Project Notes:

Project Title: **How Synaptic Pruning Mediates the Relationship Between Gut Bacteria and ASD/ADHD**
Name: **Yerin Kim**

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
Psychostimulants (how they work, drawbacks)	Watching a YouTube video explaining function	https://youtu.be/nhG5a5sET10?si=WS2YPOB-CSkVHrFQ	11/23
Different types of ADHD	Reading an official ADD article describing each type of ADHD (symptom-wise differences)	https://add.org/adhd-types/	9/10
Short chain fatty acids (SCFAs)	Watching YouTube videos explaining their composition and function	https://youtu.be/1M-pqKeFkJY?si=WRTZzURSY33SthLg https://youtu.be/zxXCpu4NLaM?si=vDqrMFftMRI1DDU6	11/23
Synaptic pruning	Reading a Healthline article with a general overview of the topic	https://www.healthline.com/health/synaptic-pruning#an-indepth-look	9/3
Zinc Finger Nucleases	Watching a YouTube video outlining the concept	https://youtu.be/TvySiie0KEA	10/18
Purkinje Cells	Watching information YouTube video that highlights their role in the brain	https://youtu.be/QUkwqAaSrUg?si=yQ9qHdQziJVHv3Kb	12/12
GABA	Introductory YouTube Video about concept	https://youtu.be/MRr6Ov2Uyc4?si=JZEGYgCC8CF3cXw9	12/12

Literature Search Parameters:

These searches were performed between (Start Date of reading) and XX/XX/2019.
List of keywords and databases used during this project.

Database/search engine	Keywords	Summary of search
Scopus	synaptic pruning mental disorders	Previous studies conducted about the relationship between synapses and mental disorders
Nature	mental disorders diet	foods that were identified to increase chances of mental disorders, or alleviate symptoms
Nature	gut bacteria autism	Many studies regarding different populations of people (and other organisms) that had ASD and differences in their microbiome

Tags:

Tag Name	
#psychology	#gutmicrobiome
#braindevelopment	

Article #0 Notes: Title (template)

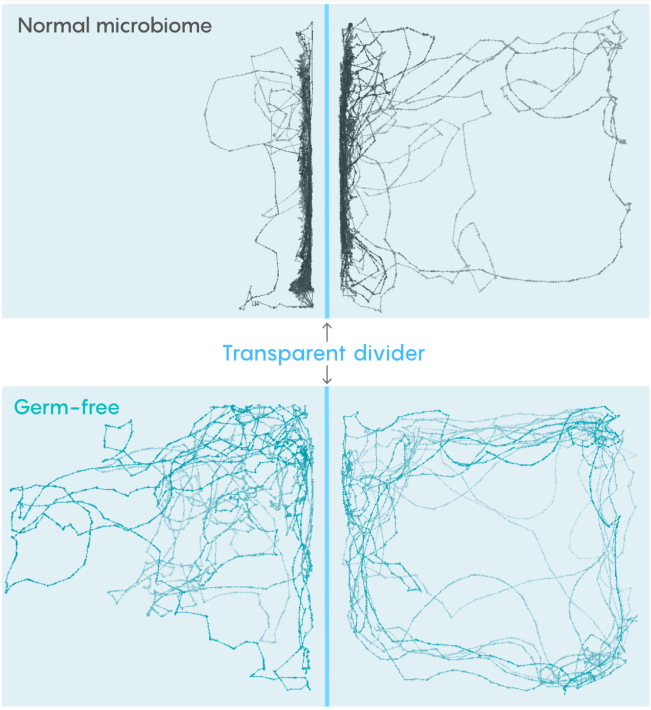
Article notes should be on separate sheets

KEEP THIS BLANK AND USE AS A TEMPLATE

Source Title	
Source citation (APA Format)	
Original URL	
Source type	
Keywords	
#Tags	
Summary of key points + notes (include methodology)	(summary) Problem: Goal: Method: Findings: (key points)
Research Question/Problem/ Need	
Important Figures	
VOCAB: (w/definition)	
Cited references to follow up on	
Follow up Questions	

Article #1 Notes: The Gut Microbiome Helps Social Skills Develop in the Brain

Source Title	The Gut Microbiome Helps Social Skills Develop in the Brain
Source citation (APA Format)	Thompson, J. (2022). The Gut Microbiome Helps Social Skills Develop in the Brain. *Quanta Magazine.* https://www.quantamagazine.org/the-gut-microbiome-helps-social-skills-develop-in-the-brain-20221115/
Original URL	https://www.quantamagazine.org/the-gut-microbiome-helps-social-skills-develop-in-the-brain-20221115/
Source type	Magazine
Keywords	gut microbiome psychology
#Tags	#psychology #gutmicrobiome #braindevelopment
Summary of key points + notes (include methodology)	Scientists have known for a while that the gut and brain are interconnected through the gut brain axis. Though there has been limited knowledge about how they work together, a recent study found that zebrafish that were exposed to healthy gut microbes only a week after birth were late to start joining shoals of fish compared to the other zebrafish who were exposed right at birth. This lack of sociability was also seen through the way their paths in the tank were more random and solitary compared to the zebrafish with normal gut microbiomes that generally swam closer to the transparent divider in the tank so they could be closer to the fish on the other side. These changes could also be seen physically in the brain: the fish that did not have a gut microbiome during early development were more packed with connections between neurons in the forebrain that affect social behavior, and less microglia, which are responsible for getting rid of waste in the brain and pruning unnecessary synapses. Even though it is still unclear how gut microbiota communicate with and create changes in the brain, and if the effect pertains to humans as well, this study still clearly shows that there is definitely a relationship between the two, and it would be interesting to further the studies on how the two communicate with each other, and the specific effects caused by specific bacteria. If this can be identified, it may open up new pathways to treatment for neurological/mental disorders.
Research Question/Problem/ Need	How does delayed development of the gut microbiome affect the social psychology of zebrafish?

Important Figures	 This visual shows how zebrafish with a normal microbiome primarily swam around the transparent divider near the fish on the other side, while the zebrafish without a gut microbiome had much more sporadic swimming pathways.
VOCAB: (w/definition)	Inoculate: to immunize (an organism) against a disease by exposing them to infective material Detritus: waste/debri Vagus nerve: cranial nerve that carries signals between brain, heart, and digestive system
Cited references to follow up on	Paper about lack of gut microbiome and decreased sociability: https://journals.plos.org/plosbiology/article?id=10.1371/journal.pbio.3001838
Follow up Questions	How does the gut and brain communicate with each other? What specific effects on the brain are caused by specific bacteria? What role does microglia play in mental disorders?

Article #2 Notes: Spreading the Word on a Possible Alzheimer's Treatment*

Source Title	Spreading the Word on a Possible Alzheimer's Treatment
Source citation (APA Format)	Fields, R. D. (2020, May 27). *Spreading the Word on a Possible Alzheimer's Treatment*. *Quanta Magazine.* https://www.quantamagazine.org/spreading-the-word-on-a-possible-alzheimers-treatment-20200527/
Original URL	https://www.quantamagazine.org/spreading-the-word-on-a-possible-alzheimers-treatment-20200527/
Source type	Scientific magazine
Keywords	Alzheimer's, brain waves, microglia
#Tags	#microglia #brainwaves #exploration
Summary of key points + notes (include methodology)	Alzheimer's was previously discovered to cause weaker and more infrequent 40-hertz brain waves than in people without Alzheimer's. Using this information, neuroscientist Li-Huei Tsai and her lab used optogenetic simulation on mice which shoots lasers directly into the neurons and made them fire 40 Hz impulses. This led to a decrease in amyloid plaques, an identifier for Alzheimer's. However, they recognized that this was not a realistic treatment option for humans, so instead, they used a different method to increase the power of gamma waves. When they used visual simulation of a strobe of flashing lights, not only did the 40 Hz waves intensify, but the amyloid plaques were also removed. To find out what the direct cause of this was, they moved their focus to microglia which were discovered by Alois Alzheimer himself to be often found near amyloid plaques, and additional research confirmed that they got rid of the plaques. Microglia can sense electrical activity in the brain and are prompted to fix the wiring when waves become irregular. Furthermore, extending the period of the visual simulation prevented neurons and synapses from disappearing. Sound simulation had similar results in the auditory cortex, and in the hippocampus, the subject mice had increased memory. To understand more of the biological reasoning of how the brain waves cause microglia to remove plaques and protect neurons, further research by a team at Georgia Institute of Technology found that gamma visual simulation caused microglia to produce more cytokines, which regulate neuroinflammation. The article concluded by hinting at the possibility of other types or ranges of light

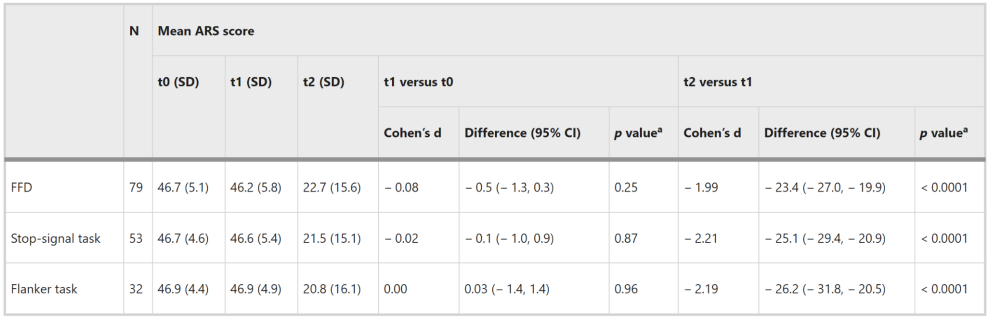
	and sound simulations to treat different neurological diseases.
Research Question/Problem/ Need	How can specific brain wave frequencies be used to treat Alzheimer's and what is the specific process that leads to the improvement?
Important Figures	N/A
VOCAB: (w/definition)	Oscillate: change in size or position around a central point Optogenetic: technology that allows fast and specific control of precise events in biological systems
Cited references to follow up on	Study in mice showing decreased amyloid plaques after firing 40 Hz waves: https://www.nature.com/articles/nature20587 Study in humans showing strobe lights increase brain waves and decrease AP: https://www.cell.com/neuron/fulltext/S0896-6273(19)30346-0?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0896627319303460%3Fshowall%3Dtrue
Follow up Questions	What are the drawbacks and/or negative symptoms of using strobe lights to increase brain waves at a certain frequency? What are other methods that have been known to decrease amyloid plaques and how does this method compare? How can other methods be used to increase microglia production of cytokines without affecting brain waves?

Article #3 Notes: Correlation between brain function and ADHD symptom changes in children with ADHD following a few-foods diet: an open-label intervention trial

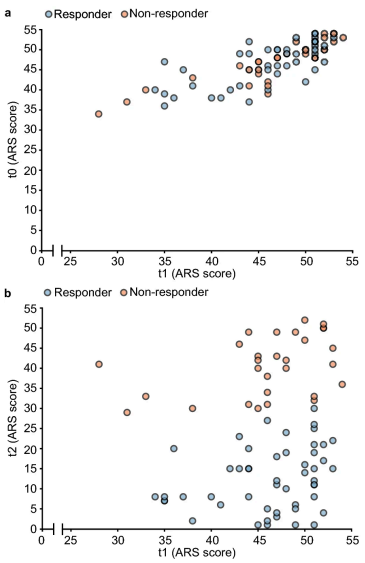
Article notes should be on separate sheets

Source Title	Correlation between brain function and ADHD symptom changes in children with ADHD following a few-foods diet: an open-label intervention trial
Source citation (APA Format)	Hontelez, S., Stobernack, T., Pelsser, L. M., van Baarlen, P., Frankena, K., Groefsema, M. M., Kleerebezem, M., Rodrigues Pereira, R., Postma, E. M., Smeets, P. A. M., Stopyra, M. A., Zwiers, M. P., & Aarts, E. (2021). Correlation between brain function and ADHD symptom changes in children with ADHD following a few-foods diet: An open-label intervention trial. *Scientific Reports*, *11*(1), Article 1. https://doi.org/10.1038/s41598-021-01684-7
Original URL	https://www.nature.com/articles/s41598-021-01684-7
Source type	Scientific journal
Keywords	dietary intervention adhd brain activity
#Tags	#adhd #brainactivity #diet
Summary of key points + notes (include methodology)	(summary) Problem: Drugs for ADHD are not completely effective and have multiple side effects, so new treatment types should be considered. Goal: Since it is already known that ADHD negatively affects brain functioning, the study aimed to investigate the effect of the few foods diet on brain activation, especially in the indicated regions of interest. Method: To analyze differences in ADHD behavior, ADHD Rating Scale scores were compared at baseline and after the FFD, as well as inhibition task reaction times. Additional fMRIs were taken during the response inhibition tasks to see where brain activity increased. Findings: There was a significant decrease in ARS scores in 63% of the subjects, and a slight decrease in reaction time during the interference inhibition tasks (no real improvement in task performance/accuracy). There were no significant changes in

	the brain ROIs during the tasks; however, when activity throughout the whole brain was considered, both response inhibition type tasks caused an increase in activity in the precuneus (which also aligned with the ARS score changes). There were also significant decreases in ODD symptoms, which is often copresent with ADHD.
	
	(key points)
	- ADHD affects the following brain regions: frontal, parietal, temporal, occipital lobes and cerebellar and sub-cortical regions (activated during response inhibition).
	- The few foods diet includes: rice, turkey, vegetables, pears, olive oil, ghee, salt, rice drink with added calcium and water
	  - The extended FFD also includes: lamb, butter, small portions of wheat, corn, potatoes, some fruits, honey
	- Precuneus plays a role in visuospatial processes, as well as brain's default network (alert but not participation in task).
	  - Depending on activity, may be over- or under-activated in people with adhd.

Research Question/Problem/ Need	How effective is the few foods diet on ADHD, and how can its effect be explained through changes in brain activity?
Important Figures	 This table shows how there was a significant decrease between t1 (baseline) and t2 (after FFD) ARS scores. The Cohen's d further supports this as the negative value indicates how the mean of the t2 scores were quite less than the t1 mean score, and the p-value for t2 versus t1 also indicates that they are statistically significant.

	N	Mean ARS score								
		t0 (SD)	t1 (SD)	t2 (SD)	t1 versus t0			t2 versus t1		
					Cohen's d	Difference (95% CI)	*p* value[a]	Cohen's d	Difference (95% CI)	*p* value[a]
FFD	79	46.7 (5.1)	46.2 (5.8)	22.7 (15.6)	− 0.08	− 0.5 (− 1.3, 0.3)	0.25	− 1.99	− 23.4 (− 27.0, − 19.9)	< 0.0001
Stop-signal task	53	46.7 (4.6)	46.6 (5.4)	21.5 (15.1)	− 0.02	− 0.1 (− 1.0, 0.9)	0.87	− 2.21	− 25.1 (− 29.4, − 20.9)	< 0.0001
Flanker task	32	46.9 (4.4)	46.9 (4.9)	20.8 (16.1)	0.00	0.03 (− 1.4, 1.4)	0.96	− 2.19	− 26.2 (− 31.8, − 20.5)	< 0.0001

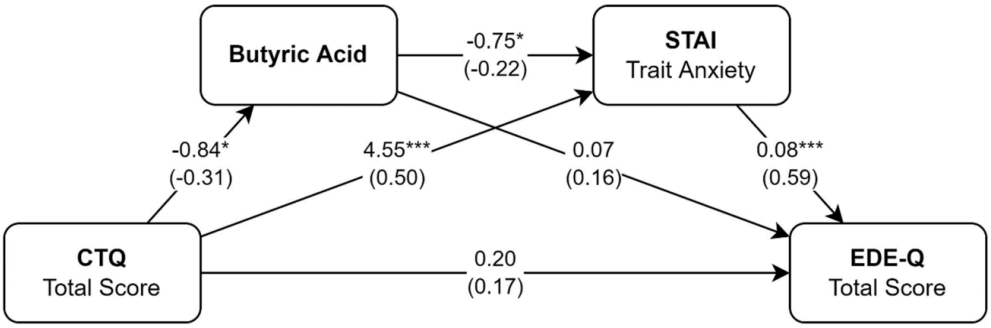
	 This scatter plot further supports how there was a significant decrease in ARS scores before and after the FFD intervention. However, it also helps to point out the fact that a little less than half of the participants did not show a significant change in ARS scores/behavior after the FFD.
VOCAB: (w/definition)	Open-label: both researchers and participants are aware of intervention Functional MRIs (fMRIs): as opposed to MRIs, fMRIs solely scan the brain, and they also detect metabolic activity over time using blood flow (blood oxygen levels). Inhibition: forcefully restraining an instinctual response Mean beta weight (of brain): a combination of the different analyses in tiny 3D sections (voxels) of the brain to give an overall result. Covariate: an additional (not primary) independent variable that may affect the outcome of the dependent variable
Cited references to follow up on	6 (“most stringent” FFD): https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0169277 9 (developing personalized diets for maximum ADHD effectiveness): https://adc.bmj.com/content/84/5/404 26 (more info about precuneus?): https://www.sciencedirect.com/science/article/pii/S0924977X19304365?via%3Dihub
Follow up Questions	How does this study put the placebo effect into account? What is the role of the precuneus? What is the difference between researcher’s observation ratings and teacher ratings? Is the teacher referred to here just their primary school teacher? ~~What do blood oxygen levels indicate in the brain?~~ What is the difference between combined, inattentive, and hyperactive/impulsive ADHD? ~~What is the main role of the precuneus?~~ (implied through article) How would the results change if the subject were in a different age group (e.g. the elderly)?

	(project-like) How can the fMRI scanning process be made more accurate and adaptable to movement and other technical issues? (project-like?) How do the compounds in specific foods lead to a change in brain functioning? How were the FFD foods chosen? What was the criteria?

Article #4 Notes: Gut microbiota metabolites mediate the interplay between childhood maltreatment and psychopathology in patients with eating disorders

Article notes should be on separate sheets

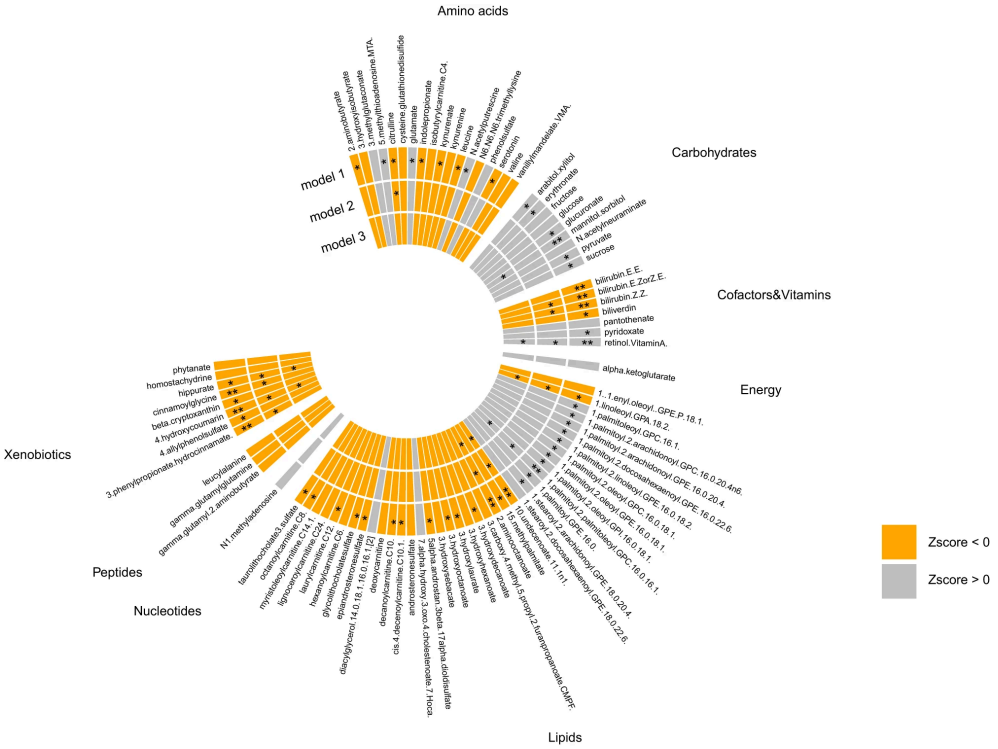
Source Title	Gut microbiota metabolites mediate the interplay between childhood maltreatment and psychopathology in patients with eating disorders
Source citation (APA Format)	Castellini, G., Cassioli, E., Vitali, F., Rossi, E., Dani, C., Melani, G., Flaccomio, D., D'Andria, M., Mejia Monroy, M., Galli, A., Cavalieri, D., Ricca, V., Bartolucci, G. L., & De Filippo, C. (2023). Gut microbiota metabolites mediate the interplay between childhood maltreatment and psychopathology in patients with eating disorders. *Scientific Reports*, *13*(1), Article 1. https://doi.org/10.1038/s41598-023-38665-x
Original URL	https://www.nature.com/articles/s41598-023-38665-x
Source type	Scientific journal
Keywords	gut brain axis mental disorder
#Tags	#mentalillness #gutmicrobiome #metabolites
Summary of key points + notes (include methodology)	(summary) Problem: Eating disorders are dangerous mental illnesses, but their complex causes and lack of biological knowledge makes it difficult to make effective treatments. Goal: This study aimed to bridge the connection between the early childhood trauma, the gut microbiome, and the symptoms of multiple different types of EDs. Method: To analyze childhood maltreatment experiences, the subjects went through clinical evaluations and the Childhood Trauma Questionnaire. Findings: In terms of acids, childhood maltreatment was overall linked to butyric acid, which was also a predictor of trait anxiety; both were found to be significant chains in the connection between EDs and early trauma. Additionally, the people with EDs had significantly less diverse gut microbiota than the HC, with varying types of gut microbiota among people with different types of eating disorders.

	(key points) - Childhood maltreatment was negatively correlated with shorter SCFAs.
Research Question/Problem/ Need	What changes in the gut are linked to early childhood trauma that also affect different types of eating disorders and their correlating behaviors?
Important Figures	 Butyric acid provides scientific explanation for how childhood trauma leads to eating disorders.
VOCAB: (w/definition)	Etiopathogenesis: cause and development of a disease or abnormal condition Trait anxiety: Tendency to feel anxiety Serial medication: predicts a consequential (one affects the next) chain relating different factors to each other that has a specific direction of flow Stratification: categorizing things into different groups Alpha diversity: the variation of species/organisms/things present on a small scale (smaller, specified population)
Cited references to follow up on	18 (ghrelin receptor signaling): https://doi.org/10.1096%2Ffj.201901433R 17 (anorectic hormones, esp induced by SCFAs): https://doi.org/10.1038%2Fs41575-019-0157-3
Follow up Questions	What are the other studied effects of short chain fatty acids on brain function/mental processing and on overall human health? What is the difference between shorter and longer SCFAs? What is the hypothalamic pituitary adrenal axis and what role does it play? Are there any current medications for people with eating disorders, and if so, how do they help the patient and what are their side effects? What are benzodiazepine anxiolytics? What is their role and relation to EDs?

Article #5 Notes: Circulating metabolites modulated by diet are associated with depression

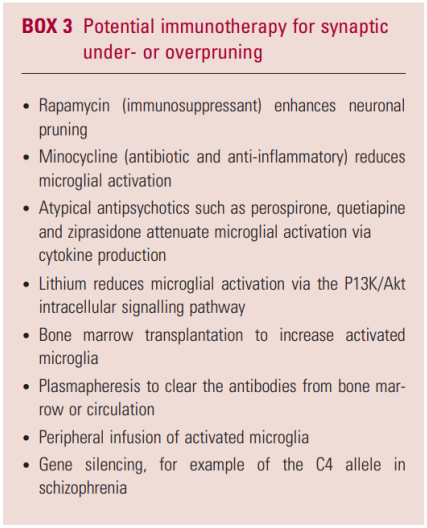
Article notes should be on separate sheets

Source Title	Circulating metabolites modulated by diet are associated with depression
Source citation (APA Format)	van der Spek, A., Stewart, I. D., Kühnel, B., Pietzner, M., Alshehri, T., Gauß, F., Hysi, P. G., MahmoudianDehkordi, S., Heinken, A., Luik, A. I., Ladwig, K.-H., Kastenmüller, G., Menni, C., Hertel, J., Ikram, M. A., de Mutsert, R., Suhre, K., Gieger, C., Strauch, K., … Amin, N. (2023). Circulating metabolites modulated by diet are associated with depression. *Molecular Psychiatry*, 1–14. https://doi.org/10.1038/s41380-023-02180-2
Original URL	https://www.nature.com/articles/s41380-023-02180-2
Source type	Scientific journal
Keywords	gut brain axis mental disorder
#Tags	#metabolites #mentalillness
Summary of key points + notes (include methodology)	As cases of depression have been increasing during the pandemic, and uncertainty remains about the exact causes and the effectiveness of current treatments, this study sought out to discover which metabolites are positively (or negatively) linked to depression and what food sources they come from to provide insight on dietary recommendations for people with depression. To study this, they analyzed various databases which had information regarding metabolites and genomes in people with depression, food sources for those metabolites, the impact of antidepressant therapies, and the gut microbiota that were correlated with the specific microbiomes. They identified strong correlations between six metabolites and depression, among which one of them was vitamin A, which showed a positive correlation (higher levels of retinol and depression). They also found out that metabolites that were previously discovered to be linked with depression and were part of the amino-acid pathway (ex. Serotonin, leucine) were very likely to be expressed due to antidepressant medication.
Research Question/Problem/	What are the different metabolites that are linked to depression and what food

Need	sources do they come from?
Important Figures	 These were the metabolites that were tested, with the stars indicating the metabolites with high correlation.
VOCAB: (w/definition)	Elucidate: Make clear Metabolome: Small molecules needed for metabolism Confounders: Affects both independent and dependent variables
Cited references to follow up on	23 (Depression and association with various compounds): https://doi.org/10.1002%2Fajmg.b.32680 47 (Depression and overdose of Vitamin A): https://doi.org/10.4088%2FJCP.10r05993 52 (Brain shrinkage w/ Vitamin A): https://doi.org/10.1177%2F1073858404263520 83 (Lecithin as a cause of depression): https://doi.org/10.1097%2F00006842-197405000-00008
Follow up Questions	Why do some metabolites have different effects on current depressive symptoms and lifetime clinical depression? How does depression cause brain damage (white matter hypersensitivity) and what long-term effects does this have on the person's health? Can any of these changes in metabolite concentrations be sensed early on, and if so, how can this be implemented to detect depression in its early stages?

Article #6 Notes: Do patterns of synaptic pruning underlie psychoses, autism, and ADHD?

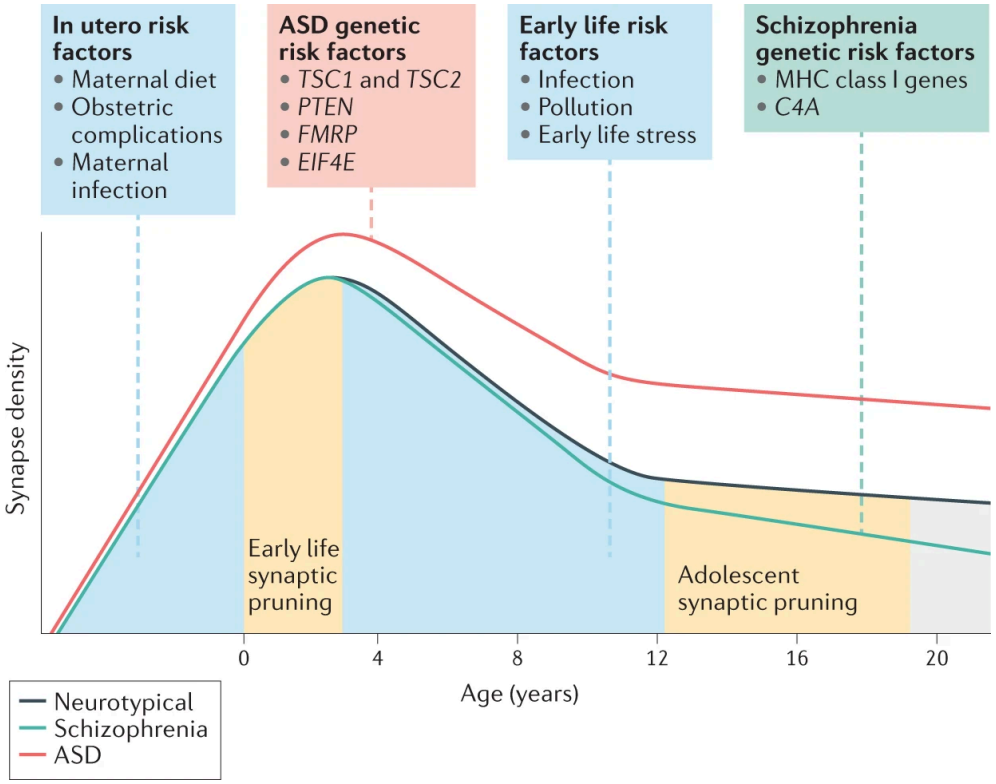
Source Title	Do patterns of synaptic pruning underlie psychoses, autism, and ADHD?
Source citation (APA Format)	Silva, P. N. de. (2018). Do patterns of synaptic pruning underlie psychoses, autism and ADHD? *BJPsych Advances*, *24*(3), 212–217. https://doi.org/10.1192/bja.2017.27
Original URL	https://www.cambridge.org/core/journals/bjpsych-advances/article/do-patterns-of-synaptic-pruning-underlie-psychoses-autism-and-adhd/10BB01A1F04C0D8EA449580DA5690144
Source type	Journal article
Keywords	synaptic pruning psychiatric conditions
#Tags	#mentaldisorder #synapticpruning #backgroundinfo
Summary of key points + notes (include methodology)	(summary) Problem: Many major psychiatric conditions have biological symptoms in early developmental stages, but many go unnoticed and are not well studied. Goal: Identifying biomarkers can improve early detection of mental illnesses and also help guide the direction of treatment. Specifically, identifying the connection between abnormal amounts of synaptic pruning and specific mental disorders can be applied to specific microglial activity enhancers and suppressors. Method: Different types of brain imaging techniques were used amongst patients with the psychiatric disorder and their healthy siblings such as PET scans, MRIs (+DTIs) to compare grey matter volume loss. Findings: There are excessive amounts of synaptic pruning in all brain regions in schizophrenia and some regions in bipolar disorder. There is not enough pruning during all phases in autism and during the childhood phase of ADHD. (key points) - Grey matter loss is associated with and can be a measure of the amount of synaptic pruning occurring in the brain. - Unwanted synapses are “tagged” with a protein marker for elimination, and astrocytes help identify these. - Microglial activity can be measured using PET scans, particularly ligand PK11195 which provides a proxy measure.

	- An allele of the C4 genes (C4A) is more likely to be present in patients with schizophrenia.
Research Question/Problem/ Need	How does the amount of synaptic pruning connect to various mental disorders and how can this information be utilized to help treat those disorders?
Important Figures	 **BOX 3** Potential immunotherapy for synaptic under- or overpruning • Rapamycin (immunosuppressant) enhances neuronal pruning • Minocycline (antibiotic and anti-inflammatory) reduces microglial activation • Atypical antipsychotics such as perospirone, quetiapine and ziprasidone attenuate microglial activation via cytokine production • Lithium reduces microglial activation via the P13K/Akt intracellular signalling pathway • Bone marrow transplantation to increase activated microglia • Plasmapheresis to clear the antibodies from bone marrow or circulation • Peripheral infusion of activated microglia • Gene silencing, for example of the C4 allele in schizophrenia Although there weren't any visuals in this article, I included this box summarizing the different types of approaches that could be used to mediate rates of synaptic pruning in patients, which could be used as a form of treatment to regulate symptoms of mental disorders.
VOCAB: (w/definition)	Prodromal: Relating to the period between first signs and full development of an illness. Phagocytosis: The process of a cell engulfing an unwanted thing to destroy it. Encephalitis (encephalitic): Inflammation of the brain. Parsimonious: Simplest, and hence, most likely to be accurate theory. Ligands: an ion or molecule that bonds with a metal atom.
Cited references to follow up on	Schizophrenia genes, gene expression and neuropathology: on the matter of their convergence. (https://www.nature.com/articles/4001558) Mapping Continued Brain Growth and Gray Matter Density Reduction in Dorsal Frontal Cortex: Inverse Relationships during Postadolescent Brain Maturation (https://www.jneurosci.org/content/21/22/8819)
Follow up Questions	Is there a specific (quantitative?) criteria to determine if a synapse should be 'tagged' for elimination? If so, what is it and how general is it? What are the other major roles of the microglia? What are the pros and cons of using grey matter volume loss vs the ligand PK11195 as proxy measures for synaptic pruning? What are the other implications based on amount of grey matter volume in the brain? What are the other biological (or physical?) similarities between autism and ADHD?

Article #7 Notes: Mechanisms governing activity-dependent synaptic pruning in the developing mammalian CNS

Source Title	Mechanisms governing activity-dependent synaptic pruning in the developing mammalian CNS
Source citation (APA Format)	Faust, T. E., Gunner, G., & Schafer, D. P. (2021). Mechanisms governing activity-dependent synaptic pruning in the developing mammalian CNS. *Nature Reviews Neuroscience*, *22*(11), Article 11. https://doi.org/10.1038/s41583-021-00507-y
Original URL	https://www.nature.com/articles/s41583-021-00507-y
Source type	Journal article
Keywords	synaptic pruning microglia neurons astrocyte neural activity
#Tags	#backgroundinfo #synapticpruning #neurologicalprocesses
Summary of key points + notes (include methodology)	(summary) This article explained the various processes that lead to synaptic pruning, mainly spontaneous vs. experience-driven neural activity induced pruning, immune-function induced pruning, and apoptosis, as well as the different cell types that performed the action (microglia, astrocytes, etc), and the different factors that may have triggered the action (neural activity, proteins, genes, environmental factors). Finally, they described how irregular patterns in synaptic pruning may be the cause of neurological disorders such as ASD and schizophrenia. (key points) - Activity-induced pruning can happen at different stages of life based on what brain region it's taking place in, what subtype of neuron it is, and when it's taking place (which stage). - Spontaneous neural activity regulates S.P. during development of the cerebellum. - Cadherin-catenin complexes help stabilize synapses. (may be interesting if there are foods/bacterias that are known to increase amount of this) - NP1 and NP2 regulated synapse plasticity? - Microglial S.P. occurs in visual cortex, retinogeniculate system, auditory brainstem, auditory cortex, primary and secondary somatosensory

	cortices, and nucleus accumbens. (where to focus brain imaging?)
	- Microglia do not only use phagocytosis to prune synapses, they also weaken climbing fiber synapses to increase chance of "winning" ones.
	- Astrocytes also perform activity-induced synaptic pruning through phagocytosis.
	  - There are more astrocytes, so they end up doing more pruning overall, but microglia are more specialized and faster at degradation.
	- ASD brains have not enough S.P., schizophrenia has too much.
	  - The genes related to pruning are C1QA, C3, and C3R.
	  - Altered mRNA translation may cause autophagy which may be the cause of irregular S.P.
	- Glial cells perform pruning of axons and sensory endings in Drosophila.

Research Question/Problem/ Need	What are the different processes that lead to synaptic pruning and how are they caused? What are the implications of irregular synaptic pruning (specifically in neurological disorders)?
Important Figures	 Autism Spectrum Disorder has significant higher synaptic density than neurotypical brains, while Schizophrenic brains have notably lower synaptic density. This connects to the conclusion that ASD often has under pruning and schizophrenia has over pruning.
VOCAB: (w/definition)	Spontaneous neural activity: Neural activity caused without a stimulus. Experience-driven neural activity: Neural activity caused by an external

	factor/stimulus. Cleave: split or sever Endogenous: having an internal cause/origin Synaptogenesis: The process of forming and maintaining a synapse. Autophagy: The process of degrading proteins and organelles.
Cited references to follow up on	158 (genes associated with synaptic pruning): https://pubmed.ncbi.nlm.nih.gov/25180572/ 234 (glial synaptic pruning): https://pubmed.ncbi.nlm.nih.gov/18172512/
Follow up Questions	Are there barriers that could cause miscommunication between neuronal activity (use of synapse) and the cells performing synaptic pruning? (ex. accidentally get rid of a necessary synapse) What are (somatic) climbing fiber synapses and what is their significance? How many different types of synapses are there and how are they different? - What are Purjinke Cells and their significance? - Difference between glutamatergic and GABAergic synapses? Would diet be considered spontaneous or experience-driven neural activity? What is the complement cascade? What is it most well known for? What is immunofluorescence microscopy and how does it show S.P.? - Positron emission tomography? What is the difference between spine and synaptic pruning? What are T helper 17 cells and their relationship with ASD?

Article #8 Notes: The translational genetics of ADHD and related phenotypes in model organisms

Source Title	The translational genetics of ADHD and related phenotypes in model organisms
Source citation (APA Format)	Cabana-Domínguez, J., Antón-Galindo, E., Fernàndez-Castillo, N., Singgih, E. L., O'Leary, A., Norton, W. H., Strekalova, T., Schenck, A., Reif, A., Lesch, K.-P., Slattery, D., & Cormand, B. (2023). The translational genetics of ADHD and related phenotypes in model organisms. *Neuroscience & Biobehavioral Reviews*, *144*, 104949. https://doi.org/10.1016/j.neubiorev.2022.104949
Original URL	https://www.sciencedirect.com/science/article/pii/S0149763422004389?via%3Dihub
Source type	Scientific review article
Keywords	ADHD animal models rodents zebrafish fruit fly genetics epigenetics
#Tags	#modelorganism #adhd #behavioraltests
Summary of key points + notes (include methodology)	(summary) Problem: The specific molecular explanation of psychological disorders, such as ADHD, are not well known due to their complex causes. Goal: The goal of this paper is to analyze various studies that used different types of model organisms to gain further information about the biology of ADHD, in particular, the genetics and epigenetics related to it. Method: Multiple behavioral tests, gene editing, and exposure to different toxins and drugs were performed on mus musculus, drosophila melanogaster, and danio rerio to identify ADHD behaviors and ADHD-related genes specific to each organism, as well as chemical or environmental factors that increased symptoms/likelihood of ADHD. Findings: Although there are most known symptoms and linked genes to mice models of ADHD, there are also many significant tests and genes known for ADHD models of danio rerio and drosophila. There are also studies that show a link between environmental factors and ADHD through epigenetics, but more research is required for direct causations. (key points)

	- most of the genes that are correlated with ADHD are targeting genes involved in dopamine transmission (reward pathway), an important neurotransmitter in ADHD
	- treatment for ADHD symptoms includes methylphenidate, amphetamine, and atomoxetine (maybe use to counter-check effects of experimental groups with the induced ADHD symptoms?)
	- There are more strains that are known to cause hyperactivity compared to the other 2 ADHD symptom types as it is easier to identify hyperactivity (be aware of this 'bias' when looking at databases)
	- ADHD and ASD are both early-onset neurodevelopmental disorders with high comorbidity and genetic overlap.
	- ADHD can cause verbal and visuo-spacial working memory deficits
	- Zebrafish are a common model organism for developmental biology due to their quick development and transparency as embryos.
	  - Chemical compounds can also be exposed through immersion and not direct injection.
	- Zebrafish larvae start moving consistently after 5 days, and adult movement pattern forms after ~1 month.
	  - Video Tracking can be used to find specific measurements.
	- HYPERACTIVITY IN ZEBRAFISH: "increase in distance swum, heightened acceleration during swim bouts"
	  - also two choice serial reaction time task
	- IMPULSIVITY IN ZEBRAFISH: The 5-CSRTT test can be performed on the zebrafish, which tests their patience of hitting LED lights for food as a measure of impulsivity.
	- INATTENTION IN ZEBRAFISH:
	  - Orientation - male zebrafish permitted to eavesdrop based on different stimuli?
	  - Sustained attention - object recognition test, measuring time spent interacting with object on video screen
	- Main ADHD candidate genes are adhesion G protein-coupled receptor L3.1 (lphn3.1/adgrl3.1) and period 1b (PER1B IS MORE WELL STUDIED) (ALSO IN TABLE BELOW)
	  - both affect ADHD-like behavior through dopamine neurotransmission
	- Zebrafish exposed to polychlorinated biphenyls (PCBs) or perfluorooctane sulphonate have been linked to increased ADHD (also in humans)
	  - "decreased response to visual startle stimulus that could be a measure of attention"
	- Too much acetaminophen use during pregnancy may increase likelihood of child showing ADHD symptoms
	- JUST INTERESTING: Irregular circadian rhythms are often the cause of many psychiatric disorders, including ADHD
	- HYPERACTIVITY IN FRUIT FLIES: data regarding locomotor activity (using Drosophila Activity Monitoring) and sleep help analyze this
	  - Also grooming?
	- INATTENTION IN FRUIT FLIES: vision-based behavioral paradigms

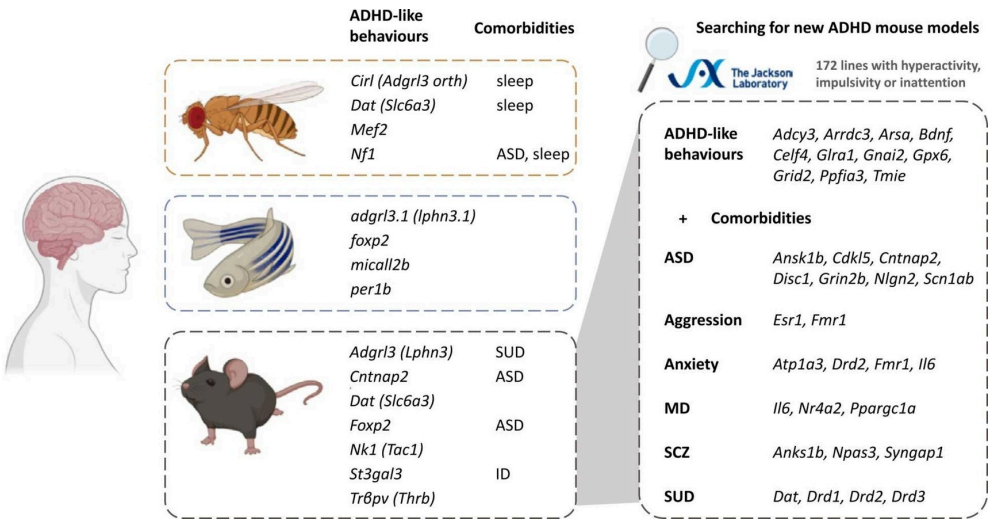
	- IMPULSIVITY IN FRUIT FLIES: courtship disinhibition(?) - Main ADHD candidate genes are SLC6A3 or DAT. - HABITUATION is related to inattention in ADHD, as it is mainly caused by the inability to separate already known and new information - Exposure to toxins such as BPA may contribute to ADHD - shown through fruit flies
Research Question/Problem/ Need	How can different model organisms be used to explain the underlying biological mechanisms that cause ADHD in current and future research endeavors?
Important Figures	 The leftmost list column shows genes that result in ADHD-like behaviors for each model organism. The second column shows comorbid (occurring together) disorders/symptoms. Finally, the third column shows additional genes/models that result in at least one of the three main ADHD symptom clusters, along with the ones that show additional comorbidities below.

Table 1
Summary of tests performed to study ADHD-related phenotypes and comorbid disorders in rodents, zebrafish and fruit flies.

		Tests used		
Disorder	Traits	Rodents	Zebrafish	Fruit fly
ADHD-related phenotypes	Hyperactivity	Open-field test	Locomotive assays	Activity monitoring, capillary feeder (CAFE) assay, open-field assay
	Impulsivity	5-choice serial reaction time task, Go/NoGo, continuous performance test, delay discounting, variable delay to signal	Locomotion (swimming) monitoring, 5-choice serial reaction time task	Courtship disinhibition assay
	Inattention	5-choice serial reaction time task, continuous performance test, Go/NoGo, variable delay to signal	5-choice serial reaction time task, object recognition task, social attention paradigm	Tethered flight paradigms, Buridan's paradigms, optomotor maze
Autism spectrum disorder	Impaired social behavior and communication, stereotypic behavior, cognitive rigidity	Three-chambered social approach, partition test, nesting behavior, ultrasonic vocalizations, open-field test, Morris water maze, T/Y maze	Shoaling assays, Y maze, interaction with conspecifics, visually-mediated social preference test	Habituation learning assay, grooming, social behavior assay, courtship song assay, Y-maze
Aggressive behavior	Aggression, social dominance	Resident intruder test, Dyadic social interaction test, social dominance test	Dyadic fight test, interaction with mirror image assay	Dyadic fight test
Anxiety	Anxiety-related behaviors, thigmotaxis	Open field, elevated plus maze, elevated zero maze, light dark box, stress-induced hyperthermia, vogel test, defensive burying, four plate test	Active avoidance conditioning	Open-field assay
Major depression	Anhedonia, despair	Sucrose preference test, Porsolt forced swim test, Tail-suspension test, progressive ratio, female urine sniffing test		Learned helplessness paradigm
Schizophrenia	Impaired sensorimotor gating	Prepulse inhibition test	Prepulse inhibition test	Larval prepulse inhibition test
Substance use disorders	Reward	Drug-induced locomotor activity or conditioned place preference	Place preference paradigm	Appetitive taste memory test, associative learning assay

This table provides a clear overview of how the symptoms of the three different types of ADHD can be tested in each of the three model organisms, as well some other comorbid disorders.

VOCAB: (w/definition)

SNP: single nucleotide polymorphism (whole genetic sequence is same except for 1 base)
Etiology: The cause(s) of a disease or condition
Paradigm: A typical example or model
Motor impulsivity: (in zebrafish with ADHD) Sharp bouts of acceleration followed by periods of inactivity
Habituation: distinguishes information that is new vs already known

Cited references to follow up on

Demontis et al., 2019b (new 12 independent loci regarding "underlying biology of ADHD): https://www.nature.com/articles/s41588-018-0269-7
Lee et al., 2019 (genetic studies showing "shared heritability and genetic overlap" between ADHD and ASD): https://doi.org/10.1016/j.cell.2019.11.020
Albadri et al., 2017 (study on tools for zebrafish that use light to observe neural activity): https://link.springer.com/chapter/10.1007/978-3-319-60192-2_4
Forster et al., 2018 (also study on light to observe zebrafish neural activity):
Yang et al., 2018 (most recent article that identified increase in swimming distance in ADHD zebrafish): https://doi.org/10.1016/j.ymeth.2018.08.012
Spulber et al., 2014 (most recent article that identified motor impulsivity in ADHD zebrafish): https://doi.org/10.1371/journal.pone.0094227
Huang et al., 2015 (lots of per1b linked to ADHD in zebrafish info): https://doi.org/10.1523/JNEUROSCI.2551-14.2015

Follow up Questions

~~What is the difference between knockout and knockdown genes?~~
How does inflammation in the brain affect cognitive processes? What are the external symptoms?

	What is the difference between unconditioned and conditioned behaviors? How overlapping are the symptoms of ADHD and a dysfunctional circadian rhythm (especially in zebrafish)? - Has the “fixing" of circadian rhythms been shown to directly improve ADHD? Is it possible to purchase per1b mutant zebrafish?

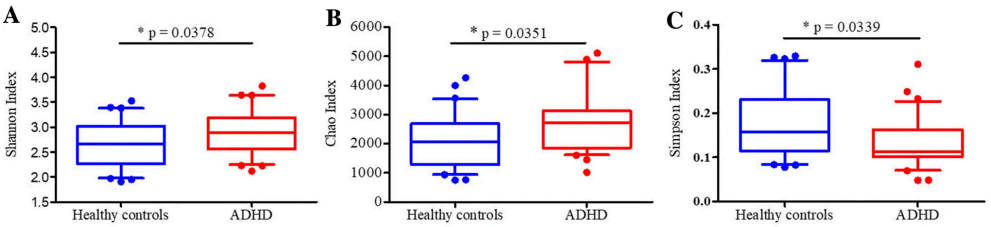
Article #9 Notes: Gut microbiota and dietary patterns in children with attention-deficit/hyperactivity disorder

Source Title	Gut microbiota and dietary patterns in children with attention-deficit/hyperactivity disorder
Source citation (APA Format)	Wang, L.-J., Yang, C.-Y., Chou, W.-J., Lee, M.-J., Chou, M.-C., Kuo, H.-C., Yeh, Y.-M., Lee, S.-Y., Huang, L.-H., & Li, S.-C. (2020). Gut microbiota and dietary patterns in children with attention-deficit/hyperactivity disorder. *European Child & Adolescent Psychiatry*, *29*(3), 287–297. https://doi.org/10.1007/s00787-019-01352-2
Original URL	https://link.springer.com/article/10.1007/s00787-019-01352-2
Source type	Scientific article
Keywords	ADHD, Gut-Brain Axis, 16S rRNA sequencing, Microbiome, Biomarker
#Tags	Bacteria, ADHD, Procedure/Method
Summary of key points + notes (include methodology)	(summary) Problem: ADHD is a common neurodevelopmental disorder that affects various aspects of life for a large number of people, but despite its commonality, the pathophysiology is not clearly known, specifically how it may be affected by diet. Goal: To determine if imbalanced gut microbiomes play a role in the biological causes correlated with ADHD. Method: Collect fecal samples from adolescent ADHD patients, analyze using 16S rRNA amplicon sequencing, and compare with clinical diagnoses and dietary patterns of ADHD. Findings: Although the actual amount of bacteria diversity between ADHD patients and healthy controls is not too varied (ADHD has higher diversity), ADHD patients have different abundances of some specific bacteria. A few types of bacteria were linked to differences in ADHD symptoms as well. (key points) - At phylum level, ADHD group had higher relative abundance of *Fusobacteria*, *Actinobacteria**, and *Proteobacteria** (*non-significant) - At genus level, *Fusobacterium* had a greater relative abundance in ADHD group. - At species level, relative abundance of *Bacteroides uniformis, Bacteroides ovatus,* and *Sutterella stercoricanis* were higher in ADHD group than HC.

<table>
<tr><td></td><td>

Also were correlated with ADHD symptoms and dietary patterns.
B. uniformis and B. ovatus were also more abundant in ADHD patients in Aarts et al. study.

It is possible that bacterial abundance in ADHD patients may be affected by different cultures, age groups, socio-environment status, etc.
Also unclear if difference in bacterial diversity/abundance is a cause of ADHD, or if ADHD causes the changes.

</td></tr>
<tr><td>Research Question/Problem/ Need</td><td>How is bacteria in the gut microbiome correlated to the pathophysiology of ADHD?</td></tr>
<tr><td>Important Figures</td><td>


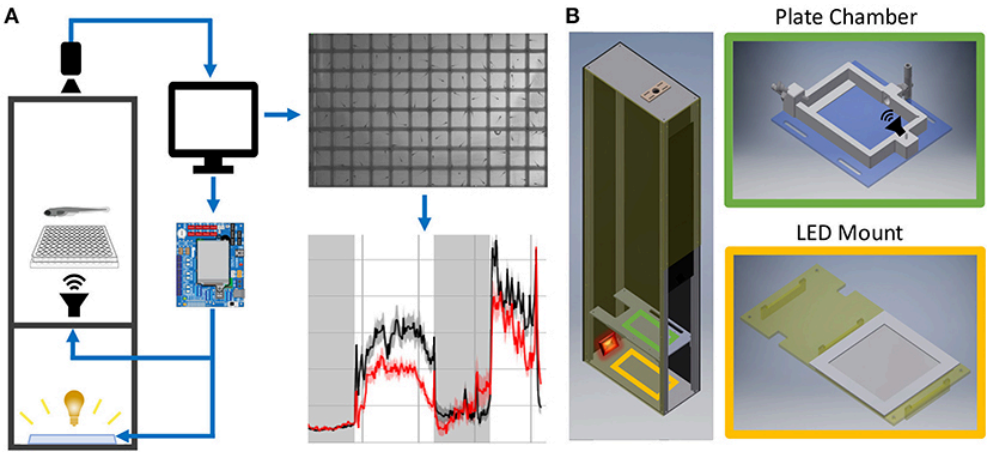
(Fig 1a, b, c) Shannon index and Chao index both display diversity of bacteria, so a and b are expressing that there is a higher number of bacterial species in the group with ADHD. The Simpson index works oppositely number-wise, as 0 represents infinite diversity and 1 represents no diversity. So it follows the pattern that there is a greater abundance of bacterial species in ADHD.
<table>
<tr><th>Genera</th><th>ADHD</th><th>Healthy controls</th><th>p value[a]</th></tr>
<tr><td>Bacteroides</td><td>59.78 (48.16–67.46)</td><td>61.72 (50.91–66.43)</td><td>0.717</td></tr>
<tr><td>Prevotella</td><td>0.02 (0.00–1.16)</td><td>0.06 (0.01–7.11)</td><td>0.116</td></tr>
<tr><td>Parabacteroides</td><td>3.83 (1.71–4.59)</td><td>3.46 (1.77–6.73)</td><td>0.865</td></tr>
<tr><td>Phascolarctobacterium</td><td>1.88 (0.32–3.98)</td><td>1.82 (0.75–4.96)</td><td>0.734</td></tr>
<tr><td>Escherichia Shigella</td><td>0.68 (0.11–5.24)</td><td>1.82 (0.33–3.35)</td><td>0.460</td></tr>
<tr><td>Alistipes</td><td>4.32 (0.02–7.37)</td><td>0.68 (0.21–2.49)</td><td>0.437</td></tr>
<tr><td>Veillonella</td><td>0.54 (0.06–2.04)</td><td>0.39 (0.05–1.84)</td><td>0.620</td></tr>
<tr><td>Sutterella</td><td>0.34 (0.01–2.42)</td><td>0.28 (0.00–3.90)</td><td>0.858</td></tr>
<tr><td>Fusobacterium</td><td>0.28 (0.02–3.28)</td><td>0.02 (0.00–0.45)</td><td>0.041*</td></tr>
<tr><td>Akkermansia</td><td>0.01 (0.00–1.52)</td><td>0.00 (0.00–0.34)</td><td>0.304</td></tr>
</table>
(Table 3) This table shows the mean relative abundance of different bacterial genera in in ADHD group and HC (%s). However, it should be noted that the only bacteria genus with a significant p-value is the Fusobacterium, which was shown to be much more abundant in people with ADHD.
</td></tr>
<tr><td>VOCAB: (w/definition)</td><td>
Pathophysiology: The study of how a disease or condition affects the patient both physically and biologically.
Phylogenetic: Study of evolutionary relationships between organisms
Alpha diversity: Abundance/variety of species within a community (local scale)
- Beta diversity: …comparative amongst different communities
OTU: A collection of 16S rRNA sequences that have a certain percentage of sequence divergence.
Phyla: Group/rank of classification between kingdom and class.
- Genera: More specific rank of classification between family & species.
</td></tr>
<tr><td>Cited references to follow up on</td><td>28 (previous study on similar topic of using 16S rRNA sequencing to identify</td></tr>
</table>

	bacteria present in ADHD patients): http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=28863139 25 (study about how 16S rRNA can be used to identify bacterial taxa in given sample): http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=24808895
Follow up Questions	How are the different indices for diversity analysis specifically calculated? Is *Fusobacterium* present in any common foods? Is it dangerous at all to the human body (what biosafety level is it at)? (more of an interpretive question-maybe ask author?) Is it more likely that the differences in bacterial abundance was caused by or a cause of ADHD?

Article #10 Notes: A Customizable Low-Cost System for Massively Parallel Zebrafish Behavioral Phenotyping

Source Title	A Customizable Low-Cost System for Massively Parallel Zebrafish Behavioral Phenotyping
Source citation (APA Format)	Joo, W., Vivian, M. D., Graham, B. J., Soucy, E. R., & Thyme, S. B. (2021). A Customizable Low-Cost System for Massively Parallel Zebrafish Behavioral Phenotyping. *Frontiers in Behavioral Neuroscience*, *14*. https://www.frontiersin.org/articles/10.3389/fnbeh.2020.606900
Original URL	https://www.frontiersin.org/articles/10.3389/fnbeh.2020.606900/full
Source type	Science journal article
Keywords	zebrafish, high-throughput screens, automated behavior, prepulse inhibition, neuropsychiatric disease, high-speed tracking, DanioVision, ZebraBox
#Tags	#method #procedure #observation
Summary of key points + notes (include methodology)	(summary) Problem: Zebrafish are increasing in population as a model organism for their efficient growth and easily observable structure, but many methods currently created are costly and too individualized. Goal: The goal was to create a zebrafish behavioral testing setup that was not very costly, yet was also accurate, efficient, and could be adapted for different standards. Method: The setup created and tested in this study consisted of a LED panel and mini projector at the bottom to generate visual stimuli, a surface transducer for acoustic stimuli, a camera to track motion, and a computer to collect and analyze data. Findings: The setup was able to accurately take in and analyze large inputs of data with minimal materials and relatively low cost. When put to the test, it was identified that the density of zebrafish in petri dishes did not affect their behavior, but wild zebrafish had vast ranges of behavior. (key points) - zebrafish at larva stage express diverse behaviors in 96-well plate format - DanioVision and ZebraBox are current commercial zebrafish observation systems, but they are costly and individualized (only specific types of stimuli)

	- custom LABVIEW software (Python based) on computer analyzes data
	  - each analysis run takes between 1.5 and 3.5 hrs
	- Acoustic, visual, and thermal stimuli available (can even be modified for additional parameters)
	- Larvae were grown in 150x55 mm petri dishes with standard methylene blue water, with density of <150 fish per plate, at 28°C, and a 14h/10h light/dark cycle.
	  - Behavioral experiments conducted on light/dark cycle
	  - Dead material and debris were removed twice before 4 days post-fertilization, and behavioral tests were conducted 4-7 days post-fertilization.
	- Zebrafish were sealed in oxygen permeable film to prevent water evaporation during multi-day experiments.
	  - Typically, larvae were loaded into observation boxes on afternoon of 4 days post-fertilization and data analyses started at 11 pm.
	- Strictly standardized mean difference (SSMD) values were calculated to estimate behavioral differences across all parameters, with 0 indicating no effect (test to identify difference between ADHD and healthy controls?)
	- Mini-projector can test optomotor response

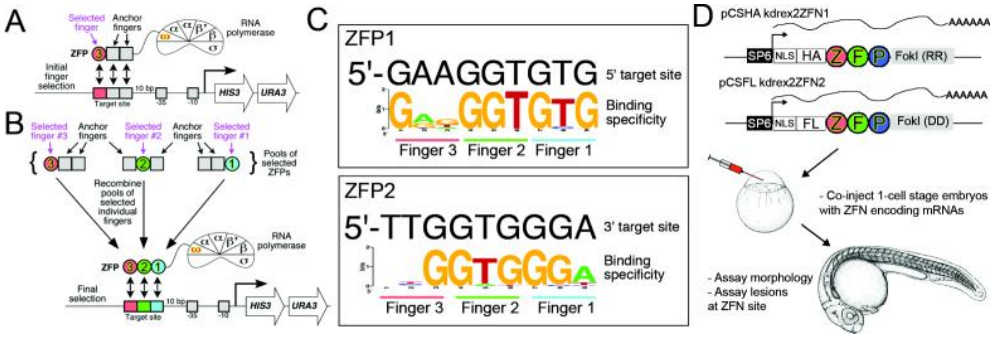
Research Question/Problem/ Need	How can an efficient and cost-effective testing set-up be made to observe zebrafish behaviors?
Important Figures	 This figure (Figure 1) shows a general overview of how the testing box is set up with the 96-well plate, surface transducer, and LED panel, with a very simple diagram of how the computer uses the LABVIEW system to analyze data.
VOCAB: (w/definition)	Phenotyping: Determining or predicting the phenotype of an organism Conserved signaling pathways: Signaling pathways w/ similar function present in different organisms Transducer: Electronic device that transforms energy from one form to another Modular: Constructed around a basic formula, but can also be modified for different functions Latency: Delay between user initiation and event actually occurring

Cited references to follow up on	Thyme et al., 2019 (previous observation system design): https://pubmed.ncbi.nlm.nih.gov/30929901 Randlett et al., 2019 (zebrafish response to visual stimuli): https://pubmed.ncbi.nlm.nih.gov/30955936 Brown et al., 2012 (genetic diversity in wild-type zebrafish): https://pubmed.ncbi.nlm.nih.gov/22203992/
Follow up Questions	What are the benefits of the commercial systems that are not present in the system specified in this study? Does accuracy increase when less fish are being recorded or not necessarily? What is the difference between C-bends and O-bends? Is there a minimum number of zebrafish in one petri dish to ensure they are able to socialize enough? How are zebrafish with and without normal swim bladder morphology different in terms of their behavior? Why is this important to differentiate in this system? Is 14h/10h the optimal light/dark cycle? How is this maintained?

Article #11 Notes: Targeted gene inactivation in zebrafish using engineered zinc-finger nucleases

Source Title	Targeted gene inactivation in zebrafish using engineered zinc-finger nucleases
Source citation (APA Format)	Meng, X., Noyes, M. B., Zhu, L. (Julie), Lawson, N. D., & Wolfe, S. A. (2008). Targeted gene inactivation in zebrafish using engineered zinc finger nucleases. *Nature Biotechnology*, *26*(6), 695–701. https://doi.org/10.1038/nbt1398
Original URL	https://pubmed.ncbi.nlm.nih.gov/18500337/
Source type	Scientific article
Keywords	mutagenesis, zinc finger nucleases, zebrafish, gene editing
#Tags	#method #mutations

Summary of key points + notes (include metho\dology)	(summary)
	Problem: Directly editing a specific gene in vertebrae organisms is not easily doable.
	Goal: The goal is to use zinc finger nucleases to make changes in specific genes in model organisms, particularly zebrafish.
	Method: Engineer ZFNs that can recognize common (ortholog) genes in zebrafish, then co-inject them into zebrafish embryos.
	Findings: The ZFNs can perform mutations at targeted sites and they can also be passed down through the germline, and they cause mild mutagenesis to the genome overall.
	
	(key points)
	- Mutations can occur through ZFNs when non-homologous end joining is performed after ZFN cleavage
	- mRNA injections are performed into stage 1-cell stage embryos, and they will still transmit through following generations
	- observation for injected embryos is needed 24 hrs after injection
	  - check for monsters
	- embryos injected with ZFN in this study showed lesions at specific target site and only mild mutagenesis to genome
	  - but there is evidence supporting possibility of other alleles being affected
	- degree of penetrance of ZFN mutation was consistent through breeding,

	indicating that the mutations are stable within germline - Embryos were separated (normal vs “monster”) 26 hpf - Genome sequences
Research Question/Problem/ Need	What is the most efficient and effective way to mutate specific genes in the zebrafish genome?
Important Figures	 This figure shows the process of ZFNs reacting with the genetic sequences to create a mutation. It specifically shows how the ZFN binds to the three base pairs in the DNA. Additionally, D in particular shows the specific process of inserting the ZFNs in regard to the zebrafish.
VOCAB: (w/definition)	Ortholog: Genes in different species that evolved from common ancestral gene Chimeric: containing multiple sets of DNA Dimerization: Multiple proteins bind to create a functional unit Heterozygosity: two different alleles at locus Mosaic: two or more cell populations with different genotypes in one organism Mutagenic: causing permanent chance in organism’s genes Stringency: How precisely DNA/RNA strands bind to each other based on their similar features Epitope: Part of antigen where antibody attaches Denature: Unfolding/breaking apart protein from its 3D structure Propensity: Tending to behave in a certain way
Cited references to follow up on	12 (ZFPs can be engineered to recognize a wide variety of target sequences): https://pubmed.ncbi.nlm.nih.gov/17406455/ 18 (imaging of wild type and Tg embryos): https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1458922/ 27 (standard method of microinjection of ZFN in embryos): https://pubmed.ncbi.nlm.nih.gov/10503230 21 (toxicity of ZFNs): https://pubmed.ncbi.nlm.nih.gov/17603476
Follow up Questions	What are the chances of ZFN attaching to the correct genetic sequence, but in the wrong locus/location, causing mutations in other alleles? **Why is there a minimum and maximum amount for ZFP chains? (particularly questioning the maximum, since isn’t more specific the better?) **from video**

	How does non-homologous end joining work? (I assume it's like a chemical(?) reaction since it is error-prone) What is the significance of nuclear localization signals, ~~epitope tags~~, and FokI cleavage domain variants in ZFPs? How is Solexa sequencing technology accessed? **How can non-morphologically normal (monster) zebrafish be identified?** Why was there such a high percentage of these "monster" zebrafish post-injection and why did only a small group of injected embryos reach adulthood? **Why is it significant to look for purines (and even more specifically, guanines) in ZFP sites?** What is the randomized aspect of the ZFNs and how are they still able to bind to the target site? How can ZFNs be harmful to organisms? What are the worst possible symptoms?

Patent #1 Notes: Method and system for diagnosis of neuropsychiatric disorders including attention deficit hyperactivity disorder (adhd), autism, and schizophrenia

Source Title	Method and system for diagnosis of neuropsychiatric disorders including attention deficit hyperactivity disorder (adhd), autism, and schizophrenia
Source citation (APA Format)	Pettegrew, J., & Panchalingam, K. (2010, January 14). Method and system for diagnosis of neuropsychiatric disorders including attention deficit hyperactivity disorder (adhd), autism, and schizophrenia.
Original URL	https://patents.google.com/patent/US20100010336A1/en?q=(synaptic+pruning)&oq=synaptic+pruning
Source type	Patent
Keywords	ADHD, autism, schizophrenia, neuropsychiatric disorders, biomarkers, neurodevelopment, magnetic resonance spectroscopy
#Tags	#neurodevelopmentalDisorderDetection #otherNeurologicalDisorders
Summary of key points + notes (include methodology)	(summary) This invention describes a method and system for diagnosing and treating neuropsychiatric disorders using phosphorus magnetic resonance spectroscopic imaging (31P MRSI). The invention focuses on two main applications: Diagnosing Chronic Alcoholism: The method examines molecular alterations in the brain, including: Membrane phospholipid and high-energy phosphate metabolism, Synaptic transport vesicles, Phosphorylated proteins, Metabolites with N-acetyl moieties and gangliosides. These alterations are measured using 31P MRSI and compared between individuals with chronic alcoholism (both cognitively impaired and unimpaired) and healthy controls. The presence of specific molecular changes can be used to diagnose chronic alcoholism and potentially distinguish between cognitively impaired and unimpaired subgroups. Treating Depression: The invention proposes using acetyl-L-carnitine (ALCAR) to treat depression. Studies show that ALCAR treatment in depressed patients leads to: Normalization of PME(s-Tc) levels in the prefrontal region (brain area associated with mood regulation) and elevation of PCr levels in various brain regions. These changes are associated with clinical improvement in depression symptoms. ALCAR is proposed as a potential treatment for depression due to its effects on brain energy metabolism, membrane structure/function, and neurotrophic factors.

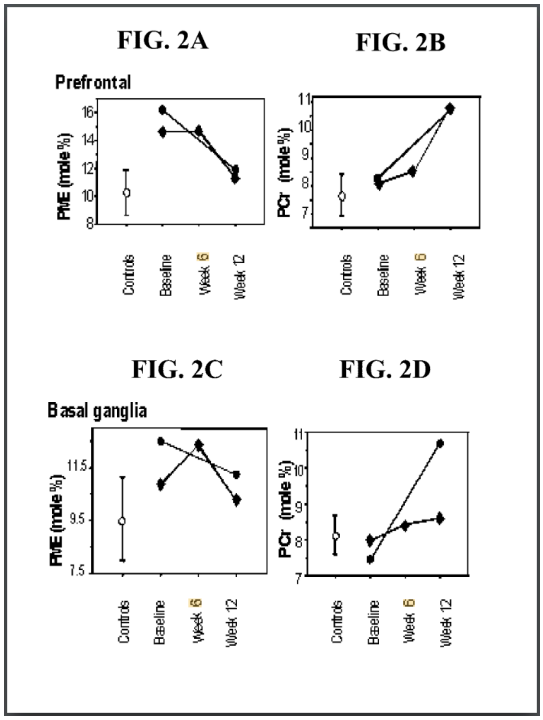
	(key points) The invention uses 31P MRSI to identify molecular changes in the brain associated with chronic alcoholism and depression. For chronic alcoholism, the invention offers a potential method for diagnosing the disorder and distinguishing between cognitively impaired and unimpaired subgroups. For depression, the invention proposes ALCAR as a treatment option based on its ability to normalize brain metabolite levels and improve symptoms. Potential Benefits: ● Improved diagnosis and treatment of chronic alcoholism and depression. ● Development of new therapeutic strategies based on the identified molecular changes. ● Personalized medicine approaches based on individual brain chemistry. Future Directions: Further research is needed to validate the diagnostic accuracy of the proposed method for chronic alcoholism. Clinical trials are necessary to confirm the efficacy and safety of ALCAR treatment for depression. Investigating the underlying mechanisms of action for both diagnostic and therapeutic applications would provide valuable insights for future development.
Research Question/Problem/ Need	Can 31P MRSI detect brain chemistry changes to diagnose and treat chronic alcoholism and depression?
Important Figures	 The figure includes four panels: Fig. 2A: Shows the levels of PME in the prefrontal cortex, a brain region involved in mood regulation and executive function.

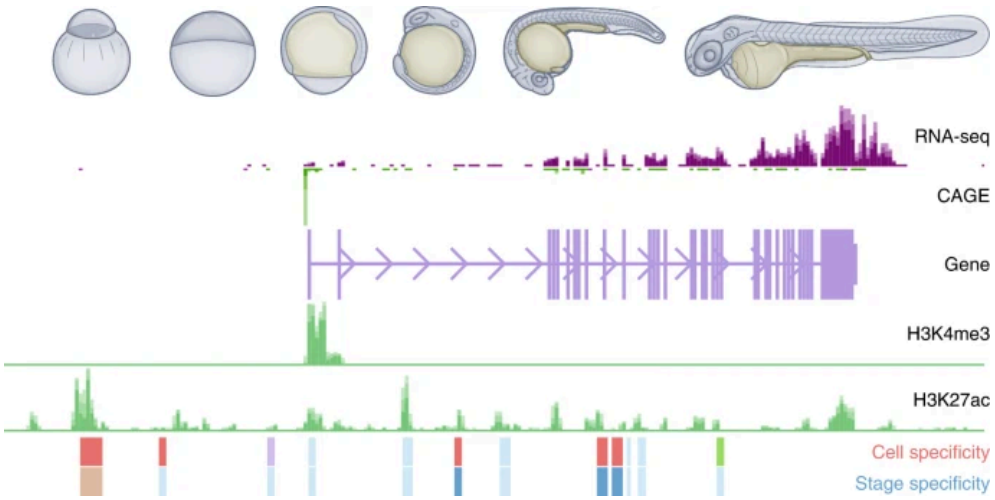
	Fig. 2B: Shows the levels of PME in the basal ganglia, a group of brain structures involved in movement and learning. Fig. 2C: Shows the levels of PCr in the prefrontal cortex. Fig. 2D: Shows the levels of PCr in the basal ganglia. Key findings: PME: In the prefrontal cortex (Fig. 2A), PME levels are higher in both CA-UI and CA-CI groups compared to controls. This suggests that chronic alcoholism, regardless of cognitive impairment, leads to changes in membrane phospholipid metabolism in the prefrontal cortex. In the basal ganglia (Fig. 2B), PME levels are lower in the CA-CI group compared to controls and CA-UI. This suggests that cognitive impairment in chronic alcoholism may be associated with specific changes in basal ganglia metabolism. PCr: In both the prefrontal cortex (Fig. 2C) and basal ganglia (Fig. 2D), PCr levels are lower in the depression group compared to controls. This suggests that depression is associated with decreased energy metabolism in these brain regions. Overall, the figure suggests that 31P MRSI can detect brain chemistry changes associated with chronic alcoholism and depression. These changes may have potential diagnostic and treatment implications.
VOCAB: (w/definition)	Phosphorus magnetic resonance spectroscopic imaging (31P MRSI): A technique used to study brain chemistry by measuring phosphorus metabolites. (Synonyms: P-MRS, phosphorus MRI) Phosphomethyl ester (PME): A metabolite involved in membrane phospholipid metabolism. (Synonyms: PME(s-Tc)) Phosphocreatine (PCr): A high-energy phosphate metabolite that provides energy for brain cells. (Synonyms: creatine phosphate)
Cited references to follow up on	Aberg-Wistedt A, Ross S B, Jostell K G & Sjoqvist B. A double-blind study of a 5-HT uptake inhibitor in endogenous depression. Acta Psychiatr Scand 66:66-82, 1982. Aitchison J. The Statistical Analysis of Compositional Data, Chapter 7, London: Chapman and Hall, 1986, Alexopoulos G S, Meyers B S, Young R C, Kakuma T, Feder M, Einhorn A & Rosendahl E. Recovery in geriatric depression. Arch Gen Psychiatry 53:305-312, 1996. Altshuler L L, Post R M, Leverich G S, Mikalauskas K, Rosoff A and Ackerman L (1995) Antidepressant-induced mania and cycle acceleration: A controversy revisited[see comment]. Am. J. Psychiatry 152, 1130-1138.
Follow up Questions	How accurate is 31P MRSI in identifying individuals with chronic alcoholism, both cognitively impaired and unimpaired, compared to other diagnostic methods? How does ALCAR treatment normalize brain metabolite levels and improve depression symptoms? Are there specific molecular pathways involved? What are the long-term safety and efficacy of ALCAR treatment for depression,

	and how does it compare to other treatment options?

*generated by ChatGPT

Article #12 Notes: Decoding the zebrafish genome

Source Title	Decoding the zebrafish genome
Source citation (APA Format)	Lawson, N. D. (2022). Decoding the zebrafish genome. *Nature Genetics*, *54*(7), Article 7. https://doi.org/10.1038/s41588-022-01080-5
Original URL	https://www.nature.com/articles/s41588-022-01080-5
Source type	Scientific journal (Nature) News Article
Keywords	zebrafish, genome, promoter
#Tags	#zebrafish #genetics #background
Summary of key points + notes (include methodology)	(summary) Problem: The zebrafish genome, especially the non-coding sequence, is not well known, even though it makes up a large portion of genes. Goal: To be able to map out the zebrafish genome and analyze the importance of non-coding genes. Method: The DANIO-CODE consortium and its affiliated researchers used various assays that had been used before with the human genome such as chromatin immunoprecipitation, high-throughput sequencing, assay for transposase-accessible chromatin with sequencing, etc. Findings: They were able to create public datasets that spanned 15 developmental stages of zebrafish, and identify specific elements such as over 100,000 with predicted enhancer activity. (key points) - 99% of human genome is non-coding, “non-functional” - zebrafish are an attractive model organism because of their rapid embryogenesis and externally fertilized transparent embryos - >70% of human genes have zebrafish equivalents - genetic information and properties regarding zebrafish changes based on development
Research Question/Problem/ Need	How can the zebrafish genome be further studied, and in turn, how can cis-regulatory elements be analyzed for their significance/role?

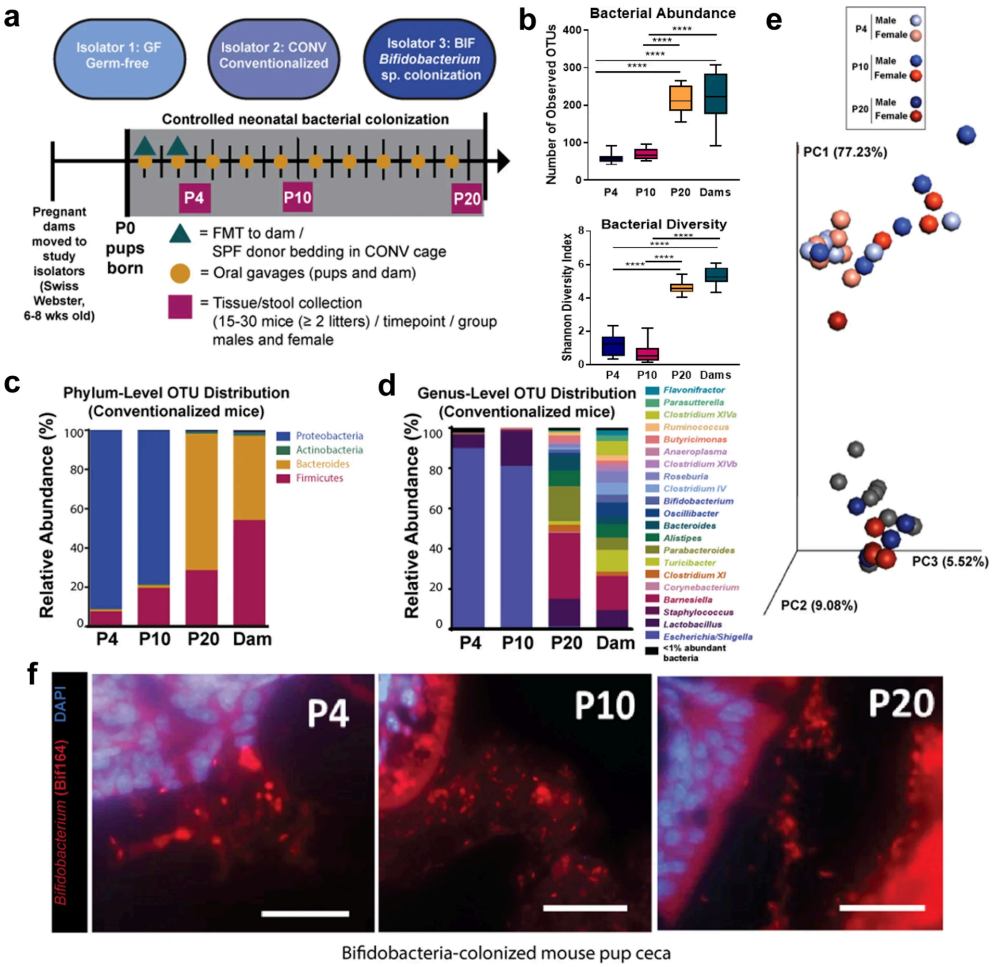
Important Figures	 This figure shows the changing complexity of genetic information and characteristics based on the developing stages of the zebrafish. It also highlights the functional elements that are unique to certain developmental features during embryogenesis.
VOCAB: (w/definition)	Glean: To extract info from various sources Perturbation: Alteration of function Amenable: Compliant / responsive to Enhancers: Increase transcription of gene Syntenic: Having similar chromosomal sequences
Cited references to follow up on	DANIO-CODE consortium (8): https://doi.org/10.1089%2Fzeb.2015.1179 Annotating non-coding elements in zebrafish genome (9): https://doi.org/10.1038/s41588-022-01089-w
Follow up Questions	What are forward and reverse genetic approaches? What is the benefit/specialty of each? What is chromatin immunoprecipitation? Purpose? What are examples of intrachromosomal interactions and what can they indicate about the organism? What is the difference between CAGE-defined and Ensembl-defined transcriptional start sites?

Article #13 Notes: Bifidobacteria shape host neural circuits during postnatal development by promoting synapse formation and microglial function

Source Title	Bifidobacteria shape host neural circuits during postnatal development by promoting synapse formation and microglial function
Source citation (APA Format)	Luck, B., Engevik, M. A., Ganesh, B. P., Lackey, E. P., Lin, T., Balderas, M., Major, A., Runge, J., Luna, R. A., Sillitoe, R. V., & Versalovic, J. (2020). Bifidobacteria shape host neural circuits during postnatal development by promoting synapse formation and microglial function. *Scientific Reports*, *10*(1), Article 1. https://doi.org/10.1038/s41598-020-64173-3
Original URL	https://www.nature.com/articles/s41598-020-64173-3
Source type	Scientific journal article
Keywords	Bacteria, Synaptic Pruning, Development, Microglia
#Tags	#gutmicrobiome #synapticpruning #development

Summary of key points + notes (include methodology)	(summary)
	Problem:
	- gaps in current studies:
	  - gut brain axis communication research is mainly done around complex microbial communities, which doesn't indicate anything about specific bacterial species or the specific pathways
	  - use adult animals to model the relationship, even though adult and postnatal microbiomes and brains are vastly different
	Goal:
	- to identify the role of *Bifidobacterium* colonization on neurodevelopment
	- provide insight about how brain function and behavior is developed in mammalian brain
	Method:
	- 3 groups (Germ-free, colonized with *Bifidobacterium* species or typical complex microbiota
	- examined cerebellum, cortex, and hippocampus
	Findings:
	- bacteria-colonized mice had decreased expression of synapse-promoting

	genes (possibly overexpressed in mice w/out microbial signaling), increased amount of markers signifying more abundant active microglia, and normal synaptic density and neuronal activity - measured by density of VGLUT2+ puncta and Purkinje cell firing rate - GF mice had observed synaptic deficits - measured morphologically and functionally (key points) - colonization of intestinal microbiota correlated with organization of fundamental neural circuitry during the postnatal period - gba in this period is especially important for proper neuronal development - Early life microbiomes to early life models will be most similar to actual/natural gut microbiome and brain relationship model - *Bifidobacterium* is an early life microbe that exerts neuromodulatory results - the cerebellum is good for studying microbiota affected changes such as synaptic functionality and circuit development - well-described circuit organization and in vivo neuronal firing properties - colonized mice were colonized using bedding exposure and through their dams - routine agar plating of feces of mice was used to check that the mice had no microbial colonization - genes controlling synapse development and plasticity in the brain were identified using PCR arrays - SYNAPSE RELATED GENES ARE UPREGULATED IN EARLY AGES OF GERM-FREE MICE RELATIVE TO COLONIZED MICE
Research Question/Problem/ Need	How does the gut microbiome affect neurological development in terms of the synaptic pruning process?

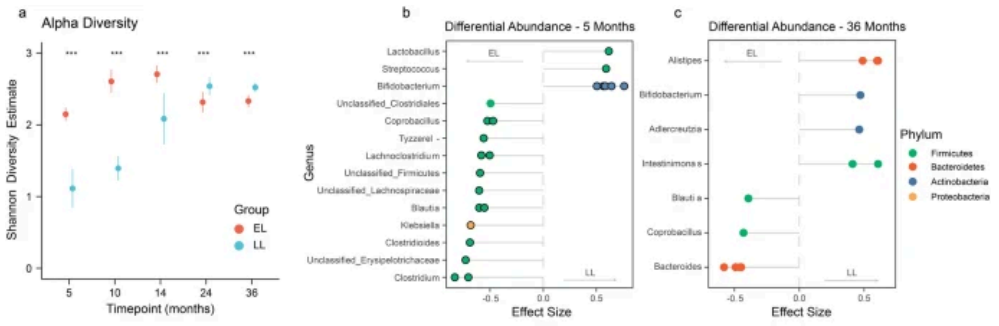
Important Figures	 Bifidobacteria-colonized mouse pup ceca This is Figure 1 of the paper. 1a shows the experimental timeline with the number of days after the mice were born when they were exposed to general bacteria, as well as the Bifidobacteria. 1b shows the bacterial abundance and diversity at different points after birth; the vast change between day 10 and day 20 could be due to difference in diet, as that period of time is when the pups have a significant increase in fiber intake from solid foods. 1c shows the different bacterial genera that dominate p4 and p10 conventionalized mouse gut; there is a significant decrease when compared with the p20 and dam microbiomes. 1d and 1e help support/refute previous claims made in the past (conventionalized mice have bacterial communities that mirror their donor microbiome profile, and microbiomes of male and female conventionalized mice are actually very similar contrary to previous studies.
VOCAB: (w/definition)	Gnotobiotic: relating to or living in a controlled environment with one or a few kinds of organisms Gavage: administration of food/drugs by force
Cited references to follow up on	4 (relationship between colonized gut and neuron structures): https://doi.org/10.1016/j.molmed.2014.05.002 32 (microbiota affects gene expression and neuronal activity in cerebellum):

	https://doi.org/10.1038/nn.4030 34 (exposure to dietary fiber in solid foods increases Bacteroidetes colonization): https://doi.org/10.1016/j.chom.2017.11.004 25 (studies that show correlation with SP related genes and gut microbiome): https://doi.org/10.1111/nmo.12295
Follow up Questions	What is the significance of Purkinje Cells and what does their firing rate indicate about neuronal activity? What are the prenatal, neonatal, and postnatal stages for zebrafish? - What is the mid-stage of synaptic reorganization and pruning for zebrafish? What are the other known roles/characteristics of *Bifidobacterium*?

Article #14 Notes: Early-life differences in the gut microbiota composition and functionality of infants at elevated likelihood of developing autism spectrum disorder

Source Title	Early-life differences in the gut microbiota composition and functionality of infants at elevated likelihood of developing autism spectrum disorder
Source citation (APA Format)	Zuffa, S., Schimmel, P., Gonzalez-Santana, A., Belzer, C., Knol, J., Bölte, S., Falck-Ytter, T., Forssberg, H., Swann, J., & Diaz Heijtz, R. (2023). Early-life differences in the gut microbiota composition and functionality of infants at elevated likelihood of developing autism spectrum disorder. *Translational Psychiatry*, *13*(1), Article 1. https://doi.org/10.1038/s41398-023-02556-6
Original URL	https://www.nature.com/articles/s41398-023-02556-6
Source type	Science journal article
Keywords	Gut-Brain Axis, Autism Spectrum Disorder, Gut Microbiota
#Tags	#bacteriaspecies #analyzingmicrobiome #detection
Summary of key points + notes (include methodology)	(summary) Problem: More and more studies have been identifying that the gut microbiome affects activity in the brain, but Goal: To identify distinct characteristics of the gut microbiota of people with ASD (or a higher likelihood of developing it) so that it can be used to detect the disorder before behavioral symptoms are evident. Method: They used an integrated shallow shotgun metagenomic sequencing and H nuclear magnetic resonance spectroscopy-based untargeted metabolomics method to analyze the microbial profiles of the infants, while MSEL and ADOS-2 tests were used to test Findings: Infants with a higher chance of developing ASD had increased amounts of *Bifidobacterium* and more *Clostridium* and *Klebsiella* species compared to the infants who were less likely. They also scored lower on behavioral intelligence tests compared to the low likelihood group, supporting that there are noticeable

	characteristics of the gut microbiome in infants who are likely to have ASD.
	
	(key points)
	- higher vs lower likelihood of ASD determined through family tree
	- people with ASD often have more GI symptoms than neurotypical individuals
	- fecal microbiota transplantation has been used as a method that produced improvements in ASD symptoms and GI issues
	- people with ASD have detailed food preferences, which may often lead to lower gut microbiota diversity
	- Shallow shotgun metagenome sequencing
	  - DNA was extracted, then quantified, then libraries were set up to be sequenced
	- H NMR spectroscopy
	  - fecal samples were defrosted, diluted, then homogenized, centrifuged, then one-dimensional pulse sequence
	- Stats: calculated mean relative abundances, then plotted the most abundant genera of each group at the specific time points
	- Early Learning Composite Scores (ELCS) improved for infants with a low chance of developing ASD, while there was no significant increase and even some decrease in infants with a high chance
	- amounts of GABA was significantly lower in infants who are more likely to develop ASD

Research Question/Problem/ Need	How can the gut microbiome be used for early detection of ASD? What are the specific characteristics that are unique to the neurodevelopmental disorder?
Important Figures	 A) Alpha diversity is greater in infants with elevated likelihood of ASD, but then it dips down, even below the lower likelihood groups. B & C) These graphs show the bacteria that are significantly higher in elevated likelihood vs lower likelihood groups.
VOCAB: (w/definition)	Omics: group of biological sciences that attempt to explain the different parts/molecules of a biological structure through their function and contribution Murine: belonging to family Murinae (mice and rodents) Homogenize: reduce a substance into extremely small particles and then distribute evenly throughout sample Enumerated: counted systematically

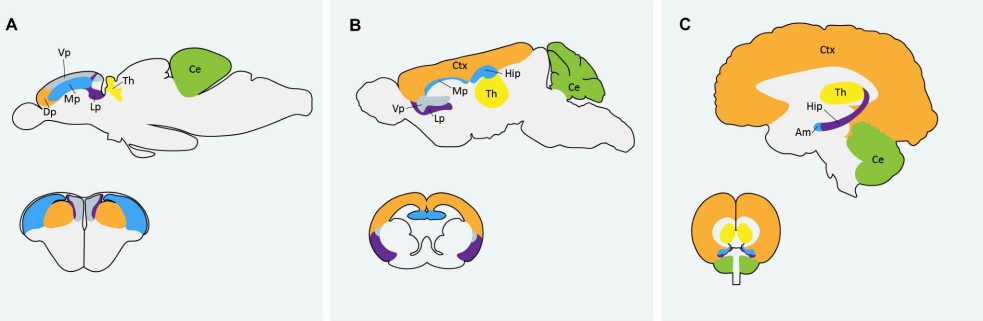
Cited references to follow up on	6 (multiple different types of causes for ASD): 19-22 (lower expression of possibly good bacteria in people with ASD): 26 (inserting high or low expressed bacteria in ASD into mice): 49 (lower amounts of GABA is children with ASD):
Follow up Questions	How is it determined which bacteria/microbiota to transplant into people with ASD symptoms? I.e. How do they know what will be effective? How long does the full process of shallow shotgun metagenome sequencing take? What is the difference between shallow shotgun metagenome sequencing and H NMR spectroscopy in terms of the results that they yield? What is the typical role/significance of GABA in the brain?

Article #15 Notes: Using Zebrafish to Model Autism Spectrum Disorder: A Comparison of ASD Risk Genes Between Zebrafish and Their Mammalian Counterparts

Source Title	Using Zebrafish to Model Autism Spectrum Disorder: A Comparison of ASD Risk Genes Between Zebrafish and Their Mammalian Counterparts
Source citation (APA Format)	Rea, V., & Van Raay, T. J. (2020). Using Zebrafish to Model Autism Spectrum Disorder: A Comparison of ASD Risk Genes Between Zebrafish and Their Mammalian Counterparts. *Frontiers in Molecular Neuroscience*, *13*. https://www.frontiersin.org/articles/10.3389/fnmol.2020.575575
Original URL	https://www.frontiersin.org/articles/10.3389/fnmol.2020.575575/full
Source type	Science journal article
Keywords	Autism Spectrum Disorder, DNA, mutation, behavior tests
#Tags	#zebrafishAsModelOrganism #ASDBehaviorTests
Summary of key points + notes (include methodology)	(summary) Problem: ASD is a very prevalent neurological disorder that affects cognitive function and behaviors, but the causes are numerous, very complex, and not well understood. Goal: The goal is to identify how zebrafish can be used as a model organism for ASD and specifically observe 12 ASD risk genes in zebrafish. Method: Behavioral tests, primarily observing zebrafishes' behaviors in a tank, were used to identify their ASD symptoms, and gene knockout and morpholino

	knockdown was used to identify human ASD gene orthologs.
	Findings: A number of behavioral tests were identified that could be used to indicate the symptoms/symptom severity of ASD in zebrafish, and 12 gene orthologs were identified.
	
	(key points)
	- zebrafish are physiologically and genetically similar to humans
	  - genome is over 70% similar
	  - have been used before to visual neural development
	- genetic manipulation w CRISPR is fairly simple in zebrafish
	- major brain similarities
	  - 62% of 858 human ASD risk genes for humans have zebrafish parallels
	  - zebrafish brains have neurons, astrocytes, oligodendrocytes, microglia, and similar regions as well
	  - ASD related regions
	  - human cortex : zebrafish dorsal
	  - human amygdala : zebrafish medial pallium
	  - some human genes have two zebrafish orthologs because of duplication
	- Behavioral tests for zebrafish
	  - Visually mediated social preference test
	  - comparing fishes' time spent with near familiar and unfamiliar fish
	  - 3-Chamber social choice test
	  - comparing fishes' time spent near empty vs populated tank, then familiar vs unfamiliar fish tank
	  - Shoaling behavior
	  - not only observing number of dpf for fish to cluster into schools, but also distance between fish and time spent in and out of shoal
	  - Thigmotaxis
	  - comparing fishes' time spent in the center vs outer wall zone of tank
	- Valproic Acid is a drug that can induce ASD

Research Question/Problem/ Need	How can zebrafish be used to model ASD in humans in terms of their linked genes and behavioral symptoms?

Important Figures	 This figure shows how there are many similar regions in the brain among zebrafish (A), mice (B), and human brains (C), supporting their capability of being effective human models for cognitive processes.
VOCAB: (w/definition)	Pleiotropic: producing more than one effect Idiopathic: relating to a disease or condition that occurs spontaneously or due to an unknown cause Topologically: relating to the way that parts of a whole are arranged in relation to each other Teleost: bony fish
Cited references to follow up on	Sgritta et al., 2019 (GI issues and microbial profile in ASD): https://www.cell.com/neuron/pdf/S0896-6273(18)31009-2.pdf Stilling et al., 2018 (bacterial metabolites affect cognitive processing): https://elifesciences.org/articles/33070 Shams et al., 2018 (zebrafish similarity to humans): https://pubmed.ncbi.nlm.nih.gov/28887224
Follow up Questions	What are Prader-Willi and Angelman syndromes? How do they compare with ASD? What is the process of neurulation and why is it significant? What is the role/significance of siRNA? What are morpholinos / morpholinos knockdown? - Are there different types of methods to knock- down genes? How do they differ? What is the percent of zebrafish that develop ASD when each of the genes are knocked out? I.e. how closely correlated are the specific genes to actual ASD?

Article #16 Notes: Autism Spectrum Disorder

Source Title	Autism Spectrum Disorder
Source citation (APA Format)	National Institute of Mental Health. (n.d.). *Autism Spectrum Disorder*. Retrieved November 8, 2023, from https://www.nimh.nih.gov/health/topics/autism-spectrum-disorders-asd
Original URL	https://www.nimh.nih.gov/health/topics/autism-spectrum-disorders-asd#
Source type	Descriptive overview article
Keywords	Autism Spectrum Disorder, Hyperactivity, Neurological Disorder, Developmental Disorder
#Tags	#backgroundInfo #causesOfASD

Summary of key points + notes (include methodology)	(summary)
	Autism Spectrum Disorder is a neurodevelopmental disorder that affects a person's ability to socialize and learn. Symptoms include difficulty with communication, interaction, repetitive and restrictive behaviors, as well as excelled memory. The causes of this disorder are complex and not completely known, but genetics are likely to play a role.
	
	(key points)
	- Diagnostic and Statistical Manual of Mental Disorders (DSM-5) is used to diagnose ASD
	- Major symptoms
	  - social
	  - lack of eye contact, even during conversation
	  - less responsive, difficulty maintaining conversations
	  - difficulty understanding others' point of view
	  - restrictive/repetitive
	  - repeating certain behaviors/phrases
	  - overly absorbed into specific topics
	  - upset when routine is interrupted
	  - increased sensitivity to external stimuli
	  - may have sleep problems
	  - academic
	  - strong memory
	  - strong visual and auditory understanding
	- Potential causes

	- genetics - older parents - lower birth weight - Treatment includes medication and behavioral, psychological, and educational interventions
Research Question/Problem/ Need	What is Autism Spectrum Disorder and its major causes and symptoms?
Important Figures	n/a
VOCAB: (w/definition)	Echolalia: repetition of words or phrases Screening: testing of person or group of people for presence of disease or other condition
Cited references to follow up on	more sources - medication for ASD: http://www.fda.gov/drugsatfda - current studies about ASD: https://clinicaltrials.gov/ct2/results?term=autism&Search=Apply&recrs=b&recrs=a&age_v=&gndr=&type=&rslt=&fund=0 - ASD Federal Resource: https://www.nichd.nih.gov/health/topics/autism
Follow up Questions	How does low birth weight affect likelihood of ASD? I.e. how are they correlated? What are the specific types of medication and how do they target the symptoms of ASD? Do symptoms tend to be less or more apparent as the individuals with ASD grow older?

Article #17 Notes: Pharmacological Therapies for Autism Spectrum Disorder: A Review

Article notes should be on separate sheets

Source Title	Pharmacological Therapies for Autism Spectrum Disorder: A Review
Source citation (APA Format)	LeClerc, S., & Easley, D. (2015). Pharmacological Therapies for Autism Spectrum Disorder: A Review. *Pharmacy and Therapeutics*, *40*(6), 389–397.
Original URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4450669/
Source type	Science journal article (review)
Keywords	Autism Spectrum Disorder, Medication, Clinical Studies
#Tags	#typesOfMedication #comorbidSymptoms

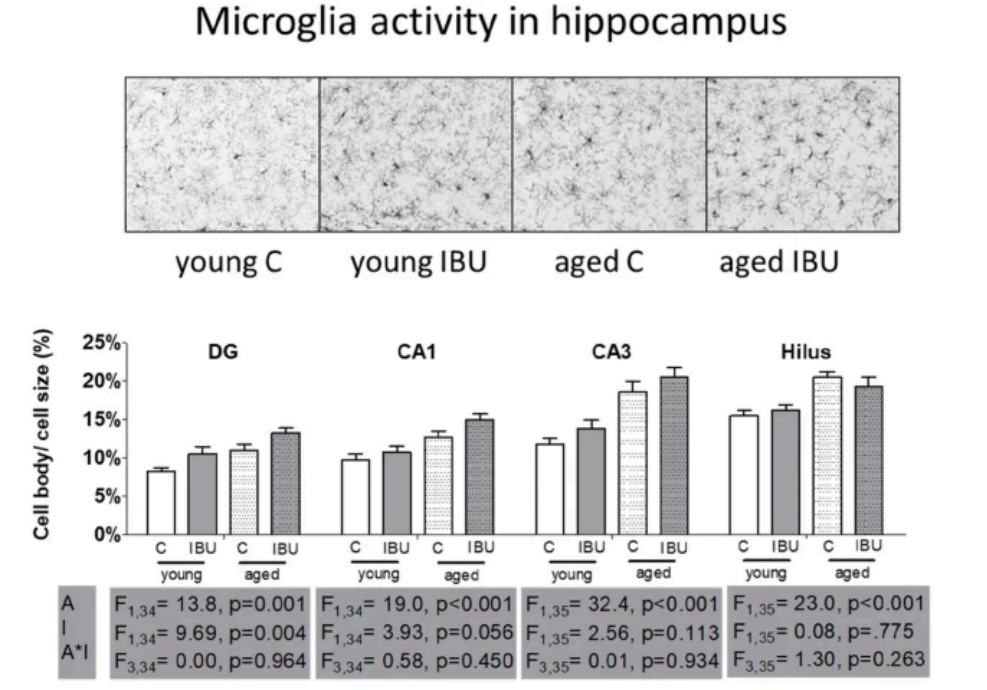
Summary of key points + notes (include methodology)	(summary)
	Problem: ASD symptoms delay development of social, speech, and behavioral skills.
	Goal: To identify and explain medication options that can be used alongside behavioral therapy to alleviate particular symptoms.
	Method: To identify the effects of the drugs, studies gave doses of these medications to people with ASD and other comorbid disorders and tested their behavioral symptoms after a certain period.
	Findings: There are many prescription based drugs that can be used to treat the different categories of symptoms for people with ASD.
	
	(key points)
	- treatment for hyperactivity and inattention
	  - Methylphenidate
	  - blocks reuptake of norepinephrine and dopamine and increases release
	  - more ADHD > ASD improvements
	  - negative drawbacks like decreased appetite, increase irritability, social withdrawal, restlessness
	  - Venlafaxine
	  - blocks reuptake of serotonin and norepinephrine
	  - linked with depression, anxiety, and panic disorder treatments
	  - also improved self-injury behavior

Research Question/Problem/ Need	What are the different types of medication that can be prescribed for people with ASD to target specific symptoms?
Important Figures	n/a
VOCAB: (w/definition)	reuptake: neuron reabsorbing neurotransmitter crossover study: two or more treatments are given to subjects in randomized orders intravenous: situated or occurring in a vein / by entering a vein diuresis: increased excretion of urine
Cited references to follow up on	39 (studying methylphenidate's effect on ASD and ADHD): https://pubmed.ncbi.nlm.nih.gov/11055460 40 (testing different doses of methylphenidate): https://pubmed.ncbi.nlm.nih.gov/17276750 43 (clinical study with low dose of venlafaxine): https://pubmed.ncbi.nlm.nih.gov/16307837
Follow up Questions	What are the major effects of norepinephrine? What are monoamines & their significance? How does the time of administration for these medications influence its effectiveness?

Article #18 Notes: Acute pre-operative ibuprofen improves cognition in a rat model for postoperative cognitive dysfunction

Article notes should be on separate sheets

Source Title	Acute pre-operative ibuprofen improves cognition in a rat model for postoperative cognitive dysfunction
Source citation (APA Format)	Oberman, K., Hovens, I., de Haan, J., Falcao-Salles, J., van Leeuwen, B., & Schoemaker, R. (2021). Acute pre-operative ibuprofen improves cognition in a rat model for postoperative cognitive dysfunction. *Journal of Neuroinflammation*, *18*(1), 156. https://doi.org/10.1186/s12974-021-02206-y
Original URL	https://jneuroinflammation.biomedcentral.com/articles/10.1186/s12974-021-02206-y
Source type	Science journal article
Keywords	Cognition, Inflammation, Neuroinflammation, Ibuprofen
#Tags	#NSAIDsForCognition #synapticPruningNSAIDs
Summary of key points + notes (include methodology)	(summary) Problem: Inflammation has an impact on development of post operative cognitive dysfunction (POCD), which can impair memory, neurological processes, attention etc. Goal: To identify if NSAIDs, specifically ibuprofen, plays a role in alleviating POCD, and identifying the specific mechanisms that cause this result. Method: Rats were injected with ibuprofen (or just normally cared for) before surgery. Blood and fecal samples were routinely analyzed, behavioral testing was performed 9-14 days post-op, and the specific components of the brain was through immunohistochemistry on day 14. Findings: Ibuprofen improved memory, hippocampal neurogenesis, and hippocampal microglia activity. Gut microbiome was not significantly affected. (key points) - Ibuprofen previous results - reduces lipopolysaccharide-induced cognitive dysfunction and

	neuroinflammation in rats - improves cognitive function post operation - correlated with specific microbial profiles - open field test used to assess anxiety and exploratory behavior - more time in center of field indicates less anxiety (LIKE THIGMOTAXIS!) - samples were stained for ionized-binding adaptor protein (IBA)-1 and doublecortin X to identify microglia and young neurons - specifically scanned for hippocampus - Statistical tests used - Mean, two way anova, one way anova, permanova, beta-diversity - Novel object recognition and novel location recognition for for short-term object and spatial memory - no difference in NOR scores for groups - ibuprofen leads to improved location recognition - microglia activity increased with ibuprofen - microglia positively correlate with neurogenesis - both correlate positively with long term spatial memory
Research Question/Problem/ Need	How can NSAIDs be used to alleviate POCD in terms of behavior and changes in neural activity?
Important Figures	 This figure shows microglial activity in the hippocampus region between the control group and ibuprofen group, as well as young vs aged mice. There are increases in microglial cell size for most of the ibuprofen groups.
VOCAB: (w/definition)	Ligation: to join together with chemical process

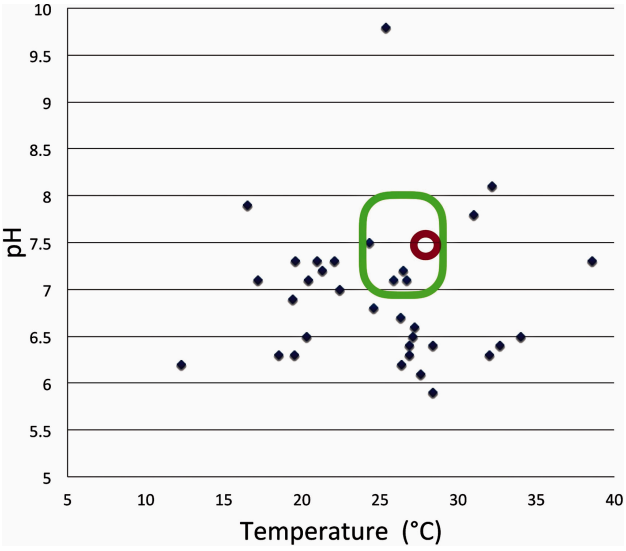
	Endothelial cells: single layer of cells that lines blood vessels and regulates exchange between bloodstream and tissues Neurogenesis: growth and development of tissue part of nervous system Corroborate: to support with evidence
Cited references to follow up on	19 (cognitive effects of ibuprofen on mice): https://doi.org/10.3389/fphar.2019.00632 21 (ibuprofen and gut): https://doi.org/10.1016%2Fj.cmi.2015.10.003 20 (ibuprofen study with decreased microglial activity): https://doi.org/10.1186%2Fs12974-018-1163-z 25 (ILI-b response and microglia activation): https://doi.org/10.1016/j.bbi.2014.02.002
Follow up Questions	What are the symptoms of lipopolysaccharide-induced cognitive dysfunction? Why was the hippocampus region chosen for IHC imaging? Why have previous studies led to decreased microglial activation, while this one shows an increase? What might the underlying factors be? How much excessive microglial activity leads to inflammation?

Article #19 Notes: Zebrafish: Housing and husbandry recommendations

Article notes should be on separate sheets

Source Title	Zebrafish: Housing and husbandry recommendations
Source citation (APA Format)	Aleström, P., D'Angelo, L., Midtlyng, P. J., Schorderet, D. F., Schulte-Merker, S., Sohm, F., & Warner, S. (2020). Zebrafish: Housing and husbandry recommendations. *Laboratory Animals*, *54*(3), 213–224. https://doi.org/10.1177/0023677219869037.
Original URL	https://journals.sagepub.com/doi/10.1177/0023677219869037
Source type	Science journal article (review)
Keywords	Zebrafish, Husbandry, Temperature, Feed, Condition
#Tags	#takingCareOfZebrafish #controlVariables

Summary of key points + notes (include methodology)	(summary)
	Problem: Current care procedures for zebrafish vary greatly between facilities, which can lead to fluctuations in results that use these organisms.
	Goal: The goal is to create more standardized protocols regarding the way fish are taken care of.
	Method:
	Findings:
	
	(key points)
	- Transportation and reception
	  - safe shipment without contamination
	  - regulate temp, water, and air condition
	  - embryos > adults
	- Water and housing
	  - most tanks come with filter systems, germicidal irradiation, light, and temp controls
	  - overflow system with recirculating water
	- Temperature
	  - 28.5° C is most often used as a standard temp for zebrafish development
	  - temp can influence the rate of their development
	- Dark-light cycle

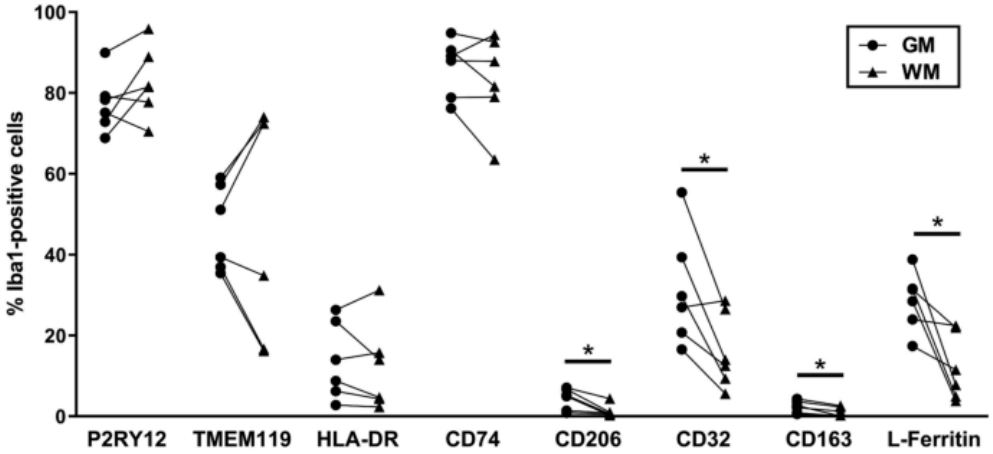
	- typically 10h dark and 14h light - other combinations may affect physiological processes, like breeding - Water quality - 0.1 mg/l can be toxic for fish, so should be removed by stirring and aerating - chloramine should be removed - many facilities used conditioned deionised water - often done using reverse osmosis - Stocking density - embryos hatch after 60 hpf and settle at bottom of petri dish until swim bladder is formed - (not proven) lower densities lead to more females and higher densities to more males - typically 4-10 adult per liter, but 3-12 should work - Welfare - reproductive success and cortisol levels are indicators - Feeding - mix of dry and live feeds 2-3 times per day - can fluctuate based on development - Sanitation and hygiene - no cross contamination - recommended to heat items to at least 60°C for 1 hr before coming into physical contact with fish - work in cleaner tanks before dirtier ones - no algae, which can be a sign of biofilm
Research Question/Problem/ Need	How can zebrafish care conditions be standardized to produce more repeatable projects and consistent results?
Important Figures	 This figure shows the pH and temperatures of 35 natural zebrafish habitats. The green square represents the range at which zebrafish are recommended to be

	grown in facilities. The range for pH is 6.5 to 8, while the recommended temperature range is 24-29°C.
VOCAB: (w/definition)	Irradiation: exposure to radiation Poikilothermic: an organism whose body temperature fluctuates to be similar or slightly higher than the temperature of the environment Water hardness: the concentration of divalent metals in water Autoclave: a strong heated container for sterilization
Cited references to follow up on	25 (O2, CO2, N conditions for fish): https://www.ncbi.nlm.nih.gov/pubmed/27443942 29 (temp influences (zebrafish) development): https://www.ncbi.nlm.nih.gov/pubmed/23382349 36 (importance of D-L cycle for embryos): https://www.ncbi.nlm.nih.gov/pubmed/24367902 41 (zebrafish cortisol release and stress): https://doi.org/10.1016/j.aquaculture.2006.04.020
Follow up Questions	What are the less obvious signs that zebrafish transportation has been contaminated? What is germicidal irradiation and why is it important for the fish? How is the light transitioned for dusk and sunrise? What is conditioned deionised water and why is this important for fish?

Article #20 Notes: Quantitative immunohistochemical analysis of myeloid cell marker expression in human cortex captures microglia heterogeneity with anatomical context

Article notes should be on separate sheets

Source Title	Quantitative immunohistochemical analysis of myeloid cell marker expression in human cortex captures microglia heterogeneity with anatomical context
Source citation (APA Format)	Swanson, M. E. V., Murray, H. C., Ryan, B., Faull, R. L. M., Dragunow, M., & Curtis, M. A. (2020). Quantitative immunohistochemical analysis of myeloid cell marker expression in human cortex captures microglia heterogeneity with anatomical context. *Scientific Reports*, *10*(1), Article 1. https://doi.org/10.1038/s41598-020-68086-z
Original URL	https://www.nature.com/articles/s41598-020-68086-z
Source type	Science journal article
Keywords	Immunohistochemistry imaging, Antigens, Microglia, Perivascular Macrophages
#Tags	#markersForMicrogliaIHC #phagotyosisDetection
Summary of key points + notes (include methodology)	(summary) Problem: Current IHC images are not able to pick up microglia with different functions. Goal: To identify different markers that can be used in IHC imaging to detect distinct microglia types / types of activity Method: Immunohistochemistry on post-mortem human middle temporal gyrus sections from neurotypical individuals. Findings: HLA-DR had mostly similar results to when other proteins such as CD206, CD32, and CD163 were stained, but none were completely the same. Perivascular macrophages detect more phagocytic and antigen presentation. (key points) - L-Ferritin detects dystrophic microglia - Myeloid cell proteins were chosen by referring to previous studies that showed that they binded more to cells unique to the brain, or were only

	expressed by microglia and perivascular macrophages in general - Perivascular macrophages live in perivascular area of blood brain barrier - Microglia can go through morphologies due to damage or disease in order to maintain proper function in the brain - ramified, hypertrophic, dystrophic, rod, and amoeboid - rod microglia are hypothesized to support signaling in grey matter - amoeboid microglia phagocytose large debris often - P2RY12, TMEM119, and L-Ferritin were only observed in microglia - CD32 and CD163 are correlated with phagocytosis
Research Question/Problem/ Need	How can the different types of microglia (based on differences in function) be identified using IHC staining?
Important Figures	 This figure shows the number of cells counted based on the markers of interest in gray matter vs white matter. Data from the case are joined together. Significance determined through paired t-tests.
VOCAB: (w/definition)	Gyrus: ridge or fold between two clefts in the brain Perivascular: Situated or occurring around a blood vessel Amoeboid: relating to amoeba Parenchyma: functional tissue of an organ (not just the connective and supporting tissue) Ramified: forming extensions/branches
Cited references to follow up on	27 (use of HLA-DR as activation marker for microglia): http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=31454549 33 (cause of microglia morphologies): http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=25257319 38 (rod microglia support signaling, possibly related to SP?): https://actaneurocomms.biomedcentral.com/articles/10.1186/s40478-015-0209-z 30 (antigen and microglia presentation related markers):

	http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=26286145
Follow up Questions	What are myeloid cells and how are the proteins they express different from other proteins? How are the types of morphologies different from each other / what are their different results? How can these staining techniques be used to identify changes in synaptic pruning? How can the connection be made?

Patent #2 Notes: Compositions and methods for treating disorders characterized by a defect in gpr56 expression or activity

Source Title	Compositions and methods for treating disorders characterized by a defect in gpr56 expression or activity
Source citation (APA Format)	Piao, X. (2020, January 23). Compositions and methods for treating disorders characterized by a defect in gpr56 expression or activity.
Original URL	https://patents.google.com/patent/WO2020018913A1
Source type	Patent
Keywords	GPR56, ASD (Autism spectrum disorder), synaptic pruning, Microglia, neurodevelopmental disorders, TG2 (Transglutaminase 2), RhoA signaling, mTOR signaling
#Tags	#proteinAffectingASD #treatmentPathway
Summary of key points + notes (include methodology)	(summary) GPR56 is a protein involved in various biological processes, and its malfunction can contribute to several diseases, including metabolic disorders, inflammatory bowel disease, and cancer. Existing treatments for these conditions often have limitations, prompting the search for new therapeutic approaches. (key points) This patent proposes compositions and methods for treating disorders linked to GPR56 dysfunction. These include: - GPR56 agonists: Molecules that activate GPR56, potentially mimicking its natural function and alleviating symptoms. - GPR56 positive allosteric modulators (PAMs): Substances that enhance the activity of GPR56 without directly binding to it, potentially offering a different approach to treatment. The patent describes various ways to deliver the GPR56-targeting agents, such as oral, intravenous, or topical administration. The patent suggests that these compositions and methods could be used to treat a range of disorders: - Metabolic disorders: Type 2 diabetes, obesity, non-alcoholic fatty liver disease. - Inflammatory bowel disease: Ulcerative colitis, Crohn's disease. - Cancer: Colon cancer, pancreatic cancer, breast cancer. - Other conditions: Bone diseases, neurodegenerative diseases.

	Benefits: The proposed approach offers several potential advantages: - GPR56 plays a crucial role in various diseases, making it a promising therapeutic target. The patent explores different compositions and methods, providing flexibility for tailoring treatment to specific needs. Compared to existing treatments, GPR56-targeting agents might offer better symptom control and fewer adverse effects.
Research Question/Problem/ Need	Can GPR56 agonists or PAMs effectively treat disorders characterized by GPR56 dysfunction?
Important Figures	n/a
VOCAB: (w/definition)	GPR56 (G protein-coupled receptor 56): The protein targeted by the compositions and methods described in the patent. It plays a role in various biological processes and its malfunction is linked to several diseases. Agonist: A molecule that activates a receptor, in this case GPR56. GPR56 agonists mimic the natural ligand (activating molecule) of GPR56, potentially triggering its desired function. Positive allosteric modulator (PAM): A substance that enhances the activity of a receptor without directly binding to it. In this case, GPR56 PAMs would increase the response of GPR56 to its natural ligand, even at low concentrations.
Cited references to follow up on	DATABASE UniProtKB [online] 15 March 2004 (2004-03-15), "Adhesion G-protein coupled receptor G1", Database accession no. AGRG1_HUMAN STOVEKEN ET AL.: "Gedunin- and Khivorin- Derivatives are Small-Molecule Partial Agonists for Adhesion G Protein-Coupled Receptors GPR56/ADGRG1 and GPR114/ADGRG5", MOLECULAR PHARMACOLOGY, vol. 93, no. 5, May 2018 (2018-05-01), pages 477 - 488, XP055676790, DOI: 10.1124/mol.117.111476
Follow up Questions	How specific are the proposed GPR56 agonists and PAMs to GPR56? Are there potential off-target effects on other receptors? What is the expected efficacy of these compositions in treating the mentioned disorders? How does it compare to existing treatments? How exactly do the proposed GPR56 agonists and PAMs work to alleviate symptoms in different disorders? Is there a specific signaling pathway involved?

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Patent #3 Notes: Beta-2 chimaerin as a mediator of axonal and synaptic pruning

Source Title	Beta-2 chimaerin as a mediator of axonal and synaptic pruning
Source citation (APA Format)	Kolodkin, A., Kazanietz, M., & Riccomagno, M. (2013, December 19). Beta-2 chimaerin as a mediator of axonal and synaptic pruning.
Original URL	https://patents.google.com/patent/WO2013188666A1
Source type	Patent
Keywords	Beta-2 chimaerin, Axonal pruning, Synaptic elimination, Neurological diseases, Beta-Chimaerin modulators, Rac GTPase, Neuropilin-2
#Tags	#proteinAffectingSynapticPruning #regulatingNeurologicalFunctioning
Summary of key points + notes (include methodology)	(summary) This patent describes the use of a protein called beta-2 chimaerin to promote the natural process of "axonal and synaptic pruning" in the brain. Pruning removes unnecessary connections between brain cells, which is important for healthy brain function. (key points) Beta-2 chimaerin is identified as a protein involved in pruning. The patent details its structure and function. Methods are provided for producing and purifying beta-2 chimaerin. This paves the way for its potential use in therapeutic applications. The patent suggests that beta-2 chimaerin could be used to treat or prevent neurological diseases. Examples include Alzheimer's, Parkinson's, and schizophrenia, where abnormal pruning is implicated. Potential benefits: Stimulating pruning could help clear away harmful protein aggregates associated with neurodegenerative diseases. Promoting healthy pruning patterns could improve cognitive function and memory. Limitations and unknowns: The patent focuses on the basic science of beta-2 chimaerin. More research is needed to understand its safety and effectiveness as a treatment. The exact role of beta-2 chimaerin in different brain diseases is still being

	investigated. Overall, this patent presents a promising avenue for developing new therapies for neurological diseases by targeting the natural process of brain cell pruning.
Research Question/Problem/ Need	Can beta-2 chimaerin, a regulator of brain cell pruning, be harnessed to treat neurological diseases linked to abnormal pruning patterns?
Important Figures	n/a
VOCAB: (w/definition)	Recombinant cells: Cells that have been engineered to express a specific protein, such as beta-2 chimaerin. Guanylate nucleotide exchange factor (GEF) activity: The ability of beta-2 chimaerin to activate another protein involved in pruning. Catalytic domain: The part of the protein that performs its enzymatic activity, potentially involved in cleaving proteins during pruning
Cited references to follow up on	BRUINSMA, S. P. ET AL.: "Chimaerin and Rac regulate cell number, adherens junctions, and ERK MAP kinase signaling in the Drosophila eye", PNAS, vol. 104, no. 17, 2007, pages 7098 - 7103 LEUNG, T. ET AL.: "Cerebellar beta2-chimaerin, a GTPase-activating protein for p21 ras-related Rac is specifically expressed in granule cells and has a unique N-terminal SH2 domain", THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 269, no. 17, 1994, pages 12888 - 12892 WEGMEYER, H. ET AL.: "EphA4-dependent axon guidance is mediated by the RacGAP alpha 2-chimaer in", NEURON, vol. 55, 2007, pages 756 - 767
Follow up Questions	How specific is beta-2 chimaerin for axonal and synaptic pruning compared to other processes in the brain? What are the potential delivery methods for beta-2 chimaerin to its target sites in the brain? Can the identified PH domain and catalytic domain be further characterized to understand their precise functions in pruning?

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