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Commentary
https://doi.org/10.63501/vrg3j806

Mitochondrial–Synaptic Crosstalk: An Integrated Framework for Earlier Detection of Neurodegenerative Disease

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ABSTRACT

Synaptic dysfunction is increasingly recognized as one of the earliest detectable pathophysiological events in many neurodegenerative disorders, often preceding overt neuronal loss. Separately, mitochondrial impairment—deficits in bioenergetics, dynamics, and quality control—is a recurring early feature across Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and Huntington's disease (HD). Accumulating evidence suggests that mitochondrial–synaptic crosstalk is causally relevant to early synaptic failure rather than merely correlative. Exploiting this axis may therefore enable sensitive, disease-agnostic biomarkers for preclinical or prodromal detection. In this Perspective, we synthesize mechanistic links between mitochondria and synapses, review emerging in vivo and fluid biomarkers that capture this interface, and propose an integrated translational roadmap combining synaptic imaging, mitochondrial molecular signatures, and functional assays for earlier and more specific detection of neurodegenerative disease.

KEYWORDS: *Neurodegenrative, Synapse, Mitochondria*

WHY MITOCHONDRIA AND SYNAPSES TOGETHER MATTER FOR EARLY DETECTION:

Neurons are energetically demanding cells, and synapses represent focal hotspots of ATP consumption, Ca^{2+} buffering, and localized reactive oxygen species (ROS) signaling. Mitochondria supply ATP, regulate Ca^{2+} transients, and shape redox environments essential for neurotransmission and synaptic plasticity (1). Disruption of mitochondrial trafficking, mitophagy, or respiratory chain function preferentially impairs synaptic performance long before neuronal cell body degeneration becomes apparent, positioning the mitochondria–synapse interface as a biologically plausible sentinel of early neurodegenerative disease (1)(2).

MECHANISTIC EVIDENCE LINKING MITOCHONDRIAL PERTURBATIONS TO SYNAPTIC FAILURE:

Multiple convergent mechanisms link mitochondrial dysfunction to early synaptic vulnerability:

- Impaired mitochondrial transport reduces ATP availability and disrupts Ca^{2+} handling at presynaptic terminals, impairing vesicle cycling and plasticity (1)(3).
- Defective mitophagy allows the accumulation of dysfunctional mitochondria, increasing local

oxidative stress and lipid peroxidation, which selectively damage synapses (4)(5).
- Disease-specific protein–mitochondria interactions, such as α-synuclein–mitochondrial coupling in PD, directly compromise both mitochondrial integrity and synaptic function (2)(6).

Collectively, these data support a model in which mitochondrial dysfunction is an upstream or parallel driver of synaptic decline rather than a secondary consequence of neuronal loss.

SYNAPTIC DYSFUNCTION AND ITS DETECTABILITY IN VIVO:

Synaptic pathology is now measurable in living humans. PET tracers targeting synaptic vesicle protein 2A (SV2A), such as ^{11}C-UCB-J, demonstrate synaptic density reductions in early AD and in individuals at risk, correlating with cognitive impairment (7)(8). Postmortem validation confirms disease- and region-specific SV2A loss across neurodegenerative disorders, including reductions exceeding 50% in some early disease states (9). Complementary fluid biomarkers, including CSF neurogranin, SNAP-25, and synaptotagmin, track synaptic damage and predict progression in prodromal disease (10)(11). However, synaptic biomarkers alone do not elucidate upstream mitochondrial contributors to synaptic failure.

MITOCHONDRIAL SIGNATURES AS ACCESSIBLE BIOMARKERS

Mitochondrial dysfunction can be interrogated using several emerging biomarker modalities:

- ***Cell-free Mitochondrial DNA (ccf-mtDNA*):** Altered CSF and plasma ccf-mtDNA levels have been associated with neurodegenerative diseases, though findings are inconsistent and highly sensitive to preanalytical and biological confounders (12)(13).
- ***Mitochondrial Proteins in Extracellular Vesicles:*** Neuron-enriched exosomal mitochondrial proteins and RNAs may reflect CNS mitochondrial stress, though marker specificity and methodological heterogeneity limit reproducibility (14)(15).
- ***Peripheral Mitochondrial Functional Assays:*** Such as respirometry of fibroblasts or blood cells, may capture systemic mitochondrial phenotypes that parallel CNS vulnerability in selected disease subtypes (16).

Individually, these biomarkers exhibit variability, but their combined interpretation with synaptic measures may enhance interpretability and predictive value.

IN VIVO MITOCHONDRIAL PET IMAGING: COMPLETING THE MULTIMODAL FRAMEWORK:

Mitochondrial PET imaging provides a critical imaging complement to synaptic PET. The tracer ^{18}F-BCPP-EF enables in vivo quantification of mitochondrial complex I (MC-I) activity:

- Reduced MC-I activity has been demonstrated in the parahippocampal region in early AD, preceding or occurring independently of glucose hypometabolism (17).
- MC-I activity correlates negatively with tau deposition but not amyloid burden, suggesting mitochondrial dysfunction reflects neuronal injury rather than amyloid accumulation (18).
- MC-I density correlates with cognitive performance even in healthy adults, supporting functional relevance (19).

Notably, comparative imaging studies show that mitochondrial PET markers may demonstrate greater longitudinal sensitivity than SV2A PET in early disease stages, reinforcing the rationale for integrated mitochondrial–synaptic imaging strategies (20).

THE VALUE AND LIMITS OF MULTIMODAL INTEGRATION:

Concurrent assessment of synaptic integrity and mitochondrial function may outperform either modality alone:

- SV2A PET or CSF neurogranin localizes synaptic loss (the "where").
- ^{18}F-BCPP-EF PET, ccf-mtDNA, and mitochondrial exosomal markers inform upstream mitochondrial stress (the "why") (7)(12)(17).

Although early cohort studies suggest feasibility, the superiority of combined biomarkers remains hypothesis-generating and requires prospective validation.

BIOLOGICAL AND TECHNICAL CAVEATS:

Important limitations must be acknowledged:

- Mitochondrial dysfunction is heterogeneous across diseases and individuals (14)(21).
- ccf-mtDNA levels are influenced by inflammation, comorbidities, and treatment effects, limiting specificity (12)(13).
- Exosome-based biomarkers exhibit limited CNS specificity and lack standardized isolation protocols (15).
- No cfDNA-based biomarker is currently approved for neurodegenerative disease, underscoring the translational gap.

ROADMAP FOR CLINICAL TRANSLATION:

- Short-term (1–3 years): Pilot multimodal observational studies combining SV2A PET or CSF synaptic markers with mitochondrial PET and fluid mitochondrial biomarkers (7)(12)(17).
- Medium-term (3–7 years): Multicenter validation, harmonization of assays, predictive modeling, and cost-effectiveness analyses (14)(20).
- Long-term (>7 years): Biomarker-guided stratification for trials targeting mitochondrial resilience or synaptic preservation, with biomarker modulation as a surrogate endpoint.

CONCLUSION:

Mitochondrial–synaptic crosstalk constitutes a biologically coherent and measurable axis linking upstream cellular stress to downstream functional decline. Integrating synaptic and mitochondrial biomarkers, particularly through combined PET imaging and fluid assays, offers a promising path toward earlier, mechanism-informed detection and stratification of neurodegenerative disease.

Ethical Approval:

Not applicable (no new human or animal subjects were involved; this narrative is based on published data).

Conflict of Interest:

None

Declaration of AI Use:

This letter was drafted and revised with the assistance of an AI language model (ChatGPT, GPT-5, OpenAI) to refine grammar, reorganize structure, and enhance clarity. All intellectual content, interpretation, and final approval of the text are solely the responsibility of the authors.

Funding:

None

REFERENCES

1. Sheng, Z. H., & Cai, Q. (2012). Mitochondrial transport in neurons: impact on synaptic homeostasis and neurodegeneration. *Nature Reviews. Neuroscience*, *13*(2), 77–93. https://doi.org/10.1038/nrn3156
2. Exner, N., Lutz, A. K., Haass, C., & Winklhofer, K.

F. (2012). Mitochondrial dysfunction in Parkinson's disease: molecular mechanisms and pathophysiological consequences. *The EMBO journal*, *31*(14), 3038–3062. https://doi.org/10.1038/emboj.2012.170

3. Devine, M. J., & Kittler, J. T. (2018). Mitochondria at the neuronal presynapse in health and disease. *Nature Reviews. Neuroscience*, *19*(2), 63–80. https://doi.org/10.1038/nrn.2017.170
4. Pickrell, A. M., & Youle, R. J. (2015). The roles of PINK1, parkin, and mitochondrial fidelity in Parkinson's disease. *Neuron*, *85*(2), 257–273. https://doi.org/10.1016/j.neuron.2014.12.007
5. Martinez-Vicente M. (2017). Neuronal Mitophagy in Neurodegenerative Diseases. *Frontiers in molecular neuroscience*, *10*, 64. https://doi.org/10.3389/fnmol.2017.00064
6. Zhu, Y., Duan, C., Lü, L., Gao, H., Zhao, C., Yu, S., Uéda, K., Chan, P., & Yang, H. (2011). α-Synuclein overexpression impairs mitochondrial function by associating with adenylate translocator. *The international journal of biochemistry & cell biology*, *43*(5), 732–741. https://doi.org/10.1016/j.biocel.2011.01.014
7. Visser, M., O'Brien, J. T., & Mak, E. (2024). In vivo imaging of synaptic density in neurodegenerative disorders with positron emission tomography: A systematic review. *Ageing research reviews*, *94*, 102197. https://doi.org/10.1016/j.arr.2024.102197
8. Chen, M. K., Mecca, A. P., Naganawa, M., Finnema, S. J., Toyonaga, T., Lin, S. F., Najafzadeh, S., Ropchan, J., Lu, Y., McDonald, J. W., Michalak, H. R., Nabulsi, N. B., Arnsten, A. F. T., Huang, Y., Carson, R. E., & van Dyck, C. H. (2018). Assessing Synaptic Density in Alzheimer Disease With Synaptic Vesicle Glycoprotein 2A Positron Emission Tomographic Imaging. *JAMA neurology*, *75*(10), 1215–1224. https://doi.org/10.1001/jamaneurol.2018.1836
9. Shanaki Bavarsad, M., Spina, S., Oehler, A., Allen, I. E., Suemoto, C. K., Leite, R. E. P., Seeley, W. S., Green, A., Jagust, W., Rabinovici, G. D., & Grinberg, L. T. (2024). Comprehensive mapping of synaptic vesicle protein 2A (SV2A) in health and neurodegenerative diseases: a comparative analysis with synaptophysin and ground truth for PET-imaging interpretation. *Acta neuropathologica*, *148*(1), 58. https://doi.org/10.1007/s00401-024-02816-9
10. Thorsell, A., Bjerke, M., Gobom, J., Brunhage, E., Vanmechelen, E., Andreasen, N., Hansson, O., Minthon, L., Zetterberg, H., & Blennow, K. (2010). Neurogranin in cerebrospinal fluid as a marker of synaptic degeneration in Alzheimer's disease. *Brain research*, *1362*, 13–22. https://doi.org/10.1016/j.brainres.2010.09.073
11. Zhang, H., Therriault, J., Kang, M. S., Ng, K. P., Pascoal, T. A., Rosa-Neto, P., Gauthier, S., & Alzheimer's Disease Neuroimaging Initiative (2018). Cerebrospinal fluid synaptosomal-associated protein 25 is a key player in synaptic degeneration in mild cognitive impairment and Alzheimer's disease. *Alzheimer's research & therapy*, *10*(1), 80. https://doi.org/10.1186/s13195-018-0407-6
12. Risi, B., Imarisio, A., Cuconato, G., Padovani, A., Valente, E. M., & Filosto, M. (2025). Mitochondrial DNA (mtDNA) as fluid biomarker in neurodegenerative disorders: A systematic review. *European journal of neurology*, *32*(1), e70014. https://doi.org/10.1111/ene.70014
13. Lowes, H., Kurzawa-Akanbi, M., Pyle, A., & Hudson, G. (2020). Post-mortem ventricular cerebrospinal fluid cell-free mtDNA in neurodegenerative disease. *Scientific reports*, *10*(1), 15253. https://doi.org/10.1038/s41598-020-72190-5
14. Park, C., Weerakkody, J. S., Schneider, R., Miao, S., & Pitt, D. (2024). CNS cell-derived exosome signatures as blood-based biomarkers of neurodegenerative diseases. *Frontiers in neuroscience*, *18*, 1426700. https://doi.org/10.3389/fnins.2024.1426700
15. Théry, C., Witwer, K. W., Aikawa, E., Alcaraz, M. J., Anderson, J. D., Andriantsitohaina, R., Antoniou, A., Arab, T., Archer, F., Atkin-Smith, G. K., Ayre, D. C., Bach, J. M., Bachurski, D., Baharvand, H., Balaj, L., Baldacchino, S., Bauer, N. N., Baxter, A. A., Bebawy, M., Beckham, C., … Zuba-Surma, E. K. (2018). Minimal information for studies of extracellular vesicles 2018 (MISEV2018): a position statement of the International Society for Extracellular Vesicles and update of the MISEV2014 guidelines. *Journal of extracellular vesicles*, *7*(1), 1535750.

https://doi.org/10.1080/20013078.2018.1535750
16. Swerdlow R. H. (2018). Mitochondria and Mitochondrial Cascades in Alzheimer's Disease. *Journal of Alzheimer's disease: JAD*, *62*(3), 1403–1416. https://doi.org/10.3233/JAD-170585
17. Terada, T., Obi, T., Bunai, T., Matsudaira, T., Yoshikawa, E., Ando, I., Futatsubashi, M., Tsukada, H., & Ouchi, Y. (2020). In vivo mitochondrial and glycolytic impairments in patients with Alzheimer disease. *Neurology*, *94*(15), e1592–e1604. https://doi.org/10.1212/WNL.0000000000009249
18. Terada, T., Therriault, J., Kang, M. S. P., Savard, M., Pascoal, T. A., Lussier, F., Tissot, C., Wang, Y. T., Benedet, A., Matsudaira, T., Bunai, T., Obi, T., Tsukada, H., Ouchi, Y., & Rosa-Neto, P. (2021). Mitochondrial complex I abnormalities is associated with tau and clinical symptoms in mild Alzheimer's disease. *Molecular neurodegeneration*, *16*(1), 28. https://doi.org/10.1186/s13024-021-00448-1
19. Wigstrom, T. P., Roytman, S., Bohnen, J. L. B., Paalanen, R. R., Griggs, A. M., Vangel, R., Barr, J., Albin, R., Kanel, P., & Bohnen, N. I. (2024). Impaired mitochondrial function in bipolar disorder and alcohol use disorder: a case study using ^{18}F-BCPP-EF PET imaging of mitochondrial Complex I. *Psychoradiology*, *4*, kkae014. https://doi.org/10.1093/psyrad/kkae014
20. Lu, X., Ji, B., Huang, G., & Ding, H. (2024). Advances in synaptic PET imaging and intervention with synapse-targeted small-molecular drugs for dementia diagnosis and therapy. *Fundamental research*, *5*(1), 63–71. https://doi.org/10.1016/j.fmre.2024.04.013
21. Burnham, S. C., Coloma, P. M., Li, Q. X., Collins, S., Savage, G., Laws, S., Doecke, J., Maruff, P., Martins, R. N., Ames, D., Rowe, C. C., Masters, C. L., & Villemagne, V. L. (2019). Application of the NIA-AA Research Framework: Towards a Biological Definition of Alzheimer's Disease Using Cerebrospinal Fluid Biomarkers in the AIBL Study. *The journal of prevention of Alzheimer's disease*, *6*(4), 248–255. https://doi.org/10.14283/jpad.2019.25