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Determinants of theory of mind performance in Alzheimer's disease: A data-mining study

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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 (EF) 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 EF 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.

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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, pp. 5–25). 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 (AD) (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 sub-optimal 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 (CAAE-17850513.2.0000.5149) and all patients or their legal representatives provided written informed consent.