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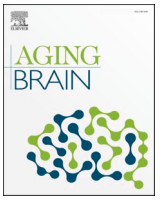

Brain structure variation and individual differences in theory of mind among older adults

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ABSTRACT

The theory of mind (ToM) is not substantially influenced by aging, suggesting the emergence of various compensatory mechanisms. To identify brain regions subserving ToM in older adults, we investigated the associations of individual differences in brain structure with performance on the Reading the Mind in the Eyes Test (RMET), a widely used measure of ToM, using voxel-based morphometry (VBM) and tract-based spatial statistics (TBSS). In contrast to findings obtained from young adults, where multiple cortical regions are implicated in ToM, VBM analysis revealed a significant positive correlation between RMET score and gray matter (GM) volume only in the right middle temporal gyrus, a region implicated in social cognition. Alternatively, TBSS revealed significant positive correlations between RMET score and the fractional anisotropy (FA) values in widespread white matter (WM) tracts, including the bilateral uncinate fasciculus, a region previously linked to RMET performance in young adults. We speculate that individual differences in WM integrity are strong influences on ToM among older adults, whereas the impact of individual differences in GM volumes is relatively limited.

Introduction

The theory of mind (ToM) refers to an individuals' awareness of the minds of others and the ability to deduce others' mental states, a capacity essential for social cognition and interaction [23]. Several neuroimaging studies proposed that the medial prefrontal cortex as well as the precuneus and temporoparietal junction would form the core ToM network [2,26]. Moreover, various age-related changes have been described in the aforementioned brain areas [4,5,13,15,19], e.g., volume reduction [4,15], reduced activation of the medial prefrontal cortex [19], and weaker temporoparietal junction connectivity with the temporal pole [13].

The Reading the Mind in the Eyes Test (RMET) is a widely used measure of ToM [3]. Several studies investigated age-related changes in performance of RMET, but have yielded mixed results, with some reporting deterioration with age [10,11,20,27] and others reporting relatively stable by aging [8]. Interestingly, Castelli and colleagues (2010) found no significant difference in RMET performance score between young and older adults and similar neural activation patterns, with both groups demonstrating task-

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specific activation of the posterior STS and temporal pole. However, older adults also exhibited greater activation in the left inferior frontal gyrus (IFG), suggesting that activity in this region may compensate for any age-related declines in ToM. The scaffolding theory of aging and cognition (STAC) posits that the aging process may impair certain cognitive capacities while others are relatively preserved by compensatory reorganization of brains networks [21]. Thus, according to STAC, brain regions subserving ToM should demonstrate greater dynamic reorganization.

Recent progress in magnetic resonance imaging (MRI) technology has facilitated the identification of brain structures and activity patterns associated with RMET performance [25,32]. For example, Yin et al. [32] found an association between gray matter (GM) density of the left pSTS and RMET performance among young people. Effective social cognition requires the integration of multiple information streams, so white matter (WM) connectivity among distributed brain regions may be critical for this capacity [30]. Consistent with this notion, Coad et al. [6] found a relationship between fractional anisotropy (FA) in the right uncinate fasciculus (UF) and RMET performance among young people. Moreover, Cabinio et al. [4] found that GM volume decreased with age in brain areas related to RMET score including the left IFG, but that RMET score was relatively well preserved, again suggesting a compensatory mechanism maintaining RMET performance in older adults [5]. Michaelian et al. [17] reported that RMET score in healthy old adults was associated with the volume of the hippocampus, a structure that supports various memory processes including social memory [18].

While these studies have identified possible neural correlates of ToM in older adults, each has limitations. First, these studies only identified regions showing reduced volume with age, which are unlikely to compensate for age-related deficits in function. Second, there is still no explanation for RMET score stability with aging. Third, these studies enrolled relatively small participant samples (i.e., 36 in Cabinio *et al.* and 52 in Michaelian *et al.*), reducing statistical power.

To identify GM and WM structures that may contribute to ToM in the elderly, we recruited a larger sample (i.e., 94 older adults) and investigated the individual differences in GM and WM structure associated with RMET score by voxel-based morphometry (VBM) and tract-based spatial statistics (TBSS), respectively. Voxel-based morphometry is a fully automated, whole-brain, unbiased, MRI-based technique capable of detecting regional differences in brain tissue composition, while TBSS is a well-established, fully automated voxel-wise statistical analysis method sensitive to changes or differences in WM integrity (as measured by FA). We expected that individual differences in both GM volume and WM connectivity could reveal neural structures responsible for sparing RMET performance in older adults.

Material and methods

Participants and psychological assessment

This study recruited 94 older participants (46 males, 48 females, mean age 73.9 years, range 65–85 years; mean education duration 13.9 years, range 9–18 years) via advertisement. The optimal sample size was determined by G*Power analysis [9]. Accordingly, a sample size of 84 participants was required to reach a statistical power of 0.8 with a medium effect size ($\rho = 0.3$) for revealing correlations between task (RMET) performance and individual differences in brain structure with a two tailed $\alpha = 0.05$. Assuming an exclusion rate of approximately 10%, we determined that a final sample size of 94 was required. All participants were right-handed without histories of major neurological or psychiatric disorders. All procedures were approved by the Ethics Committee of Kyoto University Unit for Advanced Study of Mind (3-P-17), and the participants provided written informed consent. All participants completed the Japanese version of the Mini-Mental State Examination (MMSE) for screening of general cognitive impairment.

All participants also completed the Japanese print version of the RMET and the accompanying Gender test (downloaded from the Autism Research Center webpage: https://www.autismresearchcentre.com/tests/eyes-test-adult/ [3]). The RMET consists of 36 pictures of the eye region of different human faces. Four possible adjectives are provided for each image and participants are asked to decide which one best describes the emotion displayed on the image. The Gender test consists of the same 36 pictures without adjectives and participants are required only to judge the gender. We used the Gender test to confirm that participants had no deficits in visual face processing. The number of correct answers was recorded as the dependent variable for further analyses.

MRI acquisition

The participants were scanned using a 3.0-Tesla Siemens MAGNETOM Verio MRI scanner with a 32-channel head coil. Structural images were acquired using a T1-weighted magnetization-prepared rapid-acquisition gradient echo (MP-RAGE) pulse sequence with the following parameters: TR = 2250 ms, TE = 3.51 ms, TI = 900 ms, flip angle = 9°, matrix size = 256 × 256, slice thickness = 1 mm, and field of view = 256 mm. Diffusion tensor imaging (DTI) was conducted using a multiband accelerated spin-echo echo planar imaging sequence with the following parameters: TR = 3600 ms, TE = 89 ms, matrix size = 120 × 120, field of view = 204 mm, and MB-factor = 3. Eighty-four contiguous slices were acquired in the axial orientation at 1.7 mm thickness from each participant. Three different b-values were used, b = 0 (17 volumes), b = 700 s/mm^2 (40 directions), and b = 2000 s/mm^2 (80 directions).

Gray matter analysis by VBM

Structural MRI data were analyzed using Statistical Parametric Mapping 12 software (SPM12, Wellcome Trust Centre for Neuroimaging, London, UK) and the Computational Anatomy Toolbox (CAT12) extension, which integrates preprocessing steps, including segmentation, bias correction, and spatial normalization, into a single generative model. The MR images were segmented into GM,

WM, and cerebrospinal fluid (CSF) using SPM12 probability templates. Intensity non-uniformity bias correction was applied to aid in segmentation by correcting for scanner-induced smooth spatial intensity differences. The GM images were normalized to Montreal Neurological Institute (MNI) space using a set of nonlinear functions. A modulation step was also incorporated into the preprocessing pipeline to correct for the expansion and contraction of brain regions caused by spatial normalization. The required modulation was performed by multiplying the warped tissue probability maps by the Jacobian determinant of the warp on a voxel-by-voxel basis. The Jacobian determinant represents the relative volume ratio before and after warping, thus allowing voxel intensities, and sizes in the segmented GM map to reflect pre-warp regional and total GM volumes. As a final preprocessing step, all normalized, segmented, and modulated images were smoothed with an 8-mm full-width half-maximum Gaussian kernel. Additionally, the global volumes of GM, WM, and CSF in each scan were calculated as the total number of voxels multiplied by the voxel size. Total intracranial volume (TIV) was calculated by summing the GM, WM, and CSF for each subject.

The preprocessed GM data were analyzed using SPM12 within the framework of the general linear model. To avoid possible edge effects around the borders between GM and WM and to include only relatively homogeneous voxels, all voxels with a GM value < 0.1 (of a maximum value of 1) were excluded.

White matter analysis by TBSS

The DTI data were analyzed using the FSL package (FMRIB Software Library v6.0; https://fsl.fmrib.ox.ac.uk/fsl/fslwiki). The raw DTI data for each subject were first corrected for head movement and eddy current distortions using an affine registration to the b = 0 (b0) image. The diffusion tensor models were then fitted at each voxel, resulting in maps of three eigenvalues ($\lambda1$, $\lambda2$, $\lambda3$) that allowed calculation of FA maps for each subject.

Tract-based spatial statistics were used to perform a skeleton-based analysis of WM FA [28]. The FA maps of all subjects were aligned into a common space using the nonlinear registration tool FNIRT, which uses a b-spline representation of the registration warp field [24]. A mean FA image was then created and thinned to create a mean FA skeleton representing the center of all tracts common to the group. Each subject's aligned FA data were then projected onto this skeleton and the results analyzed using voxel-wise cross-subject statistics.

Statistical analyses

For the VBM analysis, using SPM12 and the CAT12 extension, we performed a multiple regression analysis by entering the RMET score as a covariate of interest to identify ToM-associated brain regions with increased or reduced GM volume. In addition, sex and TIV were included as covariates to control possible confounding factors for the GM volume. We set the significance threshold at $p < 0.05$ (family-wise error [FWE]-corrected using the threshold-free cluster enhancement [TFCE] method described by Smith and Nichols [29]). The peak voxels within clusters with reliable associations with RMET are described in the MNI coordinates.

For the TBSS analysis, using the FSL package, we performed a multiple regression analysis through the general linear model. Specifically, we entered the RMET score as a covariate of interest to identify RMET score-associated regions with increased or reduced FA. Furthermore, we included sex as a covariate in the model. We reported on clusters with a significance of $p < 0.05$ (FWE-corrected using TFCE method, Smith and Nichols [29]).

Results

Psychological assessments

Mean MMSE score was 28.9 out of 30 (range 22–30), with ten participants (approximately 10%) scoring below the cutoff of 28 points used in previous studies (e.g., Peng et al. [22]) to eliminate participants with potential cognitive impairments. Therefore, we included only the remaining 84 participants in the following analyses (40 males and 44 females, mean age 73.4, age range 65–85; mean education 14.2 years, range 9–18 years; mean MMSE 29.4, MMSE range 28–30). Note that this sample is still sufficient for calculating correlations with two tailed $\alpha = 0.05$, statistical power of 0.8, and moderate effect size ($\rho = 0.3$). Mean RMET score was 20.5 and ranged from 5 to 27 (SD = 3.88).[1] This broad range suggested that it would be possible to calculate correlation coefficients reflecting the associations between task performance and individual differences in WM and (or) GM structure without ceiling or floor effects. In contrast, the mean Gender score was 34.7 out of 36 (range 30–36; SD = 1.51), indicating that no participant was impaired in visual face processing.

Associations between regional gray matter volumes and RMET scores

Voxel-based morphometry revealed a significant positive correlation between RMET score and GM volume in the right the middle temporal gyrus (MTG) across all participants (BA 37; Table 1, Fig. 1). In contrast, there were no other significant negative correlations between RMET score and regional GM volume. The normalized voxel values within a sphere of 4-mm radius surrounding the peak

[1] We observed similar results when the outlier, scoring 5 in the RMET (3SDs below the mean), was excluded from the analyses.

voxel are illustrated as a scatter plot in Fig. 1.

Associations between regional white matter tract integrity and RMET scores

Regression analysis revealed significant positive correlations between RMET score and FA values in widespread WM tracts, including the bilateral anterior thalamic radiation, bilateral corticospinal tract, bilateral cingulum, forceps major, forceps minor, bilateral inferior fronto-occipital fasciculus, bilateral inferior longitudinal fasciculus, bilateral superior longitudinal fasciculus, and bilateral uncinate fasciculus (JHU White-Matter Tractography Atlas, FSL; Fig. 2). Alternatively, we found no significant negative correlations between RMET score and FA values in any WM tract.

Discussion

Using VBM and TBSS, we investigated if individual differences in GM volume and WM tract integrity influence ToM as measured by RMET score in older adults. We found a significant positive correlation between RMET score and GM volume in the right MTG, but in no other region previously implicated in ToM. Alternatively, we found significant positive correlations between RMET score and FA values in widespread WM tracts, including the bilateral uncinate fasciculus (UF). These results suggest that structural differences in multiple WM tracts may underlie the inter-individual variation in ToM among older adults, and further that some of these changes may be adaptive for sustaining ToM during aging.

In contrast to Cabinio et al. [4], we found significant correlations between RMET performance and FA in widespread WM tracts among the elderly, although these studies cannot be directly compared as Cabinio et al. [4] focused only on brain areas showing substantial age-related changes in structure. Alternatively, our findings support the conclusions of Wang et al. [30] that WM integrity is essential for social cognition. In our study, RMET score correlated significantly with the FA values of areas implicated in social cognition as well as tracts involved in motor function (the corticospinal tract, CST). It was recently reported that children with autism spectrum disorder (ASD) exhibited reduced FA in the CST compared to typically developing children [33]. We suggest that this association between CST and ToM may reemerge with aging. Although our study cannot provide any further details on this issue, it is clear that individual differences in WM integrity, including in motor pathways, are critical determinants of ToM in the elderly.

While ToM was highly dependent on the integrity of widespread WM tracts, GM volume in only one specific region was significantly associated with ToM. This finding is at odds with those in young adults, where the structures of multiple GM regions implicated in social cognition are associated with RMET performance (e.g., Yin et al. [32]). A possible explanation for this result is reduced functional specificity of brain areas with age, thereby reducing the sensitivity of VBM analysis for the identification of regional contributions. Another possible explanation for the absence of significant correlations is a floor effect due to age-related reductions in regional GM volume. In any case, the impact of individual differences in GM volumes on RMET task performance differs markedly between older and younger adults. Specifically, this dependence appears to shift away from GM variation toward WM variation with age.

The only region where RMET score correlated with GM volume was the right MTG. While MTG is, not included in the core ToM network, obviously important for ToM [2,26], there is ongoing debate as to exactly how MTG volume influences ToM. For example, some studies have reported larger MTG volume in ASD [16,31] whereas others have reported smaller MTG volume in ASD [7,12].

In contrast to the findings reported by Michaelian et al. [17], we did not find a significant association between hippocampal volume and RMET score among this cohort of elderly adults, suggesting that the hippocampus is not recruited for ToM. This inconsistency may be due to group differences in general cognitive capacity as we used a higher MMSE cutoff (28) compared to Michaelian et al. [17] (24 points). Thus, the group examined by Michaelian et al. [17] may have included individuals with mild cognitive impairment. We suggest that impaired individuals may rely on hippocampal function for ToM, while the healthy aged may be able to perform RMET without the assistance of the hippocampus. Future studies are required to distinguish among these potential explanations.

In conclusion, our results indicate that individual differences in the WM integrity significantly influence the ToM among older adults, whereas the impact of individual differences in the GM volume remains relatively limited. By drawing this conclusion, we do not wish to imply that GM and WM fulfill separate roles in the ToM. Instead, we think that the ToM is supported by a specific neural circuit comprising GM and WM, for which both connections and hubs are indispensable [1,14]. In future studies, analyses of the linkages between GM and WM could potentially provide additional insights into how aging affects the ToM neural correlates.

CRediT authorship contribution statement

Yuki Otsuka: Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Ryusuke Nakai:** Data curation, Formal analysis, Investigation, Methodology, Software, Visualization, Writing – original draft. **Miho Shizawa:** Conceptualization, Funding acquisition, Investigation, Project administration,

Table 1
Results of VBM analysis showing a positive correlation between RMET score and gray matter volume ($p < 0.05$, corrected).

Brain area	T-value	Peak cluster MNI coordinates (x, y, z)			Cluster size (voxels)
Right middle temporal gyrus	1465.42	58	−56	0	584
		58	−40	−3	

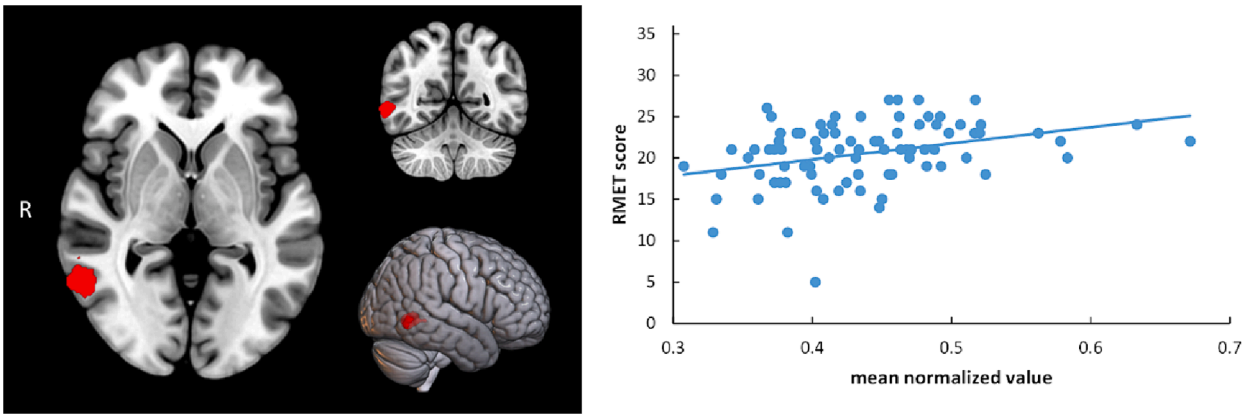

Fig. 1. Right middle temporal gyrus (MTG) volume was positively correlated with theory of mind (ToM) capacity among the elderly. Correlations between gray matter (GM) volume as measured by voxel-based morphometry (VBM) and RMET score were calculated and a $p < 0.05$ (FWE-corrected using the TFCE method) was considered significant. The scatter plot shows the correlation between normalized voxel values of the right MTG (peak at 58, −56, and 0) and RMET score. MTG, middle temporal gyrus; RMET, Reading the Mind in the Eyes Test; TFCE, threshold-free cluster enhancement.

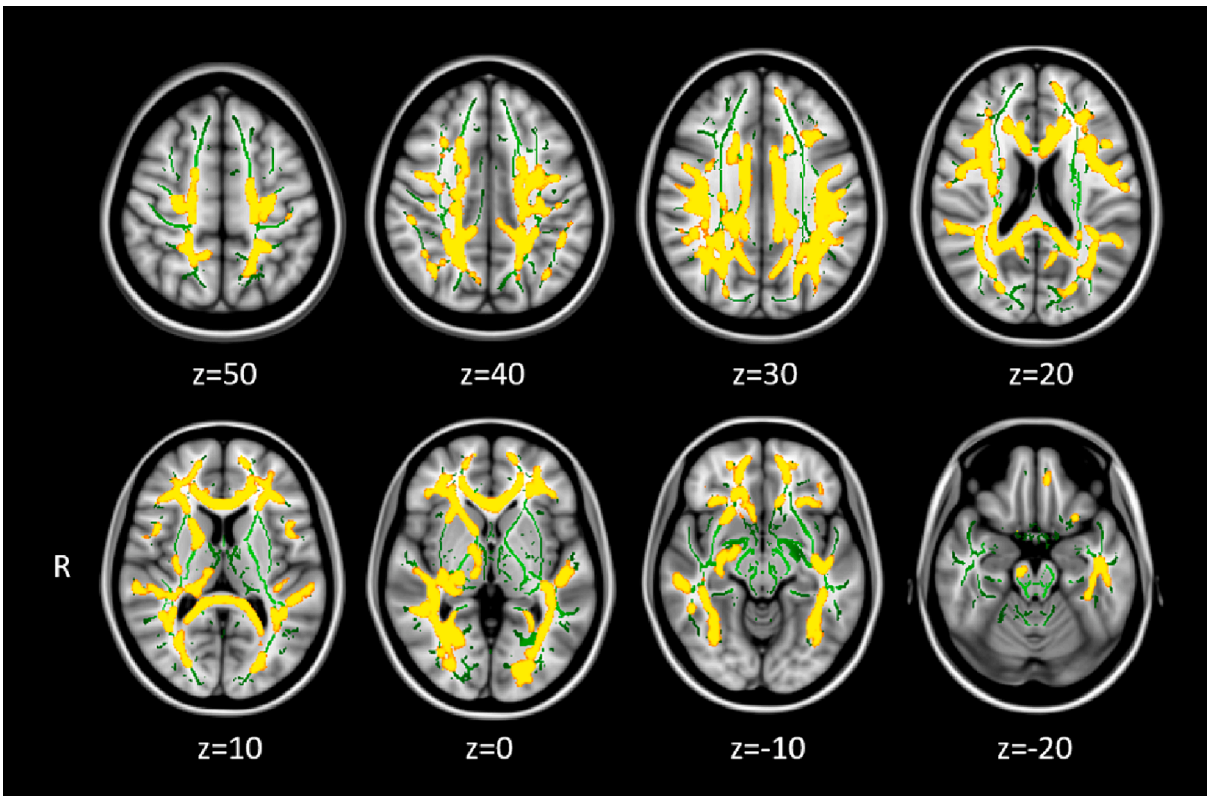

Fig. 2. Theory of mind capacity was positively correlated with widespread white matter (WM) connectivity as measured by tract-based spatial statistics (TBSS) and expressed as fractional anisotropy (FA). FA values in widely dispersed WM tracts were positively correlated with RMET score ($p < 0.05$, FWE-corrected using the TFCE method).

Writing – review & editing. **Shoji Itakura:** Conceptualization, Data curation, Methodology, Project administration, Supervision, Writing – review & editing. **Ayumi Sato:** Conceptualization, Funding acquisition, Methodology, Project administration, Writing – review & editing. **Nobuhito Abe:** Formal analysis, Methodology, Project administration, Software, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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