Project Notes:

Project Title:
Name: Karapakula, Parnitha

Note Well: There are NO SHORT-cuts to reading journal articles and taking notes from them. Comprehension is paramount. You will most likely need to read it several times, so set aside enough time in your schedule.

Contents:

Knowledge Gaps:

This list provides a brief overview of the major knowledge gaps for this project, how they were resolved and where to find the information.

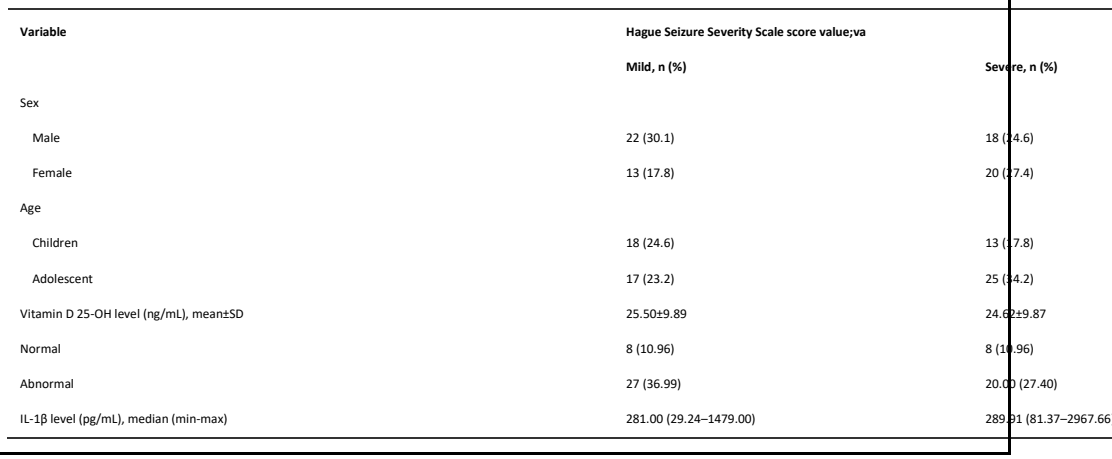
Knowledge Gap	Resolved By	Information is located	Date resolved
Alzheimer's disease and epilepsy issues for diagnosis	Reading article	Article #6	09/13/2025
Genes related to dementia and inflammation	Reading article	Article #7	09/15/2025
How to stain for Amyloid beta	Reading Article	Article #	10/02/2025

Literature Search Parameters:

These searches were performed between 8/20/2025 and XX/XX/2026.
List of keywords and databases used during this project.

Database/search engine	Keywords	Summary of search
WPI Gordon Library	Mitochondria, epigenetics, brain	Found articles that delve into the methylation of mitochondrial DNA
WPI Gordon Library	Epilepsy AND dementia	Articles looked at comorbidity between disorders and the possible reasons for it.
WPI Gordon Library	Amyloid staining	Articles showed ways to stain for amyloid beta and other dementia pathologies

Article #1 Notes: Neuroprotective and inflammatory biomarkers in pediatric drug-resistant epilepsy: Interplay between GDNF, IL-1β and vitamin D 25-OH

Source Title	**Neuroprotective and inflammatory biomarkers in pediatric drug-resistant epilepsy: Interplay between GDNF, IL-1β and vitamin D 25-OH**
Source citation (APA Format)	Saing, J. H., Sari, D. K., Supriatmo, S., Fithrie, A., Rusda, M., Amin, M. M., & Pratama, M. A. (2024). Neuroprotective and inflammatory biomarkers in pediatric drug-resistant epilepsy: Interplay between GDNF, IL-1β and vitamin D 25-OH. *Narra J*, *4*(3), e1581. https://doi.org/10.52225/narra.v4i3.1581
Original URL	https://narraj.org/main/article/view/1581
Source type	Journal Article
Keywords	Drug-resistant epilepsy, biomarker, vitamin D 25-OH, IL-1β, GDNF
#Tags	
Summary of key points + notes (include methodology)	In this study, 73 pediatric patients with drug-resistant epilepsy were analyzed using HASS (Seizure Severity Test) and GASE (Seizure Frequency Test) to see if there were any correlations with the levels of GDNF (Glial-cell Derived Neurotrophic Factor), Vitamin D 25-OH, and IL1-beta (Interleukin 1 Beta). Of these, they only found that GDNF and Seizure severity had a positive correlation. This shows that there is a significant association between seizure severity and GDNF level.
Research Question/Problem/ Need	Is there an association between GDNF, Ilb, vitamin D 25-OH and severity or frequency of epilepsy in children with drug resistant epilepsy?
Important Figures	

Variable	Hague Seizure Severity Scale score value;va	
	Mild, n (%)	Severe, n (%)
Sex		
Male	22 (30.1)	18 (24.6)
Female	13 (17.8)	20 (27.4)
Age		
Children	18 (24.6)	13 (17.8)
Adolescent	17 (23.2)	25 (34.2)
Vitamin D 25-OH level (ng/mL), mean±SD	25.50±9.89	24.62±9.87
Normal	8 (10.96)	8 (10.96)
Abnormal	27 (36.99)	20.00 (27.40)
IL-1β level (pg/mL), median (min-max)	281.00 (29.24–1479.00)	289.91 (81.37–2967.66

	GDNF level (pg/mL), median (min-max) 1370.00 (30.00–8160.00) 3315.00 (40.00–11490. Open in a new t Results and numbers found in the study. Includes variables that changes and the different seizure scale scores
VOCAB: (w/definition)	- Immunosorbent: a substance that has antibodies or antigens specifically attached to it - Interleukin – 1 beta: a cytokine produced by white blood cells to induce fever, promote inflammation, and stimulate immune activity - Heteroscedasticity: Condition where error variance in a regression is not constant across all levels of the independent variables - Epileptogenesis: The process of a non-epileptic brain undergoing changes that eventually lead to epilepsy
Cited references to follow up on	1. Paolone G, Falcicchia C, Lovisari F, et al. Long-Term, Targeted Delivery of GDNF from Encapsulated Cells Is Neuroprotective and Reduces Seizures in the Pilocarpine Model of Epilepsy. J Neurosci 2019;39(11):2144–2156. 2. Tombini M, Assenza G, Quintiliani L, et al. Epilepsy and quality of life: What does really matter? Neurol Sci 2021;42(9):3757–3765.
Follow up Questions	Is GDNF levels only correlated with the severity of epilepsy in children? GDNF is related to survival of dopaminergic neurons, what is the association between dopamine and epilepsy? Is there a connection between dopaminergic neurons and regulation GABAergic signals?

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- 20-30% of pediatric epilepsy cases are DREs
- Neuroinflammation = microglia +astrocyte activation →causes neuronal hyperactivation
- Interleukin 1 beta is proinflammatory
- Glial Cell Derived Neurotrophic Factor is neuroprotective
- Vitamin D deficiency prevalent in epilepsy + anticonvulsant users
- Cross Sectional with 73 patients ages 1-18
- Kolmogorov Smirnov test, Pearson test, multiple linear regression, SPSS software
- GDNF + epilepsy severity association was significant
- No association seen between seizure frequency
- GDNF reduces seizure severity in animal models
- Seizure frequency does not reflect seizure severity

Article #2 Notes: Mitochondrial DNA methylation and mitochondria-related epigenetics in neurodegeneration

Article notes should be on separate sheets

Source Title	Mitochondrial DNA methylation and mitochondria-related epigenetics in neurodegeneration

Source citation (APA Format)	Coppedè, F. (2024). Mitochondrial DNA methylation and mitochondria-related epigenetics in neurodegeneration. *Neural Regeneration Research*, *19*(2), 405–406. https://doi.org/10.4103/1673-5374.379045
Original URL	https://journals.lww.com/nrronline/fulltext/2024/02000/Mitochondrial_DNA_methylation_and.33.aspx
Source type	Journal Article
Keywords	None provided by article
#Tags	
Summary of key points + notes (include methodology)	This article investigates all associations researched previously between neurodegenerative disorders and mitochondrial epigenetic changes. The existence of epigenetics in mtDNA is widely questioned yet researched. Many studies have shown specific location of methylation and have linked them to disorders and nuclear gene dysregulation. The articles identifies this as a potential opportunity to study this as a biomarker of disease.
Research Question/Problem/ Need	What is the evidence to show correlation between mtDNA methylation and neurodegenerative diseases
Important Figures	https://images.journals.lww.com/nrronline/Original.01300535-202402000-00033.F1.jpeg - key findings by disease and model
VOCAB: (w/definition)	D-loop: (displacement loop) A non-coding region in the mtDNA that plays a crucial role in replication and transcription. A triple stranded region, with the 7S DNA (primer for synthesis) displacing portion of the double-stranded mtDNA Redox cofactors: molecules that participate in redox reaction, facilitating the transfer of electrons between molecules in a cell TARDBP Gene: codes for a protein that affects mRNA and is involved in ALS and FTD disorder pathology Cytochrome: group of proteins that play a vital role in energy transfer within cells Transgenic: an organism that contains genetic material introduced atrificially
Cited references to follow up on	1. Devall M, Soanes DM, Smith AR, Dempster EL, Smith RG, Burrage J, Iatrou A, Hannon E, Troakes C, Moore K, O'Neill P, Al-Sarraj S, Schalkwyk L, Mill J, Weedon M, Lunnon K (2022) Genome-wide characterization of mitochondrial DNA methylation in human brain. Front Endocrinol (Lausanne) 13:1059120. 2. Stoccoro A, Mosca L, Carnicelli V, Cavallari U, Lunetta C, Marocchi A, Migliore L, Coppedè F (2018) Mitochondrial DNA copy number and D-loop region methylation in carriers of amyotrophic lateral sclerosis gene mutations. Epigenomics 10:1431–1443.
Follow up Questions	How does mtDNA methylation affect the FTD-ALS spectrum? - FTD and ALS fall on the same spectrum so does the presence of methylation cause a leaning toward one disorder over the other?

	How does mtDNA methylation work when no histones are present? Evolutionarily, how did mtDNA epigenetics aid in the continued prescence of the mitochondrion despite its origin as a smaller bacterium eaten by a bigger bacterium?

- Mitochondria abundant in muscle, liver, brain
- Oxidative mitochondrial DNA damage associated with neurodegeneration
- mtDNA is circular, double stranded, encodes 13 subunits of the mitochondrial respiratory chain and 22 transfer RNAs and 2 ribosomal RNAs
- Mitochondrial epigenetics' existence is debated
- peaks of mtDNA methylation have been observed at several sites, including sites within the regulatory D-loop region, which regulates mtDNA transcription and replication, and within the *MT-ND2*, *MT-ND4*, *MT-ND*5, and *MT-ATP6* genes, which encode subunits of complex I (nicotinamide adenine dinucleotide dehydrogenase) or complex V (adenosine triphosphate synthase), respectively
- Entorhinal cortex shows higher mtDNA methylation of the D-loop
- SOD1 mutations showed impaired D-loop methylation levels
- Air pollution associated with changes in methylation, mutations and copy number (which usually ranges between 2 to 10 in each mitochondrion)
- Epigenetic clocks
- oxidative stress and mitochondrial dysfunction can generate retrograde mitochondrial-to-nuclear signals that, acting through epigenetic mechanisms, can regulate the expression of nuclear genes.
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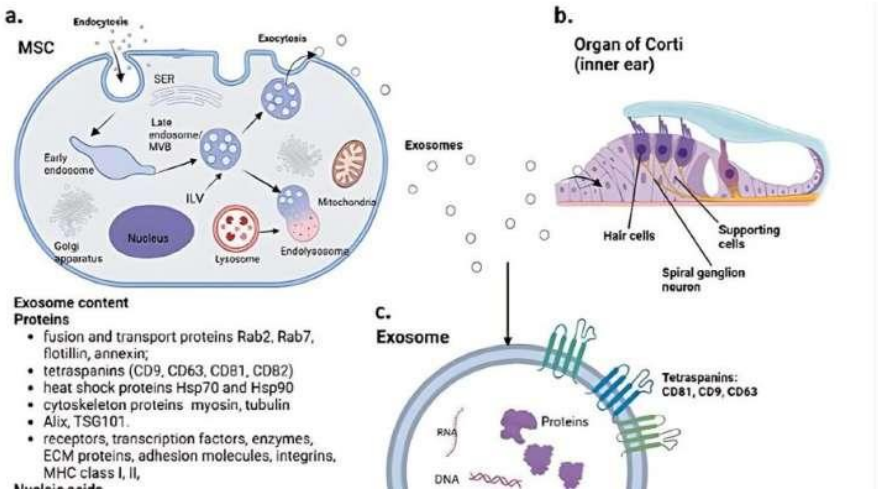
Article #3 Notes: Exosome therapy offers a promising new approach to sensorineural hearing loss

Article notes should be on separate sheets

Source Title	**Exosome therapy offers a promising new approach to sensorineural hearing loss**
Source citation (APA Format)	FBIH, A. of B. M. S. of. (n.d.). *Exosome therapy offers a promising new approach to sensorineural hearing loss*. Retrieved August 24, 2025, from https://phys.org/news/2025-06-exosome-therapy-approach-sensorineural-loss.html
Original URL	https://phys.org/news/2025-06-exosome-therapy-approach-sensorineural-loss.html
Source type	News Article

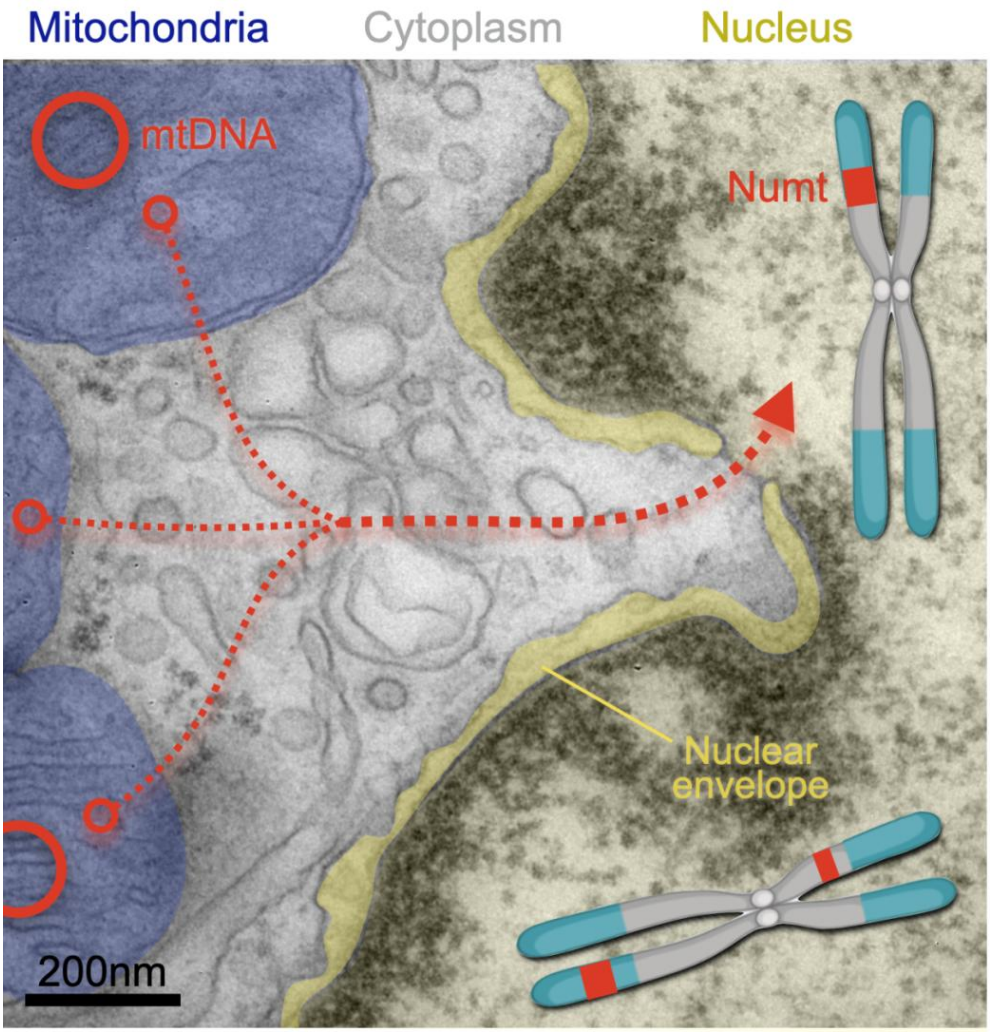
Keywords	None provided by article
#Tags	
Summary of key points + notes (include methodology)	This article discusses a recent study on using mesenchymal stem cell (MSC) derived exosomes to treat sensorineural hearing loss (SNHL). Currently, SNHL's treatments cannot restore the ability hear and MSC transplants have been shown to do so but using live cells often involves unwanted immune responses. To avoid this, exosomes, vesicles made by cells that contain RNA, lipids, and more, can be used to restore function to the inner ear. This treatment has shown promise in animal models and in an early clinical case.
Research Question/Problem/ Need	Can MSC-derived exosomes be used to restore hearing in cases of SNHL?
Important Figures	Diagram of how the exosome treatment works: 
VOCAB: (w/definition)	Aminoglycosides: a class of potent, bactericidal antibiotics used to treat serious bacterial infections. Mesenchymal Stem Cells: multipotent stem cells found in bone marrow and other tissue, capable of differentiating into various types of cells like bone, cartilage, fat, and muscle cells. Exosome: tiny extra cellular vesicles released by cells that act as messengers to transfer proteins, DNA, RNA, and lipids to other cells. Blood-labyrinth barrier: Specialized structure within the inner ear that regulates the passage of substances between the bloodstream and the inner ear fluids. Ototoxins: substances that can be toxic to the ear and potentially cause hearing loss
Cited references to follow up on	Maria Perde-Schrepler et al, Mesenchymal stem cell- derived exosomes as cell-free therapeutics for sensorineural hearing loss, *Biomolecules and Biomedicine* (2025). DOI: 10.17305/bb.2025.11517
Follow up Questions	Would the exosome of a normal (non-MSC) cell still create the same effect?

	What is contained specifically in the exosomes used in this treatment? Can these exosomes restore hearing to original capacity? How can exosomes be delivered without the need for a surgery?

- 6% of the population has SNHL (most common type of permanent hearing loss)
- Caused by prolonged noise exposure, medications, genetic conditions, and autoimmune disorders
- Hair cells lose the ability to regenerate early in embryonic development
- Cochlear implant only improves sound perception. They also impair residual hearing and limit sound clarity in noisy environments
- Pluripotent stem cells raise concerns about ethics, tumors, and immune rejection
- MSCs are derived from adult tissues like bone marrow and umbilical cords
- Exosomes influence gene expression and promote tissue repair
- Exosomes are small enough to cross the Blood Labyrinth Barrier
- Treatment shows promise in animal models and a clinical case
- Uses microRNAs and heat shock proteins
- Need to make exosome isolation, production, etc. more consistent and efficient

Article #4 Notes: Mitochondria are flinging their DNA into our brain cells

Source Title	Mitochondria are flinging their DNA into our brain cells
Source citation (APA Format)	*Mitochondria Are Flinging Their DNA into Our Brain Cells*. (2024, August 30). Columbia University Irving Medical Center. https://www.cuimc.columbia.edu/news/mitochondria-are-flinging-their-dna-our-brain-cells
Original URL	https://www.cuimc.columbia.edu/news/mitochondria-are-flinging-their-dna-our-brain-cells
Source type	News Article
Keywords	None provided by article
#Tags	
Summary of key points + notes (include methodology)	This news source looks at a study where they looked at NUMTs and how mitochondria's flinging of their genes into the nucleus affects the lifespan of people. Nuclear mitochondrial DNA insertion (NUMTs) is usually found in the brain and prefrontal cortex. Previous studies thought this only happened rarely in humans, but we now understand that it can happen several times during a person's life. This study found that the more DNA insertions that were present, the more likely you were to die earlier. The study found that stress accelerates

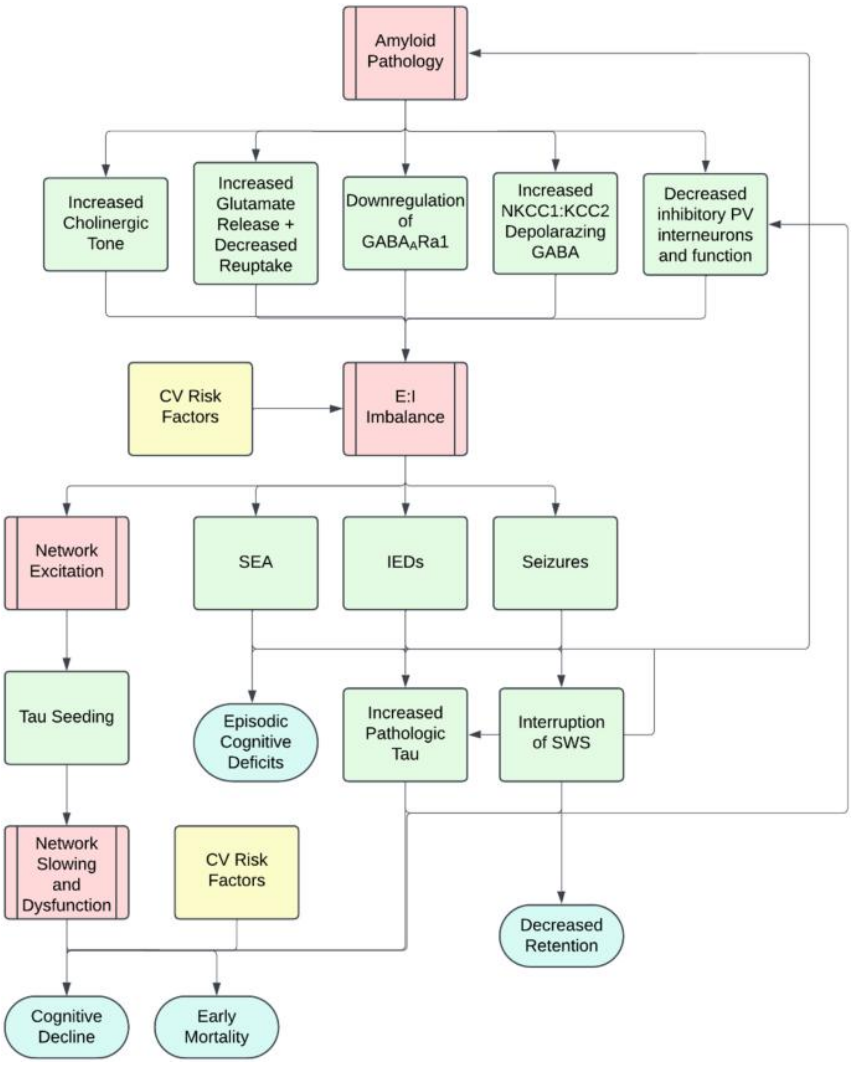
	these insertions. This was found using longitudinal studies of human skin cells.
Research Question/Problem/ Need	How does NUMTogenesis affect lifespan?
Important Figures	 Diagram of NUMT insertion in the body
VOCAB: (w/definition)	1) Retrotransposons: mobile genetic elements that "copy and paste" themselves into new locations in the genome via an RNA intermediate 2) ROSMAP: long-running, integrated study of aging and Alzheimer's disease conducted by the Rush Alzheimer's Disease Center 3) NUMT: Nuclear-mitochondrial segments; segments of mtDNA inserted into the nuclear DNA (new-mites)
Cited references to follow up on	Zhou, W., Karan, K. R., Gu, W., Klein, H.-U., Sturm, G., Jager, P. L. D., Bennett, D. A., Hirano, M., Picard, M., & Mills, R. E. (n.d.). *Somatic nuclear mitochondrial DNA insertions are prevalent in the human brain and accumulate over time in fibroblasts*. PLOS Biology. https://journals.plos.org/plosbiology/article/metrics?id=10.1371%2Fjournal.pbio.

	3002723#citedHeader
Follow up Questions	Can the process of NUMTogenesis be used to our advantage? Can we block the process of NUMTogenesis?

- Mitochondria used to be bacteria “alien”
- More NUMTs meant more likely to die
- We used to think this was rare
- Happen frequently in brain cells but not found in blood cells
- Can be passed down, so many of us have some NUMTs (mostly benign)
- Most NUMTogenesis happens in the PFC (prefrontal cortex)
- More stress causes more NUMTs

Article #5 Notes: **The Bidirectional Relationship Between Epilepsy and Alzheimer’s Disease**

Source Title	**The Bidirectional Relationship Between Epilepsy and Alzheimer’s Disease**
Source citation (APA Format)	Stewart, D., & Johnson, E. L. (2025). The bidirectional relationship between epilepsy and Alzheimer’s disease. *Current Neurology and Neuroscience Reports*, *25*(1). https://doi.org/10.1007/s11910-025-01404-y
Original URL	https://doi.org/10.1007/s11910-025-01404-y
Source type	Journal Article
Keywords	None provided by article
#Tags	
Summary of key points + notes (include methodology)	Using recent studies and meta-analyses, this review article looked at the many ways the diseases Epilepsy and Alzheimer’s Disease (AD) interact and explored their bidirectional comorbidity. This relationship showed that the pathologies of Epilepsy and AD are related. Each of them exacerbates risk factor of another which increases overall risk. This research summarizes lots of data from various sources to show that this comorbidity can be used to help diagnose and treat these disorders.
Research Question/Problem/ Need	What are the findings of recent papers regarding the bidirectional relationship between Alzheimer’s and Epilepsy
Important Figures	



Flow chart of Epilepsy and AD association and risks

VOCAB: (w/definition)

1) Epileptiform: Brain wave patterns that are characteristic of epilepsy
2) Levetiracetam: Anti-epileptic that is used to prevent and control seizures
3) Prodromal: relating to the period between initial symptoms and the full development
4) Cholinergic: refers to the neurotransmitter system of acetylcholine
5) Atropine: anticholinergic medication
6) Muscarinic: a cholinergic receptor that mediates the parasympathetic nervous system responses
7) Parvalbumin: A calcium bind protein with roles in muscle relaxation and in the brain

Cited references to follow up on

Chen L, Yang W, Yang F, et al. The crosstalk between epilepsy and dementia: a systematic review and meta-analysis. Epilepsy Behav. 2024;152:109640. https://doi-org.ezpv7-web-p-u01.wpi.edu/10.1016/j.yebeh.2024.10964

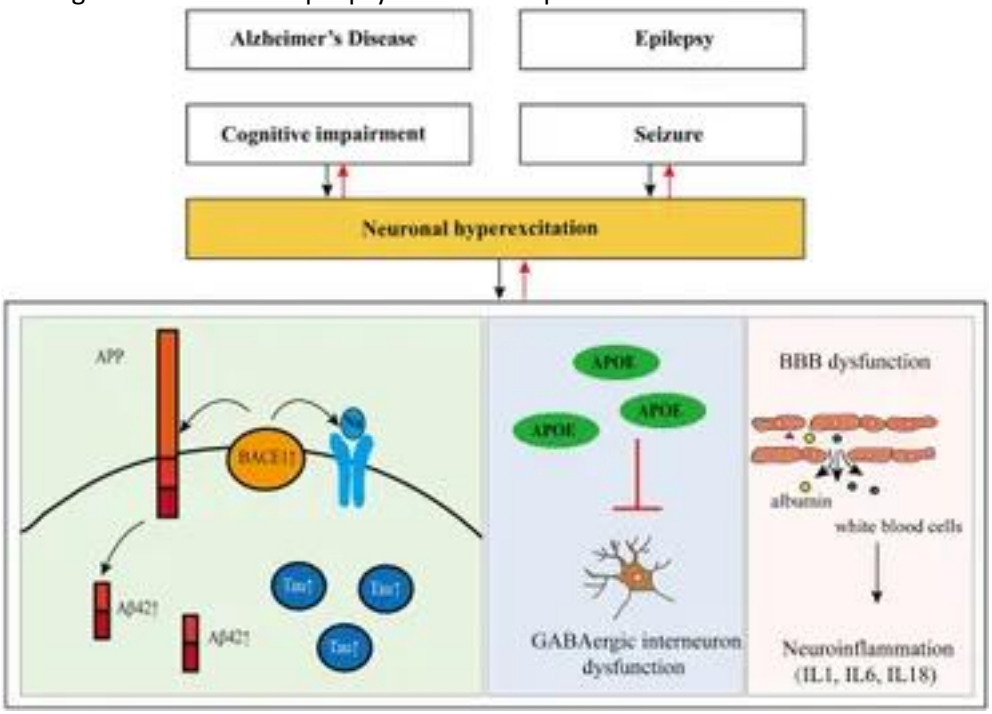
	Arnaldi D, Donniaquio A, Mattioli P, et al. Epilepsy in neurodegenerative dementias: a clinical, epidemiological, and EEG study. J Alzheimers Dis. 2020;74(3):865–74. https://doi-org.ezpv7-web-p-u01.wpi.edu/10.3233/JAD-191315.
Follow up Questions	Can EEGs be used to identify AD early? How does drug-resistant epilepsy differ from regular epilepsy in comorbidity? Could anti-seizure medication help with the progression of AD?

Notes:

- Epilepsy is considered a late-stage consequence of AD (Alzheimer's Disease)
- Epilepsy is onsetting earlier than cognitive symptoms
- Late onset epilepsy coincides with dementia risk (cognitive impairment risk)
- Epilepsy WITH other risk factors show significant comorbidity with AD
- Epilepsy after AD is mostly focal seizures (not gran-mal)
- Sleep is a huge factor to detect and for risk
- Amyloid and Tau pathology may be key
- Interneurons increased

Article #6 Notes: Alzheimer's disease and epilepsy: An increasingly recognized comorbidity

Source Title	Alzheimer's disease and epilepsy: An increasingly recognized comorbidity
Source citation (APA Format)	Yang, F., Chen, L., Yu, Y., Xu, T., Chen, L., Yang, W., Wu, Q., & Han, Y. (2022). Alzheimer's disease and epilepsy: An increasingly recognized comorbidity. *Frontiers in aging neuroscience*, *14*, 940515. https://doi.org/10.3389/fnagi.2022.940515
Original URL	https://doi.org/10.3389/fnagi.2022.940515
Source type	Review Journal Article
Keywords	Alzheimer's disease, epilepsy, comorbidity, seizure, cognition
#Tags	
Summary of key points + notes (include methodology)	Alzheimer's disease (AD) and epilepsy are increasingly recognized as interconnected conditions. People with AD—especially those with early-onset forms—are significantly more prone to seizures and epileptiform activity. These seizures often go unnoticed due to their subtle, non-motor symptoms, such as confusion or brief lapses in awareness, which can mimic AD-related cognitive decline.
Research Question/Problem/	What is the relationship between Alzheimer's disease and epilepsy, and how

Need	might understanding this comorbidity improve diagnosis and treatment outcomes?
Important Figures	Pathogenesis of AD and epilepsy – relationship  Studies that looked at Epilepsy and Dementia/ AD **Authors** | **Study type** | **Study population** | **Number of samples** | **Age mean (SD)** | **Seizures/ Epileptiform discharges incidence** | **Events confirmed type** Sjogren et al. (1952) | Retrospective | AD (autopsy) | 18 | 53.0 ± 5.0 | 22% (4/18) | Clinical Hauser et al. (1986) | Retrospective | AD (autopsy) | 81 | – | 20% (16/81) | Clinical Mendez et al. (1994) | Retrospective | AD (autopsy) | 446 | 64.1 ± 8.8 | 17% (77/446) | Clinical Mendez and Lim (2003) | Systematic review | AD | 874 | – | 10–20% | – Amatniek et al. (2006) | Prospective | Probable AD | 236 | – | 7.7% (12/236) | Clinical or EEG Hommet et al. (2007) | Prospective | Clinical AD | 197 | ≥65 | 2.5% (5/197) | Clinical Bell et al. (2011) | Prospective | Clinical AD | 28,089 | 42–101 | 2.1% | – Vossel et al. (2013) | Retrospective | aMCI and probable AD | 1,257 | 68.0 ± 7.8 (aMCI-Epilepsy) 69.1 ± 9.0 (AD-Epilepsy) | 4.3% (54/1257) | Clinical or EEG or LTM-EEG Nicastro et al. (2016) | Systematic review | AD | 3,555,817 | – | 0.5–64% | – Horváth et al. (2016) | Systematic review | AD | 3,506,623 | – | 0.5–64% | – Vossel et al. (2016) | Prospective | Probable AD | 33 | 61.7 ± 67.4 | 42.4% (14/33) | LTM-EEG or M/EEG Zarea et al. (2016) | Prospective | ADEOAD | 132 | 44.8 (24–63) | 47.7% (63/132) | Clinical Beagle et al. (2017) | Retrospective | Probable AD | 1,320 | 62–78 | 13.4% (177/1320) | Clinical or EEG Baumanaa et al. (2018) | Retrospective | AD (autopsy) | 61 | 81.4 ± 8 (AD-Epilepsy) | 17% (11/61) | Clinical Horváth et al. (2018) | Cross-sectional | Probable AD | 42 | 68.5 ± 4.1 (AD-Seizures) 68.6 ± 10.9 (AD-Epileptiform discharges) | 52% (22/42) | Ambulatory EEG Lam et al. (2020) | Cross sectional | Probable AD -NoEp | 41 | 76.3 ± 7.2 | 22% (9/41) | Ambulatory EEG AD, Alzheimer's disease; aMCI, amnestic mild cognitive impairment; ADEOAD, autosomal dominant early-onset Alzheimer's disease; AD-NoEp, probable AD with no history/risk factors for epilepsy; EEG, electroencephalogram; LTM-EEG, long-term monitoring with video-EEG; M/EEG, magnetoencephalography with simultaneous EEG.
VOCAB: (w/definition)	1. Epileptiform Discharges: Abnormal electrical patterns in the brain that can be detected by an EEG (electroencephalogram) 2. Transient Epileptic Amnesia – A seizure-related condition causing brief episodes of memory loss 3. Myoclonic Seizures – Sudden, brief muscle jerks often seen in neurodegenerative conditions
Cited references to follow up on	Amatniek, J. C., Hauser, W. A., DelCastillo-Castaneda, C., Jacobs, D. M., Marder, K., Bell, K., et al. (2006). Incidence and predictors of seizures in patients with Alzheimer's disease. *Epilepsia* 47, 867–872. doi: 10.1111/j.1528-

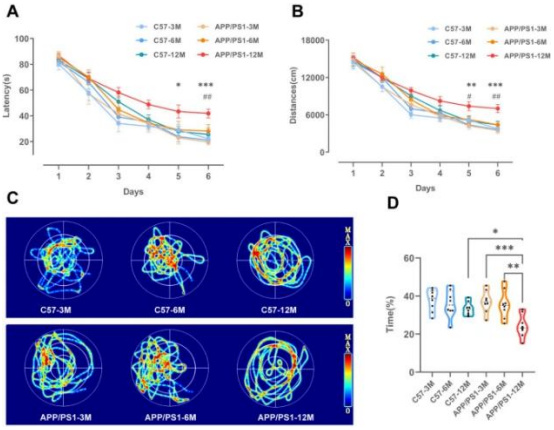
	1167.2006.00554.x Baker, J., Libretto, T., Henley, W., and Zeman, A. (2019). The prevalence and clinical features of epileptic seizures in a memory clinic population. *Seizure* 71, 83–92. doi: 10.1016/j.seizure.2019.06.016
Follow up Questions	1. How does amyloid beta molecularly trigger epilepsy activity on a cell level? 2. Is wearable EEG tech a possible tool to help with detection in dementia? 3. What is the effect of epilepsy medication in AD patients? 4. How does the genetics of both disorders interplay to exacerbate symptoms?

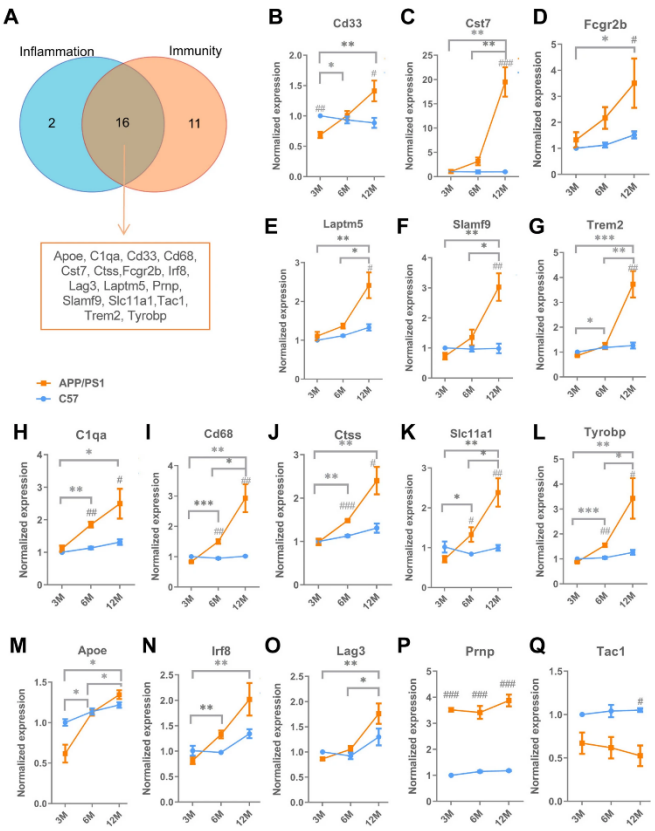
Notes:

- AD (Alzheimer's disease) is the most common type of dementia
- Most cases happen after age 65 (late-onset)
- Epilepsy hast highest incidence is patients older than 65
- AD is a common cause of new-onset epilepsy
- Recurrent seizures have relationship between cognitive decline (https://pmc.ncbi.nlm.nih.gov/articles/PMC9685172/#ref124)
- Patients with AD were 5 to 10 times more likely to develop seizures than without AD
- Early-onset AD shows higher seizure prevalence than late onset AD
- AD seizures are subtle and usually non-motor
- They can exacerbate cognitive decline
- Risk factors: Younger age at AD onset, Down syndrome, sharp cognitive decline, epileptiform EEG, certain medications
- Stroke Brain injury and metabolic disturbances also contribute
- Focal non-motor seizures are most common
- Transient epileptic amnesia (TEA) and myoclonic seizures also occur (especially related to down syndrome AD)
- Levetiracetam and lamotrigine are preferred medications for seizure treatment due to efficacy and tolerability
- AD and epilepsy have overlapping pathophysiology and clinical features
- Early detection and treatment of seizures in AD may improve outcomes
- Future therapies targeting shared mechanism hold promise

Article #7 Notes: **Integrative Analysis of the Age-Related Dysregulated Genes Reveals an Inflammation and Immunity-Associated Regulatory Network in Alzheimer's Disease**

Source Title	**Integrative Analysis of the Age-Related Dysregulated Genes Reveals an Inflammation and Immunity-Associated Regulatory Network in Alzheimer's**

	Disease
Source citation (APA Format)	Wu, Z., Dong, L., Tian, Z., Yu, C., Shu, Q., Chen, W., & Li, H. (2024). Integrative analysis of the Age-Related dysregulated genes reveals an inflammation and Immunity-Associated regulatory network in Alzheimer's disease. *Molecular Neurobiology*, *61*(8), 5353–5368. https://doi.org/10.1007/s12035-023-03900-z
Original URL	https://doi.org/10.1007/s12035-023-03900-z
Source type	Journal Article
Keywords	None provided by the article – Dementia, Inflammation, Genetics, Transcriptomics, RNA
#Tags	
Summary of key points + notes (include methodology)	This study investigates age-related gene expression changes in Alzheimer's disease (AD) using APP/PS1 mouse models at 3, 6, and 12 months. Researchers identified key mRNAs and lncRNAs linked to inflammation and immunity, especially during early and late stages of AD. They constructed a comprehensive lncRNA-miRNA-mRNA regulatory network, highlighting four lncRNAs, eight miRNAs, and four mRNAs, that may orchestrate immune responses in AD progression. The findings offer new molecular targets and a framework for understanding early-stage AD mechanisms.
Research Question/Problem/ Need	How does age-related changes in gene expression contribute to inflammation and immune response during AD progression?
Important Figures	Morris Water Maze results  Genes related to inflammation and prevalence in Ad mice vs. control mice

	
VOCAB: (w/definition)	1. Incubation Period- Period of time when a disease is in its preclinical/asymptomatic stage 2. Competing endogenous RNA (ceRNA) – RNA molecules that regulate each other by binding to shared microRNA (miRNA) 3. C57BL/6 – Standard Mice genetics for creating mutations. This acts as a control in this study (like iso-31 in drosophila) 4. Escape Latency – time it takes a rodent to solve the Morris Water Maze 5. Microarray analysis- checks the activity levels of thousands of genes at once
Cited references to follow up on	Wang K, Liu H, Hu Q, Wang L, Liu J, Zheng Z, Zhang W, Ren J, Zhu F, Liu GH (2022) Epigenetic regulation of aging: implications for interventions of aging and diseases. Signal Transduct Target Ther 7(1):374. https://doi-org.ezpv7-web-p-u01.wpi.edu/10.1038/s41392-022-01211-8 Zhou Y, Ge Y, Liu Q, Li YX, Chao X, Guan JJ, Diwu YC, Zhang Q (2021) LncRNA BACE1-AS promotes autophagy-mediated neuronal damage through the miR-214-3p/ATG5 signalling axis in Alzheimer's disease. Neuroscience 455:52–64. https://doi-org.ezpv7-web-p-u01.wpi.edu/10.1016/j.neuroscience.2020.10.028
Follow up Questions	1. How does microglial activation influence these transcriptome changes 2. Epigenetic changes aid in treating AD and other dementias? 3. What about using risk genes rather than disease genes to see the

	differences in progression based on environmental differences?

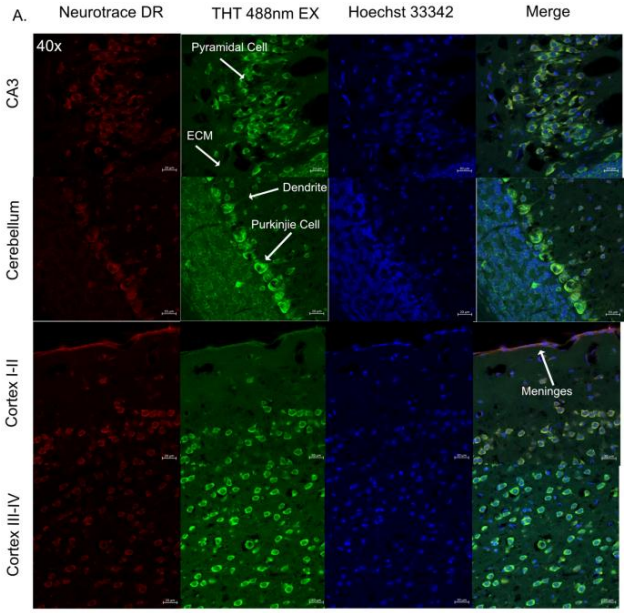
Notes:

- AD has a long incubation period
- Researchers understand the shift in RNA networks between people with AD and without AD
- Knowledge Gap: How does RNA change as AD progresses in a patient
- Study looks at the transcription differences between unaffected, preclinical, and late-onset stages in mice
- 16 of the mRNAs were associated with inflammation and immunity
- Orchestration of immune and inflammatory responses important for early stages
- Age-related AD risk genes were found
- Constructed a comprehensive regulatory ceRNA network linked to inflammation and immune system in AD
- Noncoding RNAs (ncRNAs) regulation is an epigenetic mechanism
- Long ncRNAs (lncRNAs) are longer than 200nt
- Used APP (amyloid precursor protein)/ PS1(presenilin 1) gene mutation mice
- Used a Morris Water Maze Test – Spatial learning trials to find a invisible platform within 90 seconds. 3 times a day for 6 days.
- Escape latency and swimming velocity were recorded
- 1 day rest was given then they recorded the data points
- Test was done for 3-, 6-, and 12-month groups
- The mice were then sacrificed, and their hippocampi were isolated at preserved for microarray analysis.
- 3 hippocampus samples from each group randomly
- Statistically significant differences in RNA changes
- Created a protein-protein interaction network and used STRING database to predict
- Used Chi plot – looked at how connected gene was in the network (degree) and was called a key AD gene
- Used Metascape to understand what those genes do
- Checked their key AD genes to see if it was supported by AlzData Genomic analysis evidence
- Used Mfuzz clustering method to analyze correlation of changes over ages
- Used cytoscape to create complex lncRNA network to visualize the network
- Used quantitative PCR to compare gene expression
- They then looked at the immunohistochemistry
    - Brain slices were stained for amyloid beta and visualized it with DAB staining to see antibody interaction
- Used t-tests and ANOVA
- Fig 1 shows that APP/PS1 mice age, their ability to learn and remember gets worse
- Gene differences between APP/PS1 and C57
    - 3 months -> 436 genes --- filtering for the most key genes---> 72 genes
    - 6 months -> 554 genes --- filtering for the most key genes---> 59 genes

    - 12 months -> 340 genes --- filtering for the most key genes---> 86 genes
- Gene differences between age groups in APP/PS1
    - 12vs 3 months -> 548 genes --- filtering for the most key genes---> 169 genes
    - 12 vs 6 months -> 358 genes --- filtering for the most key genes---> 43 genes
    - 6 vs 3 months -> 444 genes --- filtering for the most key genes---> 154 genes
- Pathway shows that regulators of cell development immune response and more intensify over time
- CFG analysis shows that inflammation and immunity genes in mice are more prominent at 6 and 12 months
- 16 genes have significant age-related changes showing importance in disease progression
- Limitations:
    - Regulatory network is typical but incomplete
    - Correlation didn't include negatively regulated lncRNA-mRNAs
- They found identifying age-related risk genes related to AD
- They created a lncRNA network that governs immune and inflammatory function by analyzing gene expression profiles and validation through qPCR. They identify 16mRNAs linked to inflammation and immunity. This research helps look at how immune and inflammatory responses affect early stages of AD

Article #8 Notes: **Thioflavin-T: application as a neuronal body and nucleolar stain and the blue light photo enhancement effect**

Source Title	**Thioflavin-T: application as a neuronal body and nucleolar stain and the blue light photo enhancement effect**
Source citation (APA Format)	Min, JH., Sarlus, H., Oasa, S. *et al.* Thioflavin-T: application as a neuronal body and nucleolar stain and the blue light photo enhancement effect. *Sci Rep* **14**, 24846 (2024). https://doi.org/10.1038/s41598-024-74359-8
Original URL	https://doi.org/10.1038/s41598-024-74359-8
Source type	Journal Article
Keywords	None provided by the article Staining, Amyloid, Neurons, NISSL
#Tags	
Summary of key points + notes (include methodology)	THT effectively stains neuronal cell bodies in various parts of the brain and shows a clear contrast between cells and the extracellular matrix. It also stains the nucleus in fixed tissue and live cells which was demonstrated in microglia and

	astrocytes. This molecule works with antibody-based staining and is selective for neurons. They also discovered that THT fluorescence is enhanced when exposed to blue light and is long-lasting. Overall, this study recommends THT as a versatile, cost-effective dye that can be used for amyloid and neuronal cell visualization.
Research Question/Problem/ Need	Is THT effective in staining neuronal cell bodies and nuclei when it is mostly used for amyloid fibril staining? How does Blue Light affect the fluorescence of THT?
Important Figures	 The above figure shows the different stains tested and how they show up in different parts of the brain. We can see that THT is effective in showing different cells and creating contrast between cells and the extracellular matrix.
VOCAB: (w/definition)	1) Fluorophores – Molecules that absorb light of a specific wavelength and re-emit it at a higher wavelength 2) Congo red – A dye commonly sued to stain for amyloid and is used as a diagnostic tool 3) Benzothiazole compounds – aromatic structures used in products from building to pharmaceuticals. It is used in Alzheimer's imaging agents and neurodegenerative disease treatment 4) Hyaline cartilage – bluish white cartilage present in joint, respiratory tract, and immature skeleton 5) Cardiac perfusion – the flow of blood through the heat 6) Intra-cisternal – injection of a therapeutic into the cerebrospinal fluid filled subarachnoid space between the cerebellum and medulla oblangata.
Cited references to follow up on	Verma, S., Ravichandiran, V. & Ranjan, N. Beyond amyloid proteins: Thioflavin T in nucleic acid recognition. *Biochimie* **190**, 111–123 (2021). Note: The following were older due to citing preliminary articles talking about the effectiveness in THT for staining. Might still be useful to understand the staining

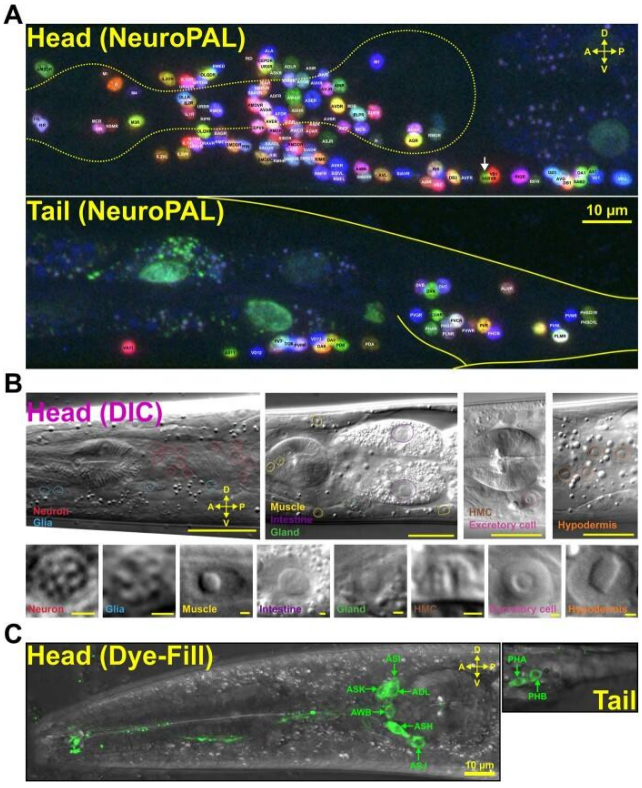
	processes. Biancalana, M. & Koide, S. Molecular mechanism of Thioflavin-T binding to amyloid fibrils. *Biochim. Biophys. Acta* **1804**, 1405–1412 (2010). Kádár, A., Wittmann, G., Liposits, Z. & Fekete, C. Improved method for combination of immunocytochemistry and Nissl staining. *J. Neurosci. Methods* **184**, 115–118 (2009).
Follow up Questions	1. Why does THT work on neuronal bodies and amyloids? What is the mechanism behind this binding? 2. How does the fluorescence of THT work and why does blue light aid it?

Notes:

- Thioflavin-T (THT) is important for amyloid staining and fluorescent staining
- THT can stain for cell bodies AND nucleoli
- THT is the gold standard in invitro and in vivo
- Applicable in many different neurodegenerative diseases
- THT can bond to mRNA (useful in terms of protein expression)
- NISSL staining has some carcinogenic properties
- THT is less expensive compared to other stains
- Mice brains dehydrated using a sucrose solution
- MedChemExpress was the source of the THT
- After staining, images were taken without blue light to avoid the enhancement
- Looked at the difference of emission spectra using nanometers
- Pearson's Correlation and Spearman's Rank Coefficient to check for strength of relationship in different parts of the brain
- T-test conducted
- FIJI used (I already have experience with this!)
    - Talk to Dr. Mansi Agrawal for more tips on staining and FIJI!
- THT is equivalent in neuronal cell staining compared to fluro-NISSL stains
-

Article #9 Notes: **Methods for analyzing neuronal structure and activity in *Caenorhabditis elegans***

Source Title	**Methods for analyzing neuronal structure and activity in *Caenorhabditis elegans***
Source citation (APA Format)	Emmons, S. W., Yemini, E., & Zimmer, M. (2021). Methods for analyzing neuronal structure and activity in Caenorhabditis elegans. *Genetics*, *218*(4), iyab072. https://doi.org/10.1093/genetics/iyab072
Original URL	https://doi.org/10.1093/genetics/iyab072

Source type	Review article
Keywords	synapse, connectome, Ca^{2+}-imaging, fluorescent reporter gene, graph theory, nervous system, nematode, WormBook
#Tags	
Summary of key points + notes (include methodology)	This article was a summary of the many, many technologies and methods that have been historically used to identify neurons and study the brain in c elegans. Since c elegans is transparent, it's easy to visualize using fluorescent markers. These are being further enhanced to look at specific types and structures of neurons. Also, since c elegans are a simple organism, many studies have been looking at connectomes to map the connections between different neurons. Overall, c elegans is a great organism to study the nervous system and its disorders and has many possible methods that can be used to study various aspects (anatomy, physiology, function, cells, etc..)
Research Question/Problem/ Need	What are some methods to look at neuronal structure and activity in c elegans?
Important Figures	 Examples of the outcomes of different staining methods in different parts of c elegans bodies.
VOCAB: (w/definition)	- Foray: A raid - Connectomics: a field of neuroscience focused on mapping all the connections in the nervous system

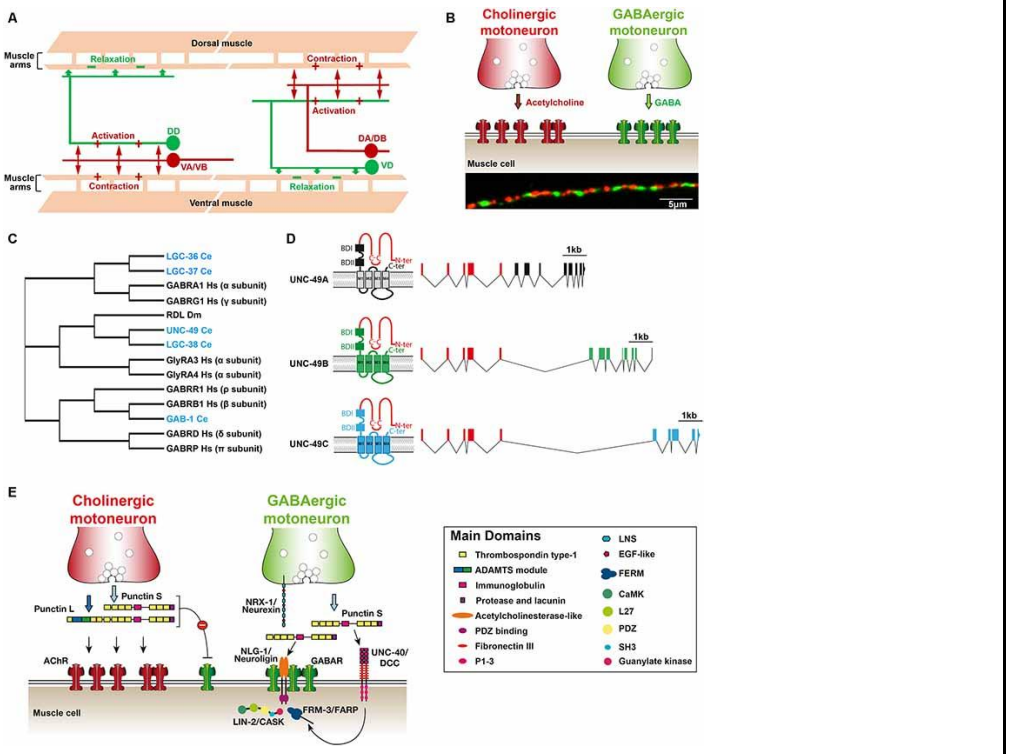
	- Electron micrographs: images created by electron microscopes - Node degree: number of edges connected to a node in a network -
Cited references to follow up on	Cook SJ, Crouse CM, Yemini E, Hall DH, Emmons SW, et al. 2020. The connectome of the *Caenorhabditis elegans* pharynx. J Comp Neurol. 528:2767–2784. Abdelfattah AS, Kawashima T, Singh A, Novak O, Liu H, et al. 2019. Bright and photostable chemigenetic indicators for extended *in vivo* voltage imaging. Science. 365:699–704.
Follow up Questions	How can connectomes be used to identify Alzheimer's activity? Does Alzheimer's cause problems with neuronal connections and pathways? Does epilepsy play a role in changing the behavior of certain pathways? Can connectomes show us insight into this?

Notes:

- C elegans is hermaphrodite
- Electron micro graphs for creating connectomes
- Nomarski microscopy was used to identify neurons in c elegans
- Fluorescent identification has been important
-

Article #10 Notes: Molecular Architecture of Genetically-Tractable GABA Synapses in C. elegans

Source Title	Molecular Architecture of Genetically-Tractable GABA Synapses in C. elegans
Source citation (APA Format)	Zhou, X., & Bessereau, J. (2019). Molecular Architecture of Genetically-Tractable GABA Synapses in C. elegans. *Frontiers in Molecular Neuroscience*, *12*. https://doi.org/10.3389/fnmol.2019.00304
Original URL	https://doi.org/10.3389/fnmol.2019.00304
Source type	Journal Article
Keywords	None provided by article
#Tags	
Summary of key points + notes (include methodology)	This mini review looked at how c elegans serves as a model for GABAergic synapses. They highlight the simplicity of the c elegans nervous system while showing the many parallels to human systems. The study looked mostly at a GABA receptor UNC-49 and the organizer protein Ce-Punctin/MADD-4. These molecules have to coordinate to cluster GABA receptors and define synaptic identity. Overall, this study acts as a justification to why c elegans should be used a model for GABA

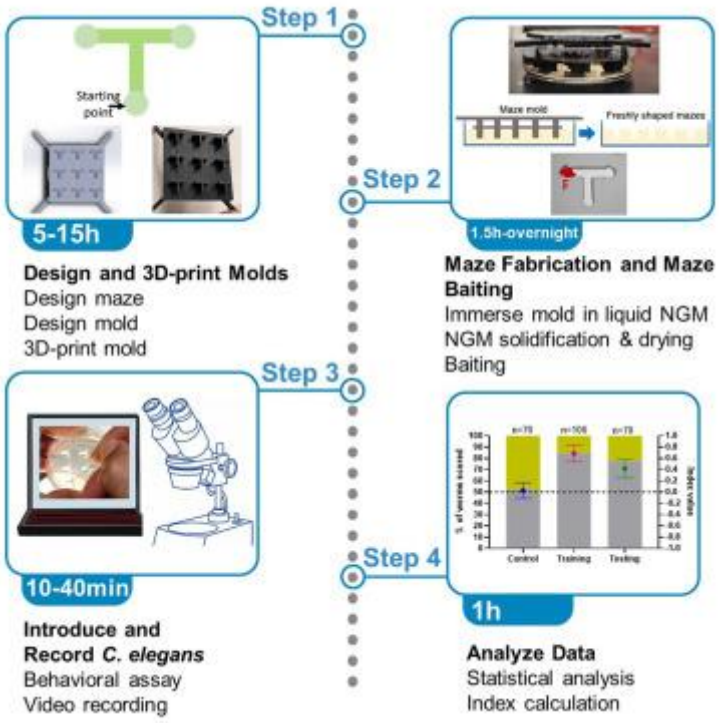
	studies and by relation shows important information on Epilepsy.
Research Question/Problem/ Need	How do the molecular and genetic mechanisms of c elegans change the GABAergic synapses?
Important Figures	 Summary diagram of the organization of the c elegans neuro muscular network. It shows the different neurons and synapses and explains how the cause neurochemical changes.
VOCAB: (w/definition)	1) Anterograde Synaptic Organizer: Presynaptic molecule that guides postsynaptic specialization 2) Ce-Punctin/MADD-4: Protein that determines whether a synapse is excitatory or inhibitory in c elegans 3) Gephyrin: Scaffolding protein in mammals that anchors GABA receptors and not found in c elegans
Cited references to follow up on	Hobert, O. (2018). The neuronal genome of *Caenorhabditis elegans*. *WormBook* 13, 1–106. doi: 10.1895/wormbook.1.161.1 Older but useful: Schultheis, C., Brauner, M., Liewald, J. F., and Gottschalk, A. (2011). Optogenetic analysis of GABAB receptor signaling in *Caenorhabditis elegans* motor neurons. *J. Neurophysiol.* 106, 817–827. doi: 10.1152/jn.00578.2010
Follow up Questions	How is Punctin secreted? How do cholinergic and GABAergic signaling markers create cross talk?

Notes:

- Unc = uncoordinated
- Many of the unc genes are related to GABA (unc 25, unc 49, unc 47, and more)
- 302 neurons in c elegans

Article #11 Notes: A maze platform for the assessment of *Caenorhabditis elegans* behavior and learning

Source Title	A maze platform for the assessment of *Caenorhabditis elegans* behavior and learning
Source citation (APA Format)	Gourgou, E., & Hsu, A.-L. (2021). A maze platform for the assessment of Caenorhabditis elegans behavior and learning. *STAR Protocols*, 100829. https://doi.org/10.1016/j.xpro.2021.100829
Original URL	https://doi.org/10.1016/j.xpro.2021.100829
Source type	Journal Article - Protocol
Keywords	Model Organisms Neuroscience Behavior
#Tags	
Summary of key points + notes (include methodology)	This paper presents a protocol for designing, fabricating, and using a 3d-printed maze to study spatial learning in c elegans. This is meant to be a low cost, reproducible tool for behavioral research. Using CAD, a t maze mold was designed and 3d printed. These mazes were imprinted into nematode growth medium to ensure environmental similarity for the worms. They baited one side of the maze with an attractant (chemotaxis) and recorded which arm of the maze the worms chose. They then found the decision index, chemotaxis index, and learning indexes. Statistically analyzed these using binomial distribution tests to determine significance. These mazes are a novel and accessible method for understanding cognitive and sensory behaviors in a structured environment.
Research Question/Problem/ Need	Need: Researchers need an accessible maze to test various c elegans behaviors.

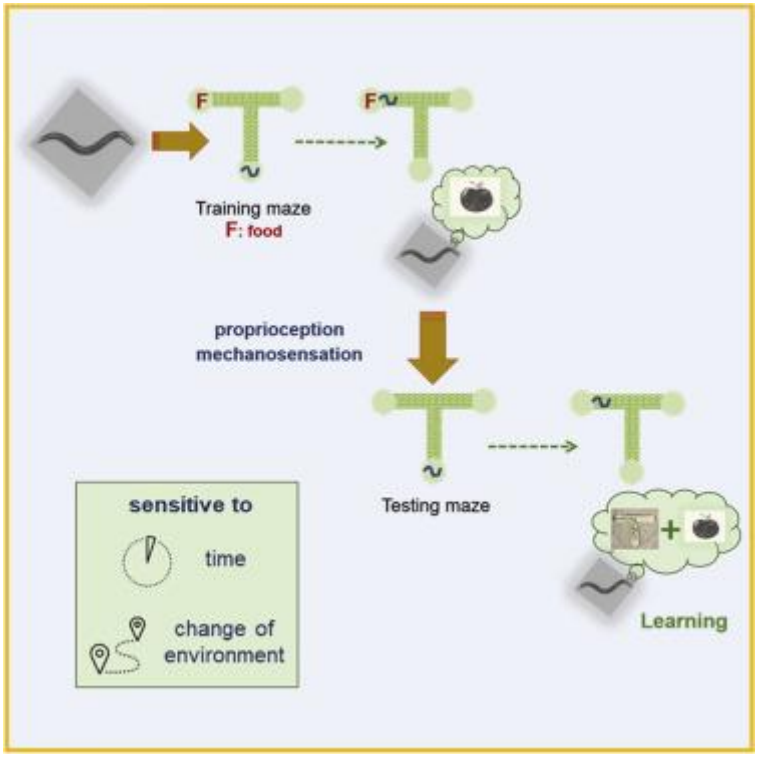
Important Figures	 Graphical abstract of this studies methods and process. This figure gives a preview and summary of what happened in this paper
VOCAB: (w/definition)	1) Stereolithography: 3D printing process that uses a laser to selectively harden a liquid photopolymer resin layer by layer to create a solid object 2) Auxiliary: Providing supplementary or additional help and support
Cited references to follow up on	Gourgou et al., 2021 E. Gourgou, K. Adiga, A. Goettemoeller, C. Chen, A.-L. Hsu Caenorhabditis elegans learning in a structured maze is a multisensory behavior
Follow up Questions	How can this maze be used in Alzheimer's symptom testing? How does this maze test learning?

Notes:

- Do not use the maze >2days post fabrication
- Do not refrigerate the mazes
- Use agar pad on top to prevent them from escaping

Article #12 Notes: *Caenorhabditis elegans* learning in a structured maze is a multisensory behavior

Source Title	*Caenorhabditis elegans* learning in a structured maze is a multisensory behavior

Source citation (APA Format)	Gourgou, E., Adiga, K., Goettemoeller, A., Chen, C., & Hsu, A.-L. (2021). Caenorhabditis elegans learning in a structured maze is a multisensory behavior. *IScience*, *24*(4), 102284. https://doi.org/10.1016/j.isci.2021.102284
Original URL	https://doi.org/10.1016/j.isci.2021.102284
Source type	Journal Article
Keywords	Behavioral Neuroscience Biological Sciences Neuroscience
#Tags	
Summary of key points + notes (include methodology)	This study shows that c elegans can learn to naviagte in a maze using sensory cues. They used a t maze as seen in article 11. They tested wild type against many mutants to figure out which sensation they were relying on to solve the maze. This was found to be mechanosensory cues. As nematodes age, their ability to learn decreased. They also found that this maze tests short term memory and learning only with their memory lasting only 8 to 10 minutes. Overall, this study shows a simple way to test spatial learning through mechanosensation.
Research Question/Problem/ Need	Can c elegans learn and remember spatial information is a structured environment? What sensory mechanisms does it use to do so?
Important Figures	

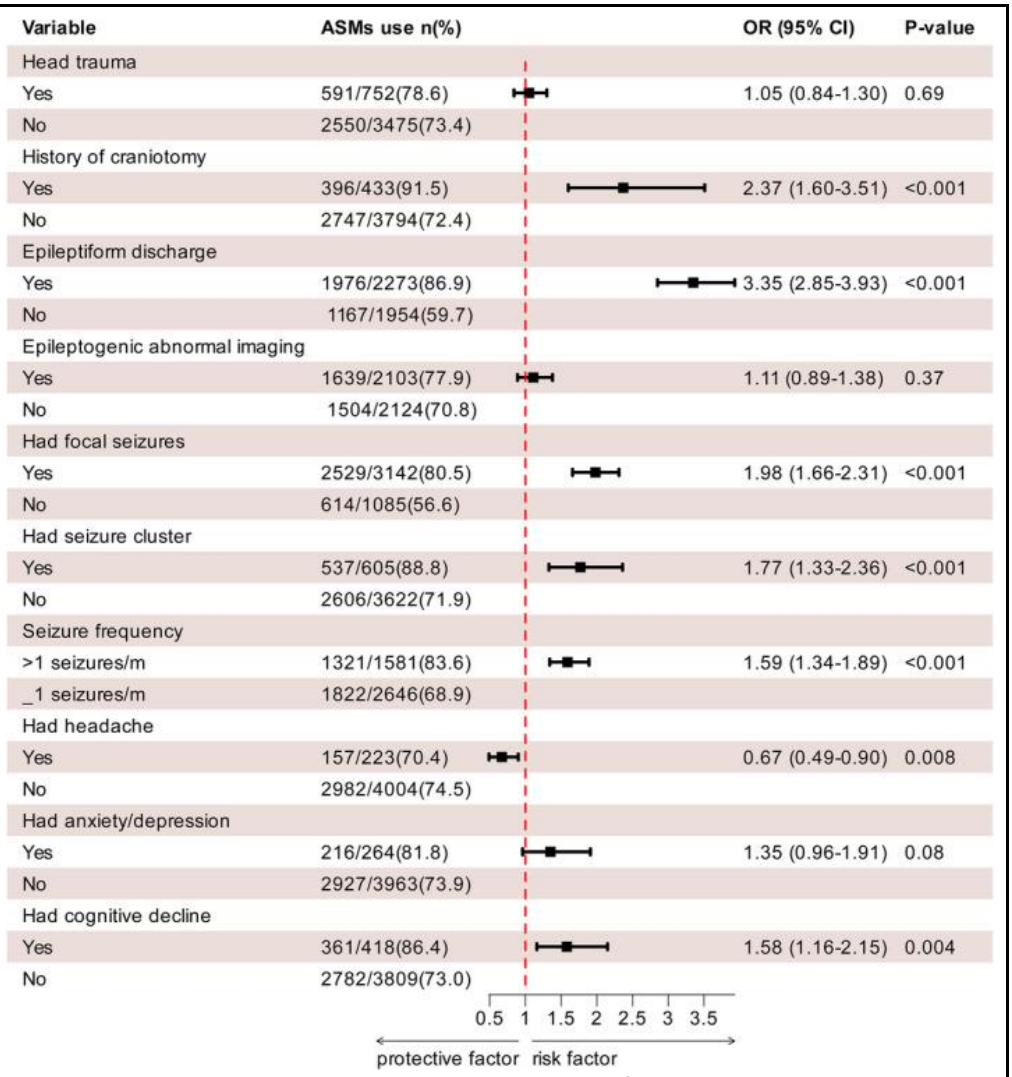
	Graphical abstract of the study and its methods
VOCAB: (w/definition)	1) Imprinting: Rapid learning where an animal forms a strong attachment with the first moving object it encounters during a critical period 2) Osmolarity: Total concentration of solute particles in a solution 3) Microfluidic device: manipulates fluids in small channels 4) Sensory modality: sensory input like touch, sound of chemical cues
Cited references to follow up on	Amano, H. · Maruyama, I.N. **Aversive olfactory learning and associative long-term memory in Caenorhabditis elegans** *Learn. Mem.* 2011; **18**:654-665 Crossref Scopus (60) PubMed Google Scholar Cook, S.J. · Jarrell, T.A. · Brittin, C.A. ... **Whole-animal connectomes of both Caenorhabditis elegans sexes** *Nature.* 2019; **571**:63-71 Crossref Scopus (409) PubMed Google Scholar
Follow up Questions	Can this t maze be used to study Alzheimer's? Do c elegans have long term spatial memory?

Notes:

- T maze shows response learning
- Mechanosensory cues for c elegans
- Worm only has 302 neurons
- Study shows spatial navigation suing mechanosensation
- Had training maze then transferred to testing maze to see if worms remember where the food was last time
- 8-10 minutes learening retention

Article #13 Notes: Clinical characteristics, etiology, and treatment of young adult-onset epilepsy: A 24-year retrospective study

Source Title	Clinical characteristics, etiology, and treatment of young adult-onset epilepsy: A 24-year retrospective study
Source citation (APA Format)	Zhang, X., Xiang, F., Wang, Z., Li, Y., Shao, C., Lan, X., Lang, S., & Wang, X. (2024). Clinical characteristics, etiology, and treatment of young adult-onset epilepsy: A 24-year retrospective study. *Epilepsia Open*, *10*(1), 298–306. https://doi.org/10.1002/epi4.13126
Original URL	https://doi.org/10.1002/epi4.13126
Source type	Journal Article
Keywords	antiseizure medication, epilepsy, etiology, young adult-onset
#Tags	
Summary of key points + notes (include methodology)	This was retrospective study that examined 4227 patients with young adult-onset epilepsy over 24 years. They found that structural causes were the leading etiologies while nearly half had unknown causes. Most patients had focal seizures, about half had epileptiform discharges on EEG or neuroimaging abnormalities. Cognitive decline was found to be the most common comorbidity. More than half the patients received monotherapy and half achieved seizure control. Porr treatment led to worse outcomes. Overall, they found important information on etiology and importance of medication use.
Research Question/Problem/ Need	How does response to antiseizure medication change based of clinical characteristics of young adult-onset epilepsy?
Important Figures	



Factors associated with medication use and its significance

VOCAB: (w/definition)	1. Status Epilepticus: Continuous seizure lasting over 5minutes (tonic-clonic) or 0ver 10 minutes (focal) or repeated seizures without recovery 2. Multivariate logistic regression: Analyzes several factors on binary outcome 3. Neoplasia: Abnormal tissue growth (kind of like a tumor)
Cited references to follow up on	Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, et al. ILAE official report: a practical clinical definition of epilepsy. Epilepsia. 2014;55(4):475–482. [DOI] [PubMed] [Google Scholar] Chun CT, Seward K, Patterson A, Melton A, MacDonald-Wicks L. Evaluation of available cognitive tools used to measure mild cognitive decline: a scoping review. Nutrients. 2021;13(11):3974. [DOI] [PMC free article] [PubMed] [Google Scholar]
Follow up Questions	Are there any specific types of lesions that are more likely to influence medication over others?

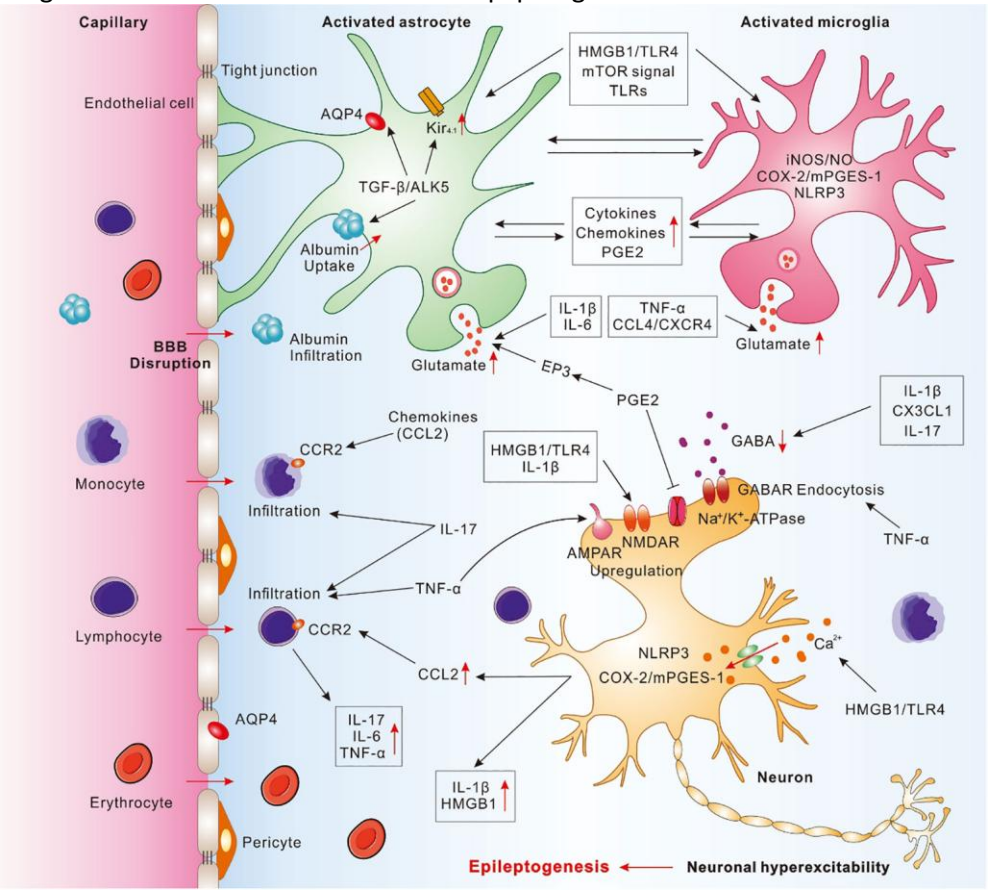
	Is there a critical window of medication delivery? How does structural etiology compare between different onsets?

Notes:

- 24 year study (1999 to 2023)
- Onset between 18 to 44 years old
- Cognitive decline comorbidity is higher than headache or anxiety
- Epilepsy was often caused by head trauma
- Age on onset and etiology are closely related
- Data was from people who attended epilepsy clinic in 1999
- 4227 patients were examined
- Patients encouraged to keep an epilepsy diary
- Multivariate Logistic Regression was used
- Cognitive decline rate of 15.5% five years after onset!
- Geographical differences between china and europe in terms of etiology
- Retrospective study

Article #14 Notes: Neuroinflammation in epileptogenesis: from pathophysiology to therapeutic strategies.

Source Title	Neuroinflammation in epileptogenesis: from pathophysiology to therapeutic strategies.
Source citation (APA Format)	Li, W., Wu, J., Zeng, Y., & Zheng, W. (2023). Neuroinflammation in epileptogenesis: from pathophysiology to therapeutic strategies. *Frontiers in Immunology*, *14*. https://doi.org/10.3389/fimmu.2023.1269241
Original URL	https://doi.org/10.3389/fimmu.2023.1269241
Source type	Review Article
Keywords	None provided
#Tags	
Summary of key points + notes (include methodology)	In this review article, the authors discuss the many different ways to approach epileptogenesis and neuroinflammation's relatonship. Immune responses have been seen in the starting of epilepsy and neuronal hyperactivation. Mainly, Microglia, astocytes, and peripheral immune cells have been found to be related. The article also discusses pro-inflammatory molecules that are related to this process and ways that these could be used as therapeutic targets to decrease hyperactivation.
Research Question/Problem/ Need	What is the relationship between epileptogenesis and neuroinflammation?

Important Figures	Diagram of BBB and Cell interactions in epilpetogenesis 
VOCAB: (w/definition)	1) Elucidated: make clear 2) Aberrant: departing from an accepted standard 3) Chemokines: any class of cytokines with functions that include attracting white blood cells to sites of infections 4) Nicotinamide: form of vitamin b3 5) Interstitial fluid: liquid that fills the spaces between cells, acting as a medium for transporting oxygen, nutrients, and waste products 6) Nestin: Protein that serves as a key structural component of the cytoskeleton, particularly in neural stem cells where it is crucial for self-renewal and proliferation 7) Mesial: Relating to the midline of the body
Cited references to follow up on	4. Rabidas SS, Prakash C, Tyagi J, Suryavanshi J, Kumar P, Bhattacharya J, et al. A comprehensive review on anti-inflammatory response of flavonoids in experimentally-induced epileptic seizures. *Brain Sci* (2023) 13, 102. doi: 10.3390/brainsci13010102
Follow up Questions	How does the BBB disruption related to epilepsy affect Alzheimer's risk? How can we regulate the peripheral immune cell infiltration to decrease epileptogenesis?

Notes:

- 30% of epileptic patients are resistant to current medications
- Epilpetogenesis Hypothesis is that neuroinflammation, immune activation, and peripheral immune cell infiltration from the blood to the brain causes seizures
- Imbalance between glutamatergic and GABAergic signaling
- Aberrant ion channel activation
- Blood Brain Barrier (BBB) is disrupted during epilpetogenesis
- Micro glia makes high levels of nitric oxide. This then activates nicotinamide adenine dinucleotide (NADPH) oxidase→NADPH is related to ATP formation and oxidase breaks it down. Less ATP formed??
-

Article #15 Notes: Epigenetics and Neuroinflammation Associated With Neurodevelopmental Disorders: A Microglial Perspective.

Source Title	Epigenetics and Neuroinflammation Associated With Neurodevelopmental Disorders: A Microglial Perspective.
Source citation (APA Format)	Komada, M., & Nishimura, Y. (2022). Epigenetics and Neuroinflammation Associated With Neurodevelopmental Disorders: A Microglial Perspective. *Frontiers in Cell and Developmental Biology*, *10*, 852752. https://doi.org/10.3389/fcell.2022.852752
Original URL	https://doi.org/10.3389/fcell.2022.852752
Source type	Journal Article
Keywords	microglia, microRNA, DNA methylation, zebrafish, rodents, fetal alcohol syndrome, autism spectrum disorders, Rett syndrome
#Tags	
Summary of key points + notes (include methodology)	This article explains how microglia, the brain's immune cells, are involved in neurodevelopmental disorders through inflammation and epigenetic changes. It shows that things like DNA methylation and microRNAs can affect how microglia behave, which can disrupt brain development and contribute to conditions like autism and Rett syndrome.
Research Question/Problem/ Need	How are neuroinflammation, epigenetics, and microglia related in neurodevelopmental disorders?
Important Figures	https://images-provider.frontiersin.org/api/ipx/w=370&f=webp/https://www.frontiersin.org/files/Articles/852752/fcell-10-852752-HTML/image_m/fcell-10-852752-g001.jpg

	Diagram of involvement of epigentic dysregualtion in neurodevelopmental disorders
VOCAB: (w/definition)	Microglia: Immune cells of the central nervous system that regulate inflammation and brain development. Neuroinflammation: Inflammatory response within the brain or spinal cord, often involving microglia. DNA methylation: Epigenetic modification that can silence or reduce gene expression. MicroRNA (miRNA): Small non-coding RNAs that regulate gene expression post-transcriptionally. Neurodevelopmental disorders (NDDs): Disorders that affect brain development, cognition, and behavior (e.g., ASD, Rett syndrome).
Cited references to follow up on	Cronk, J. C., Derecki, N. C., Ji, E., Xu, Y., Lampano, A. E., Smirnov, I., et al. (2015). Methyl-CpG Binding Protein 2 Regulates Microglia and Macrophage Gene Expression in Response to Inflammatory Stimuli. *Immunity* 42, 679–691. doi:10.1016/j.immuni.2015.03.013
Follow up Questions	Which epigenetic mechanisms most strongly influence microglial activation during early brain development? Are epigenetic changes in microglia reversible with therapeutic intervention? How well do animal model findings translate to human neurodevelopmental disorders? Could targeting microglial epigenetics reduce neuroinflammation in NDDs?

Notes:

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Article #16 Notes: Alzheimer's Disorder: Epigenetic Connection and Associated Risk Factors.

Source Title	Alzheimer's Disorder: Epigenetic Connection and Associated Risk Factors.
Source citation (APA Format)	Sharma, V. K., Mehta, V., & Singh, T. G. (2020). Alzheimer's Disorder: Epigenetic Connection and Associated Risk Factors. *Current Neuropharmacology*, *18*(8), 740–753. https://doi.org/10.2174/1570159X18666200128125641
Original URL	https://doi.org/10.2174/1570159X18666200128125641

Source type	Journal Article
Keywords	Alzheimer's disease, epigenetics, DNA methylation, histone modification, non-coding RNA, environmental risk factors, neurodegeneration
#Tags	
Summary of key points + notes (include methodology)	This article explains how epigenetic changes—factors that control gene activity without changing DNA—may contribute to Alzheimer's disease. It shows how lifestyle and environmental factors can affect these changes and increase Alzheimer's risk, suggesting epigenetics could be important for understanding and treating the disease.
Research Question/Problem/ Need	How do epigenetic modifications contribute to the onset and progression of Alzheimer's disease?
Important Figures	https://www.eurekaselect.com/images/graphical-abstract/cn/18/8/big-004.jpg Graphical abstract of epigenetics in dementia
VOCAB: (w/definition)	Epigenetics: Regulation of gene expression through reversible chemical modifications without altering the DNA sequence. DNA methylation: Addition of methyl groups to DNA that usually suppresses gene transcription. Histone modification: Chemical changes to histone proteins that affect chromatin structure and gene accessibility. Non-coding RNA (ncRNA): RNA molecules that regulate gene expression but do not encode proteins (e.g., miRNA). Amyloid-β: A peptide that accumulates in plaques in the brains of Alzheimer's patients. Tau protein: A microtubule-associated protein that forms neurofibrillary tangles when abnormally phosphorylated.
Cited references to follow up on	Lane, C.A.H.J.; Hardy, J.; Schott, J.M. Alzheimer's disease. *Eur. J. Neurol.,* **2018**, *25*(1), 59-70. [http://dx.doi.org/10.1111/ene.13439] [PMID: 28872215]
Follow up Questions	Which epigenetic modifications are most consistently altered in Alzheimer's patients? Can lifestyle-based interventions reverse harmful epigenetic changes linked to AD? How early do epigenetic changes appear during Alzheimer's disease progression?

	What challenges exist in translating epigenetic therapies to clinical use?

Article #17 Notes: Molecular mechanisms of transgenerational epigenetic inheritance

Source Title	Molecular mechanisms of transgenerational epigenetic inheritance
Source citation (APA Format)	Fitz-James, M. H., & Cavalli, G. (2022). Molecular mechanisms of transgenerational epigenetic inheritance. *Nature Reviews Genetics*, *23*(6), 325–341. https://doi.org/10.1038/s41576-021-00438-5
Original URL	https://doi.org/10.1038/s41576-021-00438-5
Source type	Journal Article
Keywords	transgenerational epigenetic inheritance, epimutations, DNA methylation, histone modifications, non-coding RNA, epigenome, heritable variation
#Tags	
Summary of key points + notes (include methodology)	This review looks at how epigenetics are transferred across generations. It looks mostly at dna methylation, histone modifications, that contribute to evolution. They note that TEI varies based a on species.
Research Question/Problem/ Need	How is epigenetic information transmitted across generations independent of DNA sequence?
Important Figures	https://www.nature.com/articles/s41576-021-00438-5 image of epigenetic influence during brain development and fetus development
VOCAB: (w/definition)	Transgenerational epigenetic inheritance (TEI): Transmission of epigenetic information across multiple generations beyond the immediate offspring (not solely via DNA sequence changes). Epimutations: Heritable changes in gene expression or phenotype caused by epigenetic alterations, not changes in DNA sequence. DNA methylation: Addition of methyl groups to DNA (often at CpGs) that can influence gene expression. Histone modifications: Chemical changes to histone proteins (e.g., methylation/acetylation) affecting chromatin structure and gene activity. Non-coding RNAs (ncRNAs): RNA molecules not translated into proteins but which regulate gene expression (e.g., miRNAs, piRNAs).

	Paramutation: A phenomenon where one allele induces a heritable change in another allele's expression state
Cited references to follow up on	Perez & Lehner (2019) on intergenerational and transgenerational epigenetic inheritance.
Follow up Questions	How strong is the evidence for TEI in mammals, and what are the best-supported mechanisms? What role do ncRNAs play relative to DNA methylation or histone marks in establishing TEI? How might TEI contribute to human phenotypic variation and disease risk across generations?

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Article #18 Notes: Epigenetic modification impacting brain functions: Effects of physical activity, micronutrients, caffeine, toxins, and addictive substances.

Source Title	Epigenetic modification impacting brain functions: Effects of physical activity, micronutrients, caffeine, toxins, and addictive substances.
Source citation (APA Format)	Mallick, R., & Duttaroy, A. K. (2023). Epigenetic modification impacting brain functions: Effects of physical activity, micronutrients, caffeine, toxins, and addictive substances. *Neurochemistry International*, *171*, 105627. https://doi.org/10.1016/j.neuint.2023.105627
Original URL	https://doi.org/10.1016/j.neuint.2023.105627
Source type	Journal Article
Keywords	Epigenetics, DNA methylation, histone modification, brain function, physical activity, micronutrients, caffeine, toxins, addictive substances.
#Tags	
Summary of key points + notes (include methodology)	This review looks at how epigenetic changes modulate brain functions. They discuss environment may cause alterations in the brain. This can influence things like neuroplasticity, memory, and more.

Research Question/Problem/ Need	What are the potential implications for understanding neuropsychiatric disorders and developing prevention or intervention strategies?
Important Figures	https://ars.els-cdn.com/content/image/1-s2.0-S0197018623001559-gr1.jpg Image of the common epigenetic processes
VOCAB: (w/definition)	Epigenetics: Study of heritable changes in gene expression that do not involve changes to the underlying DNA sequence. DNA methylation: Addition of a methyl group to DNA, often at CpG sites, typically reducing gene expression. Histone modification: Post-translational changes (e.g., acetylation, methylation) to histone proteins that alter chromatin structure and gene expression. Non-coding RNA: RNA molecules that do not encode proteins but regulate gene expression epigenetically.
Cited references to follow up on	M. Bai, X. Zhu, Y. Zhang, S. Zhang, L. Zhang, L. Xue, J. Yi, S. Yao, X. Zhang Abnormal hippocampal BDNF and miR-16 expression is associated with depression-like behaviors induced by stress during early life PLoS One, 7 (2012), 10.1371/journal.pone.0046921 View at publisherGoogle Scholar
Follow up Questions	Which specific epigenetic changes have been most consistently linked to improved cognitive outcomes from physical activity? How do caffeine's epigenetic effects compare to those of other bioactive compounds? Are there critical periods (e.g., prenatal, adolescence) when epigenetic influences are especially potent? What translational evidence exists linking these epigenetic changes to human clinical outcomes?

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Article #19 Notes: A new perspective on Alzheimer's disease: m6A modification

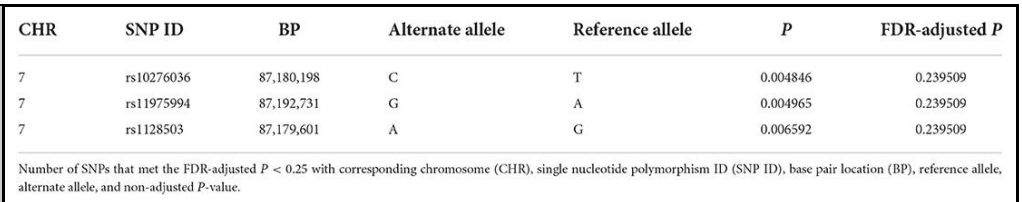
Source Title	A new perspective on Alzheimer's disease: m6A modification
Source citation (APA Format)	Xia, L., Zhang, F., Li, Y., Mo, Y., Zhang, L., Li, Q., Luo, M., Hou, X., Du, Z., Deng, J., &

	Hao, E. (2023). A new perspective on Alzheimer's disease: m6A modification. *Frontiers in Genetics*, *14*, 1166831. https://doi.org/10.3389/fgene.2023.1166831
Original URL	https://doi.org/10.3389/fgene.2023.1166831
Source type	Review Article
Keywords	Alzheimer's disease, m6A modification, RNA methylation, neurodegeneration, epigenetics
#Tags	
Summary of key points + notes (include methodology)	This review article explores the role of m6A (N6-methyladenosine) RNA modification in Alzheimer's disease (AD). m6A is a chemical modification that regulates RNA stability, splicing, and translation, and emerging evidence suggests that its dysregulation contributes to AD pathology. The article summarizes studies showing how m6A "writers," "erasers," and "readers" influence neuronal function, synaptic plasticity, and cognitive decline. By highlighting the molecular mechanisms linking m6A to neurodegeneration, the review proposes that targeting m6A-related pathways could offer novel therapeutic strategies for AD. Overall, it provides a new epigenetic perspective on understanding and potentially treating Alzheimer's disease.
Research Question/Problem/ Need	How does m6A modification influence Alzheimer's disease development and progression?
Important Figures	https://www.frontiersin.org/files/Articles/1166831/fgene-14-1166831-HTML/image_m/fgene-14-1166831-g001.jpg Shows how alzheimer's pathogenesis occurs
VOCAB: (w/definition)	m6A (N6-methyladenosine): A chemical modification of RNA that regulates its function. Writers: Enzymes that add m6A to RNA (e.g., METTL3). Erasers: Enzymes that remove m6A (e.g., FTO, ALKBH5). Readers: Proteins that recognize m6A-modified RNA and influence its fate (e.g., YTHDF proteins). Neurodegeneration: Progressive loss of neuron structure or function, including death.
Cited references to follow up on	Bhattarai, P., Thomas, A. K., Cosacak, M. I., Papadimitriou, C., Mashkaryan, V., Froc, C., et al. (2016). IL4/STAT6 signaling activates neural stem cell proliferation and neurogenesis upon amyloid-β42 aggregation in adult zebrafish brain. *Cell Rep.* 17 (4), 941–948. doi:10.1016/j.celrep.2016.09.075
Follow up Questions	Are there any human clinical studies linking m6A modifications directly to

	Alzheimer's symptoms? Which m6A regulators are the most promising therapeutic targets? How does m6A interact with other epigenetic modifications in AD?

Article #20 Notes: Genetic and molecular features of seizure-freedom following surgical resections for focal epilepsy: A pilot study

Source Title	Genetic and molecular features of seizure-freedom following surgical resections for focal epilepsy: A pilot study
Source citation (APA Format)	Louis, S., Busch, R. M., Lal, D., Hockings, J., Hogue, O., Morita-Sherman, M., Vegh, D., Najm, I., Ghosh, C., Bazeley, P., Eng, C., Jehi, L., & Rotroff, D. M. (2022). Genetic and molecular features of seizure-freedom following surgical resections for focal epilepsy: A pilot study. *Frontiers in Neurology*, *13*, 942643. https://doi.org/10.3389/fneur.2022.942643
Original URL	https://doi.org/10.3389/fneur.2022.942643
Source type	Journal Article
Keywords	epilepsy, resection, genetics, seizure-freedom, prediction, surgical outcomes, genetic variant
#Tags	
Summary of key points + notes (include methodology)	These researchers studied 201 adults with drug resistant focal epilepsy who has brain resection surgery to understand why some patients stay seizure free while others don't and to understand genetic links to this phenomenon. They wanted to use current knowledge of predicting neurological outcomes using genetics and predicting pediatric epilepsy. They did a pilot study and found that Single Nucleotide Polymorphisms in the ABCB1 gene could predict post-surgery outcomes.
Research Question/Problem/ Need	What are the genetic and molecular biomarkers that can provide insight on differential responses to brain surgery for drug-resistant epilepsy?

Important Figures	 CHR SNP ID BP Alternate allele Reference allele *P* FDR-adjusted *P* 7 rs10276036 87,180,198 C T 0.004846 0.239509 7 rs11975994 87,192,731 G A 0.004965 0.239509 7 rs1128503 87,179,601 A G 0.006592 0.239509 Number of SNPs that met the FDR-adjusted $P < 0.25$ with corresponding chromosome (CHR), single nucleotide polymorphism ID (SNP ID), base pair location (BP), reference allele, alternate allele, and non-adjusted *P*-value.
VOCAB: (w/definition)	1) Nomogram: a diagram representing the relations between three or more variable quantities by means of a number of scales, so arranged that the value of one variable can be found by a simple geometric construction, for example, by drawing a straight line intersecting the other scales at the appropriate values. 2) Engel Seizure Scale: four-class grading system used to classify the outcome of epilepsy surgery
Cited references to follow up on	The 1000 Genomes Project Consortium. A global reference for human genetic variation. Nature. (2015) 526:68–74. doi: 10.1038/nature15393 Zacher P, Mayer T, Brandhoff F, Bartolomaeus T, Duc D, Finzel M, et al. The genetic landscape of intellectual disability and epilepsy in adults and the elderly: a systematic genetic work-up of 150 individuals. Genet Med. (2021) 23:1492–7. doi: 10.1038/s41436-021-01153-6
Follow up Questions	How can this type of genetic analysis be used to show comorbidity frequencies? What is the ABCB1 gene's role in neuroinflammation?

Notes:

- 1% of US population has epilepsy
- 1/3 of them have DRE (Drug Resistant Epilepsy)
- Germline genetic variation, tissue messenger RNA, and tissue microRNA are associated with post-operative seizure freedom
- The following 10 genes were selected for further analyses in this study: *SCN1A, NBEA, PTEN, GABRA1, LGL1, DEPDC5, IL1A, ABCB1, C3, CALHM1*.
- Temporal lobe epilepsy seems to be the most common
- Fisher's exact test was performed on 14 anti-seizure medications and seizure outcome to test whether single nucleotide polymorphism results were confounded by AMSs or not
- SNPs in ABCB1 on chromosome 7 were associated with post operative seizure freedom
- ABCB1 is known as a multi-drug resistance gene that codes of P-glycoprotein

Article #21 Notes: Pentylenetetrazole derivatives

Source Title	Pentylenetetrazole derivatives
Source citation (APA Format)	Lien, L. (2012). *Pentylenetetrazole derivatives* (WIPO Patent Application No. PCT/US2012/036217). World Intellectual Property Organization. patentscope.wipo.int

Original URL	patentscope.wipo.int
Source type	Patent
Keywords	pentylenetetrazole, PTZ derivatives, central nervous system, neurological disorders, therapeutic compounds
#Tags	
Summary of key points + notes (include methodology)	This patent describes new chemical versions of pentylenetetrazole that are designed to work better or more safely in the brain. It focuses on modifying the original compound to create derivatives that could be useful for treating neurological or brain-related conditions, mainly from a drug development and research perspective.
Research Question/Problem/ Need	• How can pentylenetetrazole be chemically modified to produce safer or more effective derivatives? • Can PTZ derivatives be developed for therapeutic use in neurological or CNS-related disorders?
Important Figures	Table 1: Metabolic Stability of PTZ Derivatives in Presence of Human Liver Microsomes Figure of metabolism results
VOCAB: (w/definition)	Pentylenetetrazole (PTZ): A chemical compound known for its effects on the central nervous system and commonly used in neurological research models. Derivative: A compound chemically modified from an original substance while retaining part of its core structure. Central nervous system (CNS): The brain and spinal cord, responsible for processing and transmitting neural signals. Patent application: A legal document filed to protect intellectual property related to an invention.
Cited references to follow up on	DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; Y 1975, VOHLAND, HORST W. ET AL: "Metabolism of pentetrazole in the rat.

Compound	$t_{1/2}$ (min)	CLint (uL/min/mg)	$t_{1/2}$ increase over $t_{1/2}$ of PTZ (%)
PTZ	521	1.3	-
Compound 1	756	0.9	45.1
Compound 2	554	1.3	6.3
Compound 4	567	1.2	8.8
Compound 3	506	1.4	-2.9
testosterone	9.1	76	n/a

	Isolation and identification of the main metabolites from urine". XP002681632, retrieved from STN Database accession no. 1975:92876 abstract & VOHLAND, HORST W. ET AL: "Metabolism of pentetrazole in the rat. Isolation and identification of the main metabolites from urine". HOPPE-SEYLER'S ZEITSCHRIFT FUER PHYSIOLOGISCHE CHEMIE, 355(10), CODEN: HSZPAZ; ISSN: 0018-4888, 1974.
Follow up Questions	How do these PTZ derivatives differ functionally from the parent compound? What neurological conditions are the primary targets for these derivatives? Have any of these compounds progressed beyond patent stage into experimental or clinical testing?

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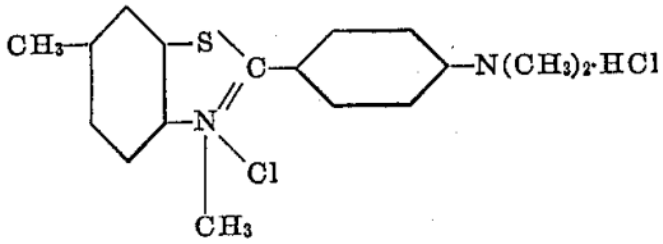
Article #22 Notes: Manufacture of Thioflavine T

Source Title	Manufacture of Thioflavine T
Source citation (APA Format)	Allemann, O. (1936). *Manufacture of Thioflavine T* (U.S. Patent No. 2,037,448). U.S. Patent and Trademark Office.
Original URL	Google patents
Source type	Patent
Keywords	Thioflavine T, fluorescent dye, chemical manufacturing, staining agents, industrial chemistry
#Tags	
Summary of key points + notes (include methodology)	This patent describes a way to make Thioflavine T, a fluorescent dye, more efficiently and reliably. While it was originally about industrial production, the dye later became important for detecting amyloid plaques in brain research.
Research Question/Problem/ Need	How can Thioflavine T be manufactured more efficiently and reliably? How can industrial dye production methods be improved for consistency and purity

Important Figures	 Figure of chemical structure of thioflavin t
VOCAB: (w/definition)	Thioflavine T: A fluorescent dye that binds to amyloid fibrils and is commonly used in microscopy. Fluorescent dye: A substance that emits light when excited by specific wavelengths. Manufacturing process: Industrial methods used to produce chemical compounds at scale. Patent: A legal document protecting an invention or process.
Cited references to follow up on	No citations
Follow up Questions	How did early manufacturing methods influence the availability of Thioflavine T for research use? How has Thioflavine T production changed with modern chemical technology? Why did Thioflavine T become especially important in neurodegenerative disease studies decades later?