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Authors
Freedman, Morris
Binns, Malcolm A
Black, Sandra E
et al.

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Object Alternation:

A Novel Probe of Medial Frontal Function in Frontotemporal Dementia

Morris Freedman, MD, FRCPC[*,†,‡], **Malcolm A. Binns, PhD**[†,§], **Sandra E. Black, MD, FRCPC**[†,‡,‖,¶], **Brian Levine, PhD**[†,‡,#], **Bruce L. Miller, MD**[**], **Joel Ramirez, MA**[‖], **Gregory M. Szilagyi, BScH**[‖], **Christopher J. M. Scott, BScH**[‖], **Alicia A. McNeely, BAH**[‖], and **Donald T. Stuss, PhD**[†,‡,#,††]

[*]Department of Medicine, Division of Neurology, Baycrest and Mt Sinai Hospital

[†]Rotman Research Institute, Baycrest

[§]Dalla Lana School of Public Health

[#]Department of Psychology, University of Toronto

[‡]Department of Medicine (Neurology), University of Toronto

[‖]LC Campbell Cognitive Neurology Research Unit, Brain Sciences Research Program, Sunnybrook Research Institute

[¶]Department of Medicine (Neurology), Sunnybrook Health Sciences Centre

[††]Ontario Brain Institute, Toronto, ON, Canada

[**]Department of Neurology, University of California, San Francisco, CA

Abstract

We studied behavioral variant frontotemporal dementia (bvFTD) using object alternation (OA) as a novel probe of cognition. This task was adopted from animal models and is sensitive to ventrolateral-orbitofrontal and medial frontal function in humans. OA was administered to bvFTD patients, normal controls, and a dementia control group with Alzheimer disease (AD). Two other frontal lobe measures adopted from animal models were administered: delayed response (DR) and delayed alternation (DA). Brain volumes were measured using the semiautomatic brain region extraction method. Compared with the normal controls, bvFTD patients were significantly impaired on OA and DR. For OA and DR, sensitivities and specificities were 100% and 51.5% (cutoff = 22.5 errors) and 9.5% and 98% (cutoff = 1.5 errors), respectively. Negative predictive value (NPV) for OA was 100% at all prevalence rates. Comparing AD with bvFTD, there were no significant differences on OA, DR, or DA. Nevertheless, positive predictive value (PPV) and NPV were good at all prevalence rates for OA (cutoff = 36.5 errors) and DA (cutoff = 6 errors); PPV

Reprints: Morris Freedman, MD, FRCPC, Rotman Research Institute, Baycrest, Brain Health Complex, Rm 656, 3560 Bathurst Street, Toronto, ON, Canada M6A 2E1 (mfreedman@baycrest.org).

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was good for DR (cutoff = 9 errors). Error scores above cutoffs favored diagnosis of AD. Performance on OA was significantly related to medial frontal gray matter atrophy. OA, together with DR and DA, may facilitate assessment of bvFTD as a novel probe of medial frontal function.

Keywords

object alternation task; medial frontal region; frontotemporal dementia; delayed response task; delayed alternation task

Behavioral variant frontotemporal dementia (bvFTD) is an important cause of social cognitive decline, especially in patients under the age of 70 years.[1] However, diagnosis can be challenging.[2] Although mutations in the microtubule-associated protein tau, progranulin, and *C9ORF72* genes serve as biomarkers, these are absent in most cases.[3] In addition, neuroimaging is not always helpful in early stages.[4] Moreover, patients may initially perform well on standard neuropsychological tests as these are sensitive primarily to dorsolateral frontal system function, whereas orbitofrontal or ventromedial frontal dysfunction may underlie social cognitive deficits that are the clinical hallmark of bvFTD.[5,6]

There is a need for the development of cognitive measures that are sensitive to pathologic changes in bvFTD and that can easily be applied in clinical settings. One approach has been to focus on tests of social cognitive function, such as Theory of Mind, that are associated with medial frontal,[7,8] including medial polar,[8,9] and orbitofrontal function.[7,10] These are sensitive to deficits in bvFTD[11] and can be incorporated into a neuropsychological assessment battery.[12] A complementary strategy is to identify neurobehavioral probes, outside the social cognitive realm, that are mediated by orbitofrontal and medial frontal systems. These “nonsocial cognitive” probes may offer new insights into the neuropsychological and functional anatomic mechanisms underlying bvFTD. They may also serve to define improved behavioral measures for diagnosis, especially if social and “nonsocial” cognitive functions in bvFTD are mediated by separate orbitofrontal and medial frontal neuronal networks.

The object alternation (OA) task provides a measure of ability to shift set and working memory for objects and is one of the few measures of nonsocial cognitive function that are sensitive to orbitofrontal and medial frontal damage in humans. This task was adopted from non-human animal models[13] and was validated as a measure of ventrolateral-orbitofrontal and medial frontal function in humans with focal brain lesions.[14]

We examined OA as a novel probe of cognitive function in bvFTD. Although experimental paradigms adopted from non-human animal models have been used to study bvFTD,[5] this is the first study to examine OA as a measure of cognitive function in this disorder.

We hypothesized that performance on OA would be highly sensitive to deficits in bvFTD. Two other measures of frontal function adopted from animal models, delayed alternation (DA) and delayed response (DR), were administered for comparison. These tasks are sensitive to frontal lesions in humans[14,15] but differ from OA in key aspects. DA and DR

require spatial working memory and are affected by dorsolateral frontal lesions. DA also involves ability to shift set and is sensitive to orbitofrontal damage.[16]

METHODS

Participants

The study was approved by the Baycrest Research Ethics Board. Informed consent was obtained from all subjects or substitute decision makers. There were 164 subjects comprising 3 groups: 21 patients with bvFTD[17] and 2 control groups composed of patients with dementia due to probable Alzheimer disease (AD)[18] (n = 42) and normal subjects (n = 101) (Table 1). Normal subjects were studied to determine whether patients with bvFTD were impaired on the experimental tasks adopted from animal models. Patients with AD were included to compare bvFTD with another form of dementia. One bvFTD patient developed motor neuron disease but had no obvious signs of this when tested. Four bvFTD patients, one of whom had a microtubule-associated protein tau mutation and 1 AD patient, had autopsy-confirmed diagnoses. In those without autopsy, longitudinal follow-up was at least 1 year in 94% of bvFTD patients and 100% in AD. In addition, 47% of patients with bvFTD and 71% with AD were followed for at least 4 years. This supported the accuracy of clinical diagnosis.

Apparatus and Procedures

As previously described, OA was administered in a modified version of the Wisconsin General Test Apparatus adapted for use with human subjects (see Figure, Supplemental Digital Content 1 http://links.lww.com/WAD/A58, which illustrates the apparatus).[14] The investigator and subject sat facing each other separated by a wooden frame. A curtain could be raised to reveal a stimulus board containing 2 reinforcement wells, each covered by a different 3-dimensional object mounted on a square black plaque. The objects differed in shape and color and remained the same throughout testing. The task was to learn that the object under which a penny was located was being alternated after each correct response. Objects were placed on the left or right according to a modified random schedule. A correction procedure was used so that a penny remained under 1 object (although not necessarily on the same side) until the subject made a correct response. A trial was completed after the subject found the penny under the target object. If the subject failed to find the penny after 10 consecutive responses on a single trial, however, the trial was ended and the penny placed under the other object. Interval between the stimulus presentations was approximately 5 seconds. As described previously,[14] the test ended after 12 consecutive correct responses or 50 trials. Outcome measure was number of errors.

DA and DR were administered as described[14] and were carried out using the same apparatus as for OA. However, the wells were covered by identical square black stimulus plaques without mounted objects (see Figure, Supplemental Digital Content 1 http://links.lww.com/WAD/A58, which illustrates the apparatus).

The procedure for DA was the same as that for OA except that the subject's task was to learn that the side on which the penny was located was being alternated after each correct response.

For DR, all subjects completed problems with 0-, 10-, and 30-second delays. A subset completed a 60-second delay condition. The investigator placed a penny underneath 1 of the 2 plaques in full view of the subject, according to a modified random schedule. Subjects were required to find the penny after a delay. On each condition, testing continued until the subject reached learning criterion of 9 correct responses in a block of 10 trials or completed 40 trials. Outcome measure was number of errors to reach criterion over all delay intervals, excluding criteria trials. Thus, if there were 9 correct responses in a block of 10 trials, learning criterion was reached at the given delay, and the error score on that block was counted as 0. Therefore, for a patient who made errors, the minimum number of errors per block of 10 trials was 2.

Neuroimaging

MRI-derived gray and white matter volumes were obtained using the semiautomatic brain region extraction (SABRE) method. This generates individualized volumetrics for each subject, segmenting the brain into multiple tissue classes[19] and parcellating the brain into 26 regions (13 left and 13 right) on the basis of a combination of 6 user-defined tracings and 7 landmarks.[20,21] Using a hypothesis-driven approach to determine the relation between brain atrophy and performance on OA, we defined regions-of-interest (ROIs) as SABRE regions contributing to the Brodmann areas previously associated with performance deficits on OA: areas 10, 24, 32, 47, and possibly 11.[14] To determine this, the Brodmann areas (included with the MRIcroN software)[22] were originally labeled on the Colin27 template[23] and transformed, along with the individual subjects' SABRE parcellations, to the ICBM 2009a "Nonlinear Symmetric" T1 template,[24,25] using the coregistration program Advanced Normalization Tools.[26] The intersections of the Brodmann and SABRE regions were then calculated. To exclude misallocation of small brain volumes to the contralateral hemisphere due to natural curvature of the brain, and the fact that SABRE processing necessitates choosing 1 representative mid-sagittal slice, there was an added criterion that each ROI contributes to > 5.9% volume of at least 1 relevant Brodmann area in at least 5% of cases. The volume criterion was set to exclude the largest misallocation error observed in our patient sample.

There were 7 SABRE ROIs: 5 frontal (medial superior, medial middle, medial ventral, lateral middle, and lateral ventral) and 2 parietal (superior and inferior). These were collapsed into 7 bilateral ROIs for analysis. Brain volumes were corrected for head size.

MRI scans were available for a subset of subjects: bvFTD (n = 12) and AD (n = 12).

Analysis

Performance on each task was measured by the count of errors. This outcome measure is non-negative and is often positively skewed. Therefore, non-Gaussian methods of analysis were used. To describe the magnitude of the differences between the bvFTD group and each of the normal control and AD groups, a nonparametric effect size estimate was calculated

using Cliff 's *d*.[27] To perform hypothesis tests comparing the bvFTD group to each of the normal control and AD groups, Poisson regression (with Pearson dispersion scaling) was used for DR and DA for which errors were relatively few. A general linear model was used on the square root transformation for OA on which errors were more frequent. In both cases, the group membership was identified by a pair of dummy variables—one indicated a normal control and the other indicated a patient with AD—which allowed comparison between each of these groups and bvFTD. Age, education, and MMSE were included as covariates. Hypothesis tests were conducted at an α-level of 0.05. No adjustment for multiple comparisons was made as the a priori goal was to characterize performance of patients with bvFTD through comparison with each of the normal control and AD groups using the 3 outcome measures selected to isolate specific cognitive processes and their neural substrates.

Receiver operating characteristic curves were generated to describe the ability of the task to differentiate bvFTD from normal controls and AD across a range of cutoff values. Optimal cutoff values are reported. We define the optimal cutoff as the midpoint between the threshold value, which maximizes the sum of sensitivity and specificity, and the next smallest observed value. As we could not locate the true border between a positive and negative test within outcome intervals that contain no observed values, we selected the midpoint of the interval as an estimate of the border's location. As indicated above, the minimum nonzero error count for DR is 2. As scores of 0 or 1 are considered error free and scores of ≥ 2 are considered error positive, the midpoint between the error-free scores and the lowest error-positive score is 1.5. Therefore, the midpoint between 0 and 2 is considered to be 1.5 for this task.

To examine the association between volume in 7 pre-specified brain regions and performance on OA, we fit a general linear model to the square root transformation of the OA score. Explanatory measures were the bilateral volume in each of the 7 regions. Years of education and MMSE score were entered as covariates. We also ran simple regression models for each of the brain regions separately to examine the effect of collinearity between the brain regions.

RESULTS

There were significant group differences in age ($F_{2,161}$ = 15.39, P < 0.0001), education ($F_{2,161}$ = 3.53, P = 0.03), and MMSE score ($F_{2,161}$ = 104.96, P < 0.0001) (Table 1). Range of MMSE scores were: bvFTD (22 to 30), AD (14 to 30), and normal controls (24 to 30). Only 2 of 21 patients with bvFTD had MMSE scores < 24.

Figure 1 summarizes group performance on OA, DR, and DA.

OA

Patients with bvFTD were impaired on OA compared with normal controls ($F_{1,158}$ = 9.45, P = 0.003; Cliff 's d = 0.29). There was no significant difference between bvFTD and AD ($F_{1,158}$ = 0.02, P = 0.90; Cliff 's d = 0.44).

DR and DA

All subjects were administered DR with 0-, 10-, and 30-second delays. Only 2 normal controls made errors on DR. Patients with bvFTD were impaired on DR compared with normal controls ($\chi^2_1 = 5.35$, $P = 0.02$; Cliff 's $d = 0.12$). There was no significant difference between the bvFTD and AD patients ($\chi^2_1 = 0.04$, $P = 0.84$; Cliff 's $d = 0.18$).

A subset of patients with bvFTD (n = 15) and AD (n = 38), and all normal controls, completed a 60-second delay on DR. Two patients with bvFTD, 1 with AD, and 1 normal control made errors only at the 60-second delay.

Patients with bvFTD were not significantly impaired on DA compared with normal controls ($\chi^2_1 = 0.01$, $P = 0.90$; Cliff 's $d = -0.13$). There was no significant difference on DA between the patients with bvFTD and AD ($\chi^2_1 = 1.35$, $P = 0.25$; Cliff 's $d = 0.51$).

Psychometric Properties

Figure 2 shows receiver operating characteristic curves for OA, DR, and DA. For OA, optimized classification of bvFTD from normal controls was at a cutoff of 22.5 errors with sensitivity and specificity of 100% and 51.5%, respectively. Comparing AD with bvFTD, the mean error score was higher in AD. Maximizing the classification between AD and bvFTD, an error score > 36.5 yielded a sensitivity of 73.8% for identifying patients with AD; specificity was 76.2%.

For DR, as all but 2 of the 101 normal controls made no errors, we selected a cutoff of 1.5 errors for the classification of bvFTD patients from normal controls to high-light that making any errors on DR strongly suggests that a subject is not normal (sensitivity = 9.5%; specificity = 98.0%). For classifying patients with AD from bvFTD, cutoff scores of 1.5 and 9 maximized accuracy about equally. Sensitivities for identifying patients with AD at error scores greater than 1.5 and 9 were 28.6% and 23.8%, respectively, and specificities for identifying patients with bvFTD were 90.5% and 95.2%, respectively.

For DA, optimal cutoff score for classification of AD from bvFTD was 6 (sensitivity = 73.8%; specificity = 71.4%). Distribution of performance on DA was similar between bvFTD patients and normal controls. Thus, no cutoff was reported.

Positive and negative predictive values (PPV and NPV) using cutoff scores identified above for OA, DR, and DA were evaluated across a range of prevalence levels. When comparing bvFTD to normal controls, NPV for OA reflected added value relative to pretest probability, whereas PPV reflected added value for DR (see Figure, Supplemental Digital Content 2 http://links.lww.com/WAD/A59, which shows PPV and NPV).

For AD versus bvFTD, there were good PPV and NPV for each of OA and DA. For DR, there was good PPV (see Figure, Supplemental Digital Content 2 http://links.lww.com/WAD/A59).

In all autopsy-confirmed cases, error scores on OA supported the diagnosis in both bvFTD and AD. The 4 bvFTD patients with autopsy confirmation had scores on OA, DA, and DR below the bvFTD versus AD cutoffs of 36.5, 6, and 1.5 errors. Thus, performance profiles across all 3 tasks were more in keeping with bvFTD than AD. The patient with autopsy-confirmed AD had an OA score above the bvFTD versus AD cutoff of 36.5 errors, although error scores on DA and DR were below the cutoff. Thus, the performance profile on OA was more in keeping with AD than bvFTD. However, it is important to stress that the number of autopsy-confirmed cases was small and thus the relation between performance on OA, DA, and DR and diagnosis in these cases can only be considered as an interesting observation.

Performance on OA and Time After Onset

All bvFTD patients were impaired on OA at a cutoff of 22.5 errors. The patient with earliest time after onset of 1 year exceeded the error criterion. The association between the performance on OA and the time after onset seems not to be linear. The most severely impaired patient was 2 years after onset (see Figure, Supplemental Digital Content 3 http://links.lww.com/WAD/A60, which shows performance scores of patients on OA in relation to time after onset).

Focal Brain Volume and Performance on OA

A general linear model was used to test the relation between ROI volumes and the performance on OA in bvFTD and AD. MMSE and education were included as covariates due to a significant group difference in MMSE score ($t_{13} = -3.01$, $P = 0.0094$) and a significant correlation between education and the performance on OA in AD ($P = 0.0031$, Pearson $r = -0.77$). There was also a borderline significant relation between performance on OA and education in bvFTD ($P = 0.0682$, Pearson $r = -0.54$). With all 7 ROIs in the model, bilateral medial superior frontal gray matter volume was associated with performance on OA ($F_{1,14} = 14.49$, $P = 0.0019$). With only medial superior frontal volume, MMSE, and education in the model, volume remained significantly associated with OA ($F_{1,20} = 16.03$, $P = 0.0007$).

Table 2 shows parameter estimates for each ROI in relation to performance on OA for the models including all regions or including each region separately. Parameter estimate for medial superior frontal region was the largest and indicated that reduced volume was associated with higher error scores on OA. Moreover, the parameter estimate for medial superior frontal region was similar whether all ROIs were included in the model or not. This suggests that this effect was not attributable to atrophy in the other ROIs.

We examined the relation between bilateral medial superior frontal gray matter volume and performance on OA in bvFTD and AD separately using a general linear model with education as a covariate. Volume was significantly associated with OA in bvFTD ($F_{1,9} = 5.52$, $P = 0.04$, $\beta = -3.19$) and AD ($F_{1,9} = 7.30$, $P = 0.02$, $\beta = -2.06$). Parameter estimates were similar to the value in the model with bvFTD and AD patients pooled and all 7 ROIs in the model.

For bvFTD and AD combined, the relation between performance on OA and white matter volume was not significant for any ROI with all 7 regions in the model ($P > 0.14$ for all regions) or with each of the 7 regions in separate models.

Figure 3 shows the contribution of medial superior frontal region to the Brodmann areas associated with performance deficits on OA, that is, areas 24 and 32 in the medial frontal lobe.

DISCUSSION

Patients with bvFTD were significantly impaired on OA, a measure of ability to shift set and working memory for objects. The magnitude of effect was characterized by moderate separation of observed distributions between bvFTD and controls.

It has been well established that OA is sensitive to ventrolateral-orbitofrontal lesions in non-human primates.[28,29] This finding was confirmed in humans with focal brain lesions.[14] The same study showed that OA was also sensitive to medial frontal lesions, thus implicating ventrolateral-orbitofrontal and medial frontal regions in the mechanisms underlying deficits on OA in humans. The neuroanatomic regions involved included the Brodmann areas 10, 24, 32, 47, and possibly 11.

Performance on OA in bvFTD and AD was significantly related to atrophy in medial superior frontal region, a SABRE region contributing to the Brodmann areas 24 and 32 in the medial frontal lobe. Functional neuroimaging and quantified MRI studies support a role for ventrolateral-orbitofrontal and medial frontal systems in mechanisms underlying human performance on OA,[30–34] although other areas may also be involved.

The OA task may be tapping into deficits in bvFTD resulting from early neuropathologic lesions in medial frontal regions[35] to which standard neuropsychological tests are relatively insensitive.[6] This suggests that OA may be useful for early detection of cognitive abnormalities in this disorder. In support of this concept, we examined patients with time after onset ranging from 1 to 6 years. There was no indication that abnormal performance, based on a cutoff of 22.5 errors, is less likely at an early time after onset. However, caution must be exerted in determining the utility of OA for early diagnosis as our study was not designed for this purpose. Moreover, medial frontal regions are not always the earliest affected areas in bvFTD.[36] Thus, tests of medial frontal function will not detect earliest change in all bvFTD patients.

Patients with AD also performed poorly on OA. This may at least partially reflect neuropathology in the medial superior frontal region. This is supported by the significant relation between performance on OA and medial superior frontal atrophy in AD. However, further studies are needed to address the relation between the performance on OA and the localization of brain damage in AD, especially with respect to more posterior lesions.

There were significant deficits on DR in bvFTD compared with normal controls. Performance on DR is impaired after bilateral dorsolateral frontal lesions in monkeys.[16] Freedman et al[14] confirmed earlier findings[15] that performance on this task is impaired after

bilateral frontal lobe lesions in humans. However, no relation was found between impaired performance on DR and specific frontal lesion sites. Despite the literature on DR tasks in humans,[14,33,37–40] the functional anatomic mechanisms underlying deficits on spatial DR tasks in patients with bvFTD remain unclear.

Patients with bvFTD were not impaired on DA despite the literature suggesting involvement of orbitofrontal[14,16,31] and medial frontal[14] systems in performance on this task. However, this test may not have been sufficiently difficult for demonstrating deficits. For example, DA and OA both measure ability to shift set. However, on the basis of DA and OA scores in normal controls, OA seems to be more difficult as controls had equal opportunity to make errors on each test but did so in greater number on OA. This may account for impairment on OA with intact performance on DA. In addition, DA and DR measure spatial working memory. Longer delays on DR may account for deficits on this task with normal performance on DA. Studies with longer intertrial intervals on DA may clarify whether performance on this measure is affected in bvFTD.

We examined psychometric properties of OA in bvFTD compared with normal controls. OA at a cutoff of 22.5 errors can achieve sensitivity of 100%. However, there is lower specificity at 51.5%. Although this specificity limits the value of OA for ruling in a diagnosis of bvFTD due to false positives, the high sensitivity indicates that an error score < 22.5 argues strongly against a diagnosis of bvFTD. Although comparing bvFTD patients with normal subjects is important to establish that OA is sensitive to deficits in bvFTD, the challenge in clinical settings is differentiation of patients with bvFTD from other dementias.

Although there was no significant group difference between AD and bvFTD in performance on OA, performance was worse in AD. Despite the absence of a significant group difference on OA when comparing bvFTD to AD, it is still valuable to identify a cutoff score that maximizes classification between AD and bvFTD. In this regard, sensitivity (73.8%) and specificity (76.2%) were relatively high at a cutoff of 36.5 errors. Therefore, an error score of > 36.5 suggests that AD is more likely than bvFTD. In contrast, an error score of < 36.5 is more in keeping with bvFTD. Further studies are needed to examine diagnostic value of the OA task when comparing bvFTD with disorders other than AD.

In addition to relatively good psychometric properties of OA when comparing AD with bvFTD, there is also relatively high sensitivity of 73.8% and specificity of 71.4% on DA at a cutoff of 6 errors. Greater than 6 errors on DA suggests that AD is more likely than bvFTD.

PPV and NPV provide information about the added diagnostic value of administering a test compared with pretest probability of a given diagnosis. Diagnosis of bvFTD is highly unlikely if error score is < 22.5. At this cutoff, NPV is substantially increased relative to pretest probability in high prevalence settings. In contrast, PPV is only slightly increased. Thus, the greater added value of administering OA may be to help rule out bvFTD, especially in samples with relatively high prevalence of this disorder. An example of such a setting is a specialized memory clinic where prevalence of bvFTD is expected to be high in the subset of patients suspected of having this disorder. The assumption is that experts in these clinics will have a high level of diagnostic accuracy such that most patients suspected

of having bvFTD will likely have this disorder. In contrast to OA, good performance on standard neuropsychological tests is not very helpful in ruling out bvFTD because these tests are relatively insensitive to bvFTD.[6]

When comparing AD with bvFTD, there is an added value of administering OA for differentiating these disorders in most clinical settings at a cutoff of 36.5 errors. The same applies to the DA task at a cutoff of 6 errors.

The major added benefit of administering DR, which is relatively insensitive to bvFTD, is to help rule out that a patient is normal. In contrast, errorless performance on DR provides little added information to help rule out bvFTD. In addition, an error score > 1.5 (or 9) has a specificity of 90.5% (or 95.2%) and favors a diagnosis of AD rather than bvFTD.

The psychometric properties of the tasks administered were based upon optimal cutoff scores selected to optimize classification of the groups studied. These scores were based upon performance of the subjects in the current study. It will be important to validate these cutoffs in independent samples.

In conclusion, OA is one of the few validated neuropsychological measures of orbitofrontal and medial frontal function in humans. This study suggests that OA is highly sensitive to cognitive deficits in bvFTD due to early involvement of medial frontal cortex. Further studies using OA, combined with other measures that may tap into orbitofrontal and medial frontal systems, such as tests of social cognition, may serve to better define the neuropsychological mechanisms underlying the cognitive dysfunction in bvFTD and may serve to enhance diagnosis using clinical measures.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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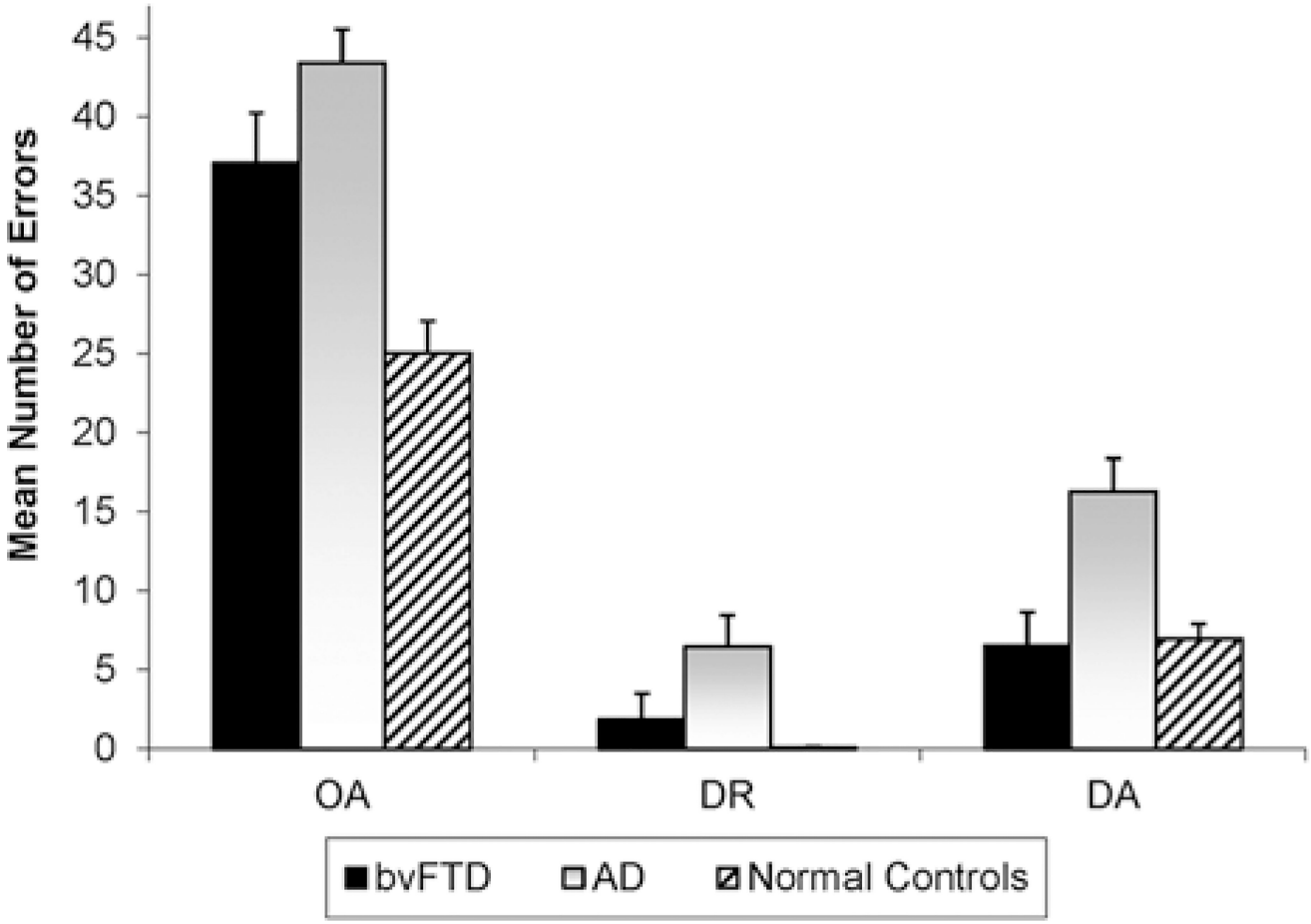

FIGURE 1.

Performance scores on OA, DR, and DA. Error bars represent SE. Number of subjects who made errors on DR over all delay intervals (0, 10, and 30 s): bvFTD (n = 2/21), AD (n = 12/42), and normal controls (n = 2/101). AD indicates Alzheimer disease; bvFTD, behavioral variant frontotemporal dementia; DA, delayed alternation; DR, delayed response; OA, object alternation.

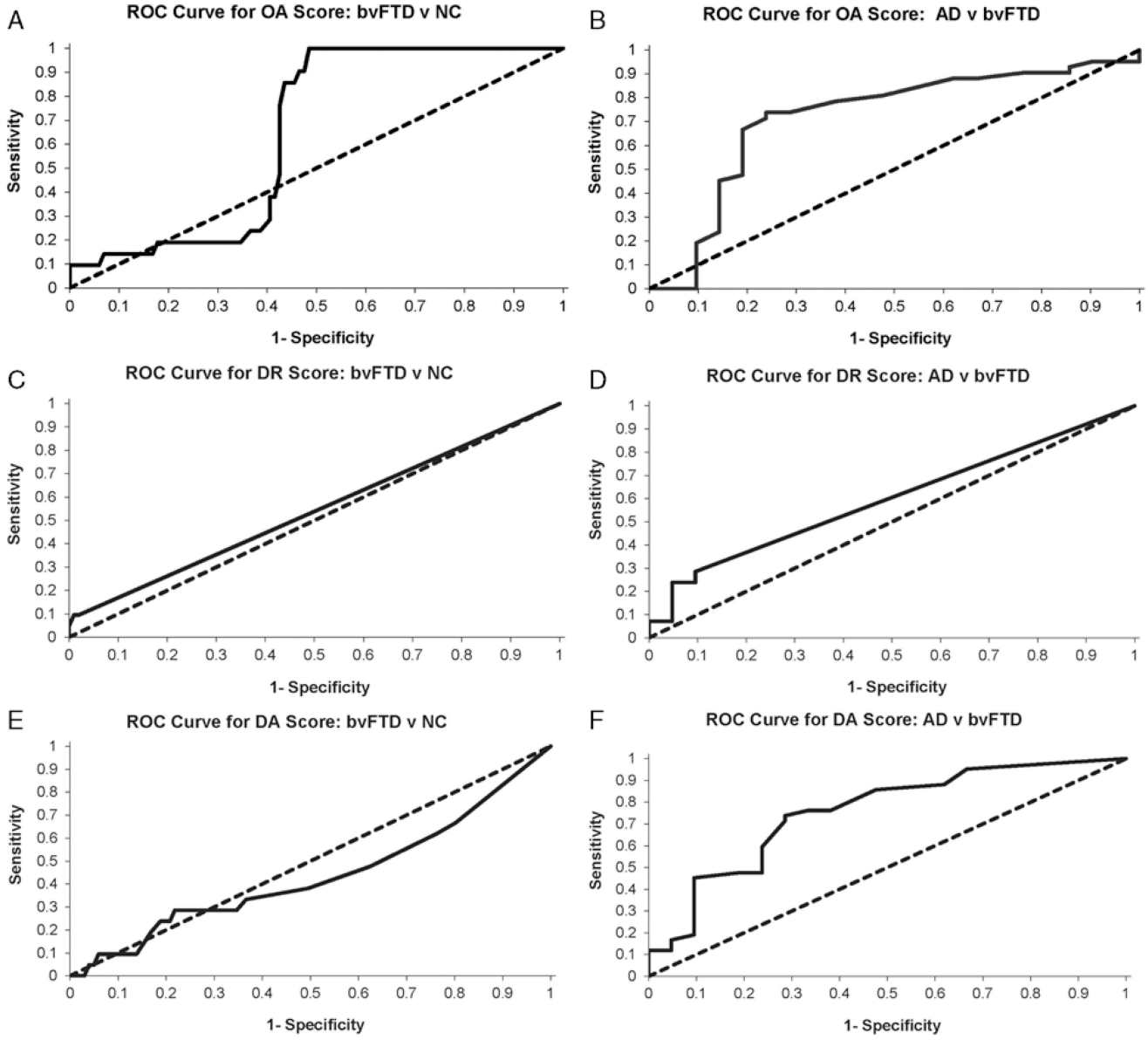

FIGURE 2.

Receiver operating characteristic curves (solid line) for OA (A, B), DR (C, D), and DA (E, F) tasks. Diagonal (dashed) line represents a hypothetical test that does not distinguish between the presence and absence of the disease. In the left side panels, the target is bvFTD, that is, sensitivity refers to the proportion of bvFTD patients scoring above each possible cutoff and 1-specificity refers to the proportion of NC scoring above a cutoff. In the right side panels, the target is AD. AD indicates Alzheimer disease; bvFTD, behavioral variant frontotemporal dementia; DA, delayed alternation; DR, delayed response; NC, normal controls; OA, object alternation.

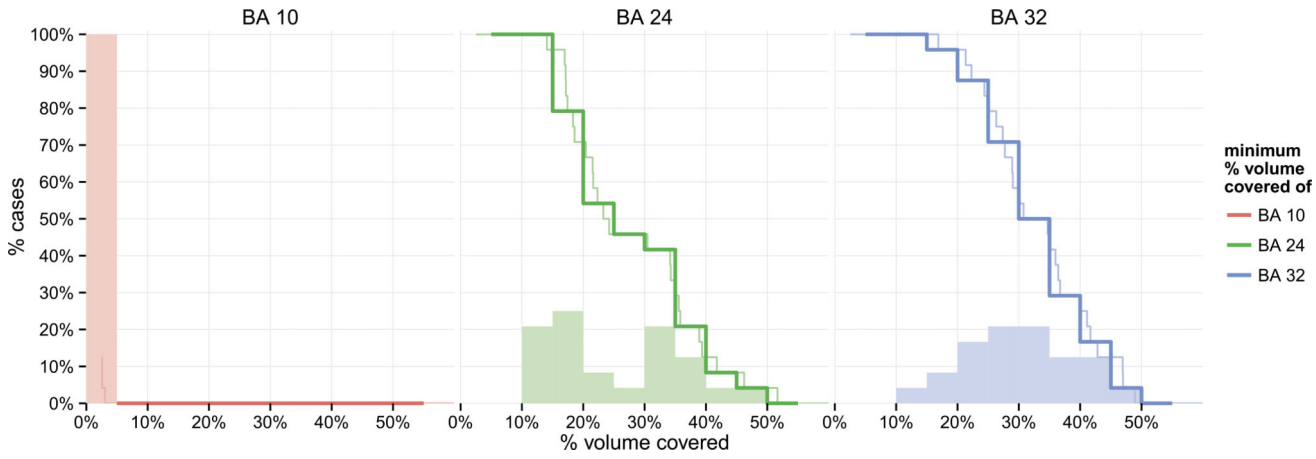

FIGURE 3.

Relative contributions of medial superior frontal (MSF) SABRE region to the Brodmann areas (BAs) (n = 24, both hemispheres). Histograms indicate percentage of cases at 5% intervals of coverage. Bold lines show the inverse cumulative proportions derived from the histogram bins corresponding to the equal or greater coverage at each threshold. Fine lines display the same inverse cumulative proportions at the actual data points. MSF was not considered to contribute to BA 10 because it did not meet reliability criterion of contributing to >5.9% of this area in either hemisphere in at least 5% of cases. BA 11 and 47 are not shown because MSF did not contribute at all to these areas.

TABLE 1

Subject Profiles

	bvFTD (n = 21)	AD (n = 42)	Normal Controls (n = 101)	Statistics	*P*
Sex (F/M)	9/12	23/19	64/37	$\chi^2_2 = 3.44$	0.1878
Age [mean (± SD)] (y)	60.0 (± 7.0)	73.7 (± 11.1)	65.7 (± 10.0)	$F = 15.39$	< 0.0001
Education [mean (± SD)] (y)	14.5 (± 3.8)	13.2 (± 4.1)	15.0 (± 3.4)	$F = 3.53$	0.0315
MMSE [mean (± SD)]	28.0 (± 2.2)	22.7 (± 4.0)	28.9 (± 1.2)	$F = 104.96$	< 0.0001

AD indicates Alzheimer disease; bvFTD, behavioral variant frontotemporal dementia; F, female; M, male; y, years.

TABLE 2

Parameter Estimates for Poisson Regression of Error Scores on Object Alternation

SABRE Region (Gray Matter)	Parameter Estimate (Full Model)	Parameter Estimate (Each Region in Separate Model)
MSF	− 3.22	− 2.28
MMF	1.28	0.01
MIF	0.62	1.04
LIF	− 0.02	1.05
LMF	0.92	− 0.44
SP	− 0.32	− 0.50
IP	0.02	− 0.13
Education *	− 0.15	—
MMSE *	− 0.18	—

* Education and MMSE not listed for regions analyzed separately because parameter estimate varied across models.

MSF indicates medial superior frontal; MMF, medial middle frontal; MIF, medial ventral frontal; LIF, lateral ventral frontal; LMF, lateral middle frontal; SP, superior parietal; IP, inferior parietal.