Dissociation in Rating Negative Facial Emotions between Behavioral Variant Frontotemporal Dementia and Major Depressive Disorder

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Objective: *Features of behavioral variant frontotemporal dementia (bvFTD) such as executive dysfunction, apathy, and impaired empathic abilities are also observed in major depressive disorder (MDD). This may contribute to the reason why early stage bvFTD is often misdiagnosed as MDD. New assessment tools are thus needed to improve early diagnosis of bvFTD. Although emotion processing is affected in bvFTD and MDD, growing evidence indicates that the pattern of emotion processing deficits varies between the two disorders. As such, emotion processing paradigms have substantial potentials to distinguish bvFTD from MDD.* **Design and Participants:** *The current study compared 25 patients with bvFTD, 21 patients with MDD, 21 patients with Alzheimer disease (AD) dementia, and 31 healthy participants on a novel facial emotion intensity rating task. Stimuli comprised morphed faces from the Ekman and Friesen stimulus set containing faces of each sex with two different degrees of emotion intensity for each of the six basic emotions.* **Measurements and Results:** *Analyses of covariance uncovered a significant dissociation between bvFTD and MDD patients in rating the intensity of negative emotions overall (i.e., bvFTD patients underrated negative emotions overall, whereas MDD patients overrated negative emotions overall compared with healthy participants). In contrast, AD dementia patients rated negative emotions similarly to healthy participants, suggesting no impact of cognitive deficits on rating facial emotions.* **Conclusions:** *By strongly differentiating bvFTD and MDD*

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patients through negative facial emotions, this sensitive and short rating task might help improve the early diagnosis of bvFTD. (Am J Geriatr Psychiatry 2016; 24:1017–1027)

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Behavioral variant frontotemporal dementia (bvFTD) is a clinical syndrome, characterized by early and prominent behavioral changes,[1] resulting from frontal and temporal lobe dysfunctions due to heterogeneous underlying neurodegenerative processes.[2] After Alzheimer disease (AD) dementia, it is the most common diagnosis in patients with early-onset dementia, with an estimated prevalence of 15.4 (95% confidence interval [CI]: 9.1–24.3) per 100,000 individuals between the ages of 45 and 64 years.[3,4] In the absence of reliable biomarkers in the early disease stage, diagnosis largely depends on clinical criteria.[1] Accurate clinical diagnosis remains a challenge as many symptoms of bvFTD overlap with those found in psychiatric disorders such as major depressive disorder (MDD), increasing the risk of misdiagnosis.[5] For example, executive dysfunction, apathy, and impaired empathic abilities are frequent in both bvFTD and MDD.[1,5–7] Notably, MDD represents the most frequent psychiatric misdiagnosis in bvFTD patients (65% in men, 50% in women), followed by bipolar disorder (20% in men, 25% in women), and schizophrenia (5% in men, 6% in women).[5] To address this diagnostic challenge, new assessment tools are thus needed.

Existing evidence indicates that emotion processing is affected in both disorders.[8,9] Importantly, however, the pattern of emotion processing disturbance appears to differ between the two disorders, providing emotion processing paradigms substantial diagnostic potential to distinguish between bvFTD and MDD. A large body of evidence has shown that bvFTD patients are impaired in perceiving emotions, particularly so for negative emotions such as anger, disgust, fear or sadness.[10–13] In contrast, MDD patients tend to exhibit a heightened perception of negative emotions rather than experience deficits in emotion recognition in general (for review, see Bourke et al.[9]). As such, MDD patients not only tend to overrate the intensity of negative emotions, but also show a negative response bias for positive, neutral, and ambiguous facial expressions (i.e., a tendency to interpret these facial expressions negatively).[9] Similarly, MDD patients show an increased vigilance and selective attention towards sad expressions and away from happy expressions.[9] To date, only one study has directly compared overall facial emotion recognition in bvFTD and MDD[14] and showed worse facial emotion recognition in bvFTD than in MDD.

Here, we administered a newly developed emotion intensity rating task in patients diagnosed with bvFTD, MDD, or AD dementia, and in healthy participants (HP) using morphed facial stimuli from the Facial Expressions of Emotion—Stimuli and Tests (FEEST).[15] We favored an emotion intensity rating task over a forced-choice emotion labeling task because emotion intensity rating tasks have proven to be particularly sensitive in detecting impairments of emotion recognition.[16] Based on the existing literature, we hypothesized that bvFTD and MDD patients would dissociate in rating the intensity of negative facial emotions. Finally, we included AD dementia patients as a clinical comparison group to ensure that impairments in perceiving the intensity of facial emotions are not influenced by cognitive deficits.

METHODS

Participants

Ninety-eight participants were recruited for the study. The sample included 25 patients who met the research diagnostic criteria for probable bvFTD,[1] 21 patients with probable AD dementia,[17] 21 inpatients with MDD according to DSM-IV criteria,[7] and 31 age-matched healthy participants. Two bvFTD patients had a coexisting motor neuron disease and two MDD patients had a bipolar disorder.

Patients with bvFTD and AD dementia were recruited from five Swiss memory clinics and the outpatient memory clinic of the Technische Universität München, Germany. The diagnosis was derived by a multidisciplinary team consisting of neurologists, neuropsychologists, and psychiatrists who performed

comprehensive neuropsychological and neuroimaging assessments. Exclusion criteria were less than 7 years of education, history of current drug or alcohol abuse according to DSM-IV,[7] psychiatric disorders according to DSM-IV,[7] head trauma (with loss of consciousness greater than 30 minutes), systemic disorders or brain diseases that could result in neuropsychological deficits, chronic pain thought to interfere with neuropsychological testing, general anesthesia within the last 3 months, and a Mini-Mental State Examination (MMSE) Score less than 20. Medication of bvFTD patients included selective serotonin reuptake inhibitors (SSRIs; N = 8), serotonin-norepinephrine-dopamine reuptake inhibitors (SNDRIs; N = 1), tetracyclic antidepressants (N = 1), atypical neuroleptics (N = 6), and benzodiazepines (N = 1). Medication of AD dementia patients included SSRIs (N = 2), serotonin-norepinephrine reuptake inhibitors (SNRIs; N = 1), tricyclic antidepressants (N = 1), and benzodiazepines (N = 1).

MDD patients were recruited from the inpatient clinic of the Psychiatric Clinics of the University of Basel, Switzerland. Additional exclusion criteria for MDD patients were score of 15 or less on the Hamilton Depression Scale (HAMD-21[18]), and/or 5 or less on the Geriatric Depression Scale (GDS-15[19]). Comorbid axis I diagnoses of DSM-IV[7] were acceptable as long as the current depressive episode was primary (one patient had an additional alcohol dependency, one patient had a generalized anxiety disorder, and one patient had a mixed personality disorder with narcissistic and emotionally unstable traits). Medication of MDD patients included SSRIs (N = 10), SNRIs (N = 10), SNDRIs (N = 1), tricyclic (N = 1) and tetracyclic (N = 7) antidepressants, agomelatine (N = 1), atypical neuroleptics (N = 10), benzodiazepines (N = 14), antiepileptics [pregabalin (N = 4) and valproic acid (N = 2)], and lithium (N = 4).

HPs were recruited from the participant pool of the Memory Clinic Basel, Switzerland. They were considered cognitively normal if they scored more than 6 points on the combined MMSE and Clock Drawing Test.[20] Exclusion criteria have been described previously.[21]

Clinical diagnosis was confirmed at a follow-up assessment, in general 1 year after the baseline assessment (mean time period of 12.73 ± 1.54 months in dementia patients and 11.04 ± 4.21 months in MDD patients) either in the clinic or, if they were unable to attend, by a standardized phone interview. Clinical diagnosis was confirmed in all patients, with the exception of one AD dementia patient and one MDD patient who could not be reached. The study was approved by the local ethics committee and all study procedures complied with the Declaration of Helsinki. In addition to participants, caregivers of bvFTD and AD dementia patients also provided informed consent.

Procedure

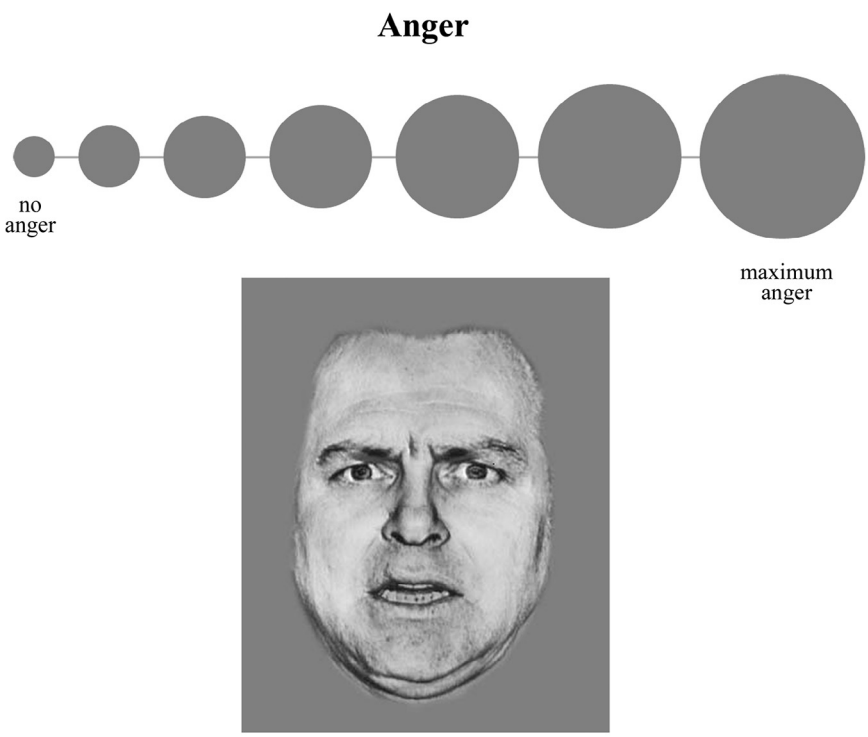
Neuropsychological Assessment

Patients were administered the German version of the Consortium to Establish a Registry for Alzheimer's Disease—Neuropsychological Assessment Battery (CERAD-NAB) as well as three additional tests of executive function and mental speed (Trail Making Tests A and B, Phonemic Fluency) (CERAD-NAB Plus).[22] In all patients, the degree of depression was measured by the HAMD-21[18] and the GDS-15,[19] and the degree of rumination was assessed by the German version of the Response Style Questionnaire (RSQ-D) 10-item rumination subscale.[23] In bvFTD and AD dementia patients, behavioral symptoms were assessed by the Frontal Behavioral Inventory (FBI[24]). Dementia severity was assessed by the Clinical Dementia Rating (CDR[25]) and the Frontotemporal Dementia Rating Scale (FRS[26]).

Emotion Intensity Rating Task

Prior to the experimental session, participants completed an adapted version of the emotion word knowledge questionnaire[27] to ensure their understanding of each of the six basic emotion terms. For example, to test their knowledge of sadness, participants were asked "How would you feel if your good friend dies?" Participants were then tested on an emotion intensity rating task comprising neutral and emotional stimuli from the morphed and caricatured continua of the FEEST.[15] These stimuli are in grayscale and the hairline is masked. A male model (model JJ) and a female model (model MO) were selected. These models show a reasonably standardized pose and lighting and are reported to be of consistent quality for each emotion.[15] All six basic emotions (i.e., anger, disgust, fear, sadness, happiness, and surprise) were presented at two different intensity levels. The low intensity level of each emotion was based on previously established

FIGURE 1. Example of a facial stimulus of the emotion intensity rating task.



threshold levels of facial emotion recognition.[21] Low intensity levels were chosen to avoid ceiling effects, particularly in MDD patients, as we assumed that these patients would show a negative response bias. Stimuli with high intensity level (i.e., low intensity level plus 50% intensity) were administered for two reasons: First, to ensure that patients, and in particular bvFTD patients, were able to recognize emotions at this intensity level, and second as a measure of response reliability as increasing rating scores were assumed with increasing intensity level of the emotional stimuli. Thus, we administered a total of 26 stimuli (6 basic emotions × 2 intensity levels × 2 sexes + neutral for both sexes). Stimuli were presented in two pseudo-randomized versions, whereby no type of emotion was shown more than twice in a row. Stimuli were displayed on a 15-inch laptop computer using E-Prime 1.2 software (Psychology Software Tools, Pittsburgh, PA). Above each facial stimulus the emotion label and a 7-point intensity rating scale ranging from *no emotion* (1) to *maximum emotion* (7) appeared on the screen (Figure 1). Participants were instructed to rate the intensity of each emotion by pointing at the appropriate circle on the screen. Stimuli remained on the screen until participants provided an answer. The task was untimed and no feedback was given. Before the experiment started, four practice trials were conducted to familiarize the participant with the procedure and clarify any questions. Moreover, HPs were retested 12 months after baseline to evaluate test–retest reliability.

Data Analyses

Comparison of Emotion Intensity Rating Scores between Groups

To analyze the emotion intensity rating task, we created mean scores for each of the six basic emotions and two composite scores [i.e., an Emotion Total (ET) score (=mean score of the six basic emotions) and a Negative Emotion Total (NET) score (=mean score of the four negative emotions)] for male and female stimuli and for stimuli at low and high intensity levels, respectively. Neutral stimuli were excluded from these

analyses. To achieve normal distribution and homogeneity of variance, cubic transformations were performed on all mean intensity rating scores.

ANCOVAs with each demographic variable (i.e., age, sex, and education) as a single predictor in the model showed that age and sex were significant predictors of the outcome variables. Therefore, we included these two variables as covariates in the models. Significant ANCOVA results of group differences ($p < 0.05$) were followed by post-hoc comparisons of adjusted means using the Tukey-Kramer option for general linear models in STATA 13.1 software (StataCorp. 2013. College Station, TX).

Discriminatory Power of the Emotion Intensity Rating Task

To determine which of the scores discriminates best between bvFTD and MDD patients, we performed receiver operating characteristic (ROC) curve analyses. Logistic regression analyses showed that age, sex, and education were not significant predictors in discriminating between bvFTD and MDD patients. Therefore, ROC analyses in these two groups were not adjusted for demographic variables.

Areas under the curves (AUC) were calculated with STATA 13.1 software to assess the discriminating power of each score with 95% CI.[28] In addition, optimal cutoff points were computed with SPSS 21.0 software (IBM Corp. 2012. Armonk, NY) according to the Youden index, where sensitivity and specificity are maximized.[29]

RESULTS

Demographic Characteristics and Neuropsychological Data

ANOVAs revealed significant group differences for education but not age and sex (Table 1). Tukey-Kramer post-hoc analyses indicated that HPs had significantly higher education than AD dementia patients. Moreover, cognitive functioning significantly differed across the three patient groups. Based on the MMSE and CERAD-NAB Plus total scores, bvFTD and AD dementia patients were cognitively more impaired than MDD patients. Notably, bvFTD and AD dementia patients did not show signs of depression (Table 1).

TABLE 1. Characteristics of Subject Sample (N = 98) Classified by Diagnostic Group

	bvFTD (N = 25)	MDD (N = 21)	AD Dementia (N = 21)	HP (N = 31)	Test (df)	Post-hoc
Age (years)	66.08 (±9.06)	62.66 (±12.88)	70.21 (±10.86)	68.42 (±8.29)	$2.24_{(3,94)}$[a]	
Sex (M/F)	19/6	9/12	12/9	20/11	$5.57_{(3)}$[b]	
Education (years)	12.20 (±2.20)	12.62 (±3.28)	11.90 (±2.91)	14.23 (±3.15)	$3.50_{(3,94)}$[a*]	AD < HP*
MMSE (0–30)	24.80 (±3.40)	28.43 (±1.63)	24.67 (±2.67)	29.39 (±0.84)	$51.41_{(3)}$[d‡]	bvFTD, AD < HP, MDD‡; HP > MDD*
CERAD-NAB Plus Score	73.92 (±15.13)	88.63 (±11.57)	72.19 (±8.85)	n/a	$18.00_{(2)}$[d‡]	bvFTD < MDD†, AD < MDD‡
CDR Box Score (0–18)	5.46 (±3.94)	n/a	3.48 (±3.08)	n/a	$1.87_{(44)}$[c]	
FBI (0–72)	27.67 (±12.17)	n/a	13.48 (±8.42)	n/a	$4.48_{(43)}$[c‡]	bvFTD > AD‡
FRS (Percentage Score)	42.33 (±22.58)	n/a	68.52 (±23.68)	n/a	$3.79_{(43)}$[c‡]	bvFTD > AD‡
HAMD-21 (0–66)	4.28 (±3.39)	20.84 (±4.37)	2.95 (±3.26)	0.26 (±0.82)	$69.02_{(3)}$[d‡]	MDD > bvFTD, AD, HP‡; HP < bvFTD, AD‡
GDS-15 (0–15)	3.16 (±2.93)	8.81 (±2.68)	1.71 (±1.74)	0.58 (±0.72)	$56.03_{(3)}$[d‡]	MDD > bvFTD, AD, HP‡; HP < bvFTD‡, AD*
RSQ (0–30)	3.72 (±4.56)	15.00 (±4.46)	3.24 (±4.81)	-	$43.44_{(2,63)}$[a‡]	MDD > bvFTD, AD‡

Notes: Values are expressed as mean (±standard deviation). *$p < 0.05$, †$p < 0.01$, ‡$p < 0.001$. AD dementia: Alzheimer disease dementia; bvFTD: behavioral variant frontotemporal dementia; CDR: Clinical Dementia Rating; CERAD-NAB Plus: Consortium to Establish a Registry for Alzheimer's Disease—Neuropsychological Assessment Battery Plus; FBI: Frontal Behavioral Inventory; FRS: Frontotemporal Dementia Rating Scale; GDS-15: 15-item Geriatric Depression Scale; HAMD-21: 21-item Hamilton Depression Scale; HP: healthy participants; MDD: major depressive disorder; MMSE: Mini-Mental State Examination; n/a: not applicable; RSQ: Response Style Questionnaire.

[a]Analysis of variance.

[b]χ^2 test.

[c]Independent sample t test.

[d]Kruskal-Wallis test.

Comparison of Emotion Intensity Rating Scores between Groups

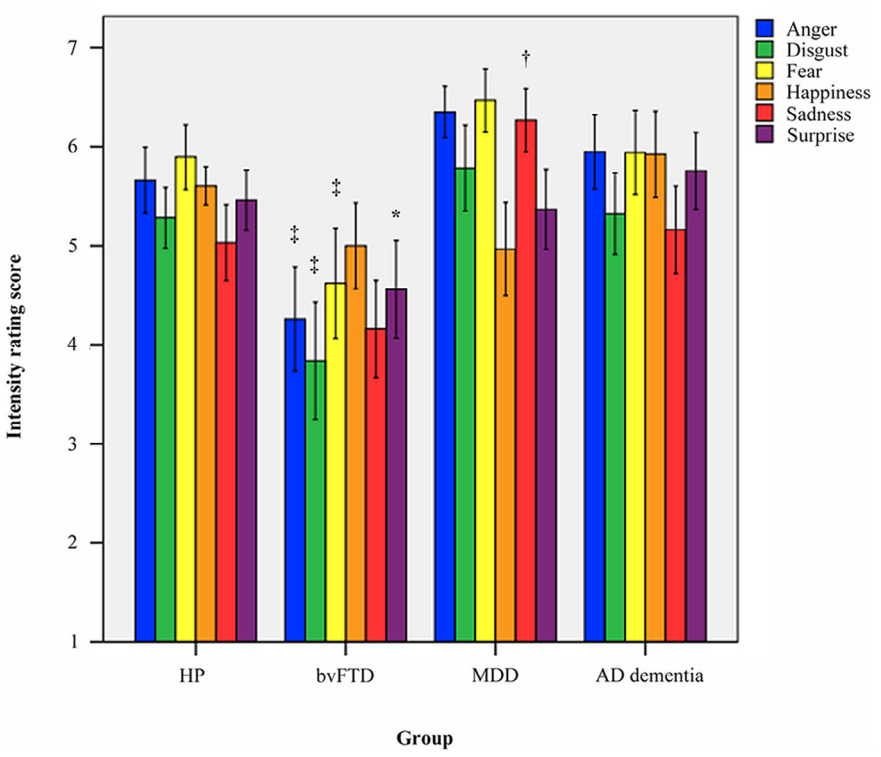
Because we found no significant group differences in terms of the two intensity levels and sex of stimuli, the stimuli were combined resulting in the following eight final scores: six emotion scores [= mean of 4 ratings; e.g., sadness score (=sadness at low intensity and high intensity levels portrayed by a female and male person)], the ET score [= mean of 24 (=6 × 4) ratings], and the NET score [= mean of 16 (=4 × 4) ratings].

Emotion Scores

ANCOVAs revealed significant main effects of group for each of the six mean emotion scores ranging from $F_{(3,92)} = 5.83$ (surprise) to $F_{(3,92)} = 18.35$ (anger) (Figure 2). Post-hoc analyses showed that four (i.e., anger, disgust, fear, and surprise) of the six emotion scores were significantly lower in bvFTD patients than in HPs, ranging between $t_{(92)} = -3.06$ (surprise) and $t_{(92)} = -4.95$ (anger) (Figure 2). In contrast, only sadness scores were significantly higher in MDD patients than in HPs ($t_{(92)} = 4.03$). Taken together, none of the emotion scores showed a dissociation of bvFTD and MDD patients from HPs.

Remarkably, all four negative emotion scores were significantly higher in MDD patients than in bvFTD patients, ranging between $t_{(92)} = 4.92$ (disgust) and $t_{(92)} = 6.86$ (anger). In contrast, the two non-negative emotion scores (i.e., happiness and surprise) did not differ between the two groups. Unlike the bvFTD and MDD patients, AD dementia patients rated all six emotions comparably to HPs (Figure 2).

FIGURE 2. **Results from ANCOVAs (df = 5, 92) depicting the mean intensity ratings of emotion scores between groups. Error bars depict 95% confidence intervals. *p < 0.05, †p < 0.01, ‡p < 0.001 compared with HP. HP: healthy participants; bvFTD: behavioral variant frontotemporal dementia; MDD: major depressive disorder; AD dementia: Alzheimer disease dementia.**



Composite Scores

Similarly to the emotion scores, we found significant main effects of group for both composite scores ranging from $F_{(3,92)} = 13.71$ (ET) to $F_{(3,92)} = 17.89$ (NET) (Figure 3). Post-hoc analyses showed that bvFTD patients had significantly lower NET and ET scores than the other groups. In contrast, MDD patients showed significantly higher NET scores than HPs ($t_{(92)} = 3.01$). Taken together, the NET score dissociated between bvFTD and MDD patients, whereas the ET score did not.

Intensity Levels

Across all emotions, all groups showed a similar mean increase in intensity rating scores from low to high intensity stimuli (bvFTD: M = 0.51 ± 0.66; MDD: M = 0.87 ± 0.41; AD dementia: M = 0.72 ± 0.35; HP: M = 0.77 ± 0.51), indicating that participants of each diagnostic group were able to reliably perceive the emotional stimuli and distinguish among the points of the 7-point intensity rating scale.

Twenty-eight HPs (90%) were retested after a mean time period of 11.40 ± 0.65 months, revealing a test–retest reliability of r = 0.89 (95% CI: 0.77–0.95) for the 24 emotional stimuli.

Discriminatory Power of the Emotion Intensity Rating Task

In contrast to the two non-negative emotion scores, all four negative emotion scores showed a high discriminatory power (Table 2). Moreover, the four negative emotions did not significantly differ in their

FIGURE 3. Results from ANCOVAs (df = 5, 92) depicting the mean intensity ratings of composite scores between groups. Error bars depict 95% confidence intervals. *p < 0.05, ‡p < 0.001 compared with HP. HP: healthy participants; bvFTD: behavioral variant frontotemporal dementia; MDD: major depressive disorder; AD dementia: Alzheimer disease dementia; ET: Emotion Total score; NET: Negative Emotion Total score.

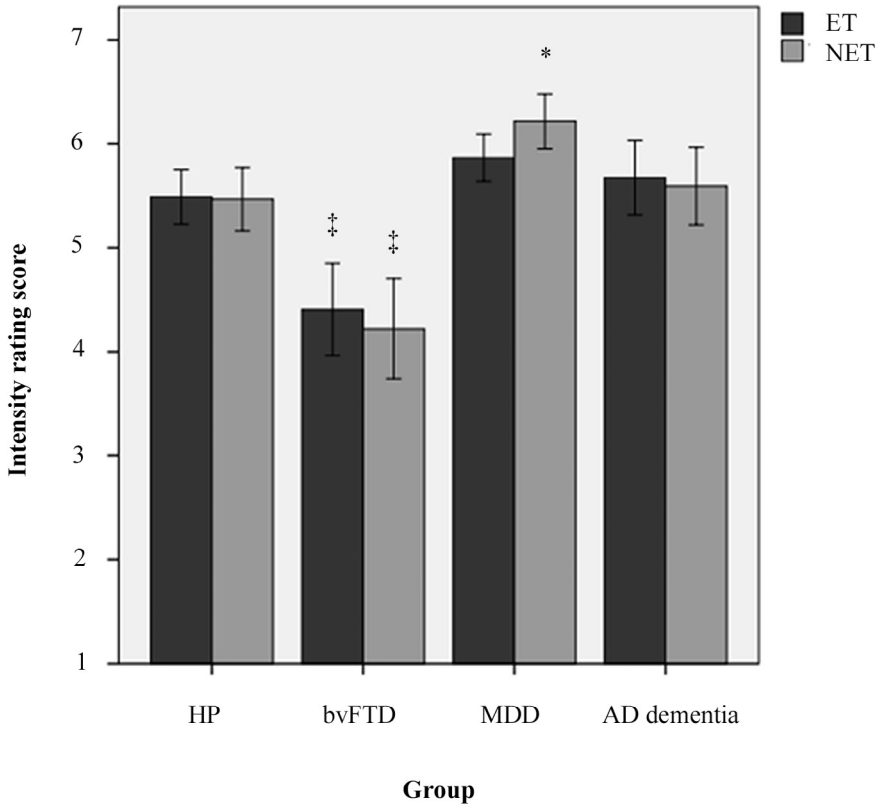


TABLE 2. Discrimination Between bvFTD and MDD Patients: Indices of the Emotion Intensity Rating Task Scores

		Cutoff	Sensitivity (%)	Specificity (%)	AUC	95% CI	LRT
Emotion scores	**Anger**	5.38	91	80	0.95	0.89–1.00	36.92[b]
	Disgust	4.88	86	80	0.86	0.75–0.97	20.28[b]
	Fear	5.63	91	64	0.92	0.84–0.99	30.18[b]
	Sadness	4.88	95	72	0.91	0.83–0.99	28.65[b]
	Happiness	3.88	91	20	0.51	0.34–0.68	0.00
	Surprise	4.38	95	40	0.72	0.58–0.87	8.17[a]
Composite scores	**ET**	5.19	91	76	0.91	0.82–0.99	28.55[b]
	NET	5.22	91	80	0.95	0.89–1.00	35.56[b]

Notes: AUC: area under the curve; bvFTD: behavioral variant frontotemporal dementia; CI: confidence interval; ET: Emotion Total score; LRT: Likelihood-Ratio χ^2 test; MDD: major depressive disorder; NET: Negative Emotion Total score.

[a]$p < 0.05$.

[b]$p < 0.001$.

discriminatory power. Both the ET score and the NET score revealed a high discriminatory power (Table 2), which did not significantly differ ($\chi^2_{(1)} = 3.52$, $p = 0.06$). Furthermore, the discriminatory power did not significantly differ between any negative emotion score and the NET score.

CONCLUSIONS

Using a novel facial emotion intensity rating task, this study is the first to uncover important differences between patients diagnosed with bvFTD or MDD in the way these patients differentiate and rate facial emotions. We found that bvFTD and MDD patients dissociate in rating negative facial emotions overall, that is, bvFTD patients underrated negative emotions overall, whereas MDD patients overrated negative emotions overall compared to healthy participants. When examined separately, the four negative emotion scores did not differ in their power to discriminate between bvFTD and MDD, with each showing a high discriminatory power between the groups. In contrast, positive (happiness) and ambiguous (surprise) emotions did not or only weakly discriminate between the two groups. Importantly, none of the emotion scores, but only negative emotions altogether as measured by the NET score, dissociated between bvFTD and MDD patients. Accordingly, we determined the NET score as the best and most reliable score to discriminate between the two patient populations. Finally, the results showed that impaired emotion rating in bvFTD patients was unlikely to be modulated by cognitive dysfunction, given the preserved perception of facial emotions in AD dementia patients.

To date, only one study has compared overall facial emotion recognition between bvFTD and MDD.[14] Using prototypical basic facial emotions,[30] the authors showed worse facial emotion recognition in bvFTD than in MDD. Here, our results expand their findings, showing that bvFTD patients are not only worse than MDD patients at recognizing facial emotions overall, but also at appraising the *intensity* of facial emotions overall.

On the other hand, several studies have contrasted facial emotion recognition in bvFTD and HP.[10–13,31] In our study, bvFTD patients perceived emotions altogether less intensively than HPs, particularly so for negative emotions. Not all types of emotions, however, were rated differently by bvFTD patients and HP; as such, happiness and sadness were similarly rated by both groups. This finding is in line with another study using prototypical Ekman faces.[11] Other studies, however, reported preserved recognition of happiness and surprise in bvFTD, (e.g., Kumfor et al.[12] and Lough et al.[13]) whereas some found the recognition of all basic emotions to be impaired.(e.g., Diehl-Schmid et al.[10]) These variable findings are probably due to differences in facial stimuli and clinical characteristics of samples across studies (e.g., disease stage and changing diagnostic criteria of bvFTD over the last years).[1,32] Based on previous neuroimaging studies in patients with neurodegenerative diseases, the reduced recognition of negative emotions observed in bvFTD may be explained by the neural basis of these emotions.[33] Each of the four negative emotions and negative emotions altogether have commonly been associated with brain regions typically affected in bvFTD such as the amygdala, the ventral striatum, or the insula.[8,34]

In contrast to bvFTD patients, negative emotions altogether were perceived more intensively by MDD patients than HPs, supporting the mood-congruent processing bias reported in previous clinical and neuroimaging studies.[9,35,36] Notably, this bias was driven by the sadness score. The response bias for sadness is in line with previous reports (for review, see Bourke et al.[9]), indicating that MDD patients tend to misperceive neutral or emotionally ambiguous stimuli as sad and/or show an increased attention towards sad expressions compared with healthy individuals. In line with the increased perception of mood-congruent negative emotions in MDD, glucose hypometabolism and/or hypermetabolism in brain regions critical for emotion processing such as the amygdala, the ventral striatum, the subgenual anterior cingulate cortex, and/or orbitofrontal cortices have commonly been reported in MDD.[36] Notably, these brain regions are also typically affected in bvFTD patients but characterized by gray matter loss.[34]

Contrary to bvFTD and MDD patients, AD dementia patients perceived all types of emotion comparably to HPs, indicating that impaired perception of facial emotions in bvFTD was unlikely to be influenced by cognitive deficits. This result is consistent with most previous studies measuring facial emotion recognition in AD dementia patients (e.g., Shany-Ur et al.[31] and Bertoux et al.[37]). The finding is further supported by neuroimaging studies showing that brain regions which are crucial for emotion processing remain relatively intact in AD dementia patients, even at advanced stages of the disease (e.g., Karas et al.[38]).

Some aspects of this study need to be borne in mind when interpreting our results. First, our MDD patients showed limited overlap in clinical characteristics with the bvFTD patients. In other words, these patients showed few cognitive deficits and typical signs of depression such as rumination. Reasons for this are probably that 1) only a minority of MDD patients shows severe cognitive deficits[39,40] and 2) the recruitment of MDD patients with severe cognitive deficits remains difficult because of their low motivation to participate in research studies overall. Nevertheless, other clinical features, such as apathy, loss of interest, and lack of motivation, largely overlapped between bvFTD and MDD patients. In order to make the two groups more comparable with regard to the severity of cognitive deficits, we conducted an additional analysis excluding ten patients with severe bvFTD based on the FRS score, also given that especially early bvFTD is often being misdiagnosed as MDD.[5,41] The discriminatory power of the NET score in this subsample (N = 36) remained equally high as in the total bvFTD-MDD subsample (N = 46). Likewise, after additionally excluding the cognitively less impaired half of the MDD patients (N = 10) based on the CERAD-NAB Plus score, the discriminatory power of the NET score remained the same.

To achieve matching cognitive deficits in bvFTD and MDD patients, future studies will require an expanded recruiting process with eligibility criteria regarding the upper and lower degree of cognitive impairment in both patient groups. In addition, and likely more difficult to achieve in terms of recruitment, MDD patients with depressive rumination would need to be excluded.

Second, compared with bvFTD and AD dementia patients, our MDD patients were more often treated with antidepressants and antipsychotics at time of testing, potentially influencing their ability in rating the intensity of facial emotions.[42] A strong negative bias was nevertheless present, despite the fact that antidepressants would decrease rather than increase the negative response bias in emotion perception, as short-time administration of these drugs have been found to reduce the processing of negative relative to positive emotions in healthy individuals.[42,43] Despite these limitations, we demonstrated that prospectively recruited typical bvFTD and MDD patients strongly dissociate in rating negative facial emotions. Ideally, the NET score, our primarily identified measure, would be used as a classifying variable in future investigations to confirm the potential of the facial emotion intensity rating task in discriminating between these two clinical populations.

Measures of emotion processing have become an essential part of a comprehensive neuropsychological assessment. Indeed, emotion recognition now forms part of the new clinical domain "social cognition" which has been included as one of the six clinical domains of neurocognitive function in the recent edition of the Diagnostic and Statistical Manual for Mental Disorders (DSM-5).[44] Sensitive tests that reliably assess aspects of social cognition within a reasonable timeframe are rare, however. Because social cognitive deficits are present to some degree in most brain disorders including neurodevelopmental, neurodegenerative, and neuropsychiatric diseases,[45] the development of novel tests such as our emotion

intensity rating task that can be used in routine clinical assessments is highly important. Our emotion intensity rating task proved to be reliable, cognitively low-demanding (i.e., rating scores were unlikely modulated by cognitive dysfunction), and completed within a short time (around 10 minutes in patients).

In conclusion, by using a novel facial emotion intensity rating task, we showed that bvFTD and MDD patients dissociate in rating the intensity of negative emotions. This finding has important clinical implications as an accurate early diagnosis of bvFTD remains notoriously difficult to establish in a proportion of cases. In such instances, different etiologies are considered by different specialists, often leading to mistreatment—such as psychiatric hospitalizations with extensive pharmacological and nonpharmacological interventions in case of a misdiagnosed "therapy-refractory MDD." In contrast, early diagnosis of bvFTD allows early counseling of carers regarding the neurodegenerative disease and initiation of a disease-appropriate treatment, increasing the resilience of carers and reducing the need for institutional care and health care costs,[46] which is becoming an increasingly important issue in our aging population. Moreover, with disease-modifying therapies for bvFTD being currently being developed, an accurate diagnosis of bvFTD at its earliest stage will become increasingly important. Here, we argue that a simple emotion intensity rating task can help improve the early diagnosis and consequently the management of this disabling disease.

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References

1. Rascovsky K, Hodges JR, Knopman D, et al: Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain 2011; 134:2456–2477
2. Mackenzie IR, Neumann M, Bigio EH, et al: Nomenclature and nosology for neuropathologic subtypes of frontotemporal lobar degeneration: an update. Acta Neuropathol 2010; 119:1–4
3. Harvey R, Skelton-Robinson M, Rossor M: The prevalence and causes of dementia in people under the age of 65 years. J Neurol Neurosurg Psychiatry 2003; 74:1206–1209
4. Vieira RT, Caixeta L, Machado S, et al: Epidemiology of early-onset dementia: a review of the literature. Clin Pract Epidemiol Ment Health 2013; 9:88–95
5. Woolley JD, Khan BK, Murthy NK, et al: The diagnostic challenge of psychiatric symptoms in neurodegenerative disease: rates of and risk factors for prior psychiatric diagnosis in patients with early neurodegenerative disease. J Clin Psychiatry 2011; 72:126–133
6. Schreiter S, Pijnenborg GH, Aan Het Rot M: Empathy in adults with clinical or subclinical depressive symptoms. J Affect Disord 2013; 150:1–16
7. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). Washington, DC: American Psychiatric Association Publishing, 1994
8. Kumfor F, Piguet O: Disturbance of emotion processing in frontotemporal dementia: a synthesis of cognitive and neuroimaging findings. Neuropsychol Rev 2012; 22:280–297
9. Bourke C, Douglas K, Porter R: Processing of facial emotion expression in major depression: a review. Aust N Z J Psychiatry 2010; 44:681–696
10. Diehl-Schmid J, Pohl C, Ruprecht C, et al: The ekman 60 faces test as a diagnostic instrument in frontotemporal dementia. Arch Clin Neuropsychol 2007; 22:459–464
11. Fernandez-Duque D, Black SE: Impaired recognition of negative facial emotions in patients with frontotemporal dementia. Neuropsychologia 2005; 43:1673–1687
12. Kumfor F, Miller L, Lah S, et al: Are you really angry? The effect of intensity on facial emotion recognition in frontotemporal dementia. Soc Neurosci 2011; 6:502–514
13. Lough S, Kipps CM, Treise C, et al: Social reasoning, emotion and empathy in frontotemporal dementia. Neuropsychologia 2006; 44:950–958
14. Bertoux M, Delavest M, de Souza LC, et al: Social cognition and emotional assessment differentiates frontotemporal dementia from depression. J Neurol Neurosurg Psychiatry 2012; 83:411–416
15. Young A, Perrett D, Calder A, et al: Facial Expressions of Emotion—Stimuli and Tests (FEEST). Bury St. Edmunds, UK, Thames Valley Test Company, 2002
16. Adolphs R, Tranel D: Impaired judgments of sadness but not happiness following bilateral amygdala damage. J Cogn Neurosci 2004; 16:453–462
17. McKhann GM, Knopman DS, Chertkow H, et al: 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 2011; 7:263–269
18. Hamilton M: A rating scale for depression. J Neurol Neurosurg Psychiatry 1960; 23:56–62
19. Sheikh JI, Yesavage JA, Brink TL: Clinical gerontology: A guide to assessment and intervention. Geriatric Depression Scale (GDS). Recent Evidence and Development of a Shorter Version 1986; 165–173
20. Thalmann B, Spiegel R, Stähelin HB, et al: Dementia screening in general practice: optimised scoring for the clock drawing test. Brain Aging 2002; 2:36–43

21. Chiu I, Gfrorer RI, Piguet O, et al: "Now I see it, now I don't": determining threshold levels of facial emotion recognition for use in patient populations. J Int Neuropsychol Soc 2015; 21:568–572
22. Schmid NS, Ehrensperger MM, Berres M, et al: The extension of the German CERAD neuropsychological assessment battery with tests assessing subcortical, executive and frontal functions improves accuracy in dementia diagnosis. Dement Geriatr Cogn Dis Extra 2014; 4:322–334
23. Treynor W, Gonzalez R, Nolen-Hoeksema S: Rumination reconsidered: a psychometric analysis. Cognit Ther Res 2003; 27:247–259
24. Kertesz A, Neelesh N, Davidson W, et al: The frontal behavioral inventory in the differential diagnosis of frontotemporal dementia. J Int Neuropsychol Soc 2000; 6:460–468
25. Morris JC: The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology 1993; 43:2412–2414
26. Mioshi E, Hsieh S, Savage S, et al: Clinical staging and disease progression in frontotemporal dementia. Neurology 2010; 74:1591–1597
27. Werner KH, Roberts NA, Rosen HJ, et al: Emotional reactivity and emotion recognition in frontotemporal lobar degeneration. Neurology 2007; 69:148–155
28. Cleves MA: From the help desk: comparing areas under receiver operating characteristic curves from two or more probit or logit models. Stata J 2002; 2:301–313
29. Perkins NJ, Schisterman EF: The inconsistency of "optimal" cutpoints obtained using two criteria based on the receiver operating characteristic curve. Am J Epidemiol 2006; 163:670–675
30. Ekman P, Friesen W: Pictures of Facial Affect. Palo Alto, CA, Consulting Psychologists, 1976
31. Shany-Ur T, Poorzand P, Grossman SN, et al: Comprehension of insincere communication in neurodegenerative disease: lies, sarcasm, and theory of mind. Cortex 2012; 48:1329–1341
32. Neary D, Snowden JS, Gustafson L, et al: Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. Neurology 1998; 51:1546–1554
33. Kumfor F, Irish M, Hodges JR, et al: Discrete neural correlates for the recognition of negative emotions: insights from frontotemporal dementia. PLoS ONE 2013; 8:e67457
34. Seeley WW, Crawford R, Rascovsky K, et al: Frontal paralimbic network atrophy in very mild behavioral variant frontotemporal dementia. Arch Neurol 2008; 65:249–255
35. Stuhrmann A, Suslow T, Dannlowski U: Facial emotion processing in major depression: a systematic review of neuroimaging findings. Biol Mood Anxiety Disord 2011; 1:10
36. Savitz J, Drevets WC: Bipolar and major depressive disorder: neuroimaging the developmental-degenerative divide. Neurosci Biobehav Rev 2009; 33:699–771
37. Bertoux M, de Souza LC, Sarazin M, et al: How preserved is emotion recognition in Alzheimer disease compared with behavioral variant frontotemporal dementia? Alzheimer Dis Assoc Disord 2015; 29:154–157
38. Karas G, Burton E, Rombouts S, et al: A comprehensive study of gray matter loss in patients with Alzheimer's disease using optimized voxel-based morphometry. Neuroimage 2003; 18:895–907
39. Gualtieri CT, Morgan DW: The frequency of cognitive impairment in patients with anxiety, depression, and bipolar disorder: an unaccounted source of variance in clinical trials. J Clin Psychiatry 2008; 69:1122–1130
40. Rock PL, Roiser JP, Riedel WJ, et al: Cognitive impairment in depression: a systematic review and meta-analysis. Psychol Med 2014; 44:2029–2040
41. Lanata SC, Miller BL: The behavioural variant frontotemporal dementia (bvFTD) syndrome in psychiatry. J Neurol Neurosurg Psychiatry 2016; 87:501–511
42. Harmer CJ, Shelley NC, Cowen PJ, et al: Increased positive versus negative affective perception and memory in healthy volunteers following selective serotonin and norepinephrine reuptake inhibition. Am J Psychiatry 2004; 161:1256–1263
43. Kerestes R, Labuschagne I, Croft RJ, et al: Evidence for modulation of facial emotional processing bias during emotional expression decoding by serotonergic and noradrenergic antidepressants: an event-related potential (ERP) study. Psychopharmacology (Berl) 2009; 202:621–634
44. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders (DSM-5). Washington, DC: American Psychiatric Association Publishing, 2013
45. Henry JD, von Hippel W, Molenberghs P, et al: Clinical assessment of social cognitive function in neurological disorders. Nat Rev Neurol 2016; 12:28–39
46. de Vugt ME, Verhey FR: The impact of early dementia diagnosis and intervention on informal caregivers. Prog Neurobiol 2013; 110:54–62