

How preserved is emotion recognition in Alzheimer Disease compared to behavioural variant frontotemporal dementia?

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Maxime Bertoux – Study concept, design, clinical and experimental data acquisition, analysis and interpretation, manuscript writing.

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Marie Sarazin – Interpretation of data, manuscript revision.

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ABBREVIATIONS

AD: Alzheimer's disease

bvFTD: Behavioural variant frontotemporal dementia

CSF: Cerebrospinal Fluid

FAB: Frontal Assessment Battery

MMSE: Mini Mental State Examination

Background: Emotion deficits are a recognised biomarker for behavioural variant frontotemporal dementia (bvFTD), but recent studies have reported emotion deficits also in Alzheimer’s disease (AD).

Methods: A hundred and twenty-three participants (33 AD, 60 bvFTD, 30 controls) were administered a facial emotion recognition test, to investigate the clinical factors influencing the diagnostic distinction on this measure. Binomial regression analysis revealed that facial emotion recognition in AD was influenced by disease duration and MMSE, whereas the same was not true for bvFTD. Based on this information, we median-split the AD group on disease duration (3 years) or MMSE (24) and compared the facial emotion recognition performance of mild-AD, moderate-AD, bvFTD patients and controls.

Results: Results showed that very mild-AD performed consistently at control levels for all emotions. By contrast, mild/moderate-AD and bvFTD were impaired compared to controls on most emotions. Interestingly, mild/moderate-AD were significantly impaired compared to very mild-AD on total score, anger and sadness subscores. Logistic regression analyses corroborated these findings with ~94% of very mild-AD being successfully distinguished from bvFTD at presentation, while this distinction was reduced to ~78% for mild/moderate-AD.

Conclusions: Facial emotion recognition in AD is influenced by disease progression, with very mild-AD being virtually intact for emotion performance. Mild/moderate-AD and bvFTD show consistent impairment in emotion recognition, with bvFTD being worse. A disease progression of over 3 years or a MMSE lower than 24 should warrant caution to put too much emphasis on emotion recognition performance in the diagnostic distinction of AD and bvFTD.

Key words: frontotemporal dementia, bvFTD, emotion, Alzheimer’s disease

INTRODUCTION

Emotion recognition deficit is a hallmark feature of behavioural variant frontotemporal dementia (bvFTD) ^[1] and has therefore substantial diagnostic potential to distinguish bvFTD from other neurodegenerative diseases, such as Alzheimer's disease (AD) ^[2]. Nevertheless, AD patients have also been reported to show emotion recognition deficits in some studies ^[3] but not others ^[4]. The current study explores the clinical factors that influence facial emotion recognition in AD, which will inform future diagnoses of both diseases. For this purpose, we compare the facial emotion recognition performance in a large sample of AD and bvFTD patients and controls. A subset of patients had patho-physiological confirmation via cerebrospinal fluid (CSF) biomarkers

METHODS

Participants.

Thirty-three AD and 60 bvFTD patients, as well as 30 age- and education-matched controls were recruited via the Memory and Alzheimer Institute of the Pitié-Salpêtrière Hospital in Paris (France). BvFTD and AD patients fulfilled the disease specific diagnostic criteria ^[5,6]. Controls were included according to the following criteria: Mini mental state examination (MMSE) score \geq 27/30; no history of neurological or psychiatric disorders; no memory complaint or cognitive impairment.

CSF biomarkers (A β ₄₂, Tau and P-Tau) were available for 32 patients (n=12 AD, n=24 bvFTD). All AD patients had an "AD CSF biomarker profile" as previously defined ^[7], whereas bvFTD patients did not. CSF data was not available for control subjects. Two bvFTD patients had known genetic mutations (1 MAPT, 1 PGRN).

According to French legislation, explicit informed consent for patients was waived. For the healthy control subjects, the study was approved by the local Ethics Committee.

Facial emotion recognition test.

Thirty-five Ekman faces were presented in a validated computerized test ^[8] and patients indicated which emotion was expressed (emotion labels were provided during the entire task). Seven different emotions were presented 5 times in a pseudorandom order (Happiness, Fear, Disgust, Neutral, Surprise, Anger and Sadness). Percentage of correct responses for each emotion and for the total emotion performance was calculated.

Statistics.

Data were analyzed using SPSS20 (IBM, Armonk, NY). Prior to any analysis, variables were plotted and checked for normality of distribution via Shapiro-Wilk tests. Demographic and neuropsychological data were analyzed across the groups via ANOVAs and Mann-Whitney tests, except for age, a normally distributed variable, which was analysed with Student *t* test.

Correlations were performed through Spearman's rank correlation coefficient.

For facial emotion recognition test, Shapiro-Wilk tests were not significant for bvFTD and control groups, indicating normal distributions. By contrast, emotion recognition performance in AD was non-normally distributed (Shapiro-Wilk: $p < .05$), which was further corroborated by a high frequency mode score (85.71) and a low Kurtosis coefficient (-0.93) in the AD group. These results suggest that the AD group is not homogeneous in its emotion

performance and that facial emotion recognition is potentially influenced by other variables.

To elucidate this further, we ran a correlation analysis on the demographic, clinical and biological variables (age, education level, disease duration, MMSE and CSF biomarkers: A β ₄₂, Tau and P-Tau) to estimate their influence on the emotion performance in AD. Results showed that MMSE ($R=0.47$; $p < .005$) and disease duration ($R=-0.51$; $p < .005$) were significantly correlated with total facial emotion recognition in AD. Interestingly, CSF-Tau level, reflecting neuronal and axonal degeneration and formation of neurofibrillary tangles

^[9,10], was also significantly correlated ($R=-0.63$; $p < .05$) with facial emotion recognition in the subgroup of AD with available tau data. No variables correlated with the emotion recognition in bvFTD. Based on the convergent links between emotion recognition and progression in AD, we decided therefore to conduct 2 analyses. In the first one, the overall AD group was contrasted with bvFTD and controls. In the second analysis, we contrasted very mild-AD and mild/moderated-AD with bvFTD and controls, by median-splitting the AD group via two proxy measures for disease severity: i) via disease duration (median=3 years) into a very mild ($n=14$, mean=1.7 year) and a mild/moderate ($n=16$, mean=5.3 year) group (3 patients were excluded from this analysis because disease duration was not available) and, ii) in a separate analysis, via low ($n=15$, MMSE mean=21.7) and high ($n=18$, MMSE mean=25.7) MMSE (median=24). Due to converging results between disease duration and MMSE analyses, only the results from the first analysis (disease duration median-split) are presented here in detail.

We also performed logistic regressions using Enter method in order to test changes in diagnostic accuracy (AD vs bvFTD) for facial emotion recognition as a function of disease progression.

RESULTS

Demographics, neuropsychological and facial emotion recognition scores for all three groups are presented in Table 1. Comparisons of bvFTD, AD and control groups revealed no significant difference for gender, education and disease duration. However, patients with AD were significantly older ($t=2.7$; $p < .05$) than bvFTD patients. Importantly, very mild-AD and mild/moderate-AD did not differ significantly on age, gender, education and the Frontal Assessment Battery (FAB) but MMSE was significantly higher in very mild-AD ($Z=-2.4$; $p < .05$).

Facial emotion recognition – AD vs. bvFTD

For this analysis, age was added as a covariate. On the total score, controls performed significantly better than AD and bvFTD ($Z=-6.9$; $p < .0001$), with bvFTD significantly impaired ($Z=-4.8$; $p < .0001$) in comparison to AD (Figure 1A). Across emotion subscores, bvFTD performed significantly worse than controls (all $p < .0001$) and AD (all $p < .01$), except for Happiness and Neutral, which were not significantly different between AD and bvFTD. AD patients were only impaired on the happiness ($Z=-1.9$; $p < .05$) and sadness subscores compared to controls ($Z=-2.4$; $p < .01$), with a non-significant trend for neutral ($p=.07$).

Comparisons between bvFTD patients with and without patho-physiological CSF confirmation showed no differences on any measure. Similarly, no significant differences were also observed for AD subgroups.

Facial emotion recognition – very mild AD vs. mild/moderate AD vs. bvFTD

Median-splitting of the AD group based on disease duration demonstrated no significant difference on total emotion recognition score between the very mild-AD group and controls, but the very mild-AD group performed significantly better ($Z=-4.9$; $p < .0001$) than bvFTD (Figure 1B). By contrast, mild/moderate-AD patients were significantly impaired compared to controls ($Z=-4.3$; $p < .0001$) and very mild-AD ($Z=-3.7$; $p < .0001$) and performed better than bvFTD ($Z=-2.5$; $p < .05$). These results were identical when median-splitting the AD group based on the MMSE score.

Analyses of the emotion subscores revealed a similar picture, with no significant difference between very mild-AD and controls. By contrast, mild/moderate-AD performed worse than controls for happiness ($p < .01$), disgust ($p < .05$), neutral ($p < .01$), surprise ($p < .05$), anger ($p < .05$) and sadness ($p < .0001$). Mild/moderate-AD also performed significantly worse than very mild-AD for sadness ($Z=-3.3$; $p = .001$) and anger ($Z=-2.4$; $p < .05$), with a trend towards

significance for disgust ($p=.09$).

Comparisons with bvFTD for emotion subscores showed that very mild-AD patients performed significantly better than bvFTD on all emotions ($p<.005$) except happiness ($p>.1$). Compared to mild/moderate-AD, bvFTD patients performed worse for anger ($Z=-2.7$; $p < .01$) and sadness ($Z=-2.3$; $p < .05$). A similar pattern was observed when median-splitting the AD group on the MMSE score.

Logistic regression analyses.

Logistic regression (ENTER method) revealed facial emotion recognition distinguished between bvFTD and AD in 76.7% of cases. This distinction increased when contrasting bvFTD and very mild-AD (94.6%) but was similar between bvFTD and mild/moderate-AD (78.9%).

DISCUSSION

Our results indicate that facial emotion recognition performance in AD is influenced by the disease duration and overall cognitive impairment as measured by the MMSE, which are both proxies of disease progression/severity. Furthermore, while this result should be further replicated in a greater sized group, facial emotion recognition in AD seems also linked to the level of Tau protein deposition, a CSF marker of neuronal and axonal degeneration and formation of neurofibrillary tangles^[9,10]. Although these findings are cross-sectional and not longitudinal, they indicate a clear decline in the recognition of emotion with the progression of AD by the convergence of clinical, cognitive and biological data. The observed differences between very mild and mild/moderate AD patients might also explain previous inconsistent AD findings^[2-4], due to different admixtures of patients at different disease stages. In addition, our results inform the diagnostic distinction of bvFTD and AD. Emotion deficits have been regarded as a hallmark

for bvFTD but not AD and thus are now included as diagnostic markers for possible bvFTD ^[5]. Our results confirm that bvFTD are consistently impaired on emotion recognition and can be distinguished from very mild-AD in over 94% of presenting cases. However, distinction from mild/moderate-AD resulted in lower accuracy (~78%). Taken together, these results suggest disease progression (disease duration or MMSE) should be taken into account during the diagnostic evaluation of facial emotion recognition in AD and bvFTD. In particular a disease duration longer than 3 years or an MMSE score lower than 24, which were the median-split cut-offs in our study, should warrant caution to put too much emphasis on facial emotion recognition performance in the diagnostic distinction between AD and bvFTD.

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Legend of Figure 1

Title: Percentage of correct answers in the facial emotion recognition test for controls, AD and bvFTD patients (A). Percentage of correct answers in the facial emotion recognition test after disease duration split in the AD group (B).

Legend:

* Indicates a significant difference. Abbreviations: AD: Alzheimer's disease; bvFTD: behavioral version of frontotemporal dementia.