Higher Peripheral TREM2 mRNA Levels Relate to Cognitive Deficits and Hippocampal Atrophy in Alzheimer’s Disease and Amnestic Mild Cognitive Impairment

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Abstract.

\textbf{Background:} Variants in triggering receptor expressed on myeloid cells 2 (TREM2) are associated with increased Alzheimer’s disease (AD) risk. Recent studies have reported inconsistent peripheral TREM2 mRNA expression levels and relationship with cognitive scores in AD and mild cognitive impairment (MCI). Additionally, no study has examined the association of peripheral TREM2 levels with neuroimaging measures in AD and MCI.

\textbf{Objective:} To determine peripheral TREM2 mRNA levels in AD, amnestic MCI (aMCI) and healthy controls, and the association with cognitive performance and brain structural changes.

\textbf{Methods:} We measured peripheral TREM2 mRNA levels in 80 AD, 30 aMCI, and 86 healthy controls using real time polymerase chain reaction. TREM2 levels were correlated with various cognitive performance and brain volumes, correcting for APOE4 status.

\textbf{Results:} TREM2 mRNA levels were significantly higher in AD compared to controls and aMCI. Levels did not differ between aMCI and controls. Corrected for APOE4, higher TREM2 levels correlated with lower Mini-Mental State Examination,
Montreal Cognitive Assessment (MoCA) and episodic memory scores, and lower total grey matter and right hippocampal volumes. Whole-brain voxel-based morphometry analysis found negative association between TREM2 mRNA levels and grey matter volumes in temporal, parietal and frontal regions. AD subjects with MoCA scores ≤20 had higher TREM2 levels correlating with smaller total grey matter, left hippocampal and right hippocampal volumes.

**Conclusion:** Peripheral TREM2 mRNA levels are higher in AD and are associated with AD-related cognitive deficits and hippocampal atrophy. Our findings suggest that TREM2 may be a potential non-invasive peripheral biomarker for AD diagnosis.

Keywords: Alzheimer’s disease, atrophy, blood-based biomarkers, hippocampus, mild cognitive impairment, TREM2

**INTRODUCTION**

The triggering receptor expressed on myeloid 2 (TREM2) is a transmembrane glycoprotein innate immune phagocytic receptor expressed on brain microglia that regulates key signaling events involved in immune response and phagocytic activity [1, 2]. Rare variants in TREM2 increase susceptibility to AD, with an odds ratio similar to that of the apolipoprotein E4 (APOE4) allele [3, 4]. In pathologically normal human brains, TREM2 is expressed in substantial abundance in the hippocampus and neocortex [3], and in AD, TREM2 appears to be overexpressed in amyloid-associated microglia in the temporal cortices [5], correlating with markers of neurodegeneration including phosphorylated tau [5].

Development of accessible fluid biomarkers remains important for improving diagnostic accuracy in neurodegenerative diseases like AD, and TREM2 has arisen as a prime molecular target given growing evidence of its role in AD pathophysiological processes [3, 6]. Cerebrospinal fluid (CSF) soluble TREM2 (sTREM2) levels were recently reported to be increased in AD compared to controls, with elevated CSF sTREM2 possibly reflecting increased brain microglia activation in response to amyloid deposition [7, 8]. While CSF remains the more ideal fluid biomarker given its direct derivation from the brain, lumbar puncture is invasive. The accessibility of blood-based biomarkers in AD is appealing, but the difficulty lies in how plausible changes in the blood reflect neurodegenerative processes in the brain, as well as the dilution of proteins and other molecules as they traffic from the brain to CSF and to the bloodstream. While it remains unlikely that a blood-based biomarker will replace more reliable CSF biomarkers, the accessibility and possibly higher sensitivity in the context of repeated measurements to track clinical change far outweighs its lower specificity [9].

This has led to preliminary efforts in exploring the potential of TREM2 as a blood-based biomarker for AD diagnosis. Higher TREM2 mRNA expression and corresponding protein levels were reported in AD patients compared to controls; correlating with lower Mini-Mental State Examination (MMSE) scores [10]. Another study found higher TREM2 levels in AD and schizophrenic patients compared to controls [11], with levels showing no correlation with MMSE scores. Reports on TREM2 mRNA levels at the pre-dementia stage remain scarce. To our knowledge, only one other study has looked at TREM2 expression in MCI subjects, finding higher TREM2 mRNA expression in blood-derived monocytes and monocyte-derived macrophages in MCI compared to AD and controls [12]. Furthermore, none of these studies looked at correlation with neuroimaging, and it remains unknown how changes in TREM2 mRNA relate to brain structural changes in AD and MCI.

To fill this gap, we aimed to study changes in TREM2 expression in amnestic MCI (aMCI) and AD patients, and its association with cognition and brain atrophy. We hypothesized that: (1) AD and aMCI would have higher TREM2 mRNA levels compared to age-matched healthy controls, and (2) higher TREM2 levels would correlate with lower cognitive performance and region-specific brain atrophy, especially temporal and hippocampal regions, given pathological evidence of increased TREM2 expression in the hippocampus in parallel with amyloid deposition [3].

**MATERIALS AND METHODS**

**Study subjects**

Participants (N = 196 (80 AD, 30 aMCI, 86 healthy controls), mean age = 67.06 years, SD = 8.14, range = 50–88 years, Table 1) were evaluated and recruited from the National Neuroscience Institute, Singapore and Singapore General Hospital between July 2013 and March 2016. Detailed clinical
evaluation including comprehensive physical examination, medical and cognitive history from the patient and a reliable informant was conducted by neurologists specialized in dementia. Diagnosis of AD was based on the NINCDS-ADRDA [13] and aMCI was diagnosed using Petersen criteria [14]. Controls included community volunteers that were cognitively normal with Clinical Dementia Rating scores included community volunteers that were cognitively normal with Clinical Dementia Rating scores.
of 0 and MMSE above or equal to 26, and not having any other significant neurological, psychiatric or systemic disease. All participants underwent venous blood taking, detailed neuropsychological assessment, and advanced neuroimaging. None of the subjects were suffering from acute infective or inflammatory illnesses at the time of blood sample collection. Finally, out of the whole sample, 38 AD, 23 aMCI and 67 cognitively healthy controls matched for age and gender with available TREM2 mRNA expression levels, APOE genotype, cognitive data and MRI meeting quality control criteria were included in the brain-genetic-cognition statistical analyses. Table 1 summarizes the subject demographics, cognitive scores and brain measures of both samples.

**Neuropsychological assessment**


**MRI acquisition and image processing**

MRI scans were performed at Duke-NUS Medical School, Singapore on a 3T Tim Trio System (Siemens, Erlangen, Germany) or a 3T Prisma Fit System (Siemens, Erlangen, Germany) after scanner upgrade (see supplementary methods for details). We obtained high-resolution T1-weighted MPRAGE (Magnetization-Prepared Rapid Gradient Echo) sequences (192 continuous sagittal slices, TR/TE/TI = 2300/2.28/900 ms, flip angle = 9°, FOV = 256 × 240 mm², matrix = 256 × 240, isotropic voxel size = 1.0 × 1.0 × 1.0 mm³, bandwidth = 240 Hz/pixel) and FLAIR (Fluid Attenuated Inversion Recovery) sequences (192 continuous sagittal slices, TR/TE/TI = 5000/387.0/1800 ms, flip angle = 15°, FOV = 256 × 256 mm², matrix = 256 × 256, isotropic voxel size = 1.0 × 1.0 × 1.0 mm³) on both scanners using the same parameters. Visual check on both T1 and FLAIR images was performed to remove images with artefacts.

The structural T1-weighted images were pre-processed using FreeSurfer (version 5.3, http://surfer.nmr.mgh.harvard.edu) [22–25]. The automated pre-processing involved removal of non-brain tissue, Talairach transformation, segmentation of subcortical structures, intensity normalization, tessellation of the grey and white matter boundaries to generate pial and white matter surfaces, and topology correction. Cortical grey and white matter volumes were found from surface-based calculation from the pial and white matter surfaces. Automated labelling based on a spatial probabilistic atlas was performed to obtain bilateral ventricular and hippocampal volumes [24]. Total intracranial volume (TIV) was estimated from the atlas scaling factor, which was computed from the determinant of the transformation from the native-space brain to the atlas [26].

Moreover, to investigate whether and how TREM2 level was associated with region-specific brain atrophy, we applied an optimized whole-brain voxel-based morphometry (VBM) protocol [27] using the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm8/) in Statistical Parametric Mapping (SPM12) (http://www.fil.ion.ucl.ac.uk/spm/). We derived the subject-level grey matter volume probability maps from T1 structural images following our previous approach [28, 29] (see Supplementary Methods).

White matter hyperintensity (WMH) volume was obtained using an in-house automatic procedure as described previously [30]. Briefly, this procedure included: 1) segmentation of T1-weighted structural images into grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF) using Statistical Parametric Mapping (SPM8; http://www.fil.ion.ucl.ac.uk/spm/); 2) removal of non-brain regions from each subject’s FLAIR images using the T1-derived GM and WM masks; 3) determination of modal pixel intensity from the skull-stripped FLAIR images; 4) threshold-based segmentation of individual FLAIR images using a threshold of 1.3 times the modal pixel intensity; 5) visual inspection of segmented FLAIR images and removal of subjects with segmentation errors; and 6) calculation of total WMH volumes for each individual.
TREM2 mRNA measurement

Total RNA from peripheral whole blood was isolated using PAXgene Blood RNA kit (Pre-AnalytiX GmbH, Switzerland), according to the manufacturer’s protocol. Complementary DNA (cDNA) was reverse transcribed from 1µg of total RNA with iScript cDNA Synthesis kit (Bio-Rad Laboratories, Hercules, CA). Real-time qPCR reactions were performed in triplicate for each sample using SYBR Green Supermix kit (Bio-Rad) in CFX96 Touch Real-Time PCR Detection System (Bio-Rad). Thermal cycling conditions included 3 min at 95°C, then 40 cycles of 10 s at 95°C and 30 s at 65°C. Melt-curve analysis was performed immediately after the amplification step to ensure only a single product had been amplified. Reference gene GAPDH was used to normalize TREM2 mRNA levels and its relative expression was determined by the $2^{-\Delta\Delta CT}$ method [31]. For more details see Methods in the Supplementary Material.

Single nucleotide polymorphism (SNP) genotyping

Genomic DNA was extracted from peripheral blood with QIAamp® DNA Blood Maxi Kit (Qiagen GmbH, Hilden, Germany) according to the standard protocol. Genotyping for APOE isoforms [rs429358 (ABI assay ID: C_3084793_20) and rs7412 (ABI assay ID: C_904973_10)] and TREM2 R47H [rs75932628 (ABI assay ID: C_100657057_10)] was performed using TaqMan SNP genotyping assays on ABI 7900HT PCR system (Applied Biosystems, Foster City, CA). APOE genotype assignments were performed as described previously [32].

Statistical analyses

Continuous variables were compared across the three groups (HC, aMCI and AD) using one-way ANOVA while categorical variables were compared using Chi-square test. All brain structure analysis was controlled for TIV and scanner type.

One-way ANCOVA was conducted to examine differences in TREM2 mRNA expression levels across the three groups. Age, gender, and ethnicity were entered as nuisance variables as they have been reported to confer potential effects on gene expression [33–36]. Significant ANOVA and ANCOVA results were followed by least significant difference (LSD) and Bonferroni’s post hoc tests. Next, we examined whether TREM2 mRNA levels were associated with cognitive deficits or brain atrophy in AD and aMCI. We tested whether TREM2 mRNA levels were associated with cognitive scores (after adjusting for age, gender, ethnicity and APOE4 status) or brain volume (after adjusting for age, gender, ethnicity, TIV, scanner type and APOE4 status) in patients with AD and aMCI using Pearson’s correlation or Spearman’s correlation. Correlation analyses were corrected for APOE4 carrier status because APOE4 is a potent risk factor for sporadic AD [37], with carriers showing greater degree of AD-related atrophy [38, 39] and higher rate of cognitive decline [40–42]. To examine the association between voxel-wise grey matter volume (GMV) and TREM2 mRNA levels in AD and MCI subjects, subject-level GMV probabilistic maps were entered into a general linear model with TREM2 mRNA levels as the covariate of interest and age, gender, ethnicity, scanner type and APOE4 genotype as nuisance covariates. We identified grey matter regions whose volumes were negatively associated with TREM2 levels at $p < 0.001$ with a cluster size threshold of 100 voxels.

To determine the influence of AD severity (based on MoCA scores) on TREM2 mRNA levels, AD patients were further divided into AD group 1 (MoCA scores ≥ 21) and AD group 2 (MoCA scores ≤ 20) based on the median level of MoCA scores in AD group. TREM2 levels of each AD subgroup were then compared to controls. Finally, similar correlation analysis of TREM2 levels with brain volumes was performed in both AD subgroups. Results were reported at the significance level of $p < 0.05$. All analyses were carried out using SPSS 20.0 (SPSS Inc., Chicago, IL, USA).

Ethics

Our study was conducted with informed consent from all individuals and approval was obtained from the Singhealth Institutional Review Board Ethics Committee, Singapore.

RESULTS

Clinical, cognitive, and brain structural characteristics

The demographics and clinical characteristics of our study cohort and a subset of age- and gender-matched subjects with available cognitive data and satisfactory imaging quality are presented in Table 1.
In the complete sample, AD subjects were significantly older and had more APOE4 carriers than aMCI and controls. There were no significant differences in terms of gender and ethnicity across all 3 groups. In the subset cohort, there were no significant differences in age, gender, and ethnicity across the diagnostic groups. There were more APOE4 carriers in the AD group than in the other 2 groups. No subjects carried the TREM2 R47H variant. On tests of global cognition, AD subjects had lower MMSE and MoCA scores than aMCI and controls. AD subjects performed worse than aMCI and controls in all neuropsychological domains, including episodic memory, attention, executive function, language and visuospatial function. Amnestic MCI subjects performed worse than controls across all cognitive domains (Table 1).

On structural brain measures, AD subjects had significantly larger ventricular volumes, with reduced total grey matter, total white matter, and left and right hippocampal volumes than the other groups. There were significant differences in total WMH volume across the three groups but not in the subset of age- and gender-matched cohort (Table 1).

**Group differences in peripheral TREM2 mRNA expression levels**

For the complete cohort, TREM2 mRNA levels differed across the three groups ($F(2,188) = 4.149$, $p = 0.017$; Fig. 1), controlled for age, gender, and ethnicity (mean ± SEM in healthy controls, aMCI, and AD were 0.81 ± 0.04, 0.74 ± 0.06, and 0.92 ± 0.05, respectively.) Post-hoc analysis after Bonferroni correction revealed higher TREM2 mRNA levels in AD than aMCI ($p = 0.012$, adjusted $p = 0.035$) and controls ($p = 0.018$, adjusted $p = 0.054$). There was no difference in levels between aMCI and controls ($p = 0.495$). Subsequent analysis in a subset of age- and gender-matched participants with adequate cognitive data and satisfactory imaging quality revealed similar findings (Supplementary Figure 1 and Supplementary Results). ROC analysis was performed between AD vs healthy controls and AD Group 2 vs healthy controls (see Supplementary results; Supplementary Figure 4).

**Association between TREM2 mRNA expression levels and cognitive deficits**

We found that higher TREM2 mRNA levels correlated with lower MMSE ($r_s = -0.449$, $p = 0.0003$), MoCA ($r_s = -0.431$, $p = 0.001$) and episodic memory ($r_s = -0.395$, $p = 0.003$) scores in AD and aMCI, controlling for age, gender, ethnicity and APOE4 status (Fig. 2, Supplementary Table 1). No significant
correlation was observed between TREM2 mRNA levels and other cognitive domains in AD and aMCI patients.

**Associations between TREM2 mRNA expression levels and brain structure**

There was a significant negative correlation between TREM2 mRNA levels and total grey matter volume \( (r = -0.412, p = 0.001) \) and right hippocampal volume \( (r = -0.264, p = 0.040) \) in AD and aMCI, controlling for age, gender, ethnicity, TIV, scanner type and APOE4 status (Fig. 3, Supplementary Table 1).

Using whole-brain voxel-wise regression, we further found that increased TREM2 levels were associated with reduced GMV in temporal, parietal and frontal brain regions in AD and aMCI subjects, controlling for age, gender, ethnicity, scanner type and APOE4 status (Supplementary Figure 3, Supplementary Table 2).

**TREM2 expression in AD subjects stratified by MOCA scores**

Given that the MoCA as a global cognition test remains a more sensitive tool for detecting cognitive impairment with less ceiling effect compared to the MMSE [43], we stratified AD patients by cognitive performance according to their total MoCA scores into two groups based on the median value: Group 1 (MoCA ≥ 21, \( n = 16 \)) and Group 2 (MoCA ≤ 20, \( n = 22 \)). We found more impaired AD patients (Group 2: MoCA ≤ 20) had higher TREM2 mRNA levels compared to healthy controls \( (p = 0.025) \) but the less impaired AD patients (Group 1: MoCA ≥ 21) did not \( (p = 0.360; \) Supplementary Figure 2), controlling for age, gender and ethnicity. There was no significant difference in TREM2 mRNA levels between Group 1 and Group 2 \( (p = 0.351) \). Similar results were observed in the complete cohort of AD subjects \( (N = 80) \).

The finding of increased TREM2 mRNA levels in more cognitively impaired AD subjects prompted us to further explore the relationship between TREM2 expression, cognition and brain structural measures in these more severe AD patients. We found that higher TREM2 mRNA expression correlated with lower total grey matter \( (r = -0.463, p = 0.030) \), left hippocampal \( (r = -0.479, p = 0.024) \), and right hippocampal \( (r = -0.414, p = 0.055) \) volumes (Fig. 4 and Supplementary Table 1) in Group 2, after controlling for age, gender, ethnicity, TIV, scanner type, and APOE4 status. This is consistent with our primary results.

**DISCUSSION**

In this study, we measured peripheral TREM2 mRNA expression levels in AD, aMCI and control subjects, and found that levels were higher in AD compared to aMCI and controls. Higher TREM2 levels in AD may reflect TREM2 upregulation in the brain as part of compensatory mechanisms by microglia in response to amyloid deposition and increased phagocytic demands from neuritic pathology and apoptotic cells [5, 6]. Given that AD continues to progress regardless, TREM2 overexpression may, in fact, be an insufficient attempt to repair brain tissue [5], and further analyses reveal that our more cognitively impaired AD patients (but not less impaired AD) had higher TREM2 levels than healthy controls.

Fig. 3. Correlation between TREM2 mRNA expression and total grey matter volume, and hippocampal volume in aMCI and AD. Higher TREM2 mRNA levels correlated with smaller total grey matter volume and right hippocampal volume residuals, controlling for age, gender, ethnicity, total intracranial volume, scanner type and APOE4 status. aMCI, amnestic mild cognitive impairment; AD, Alzheimer’s disease; GMV, grey matter volume; HIPP, hippocampus; r, Pearson correlation coefficient.
Recent evidence suggests that TREM2-expressing microglia may play protective roles by appearing in the early stages of amyloid deposition, in attempts to limit diffusion and toxicity of amyloid plaques [44]. Hence, we hypothesized that aMCI would show higher levels compared to controls, but found no differences between the two groups. A recent study by Guedes et al. [12] reported higher TREM2 mRNA levels in MCI compared to AD and controls. Their MCI subjects were generally older than our cohort and displayed relatively similar degree of cognitive impairment as our AD subjects according to MoCA scores.

Exploring TREM2 and cognition, we found that higher TREM2 levels in aMCI and AD correlated with lower MMSE, MoCA and episodic memory z-scores after controlling for age, race, gender and APOE4 status. Earlier studies reporting higher peripheral TREM2 levels in AD had conflicting results using MMSE scores, with Hu and colleagues showing negative correlation [10], and another reporting no correlation with MMSE at all [11]. Compared to the initial study by Hu et al., our study was novel in including not only aMCI, but also subjects with mild AD, as reflected by their higher MMSE scores (mean (SD) 22.1 ± 5.3). Our study adds further novelty by including additional correlation with five individual cognitive domains on detailed neuropsychological testing, as well as additional correlation with structural neuroimaging using whole-brain VBM analysis. Our findings of significant correlation between higher TREM2 levels and lower episodic memory scores, along with reduced GMV in temporal, parietal and frontal regions in aMCI and AD subjects may be reflective of increased TREM2 upregulation as part of AD pathophysiological processes.

As the first study to explore peripheral TREM2 expression with brain measures, we found that higher TREM2 levels in aMCI and AD correlated with lower overall grey matter and right hippocampal volumes. Within the AD group, more cognitively impaired subjects had TREM2 levels correlating with hippocampal and total grey matter loss, reinforcing our primary results. Overall, using cognitive and imaging measures, our findings suggest that peripheral TREM2 mRNA expression levels appear to reflect poorer episodic memory and hippocampal atrophy in AD and aMCI patients. These findings may be explained by consistent evidence in humans and AD mouse models of higher TREM2 expression in the hippocampus occurring in parallel with increased cortical amyloid burden [3, 5, 6]. Recent results have also shown that TREM2 mRNA levels are increased across Braak stages, showing correlation with markers of neurodegeneration [6, 8], consistent with our findings of more impaired AD subjects showing higher TREM2 levels and greater correlation with hippocampal atrophy than less impaired AD patients. Conversely, there was no significant association between TREM2 and WMH burden.

Possible factors driving the increase in TREM2 mRNA expression in AD peripheral blood remains to be answered. The report by Hu and colleagues finding increased TREM2 mRNA levels on monocytes [10] is of interest, given that circulating monocytes are able to infiltrate the brain in AD in response to neuronal dysfunction caused by amyloid deposition [45]. In neurodegenerative conditions like AD [46], resident microglia may become
dysfunctional, with transgenic mice models showing microglia-depleted brain regions being repopulated with new peripherally-derived monocytes expressing high CD45 and CCR2 levels taking up long-term CNS residence to assume properties of dysfunctional microglia [47]. Recent research showing TREM2-positive microglia surrounding amyloid fibrils in a protective effort found that these microglia appear to be brain-derived [44] and not from peripheral myeloid cells as suggested previously [48]. Using parabiosis methods to test the brain for cellular intruders, Wang and colleagues found minimal exchange of monocytes between blood and brain [44]. This contrasts with previous reports where TREM2-positive microglia appeared to express the peripheral myeloid cell marker CD45 and lack the brain microglia P2RY12, suggesting their peripheral origin [45, 48]. Of note, monocyte chemoattractant protein (MCP)-1 is one of the key chemokines regulating migration and infiltration of monocytes/macrophages, and is produced by amyloid-induced activated microglial cells that trigger neuro-inflamatory monocytes in the inflamed brain through CCR2 (C-C chemokine receptor type 2), a receptor for MCP-1. Both CCR2 and TREM2 have been directly implicated in AD pathology, and deficiency in CCR2 in APP/PS1 transgenic mice appears to exacerbate amyloidosis [49, 50]; whereas transplantation of CCR2-competent cells into APP/PS1/CCR2-/- mice restore cognitive functions [51]. Studies have also shown that both CCR2 and TREM2 mRNA levels were increased in AD blood-derived monocytes [10, 12], which were associated with higher uptake of amyloid fibrils. Thus, we suspect that increased expression of TREM2 peripherally could possibly be via the MCP-1/CCR2 axis, where amyloid-induced activated microglia release MCP-1, which then binds to CCR2 receptors on monocytes, promoting their recruitment from the periphery to the brain. Ultimately, whether increased activation and expression of TREM2 in the AD brain correlate with higher peripheral levels, remains to be determined, even if there are doubts to its plausibility.

One limitation of our study is the lack of corresponding TREM2 protein level measurement. This may be less important given that correlation between mRNA expression and corresponding protein levels vary according to various biological and technical factors [52], with merely ~40% explanatory power across many genome-wide correlation studies [53].

We found that TREM2 levels were higher in AD compared to aMCI and controls, and report novel findings of higher levels correlating with worse cognitive performance (particularly episodic memory) and lower hippocampal volumes. These results provide evidence for the potential role of peripheral TREM2 expression as a non-invasive AD biomarker. These results need to be validated in larger, independent cohorts, including more MCI subjects. Additional studies correlating peripheral TREM2 levels with CSF biomarkers, investigating longitudinal variation in TREM2 expression over time, as well as measurement of peripheral TREM2 in other neurodegenerative diseases are required.

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SUPPLEMENTARY MATERIAL

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