Title

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Journal

Alzheimer Disease & Associated Disorders, 37(2)

ISSN

0893-0341

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Publication Date

2023

DOI

10.1097/wad.0000000000000526

Peer reviewed

OPEN

Exploring Social Cognition Tests to Differentiate Frontotemporal Dementia from Depression

A Two-Step Pilot Study

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Abstract: Behavioral-variant frontotemporal dementia (bvFTD) is challenging to recognize, and often misdiagnosed as depression (DEP). Evidence suggests changes in social cognition (SoCog) precede general cognitive decline in bvFTD. Currently, there are no screening measures of social cognition. 17 bvFTD, 16 DEP, and 18 control participants underwent 6 SoCog tests measuring: emotion recognition; theory of mind; empathy; insight. We used χ^2, Wilcoxon rank sum, Kruskal-Wallis tests to compare groups, with decision tree analysis to identify items that best differentiated bvFTD from DEP. bvFTD performed significantly worse on all SoCog tasks compared with other groups. Decision tree analysis yielded a 5-item test with ROC area under the curve of 0.973 (95% CI: 0.928, 1.0) for differentiating bvFTD versus depression. These results suggest that it may be feasible to develop a screening measure of social cognition.

Key Words: social cognition, behavioral variant frontotemporal dementia, screening test, depression

(*Alzheimer Dis Assoc Disord* 2023;37:145–148)

Frontotemporal dementia (FTD) is a common cause of dementia in younger patients. Unfortunately, the condition is often misdiagnosed owing to overlap with depression and other common psychiatric illnesses.[1] The ability to distinguish FTD from depression is important given social, prognostic, and treatment consequences. The behavioral variant subtype of FTD (bvFTD) is characterized by symptoms including apathy; empathy loss; disinhibition; perseverative behaviors; alteration in diet or hygiene.[2] Although typical cognitive screening measures are frequently normal at early stages of illness, studies indicate that impaired social cognition is characteristic of bvFTD even in earliest stages.[3] This includes difficulties with emotion recognition;[3] loss of empathy;[4] lack of insight into their condition/deficits;[4,5] and deficits in theory of mind, or perspective-taking.[3–6] Screening measures of social cognition may be useful for identifying individuals with bvFTD and in particular, differentiating them from persons with depression.

The few available studies demonstrating social cognition differences between those with bvFTD and those with depression have used lengthy batteries not well suited for bedside use.[3] Screening questionnaires used as decision-support tools have also been investigated,[7] but do not incorporate patient performance. Exploring and developing a short, performance-based bedside screening instrument measuring social cognition would be a useful step to identify bvFTD in its earliest stages.

The goals of this study were twofold: (a) to confirm previous findings reporting differences in social cognition between patients with bvFTD and depression using an extensive test battery; (b) to explore whether bvFTD can be reliably differentiated from depression using a reduced set of test items.

METHODS

We designed a cross-sectional study comparing performance on tests of social cognition in participants with (a) bvFTD, (b) depression, and (c) controls with neither depression nor bvFTD. Following IRB approvals (from June 2015 through June 2018), participants and their study partners were recruited from the Clinic for Alzheimer Disease and Related Disorders and the Neuropsychiatry and Mood Disorder Clinics at the University of British Columbia (Vancouver, BC) and Geisinger (Danville, Pennsylvania), with additional recruitment for controls through those institutions' internal websites and through community volunteers.

Enrollment of Participants

Participants were ages 40 to 80; had visual and auditory acuity, and had ability to speak English adequate to complete testing. Exclusion criteria included previous history of neurologic or psychiatric disease, history of drug or alcohol abuse within the last 6 months. The bvFTD group met Rascovsky criteria[2] for probable bvFTD in mild to moderate stages (global score $= < 2$) based on CDR-FTLD[8] and Montreal Cognitive Assessment (MoCA) ≥ 13.[9] The Depression group met the Diagnostic and Statistical Manual of Mental Disorders Five[9] criteria for

Received for publication December 21, 2021; accepted June 30, 2022.
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Funding and support for this study was made possible by a postdoctoral fellowship award to MLL from the Association for Frontotemporal Degeneration.

The authors declare no conflicts of interest.
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DOI: 10.1097/WAD.0000000000000526

major depressive disorder, using the Mini International Neuropsychiatric Interview[9] if not previously diagnosed by a psychiatrist; have a Geriatric Depression Score[9] (GDS) score ≥ 9 at screening; and MoCA score of ≥ 19. Healthy controls had MoCA of ≥ 26 and GDS <9. Informants were required: an adult relative, friend, or care partner of the participant.

Study Procedures

Baseline demographics were obtained. Cognitive tests were administered to each participant to assess executive function: the Frontal Assessment Battery[3] and the Visual Verbal Test.[5] The Neuropsychiatric Inventory[4] was completed as part of the behavioral symptom assessment. These were followed by tests assessing social cognition.

Social Cognition Testing

We administered 6 tests measuring different dimensions of social cognition including: emotion recognition, theory of mind, predicting social consequences, empathy, and insight. The Penn Emotion Recognition Task (ER40)[10] was used to evaluate facial emotional recognition. Participants selected whether a face expressed happiness, sadness, anger, fear or was neutral. Three tasks for theory of mind were used: Reading the Mind in the Eyes (Eyes)[6] (photographs of people's eyes for which participants chose which of four word choices best describes what the person is thinking or feeling); Faux Pas[3] (vignettes assessing social faux-pas recognition and understanding); Irony and Second Order False beliefs[5] (vignettes assessing detection of irony or second order false beliefs, eg "John thinks that Mary thinks…"). Predicting social consequences was measured using the Cartoon Predictions task,[5] where participants chose the cartoon panel that was the most likely outcome of the scenario presented in the first panel. Empathy was measured from both participant and informant perspectives using the Interpersonal Reactivity Index[4] (IRI); a Likert-scale questionnaire that evaluates four domains of empathy: Perspective Taking, Emotional Concern, Fantasy, and Personal Distress. Insight was measured by taking the absolute difference between participant and informant ratings of the participant's empathy.

Statistical Methods

Descriptive statistics were calculated for all demographic and clinical variables. To avoid distributional assumptions, continuous variables were reported as median and interquartile ranges. Categorical variables were reported as percentage and frequency counts. Analysis was stratified by clinical group: bvFTD, depression, or control. χ^2 and Mann-Whitney U or Kruskal-Wallis tests were used to compare the diagnostic groups, without correction for multiple testing. Following the primary analyses, we undertook an exploratory decision tree analysis to evaluate whether a reduced item set could differentiate bvFTD from depression. R v4.0.3 (Vienna, Austria) was used for analyses.

RESULTS

Screening and Demographic Results

There were demographic differences in the groups (Table 1). The bvFTD group had more men and was older than the other groups. The control group was more educated than the other groups. The bvFTD group were more impaired on the MoCA, FAB, and VVT with higher scores on the NPI. The depressed group had higher self-ratings of depressive symptoms on the GDS.

Results of Social Cognition Testing

The bvFTD participants performed significantly worse on measures of social cognition (Table 2) including all theory of mind tests and emotion recognition for all expressions except for 'happy'. The bvFTD group self-rated their own empathy similarly to the depression and control groups; however, their informants rated them as having significantly lower empathy than both other groups. Insight was significantly impaired in bvFTD compared with the other groups in 2 subtypes of empathy: empathic concern and perspective taking. There was also a difference between the bvFTD group and depressed group in predicting social consequences. Patients with depression performed similarly to healthy controls across all social cognition tasks.

Screening Measure Development

The exploratory decision tree analysis initially selected 5 items from ER40, 3 IRI items, and 1 item from Eyes. A logistic regression model was employed to predict diagnostic status (ie, bvFTD vs. depression) and 4 items were removed owing to collinearity, yielding a total of 5 test items: 3 ER40 and 2 IRI Insight items. Area under the curve (AUC) for predicting bvFTD with these items was high at 0.973 (95% CI: 0.928, 1.0).

DISCUSSION

This study supports previous research showing that people with bvFTD perform uniformly more poorly on measures of social cognition than both people with depression and healthy controls. Our exploratory post-hoc analysis suggests that identifying such changes with a reduced item set is possible. Therefore, bedside social cognition screening measures may be feasible.

By initially administering a broad range of social cognitive tests, we were able to explore differences in social cognition between bvFTD and controls. We used a statistically driven item reduction approach to identify a potential composite measure that might be applicable in the bedside clinical setting. Our incorporation of healthy controls provides important contrast and context to the differences that were observed between the bvFTD and depression groups: the depressed group performed similarly to the healthy control group, enhancing confidence in the broader applicability of the findings. This is one of the few studies that has been able to confirm previous reports of differences in social cognition between bvFTD and depression.

Although our sample size was small, the relevant effect sizes were large. By design, study participants were already diagnosed with bvFTD and depression and thus findings cannot be extrapolated to prodromal or undiagnosed bvFTD or other psychiatric diseases, which requires further investigation. Lack of neuropathological validation of bvFTD diagnoses and the possibility of overfitting of the data owing to lack of a validation set are other significant limitations of the present study.

Although our findings are preliminary, they suggest that it may be possible to develop a quick, valid, and reliable screening measure of social cognition suitable for clinical bedside use. Longitudinal studies examining the predictive validity of a social cognition screening tool for a subsequent diagnosis of bvFTD would further establish utility.

TABLE 1. Participant Demographics

Demographics	bvFTD (n = 17)	Depression (n = 16)	Control (n = 18)	Total (n = 51)
Age	71.00 (65.00, 76.00)	54.00 (49.50, 56.00)	52.00 (48.00, 66.00)	57.00 (51.00, 70.00)*t
Sex (% female)	4 (28.57)	12 (80.00)	11 (64.71)	27 (58.70)*t
Education (y)	12.00 (12.00, 14.00)	14.00 (13.00, 16.50)	17.50 (16.00, 19.00)	14.00 (12.00, 18.00)*
Montreal cognitive assessment (0-30)	20.00 (18.00, 26.00)	25.00 (23.50, 27.00)	28.00 (27.00, 28.00)	26.00 (23.00, 28.00)*t
Geriatric Depression Scale (0-30)	6.00 (1.00, 11.00)	19.00 (12.00, 24.00)	2.00 (1.00, 5.00)	6.00 (1.00, 14.00)*t
Frontal assessment battery (0-18)	15.00 (12.00, 16.00)	16.00 (15.00, 18.00)	17.00 (16.00, 18.00)	16.00 (15.00, 18.00)*t
Visual verbal test	8.00 (7.00, 8.00)	9.00 (8.00, 9.00)	9.00 (8.00, 10.00)	9.00 (8.00, 9.00) *t
Neuropsychiatric inventory (0-144)	26.00 (13.00, 36.00)	6.00 (2.00, 15.00)	0.00 (0.00, 1.00)	8.00 (1.00, 18.00)*t

*Significant ($P < 0.05$) difference between all groups, t = significant ($P < 0.05$) difference between bvFTD and depression groups. Continuous variables reported as medians with interquartile ranges; categorical variables in frequency counts and percentages.

bvFTD indicates behavioral variant frontotemporal dementia.

TABLE 2. Results of Social Cognition Testing

	bvFTD (n = 17)	Depression (n = 16)	Control (n = 18)	Total (n = 51)	*P-value	**P-value
Emotion recognition						
Penn faces emotion recognition						
Total (% correct)	0.60 (0.55, 0.78)	0.85 (0.81, 0.90)	0.86 (0.80, 0.90)	0.85 (0.68, 0.88)	< 0.0001	0.0005
Happy (% correct)	1.00 (0.88, 1.00)	1.00 (1.00, 1.00)	1.00 (0.88, 1.00)	1.00 (0.88, 1.00)	0.1237	0.0591
Sad (% correct)	0.63 (0.38, 0.75)	0.88 (0.75, 1.00)	0.88 (0.75, 1.00)	0.75 (0.63, 0.88)	0.0004	0.0024
Angry (% correct)	0.50 (0.25, 0.63)	0.75 (0.69, 0.81)	0.69 (0.50, 0.88)	0.63 (0.50, 0.75)	0.0022	0.0012
Fear (% correct)	0.50 (0.38, 0.75)	0.88 (0.75, 0.88)	0.88 (0.75, 0.88)	0.75 (0.63, 0.88)	0.0040	0.0084
Neutral (% correct)	0.63 (0.50, 1.00)	0.94 (0.75, 1.00)	0.94 (0.75, 1.00)	0.88 (0.75, 1.00)	0.0461	0.0319
Theory of mind						
Reading the mind of the eye (% correct)	0.47 (0.36, 0.72)	0.78 (0.68, 0.81)	0.74 (0.67, 0.81)	0.72 (0.56, 0.81)	0.0014	0.0036
First and second order/sarcasm stories (% correct)						
First order	0.80 (0.70, 0.89)	1.00 (0.88, 1.00)	1.00 (0.95, 1.00)	0.95 (0.80, 1.00)	< 0.0001	0.0013
2nd order/sarcasm	0.61 (0.56, 0.74)	0.92 (0.83, 0.98)	0.95 (0.85, 1.00)	0.85 (0.70, 0.95)	< 0.0001	0.0004
Faux pas (% correct)						
Identifies faux pas	0.85 (0.73, 0.90)	0.98 (0.95, 1.00)	1.00 (0.95, 1.00)	0.95 (0.88, 1.00)	0.0002	0.0019
Identifies who said faux pas	0.76 (0.69, 0.90)	0.98 (0.95, 1.00)	1.00 (0.95, 1.00)	0.95 (0.85, 1.00)	0.0002	0.0017
Understanding inappropriateness	0.67 (0.54, 0.80)	0.95 (0.90, 1.00)	0.95 (0.90, 1.00)	0.90 (0.75, 1.00)	< 0.0001	0.0006
Intentions	0.56 (0.41, 0.60)	0.85 (0.79, 0.95)	0.88 (0.85, 0.95)	0.80 (0.60, 0.90)	< 0.0001	0.0002
Belief	0.89 (0.71, 0.95)	0.95 (0.92, 1.00)	0.98 (0.90, 1.00)	0.95 (0.88, 1.00)	0.0065	0.0208
Empathy	0.85 (0.69, 0.89)	1.00 (0.95, 1.00)	1.00 (0.95, 1.00)	0.95 (0.89, 1.00)	< 0.0001	0.0003
Empathy and insight						
Interpersonal reactivity index						
Participant (0-28)						
Fantasy	12.00 (10.00, 15.00)	19.50 (15.00, 22.50)	16.50 (9.00, 18.00)	15.00 (11.00, 20.00)	0.0977	0.0575
Empathic concern	22.00 (18.00, 25.00)	24.00 (20.00, 27.00)	23.00 (21.00, 24.00)	23.00 (21.00, 26.00)	0.4306	0.2556
Perspective taking	17.00 (15.00, 20.00)	19.00 (16.50, 23.00)	20.00 (19.00, 24.00)	19.00 (17.00, 22.00)	0.0227	0.1850
Personal distress	12.00 (4.00, 14.00)	13.50 (10.00, 16.50)	7.00 (6.00, 11.00)	11.00 (6.00, 14.00)	0.0606	0.2782
Total (0-112)	62.00 (53.00, 70.00)	77.00 (61.50, 83.00)	64.00 (61.00, 73.00)	66.00 (59.00, 76.00)	0.0668	0.0560
Study partner (0-28)						
Fantasy	5.00 (4.00, 8.00)	12.00 (8.50, 16.50)	12.50 (10.00, 16.00)	10.00 (5.00, 14.00)	0.0001	0.0016
Empathic concern	10.00 (7.00, 16.00)	24.00 (18.50, 26.00)	21.50 (19.00, 24.00)	20.00 (11.00, 24.00)	0.0005	0.0016
Perspective taking	2.00 (1.00, 6.00)	17.50 (10.00, 21.50)	14.50 (12.00, 22.00)	12.00 (2.00, 19.00)	< 0.0001	0.0010
Personal distress	16.00 (8.00, 19.00)	8.00 (6.00, 13.50)	4.00 (0.00, 8.00)	8.00 (4.00, 16.00)	0.0032	0.0497
Total (0-112)	39.00 (28.00, 41.00)	60.00 (48.50, 71.50)	56.00 (49.00, 67.00)	52.00 (39.00, 66.00)	0.0003	0.0011
Insight (0-28)						
Fantasy	9.00 (4.00, 11.00)	7.00 (4.50, 9.00)	4.50 (2.00, 7.00)	7.00 (3.00, 10.00)	0.1230	0.4108
Empathic concern	10.00 (5.00, 16.00)	3.00 (1.00, 7.00)	3.50 (2.00, 6.00)	4.00 (2.00, 9.00)	0.0041	0.0078
Perspective taking	13.00 (12.00, 16.00)	4.00 (1.00, 7.50)	6.50 (4.00, 10.00)	7.00 (4.00, 14.00)	0.0002	0.0011
Personal distress	7.00 (3.00, 14.00)	4.00 (2.00, 8.00)	5.00 (3.00, 7.00)	5.00 (3.00, 10.00)	0.2325	0.1174
Total (0-112)	30.00 (16.00, 33.00)	14.00 (9.00, 19.00)	10.50 (7.00, 18.00)	14.00 (9.00, 29.00)	0.0052	0.0129
Predicting social consequences						
Cartoon predictions (% correct)	0.70 (0.60, 0.80)	0.85 (0.70, 0.90)	0.90 (0.70, 1.00)	0.80 (0.60, 0.90)	0.0275	0.0403

Results reported as medians with interquartile ranges.

*P = difference between all groups.

**P = difference between bvFTD and depression groups; no correction for multiple comparisons.

bvFTD indicates behavioral variant frontotemporal dementia.

ACKNOWLEDGMENTS

The authors acknowledge the helpful advice of Drs Murray Grossman and Paul Eslinger on this project. They also wish to acknowledge and thank the participants and their study partners for their perseverance through the testing procedures, and the collaboration Drs Andrew Howard and Raymond Lam, Department of Psychiatry at UBC.

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