Journal of Alzheimer's Disease xx (20xx) x–xx
DOI 10.3233/JAD-150447
IOS Press

Dementia Apraxia Test (DATE): A Brief Tool to Differentiate Behavioral Variant Frontotemporal Dementia from Alzheimer's Dementia based on Apraxia Profiles

Andreas Johnen[1,*], Jana Frommeyer, Fenja Modes, Heinz Wiendl, Thomas Duning[1] and Hubertus Lohmann[1]
Department of Neurology, University Hospital Münster, Germany

Handling Associate Editor: Thomas Benke

Accepted 27 August 2015

Abstract.
Background: Standardized praxis assessments with modern, empirically validated screening tests have substantially improved clinical evaluation of apraxia in patients with stroke. Although apraxia may contribute to early differential diagnosis of Alzheimer's dementia (AD) and behavioral variant frontotemporal dementia (bvFTD), no comparable test is readily available to clinicians for this purpose to date.
Objective: To design a clinically useful apraxia test for the differentiation of AD and bvFTD.
Methods: 84 test items pertaining to twelve praxis subdomains were evaluated for their efficacy to discriminate between patients with bvFTD ($n = 24$), AD ($n = 28$), and elderly healthy controls (HC; $n = 35$). Items were then selected based on discriminative value and psychometric properties.
Results: Items indicative of mild AD comprised spatially complex imitation of hand and finger postures and to a lesser degree, pantomime of common object-use. Buccofacial apraxia including imitation of face postures, emblematic face postures, and repetition of multisyllabic pseudowords differentiated bvFTD from HC and AD. The final test version consisting of 20 items proved highly efficient for the discrimination of biologically confirmed dementia patients from HC (sensitivity 91%, specificity 71%) but also for differential diagnosis of bvFTD and AD (sensitivity 74%, specificity 93%).
Conclusions: Assessment of praxis profiles effectively contributes to diagnosis and differential diagnosis of AD and bvFTD. The Dementia Apraxia Test (DATE) is a brief and easy to administer cognitive tool for dementia assessment, has a high inter-rater reliability (Cohen's $\kappa = 0.885$) and demonstrates content validity.

Keywords: Apraxia, Alzheimer's dementia, differential diagnosis, frontotemporal dementia, neuropsychological tests

INTRODUCTION

The term apraxia commonly denotes faulty performances of gestures on command and tool-use, which are neither fully attributable to deficits in comprehension nor to motor dysfunction [1, 2]. In the tradition of Hugo Liepmann, apraxic phenomena have extensively been studied in patients after left-hemispherical

[1]These authors contributed equally to this work.

*Correspondence to: Andreas Johnen, Department of Neurology, University Hospital Münster, Albert-Schweitzer-Campus 1, 48149 Münster, Germany. Tel.: +49 251 8345304; Fax: +49 251 8345313; E-mail: a.johnen@uni-muenster.de.

ISSN 1387-2877/15/$35.00

stroke [3–5]. Accordingly, subdivisions of apraxia into domains that are considered *clinically meaningful* have almost exclusively derived from research on patients with stroke. Recently, a more descriptive taxonomy of praxis disturbances (i.e., a clear distinction between *pantomime* and *imitation* pertaining to different body-parts) has been established, which significantly improved standardized clinical assessment for patients with stroke [6]. Items for these modern clinical screening tests have been empirically selected based on their ability to quantitatively discriminate between apraxic and non-apraxic patients as well as healthy controls (HC) [7–10].

Apraxic phenomena are, however, also common in several neurodegenerative diseases even in early disease stages [11–16]. Some apraxia tests originally designed for patients with stroke have previously been applied to patients with dementia [11, 17]. However, no empirically derived test specifically designed for clinical praxis assessment in dementia exists to date. Hence, it remains indistinct which praxis domains most effectively contribute to diagnosis and differential diagnosis in neurodegenerative diseases and whether taxonomies of apraxic phenomena derived from research with stroke patients are also clinically significant in these disorders [18]. To address these issues, we systematically compared disturbances within twelve major praxis domains in patients with mild Alzheimer's dementia (AD), behavioral variant frontotemporal dementia (bvFTD), and age-matched HC. We then performed a data-driven item selection based on discriminative value and psychometric properties. As a result we here introduce the DATE (Dementia Apraxia Test), a short test to differentiate between bvFTD, mild AD, and HC based on apraxia profiles.

METHODS

Participants

Patients were recruited from the memory disorder unit at the Department of Neurology at the University Hospital Münster, Germany. All participants gave written informed consent. The study was approved by the local ethic committee (2012-365-f-S).

Patients with AD documented progressive functional decline, subjective and objective memory complaints, and fulfilled current diagnostic criteria by the workgroup of the National Institute on Aging and the Alzheimer's Association [19]. Patients with moderate or severe AD indicated by a Mini-Mental Status Examination (MMSE; [20]) <18 were not included in this study. For patients with bvFTD, current revised diagnostic criteria were applied [21]. Functional decline due to behavioral deterioration was confirmed through clinical observation and history taking of relatives, both informal and standardized using the Frontal Behavioral Inventory (FBI; [22]). Disease duration was estimated by caregivers and relatives and if possible validated through medical records. Additional diagnostic workup included detailed history taking, neurological examination, structural magnetic resonance imaging (MRI) of the brain, analyses of cerebrospinal fluid (CSF) for potential inflammation and dementia biomarkers (Aβ, total tau) as well as extended neuropsychological assessment. Potential primary dysfunction of language (e.g., aphasia) or visuoperception (e.g., agnosia) were screened using the Language Screening Test (LAST, [23]) and a subtest of the Visual Object And Space Perception Battery (VOSP, [24]), respectively. Frontal-executive functions were screened using the German version of the Frontal Assessment Battery (FAB-D, [25]). Further results of neuropsychological assessment used for diagnostic purposes are presented in Supplementary Table 1. A subsample of patients also underwent an 18-fluorodeoxyglucose positron emission tomography (FDG-PET) to detect disease specific brain hypometabolism (7/28 AD; 13/24 bvFTD, Supplementary Table 2). Exclusion criteria for both patient groups were parkinsonism or other motor symptoms (including clinical presentation of alien-limb phenomena, rigidity, tremor, dystonia, and myoclonus), history of cerebrovascular disease, stroke, brain tumor, encephalitis, or traumatic brain injury. Out of a total of 115 patients screened, 52 (AD: $n = 28$; bvFTD: $n = 24$) fulfilled the above criteria and were included in this study. Patients were subsequently classified into levels of biomarker evidence as recommended by the respective diagnostic guideline (Supplementary Table 2). HC ($n = 35$) consisted of community-dwelling elderly and relatives of patients as well as hospital staff volunteers. All HC were screened for neurological, psychiatric, and cognitive disorders and excluded if MMSE was <28.

Apraxia assessment: DATE test construction

With the goal to develop a clinical apraxia test to discriminate between mild AD, bvFTD, and HC, the DATE should cover a sufficient range of praxis domains and modalities including those that were previously shown to be impaired in patients with AD and bvFTD [11, 26]. To detect subtle disturbances in praxis

skills, tasks should challenge patients at a sufficient level of difficulty and thus incorporate a restriction of time, which has shown to be an important aspect of apraxia in early dementia [16, 27]. The final test version should be easy to administer and score in clinical routine within approximately 10 minutes (20 items). Test material (photographs and simple verbal commands) and instructions aim at a high standardization and objectivity. Moreover, instructions and test material ought to place few demands on other cognitive abilities such as language, memory and executive functions. Finally the test should demonstrate at least satisfactory objectivity, reliability, and validity.

Initial test draft

Figure 1 summarizes the praxis domains included in the initial test draft. Following the taxonomy by Goldenberg [6], the initial draft comprised the superordinate domains *imitation* and *pantomime*. The domain *actual tool* use was not examined for practical reasons. Whereas for imitation tasks, a correct response may be more or less directly deduced from visible or audible stimulus properties (e.g., a picture of a meaningless hand posture; repetition of complex words or sounds), *pantomime* performance is dependent on semantic knowledge of *how* to use the presented object (e.g., a picture of a hammer) or on experience with the conventional meaning of a gesture (e.g., participant is asked to make a gesture for "goodbye"). Items of the first test draft were selected based on clinical experience and inspired by various available apraxia tests [8, 28–30].

Imitation: Imitation items were presented visually as high-quality black and white photographs of a model showing postures of varying body-modalities and spatial complexity. Assessment of imitation tasks was preceded by sample items in which participant's errors were corrected by the examiner. Participants were asked to "imitate the posture as precisely as possible and in a smooth movement". We focused on the evaluation of novel, non-symbolic postures, which have previously shown to be more often impaired in early stages of dementia than the imitation of symbolic gestures [18, 31] possibly due to less semantic associations to guide the gesture [32, 33]. To account for possible effects of spatial complexity and body-part specificity [34], *limb imitation* was separately explored in detail for *hand postures, combined hand/finger postures, finger postures*, and *bimanual hand postures* (Fig. 1).

As *buccofacial apraxia* has recently been shown to be a potentially important clinical feature of bvFTD [11, 26] and may also be present in AD [35, 36], we also separately investigated *imitation of face postures and imitation of emotional face postures*. Conceptually related, symptoms of apraxia of *speech* were operationalized here by means of verbal repetition of multisyllabic words (*word imitation*) and pseudowords (*pseudoword imitation*; Fig. 1).

Pantomime: Pantomime of object-use was tested by presenting high-quality black and white photographs of common items and tools. Participants were asked to "imagine this object in front of you and then pretend to use it in its typical way". Two sample items were shown to make the participants familiar with the scoring system. To account for potential effects of gestural complexity and sequentiality [37], we separately assessed *pantomime of single object-use and pantomime of multiple object-use* (Fig. 1).

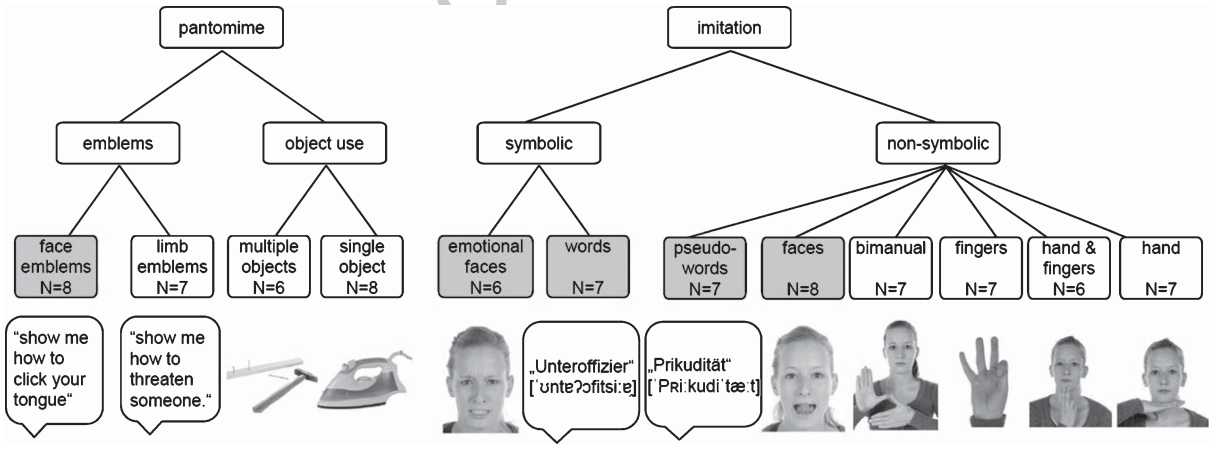

Fig. 1. Praxis domains of the DATE initial test draft and example items. Subtests concerning buccofacial/speech modality are grey-shaded in contrast to subtests concerning limb modality.

Emblematic gestures (i.e., symbolic gestures with conventional meaning without involved objects) were asked verbally both for *limb emblems* (e.g., "show me how to wave goodbye") and for *buccofacial emblems* (e.g., "click your tongue", Fig. 1).

In total, the initial test draft comprised of 84 items pertaining to 12 praxis domains (Fig. 1; see Appendix A for all items of the initial test version).

Scoring system

Participant's response to each item was rated on a 0–3 point scale based on its match with a predefined visual target state. In addition to this visual template, target state criteria consisting of clear, coherent, and defining descriptions of the spatial properties and/or sequence of the postures were provided to the rater (Appendix A). Three points were awarded, if the participant achieved the target posture in a smooth and target-oriented movement. If the participant showed a) halting movement or b) spatial corrections of limb or face positions but succeeded in achieving the target posture within a five second time period after movement onset, two points were granted. After this time period, an unspecific verbal cue was given, that the posture was not correct yet. If the participant achieved the correct target state after another ten seconds, one point was awarded; otherwise the item was rated with zero points. For the evaluation of the speech repetition items (i.e., indicative of *apraxia of speech*), a slightly adapted scoring system was used (see Appendix A for wording of instructions and original protocol sheet).

Item reduction procedure

Item reduction was achieved through a stepwise procedure as displayed in Fig. 2: In an initial step, all test items were put in a descending order by median (and subordinated mean) differences between AD and bvFTD regardless of praxis domain. We then preselected the 25 items with largest positive median differences (i.e., indicative of AD) and 25 items with largest negative median differences (i.e., indicative of bvFTD), eliminating all items with little or no discriminative value. Out of these two sets, items were then excluded based on psychometric properties until arriving at the desired test length of 20 items total (Fig. 2).

Statistics

Statistical analyses were performed with SPSS 22 (IBM). To test for between-group differences in demographic data and disease severity scores, ratios of gender, and handedness were compared between groups with χ^2-tests. Age, education, and scores of the cognitive screenings tests (MMSE, VOSP-subtest 7, LAST, FAB-D) were compared with univariate ANOVAs and *post-hoc* Games-Howell tests. Disease duration and FBI scores were compared between AD and bvFTD using independent sample *t*-tests. Sampling distributions of praxis variables were visually checked for outliers, violations of normality, and skewness within groups. Between-group differences within praxis domains of the initial test draft were tested with profile analysis using Wilk's-Λ test statistics for levels and parallelism effects. For item reduction and psychometric quality analysis, we computed Cohen's kappa coefficient κ as statistical measure of concordance for each item, based on videotapes of 15 praxis assessments rated by a second rater, blinded for patient's diagnosis. Item-total correlations $r_{it(i)}$ were computed to evaluate consistency of items within domains. Item difficulty was determined by index P_i, i.e., the quotient of scores actually reached by participants and the maximum score. For the final test scales (after item reduction), univariate ANOVAs were performed

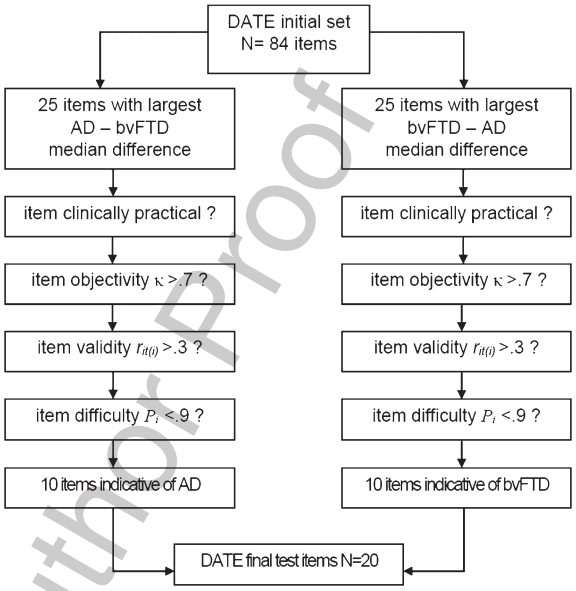

Fig. 2. Flow-diagram displaying item reduction procedure of the DATE. Items were excluded due to a) adverse experiences from clinical practice (e.g., participants repeatedly expressed discomfort with item 8 of the *buccofacial imitation* domain which demanded participants to jut their jaw forward and show their lower teeth) b) low inter-rater reliability (Cohen's kappa values <0.7) c) Low internal validity (item-total correlations <0.3) d) Ceiling effects (difficulty index >0.9). AD, Alzheimer's disease dementia; bvFTD, behavioral variant frontotemporal dementia; κ, Cohen's kappa; $r_{it(i)}$, item-total correlation P_i, item difficulty index.

to test for differences between AD and bvFTD within scales and sets of subscales (*limb apraxia* versus *buccofacial apraxia*). Cronbach's α was calculated as a measure of internal consistency of the final test version's scales. For the evaluation of construct validity Pearson's correlations r of the final test version and the Cologne Apraxia Screening (CAS; [10]) were used. Receiver operating characteristics (ROC curves) were computed to determine optimal cut-off scores and predictive validity of the final test version.

RESULTS

Demographic data and disease severity scores

All patients fulfilled core criteria with typical clinical presentations and progression of the respective dementia syndrome [19, 21]. Based on available CSF biomarker-profile, cortical atrophy on MRI and hypometabolism patterns, 15 patients with probable AD were classified with *high* and 13 with *intermediate* biomarker evidence. Likewise, within the bvFTD group, 18 patients were classified as *probable* bvFTD and 6 patients with *possible* bvFTD (Supplementary Table 2). Table 1 displays comparisons of demographic data and disease severity scores between groups. Patients with AD were slightly older than patients with bvFTD (mean difference 6.6 years, $p = 0.014$), and showed a significant difference in years of education compared with HC (mean difference 1.07 years, $p = 0.01$). There were fewer females among patients with bvFTD compared with both, AD and HC, χ^2 (2, $n = 88$) = 14.47, $p < 0.001$. As expected there were more severe behavioral disturbances within patients with bvFTD compared with AD (FBI; $p < 0.001$). Patients with bvFTD and AD did not differ significantly regarding handedness, disease duration and overall cognitive status as measured by the MMSE. We found no differential deficits regarding language abilities (LAST) and visuoperceptual functioning (VOSP-subtest 7) when comparing AD and bvFTD. Frontal-executive functions (FAB-D) were expectedly more impaired in bvFTD, however, no significant group difference compared with AD emerged (Table 1). A more detailed neuropsychological characterization of patient groups is available in Supplementary Table 1.

DATE initial test draft

Apraxia profiles: DATE initial test draft

Patients versus controls: Figure 3 displays group means of the twelve praxis domains of the initial test version. Profile analysis showed a significant *levels* effect for the three groups, indicating significant differences between groups when averaged over praxis domains, F(2, 49) = 18.16, $p < 0.001$, partial $\eta^2 = 0.426$. *Post-hoc* Games-Howell test showed that this effect was due to significantly better praxis performances of HC compared with both, AD, $p < 0.001$ and bvFTD, $p < 0.001$. Subsequent comparisons of both AD and bvFTD using separate ANOVAs and *post-hoc* Games-Howell tests revealed that both patients performed significantly worse on each of the twelve apraxia subdomains depicted in Fig. 3 compared with HC (all $p < 0.05$).

bvFTD versus AD: We additionally found a significant deviation from parallelism indicating that group

Table 1
Demographic data and disease severity scores

	AD ($n = 28$)	BvFTD ($n = 24$)	HC ($n = 35$)
Demographic data			
Age, years	71.5 (10.0)	64.9 (8.0)†	67.9 (6.1)
Gender (female/male)	16/12	3/21*†	20/15
Education, years	11 (1.3)*	11.2 (1.6)	12.0 (1.3)
Handedness (left/right)	3/25	2/22	3/32
Disease severity and cognitive screenings			
Disease duration, months	23.46 (22.6)	32.6 (21.6)	N/A
MMSE (max. 30)	23.2 (2.7)*	24.7 (5.0)*	29.2 (.8)
FBI (max. 72)	9.9 (7.1)	28.4 (10.0)†	N/A
VOSP subtest 7 (max. 10)	7.75 (2.4)	8.29 (1.7)	8.79 (1.4)[a]
LAST (max. 15)	14.39 (.79)*	14.52 (.67)*	14.95 (.23)[a]
FAB-D (max. 18)	13.43 (2.4)*	11.14 (4.6)*	17.06 (.87)[a]

AD, Alzheimer's dementia; bvFTD, behavioral variant frontotemporal dementia; HC, healthy controls; MMSE, Mini-Mental Status Examination; FBI, Frontal Behavioral Inventory; VOSP, Visual Object and Space Perception Battery; LAST, Language Aphasia Screening Test; FAB-D, Frontal Assessment Battery (German Version); [a]data available from a subsample of $n = 19$ participants; N/A, not available. Age, education, disease duration, and MMSE and FBI scores are reported as mean (SD). *$p < 0.05$ for comparison between dementia group and control group, †$p < 0.05$ for comparison between dementia groups.

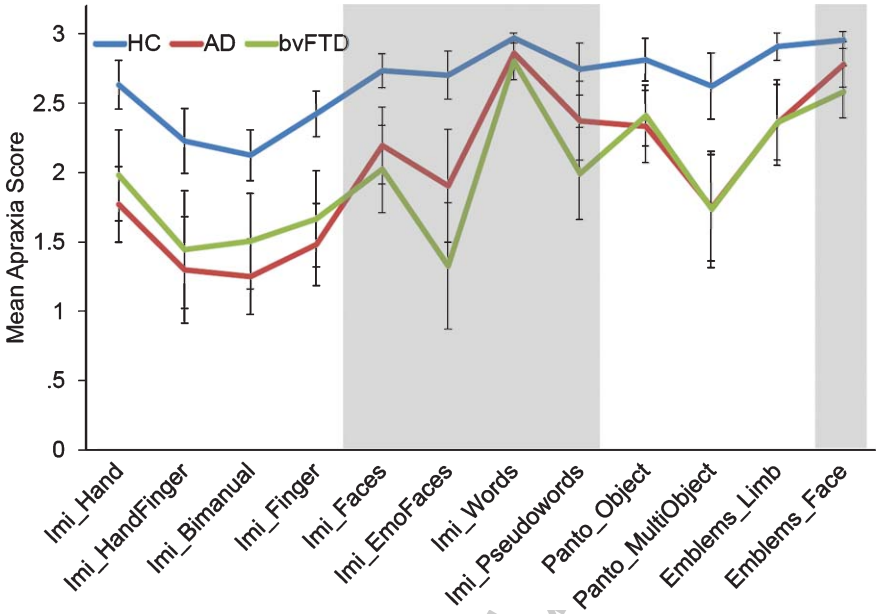

Fig. 3. Group means and profile plots for all 12 praxis domains of the DATE initial test version. Error bars indicate SDs. Buccofacial/speech domains are grey-shaded. Note that patients with bvFTD display lower group means than patients with AD in all buccofacial/speech domains. *Imi_Hand*, imitation of hand postures; *Imi_HandFinger*, imitation of combined hand and finger postures; *Imi_Bimanual*, imitation of bimanual hand and finger postures; *Imi_Finger*, imitation of finger postures; *Imi_Faces*, imitation of face postures; *Imi_EmoFaces*, imitation of emotional faces; *Imi_Words*, verbal repetition of spoken words; *Imi_Pseudowords*, verbal repetition of spoken pseudowords; *Panto_Object*, pantomime of object-use for single objects; *Panto_MultiObject*, pantomime of object-use for multiple objects; *Emblems_Limb*, emblematic limb gestures; *Emblems_Face*, emblematic face gestures.

profiles diverged across the twelve praxis domains, Wilk's $\Lambda = 0.34$, $F(22, 78) = 2.55$, $p < 0.001$, partial $\eta^2 = 0.158$. Inspection of the profile plots (Fig. 3) suggested that patients with AD scored lowest in praxis domains involving hands and fingers (i.e., *limb apraxia*), whereas patients with bvFTD were relatively more impaired across praxis domains involving face and speech modality (i.e., *buccofacial apraxia*, grey-shaded). A follow-up comparison of domains averaged over limb modality versus buccofacial/speech modality confirmed this finding by showing a significant praxis domain by group interaction for bvFTD versus AD, Wilk's $\Lambda = 0.868$, $F(1, 50) = 7.75$, $p = 0.008$, partial $\eta^2 = 0.132$.

Item reduction

Out of the 25 items indicative of AD (i.e., largest positive median and mean difference between AD and bvFTD), 10 items were selected for the final test version (Fig. 2). All of these items involved limb modality (2 *hand imitation*, 1 *finger imitation*, 1 *hand & fingers imitation*, 4 *bimanual imitation*, 1 *pantomime of single object-use*, 1 *pantomime of multiple object-use*) and were subsequently merged into two new subscales *limb imitation* (8 items) and *object pantomime* (2 items) to retain a reasonable number of items per scale for the final test version. To obtain items indicative of bvFTD, 10 items were selected in an identical procedure (Fig. 2). This resulted in a set consisting of only buccofacial/speech modality items (2 *imitation of pseudowords*, 2 *face imitation*, 4 *emotional face imitation*, 2 *face emblems*). Items from *face imitation* and *emotional face imitation* were subsequently merged into one *face imitation* subscale due to practical considerations. The DATE final test thus consisted of five subscales, two covering *limb apraxia* (DATE part 1: *limb imitation* and *object pantomime*) and three covering *buccofacial apraxia* (DATE part 2: *face imitation, buccofacial emblems*, and *imitation of pseudowords*). Item characteristics and between-group mean differences for all selected items, subscales and test parts as well as corresponding stimulus material of the DATE final test version can be viewed in Appendix B.

DATE final test version

Apraxia profiles: DATE final test version

Figure 4 and Table 2 display mean and raw scores of HC, AD, and bvFTD on scales and subscales of the final test version of the DATE after item reduction.

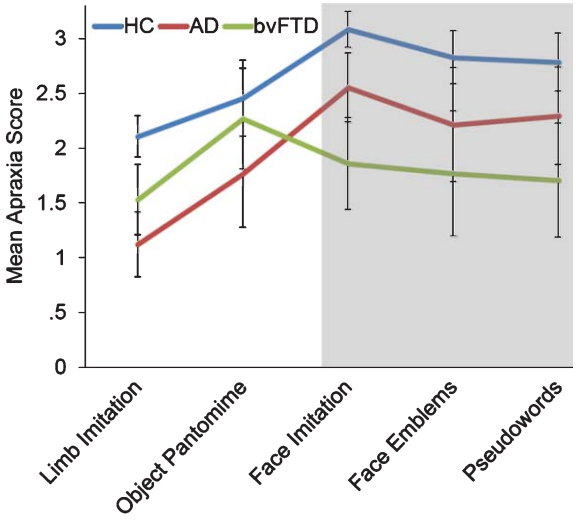

Fig. 4. Group means and profile plots of the five praxis domains of the DATE final test version. Buccofacial/speech praxis domains are grey-shaded.

Inspection of the profile plots (Fig. 4) suggests that HC performed better than both dementia groups on each final DATE scale. Differences between HC and dementia groups were significant for all subscales (for object *pantomime* only AD versus HC was significant) as well as for the combined scales *buccofacial apraxia* (Fig. 4, grey shaded), *limb apraxia* and the *DATE total test score* (Table 2).

Patients with bvFTD and AD did not differ on the *DATE total* test score. As prior to item reduction, AD and bvFTD showed diverging profiles, as AD patients performed relatively worse on scales involving limb modality, whereas bvFTD showed considerably more impairment on buccofacial subscales (Fig. 4). Although there was a statistical trend for significant differences in limb apraxia subscales between AD and bvFTD (AD < bvFTD), differences at subscale level between AD and bvFTD were only significant for *face imitation* and the combined scale *buccofacial apraxia* (Table 2). We thus directly contrasted performance of the total *buccofacial apraxia* and *limb apraxia* scales using a follow-up 2 × 2 ANOVA with apraxia modality (*buccofacial apraxia* versus *limb apraxia*) as within-subject factor and group (AD versus bvFTD) as between-subject factor. A highly significant interaction effect was found, Wilk's $\Lambda = 0.59$, $F(1, 50) = 35.75$, $p < 0.001$, partial $\eta^2 = 0.41$, confirming that patients with AD and bvFTD differed on the proportion of praxis impairments in limb versus buccofacial modality.

Criterion-referenced test interpretation and psychometric properties: DATE final test version

For criterion-referenced test interpretation, receiver operating characteristics (ROC) curves were calculated to quantify discriminative test properties and to find ideal cut-off scores to distinguish between AD, bvFTD and HC (Fig. 5).

Based on inspection of the group profiles, the *DATE total test score was* used as optimal classifier to discriminate between dementia patients (bvFTD and AD) and HC. This classifier showed an area under curve (AUC) of 0.889 and ROC revealed that the ideal cut-off point (Youden-Index 0.67) was a raw score of 41 (sensitivity: 0.79, specificity: 0.88). However, to reduce the chance of false-negative test results and increase sensitivity as recommended for a screening instrument, the cut-off score was set at 45 (Youden-Index 0.62). Using this cut-off value, the DATE revealed a sensitivity

Table 2
DATE final test version group mean raw scores and psychometric properties of scales and subscales

	AD	bvFTD	HC	AD versus HC[a]	bvFTD versus HC[a]	AD versus bvFTD[a]	α	p_i	κ[b]
Scales									
Limb imitation	9.11 (4.78)	12.25 (5.12)	16.86 (3.04)	–7.75**	–4.61**	–3.14	0.776	0.54	0.894
Object pantomime	3.54 (1.97)	4.54 (1.84)	4.91 (1.38)	–1.37**	–0.37	–1.0	0.400	0.73	0.924
Face imitation	12.53 (3.42)	8.36 (4.91)	16.11 (1.91)	–3.58**	–7.75**	4.17*	0.752	0.70	0.837
Buccofacial emblems	4.59 (1.93)	3.43 (2.27)	5.65 (0.98)	–1.06*	–2.13**	1.16	0.536	0.78	0.835
Imitation pseudowords	4.59 (1.78)	3.42 (2.08)	5.57 (1.07)	–0.98*	–2.15**	1.17	0.597	0.78	0.832
Combined scales									
Total limb apraxia	12.85 (5.29)	16.79 (6.47)	21.77 (3.58)	–9.19**	–4.98**	– 3.94	0.779	0.59	0.907
Total buccofacial apraxia	22.16 (5.13)	15.29 (7.32)	27.12 (3.58)	–4.96**	–11.83**	6.87*	0.820	0.73	0.847
Total DATE score	35.00 (8.96)	32.79 (10.99)	48.41 (5.65)	–13.41**	–15.62**	2.21	0.840	0.65	0.885

Note: Raw score means and psychometric properties of all scales, subscales and test parts of the DATE final test version. AD, Alzheimer's dementia; bvFTD, behavioral variant frontotemporal dementia; HC, healthy controls; α, Cronbach's Alpha; p_i, difficulty index; κ, Cohen's kappa. Participant group scores for each item are reported as mean (SD). See Appendix B for corresponding items. [a]values are mean difference scores, tests of significance were performed using univariate ANOVAs and Games-Howell *post-hoc* tests. [b]scores are based on $n = 15$ videos of patient assessments. $^{*}p < 0.05$, $^{**}p < 0.01$.

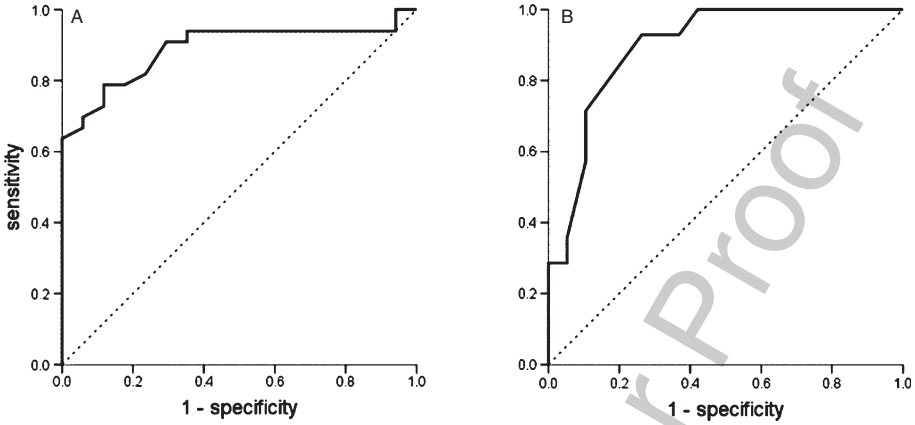

Fig. 5. ROC-curves of DATE classifiers for the discrimination between dementia patients and HC (A) and for differential diagnosis between AD and bvFTD (B). A) Solid line represents *total DATE score* as a classifier to discriminate between dementia patients (AD and bvFTD) versus HC. B) Solid line represents the difference score of *total limb apraxia* and *total buccofacial apraxia* as a classifier to discriminate between AD and bvFTD. Dashed lines represent line of no-discrimination.

of 0.91 and a specificity of 0.71 for discriminating dementia patients and HC.

For differential diagnosis of AD and bvFTD we chose to test the discriminative value of the interaction between group (AD versus bvFTD) × apraxia modality (*limb apraxia* versus *buccofacial apraxia*) as this effect showed the largest difference between the two groups (see above, DATE Final Test Version). To account for this interaction effect in a single classifier, the difference score between the two test parts (*limb apraxia* minus *buccofacial apraxia*) was used as the optimal classifier of dementia group membership (lower scores indicate larger impairment on buccofacial scales and thus bvFTD group membership). This classifier achieved an AUC of 0.897. The ideal cut-off score was found at -7 (Youden-Index 0.67) with a sensitivity of 0.74 and a specificity of 0.93 to discriminate between bvFTD and AD.

For clinical use, suggested cut-off values and calculation tables for these classifiers are included on the protocol sheets of the final test version (Appendix B).

Norm-referenced interpretation: DATE final test version

Since total test score and combined scales (*limb apraxia* and *buccofacial apraxia*) were approximately normally distributed for all participant groups, individual scores may also be interpreted with regards to distance to the mean score of HC (Table 2). For norm-referenced interpretation of the DATE, we thus suggest to conservatively interpret test scores <1 SD of the mean HC as "below average or slightly impaired" and scores <2 SD as "well below average or severely impaired".

Psychometric properties: DATE final test version

Internal consistency (Cronbach's α) of the *DATE total test score* was good ($\alpha = 0.84$) especially when considering its application in clinical populations with diffuse brain damage, indicating acceptable reliability of the test and rating criteria. As expected, subscales with fewer items (e.g., *object pantomime*, 2 items) achieved considerably lower internal consistencies than subscales with more items.

Cohen's κ revealed almost perfect agreement between raters for *the DATE total test score* ($\kappa = 0.885$) indicating high objectivity for the rating system and criteria. For subscales, concordance between raters ranged between substantial and almost perfect agreement (Table 2).

Correlations with the CAS were calculated as a measure of construct validity. The *DATE total test score* showed a positive correlation with the CAS total score, $r = 0.48$. The DATE subscale limb imitation was correlated with the *limb imitation* subscale (CAS 2.2) of the CAS, $r = 0.44$. Likewise DATE subscales *object pantomime* and *face imitation* showed positive associations with the respective CAS scales for pantomime of object-use (CAS 1.1, $r = 0.38$) and for facial imitation (CAS 2.1, $r = 0.80$). All correlations were significant at $p = 0.001$.

DISCUSSION

Although praxis disturbances are essential features of bvFTD and AD and may provide important clinical information for diagnosis [11, 37, 38], standardized and empirically validated assessment of praxis in

dementia is hindered by lack of valid and reliable tests designed for this purpose to date [18]. Moreover, it remains indistinct whether apraxic phenomena in patients with neurodegenerative disorders resemble those of patients with stroke in terms of primarily affected domains (e.g., imitation versus pantomime; limb versus face, etc.) and whether similar taxonomies of praxis [6] are clinically relevant in these patients. To address these issues empirically rather than from a theoretical viewpoint, we evaluated a large set of 84 apraxia items pertaining to 12 praxis domains for their discriminatory value to distinguish between HC and patients with AD and bvFTD.

Why another apraxia test?

Praxis disturbances are complex and multifactorial neuropsychological deficits of gesture production. Operational definitions of apraxia thus often substantially differ between studies and available tests. Relevant differences may concern imitation versus pantomime of gestures, transitivity (i.e., whether an object is involved), tested body-parts (e.g., face versus hands versus fingers), semantic content of items (symbolic versus non-symbolic), sequentiality of gestures and stimulus presentation modalities (e.g., visual stimuli versus verbal commands) [2, 3, 5]. As a consequence, results between tests and studies are hardly comparable and no gold standard for praxis assessment has yet been established, in particular for clinical testing of patients with neurodegenerative diseases [18]. The current study provides clinicians and researchers with coherent empirical data on clinical and conceptual relevance of a wide range of praxis domains in patients with AD and bvFTD. Our data thus contribute to the current understanding of gesture production deficits in patients with different neurodegenerative etiologies. Importantly, by employing a data-driven reduction of items and praxis domains, the DATE has several important advantages over previous clinical apraxia tests for application in dementia assessment. a) Items and domains of the DATE were not selected arbitrarily or primarily based on theoretical considerations about praxis impairments in patients with stroke (e.g., empirically outdated distinctions between ideatoric versus ideomotor apraxia [6]) but rather on the principle of empirically meaningful differences between patients with mild AD, bvFTD, and HC. b) Based on these differences and using only items with high psychometric quality, the DATE offers quantitative information on praxis profiles that aid in diagnosis and differential diagnosis of dementia using cut-off values. c) Despite its empirically derived structure and its highly specialized field of application, the DATE provides face validity and comparability with previous apraxia tests as e.g., scales for *limb imitation* and *pantomime* of *object-use* are included.

Apraxia profiles in AD and bvFTD: Commonalities and differences

Analysis of the initial item set as well as the DATE final test version revealed that both AD and bvFTD were significantly impaired across a wide range of praxis domains when compared with age-matched HC. Moreover, AD and bvFTD showed distinct profiles of praxis deficits. Differential performances of bvFTD and AD primarily depended on whether gestures were performed with the hands and fingers (*limb apraxia*) or the face (*buccofacial apraxia*) mostly irrespective of whether the gestures were symbolic or non-symbolic or whether *imitation* or *pantomime* was tested. Our results thus suggest that for the differentiation between AD and bvFTD, the clinically most relevant praxis dimension may be affected body-part (i.e., *limb* versus *buccofacial apraxia*).

Apraxia in AD

AD patients performed worse than bvFTD and HC on all praxis subscores involving imitation of limb postures, in particular with increasing spatial complexity (combined hand & finger and bimanual imitation). This result is in line with previous studies showing that mild AD patients are most impaired in imitation of meaningless finger and hand postures [11, 31, 39, 40]. Successful imitation of novel gestures requires intact visuospatial processing and/or internal representation of spatial relationships between body parts (and/or objects) for which parietal lobe integrity is crucial [6, 41, 42]. AD patients show marked atrophy in parietal association cortices early in the course of the disease [19], which may explain their more pronounced deficits in these praxis domains compared with bvFTD and HC. Meaningful or symbolic gestures (including pantomime of object-use, emblems, imitation of emotional facial expressions, and imitation of words) may rely to a greater extent on conceptual knowledge and semantic memory, generally facilitating performance on these tasks [43, 44]. Severe semantic memory dysfunction is associated with temporal lobe atrophy and commonly appears in later stages of AD [45]. This may account for the relatively better performance of symbolic tasks across pantomime and imitation domains within our sample of mild AD patients.

Apraxia in bvFTD

Although bvFTD primarily affects frontal and anterior temporal lobes while the parietal lobe is largely spared in early disease stages [21], patients also showed substantial deficits in almost all praxis tasks compared with HC. This result corroborates previous work regarding severe praxis deficits in bvFTD [11, 26]. Moreover, analysis of praxis profiles provided evidence of a disease specific deficit in imitation of face postures (both emotional and non-emotional), communicative gestures involving the face as well as repetition of multisyllabic pseudowords. These findings substantiate and extend previous work from our group [11]. bvFTD broadly affects social conduct and evidence suggests that abnormal processing of social stimuli is an early feature of the disease [46–50]. Within this framework, communicative gestures and in particular facial expressions may be viewed as social stimuli and production deficits on these tasks may thus be considered a novel aspect of the previously reported social cognition impairments in bvFTD. Internal simulation processes may constitute a conceptual overlap between the cognitive and neural representations of praxis and social cognition abilities [51]. A different interpretation of our results implies a more general impairment of buccofacial modality in bvFTD which is not limited to the social aspects of such stimuli: bvFTD is increasingly considered in a clinical and neuropathological continuum with motor-neuron disease [52–54]. Apraxia of speech, buccofacial apraxia and bulbar motor-dysfunction have previously been reported in motor-neuron disease [55–57]. Although more research is needed, our results of a buccofacial praxis impairment in bvFTD may point toward a possible clinical overlap of these cognitive functions. Interestingly, recent evidence suggests that such an overlap between bvFTD and motor-neuron disease also exists for social cognition deficits [58, 59].

The DATE as a neuropsychological tool for diagnosis of AD and bvFTD

Early and accurate diagnosis of neurodegenerative disorders and dementia subtype is crucial in order to ensure that patients receive optimal medical treatment and caregiving. Because of a substantial overlap in initial clinical symptoms, assessment of neuropsychological standard domains (e.g., memory, attention, executive functions) provide fundamental quantitative information for the differentiation between AD and bvFTD. However, former neuropsychological tenets such as normal memory functioning in bvFTD in contrast to AD have recently been challenged [60–62]. More specialized tests for this differentiation are necessary and are an ongoing subject of research [63–65]. Apraxic phenomena are notoriously under-represented both in clinical neuropsychological dementia assessment as well as in research on diagnostic test efficiency, probably due to the syndrome's elusive conceptualization [18]. As a result, current diagnostic criteria for AD and bvFTD lack references to praxis performance. This study provides evidence that assessment of praxis is feasible in clinical practice and that analysis of apraxia profiles is both innovative and efficient in terms of differentiation between AD and bvFTD. Compared with other neuropsychological tools commonly used to distinguish between AD and bvFTD (e.g., Go/NoGo tests, Iowa gambling task, social cognition tasks), the DATE showed comparable discriminatory value in terms of sensitivity and specificity in the current study [64]. Future studies within large study populations are needed to validate our results and directly evaluate the differential diagnostic properties of these different approaches to differentiate dementia subtypes. Nevertheless, the DATE qualifies to be employed in a diagnostic workup for patients suggestive of having AD or bvFTD and prospectively apraxia should be included in clinical diagnostic criteria.

Limitations and future prospects

Test construction and validation is a process, rather than a result of a single study. More studies are needed to investigate how the DATE relates to other established apraxia tests designed for patients with stroke to confirm its construct validity. Moreover, our results on diagnostic value and psychometric properties of the DATE need to be cross-validated in independent and international patient samples, ideally in large multicentric studies. Discriminatory efficiency of the DATE may otherwise be overestimated. All material necessary for a cross-validation is provided (Appendix B).

A second potential shortcoming of our study concerns a priori between-group differences regarding demographic variables. As patients were referred to the study in clinical routine, these differences represent naturalistic sample properties. Patients and HC differed in terms of education and there were fewer females with bvFTD. Additionally, AD patients were older than patients with bvFTD, reflecting that the mean age of onset in bvFTD is lower than in AD [66]. Little research has been conducted on potential effects of gender, age, and education on praxis performance. Regarding limb apraxia, sex has been found to have

no influence, while education and age may affect performance in HC [67]. However, the authors found an effect only for <8 years of education including illiterates but all of our participants had at least 8 years of general schooling. Age adversely influenced praxis performance in that study and it is thus possible that some praxis differences between AD and bvFTD may be confounded with age. However, performance in the *total DATE score* was similar in both patient groups despite age differences. Age differences may also not explain the group interaction effects for *limb apraxia* and *buccofacial apraxia*.

A third important caveat when interpreting our results regards possible associations of apraxia with other neuropsychological performance scores. As apraxia is a cognitive disorder, it is not independent of global cognitive performance, executive functioning, and also semantic and visuospatial abilities. Although bvFTD and AD patients in this study were similar in terms of global cognitive performance (MMSE), reported performances and diagnostic potential of the DATE needs to be interpreted with care as they may partly be linked to disturbances in some or all of the above mentioned neuropsychological domains. Despite that, our clinical impression is that apraxia assessment using the DATE is simple and requires less speech comprehension and working memory capacity than other cognitive tests specialized to distinguish between AD and bvFTD [46]. Nevertheless, future studies are needed to elucidate relationships between cognitive performance scores and gestural performance within dementia patients.

CONCLUSION

Although gestural deficits and apraxia have previously been described as early cognitive symptoms in AD and recently also in bvFTD, empirically validated apraxia tests specifically designed for clinical dementia diagnosis are not available to date. The DATE allows reliable, objective, and valid quantitative assessment of a range of gestural performance deficits that are clinically meaningful in early neurodegenerative diseases. The tool may be used in clinical routine within approximately 10 minutes. Additionally, using the DATE (in particular the relationship between *limb apraxia* and *buccofacial apraxia*) allows a differentiation between bvFTD and AD in early disease stages with good specificity and sensitivity. Future research is needed to cross-validate the DATE in larger samples and within other primary neurodegenerative diseases.

ACKNOWLEDGMENTS

Thanks to Amelie Tokaj for serving as apraxia model on photographs of stimuli material. Thanks to Patricia Goldberg and Lena Rösch for re-ratings of apraxia assessment videos. This study was supported by the Stiftung Neuromedizin, Münster, Germany.

Authors' disclosures available online (http://j-alz.com/manuscript-disclosures/15-0447r2).

SUPPLEMENTARY MATERIAL

The supplementary material are available in the electronic version of this article: http://dx.doi.org/10.3233/JAD-150447.

REFERENCES

[1] Heilman K, Rothi L (1993) Apraxia. In *Clinical Neuropsychology*, Heilman K, Valenstein E, eds. Oxford University Press, New York, Oxford, pp. 141-164.
[2] Goldenberg G (2013) *Apraxia: The Cognitive Side of Motor Control*, Oxford University Press, New York, Oxford.
[3] Leiguarda R, Marsden C (2000) Limb apraxias: Higher-order disorders of sensorimotor integration. *Brain* **123**, 860-879.
[4] Koski L, Iacoboni M, Mazziotta JC (2002) Deconstructing apraxia: Understanding disorders of intentional movement after stroke. *Curr Opin Neurol* **15**, 71-77.
[5] Petreska B, Adriani M, Blanke O, Billard AG (2007) Apraxia: A review. *Prog Brain Res* **164**, 61-83.
[6] Goldenberg G (2009) Apraxia and the parietal lobes. *Neuropsychologia* **47**, 1449-1459.
[7] Dovern A, Fink G, Weiss P (2012) Diagnosis and treatment of upper limb apraxia. *J Neurol* **259**, 1269-1283.
[8] Vanbellingen T, Kersten B, Van de Winckel a, Bellion M, Baronti F, Müri R, Bohlhalter S (2011) A new bedside test of gestures in stroke: The apraxia screen of TULIA (AST). *J Neurol Neurosurg Psychiatry* **82**, 389-392.
[9] Tessari A, Toraldo A, Lunardelli A, Zadini A, Rumiati RI (2015) STIMA: A short screening test for ideo-motor apraxia, selective for action meaning and bodily district. *Neurol Sci* **36**, 977-984.
[10] Weiss P, Kalbe E, Kessler J, Fink G, Binder E, Hesse M, Scherer A (2013) *Kölner Apraxie Screening*, Hogrefe Verlag, Göttingen.
[11] Johnen A, Tokaj A, Kirschner A, Wiendl H, Lueg G, Duning T, Lohmann H (2014) Apraxia profile differentiates behavioural variant frontotemporal from Alzheimer's dementia in mild disease stages. *J Neurol Neurosurg Psychiatry* **86**, 809-815.
[12] Burrell JR, Hornberger M, Vucic S, Kiernan MC, Hodges JR (2014) Apraxia and motor dysfunction in corticobasal syndrome. *PLoS One* **9**, e92944.
[13] Vanbellingen T, Lungu C, Lopez G, Baronti F, Müri R, Hallett M, Bohlhalter S (2012) Short and valid assessment of apraxia in Parkinson's disease. *Parkinsonism Relat Disord* **18**, 348-350.
[14] Nagahama Y, Okina T, Suzuki N (2014) Impaired imitation of gestures in mild dementia: Comparison of dementia with Lewy bodies, Alzheimer's disease and vascular dementia.

J Neurol Neurosurg Psychiatry, doi: 10.1136/jnnp-2014-309436

[15] Ozkan S, Ozbabalik Adapinar D, Tuncer Elmaci N, Arslantas D (2013) Apraxia for differentiating Alzheimer's disease from subcortical vascular dementia and mild cognitive impairment. *Neuropsychiatr Dis Treat* **9**, 947-951.

[16] Crutch SJ, Rossor MN, Warrington EK (2007) A novel technique for the quantitative assessment of apraxic deficits: Application to individuals with mild cognitive impairment. *J Neuropsychol* **1**, 237-257.

[17] Smits LL, Flapper M, Sistermans N, Pijnenburg Y, a L, Scheltens P, van der Flier WM (2014) Apraxia in mild cognitive impairment and Alzheimer's disease: Validity and reliability of the Van Heugten test for apraxia. *Dement Geriatr Cogn Disord* **38**, 55-64.

[18] Lesourd M, Le Gall D, Baumard J, Croisile B, Jarry C, Osiurak F (2013) Apraxia and Alzheimer's Disease: Review and Perspectives. *Neuropsychol Rev* **23**, 234-256.

[19] McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR, Kawas CH, Klunk WE, Koroshetz WJ, Manly JJ, Mayeux R, Mohs RC, Morris JC, Rossor MN, Scheltens P, Carrillo MC, Thies B, Weintraub S, Phelps CH (2011) The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* **7**, 263-269.

[20] Folstein M, Folstein S, McHugh P (1975) Mini-mental state: A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* **12**, 189-198.

[21] Rascovsky K, Hodges JR, Knopman D, Mendez MF, Kramer JH, Neuhaus J, van Swieten JC, Seelaar H, Dopper EGP, Onyike CU, Hillis AE, Josephs K, a, Boeve BF, Kertesz A, Seeley WW, Rankin KP, Johnson JK, Gorno-Tempini M-L, Rosen H, Prioleau-Latham CE, Lee A, Kipps CM, Lillo P, Piguet O, Rohrer JD, Rossor MN, Warren JD, Fox NC, Galasko D, Salmon DP, Black SE, Mesulam M, Weintraub S, Dickerson BC, Diehl-Schmid J, Pasquier F, Deramecourt V, Lebert F, Pijnenburg Y, Chow TW, Manes F, Grafman J, Cappa SF, Freedman M, Grossman M, Miller BL (2011) Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain* **134**, 2456-2477.

[22] Kertesz A, Davidson W, Fox H (1997) Frontal behavioral inventory: Diagnostic criteria for frontal lobe dementia. *Can J Neurol Sci* **24**, 29-36.

[23] Flamand-Roze C, Falissard B, Roze E, Maintigneux L, Beziz J, Chacon A, Join-Lambert C, Adams D, Denier C (2011) Validation of a new language screening tool for patients with acute stroke: The language screening test (LAST). *Stroke* **42**, 1224-1229.

[24] Warrington EK, James M (1991) *The visual object and space perception battery*, Thames Valley Test Company, Bury St. Edmunds.

[25] Benke T, Karner E, Delazer M (2013) FAB-D: German version of the Frontal Assessment Battery. *J Neurol* **260**, 2066-2072.

[26] Chandra SR, Issac TG, Abbas MM (2015) Apraxias in neurodegenerative dementias. *Indian J Psychol Med* **37**, 42-47.

[27] Willis L, Behrens M, Mack W, Chui H (1998) Ideomotor apraxia in early Alzheimer's disease: Time and accuracy measures. *Brain Cogn* **38**, 220-233.

[28] Weiss PH, Kalbe E, Kessler J, Fink GR (2013) *Kölner Apraxie-Screening*. Hogrefe, Göttingen.

[29] Power E, Code C, Croot K, Sheard C, Gonzalez Rothi LJ (2010) Florida Apraxia Battery-Extended and Revised Sydney (FABERS): Design, description, and a healthy control sample. *J Clin Exp Neuropsychol* **32**, 1-18.

[30] Bizzozero I, Costato D, Sala SD, Papagno C, Spinnler H, Venneri A (2000) Upper and lower face apraxia: Role of the right hemisphere. *Brain* **123**(Pt 1), 2213-2230.

[31] Rousseaux M, Rénier J, Anicet L, Pasquier F, Mackowiak-Cordoliani MA (2012) Gesture comprehension, knowledge and production in Alzheimer's disease. *Eur J Neurol* **19**, 1037-1044.

[32] Rothi L, Ochipa C, Heilman K (1991) A cognitive neuropsychological model of limb praxis. *Cogn Neuropsychol* **8**, 443-458.

[33] Dumont C, Ska B, Joanette Y (2000) Conceptual apraxia and semantic memory deficit in Alzheimer's disease: Two sides of the same coin? *J Int Neuropsychol Soc* **6**, 693-703.

[34] Goldenberg G, Karnath H-O (2006) The neural basis of imitation is body part specific. *J Neurosci* **26**, 6282-6287.

[35] Capone JG, Sala S, Della, Spinnler H, Venneri A (2003) Upper and lower face and ideomotor apraxia in patients with Alzheimer's Disease. *Behav Neurol* **14**, 1-8.

[36] Cera ML, Ortiz KZ, Bertolucci PHF, Minett TSC (2013) Speech and orofacial apraxias in Alzheimer's disease. *Int Psychogeriatrics* **25**, 1679-1685.

[37] Crutch S, Rossor M, Warrington E (2007) The quantitative assessment of apraxic deficits in Alzheimer's disease. *Cortex* **43**, 976-986.

[38] Chare L, Hodges JR, Leyton CE, McGinley C, Tan RH, Kril JJ, Halliday GM (2014) New criteria for frontotemporal dementia syndromes: Clinical and pathological diagnostic implications. *J Neurol Neurosurg Psychiatry* **85**, 865-870.

[39] Parakh R, Roy E, Koo E, Black S (2004) Pantomime and imitation of limb gestures in relation to the severity of Alzheimer's disease. *Brain Cogn* **55**, 272-274.

[40] Derouesné C, Lagha-Pierucci S (2000) Apraxic disturbances in patients with mild to moderate Alzheimer's disease. *Neuropsychologia* **38**, 1760-1769.

[41] Buxbaum LJ, Shapiro AD, Coslett HB (2014) Critical brain regions for tool-related and imitative actions: A componential analysis. *Brain* **137**, 1971-1985.

[42] Hoeren M, Kümmerer D, Bormann T, Beume L, Ludwig VM, Vry M-S, Mader I, Rijntjes M, Kaller CP, Weiller C (2014) Neural bases of imitation and pantomime in acute stroke patients: Distinct streams for praxis. *Brain* **137**, 2796-2810.

[43] Falchook AD, Mosquera DM, Finney GR, Williamson JB, Heilman KM (2012) The relationship between semantic knowledge and conceptual apraxia in Alzheimer disease. *Cogn Behav Neurol* **25**, 167-174.

[44] Hodges JR, Bozeat S, Lambon Ralph MA, Patterson K, Spatt J (2000) The role of conceptual knowledge in object use. Evidence from semantic dementia. *Brain* **123**, 1913-1925.

[45] Corbett F, Jefferies E, Burns A, Ralph MA (2012) Unpicking the semantic impairment in Alzheimer's disease: Qualitative changes with disease severity. *Behav Neurol* **25**, 23-34.

[46] Bertoux M, Volle E, Funkiewiez A, de Souza LC, Leclercq D, Dubois B (2012) Social cognition and emotional assessment (SEA) is a marker of medial and orbital frontal functions: A voxel-based morphometry study in behavioral variant of frontotemporal degeneration. *J Int Neuropsychol Soc* **18**, 972-985.

[47] Bora E, Walterfang M, Velakoulis D (2015) Theory of mind in behavioural-variant frontotemporal dementia and Alzheimer's disease: A meta-analysis. *J Neurol Neurosurg Psychiatry* **86**, 714-719.

[48] Elamin M, Pender N, Hardiman O, Abrahams S (2012) Social cognition in neurodegenerative disorders: A systematic review. *J Neurol Neurosurg Psychiatry* **83**, 1071-1079.
[49] Kumfor F, Piguet O (2012) Disturbance of emotion processing in frontotemporal dementia: A synthesis of cognitive and neuroimaging findings. *Neuropsychol Rev* **22**, 280-297.
[50] Bertoux M, de Souza L, Sarazin M, Funkiewiez A, Dubois B, Hornberger M (2014) How preserved is emotion recognition in Alzheimer disease compared with behavioral variant frontotemporal dementia? *Alzheimer Dis Assoc Disord* **29**, 154-157.
[51] Buxbaum LJ, Kalénine S (2010) Action knowledge, visuomotor activation, and embodiment in the two action systems. *Ann N Y Acad Sci* **1191**, 201-218.
[52] Ng ASL, Rademakers R, Miller BL (2014) Frontotemporal dementia: A bridge between dementia and neuromuscular disease. *Ann N Y Acad Sci* **1338**, 71-93.
[53] Cerami C, Marcone a, Crespi C, Iannaccone S, Marangoni C, Dodich A, Giusti MC, Zamboni M, Golzi V, Cappa SF (2015) Motor neuron dysfunctions in the frontotemporal lobar degeneration spectrum: A clinical and neurophysiological study. *J Neurol Sci* **351**, 72-77.
[54] Devenney E, Vucic S, Hodges JR, Kiernan MC (2015) Motor neuron disease-frontotemporal dementia: A clinical continuum. *Expert Rev Neurother* **15**, 509-522.
[55] Lobo PP, Pinto S, Rocha L, Reimão S, de Carvalho M (2013) Orofacial apraxia in motor neuron disease. *Case Rep Neurol* **5**, 47-51.
[56] Maeda K, Ogawa N, Idehara R, Shiraishi T, Tatsumi H (2013) Amyotrophic lateral sclerosis presenting with apraxia of speech. *J Neurol* **260**, 1667-1669.
[57] Duffy JR, Peach RK, Strand EA (2007) Progressive apraxia of speech as a sign of motor neuron disease. *Am J Speech-Language Pathol* **16**, 198-208.
[58] Van der Hulst E-J, Bak TH, Abrahams S (2014) Impaired affective and cognitive theory of mind and behavioural change in amyotrophic lateral sclerosis. *J Neurol Neurosurg Psychiatry*, doi: 10.1136/jnnp-2014-309290
[59] Sedda A (2014) Disorders of emotional processing in amyotrophic lateral sclerosis. *Curr Opin Neurol* **27**, 659-665.
[60] Hornberger M, Piguet O (2012) Episodic memory in frontotemporal dementia: A critical review. *Brain* **135**, 678-692.
[61] Graham A, Davies R, Xuereb J, Halliday G, Kril J, Creasey H, Graham K, Hodges J (2005) Pathologically proven frontotemporal dementia presenting with severe amnesia. *Brain* **128**, 597-605.
[62] Pleizier CM, van der Vlies AE, Koedam E, Koene T, Barkhof F, van der Flier WM, Scheltens P, Pijnenburg Y (2012) Episodic memory and the medial temporal lobe: Not all it seems. Evidence from the temporal variants of frontotemporal dementia. *J Neurol Neurosurg Psychiatry* **83**, 1145-1148.
[63] Possin KL, Feigenbaum D, Rankin KP, Smith GE, Boxer AL, Wood K, Hanna SM, Miller BL, Kramer JH (2013) Dissociable executive functions in behavioral variant frontotemporal and Alzheimer dementias. *Neurology* **80**, 2180-2185.
[64] Bertoux M, Funkiewiez A, O'Callaghan C, Dubois B, Hornberger M (2012) Sensitivity and specificity of ventromedial prefrontal cortex tests in behavioral variant frontotemporal dementia. *Alzheimers Dement* **9**, S84-S94.
[65] Buhl C, Stokholm J, Gade A (2013) Clinical utility of short social cognitive tests in early differentiation of behavioral variant frontotemporal dementia from Alzheimer's disease. *Dement Geriatr Cogn Disord* **3**, 376-385.
[66] Pasquier F, Richard F, Lebert F (2004) Natural history of frontotemporal dementia: Comparison with Alzheimer's disease. *Dement Geriatr Cogn Disord* **17**, 253-257.
[67] Rodrigues Cavalcante K, Caramelli P (2009) Evaluation of the performance of normal elderly in a limb praxis protocol: Influence of age, gender, and education. *J Int Neuropsychol Soc* **15**, 618-622.