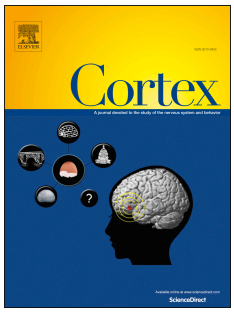
Accepted Manuscript



Determinants of Theory of Mind performance in Alzheimer's disease: A data-mining study

Siddharth Ramanan, Leonardo Cruz de Souza, Noémie Moreau, Marie Sarazin, Antônio L. Teixeira, Zoe Allen, Henrique C. Guimarães, Paulo Caramelli, Bruno Dubois, Michael Hornberger, Dr. Maxime Bertoux

PII: S0010-9452(16)30339-2

DOI: 10.1016/j.cortex.2016.11.014

Reference: CORTEX 1885

To appear in: *Cortex*

Received Date: 25 August 2016

Revised Date: 26 October 2016

Accepted Date: 23 November 2016

Please cite this article as: Ramanan S, Cruz de Souza L, Moreau N, Sarazin M, Teixeira AL, Allen Z, Guimarães HC, Caramelli P, Dubois B, Hornberger M, Bertoux M, Determinants of Theory of Mind performance in Alzheimer's disease: A data-mining study, *CORTEX* (2016), doi: 10.1016/j.cortex.2016.11.014.

Determinants of Theory of Mind performance in Alzheimer's disease: A data-mining study

Siddharth Ramanan[a], Leonardo Cruz de Souza[b], Noémie Moreau[c], Marie Sarazin[d], Antônio L Teixeira[b], Zoe Allen[e], Henrique C Guimarães[b], Paulo Caramelli[b], Bruno Dubois[f,g], Michael Hornberger[e], Maxime Bertoux[e,f,g*]

[a] Department of Neurology, Manipal Hospitals, Bangalore, India

[b] Federal University of Minas Gerais, Belo Horizonte, Brazil.

[c] Aix Marseille Université, CNRS, LPL, Aix-en-Provence, France.

[d] Centre Psychiatrie & Neurosciences, Sainte-Anne, Paris, France

[e] Norwich Medical School, University of East Anglia, UK

[f] Centre de Référence Démence Rares, Pitié-Salpêtrière, Paris, France

[g] Sorbonne Universités, Paris VI, France

*** Corresponding author**

maxime.bertoux@cantab.net

Tel. +44 (0)1603 593061

Dr. M. Bertoux

Applied Dementia Research

Norwich Medical School

Bob Champion Research and Educational Building

James Watson Road

University of East Anglia

Norwich Research Park

Norwich NR4 7UQ

Word count: 5473

Abstract

Whether theory of mind (ToM) is preserved in Alzheimer's disease (AD) remains a controversial subject. Recent studies have showed that performance on some ToM tests might be altered in AD, though to a lesser extent than in behavioural-variant Frontotemporal Dementia (bvFTD). It is however, unclear if this reflects a genuine impairment of ToM or a deficit secondary to the general cognitive decline observed in AD. Aiming to investigate the cognitive determinants of ToM performance in AD, a data-mining study was conducted in 29 AD patients then replicated in an independent age-matched group of 19 AD patients to perform an independent replication of the results. 44 bvFTD patients were included as a comparison group. All patients had an extensive neuropsychological examination. Hierarchical clustering analyses showed that ToM performance clustered with measures of executive functioning in AD. ToM performance was also specifically correlated with the executive component extracted from a principal component analysis. In a final step, automated linear modelling conducted to determine the predictors of ToM performance showed that 48.8% of ToM performance was significantly predicted by executive measures. Similar findings across analyses were observed in the independent group of AD patients, thereby replicating our results. Conversely, ToM impairments in bvFTD appeared independent of other cognitive impairments. These results suggest that difficulties of AD patients on ToM tests do not reflect a genuine ToM deficit, rather mediated by general (and particularly executive) cognitive decline. They also suggest that executive functioning has a key role in mental state attribution, which support interacting models of ToM functioning. Finally, our study highlights the relevancy of data-mining statistical approaches in clinical and cognitive neurosciences.

Keywords: theory of mind; Alzheimer's disease; behavioral variant frontotemporal dementia; data mining; data driven

1. INTRODUCTION

Social cognition refers to a complex set of behaviours such as emotion recognition and mental states inference that supports successful social interactions (Amodio & Frith, 2006). It is now considered one of the six main cognitive domains according to the most recent edition of the Diagnostic and Statistical Manual of Mental Disorder (DSM-V, American Psychiatric Association, 2013). Accordingly, strong emphasis is now placed on its assessment. Theory of mind (ToM), the ability to infer others' knowledge, belief and feelings is a key process underlying social cognition and is assessed through various neuropsychological tests varying in their design, administration and complexity. Several studies have shown evidences of social cognition and particularly ToM impairment in neurodegenerative diseases such as in behavioural-variant frontotemporal dementia (bvFTD) (for a review, see Elamin, Pender, Hardiman, & Abrahams, 2012). By contrast, social cognition was found to be relatively preserved in Alzheimer's disease (Gregory et al., 2002; Torralva et al., 2007; Bertoux, Funkiewiez, O'Callaghan, Dubois, & Hornberger, 2013), although recent studies have indicated contrary evidences suggesting ToM deficits in AD (Freedman, Binns, Black, Murphy, & Stuss, 2013; Moreau, Rauzy, Viallet, & Champagne-Lavau, 2016).

Two distinct views regarding ToM performance in AD and its relationship to general cognition have been subserved: one highlighting its inherent independence from general cognition, and the other showcasing its interdependence with general cognition. In particular, the dependency of social cognition on processes such as executive functioning (EF) and episodic memory in AD remains unclear, as past studies examining these interactions have reported inconsistent findings (Castelli et al., 2011; Cosentino et al., 2014; El Haj, Gely-Nargeot, & Raffard, 2015; Moreau et al., 2016). Though differences between studies and viewpoints can be attributed to methodological, test-choice, and sample differences, it remains important to reconcile these opposing perspectives. Such findings would have implications towards designing the next generation of ToM tests with low executive or memory demands so as to gauge true ToM deficits in AD. This is also of critical importance considering that social cognition assessment is currently one of the best cognitive domain to discriminate AD from bvFTD clinically, even when either condition presents with severe amnesia (Bertoux et al., 2015).

Recent models propose that ToM is not an isolated and specific module of human cognition. The representation and maintaining of others' mental states is rather be the result of low-level mechanisms dedicated to socially-relevant information gathered from the perceptual environment (e.g. gaze direction, body movements, emotional facial or vocal expression) interacting with high-level domain-general functions such as memory, language, or EF (Achim, Guitton, Jackson, Boutin, & Monetta, 2013; Samson, 2009; Stone & Gerrans, 2006). Complex ToM tasks that supposedly impose greater load on high cognitive functions may thus be failed because of general cognitive deficit, such as EF impairments.

The question of the neuropsychological determinants of ToM performance in AD has been previously driven by hypotheses of independency or inter-dependency with general cognition, and statistical analyses such as ANOVAs or partial correlations have been employed to confirm or refute such hypotheses. In the current study, we opted for a different approach, as such classical statistical comparisons are suboptimal to document complex and influential relationships within a large set of data. As we believe that the complex nature of the human mind requires neuroscientists to use the full spectrum of tools available in modern biology and statistics, we conducted a data-mining study aiming to explore the relationship and contribution of neuropsychological domains on ToM in AD. As past studies have shown inconsistent results, we included an independent group of AD patients in order to perform a replication of our findings, as well as a group of bvFTD patients as a contrast group.

2. MATERIALS AND METHODS

2.1 Participants

Ninety-two patients were included in this study, including 48 patients with typical AD, all satisfying the revised criteria (Dubois et al., 2007) recruited at two independent centres to perform an independent replication of the results. Of these cases, 29 (60.5%) were seen at the Centre for Psychiatry and Neurosciences of Sainte-Anne Hospital (Paris, France) and 19 (39.5%) were seen at the Department of Internal Medicine (Faculty of Medicine) at the Federal University of Minas Gerais (Belo Horizonte, Brazil). Twenty-three patients (47.9%), including 13 cases from the French cohort (44.8%) and ten cases from the Brazilian cohort (52.6%) had a clinical

diagnosis supported by abnormal levels of cerebrospinal fluid measured phospho-tau, total-tau, and beta-amyloid levels. The Innotest® Amyloid Tau Index ($A\beta_{42}$/240 + 1.18 tau) was used in this purpose (Vanderstichele et al., 2006).

As a contrast group, we included bvFTD patients (*n*=44), all satisfying the revised criteria (Rascovsky et al., 2011). These patients were seen at the Memory and Alzheimer Institute of Pitié-Salpêtrière Hospital (Paris, France). We allowed bvFTD patients with memory impairment if other core diagnostic criteria were present. Sixteen patients (36%) bvFTD cases had a clinical diagnosis supported by the absence of AD biomarker profile as revealed by cerebrospinal fluid measures. Part of the bvFTD data showcased here has been presented in a former study (Bertoux, O'Callaghan, Dubois, & Hornberger, 2016).

All patients underwent extensive neuropsychological testing as well as T1-MRI (and/or SPECT imaging). Patients presenting with motor-neuron disease, severe depression, focal lesions or severe vascular lesions were excluded. Biological and clinical data of all French patients were generated during routine clinical workup and were retrospectively extracted for the purpose of this study. As per French legislation, explicit informed consent was waived as patients and their relatives were informed that individual data might be used in retrospective clinical research studies. The recruitment of Brazilian patients was approved by the Ethics Committee of the University Federal of Minas Gerais (CAA-17850513.2.0000.5149) and all patients or their legal representatives provided written informed consent.

2.2 Neuropsychological assessments

In addition to a general cognitive screening tool (Mini Mental State Examination, MMSE: Folstein, Folstein, & McHugh, 1975; Kalafat et al., 2003), all participants underwent neuropsychological assessments as described below.

2.2.1 Assessment of memory

All French cohort participants underwent the Free and Cued Selective Reminding Test (FCSRT: Grober, Buschke, Crystal, Bang, & Dresner, 1988; Van der Linden, 2006), a memory test based on a semantic cueing method that controls for effective encoding of 16 words and facilitates their retrieval by semantic cueing. Briefly, the

word list is presented three times followed by free and cued (using semantic cueing) recall trials, and delayed free and total (free+cued) recall trials. In the current study, only performance on free recall, total recall and delayed total recall measures were considered.

All Brazilian cohort participants underwent the memory component of the Brief Cognitive Screening Battery (BCSB: Nitrini et al., 2004). Briefly, ten line drawings of common objects (e.g. shoe, spoon, key) are presented, asked to be named aloud, and recalled immediately after. The list is then presented three times with an interference trial, a delayed recall trial, and a recognition component.

Though the FCSRT and BCSB differ in terms of test items, administration and scoring, both tests produced immediate recall (or encoding), free recall and delayed recall scores. Therefore in the current study, we treated these scores across both tests as measures of the same construct of memory. Group comparisons on these measures were assessed based on cohort-specific *z*-scores.

2.2.2 Assessments of executive functions

The Frontal Assessment Battery (FAB: Dubois, Slachevsky, Litvan, & Pillon, 2000; Dubois et al., 1997), lexical and semantic fluency tests (Godefroy & Grefex, 2008), and forward and backward digit spans (Wechsler, 1997) were administered to all participants.

2.2.3 Assessment of theory of mind

All patients underwent the reduced and modified faux pas test, a part of the mini Social cognition and Emotion Assessment (mini-SEA: Bertoux et al., 2013; Bertoux, 2014), which assesses ToM through short stories, some which contain a social misconduct (faux pas). Patients have to detect the presence of a faux pas (detection) and answer questions assessing its attribution to a character of the story (attribution), its identification, knowledge, intentionality, and emotional impact on the victim (empathy) (Stone, Baron-Cohen, & Knight, 1998).

3. Statistical analyses

Analyses were conducted using R v3.3.0 (R Core Team, 2016). For group comparisons, variables were plotted and checked for normality of distribution via Shapiro-Wilk tests. Between AD groups, where variables were normally distributed,

t-tests were employed; otherwise Mann-Whitney tests were employed. *Post-hoc* comparisons between the main AD, independent AD, and the bvFTD group, were assessed using ANOVAs with Bonferroni corrections.

To determine how closely ToM, EF, and memory processes were related, we conducted a hierarchical cluster analysis, using Ward's method. As a first step, all neuropsychological test scores data were standardized (*z*-scores). Briefly, the cluster analysis defines each variable as an individual cluster; clusters are then sequentially merged as per their similarity/distance (squared Euclidean distance) in a geometric space where the number of variables set the number of dimensions. We used Bayesian Information Criterion value-guided models to determine the optimal number of clusters. The components extracted from the optimal model are then plotted on a dendrogram representing the relationships of similarity among the group of variables. The validity of the clustering architecture in AD was then assessed through a correlation analysis performed between ToM (faux-pas total score) and EF measures that were not previously included in the clustering analysis. In the Brazilian sample (n=19), (1) the number of errors from the Hayling (Part B) test (Burgess & Shallice, 1997) and (2) from the Stroop (Part B) test (Golden et al., 1978) as well as (3) a phonemic verbal fluency score (using letter A) were chosen. In the French sample, (1) the number of correct criteria identified during the modified Wisconsin Card Sorting Test (mWCST, Nelson et al., 1976; Godefroy & Grefex, 2008) and (2) the number of perseverative errors at this test were chosen (data only available for 14 patients). The validity of the clustering architecture in bvFTD was assessed in a similar way, with the number of correct criteria identified during the mWCST and (2) the number of perseverative errors at this test chosen as external variables (data only available for 42 patients).

As a second step, all EF variables (FAB, fluencies, and digit spans) were entered into a principal component analysis and a forced extraction of a single component (using varimax rotation) was performed. Individual participant loadings on this single component were then correlated with their respective ToM scores, using Spearman's rank correlation. The same method was employed for extraction of an episodic memory factor (using encoding, free and delayed recall measures).

Finally, all neuropsychological variables including the MMSE were entered into an Automated Linear Model (ALM) as predictors of ToM performance, to investigate the relationships between these variables in terms of variance contributions. ALM allows identifying the best predictive model given the data, without any a priori hypothesis. Akaike Information Criterion Corrected for small sample size was employed as a selection criterion to account for small sample size. As a major focus of the current study was on independently validating the determinants of ToM in AD, for all analyses, we report findings from the main AD cohort (French cohort) followed by findings from the second cohort (Brazil cohort).

3. RESULTS

3.1 Demographics and neuropsychological test measures (Table 1)

Between the French and Brazilian AD cohorts, no significant differences on any demographic or neuropsychological test variables were noted (all *p* values >0.1), except on the forward digit span, where the Brazilian AD cohort performed significantly better than the French AD cohort ($p<0.001$). Both AD groups differed from bvFTD on ToM assessment ($F=18.02$; $p<0.00001$) and the Brazilian AD group outperformed bvFTD patients on forward digit span ($Z=-4.97$; $p<0.001$).

Table 1. Demographic and neuropsychological test data for patient groups.

	AD (France)	AD (Brazil)	bvFTD	AD (France vs. Brazil)	
N	29	19	44	*t/Z* value	*p* value
Age (years)	72.00 (10.11)	71.15 (9.20)	65.25 (9.39)	0.29	0.76
Education (years)	11.47 (3.42)	12.94 (4.14)	11.37 (3.64)	-0.07	0.94
MMSE	23.85 (2.42)	24.68 (2.08)	24.47 (3.66)	-1.24	0.21
Neuropsychological test variables					
FAB	14.44 (2.68)	13.15 (2.75)	13.34 (3.22)	1.60	0.11
ToM (Faux pas test)	11.45 (1.96) †	11.96 (2.08) †	9.26 (2.43)	-0.83	0.40
Phonemic fluency	10.13 (3.91)	8.89 (3.49)	7.95 (6.14)	1.14	0.25

Category fluency	14.27 (5.51)	12.15 (3.21)	13.63 (5.78)	1.67	0.10
Forward digit span	5.39 (1.10)	7.47 (1.42) †	5.27 (1.26)	-5.36	0.00006
Backward digit span	4.03 (0.92)	4.15 (1.21)	3.52 (1.08)	-0.37	0.71
Encoding[a]	13.48 (2.39)	6.68 (1.41)	12.93 (3.54)	-0.41	0.67
Free recall[a]	10.82 (5.81)	6.84 (1.50)	17.68 (8.39)	-0.0003	0.99
Delayed recall[a]	8.72 (4.48)	4.31 (1.76)	12.90 (4.00)	-0.007	0.99

Note. Standard deviation shown in brackets; [a]*Post-hoc* comparisons evaluated based on cohort-specific *z*-scores, given differences in test scoring; AD, Alzheimer's disease; bvFTD, behavioural variant frontotemporal dementia; MMSE, Mini-Mental State Examination; FAB, Frontal Assessment Battery; ToM, Theory of Mind.
†, $p<0.001$ with bvFTD;

3.2 Data mining approach

Clustering results from the hierarchical cluster analysis are shown in figure 1A-C. Similar variables were joined at earlier stages (bottom of the dendrogram) and less similar ones at later stages of the analysis (top of the dendrogram). In the French AD cohort (figure 1A), two independent clusters were identified by the analysis - an episodic memory cluster (comprising of free, total and delayed recall measures) and an EF and ToM cluster (forward/backward digit spans, semantic/lexical fluency, FAB and ToM scores). In the Brazilian AD cohort (figure 1B), three independent clusters were identified by the analysis – one EF and ToM cluster (semantic/lexical fluency, backward digit span, FAB and ToM scores), one attention/short-term memory cluster (digit span forward) and one episodic memory cluster (encoding, free and delayed recall measures). When analyses were restricted to the AD patients subgroups that had CSF-biomarkers confirming the clinical diagnosis, ToM continued to cluster with EF measures and not with memory scores.

The correlation analysis performed between ToM and EF measures that were not previously included in the clustering analysis was carried to assess the validity of the clustering findings. Moderate correlations with trends of significance were observed between ToM and Hayling (r=-.43; p=.07) and Stroop (r=-.39; p=.10) errors as well as a strong and significant correlation with phonemic "A" fluency (r=.71; p<.001) in the Brazilian sample. In the French sample, moderate to strong significant correlations

with the number of criteria (r=.59; p<.05) and perseverative errors (r=-.86; p<.0005) at the mWCST were also observed. Taken together, these results support the validity of the clustering findings as they show that ToM was also significantly related to external EF measures.

In the bvFTD cohort (figure 1C), four independent clusters were identified: one EF cluster (FAB and digit spans), one episodic memory cluster (free, total and delayed recall measures), another EF cluster (lexical/semantic fluency), and an independent ToM cluster.

The correlation analysis carried to assess the validity of the clustering results showed that ToM did not correlate with the number of mWCST criteria (r=.13; p=.40) or with the number of perseverations (r=-.28; p=.12). Stability of the clusters was also observed after randomly splitting the bvFTD group in two subgroups, as the clustering architecture was identical in these subgroups.

3.3 Correlations with components (Figure 2)

From the principal components analysis (PCA), an episodic memory component and an EF component were extracted. In the French AD-cohort, ToM performance was significantly correlated with the EF component (r=0.46; p<0.05) but not with the episodic memory component (r=-0.19; p>0.1). Similarly, in the Brazilian AD-cohort, a large significant correlation between the EF component and ToM performance was observed (r=0.74; p<0.001) while a moderate coefficient trending towards statistical significance was noted between ToM and the episodic memory component (r=0.42; p=0.06). By contrast, in the bvFTD group, these correlations were non significant (all p>.5).

3.4 Automated Linear Modelling (ALM)

All neuropsychological measures were entered into an ALM (including the MMSE) as predictor variables in a forward stepwise manner, with ToM as the target variable. Plots of correlations between performance on the faux pas test and predicted values by the model are presented on Figure 2C. In the French AD-cohort, together, all neuropsychological variables predicted 48.8% of ToM performance. Of this total variance, the strongest predictors were forward digit span (explaining 42% of variance; p<0.01) and free recall (22% of variance; p<0.05). Lexical fluency and FAB

were also identified as predictors for ToM performance (20% and 16% of variance respectively), however these failed to reach statistical significance.

In the Brazilian AD cohort, all neuropsychological variables predicted 69.8% of ToM performance. Of this total variance, the strongest predictors were the FAB (explaining 79% of variance; $p<0.001$) and forward digit span (15% of variance; $p<0.05$). Delayed total recall measure was also identified as a predictor (7% of variance) but this failed to reach statistical significance.

In the AD CSF-confirmed subgroup, only one predictor (FAB) emerged to explain 51.6% of the model's variance ($p<0.01$). Interestingly, in the bvFTD cohort, no neuropsychological variables emerged as predictors of ToM (all p values >0.1).

3.5 *Post-hoc* analysis on ToM subcomponents

Similarly to a previous study (Bertoux et al., 2016), a *post-hoc* hierarchical clustering analysis was performed on AD patients in order to investigate the differential link between ToM subcomponents and EF. Due to the retrospective nature of the study, these subscores were only available for the Brazilian patients and thus, this analysis was only conducted on this sample (n=19). Four distinct clusters were identified (Supplementary figure 1): one mixed ToM and executive cluster where FAB clustered with most of the ToM subcomponents including faux pas's detection, identification, attribution, empathy and intentionality subscores; an executive and working memory cluster that included semantic and lexical fluencies as well as digit span backward; a mixed ToM and memory cluster, where faux pas' knowledge clustered with all BCSB's subscores; and a last cluster only comprising the digit span forward.

4. DISCUSSION

The data-mining approach employed in this study clearly shows that ToM performance in AD appears to be heavily linked to executive functioning. From the cluster analysis on two independent AD groups, our results indicated that ToM performance, as measured by the faux pas test, clustered closely with executive performance on measures like the FAB, digit spans, and semantic/lexical verbal fluency. Supporting these findings, correlation analyses conducted in the two independent AD groups verified that ToM performance significantly correlated only with the PCA-extracted EF component. Similarly, using an ALM on all

neuropsychological test variables, we demonstrated that attention and executive measures such as the FAB and forward digit span emerged as significant predictors of ToM performance, accounting for ~50-70% of ToM performance across both cohorts. Importantly, our findings across two independent AD cohorts were highly similar, thereby replicating our results. Finally, a last *post-hoc* analysis showed that most of the ToM subcomponents were linked to executive functioning as five dimensions of the faux pas test, namely detection, identification, attribution, intentionality and empathy, clustered with the FAB, a multidimensional measure of executive functions.

Taken together, our findings firstly suggest than ToM impairments remain closely related to executive performance in AD. Conversely, all data-driven analyses conducted in the bvFTD group corroborate and deepen previous findings, suggesting that ToM impairments in bvFTD remain largely independent of general cognition, episodic memory, and executive impairments noted in the disease (Bertoux et al., 2016; Lough & Hodges, 2002). In more detail, only intentionality and empathy subcomponents have shown to be linked to executive and attention functioning in bvFTD in a past study (Bertoux et al., 2016) while almost all subcomponents of the faux pas test were linked to executive functions in AD.

Another notable result is the link between ToM and memory functioning. Although episodic memory clustered separately from ToM in both AD groups and despite the absence of correlation between ToM and the PCA-extracted episodic memory component, the ALM showed that short-term memory and free recall score of the FCSRT are among the best predictors of ToM performance in the French AD group and may explain up to 22% of the ToM variance. This suggests that impaired verbal attention abilities and strategic memory recall could negatively impact ToM performance in AD, especially with the faux pas test that relies on verbal material.

Previous studies evaluating ToM in neurodegenerative diseases have mainly focused on bvFTD, for its early manifestations of impaired social cognition in the evolution of the disease. Indeed, past studies have shown that with early atrophy of the medial prefrontal cortex region (mPFC), a key region for theory of mind functioning (Amodio & Frith, 2006; Carrington & Bailey, 2009; Van Overwalle, 2009), bvFTD patients show severe impairments on social cognition and ToM tasks such as the faux

pas test as compared to AD (Gregory et al., 2002; Bertoux et al., 2013). These deficits persist over time and also rapidly worsen in bvFTD patients with marked mPFC atrophy compared to those with limited mPFC atrophy (Kumfor et al., 2014). By contrast, the evidence for ToM impairment in AD has lacked general consensus on whether deficits on ToM tasks are a result of an authentic impairment of ToM (Cosentino et al., 2014; Freedman et al., 2013; Moreau et al., 2016), or due to deteriorating general cognition in the disease, an approach that is compatible with the interactive models of ToM (Dodich et al., 2016; Stone et al., 2006). Few studies in support of a stand-alone ToM deficit in AD have shown that AD patients could fail on basic ToM tasks like gaze-processing (Laisney et al., 2013) and inferring someone's (first-order false) beliefs (Freedman et al., 2013; Le Bouc et al., 2012). On the other hand, studies in support of a ToM deficit secondary to deteriorating executive and general cognitive functions in AD have shown that these patients do show relatively preserved performance across simple first-order cognitive and affective belief inference tasks (Elamin et al., 2012; Fernandez-Duque, Baird, & Black, 2009; Zaitchik, Koff, Brownell, Winner, & Albert, 2006), but were impaired on more complex belief inference tasks (e.g. second-order false belief) that are supposed to place greater demands on working memory and executive functions (Gregory et al., 2002). A study adopting a neurodevelopmental perspective at examining ToM in AD suggested that performance on complex ToM tasks that are acquired later in the developmental spectrum (e.g. second-order false belief tasks), appeared to decay first in AD, and highly correlated with their performance on executive tasks of reasoning and abstraction (Castelli et al., 2011). A critical appraisal of such inconsistent results for determinants of ToM performance in AD suggests that such differences across studies largely arise due to variations in sample sizes, methodologies, and more importantly the design and complexity of the ToM task administered to the AD population (Bora, Walterfang, & Velakoulis, 2015).

Exploring the relationship between the faux pas test performance and other neuropsychological measures of general cognition, episodic memory and executive functioning, we demonstrated through a pure data-driven approach that more half of ToM variance in AD can be explained by EF & attention impairment as well as memory deficits. This is in stark contrast with what was observed in bvFTD, in which ToM emerged largely independent of executive performance as well as general

cognition and memory processing. Indeed, while only mental attribution dimensions have been shown to be linked to EF performance in bvFTD (Bertoux et al., 2016), almost all ToM subcomponents rely on EF in AD, including detection, identification and attribution of faux pas as well as mental attribution dimensions. Our results may thus bring new evidences in support of interactive models of ToM architecture, arguing that the ability to infer mental states relies on the interaction between low-level domain-specific and high-level domain-general mechanisms such as EF (Samson, 2009; Stone & Gerrans, 2006). In that view, efficient complex mental attributions are dependent on a contextual social framework integrating relevant information gathered in the environment by low-level processes (Achim et al., 2013). Because EF seem to sparsely explain ToM deficit in bvFTD (Bertoux et al., 2016; Lough & Hodges, 2002), this suggest that other mechanisms, such as contextual integration (i.e. the collection and integration of social cues) as well as social norms knowledge and awareness may play a significant role in patients' difficulties to infer mental states, especially on the faux pas test (Bora et al., 2015; Ibanez & Manes, 2012).

To our knowledge, this study is the first to have employed data-driven approaches to identify the neuropsychological determinants of ToM performance in AD. Previous studies have mainly relegated this question into the background or have used either ANOVA or partial correlations analyses to address this point. These statistical methods are appropriate to investigate an *a priori* hypothesized effect of one variable on another one, but that do not allow identifying natural grouping or pattern in data, a goal that can only be achieved using data-driven methods. Although highly focused, hypothesis-driven researches can provide interesting and powerful results in the context of known neural circuits and functions, we believe that more explanatory methods, not aiming at testing a specific hypothesis but instead enabling data-driven discovery, could provide complementary results critical for the community (Akil, Martone, & Van Essen, 2011). In that perspective, hypothesis-free automated or semi-automated statistical tools can intelligently assist in transforming vast amounts of data into useful information that can, in turn, inform about brain networks functioning (Smith, Hyvarinen, Varoquaux, Miller, & Beckmann, 2014), diagnosis procedure (Wang, Redmond, Bertoux, Hodges, & Hornberger, 2016), or cognitive architecture (Bertoux et al., 2016). Our data-driven findings suggest a strong dependence of ToM

on EF in AD, directly contradicting a recent study that highlighted the independence of ToM impairment and general cognition performance in AD (Cosentino et al., 2014). One possible reason for such differences is that (Cosentino et al., 2014) measured social cognition using a carer-reported deficit scale that may be affected strongly by caregiver bias and reflect less accurate patient-centred ToM deficits while our study used a performance-based, objective measure of ToM processing. Moreover, the confirmation of our results in a subgroup of patients with biological evidence of diagnosis and replication of our findings in an independent group of AD patients strengthened our findings. Our results are also in line with recent meta-analyses and systematic reviews that examined ToM performance across multiple tasks and found ToM to be modestly impaired in AD, with more complex ToM tasks closely linked to general cognitive impairment and executive processing(Fernandez-Duque et al., 2009; Sandoz, Demonet, & Fossard, 2014), as opposed to simple ToM tasks like first-order false beliefs (Aboulafia-Brakha, Christe, Martory, & Annoni, 2011).

From our findings, speculations may arise regarding additional cognitive processes that may possibly interfere with ToM processing in AD, as a proportion of ToM performance was not explained by EF. Although our findings showed that transversal cognitive processes such as EF or attention could critically impact on ToM processing, ToM is a multicomponent function that depends on other specific and independent cognitive mechanisms. As stated above, strong interactions with semantic memory (e.g. understanding of social rules and norms) and context processing (e.g. understanding of the social context and actors) are also important for ToM processing, particularly in the multi-dimensional faux pas test. These other dimensions of social cognition have been shown to be processed by a complex cortical network that is particularly vulnerable across different neurodegenerative diseases. Given that the field of affective neurosciences is so young, all the cognitive processes involved in ToM processing and, by extension, all the cerebral regions supporting these processes have not been described or characterized in detail yet. While mounting evidences from bvFTD have pointed to the role of mPFC atrophy and its direct association with ToM impairment (Adenzato, Cavallo, & Enrici, 2010; Bertoux et al., 2012; Bertoux et al., 2014), strong evidences suggest the involvement of a larger cerebral network dedicated to ToM processing. As examples, the role of the polar temporal pole (Ross & Olson, 2010) and the temporo-parietal junctions in inferring other's mental-states

(Schurz, Radua, Aichhorn, Richlan, & Perner, 2014) has been pointed out. Moreover, some imaging studies evidenced common cerebral activations during ToM and self-projection in other times, places or other's mind (Buckner & Carroll, 2007; Rabin, Gilboa, Stuss, Mar, & Rosenbaum, 2010); this set of overlapping regions being related to the default mode network (Raichle et al., 2001; Spreng & Grady, 2010), a functional network particularly fragile in AD (Hafkemeijer, van der Grond, & Rombouts, 2012; Simic, Babic, Borovecki, & Hof, 2014). Taken together, these results support the need for future studies to investigate components of ToM that could be selectively impaired or preserved in AD with concomitant atrophy of these regions

A number of limitations in our study warrant consideration. We used a single test of ToM when including other ToM tasks may have strengthened our findings. However, sieving through ToM tasks for their sensitivity, the meta-analysis by (Bora et al., 2015) suggested the faux pas task is the most sensitive to discriminating AD from bvFTD, as opposed to false belief tasks where performance by both groups may appear indistinguishable. In addition, this test is one of the few ToM tests allowing for a multi-dimensional assessment of ToM (exploring detection of faux pas as well as cognitive (inference of belief and knowledge) and affective (empathy) aspects of ToM. The sample size of the patient groups included in this study is also a limitation to the interpretation of our findings, as automated procedures usually require bigger sample sizes. However, given the number of different analyses conducted, all of which converge to support our findings, we believe that our interpretations are strong and valid, though further studies with larger sample size should confirm them. Another limitation is that only half of our patients had diagnostic confirmation via cerebrospinal fluid data. Results in this sample were however similar to those observed in patients with clinical diagnosis (which however include MRI evidences of medial temporal lobe atrophy). Furthermore, this study employed a replication method on an independent group of AD patients, a method rarely employed in neuropsychology that, we believe, strengthened the observed results. Finally, by choosing a group composed from Brazilian AD patients to replicate findings observed in a group of French AD patients, this study show that ToM, a cognitive function embedded in culture and local norms relies on similar processes regardless of cultural differences.

5. Conclusions

Our findings have strong implications, especially to clinical diagnosis and test development. The most recent edition of the DSM (American Psychiatric Association, 2013) has acknowledged the importance of assessing social cognition, placing emphasis on the use of standardized tests/batteries to assess social cognition functions. However, the current ToM tasks have not been designed as pure ToM assessments and rely heavily on language and EF that could critically impact performance. This study highlights the need for developing ToM tests that are more independent of executive, attention, language and memory performance, in order to capture more specific ToM impairment that some patients may have. In this line, the work by Roux and colleagues in schizophrenia (e.g. Roux, Brunet-Gouet, Passerieux & Ramus, 2016), using eye-tracking measures during ToM processing, is very interesting although such measures could be difficult to implement in clinical practice. Paradigms involving patients in real social interaction are also of great interest. They not only allow a more realistic approach of ToM evaluation but they also may capture a different form of ToM functioning, since studies have suggested that cognitive processes elicited by tasks where patients are merely spectators could be different from those involved in tasks where a real interaction was needed (de Bruin, van Elk, & Newen, 2012; De Jaegher, Di Paolo, & Gallagher, 2010; Gallotti & Frith, 2013). In these interactive tasks, ToM functioning is indeed probably more implicit and less dependent on EF since participants do not have to explicitly represent or explain the mental state they attribute (Champagne-Lavau & Moreau, 2013). The development of new ToM tests is even more crucial as recent studies have demonstrated that typical and atypical AD patients can present with mild to severe dysexecutive profiles (de Souza et al., 2013; Ramanan et al., 2016; Wong et al., 2016), thereby complicating interpretation of their ToM performance. Moreover, our results show that ToM testing should become commonplace in diagnosis of AD, but should be used with caution, in that, attention and EF tests should be administered concomitantly to control for EF contribution to ToM impairment. One interesting approach would be to deconstruct ToM in order to identify all its subcomponents (Schaafsma, Pfaff, Spunt, & Adolphs, 2015), which could provide a comprehensive theoretical basis to investigate the neural correlates of ToM processing and to design new tests tapping into these processes and cerebral regions. Finally, our findings also highlight the relevance of

using data mining techniques and visualization of grouping patterns in data in clinical neurosciences, which could complement group comparison analyses to map and visualize clusters of brain atrophy in neurodegenerative diseases. We believe that such approaches should be employed more frequently in clinical neurosciences as they can help to delineate the respective contributions of several variables in large or complex datasets.

Acknowledgements & Fundings

This work was partly supported by: CNPq (Brazil) grant (402853/2012-10). MB was supported by a Marie Skłodowska-Curie fellowship awarded by the European Commission.

Disclosures

Prof. Marie Sarazin received speaker honoraria from EISAI, Pfizer, Lundbeck, Janssen, and Novartis; she belongs to a scientific advisory board for EISAI Company. Prof. Bruno Dubois has consulted or served on advisory board for Bristol-Myers Squibb, Roche, Elan, Eli Lilly, Eisai, Janssen. His institution has received grants from Novartis and Sanofi-Aventis. Other authors do not have any competing interests.

REFERENCES

Aboulafia-Brakha, T., Christe, B., Martory, M. D., & Annoni, J. M. (2011). Theory of mind tasks and executive functions: a systematic review of group studies in neurology. *Journal of Neuropsychology, 5*(Pt 1), 39-55. doi:10.1348/174866410X533660

Achim, A. M., Guitton, M., Jackson, P. L., Boutin, A., & Monetta, L. (2013). On what ground do we mentalize? Characteristics of current tasks and sources of information that contribute to mentalizing judgments. *Psychological Assessment, 25*(1), 117-126. doi:10.1037/a0029137

Adezanto, M., Cavallo, M., & Enrici, I. (2010). Theory of mind ability in the behavioural variant of frontotemporal dementia: an analysis of the neural, cognitive, and social levels. *Neuropsychologia, 48*(1), 2-12. doi: 10.1016/j.neuropsychologia.2009.08.001

Akil, H., Martone, M. E., & Van Essen, D. C. (2011). Challenges and opportunities in mining neuroscience data. *Science, 331*(6018), 708-712. doi:10.1126/science.1199305

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 5th ed. Arlington, VA: American Psychiatric Publishing; 2013:pp 5–25.

Amodio, D. M., & Frith, C. D. (2006). Meeting of minds: the medial frontal cortex and social cognition. *Nature Reviews Neuroscience, 7*(4), 268-277. doi:10.1038/nrn1884

Bertoux, M. (2014). *Mini-SEA: Evaluation de la démence frontotemporale*. Paris: Solal - de Boeck.

Bertoux, M., de Souza, L. C., O'Callaghan, C., Greve, A., Sarazin, M., Dubois, B., & Hornberger, M. (2015). Social Cognition Deficits: The Key to Discriminate Behavioral Variant Frontotemporal Dementia from Alzheimer's Disease Regardless of Amnesia? *Journal of Alzheimer's Disease, 49*(4), 1065-1074. doi:10.3233/JAD-150686

Bertoux, M., Funkiewiez, A., O'Callaghan, C., Dubois, B., & Hornberger, M. (2013). Sensitivity and specificity of ventromedial prefrontal cortex tests in behavioral variant frontotemporal dementia. *Alzheimer's & Dementia, 9*(5 Suppl), S84-94. doi:10.1016/j.jalz.2012.09.010

Bertoux, M., O'Callaghan, C., Dubois, B., & Hornberger, M. (2016). In two minds: executive functioning versus theory of mind in behavioural variant frontotemporal dementia. *Journal of Neurology, Neurosurgery & Psychiatry, 87*(3), 231-234. doi:10.1136/jnnp-2015-311643

Bertoux, M., Volle, E., de Souza, L. C., Funkiewiez, A., Dubois, B., & Habert, M. O. (2014). Neural correlates of the mini-SEA (Social cognition and Emotional Assessment) in behavioral variant frontotemporal dementia. *Brain Imaging and Behavior, 8*(1), 1-6. doi:10.1007/s11682-013-9261-0

Bertoux, M., Volle, E., Funkiewiez, A., de Souza, L.C., Leclercq, D., Dubois, D. (2012). Social Cognition and Emotional Assessment (SEA) is a marker of medial and orbital frontal functions: a voxel-based morphometry study in behavioral variant of frontotemporal degeneration. J Int Neuropsychol Soc. 2012 Nov;18(6):972-85. doi: 10.1017/S1355617712001300.

Bora, E., Walterfang, M., & Velakoulis, D. (2015). Theory of mind in behavioural-variant frontotemporal dementia and Alzheimer's disease: a meta-analysis.

Journal of Neurology, Neurosurgery & Psychiatry, 86(7), 714-719. doi:10.1136/jnnp-2014-309445

Buckner, R. L., & Carroll, D. C. (2007). Self-projection and the brain. *Trends in Cognitive Sciences, 11*(2), 49-57. doi:10.1016/j.tics.2006.11.004

Carrington, S. J., & Bailey, A. J. (2009). Are there theory of mind regions in the brain? A review of the neuroimaging literature. *Human Brain Mapping, 30*(8), 2313-2335. doi:10.1002/hbm.20671

Castelli, I., Pini, A., Alberoni, M., Liverta-Sempio, O., Baglio, F., Massaro, D., . . . Nemni, R. (2011). Mapping levels of theory of mind in Alzheimer's disease: a preliminary study. *Aging & Mental Health, 15*(2), 157-168. doi:10.1080/13607863.2010.513038

Champagne-Lavau, M., & Moreau, N. (2013). Characteristics of current tasks that contribute to mentalizing judgments: does the engagement of the participants in the social interaction matter? Comment on Achim et al. (2013). *Psychological Assessment, 25*(4), 1404-1406. doi:10.1037/a0033433

Cosentino, S., Zahodne, L. B., Brandt, J., Blacker, D., Albert, M., Dubois, B., & Stern, Y. (2014). Social cognition in Alzheimer's disease: a separate construct contributing to dependence. *Alzheimer's & Dementia, 10*(6), 818-826. doi:10.1016/j.jalz.2013.12.021

de Bruin, L., van Elk, M., & Newen, A. (2012). Reconceptualizing second-person interaction. *Frontiers in Human Neuroscience, 6*, 151. doi:10.3389/fnhum.2012.00151

De Jaegher, H., Di Paolo, E., & Gallagher, S. (2010). Can social interaction constitute social cognition? *Trends in Cognitive Sciences, 14*(10), 441-447. doi:10.1016/j.tics.2010.06.009

de Souza L. C., Bertoux, M., Funkiewiez, A., Samri, D., Azuar, C., Habert, M-O.,… Dubois, B. (2013). Frontal presentation of Alzhiemer's disease - a series of patients with biological evidence by CSF markers. *Dementia & Neuropsychologia, 7*(1), 66-74.

Dodich, A., Cerami, C., Crespi, C., Canessa, N., Lettieri, G., Iannaccone, S., . . . Cacioppo, J. T. (2016). Differential Impairment of Cognitive and Affective Mentalizing Abilities in Neurodegenerative Dementias: Evidence from Behavioral Variant of Frontotemporal Dementia, Alzheimer's Disease, and Mild Cognitive Impairment. *Journal of Alzheimer's Disease, 50*(4), 1011-1022. doi:10.3233/JAD-150605

Dubois, B., Feldman, H. H., Jacova, C., Dekosky, S. T., Barberger-Gateau, P., Cummings, J., . . . Scheltens, P. (2007). Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. *Lancet Neurology, 6*(8), 734-746. doi:10.1016/S1474-4422(07)70178-3

Dubois B, Slachevsky A, Levy R. Démences de type frontal. *La Lettre du Neurologue. Numéro Hors Série*, Avril 1997: 16-19.

Dubois, B., Slachevsky, A., Litvan, I., & Pillon, B. (2000). The FAB: a Frontal Assessment Battery at bedside. *Neurology, 55*(11), 1621-1626.

El Haj, M., Gely-Nargeot, M. C., & Raffard, S. (2015). Destination Memory and Cognitive Theory of Mind in Alzheimer's Disease. *Journal of Alzheimer's Disease, 48*(2), 529-536. doi:10.3233/JAD-150467

Elamin, M., Pender, N., Hardiman, O., & Abrahams, S. (2012). Social cognition in neurodegenerative disorders: a systematic review. *Journal of Neurology, Neurosurgery & Psychiatry, 83*(11), 1071-1079. doi:10.1136/jnnp-2012-302817

Fernandez-Duque, D., Baird, J. A., & Black, S. E. (2009). False-belief understanding in frontotemporal dementia and Alzheimer's disease. *Journal of Clinical and Experimental Neuropsychology, 31*(4), 489-497. doi:10.1080/13803390802282688

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatry Research, 12*(3), 189-198.

Freedman, M., Binns, M. A., Black, S. E., Murphy, C., & Stuss, D. T. (2013). Theory of mind and recognition of facial emotion in dementia: challenge to current concepts. *Alzheimer Disease & Associated Disorders, 27*(1), 56-61. doi:10.1097/WAD.0b013e31824ea5db

Gallotti, M., & Frith, C. D. (2013). Social cognition in the we-mode. *Trends in Cognitive Sciences, 17*(4), 160-165. doi:10.1016/j.tics.2013.02.002

Gregory, C., Lough, S., Stone, V., Erzinclioglu, S., Martin, L., Baron-Cohen, S., & Hodges, J. R. (2002). Theory of mind in patients with frontal variant frontotemporal dementia and Alzheimer's disease: theoretical and practical implications. *Brain, 125*(Pt 4), 752-764.

Godefroy, O., & Groupe de réflexion sur l'évaluation des fonctions exécutives. (2008). *Fonctions exécutives et pathologies neurologiques et psychiatriques: évaluation en pratique clinique*. Marseille: Solal.

Grober, E., Buschke, H., Crystal, H., Bang, S., & Dresner, R. (1988). Screening for dementia by memory testing. *Neurology, 38*(6), 900-903.

Hafkemeijer, A., van der Grond, J., & Rombouts, S. A. (2012). Imaging the default mode network in aging and dementia. *Biochimica et Biophysica Acta, 1822*(3), 431-441. doi:10.1016/j.bbadis.2011.07.008

Ibanez, A., & Manes, F. (2012). Contextual social cognition and the behavioral variant of frontotemporal dementia. *Neurology, 78*(17), 1354-1362. doi:10.1212/WNL.0b013e3182518375

Kalafat, M., Hugonot-Diener, L., Poitrenaud, J. (2003). Standardisation et étalonnage français du « Mini MentalState » (MMS) version GRECO. *Rev Neuropsychol*, 13(2) :209-36.

Kumfor, F., Irish, M., Leyton, C., Miller, L., Lah, S., Devenney, E., . . . Piguet, O. (2014). Tracking the progression of social cognition in neurodegenerative disorders. *Journal of Neurology, Neurosurgery & Psychiatry, 85*(10), 1076-1083. doi:10.1136/jnnp-2013-307098

Laisney, M., Bon, L., Guiziou, C., Daluzeau, N., Eustache, F., & Desgranges, B. (2013). Cognitive and affective Theory of Mind in mild to moderate Alzheimer's disease. *Journal of Neuropsychology, 7*(1), 107-120. doi:10.1111/j.1748-6653.2012.02038.x

Le Bouc, R., Lenfant, P., Delbeuck, X., Ravasi, L., Lebert, F., Semah, F., & Pasquier, F. (2012). My belief or yours? Differential theory of mind deficits in frontotemporal dementia and Alzheimer's disease. *Brain, 135*(Pt 10), 3026-3038. doi:10.1093/brain/aws237

Lough, S., & Hodges, J. R. (2002). Measuring and modifying abnormal social cognition in frontal variant frontotemporal dementia. *Journal of Psychosomatic Research, 53*(2), 639-646.

Moreau, N., Rauzy, S., Viallet, F., & Champagne-Lavau, M. (2016). Theory of mind in Alzheimer disease: Evidence of authentic impairment during social interaction. *Neuropsychology, 30*(3), 312-321. doi:10.1037/neu0000220

Nitrini, R., Caramelli, P., Herrera Junior, E., Porto, C. S., Charchat-Fichman, H., Carthery, M. T., . . . Lima, E. P. (2004). Performance of illiterate and literate nondemented elderly subjects in two tests of long-term memory. *Journal of the International Neuropsychological Society, 10*(4), 634-638. doi:10.1017/S1355617704104062

R Core Team (2016). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/.

Rabin, J. S., Gilboa, A., Stuss, D. T., Mar, R. A., & Rosenbaum, R. S. (2010). Common and unique neural correlates of autobiographical memory and theory of mind. *Journal of Cognitive Neuroscience, 22*(6), 1095-1111. doi:10.1162/jocn.2009.21344

Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., & Shulman, G. L. (2001). A default mode of brain function. *Proceedings of the National Academy of Sciences U S A, 98*(2), 676-682. doi:10.1073/pnas.98.2.676

Ramanan, S., Bertoux, M., Flanagan, E., Irish, M., Piguet, O., Hodges, J. R., & Hornberger, M. (2016). Longitudinal Executive Function and Episodic Memory Profiles in Behavioral-Variant Frontotemporal Dementia and Alzheimer's Disease. *Journal of the International Neuropsychological Society*, 1-10. doi:10.1017/S1355617716000837

Rascovsky, K., Hodges, J. R., Knopman, D., Mendez, M. F., Kramer, J. H., Neuhaus, J., . . . Miller, B. L. (2011). Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain, 134*(Pt 9), 2456-2477. doi:10.1093/brain/awr179

Ross, L. A., & Olson, I. R. (2010). Social cognition and the anterior temporal lobes. *Neuroimage, 49*(4), 3452-3462. doi:10.1016/j.neuroimage.2009.11.012

Samson, D. (2009). Reading other people's mind: insights from neuropsychology. *Journal of Neuropsychology, 3*(Pt 1), 3-16. doi:10.1348/174866408X377883

Sandoz, M., Demonet, J. F., & Fossard, M. (2014). Theory of mind and cognitive processes in aging and Alzheimer type dementia: a systematic review. *Aging and Mental Health, 18*(7), 815-827. doi:10.1080/13607863.2014.899974

Schaafsma, S. M., Pfaff, D. W., Spunt, R. P., & Adolphs, R. (2015). Deconstructing and reconstructing theory of mind. *Trends in Cognitive Sciences, 19*(2), 65-72. doi:10.1016/j.tics.2014.11.007

Schurz, M., Radua, J., Aichhorn, M., Richlan, F., & Perner, J. (2014). Fractionating theory of mind: a meta-analysis of functional brain imaging studies. *Neuroscience & Biobehavioral Reviews, 42*, 9-34. doi:10.1016/j.neubiorev.2014.01.009

Simic, G., Babic, M., Borovecki, F., & Hof, P. R. (2014). Early failure of the default-mode network and the pathogenesis of Alzheimer's disease. *CNS Neuroscience & Therapeutics, 20*(7), 692-698. doi:10.1111/cns.12260

Smith, S. M., Hyvarinen, A., Varoquaux, G., Miller, K. L., & Beckmann, C. F. (2014). Group-PCA for very large fMRI datasets. *Neuroimage, 101*, 738-749. doi:10.1016/j.neuroimage.2014.07.051

Spreng, R. N., & Grady, C. L. (2010). Patterns of brain activity supporting autobiographical memory, prospection, and theory of mind, and their relationship to the default mode network. *Journal of Cognitive Neuroscience, 22*(6), 1112-1123. doi:10.1162/jocn.2009.21282

Stone, V. E., Baron-Cohen, S., & Knight, R. T. (1998). Frontal lobe contributions to theory of mind. *Journal of Cognitive Neuroscience, 10*(5), 640-656.

Stone, V. E., & Gerrans, P. (2006). What's domain-specific about theory of mind? *Social Neuroscience, 1*(3-4), 309-319. doi:10.1080/17470910601029221

Torralva, T., Kipps, C. M., Hodges, J. R., Clark, L., Bekinschtein, T., Roca, M., . . . Manes, F. (2007). The relationship between affective decision-making and theory of mind in the frontal variant of fronto-temporal dementia. *Neuropsychologia, 45*(2), 342-349. doi:10.1016/j.neuropsychologia.2006.05.031

Van Overwalle, F. (2009). Social cognition and the brain: a meta-analysis. *Human Brain Mapping, 30*(3), 829-858. doi:10.1002/hbm.20547

Van der Linden M (2006). *L'évaluation des troubles de la mémoire – Presentation de quatre tests de memoire épisodique (avec leur étalonnage).* Paris: Solal.

Vanderstichele, H., De Vreese, K., Blennow, K., Andreasen, N., Sindic, C., Ivanoiu, A., . . . Vanmechelen, E. (2006). Analytical performance and clinical utility of the INNOTEST PHOSPHO-TAU181P assay for discrimination between Alzheimer's disease and dementia with Lewy bodies. *Clinical Chemistry and Laboratory Medicine, 44*(12), 1472-1480. doi:10.1515/CCLM.2006.258

Wang, J., Redmond, S. J., Bertoux, M., Hodges, J. R., & Hornberger, M. (2016). A Comparison of Magnetic Resonance Imaging and Neuropsychological Examination in the Diagnostic Distinction of Alzheimer's Disease and Behavioral Variant Frontotemporal Dementia. *Frontiers in Aging Neuroscience, 8*, 119. doi:10.3389/fnagi.2016.00119

Wong, S., Bertoux, M., Savage, G., Hodges, J. R., Piguet, O., & Hornberger, M. (2016). Comparison of Prefrontal Atrophy and Episodic Memory Performance in Dysexecutive Alzheimer's Disease and Behavioral-Variant Frontotemporal Dementia. *Journal of Alzheimer's Disease, 51*(3), 889-903. doi:10.3233/JAD-151016

Wechsler D. Wechsler Adult Intelligence Scale-3rd Edition (WAIS-3). San Antonio, TX: Harcourt Assessment; 1997 (Version ECPA).

Zaitchik, D., Koff, E., Brownell, H., Winner, E., & Albert, M. (2006). Inference of beliefs and emotions in patients with Alzheimer's disease. *Neuropsychology, 20*(1), 11-20. doi:10.1037/0894-4105.20.1.11

Figure's legends

Figure 1. Dendrogram using Ward's linkage, showing the cluster architecture of faux pas (FP) performance and memory or executive scores in: (1A) AD (French cohort), (1B) an independent group of AD (Brazilian cohort) and (1C) bvFTD.
TR: Total recall; DTR: Delayed total recall; FR: Free recall; FAB: Frontal Assessment Battery; LexF: Verbal lexical fluency; SemF: Verbal semantic fluency; DSF: Digit span forward; DSB: Digit span backward; Lear.: Learning; Imm.: Immediate recall; FR: Free recall after 5min.

Figure 2. Plot of correlation for AD (French cohort), independent AD group (Brazilian cohort) and bvFTD between faux pas (FP) performance and (2A) executive functioning (EF) and (2B) episodic memory components and (2C) the values predicted by the automated linear model.