Project Notes:

Determining the Effects of Probiotics on Obsessive-Compulsive Disorder
Name: Jasmin Bella

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
How do different supplements and/or diets affect symptoms of OCD?	Read article on different supplements used in studies on reducing symptoms of OCD.	Article #4	09/03/2024
How does serotonin production work?	Read article on serotonin production and applications.	Article #5	09/07/2024
How does serotonin production correlate to OCD?	Read article on serotonin in the brain and its effects on OCD.	Article #6	09/07/2024
How do zinc and selenium affect symptoms of OCD?	Read article on effects of trace elements on serotonin levels and OCD symtoms.	Article #7	09/11/2024
How can personalized network modeling be used for other psychiatric disorders, besides depression, and how can that be correlated to attentional functioning or something else?	Read article on personalized network modeling for mental illness in general.	Article #8	09/14/2024
How does the gut-brain axis affect mental health?	Read article on GBA and its effect on mental health.	Article #9	09/17/2024
How do probiotics affect serotonin production and tryptophan, along with OCD?	Read article on the gut-brain axis and the effect of probiotics on it.	Article #10	09/19/2024

Why does glycine have negative effects on the GI system and how can that be mitigated?			
How do anti-depressants and SSRIs work?			
How do other brain chemicals (such as dopamine) correlate to OCD?			
What is oxidative stress?			
How can arsenic induce symptoms of anxiety?			
How does serotonin affect cortico-striato-thalamo-cortical circuit? How is this circuit related to OCD?			
What model organisms can accurately display the effects of probiotics on the gut-brain axis and OCD?			

Literature Search Parameters:

These searches were performed between 08/15/2024 and XX/XX/2024.
List of keywords and databases used during this project.

Database/search engine	Keywords	Summary of search
WPI Gordon Library Journals	Obsessive-Compulsive Disorder	Found Journal of Obsessive-Compulsive and Related Disorders
Microsoft Bing	Supplements reducing symptoms of OCD, food and OCD, exercise and OCD	Found multiple articles about OCD and relationship with exercise, food, and supplements
Microsoft Bing	How does serotonin production work article	Found article on serotonin production and applications
Microsoft Bing	How do zinc and selenium affect serotonin production, OCD	Found articles on minerals/trace elements and their affect on serotonin production/OCD
Microsoft Bing	Gut brain axis and mental health	Found multiple articles on gut brain axis and their relation to mental health.
Microsoft Bing	How do probiotics affect serotonin article	Found article on the effects of probiotics on serotonin production.
Microsoft Bing	Can you measure serotonin levels in c elegans	Found article on measuring neurotransmitters in C. elegans.
Microsoft Bing	OCD model C. elegans	Found articles on different animal models for OCD, however, many did not include C. elegans and only included mice or rats.
Microsoft Bing	C. elegans and probiotics	Found articles on the use of probiotics on C. elegans.
Microsoft Bing	What do OCD behaviors in C. elegans look like	Found articles to read on OCD behavior models in C. elegans.
Microsoft Bing	Patents for OCD treatment, anxiety treatment, depression treatment, SSRIs	Found multiple patents related to use of SSRIs as treatment for different mental health

		disorders.
Microsoft Bing	Why do SSRIs cause withdrawal symptoms article	Found an article on the causes of withdrawal from SSRIs.
Microsoft Bing	Glutamate and C. elegans	Found multiple sources on glutamate and C. elegans, many of which are helpful for methodology for my project.

Tags:

Tag Name	
#intro	#math
#research-question	#serotonin
#methodology	#probiotics

Article #1 Notes: 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)	
Research Question/Problem/ Need	
Important Figures	
VOCAB: (w/definition)	
Cited references to follow up on	
Follow up Questions	

Article #1 Notes: Effect of concentrated exposure and response prevention on symptoms of insomnia

Article notes should be on separate sheets

Source Title	Journal of Obsessive-Compulsive and Related Disorders
Source citation (APA Format)	Landrø, N. E. H., Pryser, S. H., Hagen, K., Hansen, B., Kvale, G., & Solem, S. (2024). Effect of concentrated exposure and response prevention on symptoms of insomnia. *Journal of Obsessive-Compulsive and Related Disorders, 42,* 100891. https://doi.org/10.1016/j.jocrd.2024.100891
Original URL	https://doi.org/10.1016/j.jocrd.2024.100891
Source type	Journal Article
Keywords	Obsessive-compulsive disorder (OCD), insomnia, D-Cycloserine
#Tags	None
Summary of key points + notes (include methodology)	Summary: Previous studies using small sample sizes showed that the compound D-Cycloserine augmented the effects of treatment for OCD when used in combination with therapies. However, a new study using a much larger sample size showed no significant differences in the reduction of OCD symptoms in the two groups that were given D-Cycloserine (100mg and 250mg) when compared to the placebo group. The study also showed reduced insomnia symptoms in participants, although whether or not a participant was diagnosed with insomnia did not affect the treatment of their OCD. Methodology: Participants had to meet certain criteria in order to take part in the study. These criteria included: not having psychosis or bipolar disorder (BPD), willingness to not take any anxiety medication during the course of the study, and not needing to travel more than one hour to get to the facility. Participants were divided into three groups, one receiving 100mg of D-Cycloserine, one receiving 250mg of D-Cycloserine, and one placebo group. The ratio of participants per group was 2:2:1 with 163 in total. Then, they each went through Bergen 4-Day Treatment (B4DT), an intensive therapy program. The scales used to measure symptoms were the Bergen Insomnia Scale (BIS), the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS), and the Patient Health Questionnaire (PHQ). Notes: Results of this study went against previous beliefs that D-Cycloserine helped to augment treatment for OCD and insomnia. They showed that the treatment of OCD was not affected by whether or not a patient had insomnia and

	that patients that received D-Cycloserine didn't have significantly different reductions in symptoms after treatment. They also showed that treatment for OCD also reduced insomnia symptoms overall.
Research Question/Problem/ Need	How does the use of D-Cycloserine (DCS) affect results of treatment for obsessive-compulsive disorder (ODC) and insomnia?
Important Figures	**Table 2** Changes in insomnia, symptoms of OCD, and depression. Measure | Pre | Post | 3 m FU | 12 m FU | F | p | *Effect size (d)* Post | 3 m | 12 m | time * group p **BIS** 250 mg | 16.15 (8.28) | 12.92 (10.60) | 12.23 (8.59) | 13.85 (9.69) | | | 0.36 | 0.46 | 0.26 | 100 mg | 19.45 (10.62) | 14.97 (10.60) | 15.29 (10.43) | 16.65 (10.98) | | | 0.42 | 0.40 | 0.26 | Placebo | 18.27 (9.71) | 15.07 (11.92) | 16.00 (9.48) | 17.12 (10.78) | | | 0.29 | 0.24 | 0.11 | Total | 17.92 (9.64) | 14.17 (10.84) | 14.21 (9.64) | 15.63 (10.48) | 12.70 | <0.001 | 0.37 | 0.38 | 0.23 | 0.87 **Y-BOCS** 250 mg | 26.60 (4.04) | 11.75 (5.44) | 13.23 (7.58) | 14.63 (7.38) | | | 3.10 | 2.20 | 2.01 | 100 mg | 27.24 (3.67) | 11.78 (5.75) | 13.25 (6.63) | 14.19 (7.09) | | | 3.21 | 2.61 | 2.31 | Placebo | 27.20 (3.83) | 14.27 (7.16) | 16.10 (7.23) | 14.30 (7.62) | | | 2.25 | 1.92 | 2.14 | Total | 26.98 (3.83) | 12.28 (6.00) | 13.83 (7.18) | 14.38 (7.26) | 246.16 | <0.001 | 2.92 | 2.29 | 2.17 | 0.28 **PHQ-9** 250 mg | 11.47 (6.04) | 7.12 (6.02) | 6.54 (5.55) | 8.61 (5.93) | | | 0.72 | 0.85 | 0.48 | 100 mg | 12.77 (5.90) | 8.78 (6.12) | 9.17 (6.29) | 10.27 (6.32) | | | 0.50 | 0.59 | 0.41 | Placebo | 11.44 (5.70) | 7.60 (5.56) | 8.48 (4.21) | 10.00 (6.07) | | | 0.68 | 0.59 | 0.24 | Total | 12.01 (5.70) | 7.91 (6.01) | 7.99 (5.77) | 9.56 (6.13) | 33.73 | <0.001 | 0.70 | 0.70 | 0.41 | 0.63 *Note.* BIS, Bergen Insomnia Scale; Y-BOCS, Yale-Brown Obsessive Compulsive Scale; PHQ-9, Patient Health Questionnaire-9. Pre, pre-treatment; Post, post-treatment; 3 m FU, 3-month follow-up; 12 m FU, 12-month follow-up. $N = 163$. This figure is important because it includes the data from the study, showing a similar reduction in OCD and insomnia symptoms across all groups.
VOCAB: (w/definition)	Augment – to make something greater by adding to it; increase
Cited references to follow up on	Crane, G. E. (1961). The psychotropic effects of cycloserine: A new use for an antibiotic. *Comprehensive Psychiatry*, 2(1), 51–59. https://doi.org/10.1016/S0010-440X(61) 80007-2
Follow up Questions	How can insomnia continue to be treated in order to prevent a relapse in OCD symptoms? How did participants fair 2-3 years after the treatment program? Can D-Cycloserine have any effects without concurrent therapy? What other medications/substances could be used to treat OCD and/or insomnia? Why was D-Cycloserine thought to be effective?

Article #2 Notes: Underground cells make ‘dark oxygen’ without light

Article notes should be on separate sheets

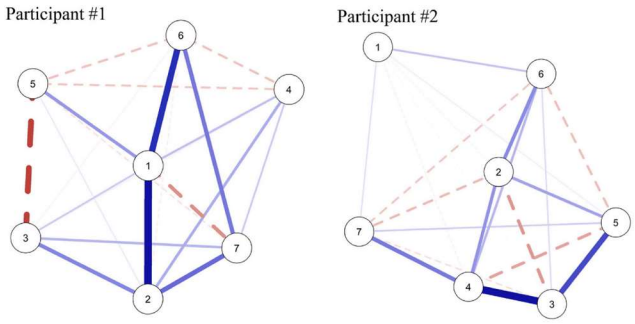
Source Title	Quanta Magazine
Source citation (APA Format)	Bolakhe, S. (2023, November 8). Underground cells make ‘Dark oxygen’ without light. *Quanta Magazine*. https://www.quantamagazine.org/underground-cells-make-dark-oxygen-without-light-20230717/#:~:text=In%20new%20research%20published%20last%20month%20in%20Nature,of%20oxygen%20even%20in%20the%20absence%20of%20light
Original URL	https://www.quantamagazine.org/underground-cells-make-dark-oxygen-without-light-20230717/#:~:text=In%20new%20research%20published%20last%20month%20in%20Nature,of%20oxygen%20even%20in%20the%20absence%20of%20light
Source type	Scientific News Article
Keywords	Methanogenic bacteria, aerobic bacteria, oxygen, water
#Tags	None
Summary of key points + notes (include methodology)	Summary: It is widely believed that deep in the ocean, there is an extreme lack of oxygen and resources, which would mean almost the complete lack of life. However, that is not necessarily the case. In deep water surrounding Alberta, Canada, microbes were found producing a large amount of oxygen, even without light. The results of the study went against the traditional belief that deeper water means less life because a greater number of microbes were actually found at greater depths. Methanogenic bacteria were found, but so were aerobes, which require oxygen, meaning that there must be oxygen dissolved in the water itself. The study suggested that the oxygen came from the methanogenic bacteria, because they produce their own from nitrites in the water, and some of that oxygen is released into the surrounding water. The process of bacteria breaking down compounds to form oxygen is called dismutation. This could lead to further research and development, especially on places like Mars.
Research Question/Problem/ Need	How do methanogenic bacteria make oxygen at great ocean depths?
Important Figures	None included
VOCAB: (w/definition)	Dismutation – the process of simultaneous oxidation and reduction
Cited references to follow up on	None

Follow up Questions	How exactly does dismutation work? Are there other types of bacteria that use dismutation to make oxygen? What other environments could these bacteria be present in? How could dismutation be artificially used and applied by humans?

Article #3 Notes: Examining attentional functioning in depression using a personalized network approach

Article notes should be on separate sheets

Source Title	Psychiatry Research Communications
Source citation (APA Format)	Kraft, B., Bø, R., Hoorelbeke, K., H.W. Koster, E., Jonassen, R., J. Harmer, C., & Inge Landrø, N. (2023). Examining attentional functioning in depression using a personalized network approach: a proof-of-principle study. *Psychiatry Research Communications*, *3*(3). https://doi.org/10.1016/j.psycom.2023.100137
Original URL	https://doi.org/10.1016/j.psycom.2023.100137
Source type	Journal Article
Keywords	Depression, attention, personalized network modeling, fatigue, network analysis, heterogeneity
#Tags	#intro
Summary of key points + notes (include methodology)	Summary: Due to the extremely dynamic and heterogenous nature of depression, the personalized network approach can help individuals understand their specific symptoms of the disorder. The personalized network approach involved participants assessing their depression symptoms on a smartphone app, and then models were created for each person. It was concluded that certain symptoms will affect the presence of other symptoms, resulting in extremely individual cases of depression. Methodology: Participants used a smartphone app over 14 days to track and assess depression symptoms. They reported symptoms five times per day at random times between 8:30am and 10:30pm, when prompted to do so. Multilevel vector auto regressive modeling (VAR) was used to create their individual networks. Participants had to have been diagnosed with Major Depressive Disorder, be between 18 and 65 years old, and fluent in Norwegian, as the study took place in Norway. They could not have mania, psychosis, or neurological disorders. The MINI International Neuropsychiatric Interview was used to assess this. The relationship between attention and different central symptoms was examined as part of the study in a lab after the 14-day period. This examination used the Attentional Network Test (ANT) on the computer to measure three areas of attention: alerting, orienting, and executive control. 92 total participants were recruited, but only 45 were able to be included at the end due to improper completion of all tasks.

	Notes: Results of the study showed that participants had varying central symptoms and peripheral symptoms of their depression, although the most common central symptoms were fatigue and a depressed mood. The least common central symptom was weight fluctuation. Participants often experienced difficulty with attention orienting when they were fatigued, and attention orienting may be associated with physical activity and social interactions. The authors also noted many considerations and other limitations from the study, such as the small sample size, limited number of depressive symptom options, and the optimal time between surveys. However, it still shows promise with personalized network modeling and establishing correlations between symptoms for individuals.
Research Question/Problem/ Need	How does reduced attentional functioning caused by depression affect individuals on a case-by-case basis?
Important Figures	 **Fig. 1.** Symptom networks for two sample participants. *Note.* Edge thickness reflects the magnitude of the association (blue = positive, red dashed = negative).1 = Sadness; 2 = Fatigue; 3 = Interest loss; 4 = Low positive affect; 5 = Concentration problems; 6 = Ruminating; 7 = Passivity. This figure is important because it shows strong correlations between certain symptoms, and not between others. It also shows the dynamic relationship between central and peripheral symptoms, and vast differences between individuals. **Table 1** Correlations between symptom centrality and attentional functioning with P-values in parentheses. | | Alerting | Orienting | Executive | |---|---|---|---| | Sadness | −0.04 (.79) | 0.03 (.87) | −0.13 (.39) | | Fatigue | 0.04 (.80) | **−0.32 (.03)** | 0.02 (.92) | | Loss of Interest | −0.10 (.53) | 0.22 (.14) | −0.14 (.36) | | Low positive affect | −0.14 (.36) | −0.07 (.67) | 0.00 (.98) | | Concentration problems | 0.17 (.27) | −0.11 (.47) | −0.09 (.56) | | Ruminating | −0.11 (.47) | 0.19 (.20) | −0.05 (.74) | | Passivity | 0.19 (.21) | 0.05 (.74) | **0.34 (.02)** | Note. P-values <.05 are denoted in boldface. Bonferroni-corrected significance level = 0.002. This figure is important because it shows the relationship between each symptom and how it affects the three areas of attention. Lower alerting and orienting scores mean poorer performance, and higher executive function scores indicate poorer

	conflict resolution.
VOCAB: (w/definition)	None
Cited references to follow up on	Not cited, but a follow up: Roefs, A., Fried, E. I., Kindt, M., Martijn, C., Elzinga, B., Evers, A. W., Wiers, R. W., Borsboom, D., & Jansen, A. (2022). A new science of mental disorders: Using personalised, transdiagnostic, dynamical systems to understand, model, diagnose and treat psychopathology. *Behaviour Research and Therapy*, *153*, 104096. https://doi.org/10.1016/j.brat.2022.104096
Follow up Questions	How could the personalized network approach be applied to other psychiatric disorders, including obsessive-compulsive disorder (OCD)? Does the personalized network approach provide an accurate representation for individuals? How can the results of the personalized network approach be applied to treatment for individuals?

Article #4 Notes: Nutritional and herbal supplements in the treatment of obsessive compulsive disorder

Article notes should be on separate sheets

Source Title	General Psychiatry
Source citation (APA Format)	Karcı, C. K., & Celik, G. G. (2020). Nutritional and herbal supplements in the treatment of obsessive compulsive disorder. *General Psychiatry*, *33*(2), e100159. https://doi.org/10.1136/gpsych-2019-100159
Original URL	https://doi.org/10.1136/gpsych-2019-100159
Source type	Journal Article
Keywords	Obsessive-compulsive disorder, supplements, zinc, selenium, glycine, vitamin B12, vitamin D, folic acid, symptom severity
#Tags	None
Summary of key points + notes (include methodology)	Summary and Notes: This article compiled the research of many studies that looked at how specific supplements and compounds affect symptoms of obsessive-compulsive disorder (OCD) and other psychiatric disorders. Research in this field has been fairly limited, causing many of the studies to contradict each other and with a limited number of studies, no strong conclusions can be drawn. Some supplements can be advantageous because they interact with serotonin and other neurotransmitters, which many people with OCD are known to be deficient in, such as Vitamins D and B12. People with OCD are often also deficient in trace elements zinc and selenium, which were both shown to decrease symptom severity, although there were very few studies on these elements, as well as N-acetyl cysteine having similar results. There were various other supplements, Glycine (led to study drop-outs because of severe effects on stomach), Myoinositol, St John's wort, Milk thistle, Valerian root, and Curcumin, but there were only one or two studies to support the reduction of OCD symptoms. Overall, many of these studies had issues due to participant's diets interfering with results, small sample sizes, and conflicting results. Certain supplements also shouldn't be taken with other drugs. This means that more research in this area is needed, because it isn't clear what supplements could be helpful in reducing symptoms of OCD. Methodology and Analysis: Many studies used the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) to quantify obsessive compulsive symptoms so that

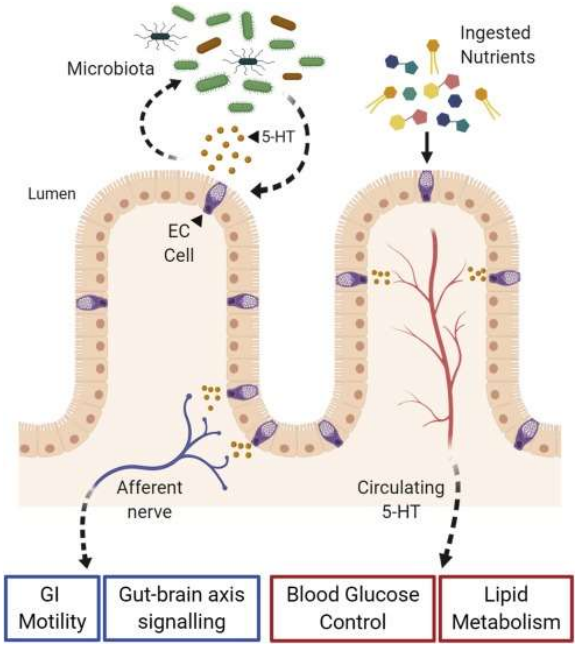
	they can be compared before and after supplements are given. They would need to compare symptoms severity pre and post supplement period. They would also need to know how much of each supplement to give each group, and for how long. It would also be helpful to control the study and understand external factors by collecting data on participants diet and lifestyle to understand how much of the supplementation could be influenced by that.
Research Question/Problem/ Need	How do different supplements and compounds correlate to and affect the severity of obsessive-compulsive disorder symptoms?
Important Figures	None included
VOCAB: (w/definition)	Aetiology – the cause of a disease; ameliorate – to make better or more tolerable;
Cited references to follow up on	Ozdemir, E., Cetinkaya, S., Ersan, S., Kucukosman, S., & Ersan, E. E. (2009). Serum selenium and plasma malondialdehyde levels and antioxidant enzyme activities in patients with obsessive–compulsive disorder. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *33*(1), 62–65. https://doi.org/10.1016/j.pnpbp.2008.10.004 Wołonciej, M., Milewska, E., & Roszkowska-Jakimiec, W. (2016). Trace elements as an activator of antioxidant enzymes. *Postępy Higieny I Medycyny Doświadczalnej*, *70*, 1483–1498. https://doi.org/10.5604/17322693.1229074 Shohag, H., Ullah, A., Qusar, S., Rahman, M., & Hasnat, A. (2012). Alterations of Serum Zinc, Copper, Manganese, Iron, Calcium, and Magnesium Concentrations and the Complexity of Interelement Relations in Patients with Obsessive–Compulsive Disorder. *Biological Trace Element Research*, *148*(3), 275–280. https://doi.org/10.1007/s12011-012-9371-3 *Sayyah, M., Andishmand, M., & Ganji, R. (2018). Effect of selenium as an adjunctive therapy in patients with treatment-resistant obsessive-compulsive disorder: A pilot randomized double blind placebo-controlled clinical trial. Archives of Psychiatry & Psychotherapy, 20(4).* Sayyah, M., Olapour, A., Saeedabad, Y. S., Parast, R. Y., & Malayeri, A. (2012). Evaluation of oral zinc sulfate effect on obsessive-compulsive disorder: A randomized placebo-controlled clinical trial. *Nutrition*, *28*(9), 892–895. https://doi.org/10.1016/j.nut.2011.11.027 Lafleur, D. L., Pittenger, C., Kelmendi, B., Gardner, T., Wasylink, S., Malison, R. T., Sanacora, G., Krystal, J. H., & Coric, V. (2005). N-acetylcysteine augmentation in serotonin reuptake inhibitor refractory obsessive-compulsive disorder. *Psychopharmacology*, *184*(2), 254–256. https://doi.org/10.1007/s00213-005-0246-6 Van Ameringen, M., Patterson, B., Simpson, W., & Turna, J. (2013). N-acetylcysteine augmentation in treatment resistant obsessive compulsive

	disorder: A case series. *Journal of Obsessive-Compulsive and Related Disorders*, *2*(1), 48–52. https://doi.org/10.1016/j.jocrd.2012.10.003 Sarris, J., Oliver, G., Camfield, D. A., Dean, O. M., Dowling, N., Smith, D. J., Murphy, J., Menon, R., Berk, M., Blair-West, S., & Ng, C. H. (2015). N-Acetyl Cysteine (NAC) in the Treatment of Obsessive-Compulsive Disorder: A 16-Week, Double-Blind, Randomised, Placebo-Controlled study. *CNS Drugs*, *29*(9), 801–809. https://doi.org/10.1007/s40263-015-0272-9 Also find sources about glycine and effects on OCD symptoms.
Follow up Questions	Are there common foods that people with OCD avoid due to symptoms, and does that lead to nutrient deficiencies and therefore severe symptoms? Is there a way to make glycine less harsh on the stomach in order for it to be a possible treatment for OCD? Could supplementation be more effective than therapy, or when used in combination, augment the effects of therapy?

Article #5 Notes: The ever-changing roles of serotonin

Article notes should be on separate sheets

Source Title	The International Journal of Biochemistry & Cell Biology
Source citation (APA Format)	Jones, L. A., Sun, E. W., Martin, A. M., & Keating, D. J. (2020). The ever-changing roles of serotonin. *The International Journal of Biochemistry & Cell Biology*, *125*, 105776. https://doi.org/10.1016/j.biocel.2020.105776
Original URL	https://doi.org/10.1016/j.biocel.2020.105776
Source type	Journal Article
Keywords	Gut microbiome, serotonin, 5-HT, 5-hydroxytryptamine, tryptophan, tryptophan hydroxylase, blood-brain barrier, SSRIs, anti-depressants
#Tags	#serotonin
Summary of key points + notes (include methodology)	Summary: Serotonin, also known as 5-HT or 5-hydroxytryptamine, is a neurotransmitter that plays many roles throughout the body, including affecting mood. It comes from the amino acid tryptophan and can be found in both the gut and brain. Serotonin reuptake inhibitors (SSRIs), a common antidepressant and treatment for depression, act on serotonin by not allowing it to leave the synaptic space within the brain. Increased serotonin in the gut and the use of SSRIs (increasing the serotonin in the brain) may be linked to weight gain, shown in mice. Overall, the findings of this study suggest that the gut microbiome and serotonin production may be linked to a plethora of human disorders that need further research. Notes: Serotonin is synthesized from the amino acid tryptophan by the rate-limiting enzyme tryptophan hydroxylase (TPH). There are two forms of TPH, Tph1, which is mainly found in gut endocrine cells, and Tph2, which is mainly found in the brain/central nervous system. 5-HT cannot cross the blood-brain barrier, meaning that the serotonin found in the gut and in the brain remain separate. The traditional roles of serotonin include controlling mood, anxiety, sleep, and some GI functions. Many anti-depressants function by preventing the removal of serotonin from the brain by blocking the serotonin transporter (SERT). This prevents serotonin from leaving the synaptic space. 5-HT in the gut is thought to affect weight gain and be affected by the gut microbiome. More 5-HT was found in obese mice than non-obese mice, which shows the possible connection to weight gain and obesity. Serotonin production in the gut may also be affected by ingested nutrients. In the brain, the long-term use of SSRIs (Serotonin reuptake inhibitors) may also

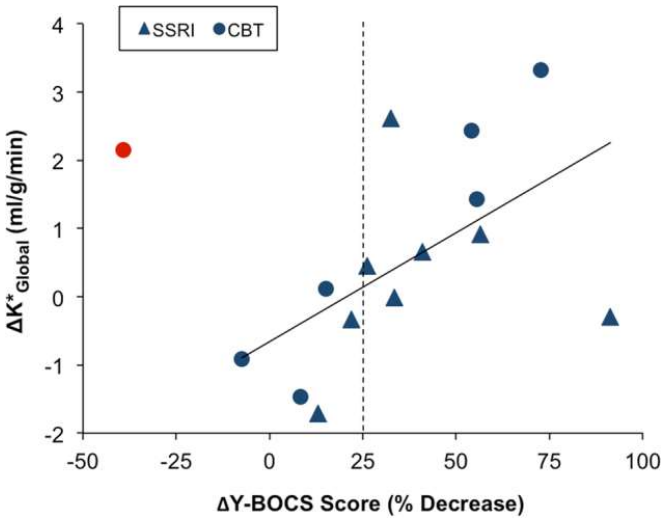
	result in weight gain. There may be a connection here to too much gut serotonin and too much brain serotonin.
Research Question/Problem/ Need	How does the gut microbiome affect serotonin production?
Important Figures	 This figure is important because it is a diagram that shows how serotonin production interacts with the gut microbiome.
VOCAB: (w/definition)	Serotonin reuptake inhibitors (SSRIs) – antidepressants that prevent serotonin from being removed from the synaptic space;
Cited references to follow up on	Gershon, M. D., & Tack, J. (2007). The serotonin signaling system: From basic understanding to drug development for functional GI disorders. *Gastroenterology*, *132*(1), 397–414. https://doi.org/10.1053/j.gastro.2006.11.002 Neufeld, K. M., Bienenstock, J., Bharwani, A., Champagne-Jorgensen, K., Mao, Y., West, C., Liu, Y., Surette, M. G., Kunze, W., & Forsythe, P. (2019). Oral selective serotonin reuptake inhibitors activate vagus nerve dependent gut-brain signalling. *Scientific Reports*, *9*(1). https://doi.org/10.1038/s41598-019-50807-8
Follow up Questions	What makes up anti-depressants that are SSRIs and could this same function be accomplished by an everyday essential vitamin or mineral? How does nutrient ingestion affect serotonin production in the gut and/or brain? How does one's diet affect their gut microbiome? Why does increased serotonin in the gut and/or brain correlate to weight gain/obesity? What is the connection between serotonin in the gut and in the brain?

Article #6 Notes: Brain serotonin synthesis capacity in obsessive-compulsive disorder: effects of cognitive behavioral therapy and sertraline

Article notes should be on separate sheets

Source Title	Translational Psychiatry
Source citation (APA Format)	Lissemore, J. I., Sookman, D., Gravel, P., Berney, A., Barsoum, A., Diksic, M., Nordahl, T. E., Pinard, G., Sibon, I., Cottraux, J., Leyton, M., & Benkelfat, C. (2018). Brain serotonin synthesis capacity in obsessive-compulsive disorder: effects of cognitive behavioral therapy and sertraline. *Translational Psychiatry*, *8*(1). https://doi.org/10.1038/s41398-018-0128-4
Original URL	https://doi.org/10.1038/s41398-018-0128-4
Source type	Journal Article
Keywords	Cognitive behavioral therapy, CBT, selective serotonin reuptake inhibitors, SSRIs, obsessive-compulsive disorder, Y-BOCS, cortico-striato-thalamo-cortical (CSTC) circuit, sertraline, PET scans
#Tags	#math
Summary of key points + notes (include methodology)	Summary: Cognitive Behavioral Therapy and Selective Serotonin Reuptake Inhibitors (SSRIs) are two main ways to treat obsessive-compulsive disorder (OCD). However, they normally only achieve an efficacy rate of 40-60%, which means that many people with OCD don't have an effective treatment. This study attempted to understand the connection between those two treatment methods and serotonin synthesis, as reduced serotonin levels are thought to be associated with OCD. The cortico-striato-thalamo-cortical (CSTC) circuit often has elevated levels of activity in patients with OCD as well. This study separated participants into two groups randomly and assigned half to receive SSRIs for 12 weeks and the other half to receive CBT for 12 weeks. PET scans were done before and after as well. Serotonin transporters (5-HTT) were reduced post-treatment, and most patients had a significant reduction in their Y-BOCS score. Additionally, the study suggested that neurotransmitters don't act alone, and dopamine may have a relationship with serotonin and OCD. The ultimate goal is to have a more effective treatment that leads to patients with OCD entering remission and having significantly reduced symptoms. Methodology: This study included 16 participants, all of whom were randomly assigned to either receive CBT or SSRIs. Before and after treatment, they received PET scans. Patients had to be medication free for at least 3 weeks or more than 5 elimination half lives of their medication, whichever was longer, but many were

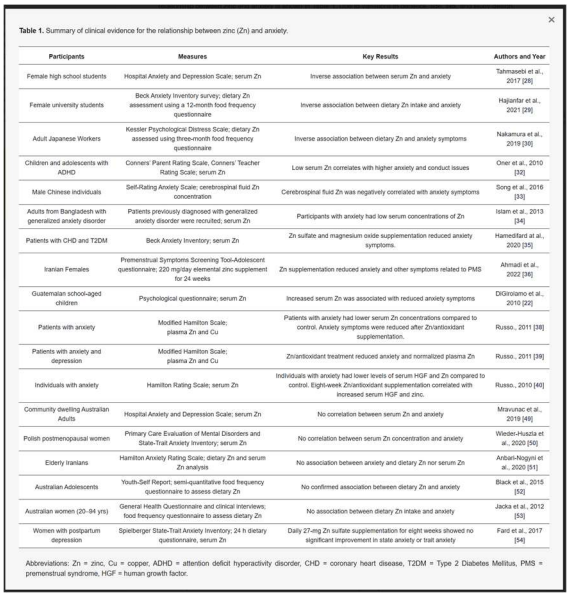
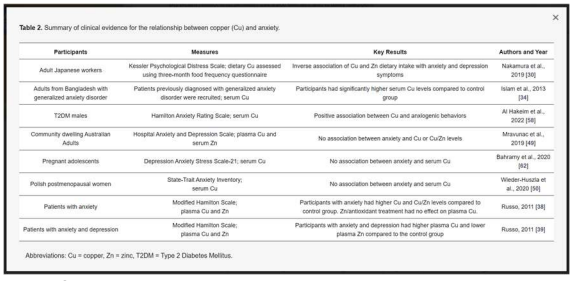
	medication free for much more time (6 months or more). Patients also couldn't have other disorders, except for depression, no substance abuse history, and a couple of other factors. The participants received their respective treatments for 12 weeks. The Yale-Brown Obsessive Compulsive Scale (Y-BOCS) was used to quantify OCD symptoms. For the patients receiving sertraline (the SSRI), they started with 25mg/day, after 1 week that increased to 50mg/day, after another week that increased to 100mg/day, after two additional weeks that increased to 150mg/day, and then after two more weeks it increased to 200mg/day. The increases were not made if patients had severe side effects. The mean final dose was 133 +/- 52 mg/day. For the patients receiving CBT, they received two 90 minutes individual sessions for the 12 weeks, with some behavioral homework for the durations in between sessions. When the PET scans were performed, patients were tested for and determined to be free of drugs such as cocaine, opiates, cannabinoids, benzodiazepines, and more. Women of fertile age were scanned during their follicular phase because serotonin levels may change throughout their menstrual cycle.
Research Question/Problem/ Need	How do Cognitive Behavioral Therapy (CBT) and Selective Serotonin Reuptake Inhibitors (SSRIs) affect serotonin synthesis in the brain and how do serotonin synthesis levels correspond to changes in OCD symptom severity?
Important Figures	Table 1 Patient demographics **Characteristic** / **CBT (*n* = 8)** / **SSRI (*n* = 8)** Age, y Mean (SD): 33.7 (9.5) / 33.4 (8.5) Range: 23–53 / 18–45 Responders/partial responders: 4/8 / 6/8 Early-onset OCD (≤10 y), No.: 5 / 5 Predominant compulsion, No. Washing: 4 / 4 Checking: 4 / 4 Lifetime history of MDE (2° to OCD symptoms), No.: 2 / 3 Past substance abuse, No.: 0 / 0 Pre / Post / Pre / Post Y-BOCS score, mean (SD): 23 (4.4) / 15.8 (7.5) / 23.6 (5.6) / 14.7 (8.2) BDI score, mean (SD): 9.8 (4.5) / 6.9 (6.0) / 14.1 (11.2) / 7.6 (9.5) Plasma free tryptophan, mean (SD), nmol/L[a]: 10.3 (2.6) / 8.4 (1.4) / 9.8 (1.7) / 9.3 (2.1) Global *K**, mean (SD), mL/g/min[a]: 5.1 (1.3) / 6.1 (1.5) / 5.8 (1.3) / 6.07 (2.0) Intravenously injected, mean (SD), mCi[a]: 9.3 (1.1) / 9.6 (0.7) / 9.6 (0.8) / 9.7 (0.4) Open in a separate window Responders/partial responders demonstrated a >25% decrease in Y-BOCS score *OCD* obsessive-compulsive disorder, *CBT* cognitive behavioral therapy, *SSRI* selective serotonin re-uptake inhibitor, *MDE* major depressive episode, *Y-BOCS* Yale-Brown Obsessive Compulsive Scale, *BDI* Beck Depression Inventory, *No.* number [a]Data not included for one patient treated with CBT This figure is important because it shows the data from before and after treatment. The reduction in the Y-BOCS score shows effective treatment.

	 This figure is important because it shows the positive correlation between serotonin levels and the decrease in the Y-BOCS score.
VOCAB: (w/definition)	PET Scan – positron emission tomography, uses a radioactive tracer to understand what organs look like in real time;
Cited references to follow up on	Stengler-Wenzke, K., Müller, U., Angermeyer, M., Sabri, O., & Hesse, S. (2004). Reduced serotonin transporter?availability in obsessive?compulsive disorder (OCD). *European Archives of Psychiatry and Clinical Neuroscience*, *254*(4). https://doi.org/10.1007/s00406-004-0489-y Kim, E., Howes, O. D., Park, J. W., Kim, S. N., Shin, S. A., Kim, B., Turkheimer, F. E., Lee, Y., & Kwon, J. S. (2015). Altered serotonin transporter binding potential in patients with obsessive-compulsive disorder under escitalopram treatment: [11C]DASB PET study. *Psychological Medicine*, *46*(2), 357–366. https://doi.org/10.1017/s0033291715001865
Follow up Questions	Does the reduction of serotonin transporters mean that more serotonin was present, occupying the available transporters? How is dopamine connected to changes in serotonin levels and how could it affect OCD symptoms? What medications are there that affect dopamine levels in the brain?

Article #7 Notes: Trace minerals and anxiety: A review of zinc, copper, iron, and selenium

Article notes should be on separate sheets

Source Title	Dietetics
Source citation (APA Format)	Totten, M. S., Davenport, T. S., Edwards, L. F., & Howell, J. M. (2023). Trace minerals and anxiety: A review of zinc, copper, iron, and selenium. *Dietetics*, *2*(1), 83–103. https://doi.org/10.3390/dietetics2010008
Original URL	https://doi.org/10.3390/dietetics2010008
Source type	Journal Article
Keywords	Zinc, copper, selenium, iron, arsenic, anxiety disorders, neurotransmitters, supplements
#Tags	None
Summary of key points + notes (include methodology)	Summary: Various trace elements, such as zinc, copper, iron, and selenium, likely have an effect on mental health and psychiatric disorders, although research in the field has been fairly limited and inconclusive. Zinc, for example, is an essential mineral, with roles in things like gene expression, immune function, wound healing, cell division, and mental health disorders. Studies have suggested that zinc plays a role in regulating neurotransmitters. Studies have shown correlations between increasing or supplementation of zinc and decreasing anxiety symptoms. These studies used diet information and blood testing to determine levels of zinc. Zinc may have an effect on glutamate and gamma-aminobutyric acid in the brain, but more research is necessary to improve understanding of its effects. Copper and zinc may have a role in anxiety disorders together. Studies showed that copper deficiencies are very rare, but copper overloads are less rare. Copper may have an effect on zinc, reducing the concentration. Too much copper may also have an effect on other biomolecules in the brain, as well as zinc. More research is needed into the relationship between copper, zinc, neurotransmitters, and anxiety disorders. Iron is a trace element that has effects on blood and oxygen transport, and there are also many iron-dependent proteins. Studies suggested that iron deficiency can have an affect on anxiety, correlating to worse symptoms. Ceruloplasmin is a copper-dependent ferroxidase that regulates iron efflux, and when removed from mice, iron levels were significantly reduced. The relationship between dietary iron and anxiety disorders needs to be further explored.

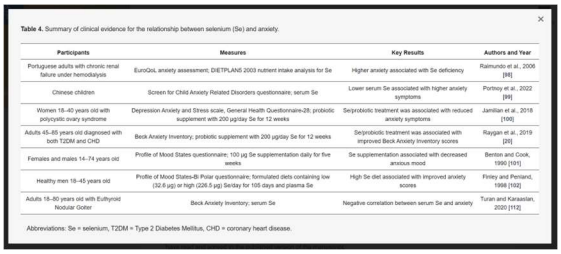
	Selenium is another trace element that functions as an antioxidant, regulates the thyroid, immune support, among other things. Selenium in relation to anxiety has been a new topic in the field, which means there is limited research available to make our understandings concrete. However, some studies show that selenium supplementation has promising effects, reducing anxiety symptoms. Since selenium plays a role in thyroid function, selenium deficiencies related to thyroid disease may be comorbid with anxiety. Not a form of treatment, but a possible way to induce anxiety symptoms is with arsenic. This article also did not go in depth about specific methodologies or analyses because it drew conclusions from previous studies.
Research Question/Problem/ Need	How do trace elements like zinc, copper, iron, and selenium affect anxiety disorders and other functions within the brain and body?
Important Figures	 **Table 1.** Summary of clinical evidence for the relationship between zinc (Zn) and anxiety. This figure is important because it outlines the results of zinc on different groups of people. Many groups had zinc lower symptoms of anxiety, while some had no effects.  **Table 2.** Summary of clinical evidence for the relationship between copper (Cu) and anxiety. This figure is important because it outlines the results of copper on different groups of people. Many groups show too much copper correlates to higher levels of anxiety.

Participants	Measures	Key Results	Authors and Year
Female high school students	Hospital Anxiety and Depression Scale; serum Zn	Inverse association between serum Zn and anxiety	Tahmasebi et al., 2017 [28]
Female university students	Beck Anxiety Inventory survey; dietary Zn assessment using a 12-month food frequency questionnaire	Inverse association between dietary Zn intake and anxiety	Hajianfar et al., 2021 [29]
Adult Japanese Workers	Kessler Psychological Distress Scale; dietary Zn assessed using three-month food frequency questionnaire	Inverse association between dietary Zn and anxiety symptoms	Nakamura et al., 2019 [30]
Children and adolescents with ADHD	Conners' Parent Rating Scale, Conners' Teacher Rating Scale; serum Zn	Low serum Zn correlates with higher anxiety and conduct issues	Oner et al., 2010 [32]
Male Chinese individuals	Self-Rating Anxiety Scale; cerebrospinal fluid Zn concentration	Cerebrospinal fluid Zn was negatively correlated with anxiety symptoms	Song et al., 2016 [33]
Adults from Bangladesh with generalized anxiety disorder	Patients previously diagnosed with generalized anxiety disorder were recruited; serum Zn	Participants with anxiety had low serum concentrations of Zn	Islam et al., 2013 [34]
Patients with CHD and T2DM	Beck Anxiety Inventory; serum Zn	Zn sulfate and magnesium oxide supplementation reduced anxiety symptoms.	Hamedifard at al., 2020 [35]
Iranian Females	Premenstrual Symptoms Screening Tool-Adolescent questionnaire; 220 mg/day elemental zinc supplement for 24 weeks	Zn supplementation reduced anxiety and other symptoms related to PMS	Ahmadi et al., 2022 [36]
Guatemalan school-aged children	Psychological questionnaire; serum Zn	Increased serum Zn was associated with reduced anxiety symptoms	DiGiroIamo et al., 2010 [22]
Patients with anxiety	Modified Hamilton Scale; plasma Zn and Cu	Patients with anxiety had lower serum Zn concentrations compared to control. Anxiety symptoms were reduced after Zn/antioxidant supplementation.	Russo., 2011 [38]
Patients with anxiety and depression	Modified Hamilton Scale; plasma Zn and Cu	Zn/antioxidant treatment reduced anxiety and normalized plasma Zn	Russo., 2011 [39]
Individuals with anxiety	Hamilton Rating Scale; serum Zn	Individuals with anxiety had lower levels of serum HGF and Zn compared to control. Eight-week Zn/antioxidant supplementation correlated with increased serum HGF and zinc.	Russo., 2010 [40]
Community dwelling Australian Adults	Hospital Anxiety and Depression Scale; serum Zn	No correlation between serum Zn and anxiety	Mravunac et al., 2019 [49]
Polish postmenopausal women	Primary Care Evaluation of Mental Disorders and State-Trait Anxiety Inventory; serum Zn	No correlation between serum Zn concentration and anxiety	Wieder-Huszla et al., 2020 [50]
Elderly Iranians	Hamilton Anxiety Rating Scale; dietary Zn and serum Zn analysis	No association between anxiety and dietary Zn nor serum Zn	Anbari-Nogyini et al., 2020 [51]
Australian Adolescents	Youth-Self Report; semi-quantitative food frequency questionnaire to assess dietary Zn	No confirmed association between dietary Zn and anxiety	Black et al., 2015 [52]
Australian women (20–94 yrs)	General Health Questionnaire and clinical interviews; food frequency questionnaire to assess dietary Zn	No association between dietary Zn intake and anxiety	Jacka et al., 2012 [53]
Women with postpartum depression	Spielberger State-Trait Anxiety Inventory; 24 h dietary questionnaire, serum Zn	Daily 27-mg Zn sulfate supplementation for eight weeks showed no significant improvement in state anxiety or trait anxiety	Farid et al., 2017 [54]

Abbreviations: Zn = zinc, Cu = copper, ADHD = attention deficit hyperactivity disorder, CHD = coronary heart disease, T2DM = Type 2 Diabetes Mellitus, PMS = premenstrual syndrome, HGF = human growth factor.

Participants	Measures	Key Results	Authors and Year
Adult Japanese workers	Kessler Psychological Distress Scale; dietary Cu assessed using three-month food frequency questionnaire	Inverse association of Cu and Zn dietary intake with anxiety and depression symptoms	Nakamura et al., 2019 [30]
Adults from Bangladesh with generalized anxiety disorder	Patients previously diagnosed with generalized anxiety disorder were recruited; serum Cu	Participants had significantly higher serum Cu levels compared to control group	Islam et al., 2013 [34]
T2DM males	Hamilton Anxiety Rating Scale; serum Cu	Positive association between Cu and anxiogenic behaviors	Al Hakeim et al., 2022 [58]
Community dwelling Australian Adults	Hospital Anxiety and Depression Scale; plasma Cu and serum Zn	No association between anxiety and Cu or Cu/Zn levels	Mravunac et al., 2019 [49]
Pregnant adolescents	Depression Anxiety Stress Scale-21; serum Cu	No association between anxiety and serum Cu	Bahramy et al., 2020 [62]
Polish postmenopausal women	State-Trait Anxiety Inventory; serum Cu	No association between anxiety and serum Cu	Wieder-Huszla et al., 2020 [50]
Patients with anxiety	Modified Hamilton Scale; plasma Cu and Zn	Participants with anxiety had higher Cu and Cu/Zn levels compared to control group. Zn/antioxidant treatment had no effect on plasma Cu.	Russo, 2011 [38]
Patients with anxiety and depression	Modified Hamilton Scale; plasma Cu and Zn	Participants with anxiety and depression had higher plasma Cu and lower plasma Zn compared to the control group	Russo, 2011 [39]

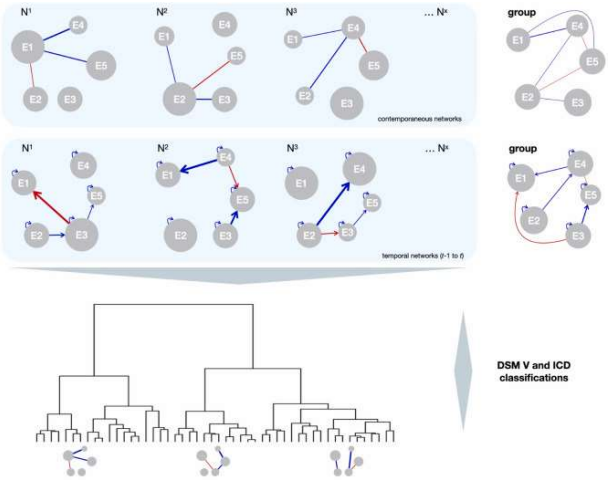
Abbreviations: Cu = copper, Zn = zinc, T2DM = Type 2 Diabetes Mellitus.

	 **Table 3.** Summary of clinical evidence for the relationship between iron (Fe) and anxiety. This figure is important because it outlines the results of iron on different groups of people. Many groups show iron deficiency corresponds to greater symptoms of anxiety.  **Table 4.** Summary of clinical evidence for the relationship between selenium (Se) and anxiety. This figure is important because it outlines the results of selenium deficiencies on different groups of people. Many groups show selenium deficiency corresponds to greater symptoms of anxiety.
VOCAB: (w/definition)	Efflux – outflow of something;
Cited references to follow up on	Młyniec, K., Gaweł, M., Doboszewska, U., Starowicz, G., & Nowak, G. (2017). The role of elements in anxiety. *Vitamins and Hormones*, *103,* 295–326. https://doi.org/10.1016/bs.vh.2016.09.002
Follow up Questions	How exactly do each of these trace elements affect different neurotransmitters in the brain, meaning, what proteins do they interact with and how do they affect neurotransmitters too? What reduction in anxiety demonstrates that the trace element may have an effect? How could different supplements (not just limited to trace elements and minerals, but also vitamins and plants) affect anxiety disorders, OCD, and comorbidities with other mental health disorders? How does arsenic cause anxiety symptoms (and could this be further looked into for causation and treatment options, for example, a statistical analysis of people with high levels of arsenic based on geographical location and anxiety or OCD incidences?)?

Article #8 Notes: A new science of mental disorders: Using personalised, transdiagnostic, dynamical systems to understand, model, diagnose and treat psychopathology

Article notes should be on separate sheets

Source Title	Behaviour Research and Therapy
Source citation (APA Format)	Roefs, A., Fried, E. I., Kindt, M., Martijn, C., Elzinga, B., Evers, A. W., Wiers, R. W., Borsboom, D., & Jansen, A. (2022). A new science of mental disorders: Using personalised, transdiagnostic, dynamical systems to understand, model, diagnose and treat psychopathology. *Behaviour Research and Therapy*, *153*, 104096. https://doi.org/10.1016/j.brat.2022.104096
Original URL	https://doi.org/10.1038/s41598-022-05078-1
Source type	Journal Article
Keywords	Personalized, transdiagnostic, dynamical systems, mental health disorders, treatment, causes
#Tags	#research-question
Summary of key points + notes (include methodology)	Summary: Treatment for mental health disorders are often ineffective. Many patients either don't respond to treatment at all, or respond but relapse within a year. This leaves the scientific community searching for a better way to treat disorders, and that may start with how we look and diagnose them. Mental health disorders are often comorbid. The goal of the personalized network to diagnose and treat disorders is to understand how different symptoms and external factors interact with one another. This includes how comorbidities interact and feed one another. The belief behind this is that symptoms constitute the disorders, there are layers to them, and understanding their complex interactions on an individual basis, because not every person will express the same disorder in the same way, can lead to more effective treatment. Methodology: This study took a large number of patients with a variety of mental health diagnoses and formed symptom networks for them. They took in information that was collected via the patients phone. The information they collected includes: physical activity, sleep quality data, time spent online, time taken to respond to text messages, ecological momentary assessment (EMA), and other data.

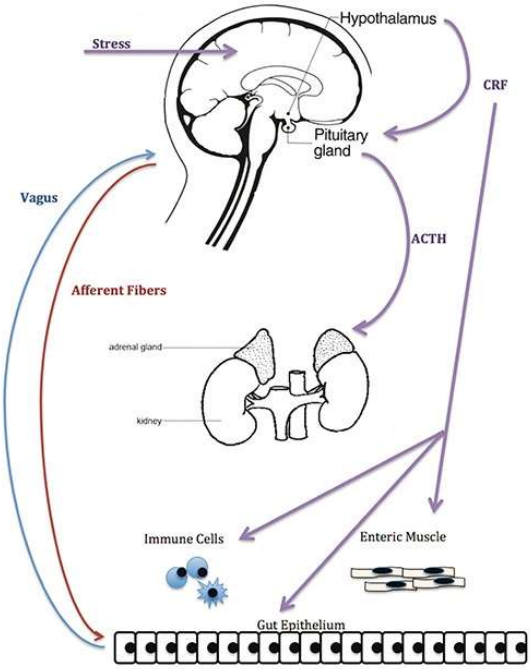
	They had a 4 week measurement period, 8 times per day, leading to a total of 224 measurements per variable per person. They used the Vector Autoregressive (VAR) model to regress each variable against all of the others from a certain time point. Other models that have been used to create symptom networks include the Group Iterative Multiple Model Estimation (GIMME) and the Dynamic Structural Equation Model (DSEM). Notes: The study noted that the smartphone survey itself that was given to participants could have been seen as a burden, which may cause inputs to be lower quality so that it could be completed faster. Another goal of the study would be to look at networks with similar structures and see if they have similar diagnoses, as well as how well the network diagnoses match up with traditional ones. If similar networks have similar diagnoses, and they match up with traditional ones, network modelling adds limited value because the same thing has already been accomplished. Centrality of symptoms can be defined in a couple of different ways in the network models. Degree is the number of edges (connections) the node (symptom) has, strength is the weight of the edges (absolute value), and expected influence is the weight with its positive or negative correlation. Treatment may focus on central symptoms or the symptoms with the most outstrength. The example given was with a patient with the strongest node being insomnia, treatment could be for insomnia and observe how that affects the rest of the network. If it is shown that network-based treatment is better than traditional treatment, clinicians would need a way to implement it quickly, rather than taking a long time for data collection.
Research Question/Problem/ Need	How can individual network models be used to better diagnose and treat different mental health disorders?
Important Figures	 This figure is important because it outlines how the networks would be structured

	and how patterns could be found.
VOCAB: (w/definition)	Transdiagnostic: a psychological mechanism that connects a group of mental disorders;
Cited references to follow up on	Bringmann, L. F., Vissers, N., Wichers, M., Geschwind, N., Kuppens, P., Peeters, F., Borsboom, D., & Tuerlinckx, F. (2013). A Network Approach to Psychopathology: New Insights into Clinical Longitudinal Data. *PLoS ONE*, *8*(4), e60188. https://doi.org/10.1371/journal.pone.0060188
Follow up Questions	Are these network models effective, and how do they compare to traditional diagnoses (possible #research-question)? Do network-based treatments have greater successes (less relapse, etc.)? How could this model be applied to a model organism? If effective, how could these models be applied to a clinical setting, allowing for quick data collection to receive a diagnosis?

Article #9 Notes: Gut microbiota's effects on mental health

Article notes should be on separate sheets

Source Title	Clinics and Practice
Source citation (APA Format)	Clapp, M., Aurora, N., Herrera, L., Bhatia, M., Wilen, E., & Wakefield, S. (2017). Gut microbiota's effect on mental health: The Gut-Brain axis. *Clinics and Practice*, *7*(4), 987. https://doi.org/10.4081/cp.2017.987
Original URL	https://doi.org/10.4081/cp.2017.987
Source type	Journal Article
Keywords	Gut-brain axis, GBA, HPA, diet, gut microbiota, human microbiome, rats, mice, Bifidobacterium, probiotics, serotonin, tryptophan, leaky gut syndrome
#Tags	#research-question
Summary of key points + notes (include methodology)	Summary and Notes: The Gut-Brain Axis (GBA) is a key connection that has been established over the past years between gut health and mental health. Gut microbiota can be influenced by many things, such as diet, genetics, method of birth, being breastfeed versus formula fed as a baby, and more. Increased levels of *Bifidobacterium* have been shown to be present in healthy guts. Not every microbiome or gut microbiota are the same, but they can generally be classified into three groups: *Bacteroides*, for people consuming high protein diets, *Prevotella,* for people consuming high carb diets, and *Ruminococcus.* These classifications are independent of body mass index (BMI), body fat percentage, gender, and geolocation. The main factors that influence them are diet and genetics. *Leaky gut syndrome* is often the result of changes in diet, periods of prolonged and high stress, antibiotics, or other factors. It allows bacteria to leak through the gut because the intestines are more permeable. This is often associated with psychiatric disorders. Probiotics may be a possible treatment for psychiatric disorders using the GBA. Different studies have shown that people given probiotics have had improvements in psychiatric symptoms. One study gave a group of healthy volunteers probiotics, and another group antidepressants, and tracked the cortisol levels and psychological effects. Cortisol levels were reduced and the probiotics acted very similarly to the antidepressants, a proven treatment for depression.

	Another part of the GBA lies with the HPA (hypothalamic-pituitary-adrenal axis), where dysregulation has been associated with depression, anxiety, and other possible disorders. Some studies showed that probiotics could regulate the HPA. Probiotics may also increase tryptophan, involved in the production of serotonin (see Article Notes #6 for a connection between tryptophan, serotonin, and OCD). Probiotics would be a good treatment for psychiatric disorders, if proven effective, because they are extremely accessible, can be found in natural food sources, and are cost-effective. They also have the potential to be more effective than current treatments, which don't have hugely high success rates.
Research Question/Problem/ Need	How can probiotics and gut microbiota use the Gut-Brain axis to affect mental health?
Important Figures	 This figure is important because it shows the relationship between immune cells, gut bacteria, and the brain (HPA).
VOCAB: (w/definition)	Microbiome – all microorganisms in the human body and their respective genetic material; microbiota – all microorganisms in a particular location (ex. Gut microbiota, microorganisms in the gut); cytokine – substance(s) excreted by cells;
Cited references to follow up on	Ait-Belgnaoui, A., Durand, H., Cartier, C., Chaumaz, G., Eutamene, H., Ferrier, L., Houdeau, E., Fioramonti, J., Bueno, L., & Theodorou, V. (2012). Prevention of gut leakiness by a probiotic treatment leads to attenuated HPA response to an acute psychological stress in rats. *Psychoneuroendocrinology*, *37*(11), 1885–1895. https://doi.org/10.1016/j.psyneuen.2012.03.024 Praveen, V., & Praveen, S. (2017). Microbiome–Gut–Brain axis: A pathway for improving brainstem serotonin homeostasis and successful autoresuscitation in

	SIDS—A novel hypothesis. *Frontiers in Pediatrics*, *4*. https://doi.org/10.3389/fped.2016.00136
Follow up Questions	How could probiotics affect serotonin production and therefore? What other factors could affect diversity among gut microbiotas? Could gut bacteria be transplanted as a form of treatment?

Article #10 Notes: Exploring the serotonin-probiotics-gut health axis: A review of current evidence and potential mechanisms

Article notes should be on separate sheets

Source Title	Food Science & Nutrition
Source citation (APA Format)	Akram, N., Faisal, Z., Irfan, R., Shah, Y. A., Batool, S. A., Zahid, T., Zulfiqar, A., Fatima, A., Jahan, Q., Tariq, H., Saeed, F., Ahmed, A., Asghar, A., Ateeq, H., Afzaal, M., & Khan, M. R. (2023). Exploring the serotonin-probiotics-gut health axis: A review of current evidence and potential mechanisms. *Food Science & Nutrition*, *12*(2), 694–706. https://doi.org/10.1002/fsn3.3826
Original URL	https://doi.org/10.1002/fsn3.3826
Source type	Journal Article
Keywords	Probiotics, serotonin signaling, neurotransmitters, chronic illness, cortisol, microbiota, gut-brain axis
#Tags	None
Summary of key points + notes (include methodology)	Summary: Current treatments for psychiatric disorders often come with side effects and are ineffective in general. Probiotics are a potential treatment that could reduce inflammation, alter gut microbiota, and affect serotonin in both the gut and the brain. Other studies have shown a connection between gut health and brain health, along the gut-brain axis, based on comorbidities with gut diseases and psychiatric disorders. Serotonin is thought to regulate appetite, peristalsis, and satiety, which all affect the absorption of nutrients. An extension of the gut-brain axis is the hypothalamus-pituitary-adrenal (HPA) axis, with gut microbiota showing their affect on stress hormones such as cortisol. Methodology: One study used rats and looked at their gut microbiota. It investigated if differences in the expression of 5-HTT (serotonin transporter) affect changes in the gut microbiota. Notes: Although serotonin cannot cross the blood-brain barrier itself, tryptophan can, which is converted into serotonin (5-HT) from 5-HTP (tryptophan product) in the brain. Obese people have been found to have higher levels of 5-HT in the gut (peripheral) than non-obese people. Because serotonin cannot cross the blood-brain axis, tryptophan does, and then initiates serotonin synthesis in the brain (tryptophan that comes from the GI system and food).

	Enterochromaffin cells (ECCs) within the GI system produce 90% of the body's serotonin, only a small amount is actually found in the brain. The hypothalamic-pituitary-adrenal (HPA) axis is one of the main parts of the GBA. Bacteria in the gut can control levels of cortisol and therefore level of stress through these axes. Bacteria in the gut can ferment and produce short-chain fatty acids (butyrate, propionate, acetate) and can affect neurotransmission. Extreme changes in the microbiota can pose a risk for chronic illnesses. Irritable bowel syndrome (IBS) is a chronic illness with a connection to gut microbiota. People with IBS have been shown to have reduced ECCs and serotonin in their gut. A study (Li, Liu, et al. (2019)) looked at prebiotics and probiotics and their effect on depression, which showed to act as antidepressants. Dysbiosis has been shown to put people at greater risk for developing a mental health disorder. This is likely because they help to maintain homeostasis with serotonin. Probiotics also likely have a role in promoting serotonin signaling.
Research Question/Problem/ Need	How can probiotics affect serotonin signaling along the gut-brain axis and affect different chronic illnesses?

Important Figures	 This figure is important because it outlines the results of different studies using probiotics and where to find the original articles.
VOCAB: (w/definition)	Peristalsis (context: serotonin was thought to be a primary regulator of this process) – movement that moves food through the digestion system; dysbiosis – an extreme change in the gut microbiota
Cited references to follow up on	Beilharz, J. E., Kaakoush, N. O., Maniam, J., & Morris, M. J. (2017). Cafeteria diet and probiotic therapy: cross talk among memory, neuroplasticity, serotonin receptors and gut microbiota in the rat. *Molecular Psychiatry*, *23*(2), 351–361. https://doi.org/10.1038/mp.2017.38 Chen, Y., Xu, J., & Chen, Y. (2021). Regulation of neurotransmitters by the gut microbiota and effects on cognition in neurological disorders. *Nutrients*, *13*(6), 2099. https://doi.org/10.3390/nu13062099

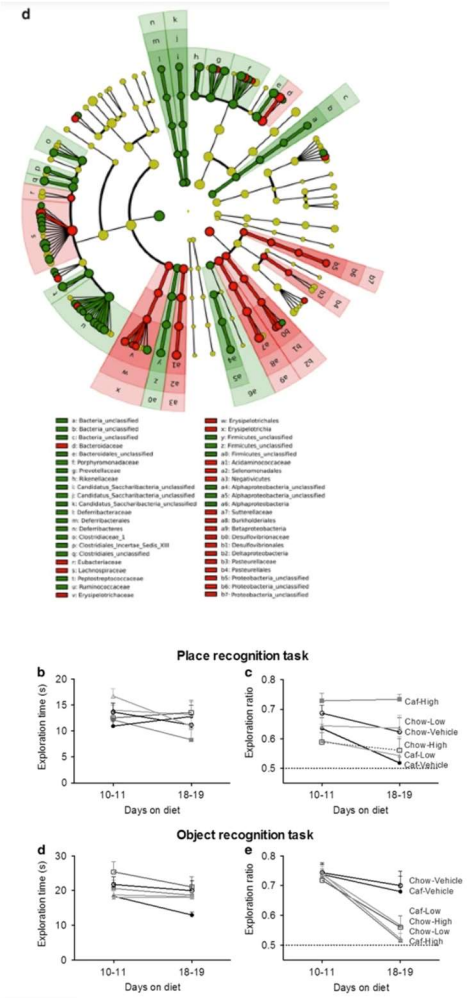
Probiotic	Study design	Duration	Targeted organ	Objective	Key findings	Reference
Lactobacilli	Mice study	8 weeks	Gut	Probiotics reduce inflammation in Multiple Sclerosis (MS)	The serotonin gene expression increased	Sajedi et al. (2021)
L. plantarum	Mice-model	14 days	Brain	Probiotics improve mental health via gut-brain axis	Promotes serotonin signaling, intestinal motility & mucin production	Chen et al. (2022)
Saccharomyces boulardii	Mice study	-	Gut	Probiotics regulate intestinal serotonin transporter	Prevent IBS and diarrhea, upregulate SERT & inhibits gut motility	Gu et al. (2022)
Bifidobacterium animalis	In vitro	-	Gut	Probiotics enhance GI motility in Zebrafish	Increased intestinal peristalsis and modulation of serotonin	Lu et al. (2019)
Streptococcus & Lactobacillus strains	Rat study	25 days	Brain and Gut	Probiotics enhance cross talk among serotonin receptors and gut	Control memory deficit & increase serotonin receptors	Beilharz et al. (2018)
Probiotic strains	In vivo model	-	Brain	Probiotics modulate serotonin signaling	Improves pathophysiological disorder	Mahesh et al. (2021)
Limosilactobacillus reuteri	Mice model	-	Gut	Probiotics upregulate serotonin signaling	Upregulation of SERT to maintain intestinal homeostasis	Engevik, Ruan, et al. (2021)

	Dăscălescu, D., & Apetrei, C. (2021). Nanomaterials based Electrochemical Sensors for Serotonin Detection: A review. *Chemosensors*, *9*(1), 14. https://doi.org/10.3390/chemosensors9010014 Aidy, S. E., Ramsteijn, A. S., Dini-Andreote, F., Van Eijk, R., Houwing, D. J., Salles, J. F., & Olivier, J. D. A. (2017). Serotonin transporter genotype modulates the gut microbiota composition in young rats, an effect augmented by early life stress. *Frontiers in Cellular Neuroscience*, *11*. https://doi.org/10.3389/fncel.2017.00222
Follow up Questions	How could probiotics from diet affect symptoms of OCD? Are probiotics from dietary changes always absorbed, or how long do they take and what percentage? How does gut serotonin affect brain serotonin? How do short-chain fatty acids affect neurotransmission?

Article #11 Notes: Cafeteria diet and probiotic therapy: cross talk among memory, neuroplasticity, serotonin receptors and gut microbiota in the rat

Article notes should be on separate sheets

Source Title	Molecular Psychiatry
Source citation (APA Format)	Beilharz, J. E., Kaakoush, N. O., Maniam, J., & Morris, M. J. (2017). Cafeteria diet and probiotic therapy: cross talk among memory, neuroplasticity, serotonin receptors and gut microbiota in the rat. *Molecular Psychiatry*, *23*(2), 351–361. https://doi.org/10.1038/mp.2017.38
Original URL	https://doi.org/10.1038/mp.2017.38
Source type	Journal Article
Keywords	Probiotics, VSL #3, bifidobacterium, lactobacilli, streptococcus salivarius, anxiety, chronic illness, infalmmation
#Tags	None
Summary of key points + notes (include methodology)	Summary: VSL #3 is a probiotic commonly used with humans and has the potential to impact gut microbiota. It is shown to have anti-inflammatory effects and impacts on chronic illnesses. This study investigated whether pre-exposure to this probiotic would prevent memory deficits after an extreme change in diet, causing a change in gut microbiota. This study also assessed the effect on anxiety-like behaviors. Methodology: 200g rats were used and fed standard rat chow. They either received a low or high dose of VSL #3 (via maple syrup) for 2 weeks before any diet changes. They were then further split up into groups based on their diet that would follow. One group would have sweets (cakes, biscuts, etc) and this group was designated the “Caf diet” group. The other group maintain their diet of standard rat chow. Rat memory was tested after 22 and 32 days of the experiment. After conclusion, the rats were anesthetized and examined. Trunk blood was used to measure glucose, blood plasma was used to measure endotoxin concentration. Also extracted fecal bacteria to analyze microbiome. Notes: VSL #3 is a probiotic mixture with strains of *bifidobacteria*, *lactobacilli*, and *streptococcus salivarius*.

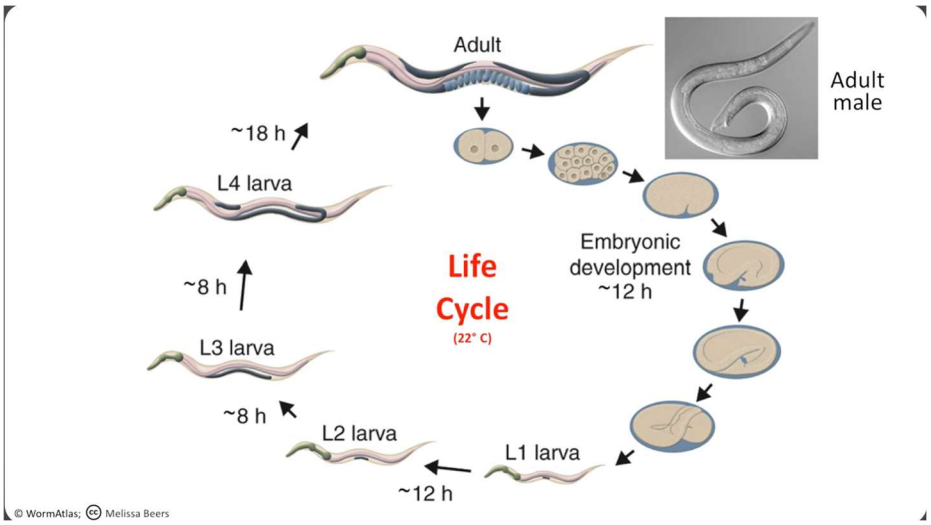
	Analysis: Used ANOVA/two-way ANOVA to analyze the data from the rats. They also used 16S ribosomal RNA sequencing to identify different bacteria species present in the gut and how those changed pre and post experiment. Results: Caf group rats consumed a significantly greater amount of energy/food (2-3 times more), were heavier, has larger livers and fat pads, but comparable blood glucose and plasma samples to Chow rats. Caf rats had increased gut serotonin (linked to obesity) and decreased brain serotonin (linked to depression).
Research Question/Problem/ Need	How does pre-treatment of probiotics affect gut microbiota and memory?
Important Figures	
VOCAB: (w/definition)	ANOVA – analysis of variance, statistical method using the means of data to determine whether or not they are statistically significant;
Cited references to follow up on	Hsu, T. M., Konanur, V. R., Taing, L., Usui, R., Kayser, B. D., Goran, M. I., & Kanoski,

	S. E. (2014). Effects of sucrose and high fructose corn syrup consumption on spatial memory function and hippocampal neuroinflammation in adolescent rats. *Hippocampus*, *25*(2), 227–239. https://doi.org/10.1002/hipo.22368
Follow up Questions	How can probiotics affect OCD? Do probiotics affect other neurotransmitters (such as dopamine) and how could this relate to OCD? What is the relationship between gut and brain serotonin, considering serotonin cannot cross the blood-brain barrier, but tryptophan can (and how does this relate to diet, for example, protein rich diets high in tryptophan)?

Article #12 Notes: Online Developmental Biology: Introduction to C. elegans

Article notes should be on separate sheets

Source Title	YouTube
Source citation (APA Format)	Pellettieri, J. (2014, February 21). *Online Developmental Biology: Introduction to C. elegans* [Video]. YouTube. https://www.youtube.com/watch?v=zc1P7lGSzdU
Original URL	https://www.youtube.com/watch?v=zc1P7lGSzdU
Source type	Video
Keywords	C. elegans
#Tags	None
Summary of key points + notes (include methodology)	Watched video to understand more background about C. elegans Notes: C. elegans are microscopic roundworms, popular model organism for biology. Part of phylum Nematoda (nematodes/roundworms), similar to Drosophila as they are part of Ecdysozoa and shed cuticle periodically. Live in soil and feed on bacteria, adult animals have 302 neurons, wired together exactly the same from one C. elegans to the next (neuron diagrams/maps available), simple structure makes good model organisms to start. Advantageous because of their simple anatomy, only 959 somatic cells. Transparent, cellular processes can be watched in-vivo. Invariant cell lineage, meaning all of the cells in one C. elegans form in the same way as in another. Embryonic development (fertilization to hatching) is approximately 12 hours. See figure below for full life cycle (about 3 days, about 300 progeny per hermaphrodite). Agar plate with bacteria for feeding, they will live in it and eat (example of bacteria is E. coli)
Research Question/Problem/ Need	What are C. elegans?

Important Figures	
VOCAB: (w/definition)	Nematodes – roundworms, C. elegans is an example; hermaphrodites – organisms that make sperm and eggs, self-fertilize;
Cited references to follow up on	None
Follow up Questions	What are specific C. elegans models for OCD? How can the bacteria that they feed on be changed to affect behaviors? What bacteria types can be used to test behavioral changes? How can neurotransmission be measured?

Article #13 Notes: Animal models for OCD research

Article notes should be on separate sheets

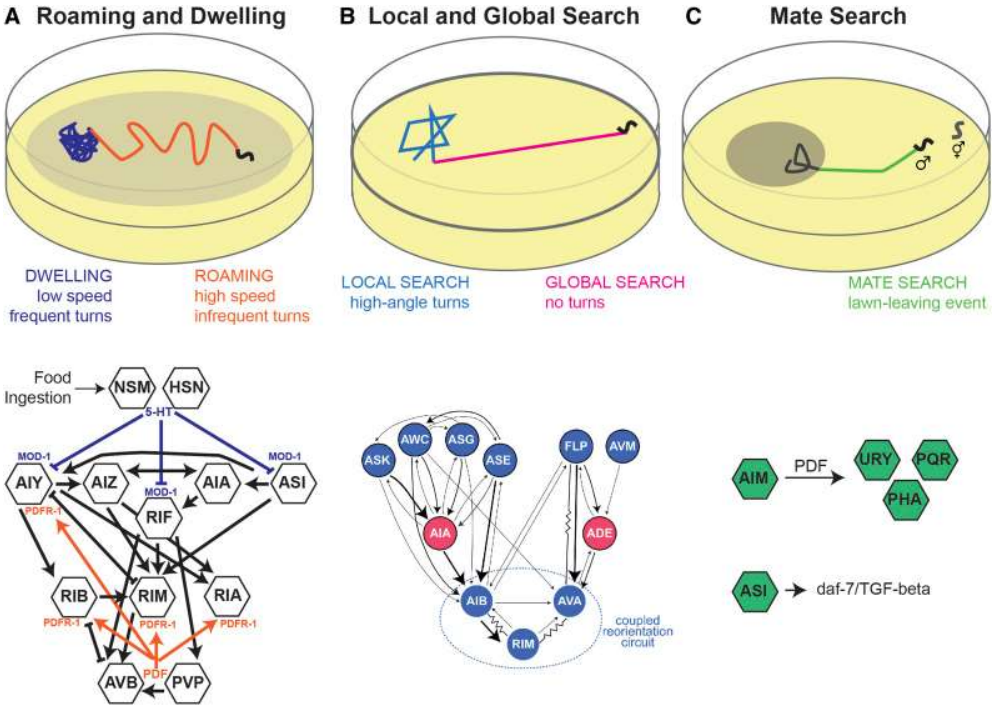
Source Title	Current Topics in Behavioral Neurosciences
Source citation (APA Format)	Chamberlain, B. L., & Ahmari, S. E. (2021). Animal models for OCD research. *Current Topics in Behavioral Neurosciences*, *49*, 55–96. https://doi.org/10.1007/7854_2020_196
Original URL	https://doi.org/10.1007/7854_2020_196
Source type	Journal Article
Keywords	Animal models, OCD, neurotransmitters
#Tags	None
Summary of key points + notes (include methodology)	Summary: Animal models for OCD have been a more recent discovery due to lack of knowledge about how it can be displayed in model organisms. However, different behavioral aspects of OCD can be broken down and observed in animal models. There are different circuits (ex. Cortico-basal ganglia-thalamic) that have been linked to OCD, as well as neuromodulators such as dopamine and serotonin. Used MRIs, PET scans, GWAS Notes: OCD is diagnosed with the presence of obsessions and/or compulsions, although they often come together it isn't mandatory for a diagnosis. OCD has been reclassified from and Anxiety Disorder to Obsessive-Compulsive and Related Disorders due to possible differences between OCD and anxiety. Anxiety disorders generally have abnormalities in the cortico-limbic circuits, OCD with the cortico-basal ganglia-thalamic loop. Anxiety is still a key symptom of OCD though. Proposals have been made to split OCD behaviors into categories (for research, possibly using behaviors from each category): contamination obsessions/cleaning rituals, taboo thoughts/checking rituals, symmetry obsessions/arranging rituals, harm-related OCD, and hoarding as a separate category. These sub-types are thought to work if different behaviors involve different areas (ex. OCD with tics has more striatal involvement), but symptoms are also very dynamic so this categorization may not be true. Using MRIs and PET scans, abnormalities have been detected in the cortico-striatal-thalamo-cortical (CSTC) circuit, with abnormal blood flow and glucose metabolism associated with increased activity in the orbitofrontal cotex (OFC). Serotonin reuptake inhibitors have been shown to resolve these abnormalities.

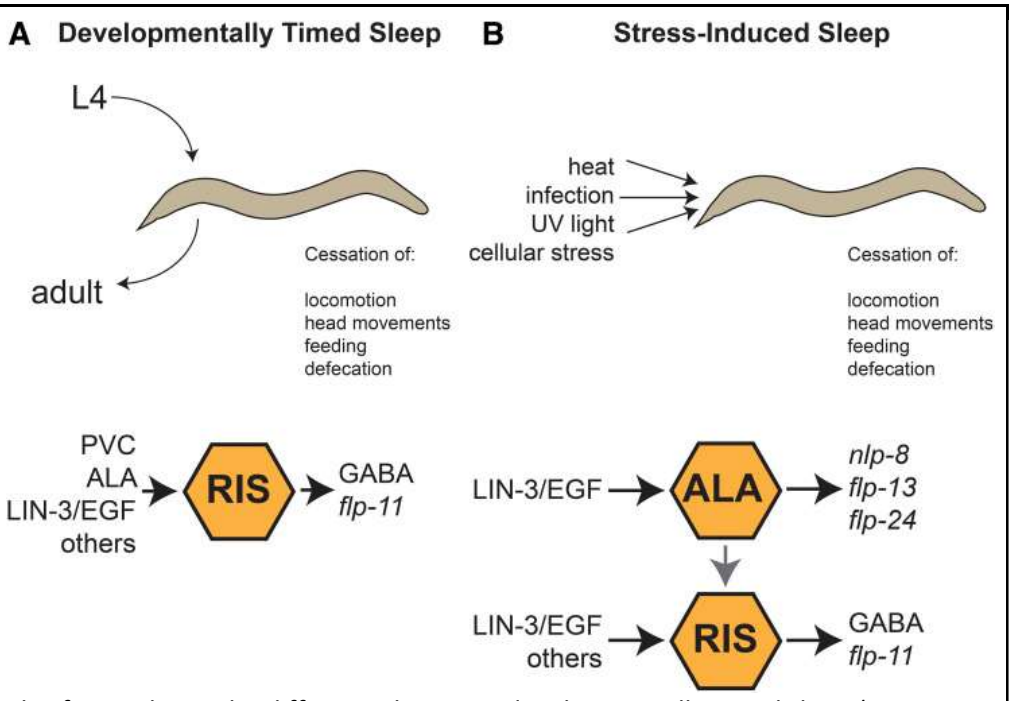
	Other areas of the brain (other cortical regions) include: anterior insula, abnormal signaling in supplementary motor areas similar to those involved with Tourette Syndrome. Abnormal activity in the amygdala has also been linked to OCD patients with comorbid anxiety/depression. Strong genetic correlation to OCD, so you can look at genome-wide association studies (GWAS). This study unfortunately did not include a C. elegans model for OCD, it mainly talked about different types of mice. However, there are some future avenues to research based on the information: Glutamate in C. elegans, relationship with OCD behaviors How do probiotics affect glutamate and GABA?
Research Question/Problem/ Need	How can animal models be used to further knowledge about causes and treatments for OCD?
Important Figures	None included for C. elegans
VOCAB: (w/definition)	Neuromodulators – chemicals that regulate/modify transmission of impulses in the brain; etiology – the cause or set of causes of a disease or condition; aberrant (as in aberrant activity) – departing from an accepted standard, abnormal;
Cited references to follow up on	Ahmari, S. E., Spellman, T., Douglass, N. L., Kheirbek, M. A., Simpson, H. B., Deisseroth, K., Gordon, J. A., & Hen, R. (2013). Repeated Cortico-Striatal stimulation generates persistent OCD-Like behavior. *Science*, *340*(6137), 1234–1239. https://doi.org/10.1126/science.1234733
Follow up Questions	What does an OCD model for C. elegans look like? How does glutamate affect OCD in C. elegans and in other organisms (mice, rats, and humans)? How does glutamate affect GABA? How does GABA affect OCD?

Article #14 Notes: Behavioral states

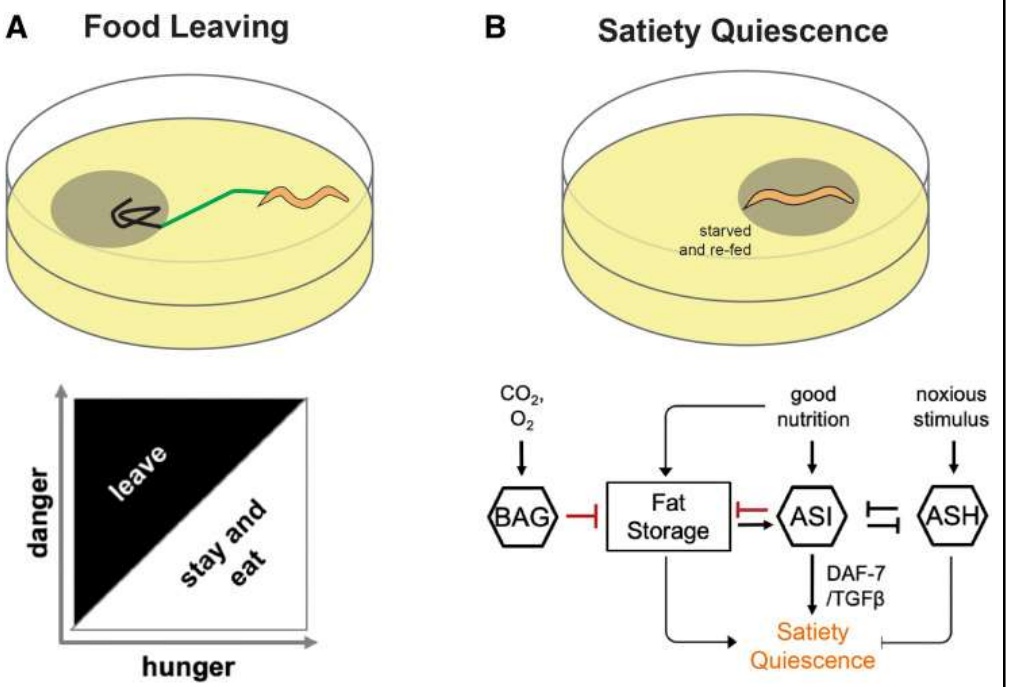
Article notes should be on separate sheets

Source Title	Genetics
Source citation (APA Format)	Flavell, S. W., Raizen, D. M., & You, Y. (2020). Behavioral states. *Genetics*, *216*(2), 315–332. https://doi.org/10.1534/genetics.120.303539
Original URL	https://doi.org/10.1534/genetics.120.303539
Source type	Journal Article
Keywords	C. elegans, behavioral model, locomotion, roaming, dwelling, metabolism, mate searching, lawn-leaving events
#Tags	None
Summary of key points + notes (include methodology)	OCD behaviors that could be used for project (look into how they can be measured and specifically applied to OCD): Locomotion – roaming and dwelling, frequency of turns, frequency of roaming vs. dwelling stages Local and global search behaviors Sleep and sleep deprivation behaviors Locomotion states: How animals can explore there environments. Different types of these states, foraging and searching behaviors. Roaming (high velocity forward movement, infrequent reversals), dwelling stages (short bouts of low velocity forward movement, frequent and short reversals). Dwelling isn't sleep because animals still move, feed, defecate, and lay eggs. Roaming/dwelling depends on food environment (odors, oxygen levels, ingestion, presence of food is digestive track, satiety levels). When they detect a lot of food, the will continue roaming, higher density of animals (based on pheromones) inhibits roaming. Dwelling driven through serotonin release, food in intestines promotes dwelling. Local and global searches: When removed from food, C. elegans exhibit two consecutive locomotion states. For the first 15 minutes, they do a local search (high frequency of high angle turns), transition to a global search/dispersal (less turning), in an attempt to search their entire area for food (this method is their foraging strategy). The mechanisms behind this state is thought to be different than the ones that control roaming/dwelling because roaming/dwelling is spontaneous (somewhat, but also dependent on food and environment). Initiation of local search is also dependent on sensory inputs (lack of food). Starvation may have an effect on glutamatergic signaling (further area of research), dopamine also may have an effect on local search. Mate searching in males: When male C. elegans are on a food lawn without

	mating partners, they are more likely to exhibit lawn-leaving events than hermaphrodites. They are trying to balance reproductive drive with need to consume food. Sleep as a behavioral state: Sleep is a behavioral state characterized by general absence of movement. With sleep deprivation (look into why sleep deprivation may occur, could observing sleep deprivation be a result of OCD induced behavior). Sleep is common in C. elegans during larval transition phase/lethargus (developmentally time sleep or DTS). Reduced responsiveness common during prolonged starvation, and they have "post-sleep coma" after a long fast and full refeeding. Other factors to consider include: behavioral quiescence during SIS, reduced responsiveness during sleep, and homeostatic regulation of sleep.
Research Question/Problem/ Need	How can different behaviors in C. elegans model OCD?
Important Figures	 This figure shows the different types of movement during roaming vs. dwelling vs. mate search stages.



This figure shows the difference between developmentally timed sleep (in between growth stages) and stress induced sleep



This figure shows how behavioral states can be regulated by metabolic states.

VOCAB: (w/definition)	Stochastically – having a random probability distribution; quiescent – marked by inactivity, tranquility at rest;
Cited references to follow up on	Bishop, N. A., & Guarente, L. (2007). Two neurons mediate diet-restriction-induced longevity in C. elegans. *Nature*, *447*(7144), 545–549.

	https://doi.org/10.1038/nature05904
Follow up Questions	Why does sleep deprivation occur in C. elegans, and could this behavior be the result of OCD? How can locomotion differ with OCD? How can roaming and dwelling stages differ with OCD? How do local and global searches differ with the inducing of OCD? How does lawn-leaving behavior differ, based on danger and hunger levels as well as reproductive desire, with OCD?

Patent #1 Notes: Method of Administration

Article notes should be on separate sheets

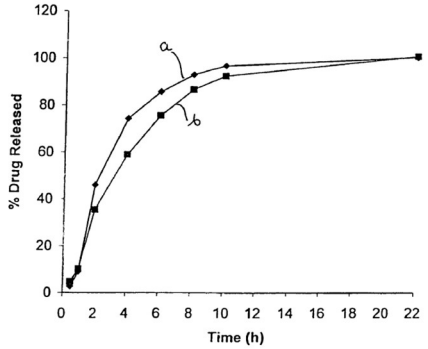
Source Title	Justia Patents
Source citation (APA Format)	Rands, P., Routledge, C., James, E., Benway, T., Joel, Z., Attwooll, V., & Good, M. (2024). *Method of Administration* (U.S. Patent Application No. 18,619,547). U.S. Patent and Trademark Office. https://patents.justia.com/patent/20240325351
Original URL	https://patents.justia.com/patent/20240325351
Source type	Patent Database
Keywords	Depression, anxiety, psilocybin, OCD, psychedelic agents, SSRIs, serotonin, dosing, treatment
#Tags	#research-question
Summary of key points + notes (include methodology)	Notes: Invention relates to administering short-duration psychedelic agents in combination with an antidepressant (ex. Selective serotonin reuptake inhibitors). Most treatments for conditions like depression, anxiety, OCD, and eating disorders involve antidepressants (often an SSRI), which are non-psychedelic agents that affect imbalances in the brain (ex. SSRIs affect serotonin by not letting it be transported from the synaptic space). The efficacy of the current treatments needs to be improved, SSRIs only end up helping about 2/3 of patients after a full year. Withdrawal is also an issue. Different psychedelics have shown some promise with psychiatric disorders (ex. Psilocybin) by improving depression/anxiety symptoms. These are being further investigated in mental health disorders that involve destructive patterns of thought processing (like OCD). Clinical trials conducted. First phase was testing psilocybin on healthy individuals, some studies looked at oral ingestion by pill versus dissolving a tablet under the tongue. Other studies have been conducted with short-duration psychedelics too. Factors that the patent looked at when treating with SSRIs and psychedelic agents at the same time were safety (serotonin toxicity was a possibility with both acting in combination), efficacy (patients that recently discontinued SSRIs may have reduced efficacy of later serotonergic treatments). Invention looked to address these factors by forming a kit and methods for treatment/dosing (including delivery method).
Research Question/Problem/ Need	How can short-term psychedelic agents be used in combination with selective-serotonin reuptake inhibitors to increase the efficacy of treatment for different

	mental health disorders?
Important Figures	None included
VOCAB: (w/definition)	Concomitant – naturally accompanying or associated;
Cited references to follow up on	None
Follow up Questions	Are there other natural sources that can do something similar to serotonin in the brain? How could withdrawal from SSRIs be mitigated (#research-question)? What other disorders could this methodology be applied to?

Patent #2 Notes: Multiparticulate controlled release selective serotonin reuptake inhibitor formulations

Article notes should be on separate sheets

Source Title	Google Patents
Source citation (APA Format)	Jeary, T., Morrissey, C., & Stark, P. (2008). *Multiparticulate controlled release selective serotonin reuptake inhibitor formulations* (U.S. Patent No. 7,465,462). U.S. Patent and Trademark Office. https://patents.google.com/patent/US7465462B1/en
Original URL	https://patents.google.com/patent/US7465462B1/en
Source type	Patent Database
Keywords	SSRIs, serotonin, Fluvoxamine, controlled release, slow-release, polymeric coating
#Tags	None
Summary of key points + notes (include methodology)	Notes: Developed a formular for slow release of SSRIs, controlled release over a period of not less than 12 hours after oral administration. Fluvoxamine was the SSRI used in this patent generally, unless it was explicitly stated otherwise. Some background on Fluvoxamine is that it is given in the form of a tablet (25/50/100mg forms), no more than 300mg per day, generally in one dose at night but can be split up if the dose is large. Peak plasma levels 3-8 hours after taking. Different release rates were recorded. One had no more than 85% being released after 6 hours, and the other no more than 80% after 12 hours (slower release). Tablet is embedded with a polymeric material/binder (ratio from 1:1 to 100:1, more specifically 5:1 to 30:1). Can be rapidly soluble in water or insoluble. Core of the tablet will contain powder mixture with SSRI, organic acid (of those listed: adipic acid, ascorbic acid, fumaric acid, malic acid, succinic acid, tartaric acid), polymeric material, core is comprised of layers of these things on top of one another. Polymeric coating on the core is part of the rate-controlling mechanism for the SSRIs, along with a filler material. Can be coated to any level that results in the desired release rate times. Tablets with slightly different concentrations/coating levels were manufactured and release rates were tested. Final adjusted treatment was tested and determined safe.
Research Question/Problem/ Need	How can slow-release SSRIs be made?

Important Figures	 This figure shows the release of an SSRI over time.
VOCAB: (w/definition)	Polymeric – relating to or of a polymeric;
Cited references to follow up on	Paradissis, G., Garegnani, J., & Whaley, R. (1992). *Extended release pharmaceutical formulations* (U.S. Patent No. 5,133,974). U.S. Patent and Trademark Office. https://patents.google.com/patent/US5133974A/en
Follow up Questions	How could slow-release SSRI administration affect withdrawal symptoms after stopping treatment, if at all? What other ways could they be made slow-release? What makes slow-release different/better, aside from release timeframe, than regular SSRIs?

Article #15 Notes: Withdrawing from SSRI antidepressants: advice for primary care

Article notes should be on separate sheets

Source Title	British Journal of General Practice
Source citation (APA Format)	Palmer, E. G., Sornalingam, S., Page, L., & Cooper, M. (2023). Withdrawing from SSRI antidepressants: advice for primary care. *British Journal of General Practice*, *73*(728), 138–140. https://doi.org/10.3399/bjgp23x732273
Original URL	https://doi.org/10.3399/bjgp23x732273
Source type	Journal Article
Keywords	Serotonin, noradrenaline, norepinephrine, dopamine, SSRIs, antidepressants, withdrawal symptoms, tapering antidepressants
#Tags	None
Summary of key points + notes (include methodology)	Notes: Withdrawal from SSRI antidepressants can be extremely severe, affecting around 56% of people who stop antidepressants for various reasons. The symptoms of withdrawal can be so severe as to increase suicidal ideation. Lack of good information about how to safely stop antidepressants and lack of support can prevent people from wanting to stop them, but there are benefits to stopping antidepressants such as reducing side effects, stopping cost, and avoiding other possible drug interactions. SSRIs increase serotonin in the brain, but they also increase noradrenaline, dopamine, and GABA. By stopping an SSRI, the brain has a quick reduction in serotonin levels which can act like a serotonin deficiency (correlation to depression/anxiety/OCD). Stronger SSRIs lead to a more severe withdrawal. Symptoms of withdrawal include: anxiety and related symptoms, suicidal ideation, hallucinations, dizziness, flue-like illness, headaches, GI distress, and much more. They are severe and need to be taken seriously. Practitioners should not make the mistake of thinking that a patient is relapsing when they are really suffering from withdrawal. To safely stop antidepressants, the current method is to do so gradually. However, some people can still experience withdrawal with this method, and it takes time. For certain reasons, one might not have ample time (due to severe side effects, etc).
Research Question/Problem/	What are the causes of and ways to mitigate severe withdrawal from SSRIs used as

Need	antidepressants?
Important Figures	None included
VOCAB: (w/definition)	Noradrenaline/norepinephrine – neurotransmitter that plays a role in body's fight or flight response, low levels correlated to anxiety/depression, release is triggered by stress, similar to adrenaline in the rest of the body Information on norepinephrine came from: Clevland Clinic. (2024, June 27). *Norepinephrine (Noradrenaline)*. Cleveland Clinic. https://my.clevelandclinic.org/health/articles/22610-norepinephrine-noradrenaline
Cited references to follow up on	Sørensen, A., Ruhé, H. G., & Munkholm, K. (2021). The relationship between dose and serotonin transporter occupancy of antidepressants—a systematic review. *Molecular Psychiatry*, *27*(1), 192–201. https://doi.org/10.1038/s41380-021-01285-w
Follow up Questions	How could the severity of withdrawal be reduced? What methods are in place to keep someone safe that needs to immediately stop an antidepressant? Is there some treatment that could be used in combination or in place of SSRIs that function as antidepressants but do not cause the same level of withdrawal? In other words, what other types of antidepressants are out there?

Article #16 Notes: Glutamate Modulators in the Treatment of Obsessive-Compulsive Disorder

Article notes should be on separate sheets

Source Title	Psychiatric Annals
Source citation (APA Format)	Pittenger, C. (2015). Glutamate Modulators in the Treatment of Obsessive-Compulsive Disorder. *Psychiatric Annals*, *45*(6), 308–315. https://doi.org/10.3928/00485713-20150602-06
Original URL	https://doi.org/10.3928/00485713-20150602-06
Source type	Journal Article
Keywords	Glutamate, glutamate receptors, serotonin, reuptake, glutamate transport, NMDA
#Tags	#research-question
Summary of key points + notes (include methodology)	Background on glutamate and OCD: Treatments for OCD are not successful for a large portion of patients, meaning that new ones need to be discovered. Many studies have suggested that the dysregulation of glutamate is correlated to OCD, with some medications having promising effects (memantine, riluzole, ketamine, D-cycloserine, glycine, N-acetylserine, topiramate, lamotrigine). However, none of these medications have stood out as possible treatments for all patients, although they are successful for some. (#research-question: using a personalized network model of symptoms to determine what medication would work best for individuals based on those symptoms). Current treatments for OCD include SSRI antidepressants, clomipramine, which have some success. Glutamate is the brain's primary excitatory neurotransmitter. It is involved in many aspects of brain function. Its main job is to control impulses from one cell to the next by exciting it (high glutamate may be associated with OCD). Primary receptors are AMPA (alpha-methyl propionic acid) and NMDA (N-methyl-D-aspartate), when they bind glutamate, they open and allow cationic current (sodium ions are common) to pass through and change the state of a cell. Glutamate needs to be cleared from the synaptic space quickly and efficiently in order not to have too much (can lead to neuronal damage/atrophy, also known as excitotoxicity). The glutamate system DIFFERS from other monoaminergic systems (dopamine, serotonin, norepinephrine – produced by a small number of cells when in the brain, also are modulators). Glutamate, however, is produced in almost every area of the brain, and is central to the functioning of circuits in the brain (not by modulating but by being a part of the function). This means that too much/too little/abnormalities with glutamate are not simple. Glutamate is similar to serotonin because it is regulated by reuptake inhibitors.

Glutamate dysregulation in OCD: Has mainly been measured through cerebrospinal fluid (CSF) from OCD patients. Two studies showed that they have elevated glutamate levels. However, there are two main things that limit what this can tell us: it doesn't tell us why the glutamate is high (is it too much synaptic activity, overwhelming the reuptake system, dysfunction of the reuptake system, or something else) and it doesn't tell us where in the brain the glutamate is coming from (what circuit) (#research-question: could C. elegans be able to show us where in the brain/neuronal circuits this would be?).

Genetics and glutamate-related genes may have some impact/correlation to this. Slc1a1 gene (has been called into question) for transport/reuptake. SAPAP/DLGAP proteins, knockout of Sapap3 gene (produces similar symptoms).

Magnetic resonance spectroscopy (MRS) can be used to measure the concentration of glutamate/related molecules. This is advantageous because it can tell us what region of the brain it is in (some early studies have shown elevated levels in the caudate nucleus and basal ganglia, but reduced in the anterior cingulate cortex; findings have not been consistently replicated).

Glutamate-modulating medications in OCD: Many FDA approved medications from glutamate-modulating that have shown therapeutic benefit in people with OCD. However, the main problem is that none of these can be said to be proven effective for OCD because of small/mixed results. This means that better-proven (although not perfect) therapies should be exhausted before using glutamate-modulators.

Treatments targeting NMDA receptor:
Memantine: FDA approved for Alzheimer's, limits excitoxicity by acting against NMDA receptor. Many reports of benefits, however, the studies done have not be large/placebo-controlled for the most part.
Ketamine: More potent than memantine, also antagonist of NMDA receptor, different effects. Clinically used as an anesthetic, abuse potential (likely not a good treatment then?) Produces an almost immediate antidepressant effect that lasts up to two weeks. Not very definitive effects (one showed no clinical statistical significance, the other was a small study that showed some benefit).
Glycine: Co-transmitter at the NMDA glutamate receptor. Small studied conducted, however, large amounts of glycine were needed which caused nausea and dropouts (not a likely effective treatment due to these side effects?).
D-cycloserine (see article #1 for this): Antagonist of NMDA receptor, has potential to enhance learning. Because CBT is a form of learning, D-cycloserine might help enhance effects of therapy (article #1 showed that it didn't, so other articles need to be read on this).
FURTHER RESEARCH NEEDED ON ALL OF THESE (some might turn out to be effective, some not, but more research is needed).

Other glutamate modulators:

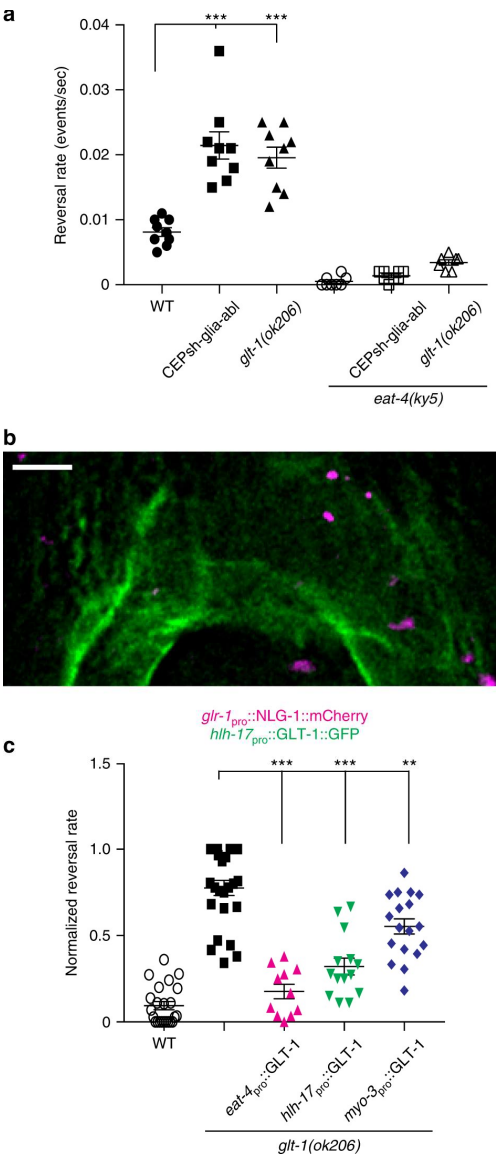
	Riluzole: Appears to have a glutamate-lowering effect by reducing glutamate release from axon terminals and increasing uptake by glutamate transporters. May be beneficial to patients who don't respond to current OCD treatments, although there are mixed/more negative leaning results. N-acetylcysteine: Modified amino acid cysteine and an antioxidant. Can modulate glutamate levels, cheap, available without a prescription, limited side-effects. May be beneficial by adding to treatment regimen that already has an SSRI. Topiramate: Modulates glutamate levels, may have greater effects on obsessions rather than compulsions, side effects may be bad. Lamotrigine: Mixed results. Overall results by targeting glutamate for treatment has had mixed results, needs more research.
Research Question/Problem/ Need	How can different medications affect glutamate and OCD?
Important Figures	None included.
VOCAB: (w/definition)	Monoaminergic -liberating or involving monoamines; atrophy - waste away, especially as a result of the degeneration of cells, or become vestigial during evolution; refractory - resistant to a process or stimulus;
Cited references to follow up on	Pittenger, C., Bloch, M. H., & Williams, K. (2011). Glutamate abnormalities in obsessive compulsive disorder: Neurobiology, pathophysiology, and treatment. *Pharmacology & Therapeutics*, *132*(3), 314–332. https://doi.org/10.1016/j.pharmthera.2011.09.006
Follow up Questions	How could the personalized network model (article #3 and #8) be used to determine what medication is effective for different individuals? What is the difference in treatments that target glutamate versus serotonin (difference in benefit?)? How could C. elegans be used to understand effects of treatment targeting glutamate? What behaviors would C. elegans display with OCD? What behaviors would C. elegans display with an effective treatment? Non-effective treatment?

Article #17 Notes: Glutamate spillover in C. elegans triggers repetitive behavior through presynaptic activation of MGL-2/mGluR5

Article notes should be on separate sheets

Source Title	Nature Communications
Source citation (APA Format)	Katz, M., Corson, F., Keil, W., Singhal, A., Bae, A., Lu, Y., Liang, Y., & Shaham, S. (2019). Glutamate spillover in C. elegans triggers repetitive behavior through presynaptic activation of MGL-2/mGluR5. *Nature Communications*, *10*(1). https://doi.org/10.1038/s41467-019-09581-4
Original URL	https://doi.org/10.1038/s41467-019-09581-4
Source type	Journal Article
Keywords	GLT1, glutamate transport, OCD, C. elegans, reversal rates
#Tags	#methodology
Summary of key points + notes (include methodology)	Notes: GLAST/EAAT1 and GLT1/EAAT2 are two glial glutamate transporters responsible for the uptake of glutamate in the brain. C. elegans share properties with mammals for these transporters. Knocking out the GLT1 protein in C. elegans results in repetitive locomotory reversals. C. elegans are not susceptible to neurotoxicity from excess glutamate (like humans are). The glutamate transporters (GLT1) regulates the amount of glutamate in the brain. Loss of GLT1 (knockout) resulted in two things: increased locomotory reversal events and clustering of reversals in repetitive bouts. They recorded locomotory information of the worms exploring their environments (with a camera) and then used a Java program to analyze it (which can be retrieved from corresponding author upon request). The study found that expressing GLT1 can restore normal reversal rates. They analyzed the probability that a worm performing a reversal event will not initiate a reversal over a period of time. Results showed that wild type had more consistent and lower reversal rates than worms mutated without GLT1. In the mutants, reversal probability was high. They also used mechanical stimulation on the C. elegans. They performed anterior mechanical stimulation to induce backward movement for approximately 3 body bends, followed by inducing forward movement. When done on wild type versus mutated, the mutated had higher reversal rates. These two tests (mechanical stimulation/escape and locomotion during exploration) showed two instances where mutated C. elegans displayed repetitive behaviors.

	The study also went into detail on levels of calcium and varying rates of this and how it correlates to repetitive behaviors. Metabotropic glutamate receptors (mGluRs) may also be involved in C. elegans' repetitive behavior, specifically MGL-2. Expressing MLG-2 resulted in more repetitive behaviors. Overall, the tests that they ran showed that too much/uncontrolled extracellular glutamate is a driver of repetitive behavior in C. elegans, a great model for mammals. Although the behaviors displayed between common models (C. elegans and mice) and people are different (grooming behaviors, reversals, obsessive thoughts, compulsions, etc.), this study showed they may be rooted in the same cause. This study also included a lot of specific methodology for conducting the experiment that can be used in my own project (#methodology).
Research Question/Problem/ Need	How can C. elegans be used as a model for OCD?

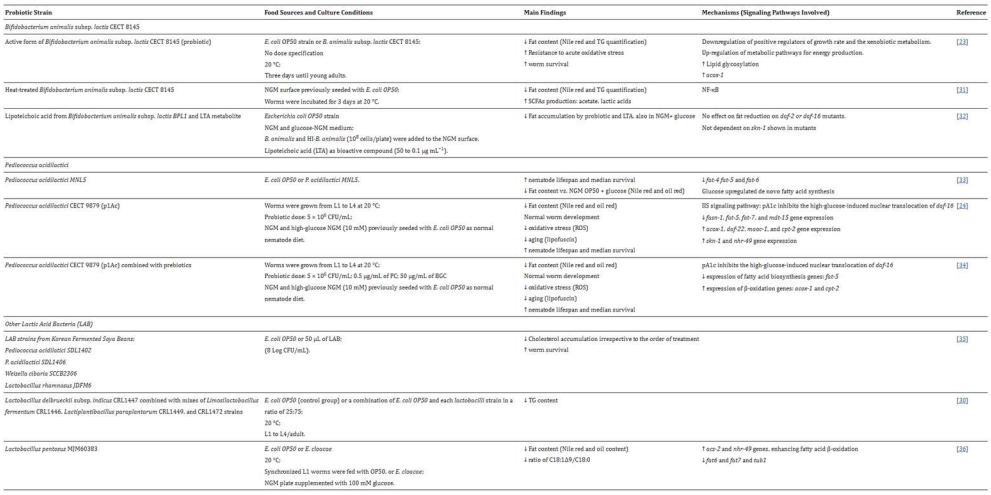
Important Figures	 This figure shows the reversal rates (wild-type is relatively low, while mutated are high).
VOCAB: (w/definition)	Astrocyte - a star-shaped glial cell of the central nervous system; glial – non-neuronal cells, but still in the brain, literally meaning “neural glue”, help to provide support and protection to neurons in the brain;
Cited references to follow up on	Mitchell, S. J., & Silver, R. A. (2000). Glutamate spillover suppresses inhibition by activating presynaptic mGluRs. *Nature*, *404*(6777), 498–502. https://doi.org/10.1038/35006649
Follow up Questions	How might the results of this study differ when probiotics are used instead of OP50? Will the reversal rates be significantly different, better or worse? If probiotics can reduce repetitive behaviors in mutated C. elegans, what does that have to say about the relationship between probiotics and glutamate (excess)?

	What does that say about probiotics as a treatment for OCD? How might the probiotics affect the wild-type?

Article #18 Notes: Caenorhabditis elegans as a Screening Model for Probiotics with Properties against Metabolic Syndrome

Article notes should be on separate sheets

Source Title	International Journal of Molecular Sciences
Source citation (APA Format)	Goyache, I., Yavorov-Dayliev, D., Milagro, F. I., & Aranaz, P. (2024). Caenorhabditis elegans as a Screening Model for Probiotics with Properties against Metabolic Syndrome. *International Journal of Molecular Sciences*, *25*(2), 1321. https://doi.org/10.3390/ijms25021321
Original URL	https://doi.org/10.3390/ijms25021321
Source type	Journal Article
Keywords	Gut microbiota, postbiotics, obesity, insulin resistance, diabetes, cardiovascular disease
#Tags	#probiotics
Summary of key points + notes (include methodology)	Notes: Using probiotics to prevent against obesity or type 2 diabetes (different metabolic disorders), study is needed to prove that they have an effect. *Bifidobacterium* may have potential anti-obesogenic or anti-diabetic properties (also look into lactic acid bacteria). Many studies have connected gut microbiota to metabolic health of the host, modifications in gut bacteria could be involved in developing the risk of diabetes or obesity, it could also possibly prevent these diseases. Lactic acid bacteria (LAB) have lipid-reducing properties, can help maintain glucose homeostasis, and more. Bifidobacteria and lactobacilli have been shown to extend the lifespan of C. elegans, other bacteria may be Bacillus subtilis DG101 (compared to E. coli OP50, chemotaxis was improved). Lacticaseibacillus casei 62 and 63 also extended lifespan. Interesting point of the study showed that inactive form of Bifidobacterium animalis forced a similar reduction in the fat as active form, may suggest their probiotic properties/efficacy is retained even in non-viable cells. This strain is anti-obesogenic. Other possible bacterial strains: Pediococcus and Weisella (reduced cholesterol when compared to E. coli OP50), other LAB bacteria can reduce fat, regulate immune system, regulate glucose, etc.

	Insulin-like signaling pathway (IGF-1) regulates aging, immunity, and lipid metabolism, a pathway that is conserved across nematodes and mammals. Probiotics with anti-inflammatory properties: inflammation is often at the center of many metabolic diseases, it is an immune response to infection/injury that aims to maintain homeostasis (ex. T2 diabetes). Main genera: Bifidobacterium, Lactobacillus, Pediococcus
Research Question/Problem/ Need	How can different types of probiotics affect C. elegans?
Important Figures	 This figure shows the results of the different bacteria species tested.
VOCAB: (w/definition)	Genera – plural of genus;
Cited references to follow up on	Brial, F., Lay, A. L., Dumas, M., & Gauguier, D. (2018). Implication of gut microbiota metabolites in cardiovascular and metabolic diseases. *Cellular and Molecular Life Sciences*, *75*(21), 3977–3990. https://doi.org/10.1007/s00018-018-2901-1
Follow up Questions	Which types of probiotics will be best for my project (talk to Dr. C)? Are there limitations based on what we have, can order, and what I am allowed to work with? How will the results of this study compare with my findings? Could inflammation be connected to OCD as well?

Probiotic Strain	Food Sources and Culture Conditions	Main Findings	Mechanisms (Signaling Pathways Involved)	Reference
Bifidobacterium animalis subsp. *lactis* CECT 8145				
Active form of *Bifidobacterium animalis* subsp. *lactis* CECT 8145 (probiotic)	*E. coli* OP50 strain or *B. animalis* subsp. *lactis* CECT 8145: No dose specification 20 °C Three days until young adults.	↓ Fat content (Nile red and TG quantification) ↑ Resistance to acute oxidative stress ↑ worm survival	Downregulation of positive regulators of growth rate and the xenobiotic metabolism. Up-regulation of metabolic pathways for energy production. ↑ Lipid glycosylation ↑ *acox-1*	[23]
Heat-treated *Bifidobacterium animalis* subsp. *lactis* CECT 8145	NGM surface previously seeded with *E. coli OP50*. Worms were incubated for 3 days at 20 °C.	↓ Fat content (Nile red and TG quantification) ↑ SCFAs production: acetate, lactic acids	NF-κB	[31]
Lipoteichoic acid from *Bifidobacterium animalis* subsp. *lactis BPL1* and LTA metabolite	*Escherichia coli OP50* strain NGM and glucose-NGM medium: *B. animalis* and HI-*B. animalis* (10^8 cells/plate) were added to the NGM surface. Lipoteichoic acid (LTA) as bioactive compound (50 to 0.1 μg mL^{-1}):	↓ Fat accumulation by probiotic and LTA; also in NGM+ glucose	No effect on fat reduction on *daf-2 or daf-16* mutants. Not dependent on *skn-1* shown in mutants	[32]
Pediococcus acidilactici				
Pediococcus acidilactici MNL5	*E. coli OP50* or *P. acidilactici MNL5*.	↑ nematode lifespan and median survival ↓ Fat content vs. NGM OP50 + glucose (Nile red and oil red)	↓ *fat-4 fat-5* and *fat-6* Glucose upregulated de novo fatty acid synthesis	[33]
Pediococcus acidilactici CECT 9879 (p1Ac)	Worms were grown from L1 to L4 at 20 °C: Probiotic dose: 3×10^8 CFU/mL: NGM and high-glucose NGM (10 mM) previously seeded with *E. coli OP50* as normal nematode diet.	↓ Fat content (Nile red and oil red) Normal worm development ↓ oxidative stress (ROS) ↓ aging (lipofuscin) ↑ nematode lifespan and median survival	IIS signaling pathway: p1Ac inhibits the high-glucose-induced nuclear translocation of *daf-16* ↓ *fasn-1, fat-5, fat-7,* and *mdt-15* gene expression ↑ *acox-1, daf-22, maoc-1,* and *cyp-2* gene expression ↑ *skn-1* and *nhr-49* gene expression	[34]
Pediococcus acidilactici CECT 9879 (p1Ac) combined with prebiotics	Worms were grown from L1 to L4 at 20 °C: Probiotic dose: 3×10^8 CFU/mL: 0.5 μg/mL of FC: 50 μg/mL of BGC NGM and high-glucose NGM (10 mM) previously seeded with *E. coli OP50* as normal nematode diet.	↓ Fat content (Nile red and oil red) Normal worm development ↓ oxidative stress (ROS) ↓ aging (lipofuscin) ↑ nematode lifespan and median survival	p1Ac inhibits the high-glucose-induced nuclear translocation of *daf-16* ↓ expression of fatty acid biosynthesis genes: *fat-5* ↑ expression of β-oxidation genes: *acox-1* and *cyp-2*	[34]
Other Lactic Acid Bacteria (LAB)				
LAB strains from Korean Fermented Soya Beans: *Pediococcus acidilactici SDL1402* *P. acidilactici SDL1406* *Weissella cibaria SCCB2306* *Lactobacillus rhamnosus JDFM6*	*E. coli OP50* or 50 μL of LAB: (8 Log CFU/mL).	↓ Cholesterol accumulation irrespective to the order of treatment ↑ worm survival		[35]
Lactobacillus delbrueckii subsp. *indicus* CRL1447 combined with mixes of *Limosilactobacillus fermentum* CRL1446. *Lactiplantibacillus paraplantarum* CRL1449. and CRL1472 strains	*E. coli OP50* (control group) or a combination of *E. coli OP50* and each *lactobacilli* strain in a ratio of 25:75: 20 °C: L1 to L4/adult.	↓ TG content		[30]
Lactobacillus pentosus MJM60383	*E. coli OP50* or *E. cloacae* 20 °C: Synchronized L1 worms were fed with OP50. or *E. cloacae*: NGM plate supplemented with 100 mM glucose.	↓ Fat content (Nile red and oil content) ↓ ratio of C18:1/19/C18:0	↑ *acs-2* and *nhr-49* genes. enhancing fatty acid β-oxidation ↓ *fat6* and *fat7* and *tub1*	[36]

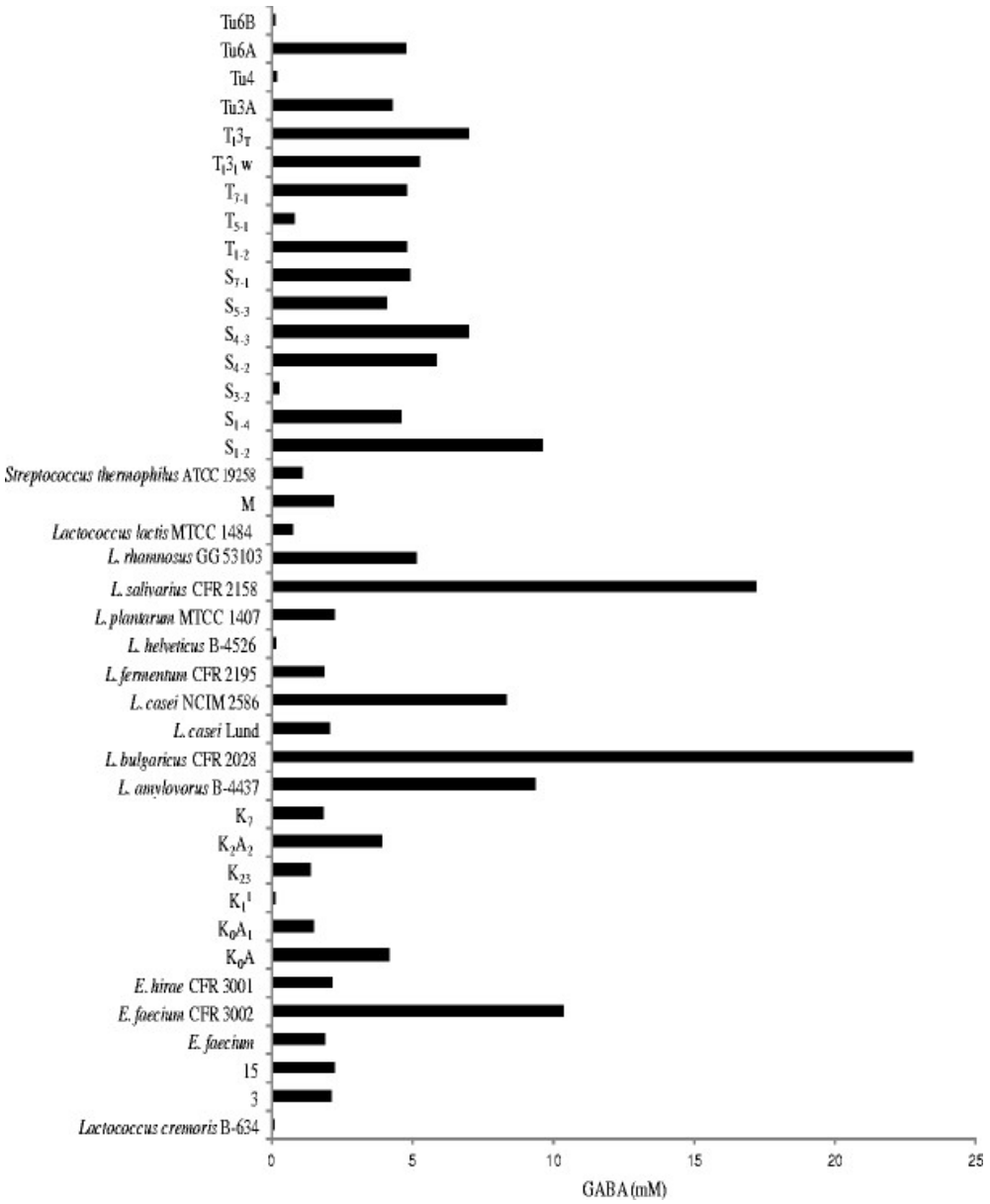
↑: increased; ↓: reduced.

Article #19 Notes: Probiotic-mediated biotransformation of monosodium glutamate to γ-aminobutyric acid: differential production in complex and minimal media and kinetic modelling

Article notes should be on separate sheets

Source Title	Annals of Microbiology
Source citation (APA Format)	Gangaraju, D., Murty, V. R., & Prapulla, S. G. (2013). Probiotic-mediated biotransformation of monosodium glutamate to γ-aminobutyric acid: differential production in complex and minimal media and kinetic modelling. *Annals of Microbiology*, *64*(1), 229–237. https://doi.org/10.1007/s13213-013-0655-4
Original URL	https://doi.org/10.1007/s13213-013-0655-4
Source type	Journal Article
Keywords	GABA, glutamate, modulation, probiotics, lactic acid bacteria, LAB
#Tags	#probiotics
Summary of key points + notes (include methodology)	Notes: GABA and glutamate are thought to be involved in all functions of the central nervous system (CNS) due to their prevalence and other testing. GABA is formed from glutamate by the action of glutamate decarboxylase. GABA has some health benefits (reduction in blood pressure, preventing diabetic conditions, treating inhibitory motor disorders, look for more mental benefits). This article looks into bio transforming glutamate into GABA through the use of probiotics (lower cost, safety, high catalytic efficiency, etc). Some studies have shown the production of GAVA from *Lactobacillus buchneri* (came from kimchi), and some others. This study examined lactic cultures from traditional fermented foods and fecal matter from healthy breast-fed infants. Also aimed to study reaction rates with monosodium glutamate (MSG, obtained from local supermarket). Created a bacteria culture broth, used thin-layer chromatography plates. Also did high-performance liquid chromatography and electrospray tandem mass spectroscopy. MSG was placed into media with bacteria (*L. bulgaricus)* and incubated at 37 degrees Celsius, samples of GABA were drawn at regular intervals. Recorded residual sugar and GABA as a function of fermentation time. Also modeled MSG consumption rate with Monod model.

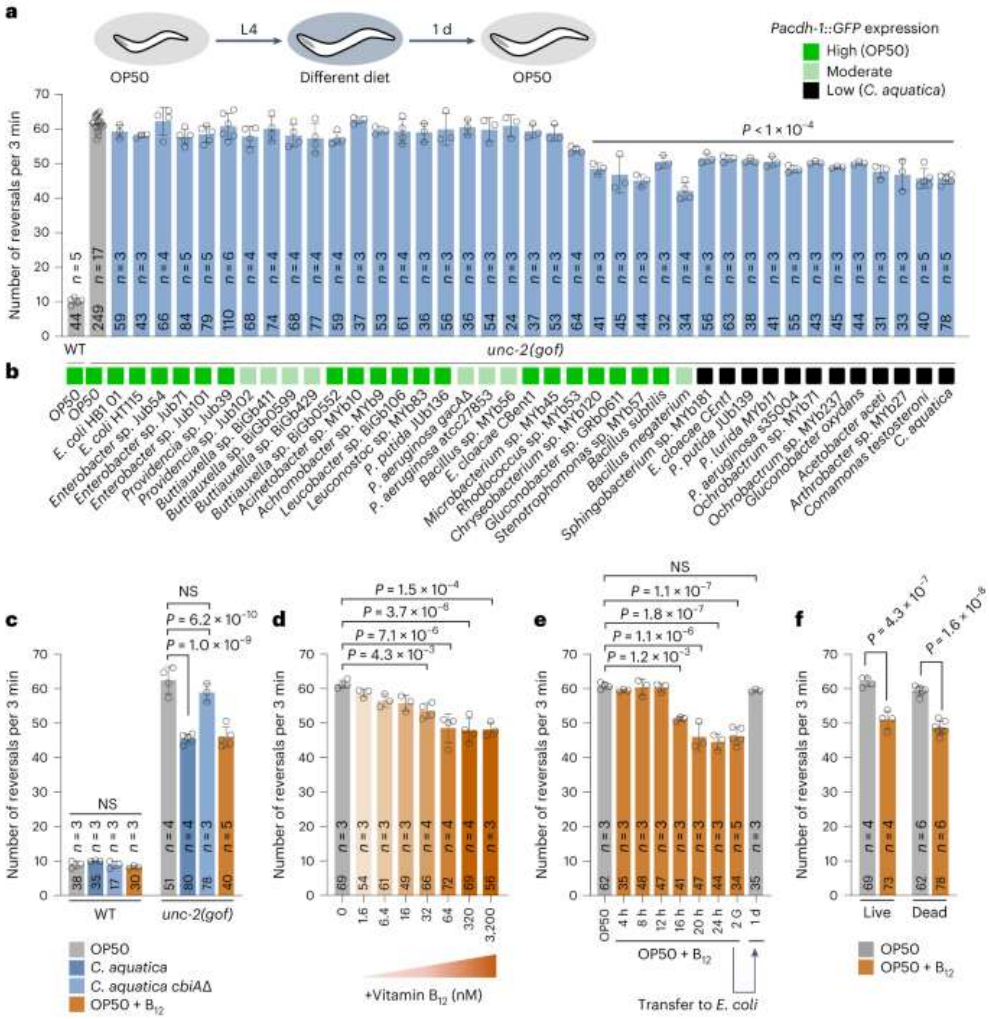
	All tested strains were positive for GABA production, however, the amount varied. *L, bulgaricus* produced the most, then *L, salivarius* and *L. amylovorus*. Also varied based on the medium, TYG produced the most with *L. bulgaricus*. Some effects of GABA on the brain: reduction in stress and anxiety, improved sleep → OCD is closely linked with anxiety symptoms. GABA and glutamate have opposite effects, inhibitory and excitatory respectively. This information came from the source below: Clevland Clinic. (2024, May 1). *Gamma-Aminobutyric Acid (GABA)*. Cleveland Clinic. https://my.clevelandclinic.org/health/articles/22857-gamma-aminobutyric-acid-gaba
Research Question/Problem/ Need	How can lactic acid bacteria (LAB) affect GABA production through fermentation?

Important Figures	 GABA Production based on bacterial strain.
VOCAB: (w/definition)	Lactic acid bacteria - LAB
Cited references to follow up on	Cho, Y. R., Chang, J. Y., & Chang, H. C. (2007). Production of gamma-aminobutyric acid (GABA) by Lactobacillus buchneri isolated from kimchi and its neuroprotective effect on neuronal cells. *Journal of Microbiology and Biotechnology*, *17*(1), 104–109. https://pubmed.ncbi.nlm.nih.gov/18051360/
Follow up Questions	How can this be related to my project and influence the choice of bacteria? How will this show up in behavioral changes in OCD when C. *elegans* are treated with probiotics? How can this be related to glutamate modulation?

Article #20 Notes: Reversal frequency in Caenorhabditis elegans Represents an integrated response to the state of the animal and its environment

Article notes should be on separate sheets

Source Title	Nature of Cell Biology
Source citation (APA Format)	Kang, W. K., Florman, J. T., Araya, A., Fox, B. W., Thackeray, A., Schroeder, F. C., Walhout, A. J. M., & Alkema, M. J. (2024). Vitamin B12 produced by gut bacteria modulates cholinergic signalling. *Nature Cell Biology*, *26*(1), 72–85. https://doi.org/10.1038/s41556-023-01299-2
Original URL	https://doi.org/10.1038/s41556-023-01299-2
Source type	Journal Article
Keywords	B12, C. *elegans*, probiotics, bacteria
#Tags	#methodology
Summary of key points + notes (include methodology)	Notes: Something that has been unclear to researches who have looked into imbalances of the gut microbiota and their relation to mental health disorders is whether the disruption/changes/imbalances in the gut are causing the disorder or are a result of the disorder. The complexities of this relationship and of human mental health in general makes it extremely difficult to understand the effects of certain specific bacteria species (including ones that have been identified as potentially beneficial). This particular study used mutated C. *elegans* with a gain-of-function (gof) mutation in the presynaptic voltage-gated calcium channel UNC-2/CaV2α. There are similar mutations in humans that have been linked to migraines. Possibly the result of imbalances in excitatory transmission (excitation-inhibition imbalance), like with autism, epilepsy, and migraines. Looked into B12 that produced bacteria that could modulate excitatory signaling in C. *elegans.* B12 has also been shown to reduce cholinergic signaling in the CNS. They looked at different bacterial diets for their ability to suppress the hyperactivity of the mutants. They used a multi-worm tracking system to look at the frequent reversals (similar to the OCD model). #methodology: To rule out the different effects that bacterial species could have on neuronal development, all of the worms were grown on standard OP50 plates until the L4 stage, then transferred to plates with the single bacteria. Then, after 24 hours, as young adults, the worms were transferred to a thin lawn of OP50 and

	the reversals quantified. They tested 40 different strains of 20 different genera, most of which were found associated with C. *elegans* in the wild. Results: They found that 18 of the 40 bacterial diets suppressed the hyper-reversals of the mutants. Some of those bacteria were known to produce B12.
Research Question/Problem/ Need	How can different species of bacteria affect behaviors in C. *elegans*?
Important Figures	 This figure shows the different species of bacteria and the results.
VOCAB: (w/definition)	None
Cited references to follow up on	Sandhu, K. V., Sherwin, E., Schellekens, H., Stanton, C., Dinan, T. G., & Cryan, J. F. (2016). Feeding the microbiota-gut-brain axis: diet, microbiome, and neuropsychiatry. *Translational Research*, *179*, 223–244. https://doi.org/10.1016/j.trsl.2016.10.002
Follow up Questions	How can some of these bacteria be used in my project? Is there a connection

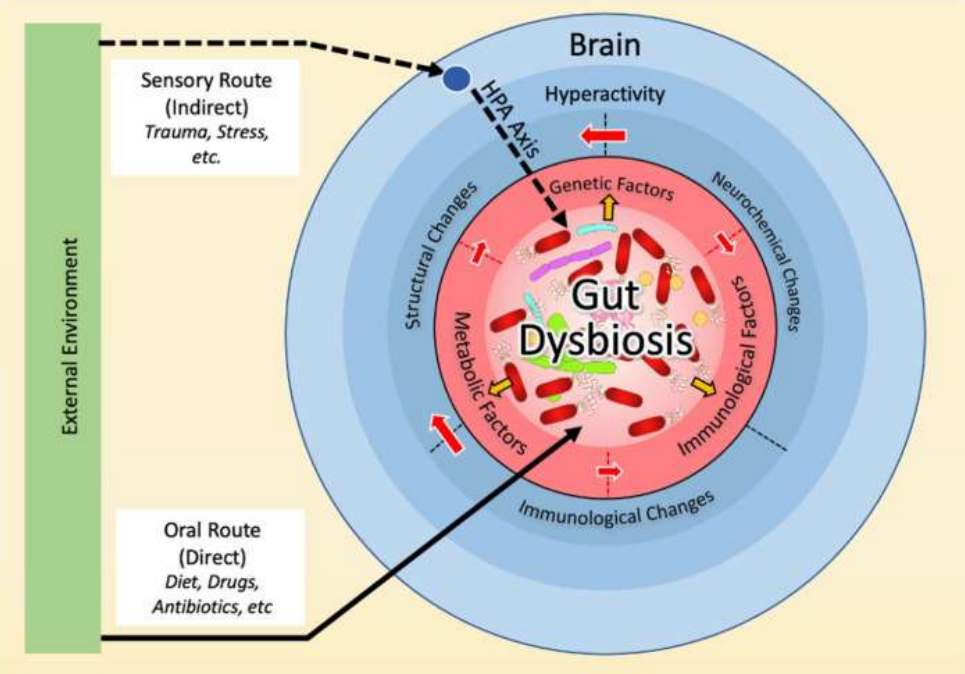
	between reversal rates in this mutated model and the OCD model? How does B12 relate to glutamate modulation?

Article #21 Notes: Microbial Reprogramming in Obsessive–Compulsive Disorders: A review of Gut–Brain communication and Emerging evidence

Article notes should be on separate sheets

Source Title	International Journal of Molecular Sciences
Source citation (APA Format)	Bendriss, G., MacDonald, R., & McVeigh, C. (2023). Microbial Reprogramming in Obsessive–Compulsive Disorders: A review of Gut–Brain communication and Emerging evidence. *International Journal of Molecular Sciences*, *24*(15), 11978. https://doi.org/10.3390/ijms241511978
Original URL	https://doi.org/10.3390/ijms241511978
Source type	Journal Article
Keywords	OCD, obsessive–compulsive disorder, microbiota, gut, gut–brain axis, probiotics, fecal transplants, microbial reprogramming
#Tags	None
Summary of key points + notes (include methodology)	Notes: Dysbiosis, an imbalance in gut microbiota, possibly linked to mental health disorders and OCD. This means that the gut is a potential target for OCD treatment. Review discussed probiotics and fecal transplants. Holistic approach to treatment is necessary due to the complex nature of OCD. OCD is often comorbid and leads to maximum indecisiveness due to the anxiety produced by obsessions and compulsions. Some genes have been identified for OCD/heritability, such as serotonin transporter SLC6A4 and dopamine receptor DRD2. It has also been associated with the cortico-striato-thalamo-cortical (CTSC) circuit, brain regions (orbitofrontal cortex, anterior cingulate cortex, and the basal ganglia), and neurotransmitters (serotonin, dopamine, glutamate). Possibly also associated with environmental factors like trauma or abuse. Some treatments have tried combining SSRIs and glutamate modulators, but overall there are lots of limitations to the current treatments (CBT and medications), like GI distress. Trillions of microorganisms in the GI tract, including bacteria, fungi, viruses, archaea, and protozoa. Classified in three categories: beneficial to the human host, pathogenic, and commensal microbes. It is essential to prevent overgrowth or lack of certain microorganisms. Dysbiosis has been associated with al disorders where OCD was comorbid with another disorder, like autism, Tourette's, anxiety disorders, eating disorders, and some GI disorders. There are strong implications that mental health disorders may be linked to the gut-brain axis, which means that it would be a great avenue, and emerging one, to study for treatments.

	GBA refers to the bidirectional communication between the gut microbiota, the GI tract, and the central nervous system (CNS). Also involves endocrine systems such as the HPA. Article described three parts of the pathway, the immune pathway, the endocrine pathway, and the nervous pathway. The endocrine pathway involves the release of products made by gut microbiota that get into circulation, like short-chain fatty acids (SCFAs), neurotransmitters, hormones, and inflammatory factors, all which have an effect on the CNS. Production of SCFAs comes from anaerobic fermentation of indigestible polysaccharides (fibers and starches) and these play a role in modulating metabolic activity in the gut. Some SCFAs are butyrate, acetate, and propionate. These have been shown to be detectable in CSF. SCFAs play a role in blood-brain barrier (BBB) integrity, which controls the passage of other molecules and nutrients. The nervous pathway involves some neurotransmitters produced by gut bacteria (dopamine, acetylcholine, GABA, noradrenaline, serotonin, and corticotrophin-releasing hormone. Enterochromaffin cells can bind to products and secrete serotonin into the lamina propria, increasing blood concentrations of 5-HT (serotonin). SCFAs are involved in the regulation of enzymes involved in synthesis or serotonin, which shows some connections. SCFAs may have an effect on neurochemistry. The immune pathway: change in gut microbiota can affect the production and availability of SCFAs, effects on inflammatory response. Lower diversity in gut bacteria has been observed in OCD patients, as well as PANS/PANDAS patients. For example, decreases in butyrate-producing genera. Small sample sizes were used, but they still show some promise and therefore should be explored more. Studies (table located in article) showed differences in bacterial levels and used different animal/human models (OCD patients, PANDAS patients, and lots of rat/mice models).
Research Question/Problem/ Need	How does dysbiosis affect symptoms of OCD and other mental health disorders?

Important Figures	 This figure shows the effects on gut dysbiosis on different areas.
VOCAB: (w/definition)	Dysbiosis – imbalances in the gut microbiome; BBB – blood-brain barrier;
Cited references to follow up on	Mahjani, B., Bey, K., Boberg, J., & Burton, C. (2021). Genetics of obsessive-compulsive disorder. *Psychological Medicine*, *51*(13), 2247–2259. https://doi.org/10.1017/s0033291721001744
Follow up Questions	How can the findings of this article relate to my project and treatment for OCD? Should the relationship between OCD and other neurotransmitters (besides glutamate) be explored? How can we measure the levels of neurotransmitters in OCD? Could I stick with my project methodology and as an extension measure the levels of different neurotransmitters?