Apathy and functional disability in behavioral variant frontotemporal dementia

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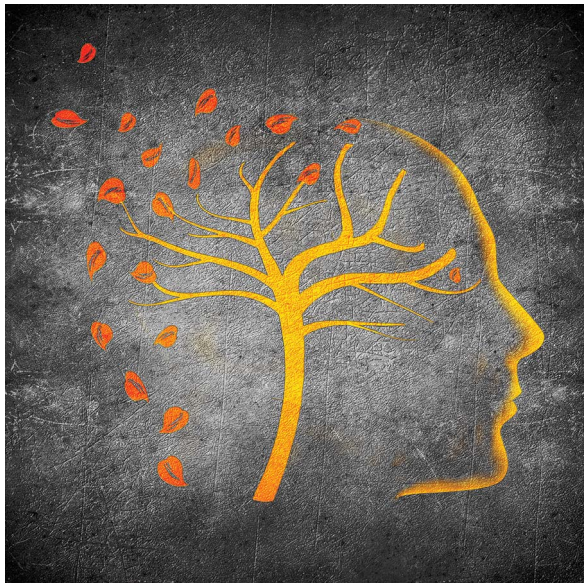
Abstract



Background

Behavioral variant frontotemporal dementia (bvFTD) has profound consequences on patients and their families. In this multicenter study, we investigated the contribution of cognitive and neuropsychiatric factors to everyday function at different levels of overall functional impairment.

Methods

In a retrospective cross-sectional study, 109 patients with bvFTD from 4 specialist frontotemporal dementia centers (Australia, England, India, and Brazil) were included. The measures administered evaluated everyday function (Disability Assessment for Dementia [DAD]), dementia staging (Clinical Dementia Rating [CDR]), general cognition (Addenbrooke's Cognitive Examination–revised [ACE-R]), and neuropsychiatric symptoms (Neuropsychiatric Inventory [NPI]). Patients were then subdivided according to functional impairment on the DAD into mild, moderate, severe, and very severe subgroups. Three separate multiple linear regression analyses were run, where (1) total DAD, (2) basic activities of daily living (BADL), and (3) instrumental activities of daily living (IADL) scores were dependent variables; ACE-R total score and selected NPI domains (agitation/aggression, euphoria, apathy, disinhibition, irritability, aberrant motor behavior) were used as independent variables. Age, sex, education, and country of origin were controlled for in the analyses.

Results

Cognitive deficits were similar across the mild, moderate, and severe subgroups but significantly worse in the very severe subgroup. NPI domain scores (agitation/aggression, euphoria, apathy, disinhibition, irritability, aberrant motor behavior) did not differ across the DAD subgroups. In the multiple regression analyses, a model including ACE-R and NPI apathy explained 32.5% of the variance for total DAD scores. For IADL, 35.6% of the variance was explained by the ACE-R only. No model emerged for BADL scores.

Conclusions

Cognitive deficits and apathy are key contributors to functional disability in bvFTD but factors underlying impairment in BADLs remain unclear. Treatments targeting reduction of disability need to address apathy and cognitive impairment to ensure greater efficacy, especially in regards to IADLs.

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At the time of the data collection, SA and SM were based at Nizam's Institute of Medical Sciences, Hyderabad, India; EM, OP, JRH were based at Neuroscience Research Australia.

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This is a retrospective cross-sectional study resulting from the secondary analysis of data from studies run at collaborating centers.

Behavioral variant frontotemporal dementia (bvFTD) has profound consequences on the lives of patients and their families.[1-3] Marked behavioral and cognitive deficits are present from early in the disease[4] and underlie the marked functional changes observed throughout the disease course. It is not surprising, therefore, that bvFTD is associated with higher rates of caregiver distress[5,6] and burden[7,8] than other forms of dementia.

Functional impairment is significantly more marked in bvFTD than other frontotemporal dementia (FTD) variants[1,9] and Alzheimer disease, even when matched for disease duration. Functional disability may also predict disease progression in bvFTD.[10] For these reasons, more generalizable understanding of factors underlying disability in bvFTD is required to provide evidence for planning of interventions, clinical decisions, and other areas of family life.

Although it has been demonstrated that apathy and cognitive scores are associated with functional decline in bvFTD,[9-11] the specific contributions of these variables to basic activities of daily living (BADL) and instrumental activities of daily living (IADL) are unknown, as large group studies including well-characterized bvFTD samples are rare. This study takes advantage of this multicenter initiative to apply a quantitative approach that can be generalized across countries.

The objectives of the present study were to (1) investigate the cognitive and neuropsychiatric profiles of patients with bvFTD according to different levels of functional impairment in a large group of patients seen across 4 international specialist centers; and (2) explore whether cognitive deficits or neuropsychiatric symptoms are directly associated with functional impairment in activities of daily living (ADL) in bvFTD.

Methods

Participants

This is a retrospective cross-sectional study resulting from the secondary analysis of data from studies run at collaborating centers. In total, 109 patients diagnosed with bvFTD according to international criteria[12,13] were included from 4 research centers: Australia, Frontier–Frontotemporal Dementia Research Centre (Sydney); Brazil, Cognitive and Behavioral Neurology Group (GNCC-SP) and Old Age Research Group (PROTER) at the University of São Paulo, and Cognitive and Behavioral Neurology Group (GNCC-MG) at the Federal University of Minas Gerais and the Neuropsychology and Dementia Unit of the Department of Neurology at the State University of Campinas (UNICAMP); England, Early Onset Dementia Clinic at the University of Cambridge; India, Nizam's Institute of Medical Sciences, Hyderabad. Samples were as follows: Australia (n = 45), Brazil (n = 31), England (n = 15), and India (n = 18).

Patients were diagnosed by experienced neurologists or psychiatrists and diagnosis was based on clinical and cognitive assessments and multidisciplinary consensus, as well as structural neuroimaging. Inclusion criteria for patients were age >40 years, education >2 years, and presence of an informant who was involved in the daily routine of the patient (formal or informal carer; usually spending more than 8 h/d with the patient). Individuals with visual, auditory, or motor deficits preventing them from understanding instructions or performing cognitive tasks; other uncontrolled clinical diseases (such as hypertension and diabetes); serious and debilitating psychiatric disorders such as major depression, schizophrenia, or bipolar disorder; clinical evidence or neuroimaging examination findings suggestive of vascular problems; or dementias or etiologies other than FTD were excluded.

Instruments

Sociodemographic and clinical variables were recorded at all centers, including age, years of formal education, marital status, and presence of other clinical conditions.

Functional disability

The Disability Assessment for Dementia (DAD)[14] was used to evaluate functional impairment, and was administered to all caregivers during an interview. It includes 40 items that assess BADL and IADL. To avoid sex bias, questions that do not apply to patients (e.g., cooking, house chores, finances) are excluded from the total score. Separate total and BADL and IADL subscores are computed. Scores vary from 0 to 100 and higher scores indicate better performance. A percentage score, as an index of functional preservation, takes into account the premorbid state of the patient, as it does not consider the tasks never performed before.

Dementia staging

To determine dementia staging, the Clinical Dementia Rating (CDR) scale[15] was completed. A predefined algorithm allows the calculation of a total score, with 0 indicating preserved performance, 0.5 mild impairment, 1.0 mild dementia, 2.0 moderate dementia, and 3.0 severe dementia.

General cognitive status

The Addenbrooke's Cognitive Examination–revised (ACE-R)[16] consists of a brief cognitive assessment battery testing 5 different cognitive domains. The highest score is 100 points, and higher scores indicate better performance.

Neuropsychiatric symptoms

The Neuropsychiatric Inventory[17] (NPI) in its short version is a 10-item questionnaire that assesses the frequency and severity of neuropsychiatric and behavioral symptoms. For the present study, we included scores for agitation/aggression, euphoria, apathy, disinhibition, irritability, and aberrant motor behavior (maximum score per domain is 12). These represent the behavioral disturbances that are most frequently observed among patients with bvFTD.[5,18-20] The English subsample did not have scores for the NPI assessment. To avoid excluding the English subsample from the descriptive analyses, scores for the NPI subdomains were input using the method of multiple imputations described by Rubin,[21] using linear regressions.

Data analyses

The χ^2 test was used to compare categorical variables between the diagnostic groups. The Kolmogorov-Smirnov test determined the absence of normal distribution in most of the continuous variables; therefore, nonparametric tests were applied. Dispersion and position indices are presented by means of interquartile ranges, such that the first quartile (Q1) represents percentile 25, the median (MD or Q2) is percentile 50, and the third quartile (Q3) represents percentile 75.

Between-group analyses (different levels of functional impairment in the DAD) were conducted with the Kruskal-Wallis test. For the investigation of the influence of neuropsychiatric symptoms and cognitive changes at different levels of functional impairment, the sample was categorized on the basis of DAD scores as mild (76–100), moderate (51–75), severe (26–50), and very severe (0–25).[1] For these analyses, considering a moderate effect size (0.3), the present sample (n = 109) generated 72% of power (moderate).

Multiple linear regression analyses[21] were performed with DAD total score, BADL, and IADL scores as numerical dependent variables, and ACE-R total score, agitation/aggression, euphoria, apathy, disinhibition, irritability, and aberrant motor behavior (NPI subscores) as independent variables, controlling for age, sex, years of education, and country. For the regression analyses, the sample from England was excluded, as we did not have NPI scores available. For statistical analysis, SPSS v.17.0 and Statistica v.7.0 were used.

Standard protocol approvals, registrations, and patient consents

Studies were approved by the local ethics committee at each research center. Informed consent was obtained from patients or caregivers.

Results

Patients from the 4 centers were matched for age, sex, education, and CDR scores. Patients from India had significantly lower cognitive ACE-R scores compared with patients from Australia and England. Functional scores (total DAD) did not differ among the countries. However, there were significant differences for BADL and IADL subscores. For BADL scores, the sample from Brazil had significantly lower scores than the samples in Australia and England. For IADL scores, the sample from India had lower scores than the samples in Brazil and England (table 1).

Cognitive and behavioral profiles: Mild, moderate, severe, and very severe scores on the DAD

We stratified the sample by levels of functional impairment on the DAD to compare cognitive and behavioral profiles according to level of functional impairment. As shown in table 2, demographic characteristics did not differ across the subgroups. The only exception was the moderate DAD subgroup, which contained a greater proportion of men compared to other DAD subgroups.

There was an overall significant group effect for degree of cognitive impairment across the subgroups. Cognitive deficits, as measured by the ACE-R, were similar for DAD score ranges mild, moderate, and severe (table 2 and figure, A), where cognitive scores seemed to be on a plateau and relatively high (mean ~67/100). Cognitive scores were significantly lower in the very severe subgroup (mean 40/100) in comparison to the other DAD score subgroups ($p < 0.001$).

In regards to neuropsychiatric symptoms (NPI domains), there were no significant differences in NPI domain scores (agitation/aggression, euphoria, apathy, disinhibition, irritability, aberrant motor behavior) across the subgroups (table 2 and figure, B).

Are cognitive deficits or neuropsychiatric symptoms underlying functional disability?

To investigate the influence of the different variables on functional disability, 3 separate multiple linear regression analyses were performed. The dependent variables were (1) total DAD, (2) BADL, and (3) IADL scores. ACE-R total score, agitation/aggression, euphoria, apathy, disinhibition, irritability, and aberrant motor behavior (NPI subscores) were included in the model as independent variables. Results were controlled for age, sex, years of education, and country.

A total of 32.5% of the variance on total DAD scores was explained by a model containing ACE-R and apathy. No model emerged to explain the variance of BADL scores. For IADL scores, 35.6% of the variance was explained by a model combining ACE-R only (table 3). The remaining NPI variables and demographic characteristics did not make an important contribution to the 3 models.

Table 1 Sociodemographic and clinical characteristics of the sample divided by country of origin

	Total, n = 109			Countries												
				Australia, n = 45			Brazil, n = 31			England, n = 15			India, n = 18			
Variables	Q1	Q2	Q3	Q1	Q2	Q3	Q1	Q2	Q3	Q1	Q2	Q3	Q1	Q2	Q3	*p* Value
Age, y	60.00	66.00	71.00	60.00	68.00	73.00	61.00	65.00	72.00	58.00	64.00	67.00	55.00	62.00	69.00	0.155
Sex, n (%)																
Male	70	(64.22)		28	(62.22)		19	(61.29)		14	(93.33)		9	(50.00)		
Female	38	(34.86)		16	(35.56)		12	(38.71)		1	(6.67)		9	(50.00)		0.075
Education, y	9.00	11.00	15.00	9.00	11.00	13.00	4.00	8.00	15.00	10.00	11.00	13.00	10.00	12.00	15.00	0.123
CDR	1.00	1.00	2.00	1.00	1.00	1.00	1.00	1.00	2.00	1.00	1.00	1.00	1.00	2.00	2.00	0.176
ACE-R (max 100)	51.00	66.00	79.00	63.00	72.00	83.00	51.00	58.00	73.00	62.00	81.00	87.00	3.00	22.00	62.00	<0.001[a]
DAD total	27.00	47.50	65.00	27.00	49.00	67.00	35.00	45.00	60.00	41.00	56.00	81.00	7.00	25.50	54.00	0.099
DAD BADL	40.00	55.00	76.00	43.00	70.00	82.00	40.00	50.00	55.00	58.00	64.00	82.00	17.00	43.50	88.00	0.014[b]
DAD IADL	15.00	35.00	60.00	13.00	34.00	53.00	20.00	40.00	60.00	31.00	50.00	80.00	5.00	18.50	26.00	0.002[c]

Abbreviations: ACE-R = Addenbrooke's Cognitive Examination–revised; bvFTD = behavioral variant frontotemporal dementia; CDR = Clinical Dementia Rating; DAD = Disability Assessment for Dementia.
Values are means. *p* Values refer to the Kruskal-Wallis test. Q1 = first quartile represents percentile 25; Q2 = second quartile represents percentile 50; Q3 = third quartile represents percentile 75.
[a] Australia and England ≠ India.
[b] Australia ≠ Brazil, England ≠ Brazil.
[c] India ≠ Brazil, India ≠ England.

Table 2 Characterization of the samples according to levels of disability on the Disability Assessment for Dementia (DAD)

	DAD percentiles												
	Mild (76%–100%), n = 13			Moderate (51%–75%), n = 34			Severe (26%–50%), n = 35			Very severe (0%–25%), n = 24			
Variables	Q1	Q2	Q3	Q1	Q2	Q3	Q1	Q2	Q3	Q1	Q2	Q3	*p* Value
Age, y	59.00	62.00	68.00	58.00	64.00	72.00	62.00	66.00	72.00	59.00	66.00	73.00	0.425
Sex, n (%)													
Male	8	(61.54)		28	(82.35)		17	(48.57)		15	(62.50)		
Female	5	(38.46)		6	(17.65)		18	(51.43)		9	(37.50)		0.034[a]
Education, y	10.50	12.00	13.00	7.00	10.00	13.00	9.00	11.00	15.00	9.00	11.50	15.00	0.134
ACE-R (max score 100)	62.00	79.00	86.00	63.00	73.50	82.00	51.00	65.50	81.00	11.00	40.00	62.00	<0.001[b]
NPI													
Agitation/aggression	0.00	0.00	1.00	0.00	0.00	3.00	0.00	1.00	4.00	0.00	0.00	2.00	0.425
Euphoria	0.00	0.00	1.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.50	0.478
Apathy	0.00	1.00	6.00	2.00	4.00	8.00	3.00	4.00	8.00	2.50	6.00	12.00	0.089
Disinhibition	0.00	0.00	0.00	0.00	1.00	3.00	0.00	2.00	4.00	0.00	0.50	2.00	0.189
Irritability	0.00	1.00	4.00	0.00	0.00	4.00	0.00	0.00	4.00	0.00	0.00	2.00	0.894
Aberrant motor behavior	0.00	0.00	6.00	0.00	0.00	6.00	0.00	0.00	6.00	0.00	6.00	10.50	0.143

Abbreviations: ACE-R = Addenbrooke's Cognitive Examination–revised; bvFTD = behavioral variant frontotemporal dementia; NPI = Neuropsychiatric Inventory.
Values are means. *p* Values refer to the Kruskal-Wallis test. Q1 = first quartile represents percentile 25; Q2 = second quartile represents percentile 50; Q3 = third quartile represents percentile 75.
[a] Severe ≠ very severe, moderate, mild.
[b] Very severe ≠ severe, moderate, mild.

A key strength of this study is the compilation of functional data from international specialist FTD centers across different continents.

Discussion

This multicenter study confirmed the disabling nature of bvFTD, and demonstrated the key contributors to level of functional impairment were apathy and level of overall cognition. Critical decline in global cognition (as measured by the ACE-R) and increased apathy were relevant to decline on ADLs overall, whereas decline in cognition had a strong influence on IADL scores. Factors underlying performance in BADLs remain unclear.

General cognition appears to be the major factor underlying disability in bvFTD.[1] Our findings differ from other studies where apathy was a major factor across ADLs in bvFTD.[1,11-22] Differences in findings may reflect the larger sample size used in this study.

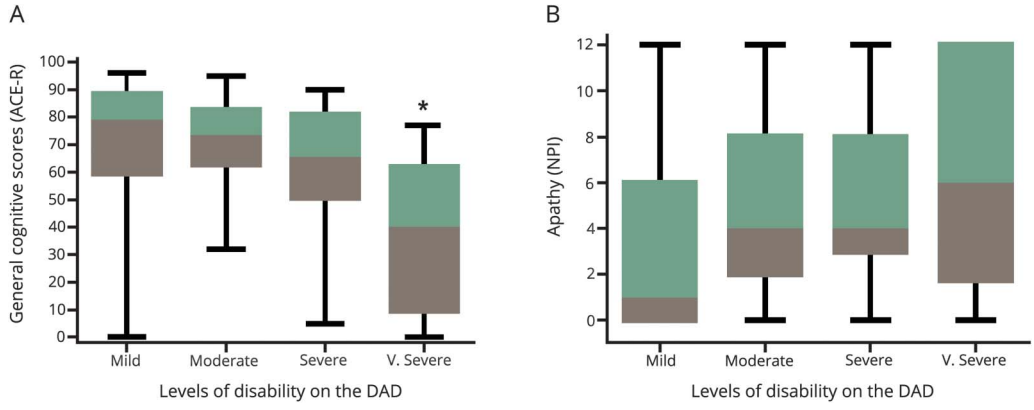
Even though general cognitive scores seem to plateau in the first 3 functional stages of bvFTD (mild, moderate, and severe as per DAD scores), the ACE-R was the main key contributor to the model explaining disability, demonstrating the role of global cognition in function. Present results reaffirm that deficits in executive or global cognitive functions are associated with ADL impairment in bvFTD.[1,6,23] Future studies should address this interaction of function and cognitive scores in more detail, bearing in mind the difficulties in applying current standardized neuropsychological tests in bvFTD. Novel techniques to evaluate cognitive function would be especially welcome.

Another implication of the complex interaction of function and cognition in bvFTD is that people may appear, at face value, to be functioning well based on their cognitive scores, while in reality they are severely disabled and dependent on others at home.[6,24,25] In addition, it is clear that cognition only partly explains the variance in functional scores. In fact, there seems to be a large amount of variability in daily functioning (especially BADLs) that is not reflected in cognitive status or measurable behaviors (e.g., NPI scores), and remains to be investigated. Our findings demonstrate the need for a multifaceted approach in assessing patients with bvFTD for the determination of appropriate clinical and social care, especially as disease progresses and BADL impairment becomes even more pronounced.

Results from this study have major implications for patient care, as they suggest that to facilitate ADL engagement patients with bvFTD may need cognitive cues as well as strong support to compensate for their lack of motivation throughout the disease. In other words, patients with bvFTD may need to have complex tasks simplified and broken into steps to reduce cognitive demands and they may benefit from intense reinforcement contingencies to improve motivation. Strategies to enhance reward may also prove useful in this patient population. Such approaches remain to be confirmed in future trials, but preliminary case study results suggest these could in fact work in FTD,[22] as shown in general dementia.[26]

In addition, pharmacologic treatment to reduce apathy may also have a positive influence on overall ADL performance, but it remains to be investigated. A key strength of this study is the compilation of functional data from international specialist FTD centers across different continents, which also enabled the analyses on a considerable sample size in FTD

Figure General cognitive scores (Addenbrooke's Cognitive Examination–revised [ACE-R]) and apathy scores (Neuropsychiatric Inventory [NPI]) for each level of functional impairment (Disability Assessment for Dementia [DAD])



(A) General cognitive scores (ACE-R) and (B) apathy scores (NPI) for each level of functional impairment (DAD). Mild, moderate, severe, and very severe. *Mean of the very severe group was lower than the mean of the other groups in the ACE-R ($p < 0.001$).

Table 3 Multiple linear regression analyses with Disability Assessment for Dementia (DAD) total, DAD basic activities of daily living (BADL), and DAD instrumental activities of daily living (IADL) scores as dependent variables

Effect	β	SE	*p* Value	Power
DAD total				
ACE-R	0.375	0.124	0.003	0.846
Agitation/aggression	0.246	1.111	0.826	0.055
Euphoria	−1.359	1.295	0.298	0.179
Apathy	−1.791	0.748	0.019	0.657
Disinhibition	0.675	0.782	0.391	0.136
Irritability	0.222	0.949	0.816	0.056
Aberrant motor behavior	−0.804	0.626	0.203	0.245
DAD BADL				
ACE-R	0.277	0.144	0.058	0.477
Agitation/aggression	−0.403	1.287	0.755	0.061
Euphoria	−2.196	1.500	0.147	0.304
Apathy	−1.645	0.866	0.062	0.466
Disinhibition	1.667	0.906	0.070	0.443
Irritability	1.090	1.099	0.324	0.165
Aberrant motor behavior	−1.149	0.725	0.117	0.347
DAD IADL				
ACE-R	0.451	0.129	0.001	0.931
Agitation/aggression	0.965	1.162	0.409	0.130
Euphoria	−0.831	1.364	0.544	0.092
Apathy	−1.350	0.792	0.093	0.391
Disinhibition	−0.275	0.821	0.739	0.063
Irritability	−0.301	0.993	0.762	0.060
Aberrant motor behavior	−0.702	0.663	0.293	0.182

Abbreviations: ACE-R = Addenbrooke's Cognitive Examination–revised; DAD = Disability Assessment for Dementia; NPI = Neuropsychiatric Inventory.
These analyses excluded the sample from England due to the absence of NPI data. Independent variables were ACE-R, NPI agitation/aggression, NPI euphoria, NPI apathy, NPI disinhibition, NPI irritability, and NPI aberrant motor behavior. The effects of age, sex, years of education, and country were controlled for in the analyses. DAD total: $R^2 = 0.325$; DAD BADL: $R^2 = 0.312$; DAD IADL: $R^2 = 0.356$.

studies, allowing for greater generalization of the results. Present findings seem to suggest that regardless of culture-specific factors, cognitive deficits and apathy contribute to functional deficits overall.

Limitations in this study include the secondary data nature of the analyses as it did not allow for a priori package training of all assessments. Nevertheless, DAD data were collected primarily by the same person (E.M.) across the United Kingdom and Australia, who also provided training for the Indian group, limiting some of the potential rater bias. A potential recruitment bias was that the study arm in Brazil recruited only patients with bvFTD who were relatively early in the disease, but this may have been balanced out by the amalgamation of data from other centers. In addition, a larger sample size would have given the study more power, given the large amount of variance in the data, particularly in the NPI.

Our results have shown that in addition to cognitive deficits, apathy is also an important factor underlying disability in bvFTD. Interventions targeting reduction of disability in bvFTD and psychoeducational programs for family and paid carers should strongly take the above factors into consideration for greater efficacy.

Author contributions

M.S. Yassuda contributed to the design and conceptualization of the study, analysis, data collection, drafting, and

revision of the manuscript. T.B. Lima da Silva contributed to the design and conceptualization, data collection, analysis, drafting, and revision of the manuscript. C.M. O'Connor contributed to the design and data collection of the study and revision of the manuscript. S. Mekala contributed to the data collection of the study and revision of the manuscript. S. Alladi contributed to the design and data collection of the study and revision of the manuscript. V.S. Bahia contributed to the data collection of the study and revision of the manuscript. V. Almaral-Carvalho contributed to the data collection of the study. H.C. Guimaraes contributed to the data collection of the study and revision of the manuscript. P. Caramelli contributed to the data collection of the study and the revision of the manuscript. M.L.F. Balthazar contributed to the data collection of the study and revision of the manuscript. B. Damasceno contributed to the data collection of the study and revision of the manuscript. S.M.D. Brucki contributed to the data collection of the study and revision of the manuscript. R. Nitrini contributed to the design, data collection of the study, and revision of the manuscript. J.R. Hodges contributed to the design, data collection of the study, and revision of the manuscript. O. Piguet contributed to the design, data collection of the study, and revision of the manuscript. E. Mioshi contributed to the design and conceptualization, data collection of the study, analysis and interpretation of the data, study supervision, and revision of the manuscript.

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