most of them were in general good health conditions, as also suggested by the relatively low FI score (median 0.15; Annex 2 in Supplementary data). Only nine of them resulted as frail (defined as presenting a FI equal to or higher than 0.25 (Kelaiditi et al., 2016)). A statistically significant correlation was found between age and FI scores (Spearman's rho 0.31; $p < 0.01$). Participants exhibited a mild impairment of the global cognitive functioning (MMSE 25.6, SD 3.5), and a substantial independence in physical function (ADL 5.9, SD 0.5; IADL 6.2, SD 1.9). Their sociodemographic and clinical characteristics according to FI scores are shown in Table 1. Overall, people who had a FI equal to or higher than the median (≥ 0.15; $n = 27$) were older and less educated than those with a score lower than the median value of 0.15 ($n = 52$).

The results of the different neuropsychological tests are shown in Table 2, together with the established thresholds for normality. As evident, a relevant proportion of participants presented an objective impairment in one or more cognitive domains. In particular, more than one third of subjects showed an impaired performance in terms of conceptual tracking and shifting abilities as measured by the TMT.

Table 3 presents the results of Spearman's correlation coefficients between the FI and the neuropsychological tests. A statistically significant correlation between FI (as a continuous variable) and TMT-B was observed (rho 0.33; $p = 0.02$), demonstrating that a higher number of deficits was associated with a greater impairment at the TMT-B. No other statistically significant correlation was found between the FI and the other tested neuropsychological measures (all $p > 0.05$). Accordingly, participants with higher FI scores exhibited a worst performance at the TMT-B compared to those with a FI < 0.15 (244.67, SD 125.81 vs. 172.89, SD 102.49; $p = 0.05$). They also tended to obtain lower (thus worst) scores at the FAS test (25.10, SD 9.18 vs. 29.22, SD 8.69; $p = 0.07$).

The interaction of the FI variable in the multiple associations between the neuropsychological tests and global cognition (as measured by the MMSE score) resulted as statistically significant or at least

Table 1
Descriptive characteristics of the study sample. Data are shown as mean ± standard deviation or %.

	All (n = 79)	FI < 0.15 (n = 52)	FI ≥0.15 (n = 27)	p
Age	71.5 ± 6.3	70.4 ± 6.6	73.2 ± 5.3	0.05
Sex (F)	55.7	51.0	69.2	0.15
Education	12.3 ± 4.6	13.2 ± 4.1	10.0 ± 4.8	< 0.01
Diabetes	16.7	13.7	23.1	0.34
Hypertension	51.9	37.3	76.9	< 0.01
Ischemic heart disease	10.1	11.8	7.7	0.71
Chronic heart failure	3.8	3.9	–	0.55
COPD	10.1	2.0	23.1	< 0.01
Cancer	20.5	17.6	26.9	0.38
Thyroid disease	27.8	13.7	57.7	< 0.01
Depression	62.8	52.9	84.6	< 0.01
FI	0.15 ± 0.09	0.10 ± 0.04	0.25 ± 0.09	< 0.01
MMSE	25.6 ± 3.5	25.7 ± 3.8	25.3 ± 3.0	0.30
ADL	5.9 ± 0.5	6.0 ± 0.1	5.7 ± 0.8	0.05
IADL	6.2 ± 1.9	6.3 ± 1.6	6.2 ± 2.4	0.82

ADL: Activities of Daily Living; COPD: chronic obstructive pulmonary disease; FI: Frailty Index; IADL: Instrumental Activities of Daily Living; MMSE: Mini Mental State Examination.

Table 3
Neuropsychological assessment in two groups of participants categorized using the FI median value as cut-point and correlations between neuropsychological measures and FI as a continuous measure (Spearman's coefficients).

	FI < 0.15 Score (mean ± SD)	FI ≥0.15 Score (mean ± SD)	p	FI (cont.)
RAVLT-I	39.17 ± 11.36	38.76 ± 12.31	0.89	−0.02
RAVLT-D	7.40 ± 4.41	7.96 ± 4.14	0.59	0.03
RAVLT-R (%)	80.53 ± 23.44	84.80 ± 22.40	0.39	0.12
RCF-c	29.02 ± 8.89	29.40 ± 8.29	0.84	0.05
RCF-I	12.47 ± 7.21	13.66 ± 6.49	0.51	0.22
RCF-D	12.36 ± 7.43	13.28 ± 6.56	0.60	0.16
TMT-A	84.43 ± 66.60	96.48 ± 58.49	0.31	0.22
TMT-B	172.89 ± 102.49	244.67 ± 125.81	0.05	0.33*
CPM	26.78 ± 6.09	26.16 ± 6.46	0.68	−0.02
FAS	29.22 ± 8.69	25.10 ± 9.18	0.07	−0.17
AN	13.21 ± 4.24	11.67 ± 4.93	0.15	−0.11

AN: animal naming; CPM: Colored Progressive Matrices; FAS: FAS verbal fluency test; FI: Frailty Index; MMSE: Mini Mental State Examination; RAVLT: Rey Auditory Verbal Test (D: delayed recall; I: immediate recall; R: recognition); RCF: Rey complex figure (D: delayed recall; I: immediate recall); TMT: Trail Making Test.
* p < 0.05.

suggestive (p value for the interaction term < 0.01) for all the considered measures. Stratified models were therefore performed (Table 4). Linear regression models showed a statistically significant association between all the adopted neuropsychological measures and the MMSE (all p < 0.05) among participants with lower FI scores. Conversely, in those with a FI ≥ 0.15, the association between the different tasks of the RCF and the MMSE was lost (all p > 0.05).

4. Discussion

In the present study, the relationships between multiple neuropsychological tests and a 35-item FI were explored. Moreover, the moderating role of the FI in the association between individual neuropsychological domains and the overall cognitive functioning was investigated.

Results show that the interpretation of the neuropsychological assessment might be biased by the frailty status of the tested individual. In fact, despite the relatively healthy condition of our sample population, a significant correlation was found between the FI and the TMT-B results, suggesting that the neuropsychological test could be influenced by the background noise of the organism's biology. In other words, it can be argued that the TMT-B is not only capturing the capacity of the individual to rapidly shift from numeric to alphabetic stimuli, but also the more general clinical status of the person. The possible weakness presented by the TMT-B was instead not present for other tests, potentially appearing as more robust at capturing the specific cognitive domains of interest. These latter tests may, thus, more robustly support the clinical identification of those cognitive disorders that are subtended by "real" neurodegenerative changes compared to those sustained by a more general disruption of the organism's homeostatic balance.

The variable sensitivity of tests at being altered by frailty might be explained in different ways. It is indeed possible that one test may not be as mono-dimensional as thought, but capture clinical aspects other than the specific cognitive domain. At the same time, it cannot be excluded that such behavior (here detected for the only TMT-B) might be more common and also shared by the other tests as soon as a frailer population is evaluated. In this case, the strongest correlation with the FI reported for the TMT-B might simply reflect its higher capacity to detect minor abnormalities compared to the other instruments. Under this scenario, it might be possible to hypothesize that neuropsychological tests might differently perceive the biasing effects of frailty according to their design and the increasing level of the organism's frailty. In this regard, it is noteworthy that previous studies had already shown an association between measures of frailty and executive functioning (Robertson et al., 2013). This link has partially been attributed to potentially shared pathophysiological processes (e.g., cardiovascular diseases and risk factors) influencing both the individual's frailty status

Table 2
Neuropsychological assessment of participating subjects.

Domain/function	Test	Cut-point*	Score (mean ± SD)	Range	Abnormal score (%)
Verbal memory and learning	RAVLT-I	≥28.53	38.96 ± 11.52	6.30-64.20	18.2
	RAVLT-D	≥4.69	7.61 ± 4.24	0.00-15.00	23.1
	RAVLT-R(%)	≥92.0	82.08 ± 22.77	0.00-100	46.8
Constructional ability and visual memory	RCF-c	≥23.75	29.09 ± 8.65	0.00-36.00	21.3
	RCF-I	≥6.44	12.82 ± 6.89	0.00-30.30	14.7
	RCF-D	≥6.33	12.67 ± 7.06	0.00-28.40	17.3
Conceptual tracking and shifting abilities	TMT-A	< 79	88.96 ± 62.07	22-300	37.3
	TMT-B	< 227	203.86 ± 118.96	45-360	41.2
Abstract thinking	CPM	≥18.96	26.54 ± 6.11	8.00-36.00	6.6
Phonemic fluency	FAS	≥17.35	27.61 ± 9.06	1.70-46.50	14.5
Semantic fluency	AN	≥9.62	12.69 ± 4.47	1.00-23.00	19.2

AN: animal naming; CPM: Colored Progressive Matrices; FAS: FAS verbal fluency test; FI: Frailty Index; MMSE: Mini Mental State Examination; RAVLT: Rey Auditory Verbal Test (D: delayed recall; I: immediate recall; R: recognition); RCF: Rey complex figure (c: copy; D: delayed recall; I: immediate recall); TMT: Trail Making Test.
* According to normative data for the Italian population (Carlesimo et al., 1996 2002; Giovagnoli et al., 1996; Zarino et al., 2014).

Table 4
Linear regression analysis exploring the relationship between neuropsychological measures and global cognitive performance (as measured by the MMSE) according to FI scores.

	FI < 0.15			FI ≥0.15		
	B	95%CI	p	B	95%CI	p
RAVLT-I	0.21	0.13 to 0.29	< 0.001	0.18	0.10 to 0.25	< 0.001
RAVLT-D	0.55	0.33 to 0.66	< 0.001	0.48	0.25 to 0.71	< 0.001
RAVLT-R(%)	0.09	0.05 to 0.13	< 0.001	0.09	0.04 to 0.13	0.001
RCF-c	0.25	0.15 to 0.35	< 0.001	0.02	−0.10 to 0.15	0.727
RCF-I	0.28	0.15 to 0.41	< 0.001	0.09	−0.09 to 0.26	0.303
RCF-D	0.28	0.16 to 0.41	< 0.001	0.12	−0.04 to 0.28	0.132
TMT-A	−0.04	−0.06 to -0.02	< 0.001	−0.04	−0.06 to -0.02	< 0.001
TMT-B	−0.02	−0.03 to -0.01	0.009	−0.01	−0.02 to -0.01	0.008
CPM	0.27	0.11 to 0.43	< 0.001	0.29	0.13 to 0.45	0.001
FAS	0.15	0.02 to 0.28	0.022	0.24	0.13 to 0.35	< 0.001
AN	0.50	0.28 to 0.72	< 0.001	0.30	0.06 to 0.54	0.016

AN: animal naming; CPM: Colored Progressive Matrices; FAS: FAS verbal fluency test; FI: Frailty Index; MMSE: Mini Mental State Examination; RAVLT: Rey Auditory Verbal Test (D: delayed recall; I: immediate recall; R: recognition); RCF: Rey complex figure (D: delayed recall; I: immediate recall); TMT: Trail Making Test.

and executive functions (Langlois et al., 2012; Robertson et al., 2013).

Interestingly, the person's biological complexity was found to act as a moderator in the relationship between specific neuropsychological functions and global cognition. In fact, increasing FI weakened the association between the constructional ability and the visual memory (as measured by the RCF) of participants with their general cognitive performance (i.e., the MMSE). That is, the ability at copying, memorizing and recalling a complex figure influenced the overall level of cognitive functioning only in those subjects presenting a lower amount of clinical and subclinical deficits.

These findings may have an important clinical implication. To date, results of neuropsychological tests are usually adjusted/corrected by sociodemographic standards, as age or education level. It is evident how this approach does not take into account the weight of the individual's clinical complexity. In an aging world, dominated by an increasing number of heterogeneous (often chronic) conditions, it makes sense to start considering the possibility of introducing a certain level of biological approximation in the evaluation of neuropsychological tests. Some time ago, the disease-oriented model of care was perhaps suitable for the monodimensional relationship assumed between the neuropsychological test and a specific cognitive domain (Fig. 1, panel A). Today with the "end of the disease era", such rigid model does not hold anymore (Tinetti and Fried, 2004). Frailty (i.e., the heterogeneous, biological complexity of the individual) becomes a crucial determinant for correctly interpreting the link between a clinical manifestation and a possible diagnosis (Cesari et al., 2016). Neglecting the existence of such underlying complexity will lead to probable mistakes. In fact, frailty may easily act as a moderating or confounding factor in the interpretation of neuropsychological test results (Fig. 1, panel B). The need of sterilizing the association from the individual's biological complexity implies the need of developing new models of correction, based on the person's health status and going beyond the traditional sociodemographic factors. Such proposal is not so futuristic as it may appear because the concept of frailty is increasingly included in the clinical practice. Moreover, it has recently been shown that frailty is implicated in the phenotypic expression of cognitive disturbances and dementia. For instance, it modifies the association between Alzheimer's disease neuropathology and Alzheimer's dementia (Wallace et al., 2019).

Our study has several limitations worth to be mentioned. The limited number of participants, the cross-sectional design, and the single site of recruitment surely represent the major weaknesses of our analyses. Further studies are needed to confirm and expand our results. Nevertheless, the model here proposed for including the evaluation of frailty in the interpretation of neuropsychological results is not substantially affected and remains theoretically valid.

In conclusion, our findings suggest that frailty may interfere with the correct reading of neuropsychological results. This influence may differ according to the frailty status of the individual and the applied neuropsychological test. The aging of the world population requires the adoption of novel methods for correcting traditional clinical practice. This includes the possibility of shifting from obsolete corrections based on poorly informative standards (as chronological age or education) towards confounders that are more inclusive of the person's biology. Such step will be consistent with the attempt of an increasingly personalized care of the aging individual.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.mad.2019.111122.

References

Carlesimo, G.A., Buccione, I., Fadda, L., Graceffa, A., Mauri, M., Lorusso, S., Bevilacqua, G., Caltagirone, C., 2002. Standardizzazione di due test di memoria per uso clinico: Breve Racconto e Figura di Rey. Nuova Riv. Neurol. 12, 1–13.

Carlesimo, G.A., Caltagirone, C., Gainotti, G., 1996. The Mental Deterioration Battery: normative data, diagnostic reliability and qualitative analyses of cognitive impairment. The Group for the Standardization of the Mental Deterioration Battery. Eur. Neurol. 36, 378–384. https://doi.org/10.1159/000117297.

Cesari, M., Marzetti, E., Thiem, U., Pérez-Zepeda, M.U., Abellan Van Kan, G., Landi, F., Petrovic, M., Cherubini, A., Bernabei, R., 2016. The geriatric management of frailty as paradigm of "The end of the disease era.". Eur. J. Intern. Med. 31, 11–14. https://doi.org/10.1016/j.ejim.2016.03.005.

Folstein, M.F., Folstein, S.E., McHugh, P.R., 1975. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J. Psychiatr. Res. 12, 189–198.

Ganguli, M., Snitz, B.E., Lee, C.-W., Vanderbilt, J., Saxton, J.A., Chang, C.-C.H., 2010. Age and education effects and norms on a cognitive test battery from a population-based cohort: The Monongahela –Youghiogheny Healthy Aging Team (MYHAT). Aging Ment. Health 14, 100–107. https://doi.org/10.1080/13607860903071014.

Giovagnoli, A.R., Del Pesce, M., Mascheroni, S., Simoncelli, M., Laiacona, M., Capitani, E., 1996. Trail making test: normative values from 287 normal adult controls. Ital. J. Neurol. Sci. 17, 305–309. https://doi.org/10.1007/BF01997792.

Katz, S., Ford, A.B., Moskowitz, R.W., Jackson, B.A., Jaffe, M.W., 1963. Studies of illness in the aged: the index of adl: a standardized measure of biological and psychosocial function. JAMA 185, 914–919. https://doi.org/10.1001/jama.1963.03060120024016.

Kelaiditi, E., Canevelli, M., Andrieu, S., Del Campo, N., Soto, M.E., Vellas, B., Cesari, M., Impact of Cholinergic Treatment Use Study/DSA Group, 2016. Frailty index and cognitive decline in alzheimer's disease: data from the impact of cholinergic treatment use study. J. Am. Geriatr. Soc. 64, 1165–1170. https://doi.org/10.1111/jgs.13956.

Langlois, F., Vu, T.T., Kergoat, M.J., Chasse, K., Dupuis, G., Bherer, L., 2012. The multiple dimensions of frailty: physical capacity, cognition, and quality of life. Int. Psychogeriatr. 24 (9), 1429–1436. https://doi.org/10.1017/S1041610212000634.

Lawton, M.P., Brody, E.M., 1969. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist 9, 179–186.

Lezak, P. of N.P. and N.M.D., Lezak, M.D., Howieson, A.P. of N. and P.D.B., Howieson, D. B., Loring, P. of N.D.W., Loring, D.W., Fischer, J.S., 2004. Neuropsychological

Assessment. Oxford University Press.
Mitnitski, A.B., Mogilner, A.J., Rockwood, K., 2001. Accumulation of deficits as a proxy measure of aging. ScientificWorldJournal 1, 323–336. https://doi.org/10.1100/tsw.2001.58.
Rascovsky, K., 2016. A primer in neuropsychological assessment for dementia. Practical Neurol (July/August), 20–25.
Robertson, D.A., Savva, G.M., Kenny, R.A., 2013. Frailty and cognitive impairment–a review of the evidence and causal mechanisms. Ageing Res. Rev. 12 (4), 840–851. https://doi.org/10.1016/j.arr.2013.06.004.
Searle, S.D., Mitnitski, A., Gahbauer, E.A., Gill, T.M., Rockwood, K., 2008. A standard procedure for creating a frailty index. BMC Geriatr. 8, 24. https://doi.org/10.1186/1471-2318-8-24.
Sorbi, S., Hort, J., Erkinjuntti, T., Fladby, T., Gainotti, G., Gurvit, H., Nacmias, B., Pasquier, F., Popescu, B.O., Rektorova, I., Religa, D., Rusina, R., Rossor, M., Schmidt, R., Stefanova, E., Warren, J.D., Scheltens, P., 2012. EFNS-ENS Guidelines on the diagnosis and management of disorders associated with dementia. Eur. J. Neurol. 19, 1159–1179. https://doi.org/10.1111/j.1468-1331.2012.03784.x.
Tinetti, M.E., Fried, T., 2004. The end of the disease era. Am. J. Med. 116, 179–185.
Wallace, L.M.K., Theou, O., Godin, J., Andrew, M.K., Bennett, D.A., Rockwood, K., 2019. Investigation of frailty as a moderator of the relationship between neuropathology and dementia in Alzheimer's disease: a cross-sectional analysis of data from the Rush Memory and Aging Project. Lancet Neurol. 18, 177–184. https://doi.org/10.1016/S1474-4422(18)30371-5.
Zarino, B., Crespi, M., Launi, M., Casarotti, A., 2014. A new standardization of semantic verbal fluency test. Neurol. Sci. 35, 1405–1411. https://doi.org/10.1007/s10072-014-1729-1.