Executive functions as predictors of functional performance in mild Alzheimer's dementia and mild cognitive impairment elderly

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Abstract

Cognitive impairment and depressive symptoms are associated with worse functionality phenotype in Alzheimer's disease (AD) and Mild Cognitive Impairment (MCI) elderly. The present study aims to investigate the association between the impairment of executive functions and episodic memory, the presence of depressive symptoms with the functionality of these patients. One hundred and eighteen participants diagnosed with AD or MCI who underwent neuropsychological examination covering various domains of episodic memory and executive functions and the answered the Geriatric Depression Scale. Caregivers answered a scale of Activities of Daily Living. The cognitive variables were reduced through factor analysis to three components (Executive Functions, Memory Episodic and Working Memory) and, along with depressive symptoms, used as predictors in a linear regression model, where only Executive Functions were related to functionality ($R^2 = 0.30$). The results suggest that executive functions are particularly relevant for functionality in these patients.

Keywords: executive functions; episodic memory, function activities, Alzheimer's dementia, cognition.

Resumo

Funções executivas como preditores do desempenho funcional em idosos com demência de Alzheimer em fase inicial e comprometimento cognitivo leve. O comprometimento cognitivo e os sintomas depressivos são associados a um pior fenótipo funcional em idosos com Alzheimer (DA) e Comprometimento Cognitivo Leve (CCL). O presente estudo almeja investigar a associação entre o comprometimento das funções executivas, da memória episódica e a presença de sintomas depressivos com o desempenho funcional nesses pacientes. Cento e dezoito idosos com DA ou CCL realizaram exame neuropsicológico, contemplando diversos domínios das Funções Executivas e Memória episódica, além da Escala de Depressão Geriátrica. Os cuidadores responderam uma escala de atividades de vida diária. As variáveis cognitivas foram reduzidas por meio de análise fatorial a três componentes (Funções Executivas, Memória Episódica e Memória de Trabalho) e junto aos sintomas depressivos utilizados como preditores em um modelo de regressão linear, onde apenas as Funções Executivas se relacionaram à funcionalidade ($R^2 = 0.30$). Os resultados sugerem que as Funções Executivas são particularmente relevantes à funcionalidade desses pacientes.

Palavras-chave: memória; funções executivas; atividades cotidianas; demência de Alzheimer; cognição.

The loss of autonomy for daily life activities performance is one of the main consequences of cognitive impairment. On the dementias, as the one which usually follows Alzheimer's disease (AD) or on its prodromal state, the Mild Cognitive Impairment (MCI), functional impairment of different intensities are usual to most of the patients, even on the mild stage of the disorders, where cognitive impairment is discrete (Brown, Devanand, Liu, & Caccappolo, 2011).

The relationship between cognitive and functional impairment is well established (Chaytor & Schmitter-Edgecombe, 2003). However, there is still inconsistency's on the specific contribution of specific cognitive domains for the performance on basic, instrumental or complex Activities of Daily Living. When an individual behave on its natural setting, different cognitive domains are used in a parallel and integrated way, which makes difficulty to identify specific patterns, normal or pathologic, of the functioning of specific domains. In this sense, the neuropsychological assessment can be particularly useful for the detection of specific cognitive impairment since its focus on the assessment of general and specific cognitive functions and its relationship with brain activity.

Neuropsychological tests are usually designed to assess

an specific cognitive construct by measuring behavior which can reproduced on artificial setting on clinical or research settings (Benton, 1994). This artificial setting, however, must be predictive of the patient's performance on ecological conditions. This psychometric property is named Ecological Validity (Tupper & Cicerone, 1990). The Ecological Validity has predictive power, integrating the cognitive assessment (which are usually built aiming diagnostic purposes) and the patient's behavior on its daily life, on a cognitive-functional relationship.

Considering the neuropsychological assessment of older adults, on the different cognitive domains assessed on the neuropsychological examination, two are particularly relevant for the functional performance: Memory (usually the most related impairment on dementia and mild cognitive impairment) and Executive Functions (related to goal-directed behaviors and also affected by dementia and MCI) as reviewed by Royall and colleagues (2007). The executive functions represent different cognitive processes which, seamlessly, allow the subject to guide its own behavior according to specific objectives, evaluate its efficiency and adequacy, discard dysfunctional strategies and maintain the most adapted ones, aiming problem-solving at its everyday functioning (Malloy-Diniz, Sedó, Fuentes, & Leite, 2008). The term Executive Functions in neuropsychology is usually described as an "umbrella" containing specific cognitive process, as controlled attention, fluency, abstract thinking, self-regulation, planning, inhibitory control, cognitive shifting and others (Chan, Shum, Toulopoulos, & Chen, 2008). The most significant brain correlate of this function are three prefrontal circuits: dorsolateral, orbitofrontal and anterior cingulate (Cummings, 1993).

Changes on executive functions are expected along the human life span. It can be described as an "inverted U" curve, where after the forty years and discrete decline is expected (Zelazo, Craik, & Boot, 2004). Some authors, as Salthouse, Atkinson and Berish (2003), suggest the much of the cognitive changes characteristic of normal ageing can be mediated by the decline of executive functions.

Changes on the process of storage and recall of episodic memories are also common on normal aging (Cansino, 2009). Subjective complaints of episodic memory, usually related to the forget of recent events, appointments or more specific details of an event are some of the most common complaints on the clinical setting. Different cognitive processes are associated with episodic memory, including short-term memory, learning, content recall and recognition. The neurocircuitry involved on episodic memory is complex, mostly involving the hippocampal formation, prefrontal, premotor and parietal cortices (Kim, 2011).

Besides cognitive impairment other clinical factor may contribute for the functional loss of older adults is the presence of mood disorders. On this population, it is of particular relevance the depressive disorders, more frequent and severe on older adults than in younger subjects, with important consequences for health and social insertion (Meeks, Vahia, Lavretsky, Kullkarni, & Jeste, 2011). Older adults diagnosed with major depressive disorder have more impairment on the performance of Activities of Daily Living even when other condition usually associated with this impairment, as the dementia, is present (Benoit et al., 2008).

On Brazilian studies of older adults, cognitive assessment is usually performed by more traditional testes, without directly concerning the ecological validity, according to a review (Vasconcelos, Brucki, & Bueno, 2007). Since there are few Brazilian studies assessing the ecological correlates of the neuropsychological assessment the present study aims to explore the relationship between neuropsychological tests related to episodic memory and executive functions in older adults diagnosed with mild AD or MCI. We also assessed the role of depressive symptoms on functional performance. We hypothesize that cognitive and behavioral aspect should predict functional performance.

Methods

Participants

For the present study 76 patients diagnosed with AD (based on the criteria proposed by McKhan et al., 1986) in this mild stage, and 42 patients diagnosed with MCI (based on the criteria proposed by Petersen et al., 2001). For the MCI group, all the participants were from the amnestic subtype (24 single domain and 18 multiple domain). The diagnoses were performed by a multidisciplinary team on a tertiary public health unit specialized in the assessment of older adults. All the participants underwent clinical examination and cognitive screening with a geriatrician and a brief neuropsychological examination with a clinical neuropsychologist. If necessary, neuroimage or complementary exams were performed. Diagnoses were based on consensus, by at least on geriatrician and one neuropsychologist. Inclusion criteria included score below the cutoff for depression (5/6) on the Brazilian 15-Item version of the Geriatric Depression Scale (Paradela, Lourenço, & Veras, 2005), no history of psychiatric or neurological disorders related by a close caregiver and after an assignment to the consent form by the patient and the caregiver. The study was approved by the Ethical Board of the institution.

Neuropsychological assessment

The neuropsychological tests used on the present study were applied on a pseudo pseudorandom order along the other measures involved on the present study. Verbal tests were not used on the interval between immediate and delayed recalls of the episodic memory test, to avoid content interference. All the tests were applied by psychologists or psychology undergraduates with appropriated training and experience. The total time for the neuropsychological assessment (including cognitive, behavioral and functional measures do not used on the study) was about 150 minutes along two or three session, according to the patient's agility on the assessment.

Category Fluency and Letter Fluency tests. A classical neuropsychological method designed to assess Executive functions, especially the ability of fluency. Three semantic categories (Animals, Fruits and Body Parts) and three letter's (F, A, S), under the time of one minute were used. The two versions were previously adapted and have normative data for Brazil (Brucki & Rocha, 2004; de Paula et al., 2010; Machado

et al., 2009).

Digit Span and Corsi Blocks. Simple tests designed for the assessment of working memory and its executive components (content manipulation). On the present study we adopted the scoring criteria proposed by Kessels, van den Berg, Ruis and Brans (2008), which consider a product score between the total correct trials and the maximum span achieved by the subject. These tests were previously adapted and validated for cognitively impaired Brazilian older adults (de Paula et al., 2010).

Frontal Assessment Battery. A screening test for frontal-executive dysfunction, containing tests of abstract thinking, fluency, selective attention, inhibitory control, motor planning and environmental autonomy, originally proposed by Dubois, Slachevsky, Litvan and Pillon (2000), and have normative values for the Brazilian older adults (Beato et al., 2012).

Tower of London Test. A classical measure for the assessment of planning skills, a component of executive functions. It is consisted of a wooden board with three pins differing in size and three colored balls which, starting from a fixed position, must be organized into a target configuration, with as few movements as possible. The version adopted on this study was standardized by Krikorian, Bartok and Gay (1994), and was previously validated for this population (de Paula et al., 2012a). Normative values were also previously published for clinical use (de Paula et al., 2012b).

Initiative/Perseveration subscale of the Mattis Dementia Rating Scale. A component related to executive functioning, containing tasks of fluency, motor programing and cognitive monitoring. The scale was adapted by Porto, Charchat-Fichman, Caramelli, Bahia and Nitrini (2003) for Brazilian older adults.

Conceptualization subscale of the Mattis dementia Rating Scale: this subscale contains items predominantly related to categorization and abstract thinking. Previously adapted by Porto and colleagues (2003).

Rey Auditory-Verbal Learning Test (RAVLT). A classical neuropsychological measure designed for the assessment of verbal learning and recall. It consists in 15-word lists which are read aloud for the patient (A1) and he must try to recall as many words as possible. The procedure is repeated four more times, for the assessment of learning, and then followed by a distractor list and then by to free recalls, one immediate (A6) and one delayed (A7). The test is concluded after a recognition task (Rec), where the subject must correctly identify the words from the target-list among 35 distractor. The total word recalled on the five trials were selected as a measure of learning. The test was adapted for Brazil by Malloy-Diniz and colleagues (2007) and validated by de Paula et al. (2012c).

Mini-Mental State Exam and Mattis Dementia Rating Scale (Mattis-Total). Global cognitive measures, used for the diagnosis and staging the cognitive impairment of the patients. On the study this two measures were used only for the participant's description, and were not used on the following procedures. They were adapted for Brazil by Bertolucci, Brucki, Campacci and Juliano (1994) and Porto et al. (2003), respectively.

Activities of Daily Living. Used as a measure of functional performance it was built as a composed measure of the Katz (Katz, Downs, Cash, & Grotz, 1970) and Lawton-Brody (Lawton & Brody, 1969) indexes of Activities of Daily Living. We used objective scoring criteria for the indexes: 2 points if the patient can perform the activity, 1 point if requires partial help for another person and 0 points if it is fully dependent of human help for correctly and safely performing the activity.

Statistical procedures

Participant's characteristics were described by descriptive statistics (mean and standard-deviations). Group comparisons between AD and MCI participants were performed by independent samples t-tests, and effect sizes estimated by the Cohen's d statistic. The predictive power of the neuropsychological tests for the functional performance of the patients was firstly explored by partial correlations, controlling for age and education. Thereafter, cognitive measures underwent exploratory factor analysis, a multivariate statistical procedure which allows to analyze the pattern of intercorrelations shown by the variables assessed. We adopted a principal components analysis, with oblique rotation (Direct Oblimin) method, for better results analysis. The factors were saved by the regression method, converting the results on standard Z scores. The Z scores were used as predictors on multiple stepwise linear regression models, with Activities of Daily Living as dependent variables. The inclusion criteria for the model were an addictive effect for the model predictive power ($p < 0.05$) and the exclusion criteria non significance ($p > 0.10$). The statistical procedures were performed on SPSS 17.0 (SPSS, 2008).

Results

Descriptive analysis of participant's data and neuropsychological measures are shown on Table 1. The groups shown significant differences in most of the adopted neuropsychological tests, with effect sizes usually moderate or high. The MCI group has also higher formal education and less depressive symptoms than AD participants. The groups did not differ between the proportion of man and woman ($\chi^2 = 0.01$, p = 0.979).

The association between cognitive and functional measures was firstly assessed by partial correlations controlling for age and education. As expected, most of the neuropsychological tests were related to functional performance, except for the Digit Span Forward ($r(115) = -0.109$, $p = 0.246$) and the component A1 of the RAVLT ($r(115) = -0.015$, p = 0.446). The strongest correlation was with the Mattis-Total ($r(115) = -0.587$, $p < 0.01$), an instrument designed for global cognitive assessment. The correlations are exposed on Table 1.

The factor analysis results on a three-components model, the first related to executive functions (including the Frontal Assessment Battery, Category and Verbal Fluency, Mattis Initiative/Perseveration and Conceptualization), a second with the RAVLT measures and a third factor composed by working memory measures. The only test which shown factor loads superior to 0.3 on more than one factor was the Tower of London, divided between the first and third factors. Together the three components explained more than 63% percent of total variance.

Table 1
Participant's Description, Neuropsychological Assessment and Group Comparisons.

	AD (n = 76, M = 36)			MCI (n = 42, M = 20)					
	Mean	SD	Min-Max	Mean	SD	Min-Max	t	d	r
Age	77.13	7.02	61-92	74.50	7.93	60-95	1.86	-	-
Education	3.68	3.63	0-15	5.57	4.53	0-15	-2.47*	-0.46	-
Geriatric Depression Scale 15	4.67	3.16	0-15	3.27	2.74	0-12	2.15**	0.47	-0.196*
Mini-Mental State Exam	19.41	4.76	13-28	23.90	3.57	17-29	-5.34**	-1.07	0.537**
Mattis-Total	96.71	17.78	86-131	118.79	12.16	95-144	-7.16**	-1.47	0.587**
Category Fluency Test	24.41	7.77	6-46	34.02	8.68	18-61	-6.19**	-1.16	0.402**
Letter Fluency Test	13.36	8.24	3-23	21.13	11.75	6-46	-4.20**	-0.77	0.281**
Tower of London	19.34	8.33	0-32	27.03	6.88	0-36	-5.94**	-1.01	0.500**
Frontal Assessment Battery	7.75	2.88	2-15	11.98	3.08	6-18	-7.44**	-1.41	0.451**
Mattis – Initiative/Perseveration	21.97	6.70	12-37	28.33	6.43	16-37	-5.00**	-0.96	0.435**
Mattis – Conceptualization	24.22	6.63	9-38	30.71	5.61	16-39	-5.36**	-1.06	0.393**
Digit Span (Forward)	27.38	14.90	9-88	36.29	16.05	20-84	-3.02**	-0.57	0.109
Digit Span (Backward)	7.85	6.18	0-24	12.67	8.21	4-35	-3.60**	-0.67	0.200*
Corsi Span (Forward)	19.00	11.14	0-48	22.72	10.56	12-70	-1.76**	-	0.282**
Corsi Span (Backward)	8.39	8.00	0-48	11.27	7.51	0-35	-1.91**	-	0.260**
RAVLT A1	2.72	1.43	0-6	3.55	1.31	1-6	-3.08**	-0.60	0.015
RAVLT A6	2.30	1.82	0-6	4.09	3.01	0-12	-4.06**	-0.70	0.258**
RAVLT A7	1.99	1.81	0-8	3.86	2.98	0-12	-4.25**	-0.78	0.355**
RAVLT Total	20.40	7.10	4-35	27.74	9.55	15-54	-4.74**	-0.88	0.224*
RAVLT REC	-1.27	6.73	-20-10	0.91	7.11	-15-12	-1.64	-0.31	0.218*
Activities of Daily Living	21.95	5.31	0-22	27.98	2.24	0-8	-8.55**	-1.59	1.000

*$p < 0.05$; **$p < 0.01$

AD: Alzheimer's disease, MCI: Mild Cognitive Impairment, RAVLT: Rey Auditory-Verbal Learning Test, M: Male, *SD*: Standard-Deviation, MIN: Minimum, Max: Maximum, *r* = partial correlation coefficient with Activities of Daily Living.

The factor structure of the neuropsychological measures is shown on Table 2.

The stepwise linear regression model which assessed the association between cognition, depressive symptoms and Activities of Daily Living was significant ($F(1, 116) = 49.27$, $p < 0.001$), explaining about 30% of total variance. On this model, containing three cognitive factors and the depressive symptoms only the Executive Functions component was significant, accounting for about 30% variance. Episodic memory ($p = 0.103$) and Working Memory ($p = 0.109$) were not significant after accounting for the first component. Depressive symptoms were not significant on the model, however, it showed a strong trend ($p = 0.053$).

Discussion

Along its own history the neuropsychology was founded and largely associated with the topographic diagnosis, the localization of lesion on the brain loci (Long & Kibby, 1995). Whit the development of neuroimage techniques the neuropsychology aimed the nosological diagnosis (of conditions like AD and MCI) or functional diagnosis (estimating the capacity and requirements for daily life functioning, school and work performance or in juridical settings). In this sense the neuropsychological exam is had a retrospective value (aiming the patient diagnosis) and a prospective value (aiming the patient prognosis). The ecological validity of the neuropsychological assessment is essential for the prospective component.

The results presented here contribute for the prospective aspect of the neuropsychological examination, suggesting that Executive Functions, represented by a combination of classical measures of this construct predicts functional performance on older adults. The other cognitive domains assessed by the present protocol (Episodic Memory and Working Memory) were not significant in our model. However, the lack of variance on Episodic Memory performance exhibited the studied population – due to floor effect (Locascio, Growdon, & Corkin, 1995) and on Working Memory by the low variability of test score found on AD and MCI (Huntley & Hoard, 2010) may explain the non-significant results.

The relationship of Executive Functions and daily life is a field of growing interest in neuropsychology. Studied as the one conducted by Espinosa et al. (2009) suggest and important association between executive functions performance and

Table 2
Rotated Pattern Matrix of the Neuropsychological Assessment Protocol.

	Executive Functions	**Episodic Memory**	**Working Memory**
Mattis – Initiative/Perseveration	**0.822**	-0.026	-0.094
Category Fluency test	**0.774**	-0.164	0.009
Mattis - Conceptualization	**0.730**	0.051	0.124
Frontal Assessment Battery	**0.652**	-0.190	0.136
Letter Fluency test	**0.617**	0.020	0.272
Tower of London	**0.386**	-0.226	**0.355**
RAVLT A7	0.058	**-0.881**	-0.021
RAVLT Total	0.203	**-0.826**	-0.118
RAVLT A6	0.071	**-0.823**	-0.016
RAVLT REC	-0.231	**-0.727**	0.188
RAVLT A1	0.096	**-0.633**	-0.061
Digit Span (Forward)	-0.165	-0.058	**0.838**
Corsi Span (Backward)	0.144	0.076	**0.729**
Digit Span (Backward)	0.136	-0.012	**0.676**
Corsi Span (Forward)	0.196	-0.013	**0.617**
Eigenvalue	**6.212**	**2.004**	**1.161**
Explained Variance (R^2)	**41%**	**13%**	**8%**

Mattis: Mattis Dementia Rating Scale.
RAVLT: Rey Auditory-Verbal Learning test.

functional performance. Some procedures like factor analysis allow the researcher to investigate whit better precision the relationship between cognitive constructs and functional variables, since they used a component or factor built on the latent structure of a set of neuropsychological tests. On this sense our findings corroborate previous studies, as Van der Elst, Van Boxtel, Van Breukle and Jolles (2008) which by factor analysis investigated the latent structure of different neuropsychological tests and found a significant predictive value for functional performance. On a population relatively similar to the one investigated on our work, Pereira, Yassuda, Oliveira and Forlenza (2008) also found a significant association between Executive Functions and functional performance, with large effect sizes.

The factor formed by Category and Fluency Tests, Frontal Assessment Battery, Tower of London and Mattis Initiative/Perseveration and Conceptualization was a good predictor of functional performance, with large effect sizes. This component represents the Executive Functions in a comprehensive way (including even a multidimensional test, the Frontal Assessment Battery). Future studies should adress the specific relationship between specific Executive Functions and different aspects of everyday functioning.

Fluency, measured by the Category and Letter Fluency tests and the Mattis-Initiative/Perseveration subscale, should be required for the production of a dynamic behavior on daily living (depending also on processing speed and semantic memory), depending of process of cognitive monitoring and cognitive shifting (avoiding repetitions and intrusions during task performance). We may consider the fluency related to a volitional component of Executive Functions, participating

on the initiation of a goal-directed behavior. Our findings are corroborated by a recent study proposed by Greenaway, Duncan, Hanna and Smith (2012), whose found and significant association between these Executive Functions assessed by Mattis-Initiative/Perseveration (mostly formed by Fluency tasks) with everyday living (moderate effect sizes). Another work from Drijgers, Verhey, Köhler and Aalten (2011), studying MCI patients, found significant differences between the Fluency of participants with and without apathy, a neuropsychiatric syndrome related to loss of volition. Their study also found a specific pattern for MCI, since AD patients did not show similar results. Considering the behaviors assessed on our study, the Fluency components should influence the initiation and cognitive monitoring of the assessed Activities of Daily Living.

In what concerns the Categorization/Abstraction components of Executive Functions, assessed in our Study by the Mattis-Conceptualization subscale, the abstract reasoning, involving similarities, has important correlates on daily living, since much of the learning of new contents and problem solving depends of an analogy thinking (Holyoak & Thagard, 1997). The processes of Categorization/Abstraction would be an important aspect of verbal reasoning, related to removing new everyday problems making adaptation of pervious cognitive schemas used on similar situations (Volle, Gilbert, Benoit, & Burgess, 2010). Most of the Activities of Daily Living assessed on our study, especially those of greater complexity (financial control, shopping and outside home walking) depends on the use of previous experiences and schemas on new contexts, involving Categorization/Abstraction.

Considering Planning Skills, its association with Activities of Daily Living performance suggests that for the correct

its execution the subject must correctly plan several steps to achieve a final goal. This Executive domain involves the correct identification of a final goal, the temporal organization of the necessary steps for a non-immediate goal, the representation of this schema on an abstract model, its online maintenance on working memory for, then, apply the necessaries behavior for achieving the targeted goal using the efferent systems (Prinz, 1997). The performance of instrumental Activities of Daily Living as preparing an meal, go out alone for a, specific place using transportation or shopping, involves a prospective component, where the subject must correctly identify the required steps for its completion. The impairment of Planning Skills would produce a confuse behavior, maladapted for its final goals, since its correct execution depends of a specific order of steps, which, if violated, may lead to failure.

Although non-significant on the current study depressive symptoms seems related to a poor functional performance. In MCI and AD older adults, depressive symptoms are usually related to different levels of impairment in Activities of Daily Licing (Wada et al., 2005). The depressive disorders are multifactorial, involving neurobiological, cognitive and behavioral aspects (Beblo, Sinnamon, & Baune, 2011). The depressive symptoms influence functional performance on different levels: it can be mediated either by cognitive impairment or by the behavioral and emotional manifestations of the disorder. Recent studies however suggest that the moderating role of depression on functional performance may be milder on pathological cognitive aging, as the dementias, and may be secondary to the impairment of Executive Functions (de Paula et al., 2012d; Sexton et al., 2011), which may explain the results found on the current study.

Our work has important limitations. The functional measure adopted for the patient's assessment is an index of different Activities of Daily Living where the patient caregiver must report its functional status. This is the most used method the assessment these behaviors in Brazil (Vasconcelos et al., 2007). However, these measures might be biased by the caregiver perception about the patient status (Onor, Trevisiol, Negro, & Aguglia, 2006). In this sense, an ecological assessment of functional performance (in an experimental setting) should allow more reliable results. The study design proposed by Farley, Higginson, Sherman and MacDougall (2011), involving ecological tests to be performed on the clinical and home setting (with objective scoring criteria) would be particularly useful. The lack of neuropsychological measures of other cognitive functions (as language or visuospatial abilities) and a global cognitive measure also restrain our conclusions. Future studies should address these issues.

Conclusion

The results of the present study suggest that in patients with mild AD and amnestic MCI the Executive Functions are particularly related to functional performance, attesting the relevance of these cognitive components for the independence on Activities of Daily Living. It is also an evidence of the ecological validity of selected neuropsychological tests. Future studies aiming the relationship between different cognitive domains and neuropsychiatric symptoms should allow a more specific analysis of the cognitive-behavioral predictors of functional performance in these patients.

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