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Theory of Mind in Mild Cognitive Impairment – Relationship with Limbic Structures and Behavioural Change

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Abstract

Objectives: Older adults presenting with mild cognitive impairment (MCI) have a higher risk of developing dementia and also demonstrate impairments in social cognition. This study sought to establish whether in people with MCI, poorer theory of mind (ToM) was associated with volumetric changes in the amygdala and hippocampus, as well as early changes in behaviour. **Methods:** One hundred and fourteen people with MCI and fifty-two older adult controls completed the Reading the Mind in the Eyes Test (RMET), while close informants (e.g., spouse/family member/friend/carer) described any current behavioural changes using the Revised Cambridge Behavioural Inventory (CBI-R). A subsample of participants completed structural magnetic resonance imaging (MRI). **Results:** The MCI group showed poorer performance on all neuropsychological tests administered, and moderate reductions on the RMET compared to the control group ($d = .44$), with greater reduction observed in those with amnestic compared to non-amnestic MCI ($p = .03$). While a robust correlation was identified between poorer RMET performance and smaller hippocampal volume in the control group ($\rho = .53$, $p = .01$), this relationship was not apparent in the MCI group ($\rho = .21$, $p = .11$). In the MCI group, poorer RMET performance was associated with poorer everyday skills ($\rho = -.26$, $p = .01$) assessed by the CBI-R. **Conclusions:** Our findings cross-validate previous reports that social cognitive deficits in ToM are a feature of MCI and also suggest that disruptions to broader neural networks are likely to be implicated. Furthermore, ToM deficits in MCI are associated with a decline in everyday skills such as writing or paying bills.

Keywords: Mild cognitive impairment (MCI), Theory of mind (ToM), Social cognition, RMET, Amygdala, Hippocampus, CBI-R

INTRODUCTION

Social cognition refers to the set of cognitive processes involved in recognising, understanding, and responding to social cues (Beer and Ochsner, 2006; Henry, von Hippel, Molenberghs, Lee, and Sachdev, 2016). It has been argued that this neurocognitive domain encompasses four broad components: (i) theory of mind (ToM), which refers to the ability to understand the mental states of others, (ii) empathy, which refers to the capacity to experience care or concern for others, (iii) social perception, which refers to the ability to recognise social cues, and (iv) social behaviour, the ability to appropriately present oneself in a social situation (Henry et al., 2016). Altogether, intact social cognitive function is pivotal in contributing to the development and maintenance of interpersonal relationships (Brodaty, 1997; Carton, Kessler, and Pape, 1999; Sodian and Kristen, 2010) throughout the lifespan.

Consistently, research has shown that certain brain regions are particularly important for specific social cognitive domains. For instance, the amygdala appears to be crucial for processing positive and negative emotional valence stimuli, and the dorsal anterior cingulate cortex has been linked to empathy and concern (Allison, Puce, and McCarthy, 2000; Berridge and

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Kringelbach, 2013; Fan, Duncan, de Greck, and Northoff, 2011; Kanwisher and Yovel, 2006; Roy, Shohamy, and Wager, 2012; Van Overwalle, 2009). More broadly, the limbic system, which encompasses core structures such as the amygdala and hippocampus, has been implicated in many aspects of social cognition (Adolphs, 2010; Laurita & Nathan Spreng, 2017; LeDoux, 2000). In addition to its role in processing emotionally salient stimuli, functional magnetic resonance imaging (fMRI) during face perception tasks has shown that the amygdala plays a key role in directing an individual's gaze towards the eyes, most significantly in fearful faces, even if a cursor is initially fixated on the mouth region (Gamer & Buchel, 2009). The hippocampus has been implicated in navigating social relationships and perception of interpersonal cues (Montagrin, Saiote, and Schiller, 2018), although research has yet to elucidate its exact role in social cognition.

In Alzheimer's disease (AD), prominent atrophy and tau deposition is observed in the hippocampus and amygdala and this may contribute to deficits in social cognition (Braak et al., 2006; Henry et al., 2008; Laisney et al., 2012; Martinez et al., 2018). These neuropathological features are even evident in earlier prodromal phases, specifically in those with mild cognitive impairment (MCI) (Markesbery, 2010). With evidence suggesting that these neuropathological features may be most pronounced in individuals with amnestic mild cognitive impairment (aMCI), a subgroup at greatest risk of progressing to AD (Fujie et al., 2008; Kohler et al., 2005; McCade et al., 2013a; Petersen, 2004; Spoletini et al., 2008).

Of clinical relevance, close informants (e.g., spouse/family member/friend/carer) of people with MCI also report changes in various aspects of behaviour such as everyday skills and motivation, which has been shown using measures such as the Revised Cambridge Behavioural Inventory (CBI-R) (Tsang, Diamond, Mowszowski, Lewis, and Naismith, 2012). These behavioural changes may in turn impact on their interpersonal relationships and perceived caregiver burden (McCade et al., 2013b; Paradise et al., 2015). It is therefore important to gain a clearer understanding of how social cognitive deficits relate to behavioural changes in people with MCI, in order to improve awareness of early disease features, and to inform early interventions focused on optimising psychosocial and interpersonal functioning.

Thus far, the majority of studies that has examined social cognitive deficits in MCI has used tests of emotion recognition such as the *Facial Expression of Emotion: Stimuli and Tests* and ToM tasks such as the *Reading the Mind in the Eyes Test* (RMET) (Elferink, van Tilborg, and Kessels, 2015; McCade et al., 2013a). Ever increasingly, however, false belief and referential communication tasks (see Moreau et al., 2015) have also been employed to assess ToM abilities. In fact, such tasks have been informative in highlighting that individuals with MCI reveal deficits in ToM abilities in natural conversation (Moreau et al., 2015). The RMET, in particular, is a well-validated social cognitive measure of relatively basic mental state decoding – requiring participants to make mentalistic inferences on the basis of observable features, specifically, *via* eye gaze cues (Baron-Cohen, Wheelwright, Hill, Raste, and Plumb, 2001; Immordino-Yang and Singh, 2013). There is now a large literature showing the RMET to be very sensitive to poorer ToM abilities in many different clinical groups (Chalah et al., 2017; Heitz et al., 2016). Furthermore, while only relatively few studies have explored this in MCI specifically, ToM abilities as indexed by the RMET have been shown to be clearly disrupted in those individuals with aMCI compared to healthy controls, even when RMET scores are adjusted for semantic fluency (Poletti & Bonuccelli, 2013). Altogether, research reveals that ToM abilities are clearly disrupted in MCI, with the greatest deficits observed in those with multi-domain aMCI (see Bora & Yener, 2017 for meta-analysis).

Importantly, to date, there has been only limited empirical assessment of the neural networks that underlie poorer ToM abilities in MCI. One study of 16 people with aMCI used fMRI to examine neural networks associated with RMET performance (Baglio et al., 2012). Possibly due to relatively small sample sizes, no neural network differences between aMCI and control participants during RMET performance were found. To the present authors' knowledge, no study to date has examined how poorer ToM abilities may specifically relate to the integrity of the hippocampus and amygdala, despite these structures showing clear, yet subtle atrophic changes in MCI (Petersen et al., 2006), and despite their clear role within the limbic system.

Aims and Hypotheses

In this study, our first aim was to cross-validate previous research showing that social cognitive function, namely, ToM, as indexed *via* the RMET is impaired in people with MCI relative to controls. Based on our prior work (McCade et al., 2013a), we hypothesised that social cognitive deficits would be evident in MCI and moreover would be most pronounced in the aMCI subgroup (compared to the naMCI subgroup). Our second aim was to determine whether poorer ToM abilities were volumetrically associated with key limbic structures. We predicted that poorer ToM abilities would be associated with smaller hippocampal and amygdalar volumes. A final exploratory aim was to determine whether ToM in MCI relates to functional and/or behavioural change, as rated by an informant.

METHODS

Sample

One hundred and fourteen individuals meeting criteria for single ($n = 34$) or multiple-domain ($n = 80$) MCI (Winblad et al., 2004) were recruited from a specialist 'Healthy Brain Ageing' Clinic at the Brain and Mind Centre, The University of Sydney, Sydney, Australia. Refer to Clinical Ratings, below, for more information on the specific diagnostic criteria used in this study. This clinic receives referrals from neurologists, psychiatrists, geriatricians, and general practitioners and preferentially targets people over the age of 50 who have new onset

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cognitive and/or mood symptoms. In addition, 52 age- and education-matched healthy volunteers were recruited from the community as control participants. All participants gave a written informed consent, and all data were obtained in compliance with the Helsinki Declaration.

Inclusion criteria for all participants were as follows: aged between 50 and 75 years; English as a first language (with respect to validity of the standardised neuropsychological assessments); and a Mini-Mental State Examination Score (MMSE; Folstein, Folstein, and McHugh, 1975) $\geq$ 24. Exclusion criteria were nonaffective psychiatric disorder (e.g., schizophrenia) or neurological disorder (e.g., head injury, prior stroke or transient ischemic attack, epilepsy, and Parkinson's disease); dementia (as determined by comprehensive clinical neuropsychological and psychiatric assessment); intellectual disability; current or past substance abuse; or impaired basic facial processing (as measured by a score of <41 on the Benton Facial Recognition Test; Benton et al., 1994).

Measures

Clinical ratings

A neurologist or geriatrician conducted a structured clinical assessment for all participants to confirm inclusion/exclusion criteria. A semi-structured clinical interview was administered to determine lifetime and current major depression.

For clinical diagnosis of MCI, all participants needed to demonstrate at least a 1.5 standard deviation decline on standardised neuropsychological tests relative to premorbid estimates. MCI diagnosis was rated on consensus by two neuropsychologists and a specialist (e.g., geriatrician, psychiatrist, or neurologist). MCI was categorised further into amnestic (aMCI, $n = 40$) and nonamnestic (naMCI, $n = 74$) subgroups. Participants met aMCI criteria where they demonstrated clear evidence of impairment on either one or more delayed recall memory tasks (i.e., not just learning deficits). By contrast, naMCI criteria were defined by deficits on tests of other cognitive domains (e.g., processing speed, working memory, language, visuospatial, or executive function). Where participants demonstrated impairment on more than one cognitive domain, they were subsequently categorised as multiple-domain MCI. Overall, this study included participants with multiple-domain aMCI ($n = 35$), single-domain aMCI ($n = 2$), multiple-domain naMCI ($n = 43$), and single-domain naMCI ($n = 32$).

Neuropsychological assessment

A standardised neuropsychological test battery, described in detail elsewhere (Duffy et al., 2014), was administered by a clinical neuropsychologist. For descriptive purposes, the MMSE was administered as a broad screening measure of cognitive functioning. Premorbid intellectual ability for each participant was estimated using the Wechsler Test of Adult Reading (Wechsler, 2001). The following tests were included as outcomes of interest for this study:

(A) Rey Auditory Verbal Learning Test (RAVLT; Lezak, 1995): to measure unstructured verbal learning [i.e., total learning over five trials (RAVLT-1-5; maximum = 60)] and delayed recall [i.e., percent retention scores (RAVLT%), calculated as (Trial 7/Trial 5)*100].

(B) Wechsler Adult Intelligence Scale–III Digit Span subtest (Digit Span; Wechsler 1997): to assess auditory working memory.

(C) Delis–Kaplan Executive Function System Color-Word Interference Test, Condition 3 (inhibition/switching) (DKEFS CWIT; Delis, Kaplan and Kramer, 2001): to measure response inhibition with concurrent cognitive flexibility, as aspects of higher-level executive functions.

(D) Controlled Oral Word Association Test (COWAT): to measure phonemic verbal fluency (letters 'F', 'A', and 'S') (COWAT-FAS; Ruff, Light, Parker and Levin, 1996) and semantic fluency (animal names) (COWAT-Animals; Tombaugh, Kozak and Rees, 1999).

(E) Boston Naming Test (Goodglass, Kaplan and Weintraub, 1983): to assess naming to confrontation.

(F) Trail Making Test Part A and Part B (TMT-A and TMT-B; Reitan, 1979): to measure psychomotor speed and set-shifting/cognitive flexibility, respectively.

In this study, the RMET (Baron-Cohen et al., 2001) was administered to assess participants' social cognitive function. The 36-item assessment requires the participant to infer mental/emotional states from a photograph showing the isolated eye region of an unknown person's face. The participant must infer the mental/emotional state of that person from four options (e.g., terrified, upset, arrogant, or annoyed). The total raw score is calculated based on the number of total correct responses. In this study, age-adjusted z scores were calculated from normative data (Baron-Cohen et al., 2001) and used for subsequent analysis.

Self-report

a) Mood: To determine depression and anxiety symptom severity, participants completed the Hospital Anxiety and Depression Scale (Zigmond & Snaith, 1983). Scores for the entire scale range from 0 to 42, whereby individual scores for each subscale (anxiety and depression) range from 0 to 21. Higher scores indicate a greater severity of symptoms.

b) Behavioural changes: To determine any current neurobehavioural changes, close informants (spouse/family member/friend/carer) of both MCI and control participants completed the CBI-R (Wear et al., 2008). This 45-item questionnaire measures observed changes in cognitive abilities, everyday function, and neuropsychiatric symptoms. Specifically, it assesses change in the domains of memory and orientation, everyday skills, self-care, abnormal behaviour, mood, delusions and hallucinations, eating habits, sleep, stereotypical and motor behaviour, and motivation. Close informants were asked to rate the frequency (0 – none; 1 – a few times per month; 2 – a few times per week; 3 – daily; and 4 – constantly) of potentially altered patterns of behaviour, over the last month.

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Table 1. Demographic and clinical data for control and mild cognitive impairment groups (mean ± *SD*)

	Control ($n = 52$)	Total MCI ($n = 114$)	aMCI ($n = 37$)	naMCI ($n = 77$)	Test statistic*	*p*-value*	Effect size, η^2*
Age, years	62.2 ± 7.1	63.4 ± 6.8	66.0 ± 7.1	62.1 ± 6.3	1.1	.31	.01
Gender (males/females), females	(14/38) 73 %	(50/64) 56 %	(19/18) 49 %	(31/46) 60 %	4.3	.04	.03
Education, years	14.0 ± 3.2	13.9 ± 3.2	14.0 ± 3.3	13.9 ± 3.2	−.1	.9	.00
Predicted IQ[a]	105.6 ± 7.3	104.4 ± 10.4	104.0 ± 10.2	104.7 ± 10.6	.0	1.0	.00
MMSE, /30	29.3 ± .9	28.4 ± 1.7	27.5 ± 2.0	28.9 ± 1.3	−3.4	.001	.07
Alcohol, drinks per week	4.0 ± 4.6	6.2 ± 8.7	4.3 ± 7.5	7.1 ± 9.1	−.9	.4	.01
HADS, anxiety[b]	5.9 ± 4.0	6.6 ± 4.6	6.3 ± 4.8	6.7 ± 4.6	−.7	.5	.00
HADS, depression[b]	4.4 ± 3.8	5.8 ± 4.0	5.4 ± 3.8	5.9 ± 4.1	−2.1	.04	.03

MCI = mild cognitive impairment; IQ = intelligence quotient; MMSE = Mini-Mental State Examination; HADS = Hospital Anxiety and Depression Scale.
* Comparative differences between the control and MCI groups only.
[a] MCI ($n = 111$); aMCI ($n = 36$); naMCI ($n = 75$).
[b] Control ($n = 52$); MCI ($n = 100$); aMCI ($n = 35$); naMCI ($n = 65$).

Magnetic resonance imaging and volume segmentation analysis

A subsample of 84 participants ($n = 17$ aMCI multiple domain; $n = 23$ naMCI multiple domain; $n = 1$ aMCI single domain; $n = 18$ naMCI single domain; and $n = 25$ controls) underwent magnetic resonance imaging (MRI) scanning using a 3T GE Discovery MR750 scanner (GE Medical Systems, Milwaukee, WI, USA) within 2 weeks of their neuropsychological assessment at the Brain and Mind Centre imaging facility. As described previously (Elcombe et al., 2015), an eight-channel phased-array head coil using a T1-weighted magnetisation-prepared rapid gradient-echo sequence was used producing (196 sagittal slices, Repetition Time (TR) = 7.2 ms; Echo Time (TE) = 2.8 ms; flip angle = 10°; matrix 256 × 256; .9 mm isotropic voxels). For each participant, two T1-weighted scans were obtained, of which the sequence with the higher signal-to-noise ratio was used. Regions of interest were the amygdala and the hippocampus. Both left and right hemispherical regional volumes, as described previously (Elcombe et al., 2015), were extracted using a semi-automated segmentation routine based on the principles of the Active Shape and Appearance Models within a Bayesian framework as implemented by 'FMRIB's Integrated Registration and Segmentation Tool (FIRST)' in FMRIB Software Library. Briefly, T1 data were reoriented, converted to Neuroimaging Informatics Technology Initiative (NIFTI) format, and skull-stripped, and the FIRST routine was applied to estimate regional volumes. As a part of the segmentation routine, data were registered to Montreal Neurological Institute (MNI) standard space and boundary correction was applied, with data visually inspected for errors. Total volume for each structure was calculated from the addition of boundary and intracranial volume corrected left and right regional volumes.

Statistical Analyses

All analyses were conducted using SPSS Version 24 (SPSS Inc., Chicago, IL, USA). To examine within- and between-group data, one-way analysis of variance with *post hoc* Tukey tests was used in addition to Levene's test for equality of variance. Similarly, an analysis of covariance was performed to examine within- and between-group data, covarying for age. Where variance differed between groups or following a non-normal distribution, the Kruskal–Wallis nonparametric or the Mann–Whitney *U* test was used, with a Bonferroni correction for multiple comparisons. Categorical data (e.g., gender) were analysed using Pearson's Chi-squared test. Continuous data were analysed using Spearman's rank-order correlation (ρ) and nonparametric partial correlations, as appropriate for the data distribution. All correlations between ToM abilities and brain structure volumes were performed list-wise, and for all analyses an α level of .05 was applied.

For imaging analyses, one aMCI case was found to be a significant outlier (for both the amygdala and hippocampus) and was thus curtailed to the next highest score in the sample.

RESULTS

Demographic and Neuropsychological Characteristics

Table 1 outlines the clinical and demographic characteristics of the sample. There were no significant differences between the MCI and control groups in terms of mean age, years of education, or estimated premorbid intellectual ability. However, as expected, the MCI group had lower scores on the MMSE ($p = .001$) and higher symptoms of depression ($p = .04$). Within the control group, there was a higher proportion of females to males ($p = .04$). Additionally, *post hoc* analyses revealed significant differences on a number of clinical variables when comparing the MCI subgroups with the control group. Specifically, participants in the aMCI subgroup ($n = 37$) were significantly older than both controls ($p = .03$) and those with naMCI ($n = 77$, $p = .01$). Moreover, lower MMSE scores were observed in the aMCI subgroup compared to both controls ($p < .001$) and the naMCI subgroup ($p = .002$).

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Table 2. Neuropsychological data for control and mild cognitive impairment groups (mean ± *SD*)

	Control ($n = 52$)	MCI ($n = 114$)	Test statistic	*p*-value	Effect size, η^2
RMET, *z* score	.2 ± 1.3	−.4 ± 1.4	4.8	.03	.03
BFRT, long form score[a]	49.0 ± 3.0	48.0 ± 4.3	−1.0	.31	.02
RAVLT 1-5, *z* score[a]	.3 ± .7	−.5 ± 1.2	−4.1	<.001	.11
RAVLT %, *z* score[a]	.2 ± .7	−.6 ± 1.4	−3.3	.001	.07
Digit Span, Age Scaled Score (ASS)[b]	11.8 ± 2.7	10.4 ± 2.9	−3.0	.003	.06
DKEFS CWIT Condition 3, ASS[c]	11.5 ± 2.1	9.9 ± 3.1	−2.8	.01	.06
COWAT-FAS, *z* score[b]	.4 ± 1.0	−.2 ± .9	−3.4	.001	.07
COWAT-Animals, *z* score[b]	.6 ± .9	−.1 ± 1.3	−3.9	<.001	.09
Boston Naming Test, ASS[d]	12.0 ± 3.0	10.0 ± 4.3	−3.0	.003	.06
TMT-A, *z* score[b]	.4 ± .7	.0 ± 1.2	−2.3	.02	.03
TMT-B, *z* score[e]	.4 ± .7	−.4 ± 1.8	−3.7	<.001	.08

MCI = mild cognitive impairment; RMET = Reading the Mind in the Eyes Test; BFRT = Benton Facial Recognition Test; RAVLT 1-5 = Rey Auditory Verbal Learning Test-total learning over 5 trials; RAVLT % = Rey Auditory Verbal Learning Test-percent retention scores (i.e., (Trial 7/Trial 5) * 100); DKEFS CWIT = Delis–Kaplan Executive Function System Color-Word Interference Test, Condition 3 (inhibition/switching); COWAT-FAS = Controlled Oral Word Association Test with letters 'F', 'A', and 'S'; COWAT-Animals = Controlled Oral Word Association Test with animal names; TMT-A = Trail Making Test Part A; TMT-B = Trail Making Test Part B.
[a] Control ($n = 44$).
[b] Control ($n = 51$).
[c] Control ($n = 46$) and MCI ($n = 87$).
[d] Control ($n = 50$) and MCI ($n = 110$).
[e] MCI ($n = 113$).

Table 2 outlines the neuropsychological characteristics of the sample. Compared to the control group, the MCI group revealed significantly poorer performance on all neuropsychological tests, with the greatest differences observed in the domains of verbal learning (RAVLT 1-5) and higher-level cognitive flexibility (TMT-B). As expected, the control and MCI groups did not differ on basic facial processing as measured by the Benton Facial Recognition Test (Benton et al., 1994). Further *post hoc* analyses revealed that the aMCI subgroup performed significantly more poorly than the control group on all neuropsychological tests ($p < .05$ for all), while the naMCI subgroup was significantly (i.e., $p < .05$) worse than controls only on tasks measuring cognitive flexibility (TMT-B), working memory (Digit Span), verbal fluency (COWAT-FAS), and semantic fluency (COWAT-Animals). In comparison with each other, the two subgroups differed only in performance on the learning and memory tasks as well as semantic fluency, with aMCI demonstrating poorer performance than naMCI (RAVLT 1-5 and RAVLT%, $p < .001$; COWAT-Animals, $p = .01$)

In addition, as outlined in Table 3, *post hoc* analyses revealed that the aMCI subgroup that underwent MRI scanning ($n = 18$) performed significantly more poorly than the control group ($n = 25$) on the learning and memory task (RAVLT 1-5 and RAVLT%, $p < .05$) and tasks of concurrent cognitive flexibility (DKEFS CWIT Condition 3 and TMT-B, $p < .05$). Similarly, the naMCI subgroup ($n = 41$) performed significantly more poorly than the control group on working memory (Digit Span, $p < .05$), one aspect of the learning and memory task (RAVLT 1-5, $p < .05$), and one task of concurrent cognitive flexibility (TMT-B, $p < .05$).

Social Cognitive Function: RMET

Table 2 shows RMET performance for the control and MCI groups. As a whole, participants with MCI demonstrated significantly poorer performance on the RMET compared to the control group, with the effect size approaching moderate in magnitude ($d = .44$). However, as shown in Table 4, when performance on this task is further compared among healthy controls and the MCI subgroups, it appears that this difference is driven by those with aMCI ($p = .03$) rather than naMCI, even when covarying for age ($p = .01$). There were no significant differences between aMCI and naMCI subgroups on the RMET.

Association Between RMET, Clinical Variables, and Regional Brain Volumes

Within the control group ($n = 25$), superior RMET performance was moderately associated with larger total hippocampal volume (Table 5), a finding which remained significant even after controlling for age ($\rho = .52$, $p = .01$). When controlling for both age and predicted IQ, this finding remained significant ($\rho = .49$, $p = .02$). Moreover, after controlling for age, semantic fluency, predicted IQ, and naming to confrontation, the results did not change ($\rho = .49$, $p = .02$). For the MCI group ($n = 59$) generally, and for the MCI subgroups (aMCI $n = 18$, naMCI $n = 41$), there were no significant correlations between RMET and hippocampal or amygdalar volume.

To determine whether the relationship between RMET and hippocampal volume could be influenced by other variables, we then examined correlations between RMET performance with demographic, neuropsychological, and neuroimaging measures (Table 6). Within the MCI group, poorer RMET performance correlated with greater age ($\rho = .29$, $p = .002$), lower levels of education ($\rho = .23$, $p = .01$), and lower predicted IQ ($\rho = .20$, $p = .04$). Furthermore, within the MCI group, greater performance on higher-level skill tasks such as Digit Span ($\rho = .21$,

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Table 3. RMET, CBI-R, neuropsychological, demographic, and clinical variables for control and mild cognitive impairment subgroup participants who underwent MRI scanning (mean ± *SD*)

	Control ($n = 25$)	aMCI ($n = 18$)	naMCI ($n = 41$)	Test statistic	*df*	*p*-value	Overall effect size, η^2
Theory of mind							
RMET, *z* score	.0 ± 1.3	−.8 ± 1.6	−.3 ± 1.4	1.8	2	.17	.04
Behavioural changes							
CBI-R, memory and orientation[a]	3.7 ± 4.2*,**	9.3 ± 6.0	7.8 ± 6.5	10.5	2	.01	.13
CBI-R, everyday skills[a]	.3 ± .6	1.1 ± 1.7	1.3 ± 2.1	5.1	2	.08	.05
CBI-R, motivation[a]	1.7 ± 1.8*	6.4 ± 5.9	3.6 ± 3.9	8.6	2	.01	.10
Neuropsychological							
BFRT, long form score	49.3 ± 3.5	49.2 ± 3.8	48.8 ± 4.2	.1	2	.93	.00
RAVLT 1-5, *z* score[b]	.4 ± .7*,**	−1.2 ± .8***	−.3 ± 1.0	26.5	2	<.001	.31
RAVLT %, *z* score[b]	.4 ± .6*	−2.1 ± 1.5	.0 ± 1.0	9.5	2	.01	.10
Digit Span, ASS[c]	12.0 ± 2.8**	10.4 ± 3.3	9.9 ± 2.4	8.0	2	.02	.09
DKEFS CWIT Condition 3, ASS[d]	11.3 ± 2.0*	9.1 ± 2.5	9.8 ± 3.2	6.6	2	.04	.06
COWAT-FAS, *z* score[c]	.4 ± 1.1	−.2 ± 1.0	−.2 ± .9	3.8	2	.15	.02
COWAT-Animals, *z* score[c]	.4 ± .6	−.4 ± 1.2	.2 ± 1.2	2.7	2	.07	.06
Boston Naming Test, ASS[e]	12.3 ± 2.9	8.2 ± 3.9	10.1 ± 4.1	6.4	2	.003	.14
TMT-A, *z* score[c]	.3 ± .8	.1 ± .9	.0 ± 1.3	.3	2	.85	.02
TMT-B, *z* score[f]	.5 ± .7*,**	−.2 ± .8	−.6 ± 1.6	13.4	2	<.001	.14
Demographic							
Age	63.4 ± 7.1	64.7 ± 6.7	62.4 ± 6.2	2.0	2	.38	.00
Gender (males/females), females	(7/18), 72%	(10/8), 44%	(18/23), 56%	3.4	2	.18	.02
Education	13.8 ± 3.1	13.1 ± 3.5	13.5 ± 3.4	.3	2	.88	.02
Predicted IQ[g]	105.4 ± 6.9	101.7 ± 11.7	103.5 ± 10.8	.9	2	.65	.01
Clinical							
MMSE	29.0 ± 1.0	27.7 ± 1.9	28.8 ± 1.4	6.2	2	.05	.05
Alcohol, drinks per week	4.4 ± 4.6	8.3 ± 11.0	3.6 ± 5.5	3.4	2	.19	.02
HADS, anxiety[h]	5.8 ± 3.7	6.8 ± 5.5	6.6 ± 4.7	.3	2	.85	.02
HADS, depression[h]	4.8 ± 4.2	5.9 ± 3.8	6.0 ± 4.3	1.6	2	.44	.01

MCI = mild cognitive impairment; aMCI = amnestic mild cognitive impairment; naMCI = non-amnestic mild cognitive impairment; RMET = Reading the Mind in the Eyes Test; CBI-R = Cambridge Behavioural Inventory – Revised; BFRT = Benton Facial Recognition Test; RAVLT 1-5 = Rey Auditory Verbal Learning Test-total learning over 5 trials; RAVLT % = Rey Auditory Verbal Learning Test-percent retention scores (i.e., (Trial 7/Trial 5) * 100); DKEFS CWIT = Delis–Kaplan Executive Function System Color-Word Interference Test, Condition 3 (inhibition/switching); COWAT-FAS = Controlled Oral Word Association Test with letters 'F', 'A', and 'S'; COWAT-Animals = Controlled Oral Word Association Test with animal names; TMT-A = Trail Making Test Part A; TMT-B = Trail Making Test Part B; IQ = intelligence quotient; MMSE = Mini-Mental State Examination; HADS = Hospital Anxiety and Depression Scale.

* Significant difference compared with the aMCI subgroup.

** Significant difference compared with the naMCI subgroup.

*** Significant difference when the aMCI subgroup is compared to the naMCI subgroup.

[a] Control ($n = 20$); aMCI ($n = 14$); naMCI ($n = 34$).

[b] Control ($n = 22$).

[c] Control ($n = 24$).

[d] Control ($n = 24$); aMCI ($n = 17$); naMCI ($n = 37$).

[e] Control ($n = 24$), aMCI ($n = 17$) and naMCI ($n = 38$).

[f] Control ($n = 24$) and naMCI ($n = 40$).

[g] aMCI ($n = 17$); naMCI ($n = 39$).

[h] aMCI ($n = 16$); naMCI ($n = 32$).

$p = .02$) and TMT-B ($\rho = .33$, $p = .0004$), correlated with greater RMET performance.

Upon further MCI subgroup analyses, greater RMET performance correlated with only greater TMT-B performance for both the aMCI ($\rho = .34$, $p = .04$) and the naMCI ($\rho = .3$, $p = .01$) subgroups. Further, MCI subgroup analysis showed that for the naMCI subgroup, poorer RMET performance correlated with lower levels of education ($\rho = .24$, $p = .03$) and younger age in the aMCI subgroup ($\rho = -.40$, $p = .02$). No other correlations were observed between the MCI subgroups' performance on the RMET, neuropsychological measures, clinical variables, and regional brain volumes.

Association Between RMET and Behavioural Changes as Measured by a Close Informant

Finally, we examined the degree to which RMET performance was related to clinical outcomes. Table 6 displays correlations between RMET performance and CBI-R subscales. Within

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Table 4. RMET, CBI-R, and neuroimaging variables for control and mild cognitive impairment subgroups (mean ± *SD*)

	Control ($n = 52$)	aMCI ($n = 37$)	naMCI ($n = 77$)	Test statistic	*df*	*p*-value	Overall effect size, η^2
RMET, *z* score	.2 ± 1.3*	−.6 ± 1.6	−.2 ± 1.3	3.3	2	.04	.04
CBI-R, memory and orientation[a]	3.8 ± 3.9*,**	9.1 ± 6.4	7.0 ± 6.0	15.3	2	<.001	.10
CBI-R, everyday skills[a]	.3 ± .6	1.0 ± 1.6	1.1 ± 2.0	4.6	2	.10	.02
CBI-R, motivation[b]	1.3 ± 1.7*	4.1 ± 4.9	3.5 ± 4.2	9.2	2	.01	.06
Hippocampus volume, mm^{3}[c]	7032.5 ± 495.0*	5934.3 ± 1332.1***	6998.2 ± 752.8	11.2	2	<.001	.11
Amygdala volume, mm^{3}[c]	2605.8 ± 302.9	2506.6 ± 521.2	2650.5 ± 336.8	.9	2	.64	.01

MCI = mild cognitive impairment; aMCI = amnestic mild cognitive impairment; naMCI = non-amnestic mild cognitive impairment; RMET = Reading the Mind in the Eyes Test; CBI-R = Cambridge Behavioural Inventory – Revised.
* Significant difference compared with the aMCI subgroup.
** Significant difference compared with the naMCI subgroup.
*** Significant difference when the aMCI subgroup is compared to the naMCI subgroup.
[a] Control ($n = 39$); aMCI ($n = 29$); naMCI ($n = 63$).
[b] Control ($n = 38$); aMCI ($n = 29$); naMCI ($n = 63$).
[c] Control ($n = 25$); aMCI ($n = 18$); naMCI ($n = 41$).

Table 5. Correlations between RMET performance, neuroimaging variables, and neuropsychological data for control and MCI groups

	Reading the Mind in the Eyes Test			
	Control		MCI	
	n	Spearman's correlation	*n*	Spearman's correlation
Total amygdala volume	25	−.24	59	−.07
Total hippocampus volume	25	.53*	59	.21

MCI = mild cognitive impairment.
*$p < .01$.

the MCI group, poorer RMET performance correlated with increased carer-reported difficulties in both the CBI-R memory and everyday skills subscales. When controlling for age within the MCI group, the correlation remained significant between both poorer RMET performance and increased difficulties on the CBI-R everyday skills ($\rho = -.25$, $p = .02$) and the memory and orientation subscale ($\rho = -.23$, $p = .03$).

DISCUSSION

This is the largest known study to examine ToM in individuals with MCI using the RMET, and to the authors' knowledge, the first to determine how ToM in MCI relates to volumetric changes in key limbic structures, namely, the amygdala and hippocampus. Broadly, these results align with prior work which has shown that deficits in areas of social cognitive function are evident in MCI involving an array of social cognitive tasks and may be more prominent in the aMCI subtype (McCade et al., 2013a, 2013b). However, the results also make an important novel contribution by showing that while the hippocampus is linked to social cognition in healthy controls, this relationship is absent in those with MCI. Of clinical significance, we further found that for individuals with MCI, poorer ToM abilities are associated with a decline in everyday skills such as difficulties in writing, handling money, or paying bills.

Our finding that ToM difficulties are pronounced in the aMCI subgroup compared to healthy controls is consistent with prior work focused on a different area of social cognition (facial affect recognition) (McCade et al., 2013a), as well as other reports employing the RMET (Poletti & Bonuccelli, 2013) and other false belief and referential communication tasks (Moreau et al., 2015). Together, these studies therefore support the importance of early assessment of social cognitive change in this subgroup that is known to be of greatest risk of progressing to dementia (Gauthier et al., 2006; Petersen, 2004). This is because the same social cognitive deficits seen in individuals with aMCI (e.g., problems recognising facial emotions and engaging in ToM inferences) have also been identified using similar methodological approaches in studies focused on mild AD (Henry et al., 2008; Kohler et al., 2005; Laisney et al., 2012; Spoletini et al., 2008; Weiss et al., 2008).

While some studies have identified intact social cognitive function (specifically emotion recognition) in aMCI subgroups, it is important to note that these studies included both single- and multiple-domain aMCI (Bediou et al., 2009; Henry et al., 2008). Because the single-domain subgroup by definition has more circumscribed impairments in memory alone, this may explain the different pattern of results identified in these studies. In the present study, we focussed on multiple-domain MCI because this subgroup has been shown to convert to dementia more frequently (Serrano, Dillon, Leis, Taragano, and Allegri, 2013). In particular, the multiple-domain aMCI subgroup appears to exhibit greater neuropathological changes, poorer patient outcomes, and greater burden on their respective carers

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Table 6. Correlations between RMET performance and demographic, neuropsychological, and clinical variables for control and MCI groups

	Reading the Mind in the Eyes Test			
	Control		MCI	
	n	Spearman's correlation	*n*	Spearman's correlation
Age	52	−.22	114	−.29*
Education, years	52	.06	114	.23**
Predicted IQ	52	.32**	111	.20**
HADS, depression	52	−.01	100	−.40
HADS, anxiety	52	.20	100	−.40
CBI-R, memory	39	−.10	92	−.23**
CBI-R, everyday skills	39	−.01	92	−.26**
CBI-R, motivation	38	−.10	92	−.17
Digit Span, ASS	51	.18	114	.21**
DKEFS CWIT condition 3, ASS	46	.17	87	.11
TMT-B, *z* score	51	.10	113	.33***

MCI = mild cognitive impairment; HADS = Hospital Anxiety and Depression Scale; CBI-R = Revised Cambridge Behavioural Inventory; DKEFS CWIT = Delis–Kaplan Executive Function System Color-Word Interference Test, Condition 3 (inhibition/switching); TMT-B = Trail Making Test Part B.
* $p < .01$;
** $p < .05$;
*** $p < .001$.

(Alexopoulos, Grimmer, Perneczky, Domes, and Kurz, 2006; Hunderfund et al., 2006; McCade et al., 2013b; Paradise et al., 2015; Petersen and Negash, 2008).

One important finding from this study was the identification of a robust relationship between ToM and hippocampal volume in the healthy control group, even after controlling for age, predicted IQ, semantic fluency, and naming to confrontation. This finding is not only consistent with other work that has shown that the hippocampus plays a critical role in social cognition (Heitz et al., 2016; Perry, Hendler, and Shamay-Tsoory, 2011; Montagrin et al., 2018) but also extends this literature in an interesting way. Specifically, the current work suggests that, beyond the hippocampus' active role in the navigation of social relationships and perception of interpersonal cues, hippocampal integrity, at least in part, may serve a more specific aspect of social cognition: ToM function in older adults who show no clinical signs of cognitive decline (Calder et al., 2003; Isaacowitz et al., 2007; Laurita & Nathan Spreng, 2017). Nevertheless, although a robust relationship between ToM and hippocampal volume in the healthy control group was identified, no relationship was observed with amygdalar volume. This finding, which is contrary to our initial hypotheses given our understanding that the amygdala is associated with the processing of positive and negative emotional valence stimuli, requires further investigation (Allison et al., 2000; Berridge and Kringelbach, 2013; Fan et al., 2011; Singer et al., 2004; Van Overwalle 2009).

The other major finding to emerge was that this relationship between ToM and hippocampal volume was not observed within the MCI group. This may suggest that the social cognitive difficulties seen in individuals with MCI (and perhaps also early dementia) may reflect a breakdown in a more distributed neural network rather than a reduction in the structural integrity of specific limbic structures implicated in social cognition such as the amygdala and hippocampus (Bell-McGinty, Lopez, Meltzer, and et al., 2005; Petersen et al., 2006; Schott, Kennedy, and Fox, 2006). For example, previous studies have demonstrated that individuals with aMCI have diminished functional connectivity within the default mode network (DMN), when compared to individuals with naMCI (Dunn et al., 2014). In fact, in other age groups with healthy adults, fMRI studies have demonstrated that significant overlap exists between the activation of the DMN and social brain networks underpinning social cognitive tasks such as the RMET (Mars et al., 2012; Schilbach, Eickhoff, Rotarska-Jagiela, Fink, and Vogeley, 2008). Additionally, growing evidence now suggests that at least some aspects of ToM also recruit the inferior–posterior sector of the posteromedial cortex, encompassing portions of the posterior cingulate and precuneus (Immordino-Yang and Singh, 2013; Sestieri, Corbetta, Romani, and Shulman, 2011). Consequently, further investigations are warranted to understand the extent of broader neural networks on poorer ToM abilities in individuals with MCI.

The present study has potentially important implications for broader clinical and psychosocial functioning in aMCI. Firstly, early changes in ToM are evident in aMCI and may even be one of the earliest clinical signs (McCade et al., 2013a, 2013b; (McCade et al., 2013a, 2013b; Phillips, Scott, Henry, Mowat, and Bell, 2010). While future research studies should continue to examine social cognition in MCI and preclinical AD to elucidate early changes in this complex cognitive process, neuropsychologists and clinicians should also more routinely assess social cognition in clinical settings early in the disease course (Henry et al., 2016). Importantly, in the present study, we found that poorer ToM abilities even in this very early stage of cognitive decline are associated with informant-observed behavioural changes. Specifically, poorer ToM abilities were associated with poorer everyday skills in social contexts (CBI-R), a result that has previously been reported in individuals with MCI (Tsang et al., 2012), although not linked to ToM deficits. However, our study adds to this knowledge by showing (for the first time) a relationship between poorer ToM abilities as well as greater difficulties with everyday skills such as writing, handling money, or paying bills in those individuals with MCI. In terms of educating carers and family members, it will therefore be important for health professionals to communicate the nature and extent of these social cognitive deficits, alongside adaptive or compensatory strategies to facilitate communication. Since prior studies have shown that broader social cognitive deficits are associated with increased carer burden, programs specifically targeting these symptoms should be developed and evaluated (McCade et al., 2013b).

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In psychiatric disorders, social cognitive training is a robust method of intervention and may even be coupled with cognitive training for targeting a more holistic range of cognitive deficits (Bogdanova, Yee, Ho, and Cicerone, 2016; Cacciotti-Saija et al., 2015).

In addition to behavioural interventions, there is now a considerable literature for disorders that are characterised by a core deficit in social functioning such as autism spectrum disorder and schizophrenia, suggesting that intranasal administration of the neuropeptide-hormone oxytocin (OT) may enhance social cognitive function, including performance on the RMET (Guastella et al., 2010; Guastella & MacLeod, 2012; Guastella et al., 2008; Guastella et al., 2015). Although poorer social cognitive function is not traditionally recognised as a core deficit in MCI (perhaps because it is not routinely assessed), a few studies have examined OT's potential in ageing, with one feasibility study in frontotemporal dementia (FTD) showing tolerance of high doses of intranasal oxytocin (INOT; up to 72 IU) even revealing improvements in apathy, empathy, and overall patient–caregiver interactions (Finger et al., 2015), when compared to FTD participants receiving placebo. Extending on this, a study investigating the role of INOT administration on all four domains of social cognitive function and carer–patient interactions to ultimately reduce caregiver burden in older people with AD is currently underway within our research team (ACTRN12617001531303). If found to be effective, and given the present results, it may be worthwhile for future research to explore the use of INOT at earlier stages of the neurodegenerative pathway, that is, MCI.

There were some limitations to this study. Firstly, the current study was cross-sectional in nature. In order to better understand the importance of the hippocampus and amygdala for social cognition in ageing and MCI, longitudinal investigation would be invaluable. In addition, the MCI sample in the present study were relatively well educated (average of 13.9 years), as were the control group, and this may limit the generalisability of our results to the broader population. In particular, since both education and IQ have been considered to be neuroprotective factors in the decline of mental function and social cognition (Brayne et al., 2010), it is possible that those with lower rates of education may demonstrate even greater social cognitive impairment than those observed in this sample. Further research in those living with MCI could perhaps investigate whether higher rates of education translate to a greater cognitive reserve or 'buffer' against more deleterious effects on a significant other (spouse/family members/friends) in relation to social cognition. Moreover, while functional skills were associated with ToM abilities, the authors note that this study did not include an extensive assessment of executive function. Specifically, key higher-level skills for everyday functioning, such as planning, organisational skills, judgment/reasoning, abstract thinking, and problem-solving, were not assessed here and may therefore be of further interest. In addition, the MRI subsample was not representative of the broader sample as they had poorer performance on tasks of cognitive flexibility compared to healthy controls, a factor that is relevant given that cognitive flexibility was associated with greater ToM ability.

Lastly, it is worth noting that while the RMET is a well-validated measure of ToM (Baron-Cohen et al., 2001; Immordino-Yang & Singh, 2013), it focuses on only one of the four core domains of social cognitive function. Thus, to further understand the extent to which specific social cognitive deficits relate to underlying brain changes in limbic structures such as the hippocampus and amygdala, additional tasks that tap into other domains of social cognition would be important to explore (McDonald et al., 2006). Furthermore, given that other brain structures such as the ventromedial prefrontal cortex are also heavily relied on for ToM, future studies should ideally include this region to further understand how it is implicated for ToM abilities in MCI.

In summary, the present study builds and extends on a growing body of evidence demonstrating that social cognitive deficits, in this case ToM, are evident in individuals with MCI, and are particularly pronounced in the aMCI subtype. The novel neuroimaging results of this study showing that ToM abilities are significantly correlated with hippocampal volume in healthy controls support the role of the hippocampus in social cognition. With the absence of this correlation in the MCI group, a breakdown in a more distributed network rather than a reduction in the structural integrity of isolated limbic structures may be implicated. These findings therefore add to a growing literature that suggests it is clinically important to include measures of social cognitive function in the routine clinical workup of individuals with suspected MCI. In addition, it may prove useful to develop and test targeted treatments directed at communication and relationship quality among patients and families, for this critical component of psychosocial interaction.

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CONFLICTS OF INTEREST

The authors have nothing to disclose.

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