Determining the Effects of Probiotics on Obsessive-Compulsive Disorder

Grant Proposal

Jasmin Bella

Massachusetts Academy of Mathematics and Science at Worcester Polytechnic Institute

Worcester, MA, USA

Abstract

Obsessive-compulsive disorder (OCD) is a chronic mental health disorder that affects a large population worldwide. It is characterized by repeated and unwanted thoughts (obsessions) and actions (compulsions) and is often comorbid with other mental health disorders such as anxiety, depression, and eating disorders. The current treatments for OCD include therapies and medication; however, they lack widespread efficacy among patients with OCD. The most common medications are antidepressants, normally a kind of selective serotonin reuptake inhibitor (SSRI). SSRIs aim to address commonly observed imbalances of serotonin in patients with mental health disorders. Likewise, patients with OCD have been observed to have an excess of glutamate in their brain, which could be a target for potential treatments.

One way to address this imbalance is through a pathway in the human body called the gut-brain axis (GBA). Recent studies have shown that the level of diversity of bacteria within the gut is correlated to areas of both mental and physical health, where greater diversity is linked to positive improvements. The goal of this project is to utilize probiotics to increase gut diversity to understand their effects on OCD. To accomplish this goal, an established *C. elegans* model for OCD was used along with various types of probiotics. Behavior was observed through periods of locomotion with and without stimulation. Preliminary data was collected on wild-type *C. elegans*, which revealed significant differences in certain behaviors with their standard diets and the administration of probiotics. This information will aid in the understanding of the GBA and mental health treatment.

Keywords: Obsessive-compulsive disorder, antidepressants, SSRIs, glutamate, probiotics

Determining the Effects of Probiotics on Obsessive-Compulsive Disorder

Obsessive-compulsive disorder (OCD) can be a chronic and debilitating mental health disorder, affecting 1 in 40 adults globally at some point in their lifetime (International OCD Foundation, 2024). It is a mental health disorder characterized by repeated and unwanted thoughts (obsessions) and actions (compulsions) (Pittenger, 2015). Obsessions are often distressing and cause discomfort, causing an individual to alleviate that discomfort through their compulsions (Pittenger, 2015). Both obsessions and compulsions can significantly affect one's daily routine and overall quality of life. For many individuals, OCD is also comorbid with mental health disorders like anxiety, depression, and eating disorders (Breteler et al., 2021; Roefs et al., 2022).

Current Treatments

Current treatments for OCD include therapy, oftentimes cognitive behavioral therapy (CBT) or exposure and response prevention therapy (ERP), and medication, usually an antidepressant (National Institute of Mental Health, n.d.; Lissemore et al., 2018). These current treatments are effective in around 40 to 60 percent of patients; however, this percentage leaves many people without proper care (Lissemore et al., 2018). Another downside to the current treatments for OCD is the lack of accessibility and flexibility. Qualified therapists are in short supply, with around 60 percent not having openings for new patients (Stringer, 2024). When it comes to antidepressants, as with most medications, side effects must be considered before using them as a form of treatment. For many people, the severity of withdrawal from antidepressants, potentially leading to worsening symptoms or suicidal ideation, is a deterrent (Palmer et al., 2023). These factors lead to around one third of adults in the United States lacking access to proper mental health care (Stringer, 2024).

Abnormalities in Neurotransmitters

Mental health disorders such as anxiety, depression, and OCD have been linked to abnormal levels of certain chemicals in the brain, such as decreased levels of serotonin (Jones et al., 2020; Lissemore et al., 2018). These abnormalities serve as the basis for the previously mentioned treatments for health disorders. For example, a common form of antidepressant used as treatment today is a selective serotonin reuptake inhibitor (SSRI), which functions by keeping serotonin in the synaptic space and, therefore, increasing the overall amount in the brain (Jones et al., 2020). Antidepressants have been shown to reduce the severity of depressive symptoms; however, they also have downsides, such as their extreme symptoms (Jones et al., 2020; Palmer et al., 2023).

Brain imaging and testing of cerebrospinal fluid (CSF) in OCD patients have also shown increased levels of glutamate in the brain (Pittenger, 2015). The high levels may be rooted in glutamate reuptake in the brain, meaning that it is not effectively transported out of the synaptic space by transport proteins (Pittenger, 2015). A significant greater amount of research is needed before ineffective glutamate transportation can be attributed to OCD.

Many of the existing research often contradicts each other based on their findings. For example, two previous studies connected the glutamate transport protein EAAT3 to OCD, yet this protein is not responsible for most of the glutamate transport done in the brain (Arnold et al., 2006; Danbolt, 2001; Dickel et al., 2006; Pittenger, 2015). Another set of proteins that may also be connected to OCD are the SAPAP and DLGAP proteins (involved in glutamate signaling regulation in mice and humans) based on their ability to cause repetitive behaviors; however, a lack of statistical significance means that neither of these proteins can be attributed to OCD without further evidence (Pittenger, 2015; Welch et al., 2007).

The Gut-Brain Axis and Probiotics

A major signaling pathway in the body that has recently shown promise in the treatment of mental health disorders is the gut-brain axis (GBA). The GBA relays information and connects the health of the gut and brain (Akram et al., 2023; Clapp et al., 2017). At the root of this pathway lies the vast number of bacterial species that comprise the human gut microbiota (Akram et al., 2023; Clapp et al., 2017). Connections have been shown between the level of diversity in gut microbiota, obesity, and mental health, where a more diverse gut is linked to improvements in the other two areas, such as a lower body fat percentage and antidepressant effects (Akram et al., 2023; Beilharz et al., 2017; Clapp et al., 2017).

Through the targeted administration of probiotics, studies have shown that gut diversity can be increased along with other benefits, such as a reduced inflammatory cortisol levels (Clapp et al., 2017). With further

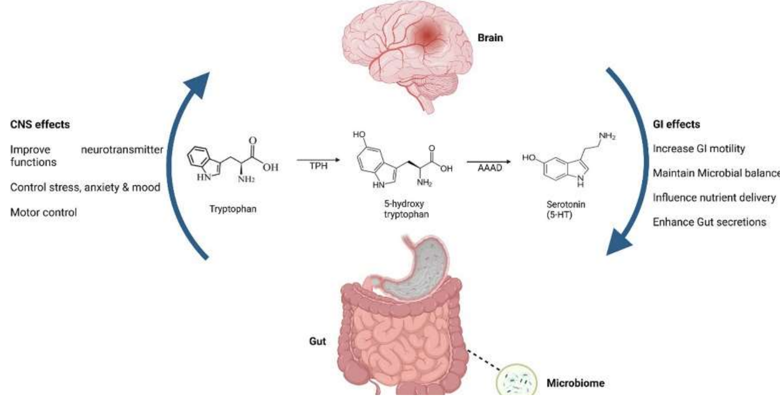

Figure 1: Gut-brain axis diagram. Diverse and balanced gut bacteria can lead to improvements in the central nervous system (CNS) and mental health through the control of stress, anxiety, and mood (Akram et al., 2023).

research on their efficacy, probiotics have the potential to be a beneficial form of treatment due to their accessible nature. They can be found in common fermented foods such as yogurt and kombucha (Clevland Clinic, 2024). These foods contain probiotic genera Lactobacillus and Bifidobacterium, two types of probiotics that have been shown to aid in immune function and digestion support (Dempsey & Corr, 2022; O'Callaghan & Van Sinderen, 2016). In addition, probiotics have been shown to reduce levels of glutamate in the brain. This connection means probiotics could be useful in glutamate modulation, potentially influencing OCD.

***C. elegans* as a Model Organism**

Commonly used model organisms for OCD that have been used in previous studies include rats and mice, as they can display repetitive behaviors characteristic of OCD, including repetitive grooming, checking, and circling (Beilharz et al., 2017; Chamberlain & Ahmari, 2021). However, *C. elegans* is another model organism that can be useful to understand the effects of probiotics on OCD. Because their diet is bacteria, they can be fed different probiotic strains to understand the effects on repetitive behaviors linked to OCD, such as repetitive reversals and feeding behaviors (Katz et al., 2019). These behaviors come from an established *C. elegans* model with a knockout mutation for a glutamate transport protein (GLT-1) that can be used of further investigate how glutamate levels can impact neurological symptoms (Katz et al., 2019). Repetitive behaviors were observed in this GLT-1 knockout model during both regular locomotion in the exploration phase and through mechanical stimulation as an escape behavior (Katz et al., 2019). This strain could be particularly useful for modeling OCD if it is in fact connected to glutamate transport in the brain. Its use as a model organism will allow for further understanding of the connections along the GBA and how this pathway can be utilized for treatment of mental health disorders in the future (Beilharz et al., 2017; Katz et al., 2019).

Section II: Specific Aims

This proposal's objective is to understand the effects of probiotics on glutamate and OCD. Our long-term goal is to ultimately develop a more effective and accessible treatment for individuals with OCD, where the central hypothesis of this proposal is that probiotics will reduce the severity of OCD behaviors in *C. elegans* and become a viable treatment method. The rationale is that patients with OCD have an imbalance in certain neurotransmitters; this proposal specifically focuses on glutamate, which probiotics may have the ability to modulate (Akram et al., 2023; Clapp et al., 2017; Pittenger, 2015) . The work proposed here will contribute to the ever-growing knowledge about the human brain and improve the quality of life of those with mental health disorders.

Specific Aim 1: Understand the effects of probiotics on a *C. elegans* model for OCD through dietary modifications.

Specific Aim 2: Understand the effects of probiotics on glutamate on a *C. elegans* model for OCD.

The expected outcome of this work is an effective probiotic treatment for OCD that is more effective and accessible to individuals globally.

Section III: Project Goals and Methodology

Relevance/Significance

For many of the 8.2 million adults in the United States alone diagnosed with OCD, finding treatment can be a difficult task (International OCD Foundation, 2024). The current shortage of mental health professionals has contributed to prolonged periods between becoming diagnosed and receiving treatment, sometimes totaling up to a year and a half (International OCD Foundation, 2024; Stringer, 2024). Additionally, traditional therapies for OCD, such as CBT and ERP, cost between 100 and 200 dollars per session (Psychology Today, n.d.). Although insurance may cover some of the cost for many individuals, finding therapists within their insurance network who also meet the needs of the individual poses another challenge (Psychology Today, n.d.). When OCD patients opt for medication-based treatments, they come with a cost, as well as the risk of side effects or extreme withdrawal, which can mean a lack of flexibility with treatments (Palmer et al., 2023).

Innovation

Although there have been some previous studies looking at the effects of probiotics on the GBA and OCD, as well as studies using *C. elegans* to model OCD, studies have not combined the two methods to further understand the effects of probiotics on OCD (Akram et al., 2023; Beilharz et al., 2017; Ghuge et al., 2023; Katz et al., 2019). This project can strengthen the conclusions from previous studies on rats to provide alternative treatment pathways (Ghuge et at., 2023).

Methodology

The *C. elegans* strains used in this project include wild-type (N2) and an OCD model (OS11091) with a GLT-1 knockout mutation. Both strains were obtained from the Caenorhabditis Genetic Center (CGC). Standard Nematode Growth Media (NGM) plates were prepared and seeded with E. *Coli* OP50 for worm stock plates. For the probiotic plates, *L. acidophilus* and *L. bulgaricus* were cultured overnight before being seeded onto NGM plates. These specific strains of lactic acid bacteria (LAB) were identified through bacteria morphology.

Worms were separated into different experimental groups which include a group grown on *E. Coli* OP50 from the egg stage to the young adult stage, a group grown on *E. Coli* OP50 from the egg stage to the L4 stage and then transferred to probiotic plates for 24 hours to develop to the young adult stage, and a group grown on probiotic plates from the egg stage to the young adult stage. These experimental groups were identified to observe the effects of probiotics at different stages of life. They have the potential to affect worm development which can show the relationship between environmental factors and the development of the disorder.

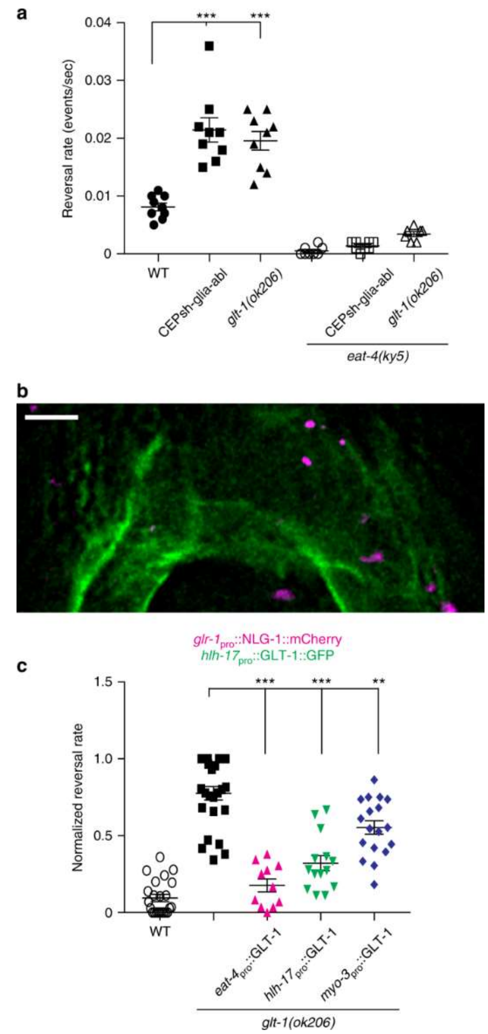

Figure 2: C. elegans reversal rates. a) Raw reversal rates (events/second) in wild-type (WT) and mutated strains of C. elegans. b) Image of GLT-1 protein and synapses. c) Normalized reversal rates relative to the minimum of the WT controls and maximum of the GLT-1 mutant strains (Katz et al., 2019).

Before conducting the two assays in this experiment, a locomotion assay and a mechanosensation assay, the worms were synchronized and grown to the young adult stage (MIT, 2015). Assays were conducted on NGM plates with a thin layer of the respective bacteria. Data collection involved using a stereo microscope camera and video software and analyses were performed manually and using an ImageJ worm tracker (Pedersen, 2011).

To conduct the locomotion assay, worms were observed for 2-minute periods. The primary behaviors observed included speed, direction, reversal events, and body bends. These behaviors provide information on symptoms of OCD in the C. *elegans* model and resulting behavior after the administration of probiotics.

The mechanosensation assay was performed with a gentle touch sensation (Chalfie et al., 2005-2018). This process involved repeated stimulation with an eyebrow hair fixed to the end of a toothpick to the anterior and posterior ends of the worm. The observation of their behaviors as a result of the mechanosensation provides insight into their response to repeated stimuli and habituation.

Specific Aim #1:

One of the goals of this proposal is to understand the effects of probiotics on a *C. elegans* model for OCD. Our approach includes using a *C. elegans* strain with a knockout mutation for the GLT-1 protein, a protein involved in glutamate transportation in the brain. Behaviors of the mutated strain can be compared to the wild-type *C. elegans* when fed probiotics to understand their effects.

Justification and Feasibility. The use of a *C. elegans* strain without the GLT-1 protein is fitting for modeling OCD due to its ability to display repetitive behaviors and the potential connection between glutamate and OCD (Katz et al., 2019). There were a higher number of reversal events from the mutated strains than the wild-type (Figure 2a and 2c), and when the GLT-1 protein was restored, reversal rates were normalized (Katz et al., 2019). This strain allows us to understand the effects of probiotics on glutamate modulation and the effects of changes in glutamate on OCD.

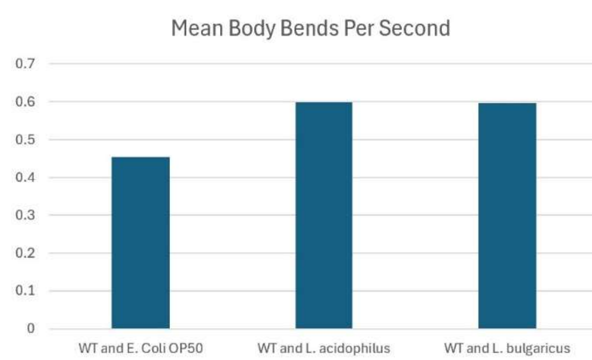

Figure 3: Mean Body Bends Per Second. One-way ANOVA conducted showed a significant difference in body bends per second, a behavior that can be used to quantify OCD, with the administration of probiotics ($p < 0.001$). Additionally, when a Tukey HSD test was conducted, there was a significant difference between the individual probiotics and the standard diet of E. Coli OP50 ($p < 0.01$); however, there was no difference between the two types of probiotics.

Summary of Preliminary Data. The wild-type worms (N2) were observed during periods of regular locomotion. The worms observed on a thin layer of *E. Coli* OP50, *L. acidophilus,* and *L. bulgaricus* for periods of 2 minutes each. The behavior of these worms was quantified manually through microscope videos and graphed using Excel (Figure 3). One-way ANOVA was conducted to understand the relationship between the administration of different probiotics and the number of body bends per second. The results of the ANOVA showed that there was a significant difference in the body bends per second across the three groups ($p < 0.001$). After the ANOVA was conducted, a Tukey HSD test was conducted to determine which groups had a significant difference. The results of this analysis showed a significant difference between the sample on *E. Coli* OP50 and each of the probiotics ($p < 0.01$); however, it showed no significant difference between the two different types of probiotics, *L. acidophilus* and *L. bulgaricus.*

Additionally, reversal events were observed and graphed using Excel (Figure 4) (Katz et al., 2019). One-way ANOVA was again conducted; however, the analysis showed that there was no significant difference in the number of reversal events per second across the treatment groups.

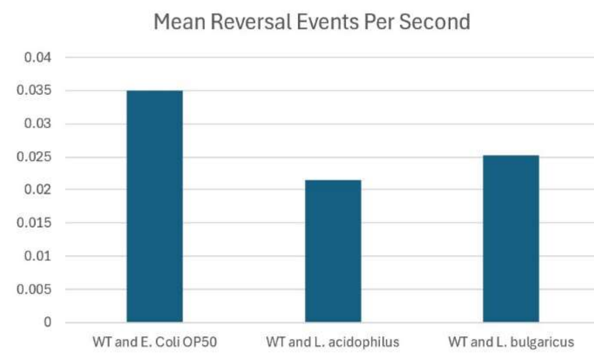

Figure 4: Mean Reversal Events Per Second. One-way ANOVA conducted showed no significant difference between the reversal events across the three treatment groups.

Expected Outcomes. The data collected from this aim will aide in determining the effects of probiotics on glutamate modulation and OCD. A decrease in the repetitive behaviors of the *C. elegans* would show that probiotics are a potentially effective treatment for OCD. These results will contribute to the understanding of the gut-brain axis and how it could be utilized to treat mental health disorders overall.

Potential Pitfalls and Alternative Strategies. This project relies on the ability to measure reversal rates using a worm analysis software. The current software, wrMTrck, functions as a plugin to the open-source Fiji software for image recognition and analysis. However, it does not currently have the capability to measure reversal rates, which means that a separate program must be written to do so. The software has the potential to pose a challenge because it needs to accurately measure the reversal rates to provide accurate results. An alternative to this could include switching to software that can analyze reversal rates, although there are limited open-source options.

Specific Aim #2:

Another goal of this project is to understand how glutamate levels in the brain are altered because of the administration of probiotics. If OCD symptoms are reduced based on testing done for the first aim, testing the levels of glutamate within the *C. elegans* to determine if there was a reduction would be a useful next step in the project. This analysis has the potential to show a correlation between glutamate modulation and OCD symptom severity, which would give further evidence for developing an effective treatment for OCD using the GBA.

Justification and Feasibility. After preliminary testing was done on CSF in OCD patients that found elevated levels of glutamate, magnetic resonance spectroscopy (MRS) was conducted to determine the exact regions of the brain where these abnormalities were present (Pittenger, 2015). This testing found elevated levels of glutamate in areas such as the basal ganglia (Pittenger, 2015). Using similar methods on *C. elegans,* MRS could help to determine whether there was an actual reduction in glutamate in the brain, in combination with a reduction of OCD symptoms. However, this technology is beyond the scope of the laboratory that this experiment is being conducted.

Expected Outcomes. The information obtained from this aim would increase our understanding of the relationship between levels of neurotransmitters in the brain and mental health disorders. It would also increase our understanding of the relationship between gut health and brain health, which could be used to develop treatments for other mental health disorders in the future.

Potential Pitfalls and Alternative Strategies. A major challenge of this aim is to obtain the equipment necessary to perform the magnetic resonance spectroscopy on the C. *elegans.* Performing this analysis on glutamate would increase the understanding of its specific role in mental health disorders, and it would also provide support for the results of the first aim. However, it is still possible to understand the effects of probiotics on OCD through the observation of behaviors only.

Section III: Resources/Equipment

The resources used in this project include *E. Coli* OP50, *L. acidophilus, L. bulgaricus*, wild-type and OCD model *C. elegans,* and agar plates with NGM. The equipment to be used includes a stereo microscope, laboratory hood, steam sterilizer, bacteria loops, and a worm pick. To measure the effects of probiotics on glutamate, equipment to perform MRS is also needed; however, this equipment is not within the current scope of the project, but it is a possible future step or extension if time allows.

Section IV: Ethical Considerations

To ensure the health, safety, and overall wellbeing of all involved in this project, proper laboratory safety measures will be taken at all times. These measures include wearing proper personal protective equipment (gloves, lab coat, goggles) when appropriate, working under a laboratory hood when culturing bacteria, sterilizing tools with bleach or isopropyl alcohol, and disposing of excess materials in the proper receptacles. In addition, the bacteria and *C. elegans* will be handled with care, not using more than the required amount of these resources.

Section V: Timeline

The initial brainstorming and research phase of this proposal began in August of 2024 and continued into November of 2024. Preliminary data collection will take place from late November to early December and the main experimentation period will run from December to February. Specific steps in the project and progress can be accessed via this link: https://wpi0-my.sharepoint.com/:x:/g/personal/jbella_wpi_edu/Edw2WPgxQjBCpo0DDNZc1wIBe3iGaE4sGlKGn__UmOJENQ?e=QjKdBL&nav=MTVfe0JCRUNGODU4LTNDODAtNEUyNy04RkM5LUYyOTczNzcwQTM1Qn0.

Section VII: References

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

Arnold, P. D., Sicard, T., Burroughs, E., Richter, M. A., & Kennedy, J. L. (2006). Glutamate transporter gene SLC1A1 associated with obsessive-compulsive disorder. *Archives of General Psychiatry*, *63*(7), 769. https://doi.org/10.1001/archpsyc.63.7.769

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

Breteler, J. K., Ikani, N., Becker, E., Spijker, J., & Hendriks, G. (2021). Comorbid depression and treatment of anxiety disorders, OCD, and PTSD: Diagnosis versus severity. *Journal of Affective Disorders*, *295*, 1005–1011. https://doi.org/10.1016/j.jad.2021.08.146

Chalfie, M., Hart, A., Rankin, C., & Goodman, M. (2005-2018). Assaying mechanosensation. In *WormBook: The Online Review of C. elegans Biology*. Pasadena, CA: WormBook. Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK235860/

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

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

Clevland Clinic. (2024, June 19). *Probiotics*. Cleveland Clinic. https://my.clevelandclinic.org/health/treatments/14598-probiotics

Danbolt, N. C. (2001). Glutamate uptake. *Progress in Neurobiology*, *65*(1), 1–105. https://doi.org/10.1016/s0301-0082(00)00067-8

Dempsey, E., & Corr, S. C. (2022). Lactobacillus spp. for Gastrointestinal Health: Current and Future Perspectives. *Frontiers in Immunology*, *13*. https://doi.org/10.3389/fimmu.2022.840245

Dickel, D. E., Veenstra-VanderWeele, J., Cox, N. J., Wu, X., Fischer, D. J., Van Etten-Lee, M., Himle, J. A., Leventhal, B. L., Cook, E. H., & Hanna, G. L. (2006). Association testing of the positional and functional candidate gene SLC1A1/EAAC1 in Early-Onset Obsessive-compulsive Disorder. *Archives of General Psychiatry*, *63*(7), 778. https://doi.org/10.1001/archpsyc.63.7.778

Ghuge, S., Rahman, Z., Bhale, N. A., Dikundwar, A. G., & Dandekar, M. P. (2023). Multistrain probiotic rescinds quinpirole-induced obsessive-compulsive disorder phenotypes by reshaping of microbiota gut-brain axis in rats. *Pharmacology Biochemistry and Behavior*, *232*, 173652. https://doi.org/10.1016/j.pbb.2023.173652

International OCD Foundation. (2024, October 15). *International OCD Foundation | Who gets OCD?* https://iocdf.org/about-ocd/who-gets-ocd/

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

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

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

MIT. (2015). C. elegans synchronization via bleaching. *MIT OpenCourseWare*, 1–2. https://ocw.mit.edu/courses/7-15-experimental-molecular-genetics-spring-2015/c4cb8b1556ac80b5d2e3599c65b5d1c4_MIT7_15S15_Synchronization.pdf

National Institute of Mental Health. (n.d.). *Obsessive-Compulsive Disorder*. National Institute of Mental Health (NIMH). https://www.nimh.nih.gov/health/topics/obsessive-compulsive-disorder-ocd

O'Callaghan, A., & Van Sinderen, D. (2016). Bifidobacteria and their role as members of the human gut microbiota. *Frontiers in Microbiology*, *7*. https://doi.org/10.3389/fmicb.2016.00925

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

Pedersen, J. S. (2011). *wrMTrck multible object tracker* [Software]. https://www.phage.dk/plugins/wrmtrck.html

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

Psychology Today. (n.d.). *Cost and insurance coverage*. https://www.psychologytoday.com/us/basics/therapy/cost-and-insurance-coverage#how-much-does-therapy-cost

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

Stringer, H. (2024). Mental health care is in high demand. Psychologists are leveraging tech and peers to meet the need. *Monitor on Psychology*, *55*(1). https://www.apa.org/monitor/2024/01/trends-pathways-access-mental-health-care

Welch, J. M., Lu, J., Rodriguiz, R. M., Trotta, N. C., Peca, J., Ding, J., Feliciano, C., Chen, M., Adams, J. P., Luo, J., Dudek, S. M., Weinberg, R. J., Calakos, N., Wetsel, W. C., & Feng, G. (2007). Cortico-striatal synaptic defects and OCD-like behaviours in Sapap3-mutant mice. *Nature*, *448*(7156), 894–900. https://doi.org/10.1038/nature06104