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Synaptic Proteome Remodeling in the Angular Gyrus Identifies Molecular Signatures of Cognitive Decline and Resilience in Alzheimer's Disease

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ABSTRACT: Synaptic degeneration is a hallmark of early Alzheimer's disease (AD) and is closely linked to cognitive impairment. The angular gyrus, a key cognitive hub, is particularly vulnerable to AD pathology. This study aimed to characterize synaptic proteomic alterations in the angular gyrus across individuals with varying cognitive outcomes and AD pathology. We analyzed synaptic fractions from post-mortem angular gyrus tissue of 100 individuals divided into four diagnostic groups (Normal, Dementia-AD, Resilient, Frail). Synaptic proteins were isolated using Syn-PER, followed by Tandem Mass Tag (TMT)-based LC-MS3 proteomic analysis. A total of 3,924 high-confidence synaptic proteins were quantified, and group-wise comparisons were performed using FDR-corrected statistical analyses. A total of 123 synaptic proteins were differentially expressed across diagnostic groups. Compared to the Normal group, the Dementia-AD group exhibited significant downregulation of key synaptic proteins (e.g., SNAP25, PSD-95) and upregulation of immune-related markers (e.g., TREM2, CD68). Resilient individuals preserved the expression of core synaptic proteins despite high AD pathology, suggesting molecular mechanisms of cognitive protection. Gene Ontology analysis revealed enrichment in pathways related to synaptic signaling, vesicle trafficking, and immune activation. These findings support a model in which cognitive decline results from both synaptic loss and neuroinflammatory processes. This study provides a comprehensive proteomic map of synaptic alterations in the angular gyrus and reveals molecular signatures associated with both cognitive decline and resilience in AD. These insights highlight potential biomarkers and therapeutic targets aimed at preserving synaptic function and delaying cognitive deterioration.

Keywords: Alzheimer's Disease, Synaptic Proteomics, Angular Gyrus, Cognitive Resilience, Tandem Mass Tag, Neurodegeneration, LC-MS3.

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most common cause of dementia worldwide. Among the earliest and most critical pathological events in AD is synaptic degeneration, a process now recognized as preceding significant neuronal loss and cognitive

symptoms. Synapses, as the primary sites of neuronal communication, are essential for maintaining cognitive integrity, and their loss has been closely correlated with cognitive impairment. Mounting evidence underscores that even slight reductions in synaptic density can predict impending cognitive decline. This is particularly relevant in light of findings from quantitative proteomic studies that have elucidated early disruptions in neurotransmission and vesicle cycling, indicating synaptic vulnerability long before classical AD markers such as amyloid plaques and neurofibrillary tangles are prominent (Haytural et al., 2020).

One brain region that exemplifies this synaptic vulnerability is the angular gyrus. Located within the parietal lobe, the angular gyrus integrates sensory information and supports critical cognitive domains, including memory retrieval, attention, and spatial reasoning. Neuroimaging and pathological studies have shown that this region is highly susceptible to AD-related degeneration. Moreover, there is emerging evidence that individuals with preserved angular gyrus integrity, even in the context of widespread AD pathology, may demonstrate relatively maintained cognitive performance. This observation introduces the concept of cognitive resilience, wherein structural or functional preservation within specific brain regions mitigates the clinical expression of neuropathology (King et al., 2022; Krivinko et al., 2018).

Proteomic approaches have significantly contributed to delineating the molecular mechanisms underlying synaptic alterations in AD. Early-stage studies using mass spectrometry-based proteomics revealed consistent downregulation of key presynaptic proteins involved in neurotransmitter release and synaptic structure. These changes are not random but represent selective vulnerability of proteins integral to cognitive function (Hesse et al., 2019). Post-mortem analyses further corroborate these findings, revealing distinct synaptic protein signatures that align more strongly with cognitive decline than with overall neuronal degeneration. Such findings suggest that the molecular architecture of the synapse undergoes targeted disruption in AD, reinforcing the notion that synaptic health may serve as a more precise indicator of disease progression (Miyamoto et al., 2020).

Adding further complexity to the disease landscape are individuals who exhibit divergent cognitive outcomes despite comparable levels of AD pathology. This phenotypic variability raises crucial questions about the mechanisms supporting resilience. Some individuals, classified as cognitively resilient, maintain performance despite severe amyloid and tau deposition. This disparity may be attributable to genetic factors, compensatory synaptic mechanisms, or alternative cognitive strategies, all of which highlight the heterogeneity of AD. Understanding the molecular basis of such resilience requires granular, region-specific studies capable of capturing these nuanced proteomic differences (Carlyle et al., 2020).

Notably, several studies indicate that the correlation between synaptic protein loss and cognitive performance is stronger than the association with amyloid or tau pathology. This suggests that synaptic protein depletion plays a foundational role in disease progression. In fact, markers such as SNAP25, PSD95, and synaptophysin have been found to correlate directly with cognitive scores in AD cohorts. These observations position synaptic proteins not only as mediators of function

but also as viable biomarkers and therapeutic targets (Colom-Cadena et al., 2020; Deng et al., 2016).

Technological advancements have further refined the study of synaptic alterations. Techniques such as tandem mass tag (TMT) labeling and high-resolution LC-MS3 have enabled detailed quantitative profiling of thousands of proteins within isolated synaptic compartments. These tools allow researchers to detect subtle but meaningful changes in synaptic biology across disease stages. Emerging methodologies, including mass synaptometry, offer single-synapse resolution, providing unprecedented insights into heterogeneity within synaptic populations (Gajera et al., 2019). When integrated with large-scale multi-region brain proteomics, such as those conducted by the AMP-AD consortium (Johnson et al., 2020), these approaches help illuminate the proteomic landscape of cognitive decline and resilience.

In this context, the present study applies quantitative proteomics to synaptic fractions of the angular gyrus to investigate molecular changes associated with cognitive outcomes in AD. By comparing four distinct diagnostic groups Normal, Dementia-AD, Resilient, and Frail this study seeks to identify protein alterations that correspond with resilience or susceptibility to cognitive impairment. Our central hypothesis is that synaptic proteomic profiles differ across cognitive phenotypes and that specific proteins mediate these differences, offering insights into mechanisms of vulnerability and protection. Through this focused approach, we aim to elucidate the molecular architecture of synaptic degeneration in AD and highlight key candidates for future biomarker and therapeutic development.

METHOD

Study Design and Sample Selection

This study analyzed synaptic protein profiles from human post-mortem brain tissue using quantitative proteomics. A total of 100 samples were obtained from the ROSMAP brain cohort, divided into four diagnostic groups based on pathological and cognitive assessments: Normal (n=25), Dementia-AD (n=25), Resilient (n=25), and Frail (n=25). These groups reflect distinct combinations of AD pathology burden and cognitive performance.

Brain Region Selection

The angular gyrus (Brodmann area 39) was selected due to its known involvement in higher-order cognitive functions such as attention, memory integration, and spatial reasoning. This region has demonstrated marked vulnerability to AD-related synaptic degeneration.

Synaptic Fractionation Protocol

Synaptic proteins were isolated using the Syn-PER reagent (Thermo Fisher Scientific), which enables differential extraction of synaptic elements from other subcellular components. This method enriches the synaptic proteome while reducing contamination from non-synaptic proteins (Benito et al., 2018). It also improves protein recovery yield and enables the detection of low-abundance synaptic proteins relevant to neurodegenerative pathophysiology (Russell et al., 2016).

Proteomics Workflow

Each sample underwent Tandem Mass Tag (TMT)-based labeling and LC-MS3 analysis. TMT labeling enables simultaneous analysis of multiple samples in a single run, enhancing reproducibility and reducing experimental bias. The use of LC-MS3 provides improved peptide quantification through tri-stage mass spectrometry, which mitigates co-fragmentation effects and enhances quantification accuracy (Paulo & Schweppe, 2021). This combination allows for comprehensive, high-resolution proteomic profiling from complex brain tissue.

Data Processing and Protein Identification

Peptide identification and quantification were performed using a curated synaptic protein inclusion list of 5,667 entries. High-confidence protein identification was defined as proteins detected in at least 50% of samples, with consistent quantification across runs. Ultimately, 3,924 high-confidence synaptic proteins were identified.

Statistical Analysis

To determine differential protein expression among diagnostic groups, the study employed ANOVA followed by post hoc pairwise comparisons. The Benjamini-Hochberg False Discovery Rate (FDR) correction was applied to control for multiple hypothesis testing (Storey et al., 2020). Proteins with FDR-adjusted p-values < 0.05 were considered significantly differentially expressed. Additional statistical robustness was provided through permutation testing. Advanced data visualization and clustering were performed using R and bioinformatics packages such as limma and pheatmap.

Functional Enrichment Analysis

Gene Ontology (GO) enrichment analysis was conducted for differentially expressed proteins using DAVID and g:Profiler. Functional annotations were categorized into biological processes and molecular functions, focusing on synaptic signaling, vesicle trafficking, immune response, and mitochondrial pathways.

This methodological pipeline integrates rigorous sample preparation, advanced proteomic technologies, and robust statistical tools to ensure precise identification of synaptic protein alterations associated with cognitive phenotypes in Alzheimer's disease.

RESULT AND DISCUSSION

Synaptic Proteome Coverage

Synaptic fractionation of angular gyrus tissue yielded 3,924 high-confidence synaptic proteins, reflecting substantial proteome depth and quality. This exceeds typical synaptic proteome coverage (1,000–2,000 proteins) observed in similar human cortical studies (Huang et al., 2019). The elevated protein yield may be attributed to high-quality post-mortem tissues and efficient fractionation. Proteins identified were subjected to quality control and validation based on reproducibility and synaptic relevance (Singh et al., 2020). Clustering analysis revealed distinct groupings by diagnostic classification, indicating that proteomic profiles align with clinical phenotypes.

Differential Expression by Group

A total of 123 proteins were found to be differentially expressed across diagnostic groups (FDR < 0.05). The most pronounced differences were observed in the Dementia-AD vs Normal comparison, with 26 proteins upregulated and 71 downregulated. Consistent with prior findings, key synaptic proteins such as synaptophysin, PSD-95, SNAP25, and STX1B were significantly downregulated (Carlos et al., 2017). These proteins are essential for synaptic plasticity and signal transmission, and their loss likely contributes to the observed cognitive impairment in AD (Ke et al., 2023).

In contrast, several upregulated proteins, including CD68 and other neuroimmune markers, suggest a compensatory or inflammatory response within the synaptic environment (Mecca et al., 2022). This immune activation may contribute to the progression of synaptic dysfunction.

Group-specific Synaptic Signatures

Resilient individuals those with high AD pathology but preserved cognition demonstrated more stable expression of core synaptic proteins. This preservation suggests underlying compensatory mechanisms that maintain synaptic function despite pathological burden (Zhuang et al., 2023).

The Frail group, in contrast, showed distinct proteomic changes unrelated to typical AD pathology, including alterations in proteins linked to metabolic dysfunction and oxidative stress. Neuroimmune signaling and endosomal trafficking pathways emerged as central to these distinctions, emphasizing alternative routes of synaptic impairment beyond classic AD pathology (Bilousova et al., 2017).

Functional Categorization

GO enrichment analysis indicated that downregulated proteins were primarily involved in synaptic vesicle trafficking, membrane fusion, and synaptic signaling (Prinkey et al., 2024). These functions are critical for neurotransmission and their disruption correlates with cognitive deficits in AD.

Upregulated proteins were enriched in neuroimmune-related categories, including complement activation and cytokine signaling. These findings support the hypothesis that inflammation contributes directly to synaptic deterioration. The combined enrichment patterns reinforce a mechanistic model in which disrupted vesicle dynamics and elevated immune signaling underlie synaptic vulnerability in Alzheimer's disease (Coomans et al., 2021).

The findings from this study reinforce the central role of synaptic degeneration in Alzheimer's disease (AD) and its direct association with cognitive decline. Across multiple diagnostic groups, we identified significant alterations in the synaptic proteome of the angular gyrus, a region critically involved in memory integration and attention. These changes underscore the vulnerability of synaptic structures in AD and provide molecular evidence supporting clinical observations of cognitive deterioration.

Synaptic protein loss has long been recognized as one of the earliest and most consistent correlates of cognitive impairment in AD. Proteins such as synaptophysin and PSD-95, both essential for synaptic transmission and plasticity, were significantly downregulated in the Dementia-AD group, aligning with previous reports that link their reduction to memory deficits and decreased synaptic function (Scaduto et al., 2022). Importantly, these changes were observed before the full onset of clinical symptoms in prior studies, suggesting that synaptic proteomic alterations precede and potentially drive cognitive decline (Woody et al., 2016).

Our results also highlight the biological substrates of cognitive resilience. Individuals classified as Resilient those maintaining cognitive function despite high pathological burden exhibited a preserved expression of key synaptic proteins. This finding supports prior evidence that proteins such as neuritin and other neuroplasticity-related factors contribute to cognitive stability in the face of neurodegeneration (Carlyle et al., 2021). Understanding the molecular mechanisms behind this resilience offers a promising avenue for therapeutic development, as enhancing or mimicking these protective pathways may help preserve cognition in at-risk populations.

Therapeutic strategies derived from these insights could involve restoring or stabilizing the expression of specific synaptic proteins or modulating their regulatory pathways. Targets may include synaptic adhesion molecules, glutamate receptor subunits, and neurotrophic factors. Experimental compounds that upregulate these pathways have already shown potential in preclinical models, and their relevance to human AD pathology is now further substantiated by the present findings (Kurbatskaya et al., 2016).

Additionally, our findings echo synaptic patterns seen in other neurodegenerative disorders. For instance, Huntington's disease and ALS also exhibit reductions in synaptic proteins and concurrent cognitive impairments (Dey et al., 2019). These commonalities suggest that synaptic dysfunction

may represent a convergent pathway across multiple conditions, reinforcing the notion that preserving synaptic health could be a universal strategy for neuroprotection (Dando et al., 2024).

Overall, this study not only deepens our understanding of AD pathology at the synaptic level but also emphasizes the translational potential of synaptic proteins as biomarkers and therapeutic targets. The proteomic changes identified in the angular gyrus represent a molecular fingerprint of cognitive decline and resilience, offering a clearer understanding of the processes underlying AD heterogeneity.

CONCLUSION

This study provides compelling evidence that synaptic proteomic alterations in the angular gyrus are tightly linked to cognitive outcomes in Alzheimer's disease (AD). By examining high-confidence synaptic proteins across cognitively normal, demented, resilient, and frail individuals, we have identified distinct molecular signatures that correspond to different trajectories of cognitive aging. In particular, the marked downregulation of core synaptic proteins such as synaptophysin, PSD-95, and SNAP25 in the Dementia-AD group illustrates the central role of synaptic failure in cognitive decline.

Importantly, individuals classified as cognitively resilient maintained the expression of many of these synaptic proteins despite significant AD pathology, suggesting that synaptic integrity underlies their preserved cognitive function. These findings not only confirm prior reports but also extend them by offering a detailed proteomic characterization of resilience at the synaptic level.

The observed upregulation of neuroimmune and inflammatory markers in AD samples further underscores the complex interplay between synaptic degeneration and immune responses in the brain. These molecular alterations suggest that both loss-of-function in synaptic transmission and gain-of-function in neuroinflammatory processes contribute to AD progression.

Overall, this research contributes a robust framework for understanding AD heterogeneity and highlights novel molecular targets for early diagnosis and therapeutic intervention. Future work should focus on validating these synaptic protein markers in cerebrospinal fluid and in vivo imaging studies, with the aim of developing precise biomarkers and resilience-enhancing therapies to combat cognitive decline in Alzheimer's disease.

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