ISSN NO. 2320-5407

Journal homepage: http://www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH

RESEARCH ARTICLE

EFFECT OF SEVERITY OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE ON COGNITIVE DYSFUNCTION IN PATIENTS ATTENDING A TERTIARY CARE CENTRE IN KERALA

DR. JESSY JOHN [1], DR.C.V.SHAJI[2], DR. P.VENUGOPAL[3]

1. Assistant professor, Dept. Of Physiology, Govt. T. D. Medical College, Vandanam, Alappuzha, Kerala -688005 ,India
2. Professor and HOD, Dept of Neurology, Govt. T. D. Medical College, Vandanam Alappuzha, Kerala,India-688005
3. Additional professor, Dept. of Pulmonary Medicine, Govt.T.D.Medical College, Vandanam, Alappuzha,Kerala, India- 688005

Manuscript Info

Manuscript History:

Received: 18 October 2015
Final Accepted: 22 November 2015
Published Online: December 2015

Key words:

cognition, cognitive impairment, COPD,hypoxemia, Neuropsychological tests,

Corresponding Author

DR. JESSY JOHN

Abstract

Cognitive dysfunction is an important systemic effect of COPD affecting various cognitive domains. The mechanisms involved in the impairment of cognition and the relevant factors are complex and not fully understood. Our study aimed to evaluate the impact of disease severity and impairment of respiratory physiology on cognitive impairment in patients with established COPD. In a hospital based cross sectional study, we examined hundred consecutive COPD patients for their lung parameters and further graded them into groups based on severity of disease by a multidimensional staging (BODE) index. All the subjects were then assessed for cognitive skills of orientation, attention, memory, visuo perceptual abilities and executive functions by neuropsychological battery of tests.

Out of the respiratory parameters resting oxygen saturation (SpO2), modified Medical Research Council (mMRC) and Chronic obstructive pulmonary disease Assessment Test (CAT) scores correlated well with most of the cognitive domains. There was a significant correlation of resting SpO2 with Mini Mental State Examination (MMSE), orientation, registration, attention, recall, language and Clock Drawing Test (CDT). mMRC correlated significantly with the tasks Trail Making Test (TMT-A and TMT-B), orientation and recall. CAT score correlated significantly with orientation and MMSE and CDT.

The decline in pulmonary function is associated with cognitive dysfunction and an impairment of cognition increases significantly with the advancement of the disease. Among the various cognitive domains, **memory, attention, symbolic representation and visual processing (CDT), reproduction of numeric sequences, cognition flexibility, and shifting capacity (TMT-A and TMT-B)** were the most affected.

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) has been traditionally considered as a disease primarily affecting the lungs however its systemic effects have been increasingly recognized with diverse manifestations involving various body systems distant from the lung causing different co morbidities of various severities (Aït-Khaled N *et*

al., 2007).The brain, in particular, may be vulnerable to the systemic effects of COPD (Moss M *et al*.,2005) causing cognitive impairment (Calverley PM *et al.*, 1996).

Cognitive function impairment was found to be associated with severe pulmonary dysfunction long ago (Ritchie K et al .,2000), although its prevalence varied from study to study (Pleis JR et al, 2006), (Anstey KJ, et al 2004). Several studies were done to assess the impact of disease severity on cognition, but had methodical limitations (Grant I, et al 2009) including lack of clinical assessment of airflow impairment (Hung WW et al 2009), lack of multiple psychometric tools (Maruta C, et al 2011) and small sample sizes (Kozora E et al 1999). Our study aimed to evaluate the impact of disease severity and impairment of respiratory physiology on cognitive impairment in patients with established COPD

Materials and Methods-

A Cross sectional study was conducted among (n=100) consecutive subjects aged >40yrs with COPD as defined in the Global Initiative for obstructive lung disease guidelines(**GOLD 2014),** attending for review in outpatient unit of department of the Respiratory medicine in Govt. T D Medical College Hospital, Alappuzha, Kerala, during January 2015 to July 2015. Selection of sample size was done from a previous study done in Turkey found that 64% of COPD patients showed cognitive impairment. Assuming 50% cognitive impairment in our setting, with a 95% confidence and 80% power of the study, Sample size= $4PQ/d^2$ =100. The purpose of the study was explained to both the groups and explicit written consent was obtained thereof. Institutional ethical clearance was obtained for the study by institutional review board.

Inclusion criteria for the study are- Selection of COPD patients aged >40 yrs, with at least high school education, treated only with necessary medications for COPD.

Exclusion criteria-patients with any known neurological disorders, history of depression (Hamilton depression rating scale HAM-D-21 > 8, not included in the study (Hamilton M. 1967)**,** Patients on continuous oxygen therapy, or with other co morbidities like, HTN, DM, CAD or previous stroke, TB, pneumonia, severe anaemia, electrolyte imbalances and patients with visual or hearing impairment.

Assessment of pulmonary physiology- An electronic portable PC based spirometer with printer (SPIROPALM 6MWT comply with ATS/ERS guidelines) and integrated pulse oximetry (NONIN) was used. The resting oxygen saturation was assessed using the pulse oximetry (NONIN) with placing probe in left index finger. The COPD patients had post-bronchodilator (20 min after inhalation of 2 puffs of salbutamol given via a metered dose inhaler through a spacer) FEV_1 less than 80% of the predicted value along with an FEV_1/FVC % not more than 70%. Post-bronchodilator increase in FEV_1 was less than 200 ml and not more than 12% of baseline value. These patients were also assessed for their health status using the COPD Assessment test [CAT] questionnaire (≥ 10 as an indicator of more symptoms) (Jones PW et al., 2011).

Measurement of COPD severity-We used the validated BMI (Body Mass Index), Obstruction, Dyspnea, Exercise Capacity (BODE) Index, which is a multi-modal measure of disease severity (Celli BR, et al 2004). The BODE Index is based on the body-mass index (*B*), the degree of airflow obstruction (*O*) measured by Forced Expiratory Volume in one second (FEV1), grade of dyspnea (*D*) assessed by the modified Medical Research Council (mMRC) Dyspnea Scale(Bestall JC et al 1999**);** (≥ 2 as an indicator of more symptoms) and exercise capacity (*E*) measured by the six-minute-walk test. Each component is assigned a specific score and the total score ranges from 0 to 10 points (higher scores indicate greater severity). It has been validated in patients with a mean age of 66 years and with an average FEV1% predicted of 45% (Celli BR et al 2004)

Cognitive assessment-Cognition impairment was evaluated using four validated psychometric questionnaires: 1) the Mini Mental Status test (MMSE), (Folstein M.F et al 1975), widely used instrument for monitoring cognitive impairment for research and clinical purposes, assesses spatial and time orientation, attention, and calculation. In the present study, MMSE was administered in their native language [Malayalam] by exact conversion of the questions of MMSE International Version in English. 2) The Clock drawing test assesses memory, attention, and symbolic representation. A 6-point scale was used. A score of ≥3 represents a cognitive deficit, while a score of 1 or 2 is considered normal (Shulman KI,et al 2006) . 3) The Trail Making test, TMT-A (Reitan RM: et al 1958) that assesses visual processing and reproduction of numeric sequences (cognitive impairment: ≥94 seconds); and 4) the TMT- B (Giovagnoli AR et al 1996), that assesses cognition flexibility and shifting capacity (cognitive impairment: ≥283 seconds).

***Statistical analysis*-** Neuropsychometric parameters of the different BODE groups were compared with the parametric ANOVA test and non-parametric (Kruskal Wallis test), as appropriate ($P<0.05$ indicated statistical significance). Pearson and Spearman Correlation analyses were run among clinical, spirometric and neuropsychometric variables in patient group, as appropriate. Values *p* at 0.01 and 0.05 levels were considered statistically significant.

Results

The mean age of the study population was 64.47 ±8.01 year with majority (n=81/100) of them being males and (n=19/100) of them being females. BODE index scores measured were categorized into four quartiles, quartile (BODE) 1 to 4 with scores of 0-2, 3-4, 5-6 and 7-10, respectively **(Table-l)**

Table -ll depicts the comparison of neuro psychometric scores among various BODE groups to assess the effect of disease severity on cognitive function. It was observed that; with higher BODE scores, the time taken to complete TMT-A and TMT-B was more. CDT scores also were increasing, showing poor performance with higher BODE scores, but not statistically significant. There was not much noticeable difference with MMSE. Among the different domains of cognition, recall was affected in higher BODE scores and copying a polygon was invariably affected in all the BODE groups. None of the results were statistically significant.

Table-lll depicts the correlate of lung function indexes such as forced expiratory volume in one second (FEV1), forced expiratory ratio (FEV1/ FVC ratio), resting peripheral oxygen saturation (SpO2), mMRC Dyspnoea scale and CAT test with the neuro psychometric scores. It was seen that resting oxygen saturation (SpO2), significantly correlated with all the domains of cognition like MMSE (p-0.004), orientation (p-0.01), registration (p-0.02), attention (p-0.04) recall (p-0.03) and language (p-0.03) and a negative correlation with CDT (p-0.01). We also found a significant correlation of mMRC with the tasks TMT-A (p-0.01) and TMT-B (p-0.02) also an inverse correlation of mMRC with domains like orientation (p-0.04) and recall (p-0.02). With the CAT score there was a significant inverse correlation with orientation (0.02) and MMSE (p-0.016) and a positive correlation with CDT (0.016).

Discussion

Cognitive impairment may interfere with COPD patients' ability to adhere to their medication regimen, adjust their medications in response to respiratory symptoms, and perform other aspects of self-management. More broadly, cognitive impairment may create difficulties with performing daily activities, especially those that involve memory or complex reasoning (Perneczky R, et al 2006). It is likely that cognitive impairment has major effects on many aspects of patient functioning and health status. Thus it becomes imperative to assess the extent of involvement of cognitive domains in these patients suffering with such chronicity. Thus, we used a multi factorial assessment of severity of disease to understand the impact of these factors on cognitive function.

The presence of a substantial deterioration in cognitive function can be more clearly observed using multi parametric psychometric measures (ie, the four different questionnaires in the present study) that are able to inform on several domains of cognition. In particular, when the Clock Drawing Test and both the TMT A and B are added to the commonly used MMSE, the subjects' cognitive dysfunction can be measured more clearly.

We have already hypothesized in our earlier study that there was a significant decline in the cognitive function in COPD patients when compared to the normal healthy individuals. And also we demonstrated the effect of hypoxia and duration of illness of COPD on cognition (John J, et al 2015).

In this study, we used a multidimensional staging system of BODE index that has already been shown to be a superior predictor of the risk of death in COPD patients compared with the FEV_1-based staging system by the ATS, and is better correlated to health status as assessed by a disease-specific index for COPD than the GOLD staging criteria **(**Celli BR, *et al* 2004**)**

With the BODE scoring system of classification, we found that, TMT-A and TMT-B were more sensitive tools, showing a deterioration in **visuospatial and motor constructional abilities** with increasing severity of the disease. Copying a polygon **involving visuospatial perception** was invariably affected in all the BODE groups, but these findings didn't show any statistical significance, could be because of small sample size. All these tests that used to assess visuo-constructive abilities require verbal understanding, memory and spatially coded knowledge in addition to constructive skills.

A poor performance on these tasks can be explained due to frontal hypoperfusion in patients with COPD. Earlier studies (Ortapamuk H et al 2006; Inc Antonelli et al 2003)**,** suggested that frontal-dominant perfusion decrease in COPD patients occurs due to the greater sensitivity of the frontal regions to hypoxia than the other cerebral regions. Further, an impairment of executive motor constructive tasks (copying and trial making) can also be attributed to the muscle wasting due to reduction in physical activity or drug induced tremor, which is frequently seen in COPD patients (Bernard S, et al 1998)**.**

On correlating the clinical parameters and lung function with neuro psychometric test scores in COPD patients, it was found that resting oxygen saturation (SpO2), the mMRC and the CAT score, was well correlated with cognitive ability. Although all the domains of cognition were variably affected, **memory, attention, symbolic representation and visual processing (CDT), reproduction of numeric sequences, cognition flexibility, and**

shifting capacity (TMT-A and TMT-B) were the most affected cognitive functions. This is consistent with a previous study (Roberto W Dal et al 2014)**,** thus, it can be further speculated that several factors, variably interacting with each other, might contribute to the progressive worsening of cognition in subjects suffering from chronic airway damage. From our study, among the various lung variables, hypoxemia played an important role over others in cognitive impairment. Our results are consistent with previous studies (D.T. Stuss et al 1997; I. Grant et al 1987). D.T Stuss et al (1997) reported that hypoxia in COPD results in a relatively focused pattern of impairment in measures of memory function and tasks requiring attention allocation.

D T Stuss et al. (1995) hypothesized that significant impairments in anterograde memory deficit might be due to the sensitivity of the hippocampal or general limbic memory region to hypoxia. Also, it was reported that both defective retrieval and inaccurate recognition affect verbal memory of COPD patients (Orth M et al 2006).

We could not find any correlation with FEV1 and FEV1/FVC with cognition.

Future concerns- Assessment of cerebral oxygenation and EEG is in progress in these patients.

There are few limitations in our study, like less sample size, institute-based sample subjects rather than planned sample collection from community and lack of quantification of their hypoxemia and hypercarbia during severe work, lung imaging techniques for better understanding the lung function, not done due to economic constraints.

In conclusion, cognition can deteriorate substantially in subjects with chronic airway flow limitation ie, COPD subjects. Several lung variables that assess the severity of the disease mMRC dysnoea scale, CAT test, resting SpO2 and BODE score, contributed to, although not individually, the progression of the cognitive impairment. Thus, its quiet evident that the decline in pulmonary function is associated with cognitive dysfunction and an impairment of cognition increases significantly with the advancement of the disease. Among the various cognitive domains, **memory, attention, symbolic representation and visual processing (CDT), reproduction of numeric sequences, cognition flexibility, and shifting capacity (TMT-A and TMT-B)** were the most affected. We believe that the assessment of cognition in subjects suffering from chronic airway disorders, in particular of the obstructive nature, should enter the routine of diagnostic procedures to grade the overall impact of patients' respiratory condition, and to decide the most effective therapeutic actions and strategies.

Conflicts of interest-The authors report no conflicts of interest in this work.

Acknowledgements –

Funded by SBMR (State Board of Medical Research) of Alappuzha zone. We also thank Dr. Oommen P. Mathew, Research Investigator, Population research centre, University of Kerala, Kariavattom P.O, Thiruvananthapuram, for his contribution in the statistical analysis of this work.

Table-I Variables and point values used for the computation of the BODE index

Variable	Points on BODE index			
	0	**1**	**2**	**3**
FEV_1 (%predicted)[a]	≥65	50-64	36-49	≤35
Six-minute walk distance (m)	≥350	250-349	150-249	≤149
MMRC dyspnea scale[b]	0-1	2	3	4
Bodymass index (kg/m^2)	≥21	≤21		

Data Adapted from Celli et al (2004). The cut-off values for the assignment of points are shown for each variable; the total possible values range from 0 to 10;

[a] The FEV_1 categories were identified by the American Thoracic Society (1995);.

[b] Scores on the modified Medical Research Council (mMRC) dyspnea scale can range from 0 to 4, with a score of 4 indicating that the patient is too breathless to leave the house or becomes breathless when dressing or undressing.

Table-II Comparison of neuro psychometric scores with respect to different grades of severity assessed by BODE score

	BODE 1& 2	**BODE 3**	**BODE 4**	**P value**
	Mean±SD	**Mean±SD**	**Mean±SD**	
Number (n)	**24**	**32**	**44**	
Orientation (max score-10)	9.5 ± 0.7	8.8 ± 2.1	8.1 ± 2.1	0.097
Registration (max score-3)	2.8 ± 0.4	2.7 ± 0.6	2.8 ± 0.4	0.882
Attention, calculation (max score-5)	3.5 ± 1.3	3.3 ± 1.4	3.2 ± 1.5	0.860
Recall (max score-3)	2 ± 0.8	2.1 ± 0.9	1.9 ± 0.8	0.631
Language-verbal (max score-8)	6.9 ± 1	7.1 ± 1	7.1 ± 0.9	0.825
Copying (max score-1)	0 ± 0	0.1 ± 0.2	0 ± 0.2	0.683
MMSE SCORE	24.7 ± 2.5	24 ± 4.8	23.2 ± 4.5	0.528
CDT SCORE	3.8 ± 1.5	4.2 ± 1.6	4 ± 1.7	0.553
TMT-A SEC	113.3 ± 71.5	152.5 ± 102.6	176.7 ± 87.5	0.604
TMT-B SEC	150 ± 50.4	178.1 ± 102	232.6 ± 112.1	0.170

Values are expressed as Means ± SD; # ANOVA, others Kruskal Wallis test**.;**

BODE-1 is defined by a score of 0-2, BODE-2, score of 3 to 4, BODE-3, score of 5 to 6, & BODE-4, score of 7 to 10, with higher scores indicating a greater risk of death;

Abbreviations- MMSE, Mini Mental Status test; CDT, clock drawing test; TMT A, Trail Making test A; TMT B, Trail Making test B. (Normal reference values- MMSE>24; CDT<3; TMT-A<94sec; TMT-B<283sec.)

Table-III Correlation between parameters of severity of COPD and psychometric tests in the Study COPD group

	Orientation	**Registration**	**Attention, calculation**	**Recall**	**Language-verbal**	**Copying**	**MMSE SCORE**	**CDT SCORE**	**TMT-A SEC**	**TMT-B SEC**
SPO2	**0.248***	**0.227***	**0.205***	**0.212***	**0.214***	0.156	**0.287**#**	**-0.254***	-0.117#	-0.052#
FEV1% pred	0.136	-0.008	0.075	0.03	0.022	-0.045	0.083#	-0.036	0.044 #	0.061#
FEV1/FVC %	0.035	-0.185	0.038	0.036	0.037	0.045	0.011#	0.088	-0.003 #	-0.21#
CAT score	**-0.229***	-0.081	-0.103	-0.051	-0.152	0.037	**-0.24* #**	**0.24***	0 #	0.016#
MMRC score	**-0.198***	0.008	-0.007	**-0.229***	-0.122	-0.174	-0.168	0.009	**0.275***	**0.353***

Values expressed as Correlation coefficient (CC); **Significant at 0.01 level;*Significant at 0.05 level; # Karl Pearson correlation, Others Spearman rank correlation; **Abbreviations,** SPO2- resting oxygen saturation; FEV1- forced expiratory volume in one second (Litres); CAT, chronic obstructive pulmonary disease (COPD) assessment test; mMRC- modified Medical Research Council (mMRC) dyspnea scale.

References-

- **Aït-Khaled N, Enarson DA, Ottmani S, El Sony A, Eltigani M, Sepulveda R**. Chronic airflow limitation in developing countries: burden and priorities. Int J Chron Obstruct Pulmon Dis. 2007;2(2):141–150.
- **Anstey KJ, Windsor TD, Jorm AF, Christensen H, Rodgers B**. Association of pulmonary function with cognitive performance in early, middle and late adulthood. Gerontology. 2004;50(4):230–234.
- **Bernard S, LeBlanc P, Whittom F.** "Peripheral muscle weakness in patients with chronic obstructive pulmonary disease" .Am J Respir Crit Care Med 1998;158:629-34
- **Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA**. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. Thorax. 1999; 54(7):581–586.

- **Calverley PM.** Neuropsycological deficits in chronic obstructive pulmonary disease. Monaldi Arch Chest Dis. 1996; 51(1):5–6.
- **Celli BR, Cote CG, Marin JM, Casanova C, Montes de Oca M, Mendez RA, et al** The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med. 2004; 350:1005–1012.
- **D.T. Stuss, I. Peterkin, D.A. Guzman, C. Guzman and A.K. Troyer**; Chronic obstructive pulmonary disease: Effects of hypoxia on neurological and neuropsychological measures. J Clin Exp Neuropsychol **19**(4) (1997), 515–524.
- **D.T. Stuss, T. Shallice, M.P. Alexander and T.W. Picton,** A multidisciplinary approach to anterior attentional functions, Annals of the New York Academy of Science 769 (1995), 191–212.
- **Folstein M.F., Folstein S.E., McHugh P.R. (1975):** "Mini-Mental State": a practical method for the grading the cognitive state of patients for the clinician." J Psychiatr Res, 12: 196 – 198.
- **Giovagnoli AR, Del Pesce M, Mascheroni S, Simoncelli M, Laiacona M, Capitani E:** "Trail making test: normative values from 287 normal adult controls". Ital J Neurol Sci 1996**;17**: 305–309.
- **Global Strategy for Diagnosis**, Management, and Prevention of COPD, Updated January 2014.
- **Grant I, Healton RK, Mc Sweeny AJ, Adam KM, Timms RM**. Neurophysiological Finding In hypoxemic chronic obstructive pulmonary disease. Arch Intern 2009;180:134- 7
- **Grant, G.P. Prigatano, R.K. Heaton, A.J. McSweeney, E.C. Wright and K.M. Adams,** Progressive neuropsychologic impairment and hypoxemia. Arch Gen Psychiatry **44** (1987), 999–1006.
- **Hamilton M.** Development of a rating scale; for primary depressive illness". Br J Soc Clin Psychol. 1967 Dec; 6(4): 278-96.
- **Hung WW, Wisnivesky JP, Siu AL, Ross JS**. Cognitive decline among patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2009; 180(2):134–137.
- **Inc Antonelli, Marra C, Giordano A, Calcagni ML, Cappa A,Basso S, et al.** "Cognitive impairment in obstructive pulmonary disease neuropsychological and spect study". J Neurol 2003;250:325-32.
- **John J, Velayudhan S, Paniker V.** Cognitive function in patients with chronic obstructive pulmonary disease attending a tertiary care centre in Kerala. Biomedicine: 2015; 35(4): 418-424.
- **Jones PW, Brusselle G, Dal Negro RW, M. Ferrer, P. Kardos, M.L. Levy .** Properties of the COPD assessment test in a cross-sectional European study. Eur Respir J. 2011; 38(1):29–35.
- **Kozora E, Filley CM, Julian LJ, Cullum CM.** Cognitive functioning in patients with chronic obstructive pulmonary disease and mild hypoxemia compared with patients with mild Alzheimer disease and normal controls. Neuropsychiatry Neuropsychol Behav Neurol. 1999; 12(3):178–183.
- **Maruta C, Guerreiro M, de Mendonça A, Hort J, Scheltens P.** The use of neuropsycological tests across Europe: the need for a consensus in the use of assessment tools for dementia. Eur J Neurol. 2011;18(2): 279–285.
- **Moss M, Franks M, Briggs P, Kennedy D, Scholey A**. Compromised arterial oxygen saturation in elderly asthma sufferers results in selective cognitive impairment. J Clin Exp Neuropsychol. 2005; 27: 139–150.
- **Ortapamuk H, Naldoken S.** "Brain perfusion abnormalities in chronic obstructive pulmonary disease: Comparison with cognitive impairment". Ann Nucl Med. 2006;20:99–106.
- **Orth M, Kotterba S, Duchna K, Widding W, Rasche K,Schulze , Weninghaus G et al .** Cognitive deficits in patients with chronic obstructive pulmonary disease (COPD). Pneumologie 2006;60:593–9.
- **Perneczky R, Pohl C, Sorg C, Hartmann J, Tosic N, Grimmer T, et al.** Impairment of activities of daily living requiring memory or complex reasoning as part of the MCI syndrome. Int J Geriatr Psychiatry. 2006;21:158–162
- **Pleis JR, Leithbridge-Cejku M**. Summary Health Statistics for US adults: National Health Interview Survey, 2006. Hyattsville, MD: Vital and Health Statistics, US Department of Health and Human Services; 2007; 20–23.
- **Reitan RM:** "Validity of the trail-making test as an indication of organic brain damage". Percept Mot Skills 1958; 8: 271–276.
- **Ritchie K, Touchon J.** Mild cognitive impairment: conceptual basis and current sonological status. Lancet. 2000; 355(9199):225–228.
- **Roberto W Dal Negro, Luca Bonadiman, Silvia Tognella, Fernanda P Bricolo, Paola Turco.** Extent and prevalence of cognitive dysfunction in chronic obstructive pulmonary disease, chronic non obstructive

bronchitis, and in asymptomatic smokers, compared to normal reference values; International Journal of COPD, 2014:9 675–683

- **Shulman KI, Herrmann N, Brodaty H, Chiu H, Lawler B, Ritchie K, et al.** "IPA survey of brief cognitive screening instruments*". Int Psychogeriatr. 2006;18:281–94.*