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Empathy and Theory of Mind in Alzheimer's Disease: A Meta-analysis

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Abstract

Objective: A large literature now shows that Alzheimer's disease (AD) disrupts a number of social cognitive abilities, including social perceptual function and theory of mind (ToM). However, less well understood is how the specific subcomponents of ToM as well as both the broader and specific subcomponents of empathic processing are affected. **Method:** The current study provides the first meta-analytic review of AD that focuses on both empathy and ToM as broad constructs, as well as their overlapping (cognitive empathy and affective ToM) and distinct (affective empathy and cognitive ToM) subcomponents. **Results:** Aggregated across 31 studies, the results revealed that, relative to controls, AD is associated with large-sized deficits in both cognitive ToM ($g = 1.09$) and affective ToM/cognitive empathy ($g = 0.76$). However, no statistical differences were found between the AD participants and controls on affective empathic abilities ($g = 0.36$). **Conclusions:** These data point to a potentially important disconnect between core aspects of social cognitive processing in people with AD. The practical and theoretical implications of these findings are discussed.

Keywords: Empathy, Affective empathy, Cognitive empathy, Theory of mind, Affective theory of mind, Cognitive theory of mind, Alzheimer's disease

Social cognition broadly refers to the complex set of cognitive processes that allow us to perceive, process, and interpret social information (Adams et al., 2019; Henry et al., 2016; Poletti, Enrici, & Adenzato, 2012). In many neurodegenerative disorders, deficits in core social cognitive abilities, such as theory of mind (ToM), empathy, social perception, and social behavior, are now recognized to be common presenting symptoms, and to be as, if not more important, than deficits in other neurocognitive domains (Christidi et al., 2018; Henry et al., 2016). This is because social cognitive deficits fundamentally disrupt the ability to build and maintain supportive social relationships, thereby eliminating the benefits that social interactions have for people living with neurocognitive impairments (see, Henry et al., 2016). It is therefore unsurprising that social cognitive impairment has been argued to be a key predictor of many important prognostic outcomes including mental health, well-being, social integration, and quality of life more broadly (Christidi et al., 2018; Henry et al., 2016).

Alzheimer's disease (AD) is the most common neurodegenerative disorder, with amnestic disturbances the most frequent initial presenting feature. However, in the mild to moderate stages of the illness, abnormalities in a number of distinct social cognitive domains are also evident. In particular, meta-analytic reviews show that there are consistent AD-related deficits in both social perception (Bora, Velakoulis, & Walterfang, 2016; Klein-Koerkamp et al., 2012) and ToM (Bora, Walterfang, & Velakoulis, 2015). Failures of social perception typically present as difficulties recognizing and responding to basic social and emotional cues, such as interpreting facial expressions, body language, or voices. Failures of ToM refer to difficulties understanding the mental states of others and appreciating that these mental states might differ from our own (Poletti et al., 2012). In AD, these social cognitive deficits have been linked to both volumetric loss and white matter pathology (Dermody et al., 2016; Guntekin et al., 2019; Kanske et al., 2015; Lee et al., 2013; Park et al., 2017; Poletti et al., 2012; Sturm et al., 2013). Consequently, it is unsurprising that both types of impairment grow more severe with disease progression (Fliss et al., 2016; Kumfor et al., 2014; Sturm et al., 2013; Torres et al., 2015).

However, while it is now well established that deficits in social perception and ToM are common presenting problems, less clear is how empathy – another core aspect of social cognition – is affected. Empathy is a multifaceted construct, which consists of both cognitive and affective components. Whereas cognitive empathy refers to the ability to understand another's emotional state, affective empathy refers to one's

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emotional response to the perceived situation of another (Bartochowski et al., 2018). A deficit in cognitive empathy may manifest as an inability to comprehend what another individual is feeling, with direct implications for how one then behaves toward that individual. Alternatively, affective empathic responses reflect one's emotional response to the perceived emotional states of others. An example here would be when an individual observes another person crying in distress, they may feel sad that they are unhappy. Importantly, these personal emotional reactions can be distinct from the other individual's experienced emotions (i.e., when one feels embarrassed for someone who is overconfident; Henry et al., 2016). In day-to-day living, an exaggerated or deficient affective empathic response has implications for interpersonal conduct and social relations with others. Since behavioral problems and breakdowns in patient–carer relationships are key predictors of institutionalization (Banerjee et al., 2003; Spitznagel et al., 2006), a clearer and more nuanced understanding of how empathic processing is affected by AD is required.

Consequently, it is of particular interest that in a recent qualitative review, Fischer, Landeira-Fernandez, Sollero de Campos, and Mograbi (2019) argued that AD is associated with impairment in cognitive but not affective empathic processing. Indeed, while prior work has identified a core neural network that appears to underlie both components of empathy (Fan et al., 2011), studies have also identified distinct neural regions for cognitive and affective empathy. For instance, Fan et al. (2011) found that overall empathy was associated with activation in the dorsal anterior cingulate cortex, anterior mid-cingulate cortex, supplementary motor area, and the bilateral anterior insula. The right anterior insula was more likely to be activated in affective empathy (the left anterior insula was activated for overall empathy), while the dorsal anterior cingulate cortex was more frequently activated during cognitive empathic tasks than for overall empathy. These findings align with Eres et al. (2015) who found that affective empathy was associated with greater gray matter density in the insula cortex, whereas cognitive empathy was associated with greater gray matter density in the midcingulate cortex/dorsomedial prefrontal cortex. Thus, it is possible that these neural regions may be differentially affected by AD (Dermody et al., 2016; Eres et al., 2015; Uribe et al., 2019). To date, there has been no meta-analytic study to quantitatively test the magnitude and significance of any AD-related effects in each of these two empathic components. This is therefore the next important step in this literature and the first aim of the present study.

For ToM, a distinction between the affective and cognitive subcomponents has also been identified. Whereas cognitive ToM requires an understanding of another's mental states, affective ToM is concerned with understanding another's emotional state (Heitz et al., 2016). Although conceptually there are differences between affective ToM and cognitive empathy (see, Singer, 2006) at the behavioral level of assessment, these two constructs are difficult to distinguish and their overlap has frequently been noted (e.g., Bensalah, Caillies, & Anduze, 2016; Dodich et al., 2016; Dvash & Shamay-Tsoory, 2014; Moreau et al., 2016; Preckel, Kanske, & Singer, 2018; Shamay-Tsoory, Aharon-Peretz, & Perry, 2009; Shamay-Tsoory et al., 2005). In particular, both affective ToM and cognitive empathy involve understanding another's emotional state. Thus, these constructs will be considered interchangeable for the purposes of this paper. A deficit in cognitive ToM affects one's ability to take the perspective of another (i.e., as shown by failures of false-belief understanding; Takenoshita et al., 2018). This in turn affects the ability to relate to others as individuals may demonstrate a failure to reciprocate socially, even when obvious social cues are given. Cognitive ToM is different from cognitive empathy as the former represents one's capability to infer another's mental state (thoughts, beliefs, perspectives), while the latter is the ability to infer another's emotional state (which may manifest as happiness, sadness, etc.).

In the only meta-analysis of the ToM-AD literature to date, Bora et al. (2015) found evidence for an AD-related deficit in ToM function that was large in magnitude ($d = 1.15$). However, it was unclear whether this was attributable to problems with both or only one of the subcomponents, as no distinction was made between affective and cognitive ToM. Importantly, it has been found that in the mild to moderate stages of AD, key brain regions involved in overall ToM processing – the precuneus, temporal poles, and posterior superior temporal sulcus – are affected (Bailly et al., 2013; Ciaramidaro et al., 2007; Enrici et al., 2011; Gomez-Isla et al., 1997; Ramos et al., 2017; Ryu et al., 2005; Schroeter et al., 2009; Sebastian et al., 2011; Stone, Baron-Cohen, & Knight, 1998). While some studies have provided evidence for AD-related impairment on one or both ToM components (Dodich et al., 2016; Moreau et al., 2016; Yamaguchi et al., 2019), others have identified no significant AD-related impairment for either (Heitz et al., 2016; Kumfor et al., 2017) or have reported evidence of a disconnect between the two (Bertoux et al., 2016; Fliss et al., 2016). For instance, one recent study reported that only the affective but not the cognitive component of ToM was impaired (Bertoux et al., 2016), while a different study reported the reverse pattern of impairment (Fliss et al., 2016). The second aim of the present study was therefore to use meta-analytic methodology to quantitatively test the magnitude and significance of AD-related effects for these two components of ToM.

In sum, the present study was designed to provide the first meta-analytic integration of the AD literature focused on empathy and ToM, in which the cognitive and affective subcomponents of both of these abilities are differentiated. Analyzing empathy and ToM, both broadly and in terms of their subcomponents, will provide a clearer and more nuanced understanding of the types of social cognitive difficulties persons with AD exhibit. Based on the prior empirical studies in this literature (Bora et al., 2015; Dermody et al., 2016; Fischer et al., 2019), it was predicted that significant deficits would be identified for the cognitive, but not the affective component of empathy, and that deficits would also

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be evident for both components of ToM. Prior literature has shown that older adults often exhibit greater social cognitive difficulties than younger adults (Grainger et al., 2019, 2020; Henry et al., 2013; Sun et al., 2017). Because of this, age was included as a predictor variable in the meta-regression analyses. Additionally, broader cognitive decline and disease duration have been linked to greater social cognitive difficulties in AD and other clinical groups (Castelli et al., 2011; Cuerva et al., 2001; Fliss et al., 2016; Henry et al., 2016; Laisney et al., 2013). As such, these clinical variables were also included as predictors of ToM and empathy impairment.

METHODS

Literature Search Strategy

The current meta-analysis was conducted in accordance with PRISMA guidelines (Moher et al., 2009). A systematic literature search was conducted across PubMed, Web of Science, MEDLINE, and PsycINFO databases in August 2019. The search terms used were as follows: AD or dementia; in combination with, emotion perception, social cognition, social perception, emotion recognition, facial expression, prosody, ToM, pragmatic impairment, lie*, joke*, mentalising, non-literal language, sarcas*, empath*, perspective taking, Peer-Report Social Function Scale. This was accompanied by a backward citation search of studies identified in relevant meta-analyses and systematic reviews (Bartochowski et al., 2018; Bora et al., 2016, 2015; Christidi et al., 2018; Henry et al., 2016; Poletti et al., 2012).

Search Eligibility Criteria

Titles then abstracts were first screened to remove ineligible studies (i.e., studies with no mention of AD, systematic reviews or meta-analyses, animal studies, or studies with no healthy age-matched control group; see Figure 1). Full-text screening was then conducted by the first author. In instances where study inclusion was ambiguous, the second author was consulted.

Studies were considered eligible for inclusion if (1) they compared AD participants to healthy age-matched controls, (2) the AD group consisted of more than one participant – (i.e., it was not a single-case study), (3) the required statistics to derive effect sizes were published or provided upon request, (4) the studies and their data were unique, (5) the study was published in a peer-reviewed journal in English, (6) the tasks assessed measured the participant's cognitive/affective abilities of ToM and/or empathy, and (7) the studies were empirical. There was no restriction placed on the year in which a study had to be published.

Theory of Mind Eligibility Criteria

For cognitive ToM, eligible studies had to include a behavioral, informant-rated, or self-report measure that assessed mental state attribution. Eligible affective ToM/cognitive empathy measures had to assess the participant's understanding of another's emotional state. In this instance, an emotional state referred to a state of arousal which externally manifested as emotions (happiness, sadness, anger, etc.). Overall ToM was measured through combining scores from the cognitive and affective ToM measures.

Empathy Eligibility Criteria

Tasks were considered eligible for affective empathy if they included a self-reported, informant-rated, or behavioral assessment of one's affective empathic capacity. Overall empathy was measured by combining scores from the cognitive empathy/affective ToM and affective empathy measures. For further detail on the categorization of these constructs, see Coundouris et al. (2020).

Data Extraction

Where available, the data extracted from the eligible studies included:

1) Sample characteristics from the control and AD groups, such as sample size, means and standard deviations for age, cognitive status as indexed by the Mini Mental State Examination (MMSE), and, for the AD participants, disease duration.
2) Means and standard deviations for cognitive and affective measures of empathy and ToM, or other data which allowed the precise effect sizes for these measures to be calculated.

When required data were unavailable, the corresponding author on the manuscript was contacted to request the data. The following studies were excluded because the data were not available (Martinez et al., 2018; Poveda et al., 2017; Rowse et al., 2013; Zaitchik et al., 2006). In certain instances, data were unavailable upon request due to specific participant groups not being assessed on the measures of interest (Cuerva et al., 2001; Dodich et al., 2016; Duclos et al., 2018; Fernandez-Duque, Baird, & Black, 2009; Youmans & Bourgeois, 2010). If participants scored at ceiling or floor on any measure, data for both control and AD participants from the measure in question were not permitted to contribute to the analyses. This decision was made because these types of data have the potential to overestimate effect sizes, and the software used to conduct the analyses does not analyze data points with a standard deviation of zero (Castelli et al., 2011; Gregory et al., 2002; Le Bouc et al., 2012; Yamaguchi et al., 2012; Zaitchik et al., 2006). However, the overall study was not excluded if it reported appropriate data for other measures. When studies tested a single control group and more than one AD group (for instance, a mild AD group and a moderate AD group), data from the two AD groups were averaged together to derive one overall score for AD performance for each dependent measure of interest in the study (Cuerva et al., 2001). Some measures did not clearly differentiate cognitive and affective ToM (Fliss et al., 2016; Heitz et al., 2016;

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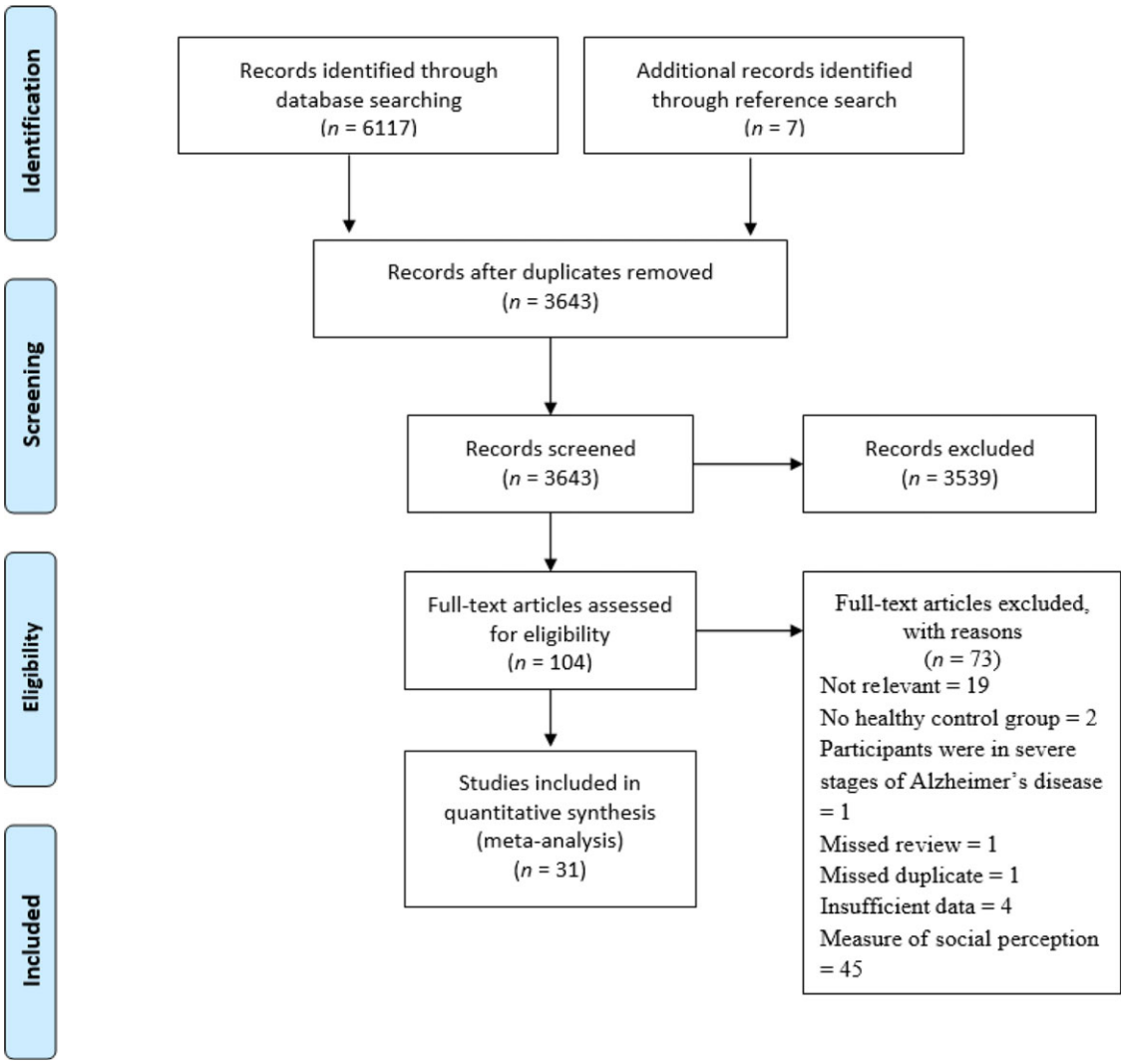

Fig. 1. PRISMA flowchart displaying study screening and selection process.

Narme et al., 2013; Scheidemann et al., 2016), and consequently contributed to analyses of overall ToM but not to either of the specific ToM subcomponents (see Table 1). Finally, all of the data extracted were independently cross-checked by a second coder. In instances where measure inclusion was ambiguous, the fourth author was consulted.

Key background characteristics of the contributing studies are reported in Table 1. A number of studies assessed a single-dependent measure using multiple tasks (i.e., a study may have reported data for multiple separate ToM tasks). In these instances, overall mean effect sizes were calculated by averaging the data across measures to create a single value to ensure that each participant contributed only once to the estimation of each mean effect. The same participants were, however, allowed to contribute to *different* overall means (i.e., the same participants were permitted to contribute both to the mean effect for affective empathy as well as the mean effect for cognitive empathy). As this resulted in mean effects not being independent, these subcategories were not compared statistically. Instead, to interpret differences between mean effect sizes, differences in effect size magnitude, as well as the percentage of variance accounted for (PVAF) by having a diagnosis of AD versus being a control participant was referred to (see, Adams et al., 2019; Coundouris et al., 2019).

Statistical Analyses

Meta-analyses were conducted using the Comprehensive Meta-Analysis Version 3 software. A Hedges *g* index of effect size was used (Borenstein et al., 2013), and effect sizes were deemed small, medium, or large when their values were equal to or larger than 0.2, 0.5, or 0.8, respectively (Cohen, 1988). The effect sizes for each study were calculated so that positive values indicated a deficit in ToM or empathy for the AD group (relative to the control group). The random effects model was used as it better accommodates heterogeneous effect distributions (Lipsey & Wilson, 2001).

A series of meta-regressions were then conducted to test whether clinical variables (i.e., MMSE scores, disease duration) or age explained variance in any of the effects identified. For each of these analyses, a minimum of 10 data points were required for each relevant predictor variable and

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Table 1 Individual study characteristics

Study	Control participants			Alzheimer's disease participants						
	N	Age *M*	MMSE *M*	*N*	Age *M*	MMSE *M*	Disease duration (years) *M*	Task	Subcomponent	Overall effect size
Amanzio et al. (2008) [48]	20	67.65	27.95	20	70.30	21.83	1.95	FB Task	CogToM	1.44
								FB Task	CogToM	
Bertoux et al. [35]	30	67.20	29.00	28	70.30	24.30	3.50	Mini-SEA Faux-Pas Recognition	CogToM	0.12
Castelli et al. [43]	16	71.38	29.19	16	70.50	23.69	–	Emotion Situation Understanding[a]	AffTom/CogEmp	0.78
								EYES Test Emotional[h]	AffTom/CogEmp	
								EYES Test Epistemic[h]	CogToM	1.14
								Deceptive Box Task	CogToM	
								Look Prediction	CogToM	
								Say Prediction	CogToM	
								Strange Stories	CogToM	
								Eye Direction Detection[a]	CogToM	
Choong & Doody (2013) [49]	11	–	–	16	–	19.30	–	FB Task	CogToM	0.96
								Cartoon Joke Task – FB/ignorance	CogToM	
								Cartoon Joke Task – Deception	CogToM	
Cuerva et al. [50][g]	10	60.60	–	14	71.55	22.40	2.35	ToM Short Stories[c]	CogToM	1.27
								ToM Short Stories	CogToM	
Dermody et al. [8]	22	68.20	–	25	66.10	–	3.51	IRI Perspective Taking	AffTom/CogEmp	1.01
								IRI Empathic Concern	AffEmp	0.12
Dodich et al. [31]	65	66.89	28.64	12	73.17	21.50	3.17	Story Based Empathy Task – Intention Attribution	CogToM	2.01
								IRI Perspective Taking[c]	AffTom/CogEmp	
								Story Based Empathy Task – Emotion Attribution	AffTom/CogEmp	1.30
								IRI Empathic Concern[c]	AffEmp	–
Duclos et al. [41] [d]	20	77.30	29.00	20	79.40	21.90	–	Peter & Mary Task (Context)	AffTom/CogEmp	1.32
								IRI Perspective Taking[c]	AffTom/CogEmp	
El Haj, Gély-Nargeot, & Raffard (2015) [51]	30	70.27	28.03	28	74.38	24.24	–	RMET	AffTom/CogEmp	0.40
								FB Task	CogToM	0.91
								FB Task	CogToM	
Fernandez-Duque et al. [42][f]	12	68.70	28.80	17	69.40	24.90	3.92	FB Task	CogToM	0.69
								IRI Empathic Concern[c]	AffEmp	–
Fliss et al. [14]	23	77.90	28.90	42	78.50	22.05	–	FB Task	CogToM	0.90
								FB Task	CogToM	
								Preference Judgment[e]	Mixed ToM	1.27
								The Eyes/Faces Test	AffTom/CogEmp	−0.10

(*Continued*)

Table 1 (*Continued*)

Study	Control participants			Alzheimer's disease participants						
	N	Age *M*	MMSE *M*	*N*	Age *M*	MMSE *M*	Disease duration (years) *M*	Task	Subcomponent	Overall effect size
Freedman et al. (2013) [52]	31	65.00	29.10	21	71.60	24.60	4.80	FB Task	CogToM	0.72
								FB Task	CogToM	
								Visual Perspective Taking (Direct Inference)	CogToM	
								Visual Perspective Taking (Transfer Inference)	CogToM	
Gregory et al. [44]	16	57.10	28.70	12	66.50	27.10	–	FB Task[a]	CogToM	1.07
								FB Task[a]	CogToM	
								Faux-Pas Recognition	CogToM	
								RMET	AffTom/CogEmp	0.00
Heitz et al. [24][d]	16	68.30	29.30	15	70.90	27.00	3.60	Faux-Pas Recognition	Mixed ToM	0.61
								RMET	AffTom/CogEmp	0.72
Henry et al. (2009) [53]	20	80.50	28.80	20	81.80	17.20	–	RMET	AffTom/CogEmp	1.81
Kumfor et al. [34]	25	64.80	–	23	66.10	–	3.30	TASIT-S-2 Social Inference	CogToM	1.08
Kumfor et al. [15]	24	67.90	–	17	67.40	–	3.30	TASIT-2 Social Inference Minimal	CogToM	0.69
Laisney et al. [54]	15	76.40	–	16	78.10	21.50	–	Preference Judgment Task	CogToM	1.16
								FB Task	CogToM	
								FB Task	CogToM	
								RMET	AffTom/CogEmp	0.66
Le Bouc et al. [45][d]	20	59.80	–	12	61.90	–	–	FB Deficit Score (Self-Perspective)	CogToM	0.54
Mograbi et al. [55]	21	78.60	28.50	22	80.10	23.40	–	Film Reactivity	AffEmp	−0.14
Moreau et al. [32]	20	75.70	28.90	20	77.90	25.00	–	FB Task – True Belief	CogToM	1.38
								FB Task – False Belief	CogToM	
Narme et al. [56]	26	68.90	27.80	13	74.50	3.77	23.60	IRI Perspective Taking	AffTom/CogEmp	0.59
								Faux-Pas Recognition	AffTom/CogEmp	
								Yoni Task	AffTom/CogEmp	
								Yoni Task	Mixed ToM	0.67
								Faux-Pas Recognition	CogToM	1.05
								IRI Empathic Concern	AffEmp	1.24
Nash et al. [57]	20	77.20	28.80	20	79.30	24.60	–	IRI Perspective Taking	AffTom/CogEmp	0.60
								IRI Empathic Concern	AffEmp	0.34
Scheidemann et al. [58]	9	79.20	28.78	9	82.89	23.67	–	Movie for Assessment of Social Cognition – Multiple Choice	Mixed ToM	3.47
Shany-Ur et al. (2012) [59]	77	68.20	29.40	32	62.30	24.40	–	TASIT-3	AffTom/CogEmp	0.96
								TASIT-3	CogToM	0.95
								UCSF Perspective Taking Task	CogToM	
Takenoshita et al. [60]	35	73.20	28.80	116	79.20	22.30	3.53	Sally-Anne Task	CogToM	0.91
Verdon et al. (2007) [62]	20	82.00	29.00	20	82.00	23.00	–	Cartoon Task – Intention Attribution	CogToM	2.65
Yamaguchi et al. [33]	45	73.20	28.00	51	80.95	16.60	–	Cartoon Task	CogToM	1.73

(*Continued*)

Table 1 (*Continued*)

Study	Control participants			Alzheimer's disease participants						
	N	Age *M*	MMSE *M*	*N*	Age *M*	MMSE *M*	Disease duration (years) *M*	Task	Subcomponent	Overall effect size
Yamaguchi et al. [46] [b]	26	73.20	28.90	36	79.20	19.90	–	Deception Cartoon Task	CogToM	1.19
Youmans & Bourgeois [63][f]	10	78.00	29.80	10	82.00	20.60	–	FB Task[i]	CogToM	2.29
Zaitchik et al. [40][d]	15	88.47	28.90	25	88.96	19.64	–	FB Picture Story Task	CogToM	0.72
								FB Real Object Task[a]	CogToM	

Note. AD = Alzheimer's disease. AffTom/CogEmp = Affective ToM/Cognitive Empathy. FB = False Belief. RMET = Reading the Mind in the Eyes Test. IRI = Interpersonal Reactivity Index. TASIT = The Awareness of Social Inference Test. ToM = theory of mind.

[a] Data from this measure were excluded from analyses due to ceiling effects.

[b] Study had a second AD participant group who were excluded from analyses due to floor effects.

[c] Measure was excluded from analysis due to insufficient data.

[d] Other ToM or empathy tasks used in this study were excluded as they measured social perception.

[e] Measure could not be separated into cognitive or affective ToM, so was used for overall ToM analyses but not subcomponent analyses.

[f] Other measures of ToM that were excluded due to having no control data.

[g] Study had data for two separate AD groups which were averaged together for analyses.

[h] Authors separated RMET task into a cognitive ToM component and an affective ToM/cognitive empathy component.

[i] A measure of ToM was excluded because data were deemed inconclusive by authors.

the social cognitive ability under assessment (see Higgins, 2008). For this reason, no meta-regressions were conducted with affective empathy as the dependent measure, as fewer than 10 studies contributed data to this subcomponent. Where sufficient data were available, meta-regressions were conducted assessing the influence of MMSE scores, disease duration, and age on overall ToM and empathy, cognitive ToM, affective ToM/cognitive empathy.

Testing for publication bias

"The file drawer problem" refers to the higher probability of significant results being published, relative to nonsignificant results (Easterbrook et al., 1991; Rosenthal, 1979). To assess whether or not publication bias influenced the results of the current study, four analyses were conducted. First, the Begg and Mazumdar rank correlation test was used to calculate the correlation between study size and effect size. Egger's test of the intercept was then used to provide a test of the same bias using precision (the inverse of the standard error) to predict the standardized mean effect size. For both these tests, a non-significant correlation/intercept would suggest no presence of bias.

Additionally, the robustness of each mean effect size to any potential bias was assessed. Orwin's "Fail safe *N*" was calculated to quantify the number of unpublished studies averaging null results that must exist to reduce the mean correlation past a specific threshold (0.10 in the present study). The trim-and-fill method was then used to establish how each respective mean effect size would change if any identified bias were removed.

Testing for within study bias

To assess any potential biases at the level of the individual study, the appraisal tool for cross-sectional studies (AXIS; Downes et al., 2016) was used. The AXIS was designed to evaluate the quality of cross-sectional studies on both methodological and more general issues. Although studies are assessed against 20 criteria that are classified as either yes (recorded as one) or no/unclear (recorded as zero), no numerical scale is provided, and thus interpretations involve degrees of subjectivity. Downes et al. (2016) describe this subjectivity as a positive aspect of the tool as it allows for more flexibility during decision making, especially as the user can assess individual aspects of a study's design.

Twelve of the AXIS criteria were met by the included studies, five criteria were met by the majority of studies, and three criteria were met by less than half of the studies appraised (see Table S1). Specifically, of the 31 studies, only one justified their sample size, nine ascertained their samples from an appropriate population base, and four undertook measures to categorize and address nonresponders. It is important to note, however, that issues of nonresponders were likely not an issue that needed to be addressed in the remaining 27 studies. Overall, while most of the studies satisfied the

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Table 2. Mean effects for ToM and empathy subcomponents comparing participants with Alzheimer's disease against healthy controls and tests for publication bias

Subcomponent	*g*	95% CIs						Orwin fail safe *N*	Begg's method kendall's Tau	Egger's method intercept a	Trim and fill imputed *g*
		Lower	Upper	PVAF	*K*	*N*	*Q*				
Overall ToM	1.03***	0.85	1.21	0.01	30	1455	88.26***	256	0.34**	2.43*	1.03***
Overall empathy	0.67***	0.40	0.94	0.02	14	680	41.01***	76	0.07	1.86	0.67***
Cognitive ToM	1.09***	0.89	1.29	0.01	24	1337	56.33***	229	0.26	2.08	1.09***
Affective empathy	0.36	−0.18	0.91	0.08	4	169	9.34*	9	0.50	17.14	0.36
CogEmp/AffToM	0.76***	0.48	1.04	0.02	13	637	32.74***	83	0.12	2.14	0.76***

Note. *$p < .05$, **$p < .01$, ***$p < .001$. CogEmp/AffToM = cognitive empathy/affective theory of mind. A positive effect size indicates that the control group performed better than the AD group. PVAF = percentage of variance accounted for by group membership. *K* = the number of studies. *N* = the number of participants that contributed to the effect. AD = Alzheimer's disease. The Orwin fail-safe *N* threshold used was 0.10. Trim and fill: look for missing studies to left of mean; using random effects model. Imputed mean is random effects.

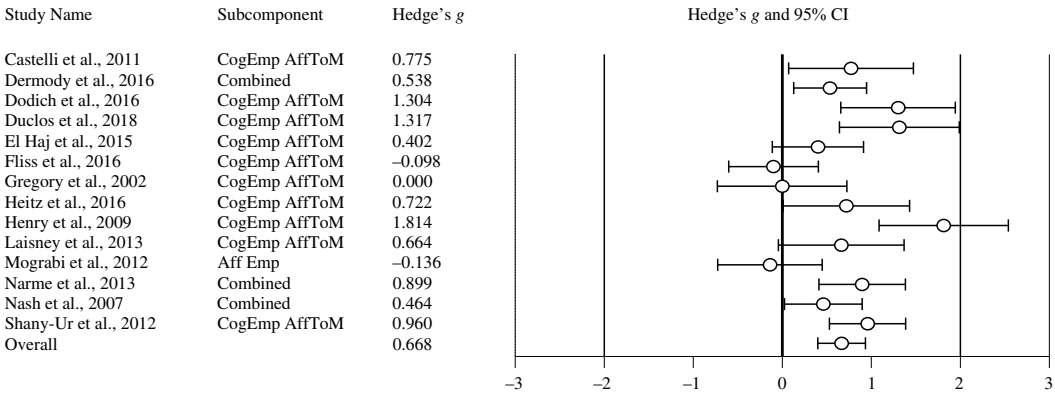

Fig. 2. Forest plot for overall ToM, displaying effect size (Hedges *g*) calculated using a random effects model. Positive effect sizes indicate better performance by controls.

majority of the AXIS criteria, there were some limitations that should be taken into consideration when evaluating this literature.

RESULTS

Literature Search

As can be seen in Figure 1, the initial literature search yielded 6117 results. After the removal of duplicates, 3643 articles remained, which were then subjected to title and abstract screening. Following this screening, 104 articles were subjected to a full-text review. Ultimately, 31 studies published between 2001 and 2019 met the inclusion criteria. This included 30 studies examining overall ToM, 14 studies examining overall empathy, 24 studies assessing cognitive ToM, 13 studies assessing cognitive empathy/affective ToM, and four studies assessing affective empathy. Overall, the studies included data from a total of 748 AD participants and 750 controls.

Participant Characteristics

An independent groups *t*-test indicated no significant difference between AD participants ($M = 74.79$, $SD = 6.60$) and controls ($M = 71.73$, $SD = 7.08$) on age ($p > .05$). The mean MMSE scores were 22.28 ($SD = 2.98$) and 28.79 ($SD = 0.47$) for AD and control participants, respectively. On average, AD participants had been formally diagnosed with the disorder for 3.31 ($SD = 0.82$) years.

Meta-analytic results

Table 2 reports the key results from the meta-analysis. Compared to healthy controls, people living with AD were significantly impaired in overall ToM, with this deficit large in magnitude ($g = 1.03$, $K = 30$; see Figure 2). People with AD were also significantly and moderately impaired in their overall empathic ability ($g = 0.67$, $K = 14$; see Figure 3). Examining the overlapping and distinct subcomponents of these constructs revealed that AD was associated with

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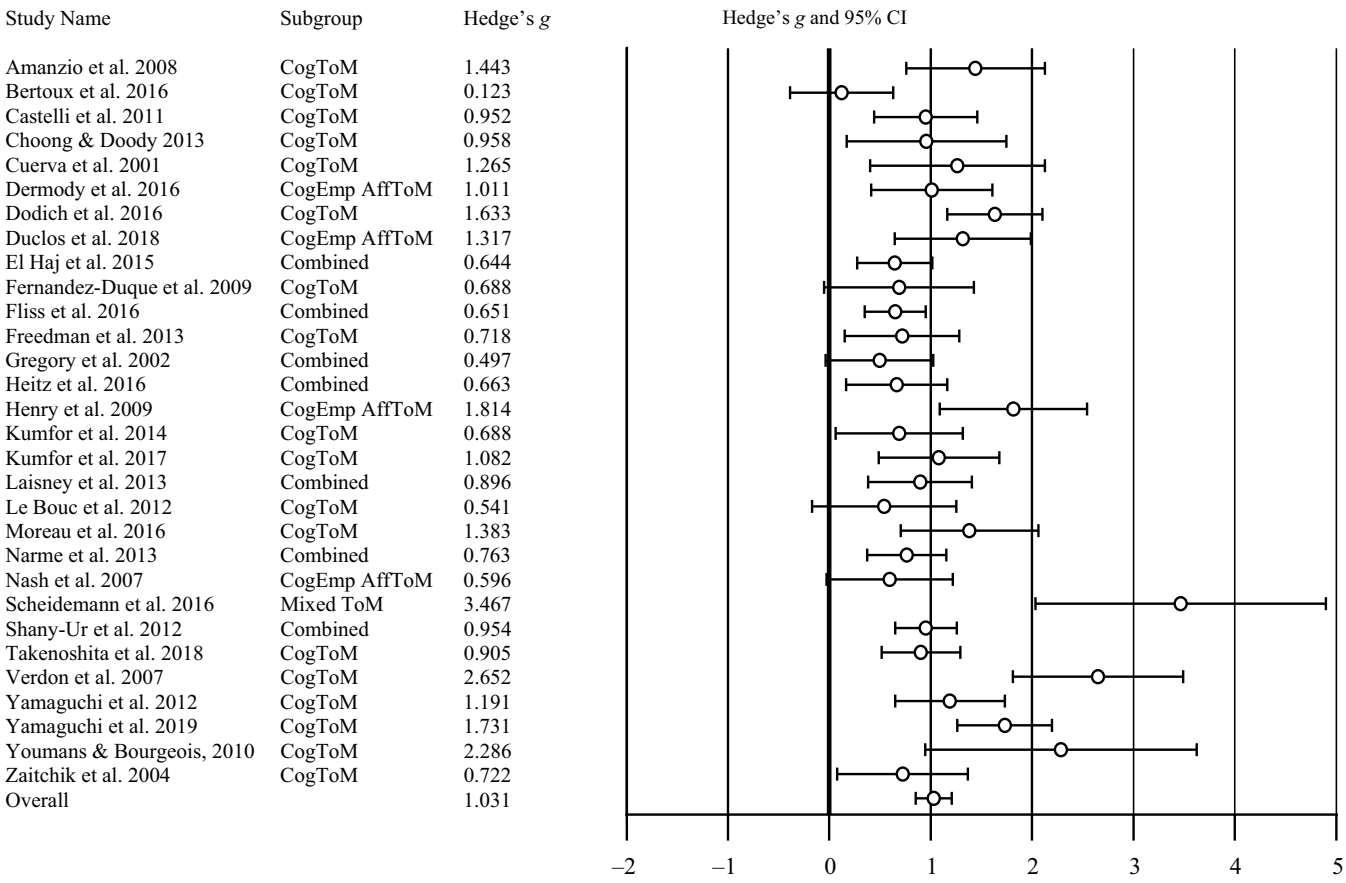

Fig. 3. Forest plot for overall empathy, displaying effect size (Hedges *g*) calculated using a random effects model. Positive effect sizes indicate better performance by controls.

significant, and large-sized deficits in cognitive ToM ($g = 1.09$, $K = 24$) and affective ToM/cognitive empathy ($g = 0.76$, $K = 13$). However, no group differences were evident for affective empathy ($g = 0.36$, $K = 4$).

Meta-Regressions

The next step in the analyses was to test whether level of cognitive impairment (as indexed by the MMSE) was a significant predictor of AD-related impairment in overall ToM, both ToM subcomponents, and overall empathy. MMSE scores accounted for significant variance in overall ToM, cognitive ToM, affective ToM/cognitive empathy, and overall empathy ($R^2 = 0.44$, between-group $Q = 4.06$, $p = .04$, $K = 25$, $R^2 = 0.65$, between-group $Q = 7.33$, $p = .007$, $K = 20$, $R^2 = 0.26$, between-group $Q = 4.63$, $p = .031$, $K = 12$, and $R^2 = 0.20$, between-group $Q = 4.44$, $p = .035$, $K = 13$, respectively). Using the same meta-regression approach, it was then tested whether disease duration predicted impairment in overall ToM and cognitive ToM ability. Disease duration did not account for significant variance in either overall ToM or cognitive ToM ($R^2 = 0.15$, between-group $Q = 1.76$, $p = .184$, $K = 11$, $R^2 = 0.05$, between-group $Q = 1.46$, $p = .226$, $K = 10$, respectively).

A meta-regression was then conducted to assess whether the age of the AD participants accounted for variance in their overall ToM and empathy, as well as their subcomponents (excluding affective empathy, for which $K < 10$). No effect of age was identified for overall ToM, cognitive ToM, affective ToM/cognitive empathy, or overall empathy ($R^2 = 0.00$, between-group $Q = 0.23$, $p = .632$, $K = 29$, $R^2 = 0.00$, between-group $Q = 0.17$, $p = .681$, $K = 23$, $R^2 = 0.00$, between-group $Q = 0.13$, $p = .717$, $K = 13$, and $R^2 = 00$, between-group $Q = 0.00$, $p = .965$, $K = 14$, respectively). These data therefore suggest that at least some of the heterogeneity between the contributing studies is attributable to variation in levels of cognitive impairment linked to AD, but that this is not the case for either disease duration or normative age.

Heterogeneity of Effect Sizes

Cochran's Q was used to measure the extent to which the studies contributing to each subcomponent's mean could be regarded as homogenous. As reported in Table 2, Cochran's Q statistics for all mean effects were significant, indicating that there is meaningful variance between the studies that are contributing to each mean (Borenstein et al., 2013).

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Testing for Publication Bias

The tests used to quantify publication bias (Begg's and Egger's methods) suggested a potential presence of publication bias for overall ToM, but not for either of the two ToM subcomponents, overall empathy, or affective empathy. Orwin's "Fail safe *N*" indicated that for overall ToM and empathy, 256 and 76 unpublished studies averaging null results would be needed to reduce the mean effect size value past 0.1 (respectively). Additionally, the trim-and-fill method indicated that the mean effect size for all constructs did not change (see Table 2 for further information). Therefore, these data suggest a potential publication bias for overall ToM, but not for overall empathy, affective empathy, cognitive ToM, or affective ToM/cognitive empathy.

DISCUSSION

This meta-analytic integration of 31 studies provides important and novel insights into how AD affects empathy and ToM, both as broad constructs and in terms of their distinct and overlapping subcomponents. The results show that, when operationalized broadly, people with AD are significantly and substantially impaired in both their capacity for empathy and ToM ($g = 0.67$ and 1.03, respectively). However, when focusing on the subcomponents of these processes, AD was associated with significant impairment in cognitive empathy/affective ToM and cognitive ToM. No significant differences were found between individuals with AD and controls on affective empathy. This disconnect between the cognitive and affective subcomponents of empathy aligns with conclusions from a recent qualitative review (Fischer et al., 2019). Similarly, some studies have found that individuals with AD are impaired in cognitive empathy (Castelli et al., 2011; Dodich et al., 2016; Duclos et al., 2018), while others have found no differences in affective empathy (Dermody et al., 2016; Nash et al., 2007). Importantly, unlike these prior studies, this study used meta-analytic methods which allowed the aggregation of mean effect sizes while controlling for sampling error (the most serious source of artefactual variance), thus providing a clearer understanding of how the different components of ToM and empathy are affected by AD. The findings of this meta-analysis therefore suggest that individuals with AD potentially maintain the capacity to react appropriately to the distress or loss of others, share in the joy and celebrations of others, or relate emotionally to others.

The current results also align with broader literature which suggests that these two empathic components differ in their demands on effortful processing, and therefore likely present different challenges for people with AD. Specifically, affective empathy is regarded as an automatic, spontaneous response that operates with minimal conscious awareness, whereas cognitive empathy has been described as a slow, effortful process requiring time and attention (Yu & Chou, 2018). As affective empathy is a less cognitively demanding process, it might be expected that this ability remains relatively preserved in AD, particularly in the earlier stages of the disease. Indeed, this distinction between automatic, reflexive mechanisms and controlled mechanisms has been identified as critical in predicting the integrity of other specific cognitive processes in AD. For instance, inhibitory deficits in AD do not appear to be the result of a general inhibitory breakdown. Instead, AD has a strong effect on tasks requiring controlled inhibition processes but relatively little effect on tasks requiring more automatic inhibition (Amieva et al., 2004). The data pertaining to ToM impairment are also interesting and important in light of the noted inconsistencies identified in prior literature, with some studies suggesting that some or all aspects of ToM function may be preserved in AD (Bertoux et al., 2016; Fliss et al., 2016; Heitz et al., 2016; Kumfor et al., 2017). The current data instead align with other studies in this literature which have shown that ToM, both broadly and when broken down into its' subcomponents, is substantially impaired in AD (Bora et al., 2015; Dodich et al., 2016; Moreau et al., 2016; Yamaguchi et al., 2019). It is important to note that a potential publication bias has occurred for overall ToM data. Both the Begg and Mazumdar rank correlation test and Egger's regression intercept were significant. This suggests that, for overall ToM data, there is a higher probability that significant results were published relative to nonsignificant results.

At the same time, however, considerable heterogeneity between the individual studies contributing to these mean effects was identified, and this was captured formally by the significant *Q* statistic for all of the aggregate mean effects. As noted earlier, because an important strength of meta-analytic methodology is the ability to control for sampling error, the fact that significant heterogeneity still emerged indicates that there are other important sources of substantive variance remaining. The current study was able to identify one of these sources, showing that cognitive impairment, as indexed by the MMSE, accounted for significant variance in the AD-related effects for overall ToM, cognitive ToM, affective ToM/cognitive empathy, and overall empathy. This finding is unsurprising, as deficits in executive control and working memory have been shown to contribute to ToM functioning in AD (Castelli et al., .2011; Cuerva et al., 2001; Fliss et al., 2016; Laisney et al., 2013; Moreau et al., 2016), and these cognitive abilities continue to deteriorate as the disease progresses. Other clinical variables such as depression, prior substance abuse, apathy, and vascular illness burden have also been argued to influence ToM and empathic functioning (e.g., Mattern et al., 2015; Njomboro, Humphreys, & Shoumitro, 2014; Sanvicente-Vieira et al., 2017; Walzak & Loken Thornoton, 2018; Weightman, Air, & Baune, 2014; Zobel et al., 2010). However, it was not possible to assess the potential influence of these variables at the meta-analytic level because they were only assessed in a minority of the contributing studies. Indeed, certain variables, such as prior substance abuse, often resulted in a participant's exclusion from the study.

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LIMITATIONS AND FUTURE DIRECTIONS

An important limitation is that, although 31 empirical studies contributed to this study, only four contributed to the specific aggregate mean effect for affective empathy. Further, while one study used a behavioral assessment of affective empathy (Mograbi et al., 2012), three studies used the Interpersonal Reactivity Index empathic concern subscale, and of these, only one had participant-reported ratings (Nash et al., 2007), while the other two had carer's answer questionnaires on behalf of AD participants (Dermody et al., 2016; Narme et al., 2013). Accurate self-reporting is reliant both on emotional insight and a willingness to disclose personal information (Murphy & Lilienfeld, 2019). It is therefore of concern that prior studies have shown that, for other cognitive domains, as well as clinical aspects of their illness more broadly, people with AD often exhibit relatively poor insight (Howorth & Saper, 2003; Mangone et al., 1991; Vogel et al., 2004), although it has yet to be established whether these difficulties extend to emotional insight. Even for people without a clinical illness such as AD, there may be difficulties relying on self-report assessments of empathy. A recent meta-analysis found that self-report and behavioral measures of cognitive empathy exhibit poor convergent validity (Murphy & Lilienfeld, 2019), indicating that a multimethod approach is critical to gain a clear understanding of this complex capacity to engage in empathy. Additional implications also arise when questionnaires are filled out on behalf of another individual. There are questions regarding the reliability of informant-reported measures as the information being reported has the potential to be influenced by characteristics of both the patient and the informant (Farias, Mungas, & Jagust, 2005; Kemp et al., 2002; Morrell, Camic, & Genis, 2019).

Most critically, Mograbi et al.'s (2012) behavioral assessment of affective empathy examined participants' empathic responses to emotional information. This study showed that people with AD exhibited lower levels of empathy relative to healthy controls in response to happy and fearful films. Importantly, they found no significant differences between either groups on angry, hopeless, neutral, or positive films. The current meta-analysis therefore highlights the need for further empirical studies to assess affective empathy in AD using a range of methodological approaches. Potentially promising behavioral assessments that might be used to index this construct include the Multifaceted Empathy Test (MET; Dziobek et al., 2008) and the EmpaToM (Kanske et al., 2015).

Additionally, future research should examine how factors such as apathy, depression, or prior substance abuse affect an individual with AD's ability to function on ToM and empathy tasks. In the current meta-analysis, data for these variables were only reported in a small minority of the contributing studies, and as such, their potential impact could not be determined. This therefore remains an important issue for future research to address.

Furthermore, the overlap between cognitive and affective processes has frequently been noted in prior literature (Bensalah et al., 2016; Bertoux et al., 2016; Dodich et al., 2016; Dvash & Shamay-Tsoory, 2014; Kumfor et al., 2017; Moreau et al., 2016; Preckel et al., 2018; Shamay-Tsoory et al., 2009, 2005; Yamaguchi et al., 2019). Although they were treated as distinct in the current meta-analysis, it is likely that these processes influence each other. For instance, an affective empathic response may facilitate the understanding of someone else's mental state. Therefore, further studies are required to understand how the relationship between these variables affects broader social function and quality of life outcomes in AD.

To conclude, it is now well accepted that in many neurological groups, social cognitive impairment is a key predictor of broader prognostic outcomes, including social function, mental health, and quality of life. A more complete and nuanced understanding of how social cognition is affected in AD is therefore now critical to inform the development of structured social cognitive interventions. The results of this meta-analysis show that while AD is associated with significant and substantial impairment in both ToM and empathy as broad constructs as well as both ToM subcomponents, affective empathy, at least when indexed via self-report, is not significantly impaired. Further work is now needed to cross-validate these findings using behavioral methods of assessment and also to test the influence of important clinical variables (i.e., apathy, depression) on ToM and empathic ability in AD.

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CONFLICT OF INTEREST

None.

SUPPLEMENTARY MATERIAL

To view supplementary material for this article, please visit https://doi.org/10.1017/S1355617720000478

References marked with an asterisk indicate studies included in the meta-analysis.

References

Adams, A.G., Schweitzer, D., Molenberghs, P., & Henry, J.D. (2019). A meta-analytic review of social cognitive function following stroke. *Neuroscience & Biobehavioral Reviews*, *102*, 400–416. doi: 10.1016/j.neubiorev.2019.03.011

*Amanzio, M., Geminiani, G., Leotta, D., & Cappa, S. (2008). Metaphor comprehension in Alzheimer's disease: novelty matters. *Brain and Language*, *107*(1), 1–10. doi: 10.1016/j.bandl.2007.08.003

Amieva, H., Phillips, L.H., Della Sala, S., & Henry, J.D. (2004). Inhibitory functioning in Alzheimer's disease. *Brain*, *127*(5), 949–964. doi: 10.1093/brain/awh045

Bailly, M., Destrieux, C., Hommet, C., Mondon, K., Cottier, J., Beaufils, E., Vierron, E., Vercouillie, J., Ibazizene, M., Voisin, T., Payoux, P., Barré, L., Camus, V., Guilloteau, D., & Ribeiro, M. (2013). Precuneus and cingulate cortex atrophy and hypometabolism in patients with Alzheimer's disease and mild cognitive impairment: MMRI and F-FDG PET quantitative analysis using FreeSurfer. *BioMed Research International*, *2015*, 8. doi: 10.1155/2015/583931

Banerjee, S., Murray, J., Foley, B., Atkins, L., Schneider, J., & Mann, A. (2003). Predictors of institutionalisation in people with dementia. *Neurology, Neurosurgery & Psychiatry*, *74*(9), 1315–1316. doi: 10.1136/jnnp.74.9.1315

Bartochowski, Z., Gatla, S., Khoury, R., Al-Dahhak, R., & Grossberg, G. T. (2018). Empathy changes in neurocognitive disorders: a review. *Annals of clinical psychiatry: Official the American Academy of Clinical Psychiatrists*, *30*, 220–232. Retrieved from europepmc.org

Bensalah, L., Caillies, S., & Anduze, M. (2016). Links among cognitive empathy, theory of mind, and affective perspective taking by young children. *Genetic Psychology*, *177,* 17–31. doi: 10.1080/00221325.2015.1106438

*Bertoux, M., De Souza, L. C., O'Callaghan, C., Greve, A., Sarazin, M., Dubois, B., & Hornberger, M. (2016). Social cognition deficits: the key to discriminate behavioural variant frontotemporal dementia from Alzheimer's disease regardless of amnesia? *Alzheimer's Disease*, *49*(4), 1065–1074. doi: 10.3233/JAD-150686

Bora, E., Velakoulis, D., & Walterfang, M. (2016). Meta-analysis of facial emotion recognition in behavioural variant frontotemporal dementia: comparison with Alzheimer disease and healthy controls. *Geriatric Psychiatry and Neurology*, *29*(4), 205–211. doi: 10.1177/0891988716640375

Bora, E., Walterfang, M., & Velakoulis, D. (2015). Theory of mind in behavioural-variant frontotemporal dementia and Alzheimer's disease: a meta-analysis. *Neurology, Neurosurgery & Psychiatry*, *86*(7), 714–719.doi: 10.1136/jnnp-2014-309445

Borenstein, M., Hedges, L., Higgins, J., & Rothstein, H. (2013). *Comprehensive Meta-Analysis Verson 3 [Computer software]*. Englewood, NJ: Biostat.

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

*Choong, C.S., & Doody, G.A. (2013). Can theory of mind deficits be measured reliably in people with mild and moderate Alzheimer's dementia? *BMC Psychology*, *1*(1). 28. doi: 10.1186/2050-7283-1-28

Christidi, F., Migliaccio, R., Santamaría-García, H., Santangelo, G., & Trojsi, F. (2018). Social cognition dysfunctions in neurodegenerative diseases: neuroanatomical correlates and clinical implications. *Behavioural Neurology*, *2018*, 1849794–1849794. doi: 10.1155/2018/1849794

Ciaramidaro, A., Adenzato, M., Enrici, L., Erk, S., Pia, L., Bara, B.G., & Walter, H. (2007). The international network, how the brain reads varieties of intentions. *Neuropsychologia*, *45*(13), 3105–3113. doi: 10.1016/j.neuropsychologia.2007.05.011

Cohen, J. (1988). *Statistical power analyses for the behavioural sciences*. New York, NY: Academic Press.

Coundouris, S.P., Adams, A.G., Grainger, S.A., & Henry, J.D. (2019). Social perceptual function in Parkinson's disease: a meta-analysis. *Neuroscience and Behavioural Reviews*, *104,* 255–267. doi: 10.1016/j.neubiorev.2019.07.011

Coundouris, S.P., Adams, A.G., & Henry, J.D. (2020). Empathy and theory of mind in Parkinson's disease: a meta-analysis. *Neuroscience & Biobehavioral Reviews*, *109*, 92–102. doi: 10.1016/j.neubiorev.2019.12.030

*Cuerva, A.G., Sabe, L., Kuzis, G., Tiberti, C., Dorrego, F., & Starkstein, S.E. (2001). Theory of mind in pragmatic abilities in dementia. *Neuropsychiatry, Neuropsychology, and Behavioural Neurology*, *14*(3), 153–158. ISSN: 0894-878X

*Dermody, N., Wong, S., Ahmed, R., Piguet, O., Hodges, J.R., & Irish, M. (2016). Uncovering the neural bases of cognitive and affective empathy deficits in Alzheimer's disease and the behavioural-variant of frontotemporal dementia. *Alzheimer's Disease*, *53*(3), 801–816. doi: 10.3233/JAD-160175

*Dodich, A., Cerami, C., Crespi, C., Canessa, N., Lettieri, G., Lannaccone, S., Marcone, A., Cappa, S.P., & Cacioppo, J.T. (2016). Differential impairment of cognitive and affective mentalizing abilities in neurodegenerative dementias: evidence from behavioural variant of frontotemporal dementia, Alzheimer's disease, and mild cognitive impairment. *Alzheimer's Disease*, *50*(4), 1011–1022. doi: 10.3233/jad-150605

Downes, M.J., Brennan, M.L., Williams, H.C., & Dean, R.S. (2016). Development of a critical appraisal tool to assess the quality of cross-sectional studies (AXIS). *BMJ Open*, *6*(12), e011458. doi: 10.1136/bmjopen-2016-011458

*Duclos, H., Bejanin, A., Eustache, F., Desgranges, B., & Laisney, M. (2018). Role of context in affective theory of mind in Alzheimer's disease. *Neuropsychologia*, *119*, 363–372. doi: 10.1016/j.neuropsychologia.2018.08.025

Dvash, J., & Shamay-Tsoory, S.G. (2014). Theory of mind and empathy as multidimensional constructs: neurological foundations. *Topics in Language Disorders*, *34,* 282–295. doi: 10.1097/TLD.0000000000000040

Dziobek, I., Rogers, K., Fleck, S., Bahnemann, M., Heekeren, H., Wolf, R., & Convit, O. (2008). Dissociation of cognitive and emotional empathy in adults with Asperger syndrome using the multifaceted empathy test (MET). *Austism and Developmentaal Disorders*, *38*(3), 464–473. doi: 10.1007/s10803-007-0486-x

Easterbrook, P.J., Berlin, J.A., Gopalan, R., & Mathews, D.R. (1991). Publication bias in clinical research. *Lancet*, *337*, 867–872. doi: 10.1016/0140-6736(91)90201-Y

*El Haj, M., Gély-Nargeot, M., & Raffard, S. (2015). Destination memory and cognitive theory of mind in Alzheimer's disease. *Alzheimer's Disease*, *48*(2), 529–536. doi: 10.3233/JAD-150467

Enrici, I., Adenzato, M., Cappa, S., Bara, B.G., & Tettamanti, M. (2011). Intention process in communication: a common brain

network for language and gestures. *Cognitive Neuroscience*, *23*(9), 2415–2431. doi: 10.1162/jocn.2010.21594

Eres, R., Decety, J., Louis, R.W., & Molenberghs, P. (2015). Individual differences in local gray matter density are associated with differences in affective and cognitive empathy. *Neuroimage*, *117*, 305–310. doi: 10.1016/j.neuroimage.2015.05.038

Fan, Y., Duncan, N.lW., De Greck, M., & Northoff, G. (2011). Is there a core neural network in empathy? An FMRI based quantitative meta-analysis. *Neuroscience & Biobehavioral Reviews*, *35*(3), 903–911. doi: 10.1016/j.neubiorev.22010.10.009

Farias, S. T., Mungas, D., & Jagust, W. (2005). Degree of discrepancy between self and other reported everyday functioning by cognitive status: dementia, mild cognitive impairment, and healthy elders. *International Journal of Geriatric Psychiatry*, *20*(9), 827–834. doi: 10.1002/gps.1367

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

Fischer, A., Landeira-Fernandez, J., Sollero de Campos, F., & Mograbi, D.C. (2019). Empathy in Alzheimer's disease: review of findings and proposed model. *Alzheimer's Disease*, *69*(4), 921–933. doi: 10.3233/jad-180730

*Fliss, R., Le Gall, D., Etcharry-Bouyx, F., Chauvire, V., Desgranges, B., & Allain, P. (2016). Theory of mind and social reserve. Alternative hypothesis of progressive theory of mind decay during different stages of Alzheimer's disease. *Social Neuroscience*, *4,* 409–423. doi: 10.1080/17470919.2015.1101014

*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 and Associated Disorders*, *27*(1), 56–61. doi: 10.1097/WAD.0b013e31824ea5db

Gomez-Isla, T., Hollister, R., West, H., Mui, S., Growdon, J.H., Petersen, R.C., Parisi, J.E., & Hyman, B.T. (1997). Neuronal loss correlates with but exceeds neurofibrillary tangles in Alzheimer's disease. *Annals of Neurology*, *41*(1), 17–24. doi: 10.1002/ana.410410106

Grainger, S.A., Rakunathan, V., Adams, A G., Canty, A.L., & Henry, J.D. (2020). An assessment of age differences in theory of mind using the virtual assessment of mentalizing ability. *Aging, Neuropsychology, and Cognition*, 1–11. doi: 10.1080/13825585.2020.1713290

Grainger, S.A., Steinvik, H.R., Henry, J.D., & Phillips, L.H. (2019). The role of social attention in older adults' ability to interpret naturalistic social scenes. *Quarterly Journal of Experimental Psychology*, *72,* 1328–1343. doi: 10.1177/174021818791774

*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*(4), 752–764. doi: 10.1093/brain/awf079

Guntekin, B., Hanoglu, L., Akturk, T., Fide, E., Emek-Savas, D.D., Rusen, E., Yıldırım, E., & Yener, G.G. (2019). Impairment in recognition of emotional facial expressions in Alzheimer's disease is represented by EEG theta and alpha responses. *Psychophysiology*, e13434. doi: 10.1111/psyp.13434

*Heitz, C., Noblet, V., Phillipps, C., Cretin, B., Vogt, N., Philippi, N., Kemp, J., de Petigny, X., Bilger, M., Demuynck, C., Martin-Hunyadi, C., Armspach, J.p., & Blanc, F. (2016). Cognitive and affective theory of mind in dementia with Lewy bodies and Alzheimer's disease. *Alzheimer's Research & Therapy*, *8*(1), 10. doi: 10.1186/s13195-016-0179-9

Henry, J.D., Phillips, L.H., Ruffman, T., & Bailey, P.E. (2013). A meta-analytic review of age differences in theory of mind. *Psychology and Aging*, *28*(3), 826–839. doi: 10.1037/a0030677

*Henry, J.D., Rendell, P.G., Scicluna, A., Jackson, M., & Phillips, L.H. (2009). Emotion experience, expression, and regulation in Alzheimer's disease. *Psychology and Aging*, *24*(1), 252–257. doi: 10.1037/a0014001

Henry, J.D., Von Hippel, W., Molenberghs, P., Lee, T., & Sachdev, P.S. (2016). Clinical assessment of social cognitive function in neurological disorders. *Nature Reviews Neurology*, *12*(1), 28–39. doi: 10.1038/nrneurol.2015.229

Higgins, J.P.T. (2008). *Cochrane handbook for systematic reviews of interventions*. Chichester, UK: John Wiley & Sons, Ltd. doi: 10.1002/9781119536604

Howorth, P., & Saper, J. (2003). The dimensions of insight in people with dementia. *Aging and Mental Health*, *7*(2), 113–122. doi: 10.1080/1360786031000072286

Kanske, P., Böckler, A., Trautwein, F,. & Singer, T. (2015). Dissecting the social brain: introducing the EmpaToM to reveal distinct neural networks and brain-behaviour relations for empathy and theory of mind. *Neuroimage*, *122,* 6–19. doi: 10.1016/j.neuroimage.2015.07.082

Kemp, N. M., Brodaty, H., Pond, D., & Luscombe, G. (2002). Diagnosing dementia in primary care: the accuracy of informant reports. *Alzheimer Disease & Associated Disorders*, *16*(3), 171–176. doi: 10.1097/00002093-200207000-00007

Klein-Koerkamp, Y., Beaudoin, M., Baciu, M., & Hot, P. (2012). Emotional decoding abilities in Alzheimer's disease: a meta-analysis. *Alzheimer's Disease*, *32*(1), 109–125. doi: 10.3233/JAD-2012-120553

*Kumfor, F., Honan, C., McDonald, S., Hazelton, J.L., Hodges, J.R., & Piguet, O. (2017). Assessing the "social brain" in dementia: applying TASIT-S. *Cortex*, *93*, 166–177. doi: 10.1016/j.cortex.2017.05.022

*Kumfor, F., Irish, M., Leyton, C., Miller, L., Lah, S., Devenney, E., Hodges, J.R., & Piguet, O. (2014). Tracking the progression of social cognition in neurodegenerative disorders. *Neurology, Neurosurgery, and Psychiatry*, *10,* 1076–1083. doi: 10.1136/jnnp-2013-3070098

*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. *Neuropsychology*, *7*(1), 107–120. doi: 10.1111/j.1748-6653.2012.02038

*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*(10), 3026–3038. doi: 10.1093/brain/aws237

Lee, T.M.C., Sun, D., Leung, M., Chu, L., & Keysers, C. (2013). Neural activities during affective processing in people with Alzheimer's disease. *Neurobiology of Aging*, *34*(3), 706–715. doi: 10.1016/j.neurobiolaging.2012.06.018

Lipsey, M.W., & Wilson, D.B. (2001). *Practical meta-analysis*. Thousand Oaks, CA: Sage Publications, Inc.

Mangone, C.A., Hier, D.B., Gorelick, P.B., Ganellen, R.J., Langenberg, P., Boarman, R., & Dollear, W.C. (1991). Impaired insight in Alzheimer's disease. *Geriatric Psychiatry and Neurology*, *4*(4), 189–193. doi: 10.1177/089198879100400402

Martinez, M., Multani, N., Anor, C.J., Misquitta, K., Tang-Wai, D.F., Keren, R., Fox, S., Lang, A.E., Marras, C., & Tartaglia, M.C. (2018). Emotion detection deficits and decreased empathy in patients with Alzheimer's disease and Parkinson's disease affect caregiver mood and burden. *Frontiers in Aging Neuroscience*, *10*, 120. doi: 10.3389/fnagi.2018.00120

Mattern, M., Walter, H., Hentze, C., Schramm, E., Drost, S., Schoepf, D., . . . & Schnell, K. (2015). Behavioural evidence for an impairment of affective theory of mind capabilities in chronic depression. *Psychopathology*, *48*, 240–250. doi: 10.1159/000430450

*Mograbi, D.C., Brown, R.G., & Morris, R.G. (2012). Emotional reactivity to film material in Alzheimer's disease. *Dementia And Geriatric Cognitive Disorders*, *34*(5–6), 351–359. doi: 10.1159/000343930

Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., & Group, P. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Medicine*, *6*, e1000097.

*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

Morrell, L., Camic, P.M., & Genis, M. (2019). Factors associated with informant-reported cognitive decline in older adults: a systemised literature review. *Dementia*, *18*(7–8), 2760–2784. doi: 10.1177/1471301218759836

Murphy, B.A., Lilienfeld, S.O. (2019). Are self-report cognitive empathy ratings valid proxies for cognitive empathy ability? Negligible meta-analytic relations with behavioural task performance. *Psychological Assessment*, *31*(8), 1062–1072. doi: 10.1037/pas0000732

*Narme, P., Mouras, H., Roussel, M., Devendeville, A., & Godefroy, O. (2013). Assessment of socioemotional processes facilitates the distinction between frontotemporal lobar degeneration and Alzheimer's disease. *Clinical and Experimental Neuropsychology*, *35*(7), 728–744. doi: 10.1080/13803395.2013.823911

*Nash, S., Henry, J.D., McDonald, S., Martin, I., Brodaty, H., & Peek-O'Leary, M. (2007). Cognitive disinhibition and socioemotional functioning in Alzheimer's disease. *The International Neuropsychological Society: JINS*, *13*(6), 1060–1064. doi: 10.1017/S135561770707184

Njomboro, P., Humphreys, G.W., & Shoumitro, D. (2014). Exploring social cognition in patients with apathy following acquired brain damage. *BMC Neurology*, *14*(18), 1–11. doi: 10.1186/1471-2377-14-18

Park, S., Kim, T., Shin, S.A., Kim, Y.K., Sohn, B.K., Park, H.J., Youn, J.H., & Lee, J.Y. (2017). Behavioural and neuroimaging evidence for facial emotion recognition in elderly Korean adults with mild cognitive impairment, Alzheimer's disease, and frontotemporal dementia. *Frontiers in Aging Neuroscience*, *9*, 389. doi: 10.3389/fnagi.2017.00389

Poletti, M., Enrici, L., & Adenzato, M. (2012). Cognitive and affective theory of mind in neurodegenerative diseases: neuropsychological, neuroanatomical and neurochemical levels. *Neuroscience & Biobehavioral Reviews*, *36*(9), 2147–2164. doi: 10.1016/j.neubiorev.2012.07.004

Poveda, B., Osborne-Crowley, K., Laidlaw, K., Macleod, F., & Power, K. (2017). Social cognition, behaviour and relationship continuity in dementia of the Alzheimer type. *Brain Impairment*, *18*(2), 175–187. doi: 10.1017/Brlmp.2016.35

Preckel, K., Kanske, P., & Singer, T. (2018). On the interaction of social affect and cognition: empathy, compassion and theory of mind. *Current Opinion in Behavioural Sciences*, *19,* 1–6. doi: 10.1016/j.cobeha.2017.07.010

Ramos Bernardes Da Silva Fiho, S., Oliveira Barbosa, J.H., Rondinoni, C., Dos Santos, A.C., Garrido Salmon, C.E., Da Costa Lima, N.K., Ferriolli, E., Moriguti, J.C. (2017). Neurodegeneration profile of Alzheimer's patients: a brain morphometry study. *NeuroImage: Clinical*, *15*, 15–24. doi: 10.1016/j.nicl.2017.04.001

Rosenthal, R. (1979). The "file drawer problem" and tolerance for null results. *Psychological Bulletin*, *86*, 638–641. doi: 10.1037/0033-2909.86.3.638.

Rowse, G., McCarthy-Jones, S., Knowles, R., Corcoran, R., & Bentall, R.P. (2013). Attributional style and theory of mind in people with Alzheimer disease and persecutory delusions. *Geriatric Psychiatry*, *21*(9), 898–905. doi: 10.1016/j.jagp.2013.01.020

Ryu, S., Kwon, M.J., Lee, S., Yang, D.W., Kim, T., Song, I., Yang, P.S., Kim, H.J., & Lee, A.Y. (2005). Measurement of precuneal and hippocampal columes using magnetic resonance volumetry in Alzheimer's disease. *Clinical Neurology (Seoul, Korea)*, *6*(4), 196–203. doi: 10.3988/jcn.2010.6.4.196

Sanvicente-Vieira, B., Romani-Sponchiaado, A., Kluwe-Schiavon, B., Brietzke, E., Araujo, R.B., & Grassi-Oliveira, R. (2017). Theory of mind in substance users: a systematic minireview. *Substance Use & Misuse*, *52*(1), 127–132. doi: 10.1080/10826084.2016.1212890

*Scheidemann, J.H., Petermann, F., & Schipper, M. (2016). Are deficits in social cognition linked to autobiographical memory in patients with Alzheimer's disease? *Zeitschrift Fur Neuropsychologie*, *27*(4), 257–262. doi: 10.1024/1016-264X/a000187

Schroeter, M.L., Stein, T., Maslowski, N., & Neumann, J. (2009). Neural correlates of Alzheimer's disease and mild cognitive impairment: a systematic and quantitative meta-analysis involving 1351 patients. *NeuroImage*, *47*(4), 1196–1206. doi: 10.1016/j.neuroimage.2009.05.037

Sebastian, L.C., Fontaine, M.G.N., Bird, G., Blakemore, S., De Brito, A.S., McCroy, J.P.E., & Viding, E. (2011). Neural processing associated with cognitive and affective theory of mind in adolescents and adults. *Social Cognitive and Affective Neuroscience*, *7*(1), 53–63. doi: 10.1093/scan/nsr023

Shamay-Tsoory, S.G., Aharon-Peretz, J., & Perry, D. (2009). Two systems for empathy: a double dissociation between emotional and cognitive empathy in inferior frontal gyrus versus ventromedial prefrontal lesions. *Brain*, *132,* 617–627. doi: 10.1093/brain/awn279

Shamay-Tsoory, S.G., Tomer, R., Berger, B.D., Goldsher, D., & Aharon-Peretz, J. (2005). Impaired "affective theory of mind" is associated with right ventromedial prefrontal damage. *Cognitive and Behavioural Neurology*, *18,* 55–67. Retrieved from ovidsp.dc2.ovid.com/sp

*Shanny-Ur, T., Poorzand, P., Grossman, S.N., Drowdon, M.E., Jang, J.Y., Ketelle, R.S., Miller, B.L., & Rankin, K.P. (2012). Comprehension of insincere communication in neurodegenerative disease: lies, sarcasm, and theory of mind. *Cortex*, *48*(10), 1329–1341. doi: 10.1016/j.cortex.2011.08.003

Singer, T. (2006). The neuronal basis and ontogeny of empathy and mind reading: review of literature and implications for future research. *Neuroscience & Biobehavioral Reviews*, *30*, 855–863. doi: 10.1016/j.neubiorev.2006.06.011

Spitznagel, M.B., Tremont, G., Davis, J.D., & Foster, S.M. (2006). Psychosocial predictors of dementia caregiver desire to institutionalize: caregiver, care recipient, and family relationship factors. *Geriatric Psychiatry and Neurology*, *19*(1), 16–20. doi: 10.1177/0891988705284713

Stone, V.E., Baron-Cohen, S., & Knight, R.T. (1998). Frontal lobe contributions to theory of mind. *Cognitive Neuroscience*, *10*(5), 640–656. doi: 10.1162/089892998562942

Sturm, V.E., Yokoyama, J.S., Seeley, W.W., Kramer, J.H., Miller, B.L., & Rankin, K.P. (2013). Heightened emotional contagion in mild cognitive impairment and Alzheimer's disease is associated with temporal lobe degeneration. *Proceedings of the National Academy of Sciences*, *110*(24), 9944–9949. doi: 10.1073/pnas.1301119110

Sun, B., Luo, Z., Zhang, W., Li, W., & Li, X. (2017). Age-related differences in affective and cognitive empathy: self-report and performance-based evidence. *Aging, Neuropsychology, and Cognition*, *25*(5), 665–672. doi: 10.1080/13825585.2017.1360835

*Takenoshita, S., Terada, S., Yokota, O., Kutoku, Y., Wakutani, Y., Nakashima, M., Maki, Y., Hattori, H., & . . . Yamada, N. (2018). Sally-Anne test in patients with Alzheimer's disease dementia. *Alzheimer's Disease*, *61*(3), 1029–1036. doi: 10.3233/jad-170621

Torres, B., Santos, R.L., Sousa, M.F., Simoesneto, J.P., Nogueira, M.M., Belfort, T.T., Dias, R., & Dourado, M.C. (2015). Facial expression recognition in Alzheimer's disease: a longitudinal study. *Arquivos de Neuro-Psiquiatri*, *5,* 383–389. doi: 10.1590/0004- 282x20150009

Uribe, C., Puig-Davi, A., Abos, A., Baggio, H.C., Junque, C., & Segura, B. (2019). Neuroanatomical and function correlates of cognitive and affective empathy in young healthy adults. *Frontiers in Behavioural Neuroscience*, *13*, 85. doi: 10.3389/fnbeh.2019.00085

*Verdon, C., Fossati, P., Verny, M., Dieudonne, B., Teillet, L., & Nadel, J. (2007). Social cognition: an early impairment in dementia of the Alzheimer type. *Alzheimer Disease and Associated Disorders*, *21*(1), 25–30. doi: 10.1097/WAD.0b013e318032487a

Vogel, A., Stokhom, J., Gade, A., Anderson, B.B., Hejl, A., & Waldemar, G. (2004). Awareness of deficits in mild cognitive impairment and Alzheimer's disease: do MCI patients have impaired insight? *Dementia and Geriatric Cognitive Disorders*, *17*(3), 181–187. doi: 10.1159/000076354

Walzak, L.C., & Loken Thornton, W. (2018). The role of illness burden in theory of mind performance among older adults. *Experimental Ageing Research*, *44*(5), 427–442. doi: 10.1080/0361073X.2018.1521494

Weightman, M.J., Air, T.M., & Baune, B.T. (2014). A review of the role of social cognition in major depressive disorder. *Frontiers in Psychiatry*, *5*(179). doi: 10.3389/fpsyt.2014.00179

*Yamaguchi, T., Maki, Y., Takatama, M., & Yamaguchi, H. (2019). Gullibility may be a warning sign of Alzheimer's disease dementia. *International Psychogeriatrics*, *31*(3), 363–370. doi: 10.1017/s1041610218000844

*Yamaguchi, T., Maki, Y., & Yamaguchi, H. (2012). Pitfall Intention Explanation Task with Clue Questions (Pitfall task): assessment of comprehending other people's behavioural intentions in Alzheimer's disease. *International Psychogeriatrics*, *24*(12), 1919–1926. doi: 10.1017/s1041610212001147

*Youmans, G., & Bourgeois, M. (2010). Theory of mind in individuals with Alzheimer-type dementia. *Aphasiology*, *24*(4), 515–534. doi: 10.1080/02687030902801573

Yu, C., & Chou, T. (2018). A dual route model of empathy: a neurobiological prospective. *Frontiers in Psychology*, *9,* 2212. doi: 10.3389/fpsyg.2018.02212

*Zaitchik, D., Koff, E., Brownell, H., Winner, E., & Albert, M. (2006). Inference of mental states in patients with Alzheimer's disease. *Cognitive Neuropsychiatry*, *9*(4), 301–313. doi: 10.1080/13546800344000246

Zobel, I., Werden, D., Linster, H., Dykierek, P., Drieling, T., Berger, M., & Schramm, E. (2010). Theory of mind deficits in chronically depressed patients. *Depression and Anxiety*, *27*, 821–828. doi: 10.1002/da.20713