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Comparative Analysis of MAPT-RNA Expression Levels Across Temporal and Visual Cortices

Buse Erdoğan

Robert College, Istanbul, Turkey

Abstract

Tau aggregation and dysregulation have been associated with various neurodegenerative disorders, such as Alzheimer's disease and various types of frontotemporal dementia. The heterogeneity of clinical presentation among tauopathies and the lack of reliable biomarkers for early diagnosis hinder the ability to diagnose tauopathies before they have reached stages at which they are mostly untreatable. For most of these disorders, the primary brain region of hyperphosphorylated or mutant tau accumulation has not been identified. Higher expression of MAPT-RNA is more likely to lead to higher deposition and potentially accumulation of mutant tau; therefore, mapping regions with high levels of MAPT-RNA could help identify potential sites of tau accumulation. Although significant heterogeneity in regions of interest (ROI) of MAPT-RNA expression and tau accumulation has been found, identifying potential ROIs that can be generalized to small populations can be valuable in diagnosis and treatment. This study is a small-scale exploratory analysis of the expression locations of the human MAPT gene RNA in postmortem brain samples from two healthy controls, aimed at seeing if the temporal or visual cortex is comparatively more susceptible to tau accumulation.

Keywords: microtubule-associated protein tau (MAPT), tau protein, taupathy, frontotemporal dementia, Alzheimer's disease (AD), MAPT-RNA expression, tau accumulation, neurodegeneration

1. Introduction

1.1. The Human MAPT Gene

The human MAPT gene, which encodes tau protein, is located on chromosome 17q21.31. The mRNA transcripts of the MAPT gene undergo alternative splicing in exons 2, 3, and 10, leading to 6 tau isoforms in the central nervous system (Buchholz & Zempel, 2024). Links have been found between more than 50 MAPT mutations and various neurodegenerative disorders

such as frontotemporal dementia with Parkinsonism-17 (FTDP17), corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), Pick's disease, and Alzheimer's disease (AD) (Strang et al., 2019). Understanding the expression of the MAPT gene is important for understanding the regulation of tau protein levels, which can lead to neurodegenerative disorders if found in excess.

1.2. Tau Proteins

Tau proteins are part of the microtubule-associated protein (MAP) family. In humans, tau proteins are most commonly present in neuronal cells, though smaller amounts are also found in peripheral tissues such as the heart, kidney, and lung (Xu et al., 2025). In the neuron, tau is abundant in the axons, though it is also present in smaller quantities in dendrites. Under physiological conditions, the tau protein's primary functions are stabilizing neuronal microtubules, facilitating axonal transportation, and modulating synaptic plasticity (Buchholz & Zempel, 2024). There are 6 brain-specific isoforms of the tau protein. These isoforms are differentiated by the number of amino-terminal inserts (0N, 1N, or 2N) or carboxyl-terminal repeat domains (3R or 4R) (Buchholz & Zempel, 2024). The loss of function, mislocalization, or toxic gain of function of pathological tau may lead to neurotoxicity and also mediate amyloid-β-induced toxicity (Wang & Mandelkow, 2016). As tau is a natively unfolded protein that doesn't tend to aggregate, mutations or post-translational modifications may lead to tau aggregation and tau-induced neurodegeneration (Gao et al., 2018). Therefore, it is important to identify brain regions in which more tau proteins are synthesized, as those regions have a higher probability of having tau pathology by simple probability.

1.3. Location of Tau Aggregates

Elevated phosphorylated tau levels in the cerebrospinal fluid are a biomarker for neurodegenerative diseases such as Alzheimer's disease. CSF p-tau181, p-tau217, and p-tau231 have been shown to be accurate predictors of cognitive impairment in AD patients (Ashton et al., 2022). It is commonly held that tau-pathology progression follows a distinct pattern, identified postmortem through approximating Braak Stages. However, recent studies have concurred that this homogeneous approach is limited and that individual differences lead to different progression patterns (St-Onge et al., 2023). Therefore, it is more effective to track pathological tau accumulation and spread by using individualized regions of interest (Sohn et al., 2015). In this study, we examine differences in MAPT gene expression in postmortem brain samples from two healthy control subjects to evaluate expression differences between the temporal and visual cortices. Since the analysis only includes healthy controls, the data in this study cannot be used to reach clear conclusions on how MAPT-RNA expression affects tau pathology. Our goal was to establish whether regional differences in MAPT-RNA expression exist at baseline based on the cortex. It has been hypothesized that reducing MAPT mRNA expression and thus tau protein levels can prevent tau aggregation and could be a potential treatment option for tauopathies (Sud et al., 2014). Both Sud and colleagues and Chakravarthy and colleagues have been successful in developing antisense oligonucleotides against MAPT, which have reduced the expression of MAPT mRNA and tau levels. Lower MAPT mRNA production may reduce the production of hyperphosphorylated tau (Chakravarthy et al., 2020). Conversely, it can be theorized that brain regions with higher MAPT-RNA expression can potentially be more susceptible to tau accumulation. These can be promising sites for further research on the diagnosis and treatment of tauopathies.

1.4. Tauopathology and MAPT Expression

Post-translational modifications are the most prominent cause of tau aggregation (Hattiholi et al., 2025). Specifically, mutations that alter phosphorylation sites of tau may lead to hyperphosphorylation. Hyperphosphorylation of tau is three times higher in the disease state compared to physiological conditions (Nisbet et al., 2015). Hyperphosphorylation of tau compromises microtubule stabilization and axonal transport by negatively regulating the binding of tau to microtubules. Hyperphosphorylation significantly reduces tau's affinity for microtubules (Geschwind, 2003). A previous study by Lee and colleagues identified the entorhinal cortex (A28/34, A35/36r) as a region with high tau-PET signaling and the first region to become tau positive, specifically in AD patients (Lee et al., 2022). Their study also identified the inferior temporal gyri as a "propagation hub," a brain region well-positioned to promote widespread tau aggregation (Lee et al., 2022). In light of such findings, our study examined MAPT expression in the temporal and visual cortices of healthy controls. This study aimed to compare subjects to understand if the specific identification of the inferior temporal gyri can be applied more generally to the temporal cortex. MAPT-RNA expression in the temporal cortex was compared to the visual cortex, which has not been suggested as a region with particularly high tau or as a propagation hub.

2. Procedure

2.1. Subjects

Samples were obtained from the Allen Institute's 1,000 Gene Survey in Cortex as part of the Allen Human Brain Atlas. The Allen Institute obtained frozen tissue samples from adult male and female control or schizophrenia subjects from the brain tissue collection of the Section on Neuropathology, Clinical Disorders Branch, GCAP, IRP, National Institute of Mental Health, NIH, Bethesda, MD, and the University of Miami Brain Endowment Bank, University of Miami Miller School of Medicine, Miami, FL. All control subjects had normal neuropathological examination results, no known history of neuropsychiatric disease, and no evidence for substance use. The male and female control subjects from whose samples were tagged for MAPT-RNA were used in this study. Both of the subjects were 41 years old (Technical White Paper: In Situ Hybridization in the Allen Human Brain Atlas, 2013).

2.2. Tissue Samples

Frozen tissue samples, sectioned into coronal slabs of 1-1.5 cm thickness, were harvested by the Allen Institute. The samples from the male subject used in this study were taken from the right hemisphere, and the samples from the female subject were taken from the left hemisphere. For the male subject, 4 slices from the temporal cortex and 4 slices from the visual cortex were analyzed; for the female subject, 3 slices from the temporal cortex and 3 slices from the visual cortex were analyzed. Visual cortex samples included Brodmann's areas 17 and 18, and temporal cortex samples included Brodmann's areas 21 and 22 (Technical White Paper: In Situ Hybridization in the Allen Human Brain Atlas, 2013).

2.3. Image Analysis

ISH expression images obtained from the Allen Institute's Allen Brain Atlas data portal were manually cropped on ImageJ/FIJI (NIH). Copies of the cropped images were separately thresholded for high and moderate expression levels. The cells appearing red in the original images exhibit high MAPT-RNA expression, the cells that appear green exhibit moderate

MAPT-RNA expression, and the cells that appear blue exhibit low MAPT-RNA expression per ISH guidelines. Accepted red-green-blue (RGB) color model hues for high-expression (red) were 1-23, and moderate-expression (green) were 53-123. The hues were selected manually on the hue-saturation-brightness (HSB) scale to represent the colors. Low-expression (blue) cells were discarded as the blue hues were too similar to the background and could result in misleading data. The circularity parameters used to extract the data were set at 0.70-1.00 since neuronal cell bodies are approximately circular-shaped. Percent areas, the total area of cells within the accepted hues divided by the total area of the cropped image, were calculated for each thresholded crop using FIJI.

Differences in percent areas were analyzed across different cortices and sexes for both expression levels. Statistics were run as two-way ANOVA tests on GraphPad Prism 10. The significance level was 0.05.

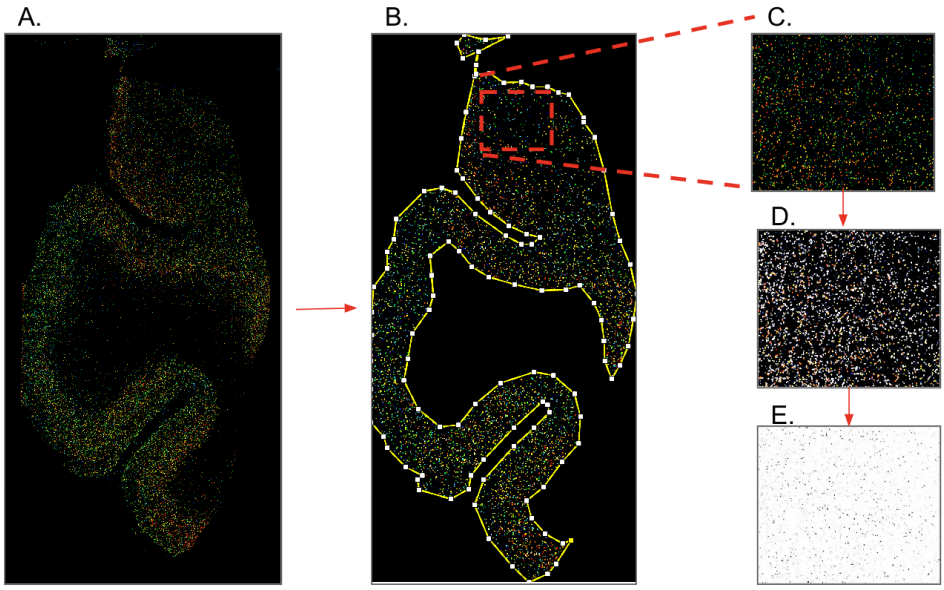

Figure 1: Image Analysis Pipeline

A. Example ISH expression image data obtained from the Allen Institute's Allen Brain Atlas data portal.
B. Manual cropping of the ISH expression image.
C. Example insert to demonstrate marker expression at low, medium, and high levels.
D. The sample was thresholded to only include the cells with the accepted green hues.
E. Masks were obtained from the analysis of accepted cells and used for percent area calculations on FIJI.

2.4. Statistical Analysis

The extracted data were organized in Google Sheets based on subject and brain region to identify differences based on these factors. T-tests and 2-way ANOVAs were then run on GraphPad Prism 10 (San Diego, CA) for all comparisons with an alpha level of 0.05. The 2-way ANOVA test included a region effect, a subject effect, and an interaction effect. The difference between visual and temporal cortex analyses, as well as the difference between the subjects for both brain

regions, was calculated. Tukey's correction was used for multiple comparisons. Importantly, the 2-way ANOVA and Tukey's correction multiple comparison analyses reflect within-subject variability across samples from only one subject. Due to the small sample size of n=1 per group, these data do not support population-level inference. The statistical tests are only descriptive. The resulting graphs from the 2-way ANOVA test were also generated on Prism 10.

3. Results

Figure 2 shows the percent area for high-level expression (red) cells in the samples from the visual and temporal cortices of both the male and female subjects. A 2-way ANOVA revealed a significant difference in high-level MAPT-RNA expression between the subjects ($F_{1, 10}$=16.37, p=0.002, **). However, no significant difference in expression was observed between the visual and temporal cortices within the subjects ($F_{1, 10}$=0.10, p=0.757). Post hoc comparisons demonstrate that the male high-level MAPT expression is higher in the visual cortex compared to the temporal cortex (p=0.002, **).

Figure 3 shows the percent areas for medium-level expression (green) cells in the samples from the visual and temporal cortices of both the male and female subjects. A 2-way ANOVA revealed a significant difference in medium-level MAPT-RNA expression between the subjects ($F_{1, 10}$=18.0, p=0.002, **). However, no significant difference was observed between the visual and temporal cortices within the subjects ($F_{1, 10}$=0.9, p=0.345). Post hoc comparisons demonstrate that the male medium-level MAPT expression is higher in the visual cortex compared to the temporal cortex (p<0.001, ***), and that the medium-level MAPT expression is higher for the female subject compared to the male subject in the temporal cortex (p=0.018, *).

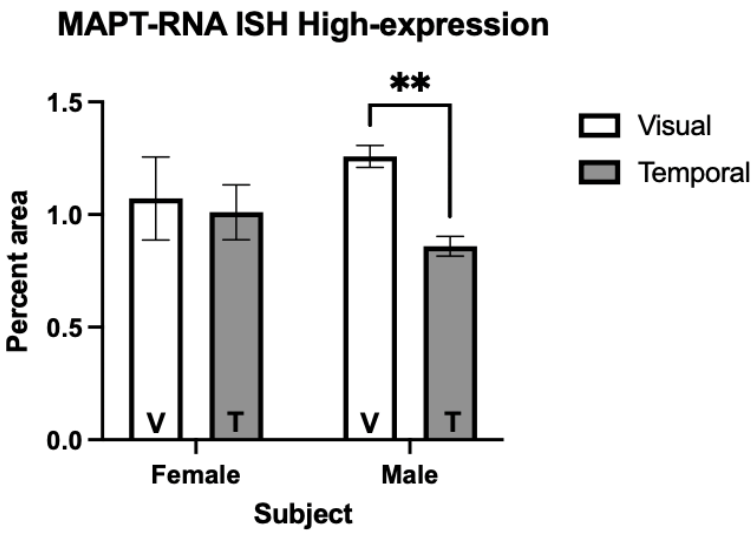

Figure 2: A 2-way ANOVA revealed a main effect of brain region. Post hoc comparisons revealed a significant difference between the visual and temporal cortices in the male subject (p=0.002, **).

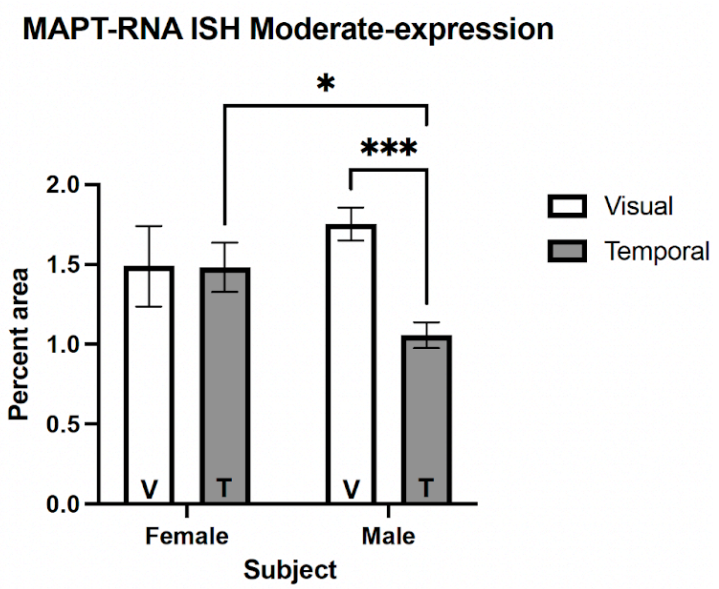

Figure 3: A 2-way ANOVA revealed a main effect of brain region and subject. Post hoc comparisons revealed a significant difference between the visual and temporal cortices in the male subject, and between the male and female subjects in the temporal cortex (p<0.001, ***) (p=0.018, *).

4. Discussion

The analysis of the results shows a significant difference in high MAPT-RNA expression between the visual and temporal cortices of the male subject, and a significant difference in moderate MAPT-RNA expression between the temporal cortices of the male and female subjects and between the visual and temporal cortices of the male subject. This might be due to the low sample size or a broader lack of homogeneity in MAPT-RNA expression among individuals. Previous studies have also highlighted the heterogeneity among individuals regarding regions of tau accumulation (St-Onge et al., 2023). The differences observed within moderate MAPT expression show that the same heterogeneity can also be seen in MAPT gene expression. Although the main demographic factor separating the subjects was their sex, it is not possible to determine if the difference in expression is a sex-related or an individual difference. Similarly, the results are unlikely to be related to the difference in the hemisphere between the subjects, especially because the sample size is not large enough for such a generalization, and there have been no previous reports of the left or right hemisphere being more susceptible to MAPT expression. Thus, more extensive studies are needed to understand the potential inter-region, inter-sex, and inter-individual differences of MAPT expression in humans and its implications for susceptibility to tau dysfunction.

Based on Lee and colleagues' study, we hypothesized that the temporal cortex would exhibit higher expression. However, in our analysis, MAPT-RNA expression was found to be higher in the visual cortex, particularly for the male subject. A primary limiting factor in this study is the low sample size, which may be one of the reasons our findings did not align with the findings from Lee and colleagues' wider-scale study. As previously stated, the sample size is too small to make a

generalization, and results may only reflect individual differences. Moreover, Lee and colleagues' study found the inferior temporal gyrus, Brodmann area 20, to be a tau propagation hub. Our sample included slices from Brodmann areas 21 and 22. This may indicate that the high MAPT expression observed is specific to the inferior temporal gyrus. The results may indicate that the areas chosen for the temporal cortex samples in this study do not exhibit the same heightened MAPT expression found in the inferior temporal gyrus. In that case, it is possible that the expression in the visual cortex was higher due to individual differences, particularly given the low sample size.

Importantly, these results also do not indicate that high MAPT-RNA expression can be linked to susceptibility to tau aggregation, as only healthy controls were included in the study. This study only analyzes differences in MAPT-RNA expression, which is only directly related to tau production, not aggregation. We aimed to identify potential sites with increased tau amount as suggestions for sites susceptible to aggregation. However, to draw a connection between tau amount and aggregation, samples from tauopathy patients would be required.

5. Conclusion

The findings of this study confirm that there are significant differences between different ROIs in individuals and also between individuals concerning MAPT-RNA expression. These differences suggest that it is difficult to determine potential tau accumulation sites that can be generalized to all individuals. However, identifying ROIs that are more susceptible to tau aggregation can be a useful diagnostic tool for smaller populations or at the individual level. More extensive future studies that have higher sample sizes and that examine a wider range of brain regions are required to identify specific trends for populations.

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Author Biography

Buse Erdoğan is a Turkish high school senior at Robert College. She plans to pursue a Bachelor's degree in neuroscience or medical sciences. She is specifically interested in neurophysiology, communication and language disorders, and neurological diseases.

Mentor Contribution Statement

Throughout the writing process, **Dr. Jorge Avila** provided extensive feedback on the organization, language, and scope of

the manuscript. He was especially involved in helping with the “Statistical Analysis” and “Results” sections, and he guided the author on which information to include and how to clearly and honestly express the results of his analysis. He specifically helped interpret and communicate the 2-way ANOVA results. He taught the author how to make figures and advised on organizing graphics to be clearer and on correctly indicating statistical significance and confidence level on graphs. He showed the author which pieces of information to include in figure captions and helped him write them correctly. It was Dr. Avila’s idea to expand on previous research done on the link between MAPT-RNA expression and the tau protein in the “Discussion” sections, which provided context for the analysis. He also helped the author access and include the Allen Institute’s white paper on their protocol in the manuscript, providing detailed information on how the specimens analyzed were obtained.