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The Philadelphia Brief Assessment of Cognition (PBAC): A Validated Screening Measure for Dementia

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Abstract

The Philadelphia Brief Assessment of the Cognition (PBAC) is a brief dementia-screening instrument. The PBAC assesses five cognitive domains: working memory/executive control; lexical retrieval/language; visuospatial/visuoconstructional operations; verbal/visual episodic memory; and behavior/social comportment. A revised version of the PBAC was administered to 198 participants including patients with Alzheimer's disease (AD) ($n=46$) and four groups of patients with frontotemporal dementia (FTD) syndromes: behavioral-variant FTD (bvFTD; $n=65$), semantic-variant primary progressive aphasia (PPA) (svPPA; $n=22$), non-fluent/agrammatic-variant PPA (nfvPPA; $n=23$), and corticobasal syndrome (CBS; $n=42$), and a group of normal controls ($n=15$). The total PBAC score was highly correlated with the MMSE. The criterion validity of the PBAC was assessed relative to standard neuropsychological test performance. Using standard neuropsychological test performance as a criterion, the total PBAC score accurately identified the presence and severity of dementia. Intra-class correlations between PBAC subscales and standard neuropsychological tests were highly significant. PBAC subscales demonstrated good clinical utility in distinguishing AD and FTD subtypes using receiver operating characteristic analysis and standard diagnostic performance statistics to determine optimal subscale cut scores. The PBAC is a valid tool and able to assess differential patterns neuropsychological/behavioral impairment in a broad range of neurodegenerative conditions.

Keywords

Alzheimer's disease; Frontotemporal lobar dementia; Frontotemporal dementia; FTD; Philadelphia Brief Assessment of the Cognition; PBAC; Neuropsychological assessment; Philadelphia (repeatable) Verbal Learning Test

INTRODUCTION

Frontotemporal dementia (FTD) is a progressive neurodegenerative disorder associated with imaging and pathological findings of frontal and temporal disease (Grossman, 2002;

Snowden, Neary, & Mann, 1996). Several FTD subgroups have been described, including patients with a disorder of social comportment and executive functioning (bvFTD), a non-fluent/agrammatic variant of primary progressive aphasia (nfaPPA), a semantic variant of PPA (svPPA), and corticobasal syndrome (CBS). The Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975) is commonly used to screen for the presence and severity of dementia; however, MMSE is insensitive to the cognitive and social deficits associated with FTD (Hodges et al., 2004; Hutchinson & Mathias, 2007). Other screening measures used to assess for Alzheimer's disease (AD) and FTD include the Frontal Assessment Battery (FAB; Dubois, Slachevsky, Litvan, & Pillon, 2000), the Addenbrooke Cognitive Examination (ACE; Mathuranath, Nestor, Berrios, Rakowicz, & Hodges, 2000; see also Galton, Erzinclioglu, Sahakian, Antoun, & Hodges, 2005); the Neuropsychiatric Inventory (NPI; Cummings et al., 1994), the Montreal Cognitive Assessment (MoCA; Nasreddine, Phillips, & Bediren, 2005); the Frontal Behavioral Inventory (FBI; Kertesz, Nadkarni, Davidson, & Thomas, 2000); and verbal fluency tests (Elfgren, Brun, & Gustafson, 1994; Pasquier, Lebert, Grymonprez, & Petit, 1995; Rascovsky, Salmon, Hansen, Thal, & Galasko, 2007). However, there is little research documenting or demonstrating the differential validity of screening instruments for assessing unique or specific patterns of neuropsychological impairment in AD and FTD subgroups.

The Philadelphia Brief Assessment of Cognition (PBAC; Libon, Massimo, et al., 2007; Libon, Xie, et al., 2007) was developed to fulfill two important functions: to provide a relatively brief measure of overall dementia severity and to provide a measure that differentiates between dementia subtypes. Thus, in addition to a total score that reflects overall dementia severity, the PBAC yields separate subscales that measure behavior/social comportment and a variety of specific cognitive functions. In a prior study using the PBAC, Libon, Xie, et al. (2007) showed that the total PBAC score was highly correlated with the MMSE in patients with AD and FTD. More importantly, AD and FTD patients with bvFTD, nfaPPA, svPPA, and CBS displayed differential impairment on PBAC subscales measuring episodic memory, behavior/social comportment, working memory/executive control, language-related skills, and visuospatial/visuoconstructional ability (Libon, Xie, et al., 2007). Prior research therefore suggests that the PBAC is sensitive to overall dementia severity and specific to the cognitive deficits that can be associated with dementia subtypes.

The current research differs from past research in that a larger sample of AD and FTD patients were studied and a normal control group was recruited. Also, a standard neuropsychological protocol was obtained on a portion of dementia patients. The purpose of the current research was to provide additional support for the criterion validity of the PBAC with correlations between the total PBAC score and performance on the Mini-Mental State Examination (Folstein et al., 1975) and performance on standard neuropsychological tests. Criterion validity was also assessed by comparing PBAC subscales between AD and FTD patient groups. Finally, the clinical utility of the PBAC was assessed with receiver operating characteristics and standard diagnostic utility statistics to determine optimal cut scores. None of these analyses appeared in our original report (Libon, Xie, et al., 2007).

METHOD

Patients

A total of 270 patients were assessed for this research. All patients were evaluated and recruited by experienced behavioral neurologists (AC, HBC, RG, MG). Dementia subgroups were classified based on modifications of previously published criteria (Grossman, 2010; McKhann et al., 2001; Murray et al., 2007; Neary et al., 1998). At least two trained reviewers of a consensus committee (inter-rater reliability, $r=.91$, $p<.001$) confirmed the presence of specific diagnostic criteria and assigned patients to FTD subgroups based on an

independent review of the semi-structured history obtained from patients and their families and a detailed neurologic examination. The PBAC was not used for the initial diagnosis of research participants.

The initial clinical diagnosis of a neurodegenerative disease was consistent with the results of a detailed clinical interview of patients and families, serum studies, structural imaging studies such as MRI or CT, clinical studies of cerebrospinal fluid (when available), and functional neuroimaging studies such as SPECT or PET (these studies were not available to the consensus committee). Exclusion criteria included the presence of other neurologic conditions such as stroke or hydrocephalus (consistent with imaging studies reviewed by a neurologist), primary psychiatric disorders (i.e., major depression, psychosis), or a systemic illness that can interfere with cognitive functioning. Some patients were taking a cholinesterase inhibitor (e.g. donepezil, rivastigmine, galantamine), memantine, a non-sedating anti-depressant (e.g., serotonin-specific re-uptake inhibitors such as sertraline), or an atypical neuroleptic agent (e.g., quetiapine) consistent with clinical care, but no patient demonstrated evidence of sedation.

In the original paper describing the PBAC 108 patients with FTD syndromes were assessed (bvFTD=49, nfaPPA=11, svPPA=19, CBS=29). In the current research we added to this sample and assessed 152 patients with FTD syndromes including 65 patients with bvFTD who presented with alterations in personality/social comportment and executive functioning; 23 patients with nfaPPA who displayed effortful speech with simplified grammatical expression but relatively good single word comprehension; 22 patients with svPPA characterized by fluent but often empty speech with prominent deficits in naming and single word comprehension; and 42 patients with CBS who had a unilateral extrapyramidal syndrome, limb apraxia, and cortical sensory loss. The current research also included 46 patients with AD (McKhann et al., 1984) presenting with striking episodic memory impairment and deficits in other cognitive domains.

A group of healthy seniors (NC; $n=15$) were recruited who were living independently in the community, not taking psychoactive medications, had no cognitive complaints, and were unimpaired in instrumental activities of daily living. NCs were not included in the previous paper on the PBAC. Patients with mild cognitive impairment ($n=23$), vascular dementia ($n=13$), ALS ($n=8$), an atypical presentation of AD (posterior cortical atrophy, $n=12$), a non-progressive language disorder ($n=9$), and Lewy body disease ($n=7$) were excluded. Table 1 summarizes the demographic features of our AD and FTD groups. This research was approved by the University of Pennsylvania Institutional Review Board and consent was obtained consistent with the Declaration of Helsinki.

The Philadelphia Brief Assessment of Cognition (PBAC)

The rationale for the construction of the PBAC was based on prior research (Libon, Massimo, et al., 2007; Libon, Xie, et al., 2007) where both principal component analysis (PCA) and between-group analyses on neuropsychological tests obtained from AD and FTD patients differentiated dementia subtype. The PBAC consists of 11 separate tests and separate scales that rate behavior and speech. These 11 tests and two rating scales yield 15 variables that are grouped into five subscales of roughly equal value: working memory/executive control, lexical retrieval/language, visuospatial/visuoconstructional ability, verbal/visual episodic memory, and behavior/social comportment. The total PBAC score ranges between 0 and 93 (see the Appendix for a complete description of PBAC administration and scoring). Administration of the PBAC requires approximately 10 minutes.

Executive Control/Working Memory (range 0–17)—Forward digit span was assessed with six trials (3–8 digits) and backward digit span was assessed with six trials (2–7 digits).

Unlike traditional digit span (Wechsler, 1987) only a single trial for any span length was administered on the PBAC. Both tests were administered until the patient erred. On a letter “F” fluency test, patients were given 60 seconds to generate as many different words as possible, excluding proper nouns and numbers (Spreen & Struss, 1990).

Lexical Retrieval/Language (range 0–19)—Visual confrontation naming was assessed by asking patients to name six line drawings from the Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983): two animals (camel/pelican), two vegetables (mushroom/asparagus), and two tools (saw/tongs). Semantic knowledge was assessed by asking patients to “point to the two pictures that are alike” and to provide the appropriate superordinate grouping without describing common perceptual features. Conversational speech was scored clinically for word-finding difficulty, circumlocution, semantic paraphasic errors, literal paraphasic errors, agrammatical speech, effortful speech, dysarthria, and impaired discourse. Reading was assessed with four irregularly spelled words. Writing was assessed by asking patients to produce a sentence about the weather, scored for accurate content, correct grammar, and absence of spelling errors. Repetition was assessed by asking patients to repeat the phrase “no ifs, ands or buts.”

Visuospatial/Visuoconstructional Skills (range 0–18)—Visuoconstructional ability was assessed by asking patients to copy a modified Rey Complex Figure (Lezak, Hanney, & Loring, 2004). Spatial orientation was assessed with a fan-like array of seven lines drawn at various angles. Below the array, six additional randomly ordered lines were drawn at oblique angles. Patients were asked to match each of these six lines to a target in criterion array.

Episodic Memory (0–21)—Verbal learning and memory were assessed with a six-word list administered over three trials. Delayed free recall for this list was assessed after a 1–2-minute filled delay. This was followed by a delayed recognition test. The stimuli contained in the recognition test consisted of the six original words and six novel words that are semantically related to each target word. On the delayed recognition test all 12 words were read and patients were asked to identify words from the original word list. Visual episodic memory was assessed by asking patients to reproduce the modified Rey Complex Figure after a 1–2-minute filled delay.

Behavior/Social Compartment Scale (range 0–18)—Alterations in social compartment and behavior was assessed through a combination of interviewing a family member and observation of the patient’s behavior during the clinical interview. Six behavioral domains were queried: apathy/poor initiation, disinhibition, agitation/irritability, ritual/obsessive behavior, lack of empathy, and poor self-insight. Each behavioral symptom was scored on a 4-point ordinal scale (3–0) reflecting severity in each domain, with examples provided at each level of severity.

Neuropsychological protocol

A subset of dementia patients ($n=56$) was administered a comprehensive neuropsychological protocol. This included standardized tests probing neuropsychological domains corresponding to those contributing to the PBAC. The neuropsychological protocol was administered on a different occasion but on average within 2.28 months regarding PBAC test administration. The neuropsychological protocol consisted of the Wechsler Adult Intelligence Scale-Revised Digit Span subtest (Wechsler, 1987), tests of letter fluency (letters “FAS”, Spreen & Struss, 1990), a 30-item version of the Boston Naming Test, a test of semantic (“animal”) fluency (Spreen & Struss, 1990), the CERAD Figure Copy Test

(Morris et al., 1989), the Philadelphia (repeatable) Verbal Learning Test (Price et al., 2009), and the Neuropsychiatric Inventory (Cummings et al., 1994; see Table 2).

On the PBAC four of the six BNT test stimuli used in the PBAC were part of the 30-item BNT used in the neuropsychological protocol. Some FTD phenotypes present with either striking semantic knowledge deficits (svPPA) or perceptual/visual spatial deficits (CBS). Thus the BNT items used in the PBAC were purposively selected because of the distinctive semantic as well as perceptual features contained in these stimulus items.

RESULTS

Demographic variables

Demographic variables were analyzed with one-way analysis of variance (ANOVA); Bonferroni tests were used for post-analysis. For age, $F(5, 207)=6.98, p<.001$, the AD group was older than bvFTD ($p<.001$), SemD ($p<.004$), CBS ($p<.001$), and NC ($p<.045$) participants. On the MMSE, $F(5, 195)=3.34, p<.001$, NC participants obtained a higher score than all patient groups ($p<.001$) except bvFTD patients; bvFTD patients obtained a higher MMSE score than SemD ($p<.017$) and CBS patients ($p<.040$). The one-way ANOVA for education was significant, $F(5, 195)=9.36, p<.001$; however, no post-hoc Bonferroni comparison reached significance (Table 1).

Criterion validity

Correlation with MMSE and neuropsychological tests—Several analyses assessed the criterion validity and the capacity of the total PBAC score to measure overall cognitive impairment. First, the total PBAC score (mean $\pm$ $SD=77.13\pm 8.18$) was highly correlated with the MMSE (mean $\pm$ $SD=21.97\pm 6.51$; $r=.766, p<.001$). Second, a single measure reflecting neuropsychological performance was obtained by converting all neuropsychological tests to z -scores relative to 25 age- and education-matched controls. These scores were averaged to obtain a Total Neuropsychology Score (TNS). Total PBAC score was significantly correlated with TNS ($r=.443, p<.003$).

Between-group comparisons—The one-way ANOVA comparing groups on the total PBAC score (Table 3) was significant, $F(5, 137)=11.98, p<.001$. Bonferroni Tests showed that the NC group outperformed all dementia groups ($p<.007$). CBS patients also obtained a lower score compared to bvFTD ($p<.001$) and nfaPPA groups ($p<.018$). Co-varying for age, education, or MMSE had no effect on these results. The criterion validity of individual PBAC index scores to assess for specific patterns of neuropsychological impairment was examined with a series of one-way ANOVAs. Because past research documents modality-specific cognitive impairment in patients with CBS (Libon, Xie, et al., 2007; Murray et al., 2007) separate analyses were conducted to assess differences on delayed verbal and visual memory tests. All one-way ANOVAs were highly significant (see Table 2). Co-varying for age, education, and MMSE had no effect on these analyses.

For the executive index the NC group outperformed all dementia groups ($p<.001$). nfaPPA and svPPA patients scored lower than bvFTD patients ($p<.010$ and $p<.048$, respectively). On the language index the NC group outperformed all dementia groups ($p<.033$). svPPA ($p<.010$) and AD patients ($p<.049$) scored lower than bvFTD patients. On the visuospatial index the NC group outperformed AD ($p<.029$) and CBS ($p<.001$) groups. Patients with CBS scored lower than all dementia groups ($p<.001$) and the AD group scored lower than the bvFTD group ($p<.025$). For verbal memory the NC group obtained a higher score than AD ($p<.001$) and svPPA ($p<.045$) groups. AD patients scored lower than bvFTD, nfaPPA, and CBS patients ($p<.001$, all contrasts). For delayed visual recall the NC group outscored AD

and CBS groups ($p < .001$ all contrasts). Both AD and CBS groups scored lower than all groups ($p < .001$). For the behavior/social comportment scale bvFTD exhibited a more pronounced behavioral disturbance than all other groups ($p < .001$ all contrasts). On the behavior/social comportment scale there were no differences between the NC and other dementia groups except for the bvFTD subgroup ($p < .001$; see Table 2).

PBAC/multi-nominal regression analysis—The ability of the PBAC subscales to assign patients to their respective diagnostic groups was assessed with likelihood ratios calculated from a series of multinomial logistic regression where NC participants were the reference group. Lower scores on the PBAC executive control subscale, $\chi^2(5)=73.84$, $p < .001$, were associated with greater likelihood of any dementia diagnoses compared to NC group ($p < .001$, all analyses). Lower scores on the PBAC language subscale, $\chi^2(5)=34.95$, $p < .001$, were associated with greater likelihood of any dementia ($p < .007$, all analyses). Lower scores on the PBAC visuospatial subscale, $\chi^2(5)=67.22$, $p < .001$, were associated with greater probability of AD ($p < .025$) and CBS ($p < .002$). Lower scores on the PBAC Verbal Memory subscale, $\chi^2(5)=52.94$, $p < .001$, were associated with greater probability of AD ($p < .001$) and svPPA ($p < .005$). Lower scores on the PBAC Visual Memory subscale, $\chi^2(5)=81.86$, $p < .001$, were associated with greater probability of AD and CBS ($p < .001$, both analyses). Finally, lower scores on the PBAC behavior/social comportment subscale, $\chi^2(5)=49.59$, $p < .001$, were associated with greater probability of bvFTD ($p < .005$).

A second group of likelihood ratios were calculated using multinomial logistic regression analyses guided by the results of the between-group analyses described above such that the reference group used for each logistic regression (i.e., the group against which all other groups are compared) was based on the group that displayed the greatest impairment on any single PBAC index. For example, when the nfaPPA group was the reference group for the PBAC executive control subscale, $\chi^2(5)=73.84$, $p < .001$, nfaPPA was differentiated from bvFTD and AD ($p < .017$) subgroups. For the PBAC language subscale, $\chi^2(5)=34.95$, $p < .001$, svPPA was differentiated from bvFTD ($p < .001$). For the PBAC visuospatial subscale, $\chi^2(5)=66.22$, $p < .006$, CBS was differentiated from all other patient subgroups ($p < .002$ all contrasts). For the PBAC verbal memory subscale, $\chi^2(5)=52.94$, $p < .001$, AD was differentiated from all other groups ($p < .039$ all contrasts). Similarly, for the PBAC visual memory subscale, $\chi^2(5)=74.09$, $p < .001$, CBS was differentiated from all other groups ($p < .001$ all contrasts) except the AD group. For the PBAC behavior/social comportment subscale, $\chi^2(5)=49.59$, $p < .001$, bvFTD was differentiated from all other patient groups ($p < .001$ all contrasts).

Intra-class correlation/Cronbach Alpha statistics—The relationship between PBAC subscale scores and neuropsychological test performance was also assessed with a series of intra-class correlations and Cronbach Alpha statistics. Tables 2 and 3 summarize robust intra-class correlations between each PBAC subscale score and performance on corresponding neuropsychological tests and robust Cronbach Alpha statistics.

PBAC clinical utility

The diagnostic ability of the PBAC subscales in differentiating FTD, AD, and NC subgroups was evaluated through the receiver operating characteristic (ROC) analysis. The executive subscale was evaluated in differentiating nfaPPA subtype from others (other FTD subtypes, AD, and NC), the language subscale in differentiating SD from other patient groups, the visuospatial subscale in differentiating CBD from patients groups, the memory measure in distinguishing AD from patient groups, and the behavior measure in distinguishing BVFTD from other groups. A ROC curve was constructed for each subscale in distinguishing the disease classifications described above and the corresponding area under the ROC curve

(AUC) was computed. The optimal cut score for each subscale in differentiating disease subtypes was calculated, along with the corresponding standard diagnostic performance statistics measuring sensitivity, specificity, positive and negative likelihood ratios (PLR, NLR), and positive and negative predictive values (PPV, NPV). Because diagnostic measures estimated from the observed data (i.e., “apparent performance”) will be better than performance from another data set, a bootstrap procedure (Steyerberg et al., 2001) was implemented to adjust for this “optimism” when generating the final estimated diagnostic performance statistics.

Estimates of sensitivity and specificity for each PBAC subscale were obtained at an optimal cut-point, determined as the point that maximizes the sum of sensitivity and specificity. Estimates for sensitivity and specificity for the optimal cut-point were first obtained for the observed data (i.e., “apparent performance”). Then 1000 bootstrap samples were drawn from the disease subgroup of interest and other disease subtypes with replacement, and sensitivity and specificity estimates were found for the optimal cut-point within each sample (i.e., “bootstrap performance”). The optimal cut-point from the bootstrap samples was then applied to the observed data to yield “test performance” estimates of sensitivity and specificity. Therefore an estimate of “optimism” can be obtained by averaging the difference between the bootstrap performance and the test performance. The final estimated diagnostic performance adjusting for “optimism” was obtained by subtracting the “optimism” estimate from the apparent performance estimate.

Using these methods the “optimism” adjusted AUC for the executive measure in distinguishing nfaPPA from other patient groups was 0.75. For the optimal cut-score for the executive subscale of 5.00 we found that the “optimism” adjusted sensitivity was 0.68, which is slightly lower than the “apparent performance” sensitivity estimate based on the observed data. Similarly, “optimism” adjusted specificity was 0.72. PPV and NPV estimates depend on disease prevalence, which was estimated from our clinical database. Complete bootstrap-based AUC and diagnostic performance statistics for the optimum cut-point of each PBAC subscale can be found in Table 4.

DISCUSSION

It should be clearly understood that the PBAC was not designed to substitute for a standard, comprehensive neuropsychological protocol. Rather, the PBAC was developed to be a brief screening test that is both sensitive to overall cognitive and behavioral impairment and specific to the unique patterns of impairment that typify AD and FTD phenotypes.

It is widely accepted that traditional cognitive screening tests such as the MMSE do not reflect dementia severity in a reasonable manner across the broad spectrum of neurodegenerative conditions that includes FTD and AD. To meet this challenge several brief screening measures have emerged. The Addenbrooke Cognitive Examination (ACE; Mathuranath et al., 2000) has been shown to differentiate between patients with AD versus FTD; AD versus mild cognitive impairment (MCI; Bak et al., 2005); and AD versus major depression (Mioshi, Dawson, Mitchell, Arnold, & Hodges, 2006), although not between FTD phenotypes. A combination of the ACE and verbal serial list learning was able to track longitudinal alterations in cognition and atrophy measured with MRI scans in patients with MCI and FTD (Ahmed, Mitchell, Arnold, Nestor, & Hodges, 2008; Kipps, Nestor, Dawson, Mitchell, & Hodges, 2008). The ACE has also been shown to be sensitive to impairment in activities of daily living in FTD (Kipps et al., 2008). The MoCA (Nasreddine et al., 2005), another brief cognitive screening test, has been shown to be more sensitive than the MMSE in detecting MCI and dementia in Parkinson’s disease (Hoops et al., 2009). The MoCA also has been found to be superior to the MMSE in identifying patients with MCI who are at risk

for developing AD (Luis, Keegan, & Mullan, 2009; Smith, Gildeh, & Holmes, 2007). However, to date the MoCA has not been used to assess patients with FTD or to differentiate between dementia subtypes. The PBAC requires only marginally more time to administer and score than other cognitive screening tests such as the MMSE. Thus the decision to use the PBAC in a busy clinical setting must be balanced against the additional specificity associated with the PBAC relative, say, to the MMSE or MoCA.

The results of the current study demonstrate a strong correlation between the total PBAC score and the MMSE, a finding previously reported (Libon, Xie, et al., 2007). A unique feature of the PBAC is the construction of subscales that reflect impaired test performance within specific cognitive domains such as working memory/executive control, language, visuospatial functioning, episodic memory, and social/behavioral functioning. In the current research PBAC subscales were able to differentiate between NCs and dementia groups. A series of logistic regression analyses using PBAC subscales were able to assign patients to their respective diagnostic groups.

A variety of analyses assessed the PBAC against performance on standardized neuropsychological tests. The current research obtained good intra-class correlations between domain-specific PBAC indices and analogous performance on neuropsychological tests. Thus patients with AD were disadvantaged on the verbal and visual memory tests. Patients with CBS were markedly impaired on visuospatial and visuoconstructional tests. Their impaired visual memory in the setting of relatively intact verbal memory presumably reflects modality-specific difficulty processing visually mediated material. Patients with svPPA scored lower on the PBAC language index, and verbal memory difficulty in svPPA may reflect a material-specific deficit processing verbal material. Finally, patients with nfaPPA displayed difficulty on executive/working memory tests. This is consistent with previous observations of executive difficulty in these patients (Libon, Massimo, et al., 2007). The executive deficit in svPPA may reflect problems associated with verbally mediated executive measures. Regardless of the basis for these findings, the benefits of the PBAC include not only its sensitivity to overall cognitive impairment, but also the capacity to capture differential patterns of cognitive and behavioral alterations in subgroups of patients with AD and FTD, a feature not available in the ACE or MoCA. This feature may be particularly useful in identifying FTD phenotypes targeted for treatment in pharmacological clinical trials. Cronbach Alpha statistics demonstrated good internal consistency for the various tests that comprise each of the PBAC subscales. Finally, ROC statistics and standard diagnostic utility statistics were able to determine an optimum total PBAC cut score and provided complementary evidence for acceptable sensitivity and specificity.

This study is not without several limitations. First, the data reported above, including subscale cut scores, would be enhanced with a larger normal control group, greater and relatively equal numbers patients in all FTD groups, and more patients assessed with the PBAC and a complete neuropsychological protocol. Second, the limited number of contributing subtests may have led to some confounds in characterizing dementia phenotypes, but the inclusion of additional subtests would have lengthened overall administration time. Third, the ability of the PBAC to detect longitudinal alterations in cognitive and behavioral functioning has not been tested. Fourth, imaging correlates between PBAC subscales and specific brain regions of interest would be desirable. Finally, while the PBAC was developed for use in patients with suspected AD and FTD spectrum syndromes, the sensitivity and specificity of the PBAC for other neurodegenerative syndromes such as Parkinson's dementia, vascular dementia, amyotrophic lateral sclerosis, and mild cognitive impairment remains to be addressed. With these limitations in mind, we

conclude that the PBAC is psychometrically sound and an efficient instrument to screen for dementia.

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APPENDIX

PBAC administration and scoring instructions

Instructions for administering and scoring each task are described below. Text in *italics* refers to what the examiner should say to the patient when administering each task.

1. Verbal List Learning

- a. Verbal List Learning Trial 1 – Say, *I am going to read a list of words. Listen carefully. When I am done, please say them back in any order you wish.* Be sure to record responses verbatim, in the order given, including repetitions and incorrectly intruded responses.
- b. Verbal List Learning Trial 2 – Say, *Now I will read the list again. Just as before, when I am done, say back as many words as you can.* Record all responses verbatim.
- c. Verbal List Learning Trial 3 – Say, *One last time, listen carefully. After I read the words, please say back as many words as you can in any order.* Record all responses verbatim. This portion of the verbal memory test is not scored.

2. Letter Fluency (letter “F”)

Say, I am going to say a letter of the alphabet. When I say begin, please tell me as many words as you can that begin with that letter. You will have 60 seconds before I tell you to stop. None of the words can be names of people, places, or numbers. For example, if I gave you the letter T, you could say “toy” or “tell”, but you would not say, “Tom”, “Toronto”, or “two”. Also, please give only one form of a word. For example, if you were to say “take” please do not say “taking.” Let’s begin. Tell me all the words you can, as quickly as you can, that begin with the letter “F”. Record all responses verbatim in 15-second intervals.

Scoring – Score ½ point for each correct response up to 16 correct responses; range 0–8.

3. Verbal Delayed Free Recall

Say, A little while ago, I read a list of words to you. I want you to tell me all the words you remember from that list. You can say them in any order. Record all responses verbatim. Discontinue the task if no response after 10 seconds.

Scoring – Score 1 point for each correct response, range 0–6.

4. Verbal Delayed Recognition

Say, I’m going to read some additional words to you. After I read each one, say “yes” if it was on the list I read to you earlier, or say “no” if it was not on that list. Record all responses verbatim.

Scoring – Score ½ point for the correct identification of each target word (word on the initial word list) and the rejection of its paired foil (word not on the initial list), range 0–3.

5. Digit Span Forward

Say, *Listen carefully, I am going to read some numbers to you. Please repeat them in the order you hear them.* Discontinue when the patient fails a trial at any span length. Record responses verbatim.

Scoring – Score ½ point for each correct trial, range 0–3.

6. Digit Span Backward

Say, *Now I will read more numbers. This time please say them backwards. For example, if I say “1-2-3”, you would say, “3-2-1”.* Discontinue after the first failed test trial. Record responses verbatim.

Scoring – Score 1 point for each correct trial, range 0–6.

7. Visual Confrontational Naming

Show the six pictures to the patient one by one. Say, *Please tell me the name of this picture.* Record all responses verbatim. Give the patient a maximum of 10 seconds to name each item.

Scoring – Score 1 point for each correct response, range 0–6.

8. Semantic Judgment

Say, *Please look at these six pictures again. Point to two pictures that are the same kind of thing.* Record the patient's selection of which two pictures are alike. Then ask, *How are two other pictures alike?* Record verbatim the patient's rationale. Repeat this procedure two more times to obtain three pairings (animals, vegetables, tools). Give the patient a maximum of 10 seconds per pairing.

Scoring – Award ½ point for the correct pairing of pictures and score an additional ½ point if the patient correctly identifies the superordinate relationship for each picture pair (i.e., animal, vegetable, tool), range 0–3.

9. Geometric Figure Copy

Say, *Please copy this design in the space provided.* Indicate to the patient the space available for copying to the right of the figure. Discontinue the task if no response after 10 seconds.

Scoring – Award 1 point for each of the 12 figure elements. To receive a point, each element must be present and in its approximate proper location, range 0–12.

10. Line Orientation

Point to each of the six lines below the horizontal, one at a time. Say, *See this line I am pointing to? Please show me which line above the horizontal line is parallel or going the same direction as the line I am showing you.* Give the patient a maximum of 10 seconds per line judgment.

Scoring – Award 1 point for each correct answer, range 0–6.

11. Delayed Figure Recall

Say, *A little while ago, you copied a design. Please draw as much of this figure as you can remember.* Indicate to the patient the space available for the recalled figure to be drawn.

After 10 seconds prompt the patient by saying, *Please draw whatever you can remember*. If still no response after 10 seconds, discontinue the task.

Scoring – Award 1 point for each of the 12 figure elements, range 0–12.

12. Word Reading

Point to each of the words, “choir”, “yacht”, “pint”, and “cough”, one at a time for the patient to read. Say, *Please read each of the following words*. Record all responses verbatim.

Scoring – Score ½ point for each correct response, range 0–2.

13. Repetition

Say, *Please repeat after me, “no, ifs, ands, or buts”*. Record response verbatim.

Scoring – To earn a point the patient’s response must be totally correct, range 0–1.

14. Sentence Writing

Say, *Please write a sentence about the weather*. Indicate to the patient the space available to write the sentence.

Scoring – Score 1 point for correct content, 1 point for correct grammar, and 1 point for correct spelling, range 0–3.

15. Conversational Speech

Listen for the presence of speech and/or language problems listed below. These speech or language problems are scored on the basis of your entire interaction with the patient.

Word-finding pauses – prolonged pauses in ongoing speech as the patient searches for a word.

Circumlocutory speech – the use of indirect expressions or more words than necessary to describe an idea; often a result of word-finding difficulty.

Semantic paraphasic errors – semantically related errors (i.e., similar in meaning to the target word; e.g., “fork” for “dish”).

Literal or phonologic paraphasic errors – errors that sound similar to the target word; the resulting error can be a word or a non-word (e.g., “mat” for “cat” or “treen” for “train”).

Agrammatical speech – speech characterized by simplified grammatical structure; for example, absence of grammatical markers such as past tense (-ed) or plural endings (-s) or of function words such as prepositions (“to”, “under”) or articles (“a”, “the”, “her”).

Effortful speech – speech that appears difficult for the patient to produce; speech is typically slow and characterized by pauses, hesitations, and restarts.

Dysarthria – a motor speech problem characterized by poor articulation of speech sounds.

Discourse deficit – speech characterized by difficulty conveying ideas in a coherent manner; ideas expressed may be disorganized, tangential, ambiguous, or irrelevant.

Scoring – Debit ½ point for each speech/language problem, range 0–4.

16. Behavior/Personality

Please rate each of the following six behavioral characteristics. These behaviors are scored on the basis of your interaction with the patient and your interview with the family.

Behavior	Mild	Moderate	Severe
Apathy	Patient needs prompts to initiate/complete volitional, previously rewarding activities	Patient needs prompts to initiate/complete everyday self-care activities (e.g., dressing, grooming)	Caregiver needs to physically assist patient to initiate and complete simple activities (e.g. go to bathroom)
Disinhibition/Impulsivity	Loss of manners and decorum, mild impulsivity	Inappropriate gestures or remarks (e.g., approaching strangers, crude jokes)	Grossly inappropriate behavior (e.g. hypersexuality, careless, risky behavior)
Agitation	Mild anxiety or irritability	Disruptive but not harmful behaviors, not easy to redirect (e.g., pacing)	Explosive, threatening, physical behaviors (e.g., hitting, pushing, etc)
Ritualistic/OCD	Simple or complex repetitive behaviors that are not disruptive of everyday activities (e.g., mild ordering, occasional simple repetitive movements)	Disruptive simple or complex repetitive behaviors (e.g., compulsive checking, hoarding)	Disruptive repetitive behaviors that cannot be re-directed, may have the potential for self-injury (e.g., picking skin that leads to bleeding)
Empathy	Inconsiderate/thoughtless concerning others' feelings	Overt disregard for people's feelings, inappropriate response to other's distress	Total disregard for physically distressful events (e.g., accidents, observable pain)
Self Insight	Diminished concern, will acknowledge limitations when pointed out by caregiver	Minimal awareness of disease/limitations; lack of appreciation for implications of disease	Complete denial of illness/ limitations

Scoring – Score each of the six behaviors using the following scale: 3=not observed, 2=mild, 1=moderate, 0=severe, range 0–18.

Table 1Demographic information: Mean (*SD*)

	Age	Education	MMSE
AD	71.98 (8.20)	14.55 (2.98)	19.45 (6.58)
bvFTD	62.82 (8.89)	15.92 (3.42)	25.59 (5.54)
nfaPPA	65.39 (10.08)	14.43 (2.39)	22.45 (6.19)
svPPA	63.73 (6.87)	16.50 (2.66)	20.59 (8.56)
CBS	63.88 (8.66)	14.25 (2.34)	21.79 (5.68)
NC	64.27 (8.55)	15.60 (2.47)	29.33 (0.81)

MMSE=Mini-Mental State Examination, AD=Alzheimer's disease, bvFTD=behavioral variant of frontotemporal dementia, nfaPPA=non-fluent agrammatic variant of primary progressive aphasia; svPPA=semantic variant of primary progressive aphasia, CBS=corticobasal syndrome, NC=normal control.

Table 2

PBAC raw scores, composite indices, and Intra-class correlations between PBAC indices and standardized neuropsychological tests: Mean (SD)

	AD	bvFTLD	nfaPPA	svPPA	CBS	NC	Significance ^d	Neuropsychological Tests	Intra-class Correlations ^b
Executive subscale	7.40 (3.83)	8.11 (3.48)	5.20 (2.99)	5.61 (3.26)	6.72 (3.22)	14.06 (2.15)	$F(5, 200) = 15.62, p < .001$	letter (FAS) fluency, digits backward	$r = .471, p < .001$
Language subscale	11.58 (4.27)	14.08 (3.37)	12.01 (3.40)	10.33 (3.07)	11.52 (4.55)	16.03 (1.51)	$F(5, 141) = 6.31, p < .001$	30-item Boston Naming Test, "animal" fluency	$r = .763, p < .001$
Visuospatial subscale	12.22 (5.92)	15.49 (3.69)	14.23 (5.66)	14.59 (5.06)	6.35 (6.43)	17.06 (3.10)	$F(5, 195) = 18.25, p < .001$	CERAD figure copy test	$r = .605, p < .032$
Verbal memory subscale	2.08 (1.25)	4.04 (1.49)	4.27 (1.57)	2.93 (1.95)	3.80 (1.76)	4.50 (1.75)	$F(5, 200) = 11.93, p < .001$	P(r)VL.T delay free recall; delay recognition discriminability	$r = .563, p < .001$
Visual memory scale	1.76 (2.57)	5.83 (3.28)	6.90 (4.08)	5.72 (3.84)	2.20 (3.01)	7.53 (3.11)	$F(5, 200) = 18.38, p < .001$	n/a	n/a
Behavior scale	16.15 (5.01)	12.22 (4.99)	16.77 (1.77)	16.54 (1.92)	16.25 (4.18)	17.93 (0.25)	$F(5, 200) = 9.48, p < .001$	NPI total score	$r = .492, p < .001$
Total PBAC score	51.57 (11.08)	60.23 (13.00)	60.65 (14.14)	58.47 (11.32)	46.73 (16.45)	77.13 (8.18)	$F(5, 137) = 11.98, p < .001$		

PBAC=Philadelphia Brief Assessment of Cognition, AD=Alzheimer's disease, bvFTLD=behavioral variant frontotemporal dementia, nfaPPA=non-fluent/agrammatic variant of primary progressive aphasia; svPPA=semantic variant of primary progressive aphasia, CBS=corticobasal syndrome, CERAD=Consortium for the establishment for Research In Alzheimer's disease; P(r)VL.T=Philadelphia (repeatable) Verbal Learning Test; NPI=neuropsychiatric inventory, n/a=not available.

^aOne-way ANOVA statistic assessing the effect of group on PBAC sub-scales.

^bIntra-class correlations between PBAC subscales and neuropsychological tests.

Table 3

PBAC Cronbach Alpha statistics

PBAC executive tests	0.673
PBAC language tests	0.686
PBAC visuospatial tests	0.756
PBAC memory Tests	0.597

PBAC=Philadelphia Brief Assessment of Cognition.

Table 4

PBAC subscale cut scores and diagnostics performance statistics: Bootstrap analysis

Subscale	Cutpoint	Sens	Spec	PLR	NLR	PPV	NPV	AUC
Executive	5.00	0.68	0.72	2.45	0.45	0.23	0.95	0.75
Language	13.50	0.86	0.55	1.92	0.25	0.17	0.97	0.75
Visuospatial	13.00	0.77	0.80	3.90	0.29	0.37	0.96	0.87
Memory	4.50	0.80	0.81	4.18	0.24	0.43	0.96	0.87
Behavior	16.00	0.85	0.77	3.70	0.19	0.74	0.87	0.84

Sens=Sensitivity; Spec=Specificity; PLR=positive likelihood ratio; NLR=negative likelihood ratio; PPV=positive predictive value; NPV=negative predictive value; AUC=area under the ROC curve.