Logbook - For a more detailed log without dates, ask to see my project construction document.

Name: Sara Waqas
Grade: 10

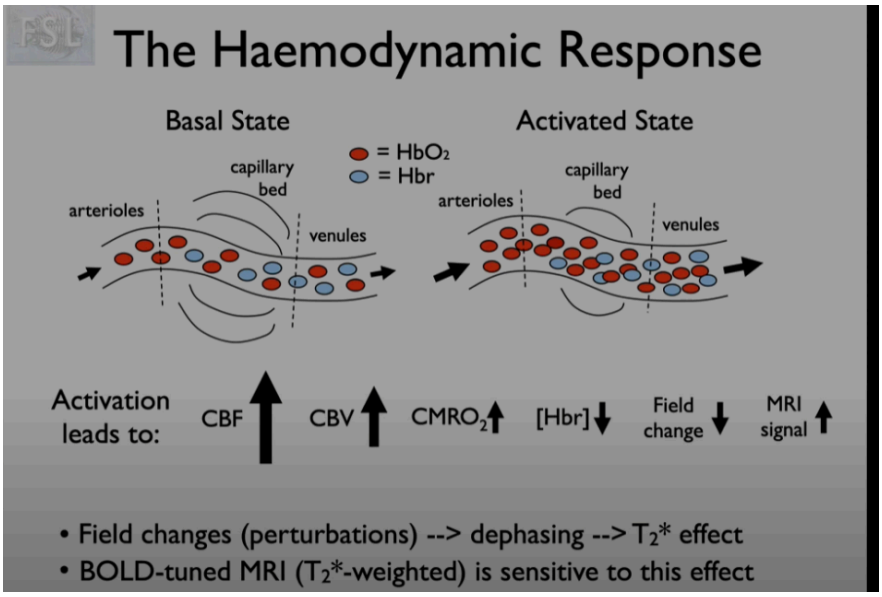
Project Type: Study
Project Title: Using fMRI and Multi-omic Analysis to Develop a Neurobiologically Precise Alternative Treatment to Schizophrenia

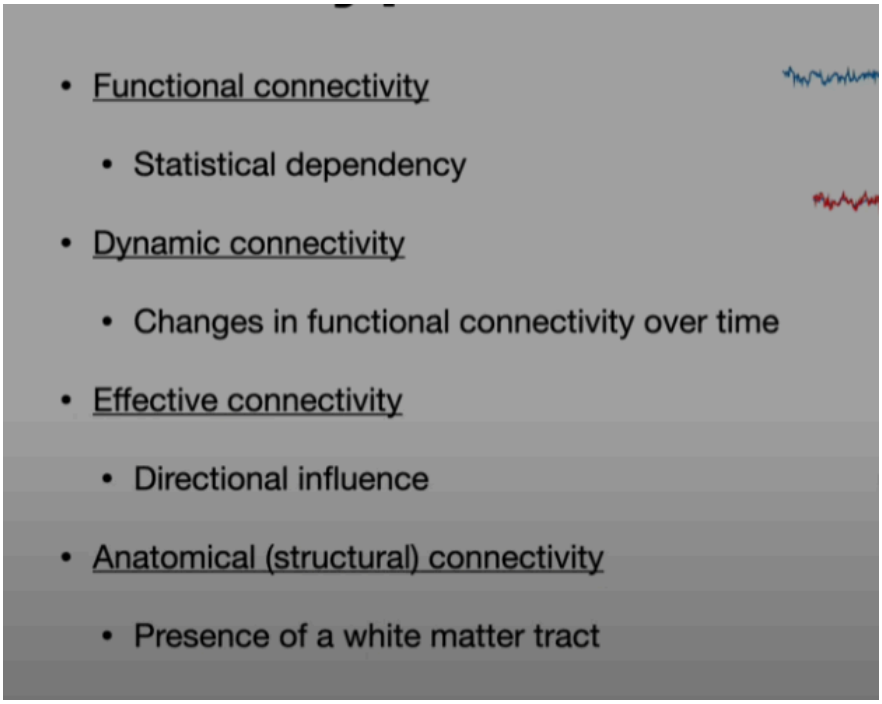
June 27th, 2024	Right now, im thinking of doing something related to the way schizophrenia is labeled as a what disease, but it has some relationships with aging Starting a huge literature dive: Brodmann area 9, The subcortical structures include the deep gray and white matter structures. Methylation of CpG islands stably silences genes So accelerated epigenetic aging is related to suicidality, that is what we get from the literature. We can basically confirm this, and then confirm the idea of schizophrenia suicidality being mroe common in those with accelerated aging. Then find very specific markers for that, but i want to know if schizophrenic suicidality is another thing yk The molecular mechanisms of suicidal behavior in psychosis remain poorly investigated, although it has been hypothesized that epigenetic processes are involved in the etiology of both psychosis and suicidality. https://www.sciencedirect.com/science/article/abs/pii/S0022395618305922 What next? What AFTER the thing can we do - molecular docking to discover treatment

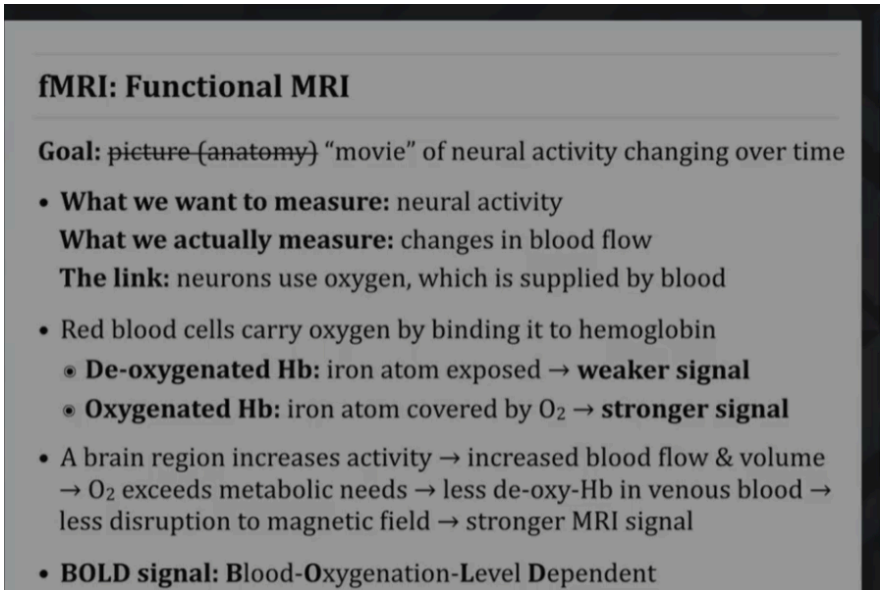
	Maybe suicidality in schizophrenia?
July 13th, 2024	Something to do with biomarkers for schizophrenia, but i want something more specific. I want to focus on a specific area or something like that. So find biomarkers associated with motor and cognitive decline that can be targeted for treatment too and increasing motor function as well as used to identify severity and predict decline. Brain biomarkers for schizophrenia are found in critical ROIs corresponding to specific brain networks, identified through brain-network-constrained multi-view SCCA, showing potential for clinical applications and correlation with symptom severity. Research about sleep spindles. Sleep spindles play a crucial role in sleep-dependent memory consolidation and are significantly altered in schizophrenia (SCZ), potentially serving as a biomarker for the disorder [2]. Patients with SCZ exhibit deficits in sleep spindle characteristics, such as density and amplitude, which correlate with impaired memory consolidation [2]. Research suggests that these spindle abnormalities are specific to SCZ and are not observed in first-degree relatives of patients, indicating that spindle deficits may be a core feature of the disorder [2]. Furthermore, reductions in sleep spindles have been linked to disruptions in thalamocortical networks, reflecting underlying neuronal and molecular mechanisms in SCZ [1] Distinct core and matrix thalamocortical circuits regulate sleep spindles. Disruption in these networks may underlie deficits in schizophrenia, impacting sleep and attentional gating. Sleep spindles, which are brief bursts of rhythmic brain activity during non-rapid eye movement sleep, play a crucial role in memory consolidation and are regulated by thalamocortical (TC) circuits. Research suggests that disruptions in these circuits are associated with schizophrenia, impacting sleep architecture and cognitive functions

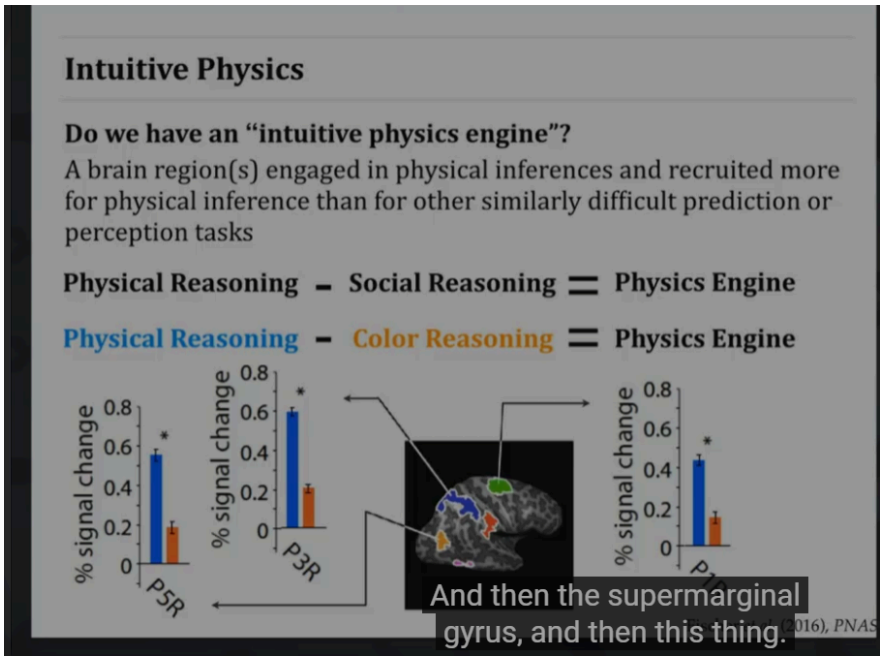
	that alterations in sleep spindle parameters, such as density and power, are observed in patients with schizophrenia, potentially reflecting underlying thalamocortical network dysfunction. \ Ok so maybe look at this network and find specific biomarkers of it's disruption. Diazepam plays a significant role in the treatment of schizophrenia, particularly in conjunction with antipsychotic drugs. Research indicates that benzodiazepines, including diazepam, are commonly used in older patients with schizophrenia, despite associations with adverse outcomes such as impaired cognition and increased hospitalization rates [3]. Additionally, studies highlight the potential of diazepam to prevent hippocampal hyperactivity and psychosis-related behaviors in animal models of schizophrenia, emphasizing the importance of GABAergic mechanisms
August 2nd, 2024	Biggest idea right now: targeted therapeutics and accurate diagnosis for schizophrenia through biomarker identification using fMRI, network science, and multiomic analysis. I'm thinking of suicidality of schizophrenic patients. paper notes: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9706110/ Genetic risk (specifically parents or siblings with schizophrenia) is considered one of the important predisposing factors. Environmental factors such as being born in winter, living in an urban environment, air pollution (PM2.5, PMC, PM10, SO2, and NO2 exposure) (Song et al., 2022), immigrating to a new country, using cannabis or recreational drugs, especially from a young age, and suffering prenatal hypoxic ischemic events and/or nutritional deficiencies (Susser et al., 1995), constitute risk factors (Tiwari et al., 2010). Certain infections (e.g., influenza, toxoplasma gondii, herpes simplex virus type 2) (Brown and Derkits, 2010) and autoimmune diseases can increase the risk. Suffering from a severe long-term stress has been demonstrated to affect the brain and raise the risk of schizophrenia. early 10% of patients with schizophrenia die from suicide. using imaging techniques for psychiatric disorders, like schizophrenia to rule out any physical abnormalities or structural

	lesions in the brain. These abnormalities could potentially cause symptoms that mimic or resemble those of schizophrenia. Essentially, imaging helps to ensure that the symptoms are not due to other underlying structural issues in the brain. nterior cranial fossa meningiomas that encroach on the frontal lobes are known to cause such symptoms as abulia, personality changes, and olfactory hallucinations which may lead to a misdiagnosis of schizophrenia. Method: computed tomography.
August 3rd, 2024	Fmri is good because it can show us cognitive function during different mental illnesses. Esp since for schizophrenia the pathophysiology is unknown. Theories rn: Anatomic, neurotransmitter, and **immune system abnormalities** have been implicated So we can choose data that has them doing an activity (research why thats important and different activities we want maybe on an individual basis) or we could do: rsfMRI is a method aimed at examining intrinsic networks in the brain while no task is performed (rest); this is to estimate correlations between brain regions. These correlations may indicate a tight functional relationship (i.e., “functional connectivity”) between those regions. ; http://afni.nimh.nih.gov/afni), the CONN toolbox (https://www.nitrc.org/projects/conn/), MELODIC (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/MELODIC), and Group ICA of fMRI Toolbox Software (GIFT; http://mialab.mrn.org/software/gift/), are commonly used to analyze rs-fMRI data. Pipelines26,27 have also been developed to analyze data almost automatically, which make the data analysis much easier for nonexperts. For easy understanding, the large amount of information contained in the rs-fMRI data can be compared with a map.28 Regional Homogeneity Analysis ReHo analysis is a voxel-based measure of the similarity between the time-series of a given voxel and its nearest neighbors,

	Using trust games, Reference Gromann, Heslenfeld and Fett Gromann and colleagues (2013) found that patients displayed reduced baseline trust of others. In addition, when playing with cooperative people, patients showed reduced caudate activity, which was inversely correlated with paranoia measures. So non resting state basically elucidates more like bejhavior so it wouldnt tell us what to treaty exactly.
August 5th, 2024	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6051935/  When the blood flow increases obviously the more iron gets a stronger mri signal so we are able to see changes in signal

	 https://radiopaedia.org/articles/diffusion-weighted-imaging-2

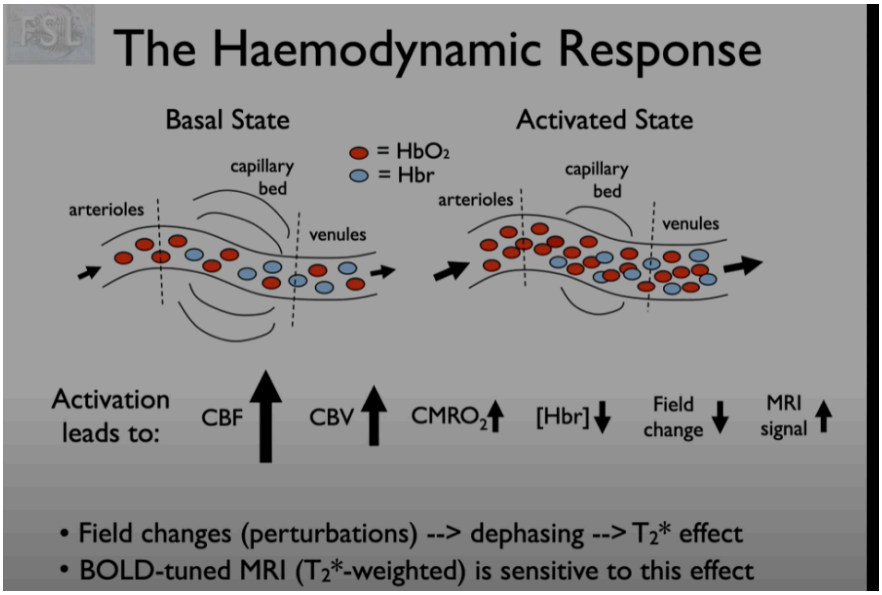


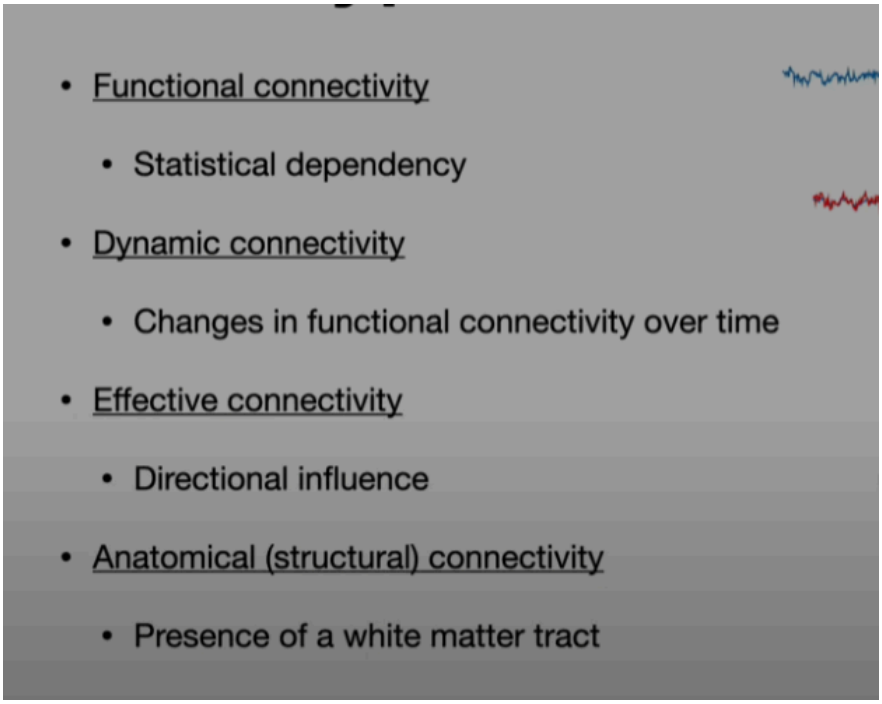


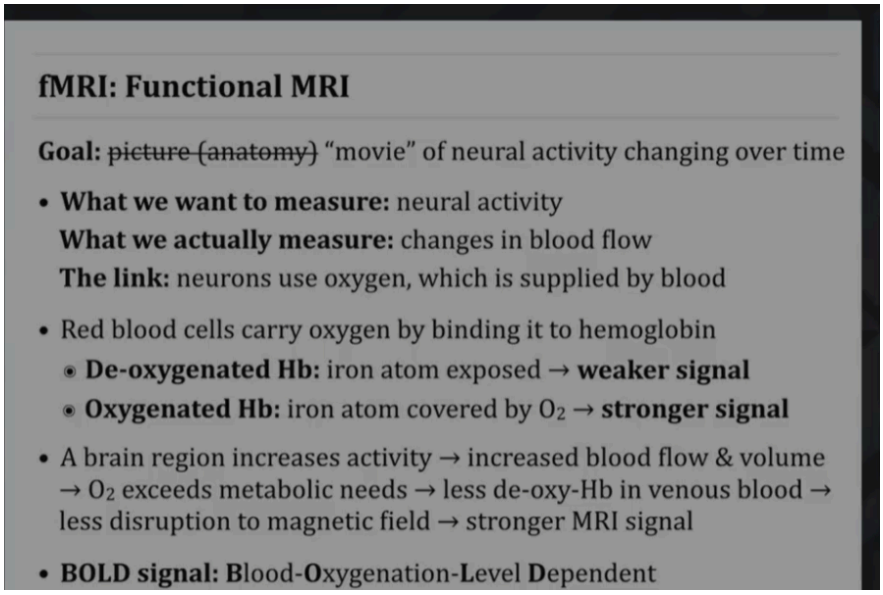
To create a baseline and take away the parts of brain responding to color and physical stuffs and not the actual physics

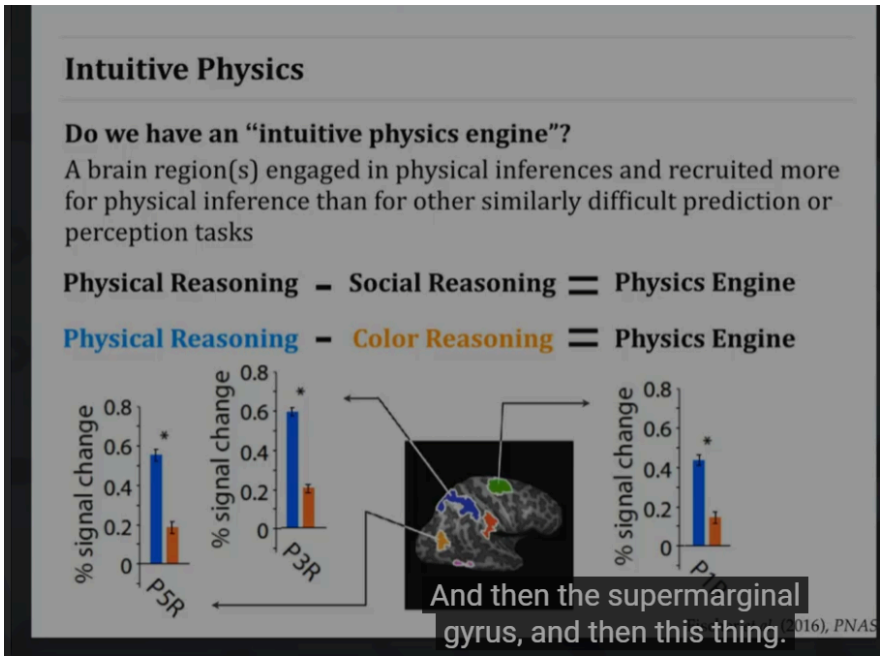
You cant make an assertion that just cus one brainr legion does something that that is whats going on; the brain part that responds to pain may also respond to social rejection, or happiness lol so yeah u have to be weary.

So you really have to look into likteraturei nto the actual regions and see what it says. If its solely about one thing like pain u can

	deduce ur original hypothesis, but if its a multitude of things then good luck. Still not perfect. Sio the methodology described is called “cognitive subtraction”. This is limited bcs it relies on SO MANY assumptions. So multivoxel pattern analysis is the best methodology.
August 6th, 2024	Looking into fMRI analysis tools. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6051935/  When the blood flow increases obviously the more iron gets a stronger mri signal so we are able to see changes in signal

	 https://radiopaedia.org/articles/diffusion-weighted-imaging-2





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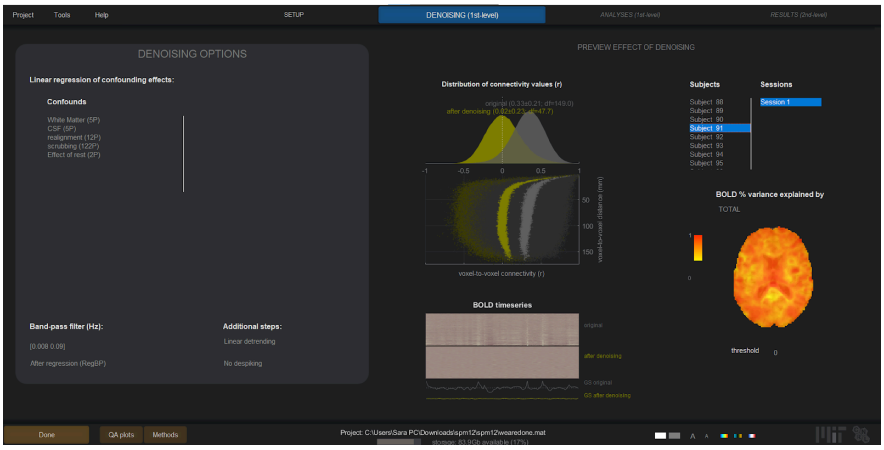
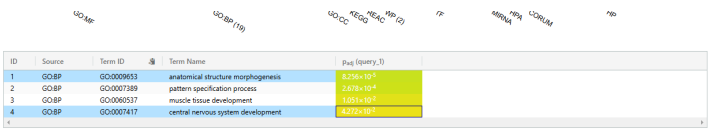
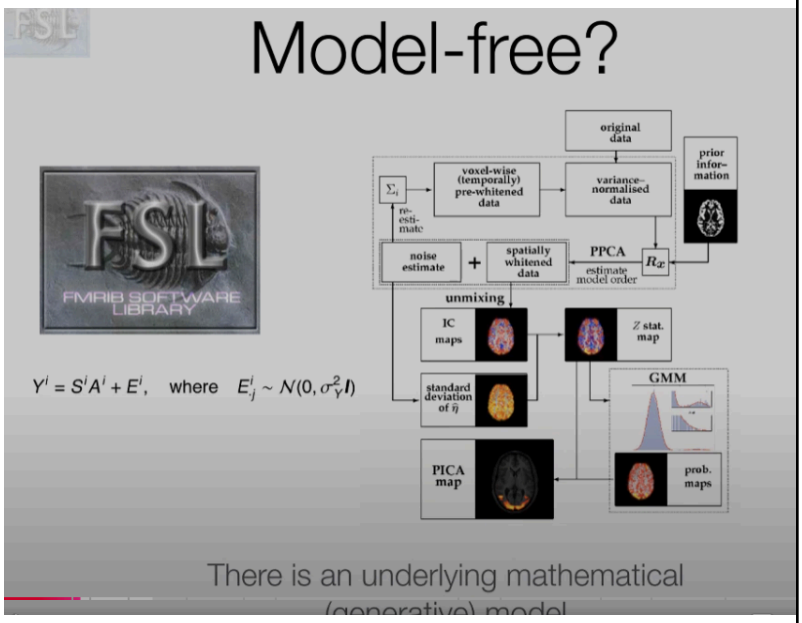
August 11th, 2024	So we have the tools, now we need to know what we want to know.. Alternative treatment targeted for schizophrenia thats a good enough rationale. Negative symptom means not in normal brain Positive means something new not in normal brain. So my analysis would tell me if there are positive or negative symptoms, IE if I need to silence or something we must induce.
August 17th, 2024	Was thinking about identifying gene variants associated with schizophrenia using the GWAP and then creating my own disease risk score based on different samples to assess who would have a severe case of schizophrenia. Then I can have targetted pathways and drug treatment.
September 2nd, 2024	So im thinking of the hippocampus dysfunction theory, so look at the working memory set AND the normal one from UCLA, see if it makes sense in terms of the genomic stuff, and then invent a better treatment. This would be a great way to identify that there are issues in hippocampus function Discovered openFMRI as a great database to refer to.
September 29th, 2024	Worked on datasets as well as different scan “cuts” of the brain: Different cuts Small movements create spurious correlations. Need to be VERY VERY specific as too much movement ruins study.

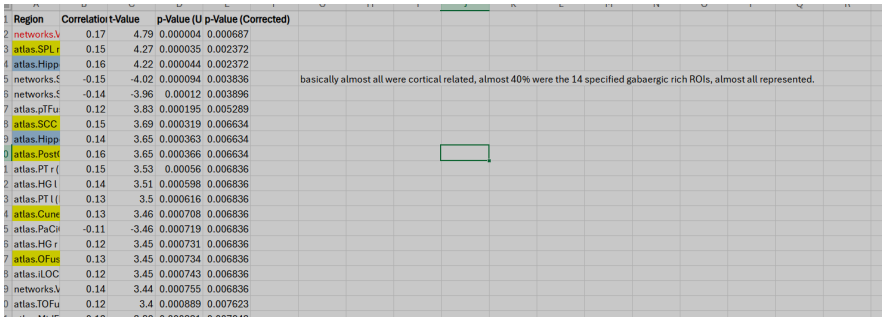
	Learn: ROI, NODES, CONNECTIVITY MAPS, parts of brain, voxels, networks Okay my idea is: First we do all samples, and then differentiate between men and females to see if there are any differences or any precise things we can do to alter the treatment. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5688947/ Last resorts: https://openneuro.org/datasets/ds003011/versions/1.2.3 https://openneuro.org/datasets/ds005073/versions/1.0.0 Hopefully we get it from the COMBINE one, but it will be hard as it is quite restricted.
October 13th, 2024	Decided I could analyze multiple sets so I can derive biomarkers a lot easier. Decided to analyze all sets despite quality and just state the quality discrepancies in my sources of error.
November 2nd, 2024	Read more into the literature and decided I should probably do multiple tests, some testing about gender specific differences, some on different DSM5 related schizophrenia diagnosis. A lot to work with after processing is complete.
November 3rd, 2024	Found the CONN toolbox and will be using that for analysis in MATLAB.
November 4th-14th	Multiple trial and errors of trying to use the CONN toolbox and failing miserably. Took many efforts to realize I needed to upload structural data as well. I decided on the 12th I need to start learning a lot about the actual white matter, grey matter, etc so I can UNDERSTAND my analysis. My pipeline requires preprocessing so skull stripping which I will explain more indepth later, then denoising so removing random variances that seem like BOLD signal but are not, then first level analysis and finally group level and actually seeing differences. Might want to do GROUP ICA. Saving the RNA SEQ for later however.
November 15th	Finished denoising, very good because I had many outliers. I need to really dive into literature is what I have learned as there is a lot of information regarding my hypothesis I need to learn about and also

	schizophrenia in general as well as BOLD signal. I'm reserving this more indepth time consuming work for later asprocessing takes longest, most trial and error, and finishing it soon is definitely ideal. The goal is before January to have all fMRI data processed as well as HOPEFULLY all RNA seq worked out (but I am more experienced in that department). 
December 22nd, 2024	This is lock down time for science fair, so I need to finish group level analysis. I will be adding covariates like age and separating my analysis so I can analyze the different groups (control and disease). I'll do the other comparison later.  Making groups.

	Made control, patient and age (mean centred) will make groups for each diagnosis as well.
December 23rd, 2024	
December 24th, 2024	Found RNA seq data,
December 25th, 2024	Found better RNA seq data, ran group ICA and dynamic ICA work
December 26th, 2024	Began RNA seq analysis, ran gorup ICA and dynamic ICA, decided to make my own ROI for gabaergic and also compare all gabaergic ROI among the entire system to see fi they are functionally connec

December 29th, 2024	Explored downregulated genes and found that genes involved in synthesized retinoic acid were consistently and severely downregulated. Could be a good target for neuroinflammation. Impaired retinoic acid signaling results in neuroinflammation, oxidative stress, mitochondrial malfunction, and neurodegeneration - also supports neurodegenerative hypothesis. So, target is uplifting retinoic acid! …Was my original conclusion. After further inspection I did realize that just targeting retinoic acid would likely prove to be helpful but nonspecific as it is likely that retinoic acid is not the catalyzing compound. Revert to gabaergic, find therapeutics that have a binding affinity ot both gabaergic interneurons AND retinoic acid receptors? https://www.nature.com/articles/nrn2212  Dysfunction was evident of central nervous system, large alterations, but what we cared about was fixing this. We know theyre different, so thia was good verification. But what can we target.
December 30th, 2024	Wanted to ensure analysis was actually rooted in sound scientific processes so went backwards and educated myself on exploratory fMRI tests. Focused on ICA (dynamic and group) ICA - exploratory, hidden structures in data - 3d spatial maps - Represenrts 1 independent signal

	- Model free  - Breaks it into components, which are features - Components are constituents of data. So if theres an auditory and visual task, one component would be audio, one visual. - Should add components to get original data - Spatial map shows activity, time series says when it is occurring.. - All spatial maps represent what is common :) Network modeling - temporal approach, helps us narrow hypothesis but it is complimentary Rest is EXPLORATORY. Our results are if we are finding any cool structures So take time space maps, concatenate, then run ICA, then get signals and times common to all data. - Components are NETWORKS. - Take each subject spatial map, then use GLM, then show sig differing contrast.
December 31st, 2024	Converted all results from seed based into an excel sheet with all information. Decided not to use voxel results as so variable and not as trusted, especially to use without confirming there is even a

	correlation with exploratory processes. Excel was color coded based on if A. it was directly related to ROIs of interest (sounds redundant but it's not haha) that were part of the sensorimotor and visual cortical areas. ROI's of interest are gabaergic rich, cortical areas part of the sensorimotor and visual cortex. Then, blue were for gabaergic rich regions that were part of sensorimotor and visual but NON cortical (which would assist in affirming hypothesis that it is not just local disruption because of proximity but distinct structures. Example of one such structure:  basically almost all were cortical related, almost 40% were the 14 specified gabaergic rich ROIs, almost all represented.
January 1st, 2025	Redefined ROIs of interest (LOL) to ensure there was no overlap with dopeminergic receptors: (atlas.Cereb6, atlas.Cereb7, atlas.Cereb8) Cerebellum crust1 leftAdditional Regions with High AAC Density ○ atlas.Accumbens l & atlas.Accumbens r (Accumbens, Left and Right) ○ Pallidum too Will not test amygdala. Will tesy pallidum.. ● Amygdala is also implicated but too related to D2 ●

Region	Correlation	t-Value	p-Value (U	p-Value (Corrected)
networks.V	0.17	4.79	0.000004	0.000687
atlas.SPL r	0.15	4.27	0.000035	0.002372
atlas.Hipp	0.16	4.22	0.000044	0.002372
networks.S	-0.15	-4.02	0.000094	0.003836
networks.S	-0.14	-3.96	0.00012	0.003896
atlas.pTFu	0.12	3.83	0.000195	0.005289
atlas.SCC	0.15	3.69	0.000319	0.006634
atlas.Hipp	0.14	3.65	0.000363	0.006634
atlas.Postc	0.16	3.65	0.000366	0.006634
atlas.PT r (	0.15	3.53	0.00056	0.006836
atlas.HG l	0.14	3.51	0.000598	0.006836
atlas.PT l (	0.13	3.5	0.000616	0.006836
atlas.Cune	0.13	3.46	0.000708	0.006836
atlas.PaCi	-0.11	-3.46	0.000719	0.006836
atlas.HG r	0.12	3.45	0.000731	0.006836
atlas.OFus	0.13	3.45	0.000734	0.006836
atlas.iLOC	0.12	3.45	0.000743	0.006836
networks.V	0.14	3.44	0.000755	0.006836
atlas.TOFu	0.12	3.4	0.000889	0.007623

	Claustrum-Insular Complex and Related Regions ● Rationale: Involved in sensory integration and emotional regulation. ● Relevant ROIs: ○ atlas.IC l & atlas.IC r (Insular Cortex, Left and Right) ○ atlas.SMG l & atlas.SMG r (Supramarginal Gyrus, Left and Right) ● atlas.pTFusC l (Temporal Fusiform Cortex, p*eft) 0.16 4.01 0.000097 0.014488 ● atlas.pTFusC r (Temporal Fusiform Cortex, p*ght) 0.15 3.85 0.000178 0.014488 ● atlas.pMTG r (Middle Temporal Gyrus, poster*ght) 0.15 3.67 0.000342 0.018589 ● atlas.aITG r (Inferior Temporal Gyrus, ante*ght) 0.13 3.43 0.000784 0.022339 ● atlas.aSTG r (Superior Temporal Gyrus, ante*ght) 0.13 3.43 0.000790 0.022339 ● atlas.toITG r (Inferior Temporal Gyrus, tem*ght) 0.13 3.42 0.000822 0.022339 ● atlas.aITG l (Inferior Temporal Gyrus, ante*eft) 0.11 3.25 0.001455 0.030292 ● atlas.Caudate l -0.12 -3.24 0.001487 0.030292 atlas.pSTG l (Superior Temporal Gyrus, post*eft) 0.10 3.08 0.002453 0.044421 These regions contribute to the regulation of motor and cognitive functions and could be influenced by GABAergic activity (Keefe et al., 2023). - very related to dopamine, so require distinction.

	The biggest thesis would be figuring out which are distinct from dopamine. Dopamine are implicated in: D2 receptors are primarily located in the striatum, substantia nigra, and hypothalamus. Based on the ROIs you provided, the most relevant regions to consider for D2 receptor involvement would include: 1. Striatum (Caudate and Putamen): ○ atlas.Caudate r (Caudate Right) ○ atlas.Caudate l (Caudate Left)
January 2nd, 2025	Approximated numbers and determined if the hypothesis still stands after exploratory processes. Decided yes as A. sensorimotor and visual cortex were implicated to be functionally abhorrent, which correlated with gabaergic theory. Moreover, when I moved on to recomputing seed based with new ROIs that were unrelated to D2 receptors as well as some ROIs related to those networks and gabaergic but non cortical areas, there was significant disruption specifically in predefined gabaergic areas, which supports our my hypothesis.
January 4th, 2025	Defined some areas that were specifically thalamical and; - Disrupted in exploratory analysis - Rich in gabaergic interneurons. Orange - thalamical disruption. ○ Lateral Occipital Cortex (LOC) ○ Intracalcarine Cortex (ICC) ○ Occipital Fusiform Gyrus (OFusG) ○ Cuneal Cortex (Cuneal) ○ Occipital Pole (OP) ○ Supracalcarine
January 18th, 2025	I want to become more knowledgeable on what the current scene for schizophrenia medication is before I move on to developing the treatment and figuring out what software I will use for it. I researched Clozapine and Abilify - I'm seeing they have not had the idea of the flavone ring I have which is quite interesting as that is a key anti inflammatory agent. Most of them have the same mechanism, they partially agonize HT4A but there are issues with that of course because it is not the root issue; this is their main

	function. While I see the value in agonising serotonin, that should be a secondary function.
January 19th, 2025	Transferred ROI data from seed based connectivity results into excel sheet and highlighted any connectivity modulations that had to do with the previously identified ROIs. Found no inter-ROI modulation but that does not mean they are not affected just that their function TOGETHER is not modulated at the exact same time series which would've been revolutionary.
January 23rd, 2025	Attempted to interpret and summarize results from RNA seq analysis: Through rna seq analysis we found that downregulation was more abhorrent than upregulation, and this was associated with downregulation of negative regulation of retinoic acid receptor signaling " Retinoic acid transcriptionally regulates downstream regulatory molecules, including enzymes, transcription factors, cytokines, and cytokine receptors." "Cytokines affect the growth of all blood cells and other cells that help the body's immune and inflammation responses." Inflammatory responses are altered due to retinoic acid - increased retinoic acid means more cytokines - NO- RA inhibits the production of inflammatory cytokines
January 24th, 2025	I researched the implications of the RNA seq analysis results: Axon development involves GABAergic interneurons, particularly parvalbumin positive chandelier cells, which synapse onto the axon initial segment. Their molecular specialization, including proteins like FGF13, is crucial for synapse formation and maintenance, influencing circuit function and stability. The paper discusses the development of GABAergic interneurons, emphasizing their axon development as crucial for establishing inhibitory circuits in the brain, which are essential for maintaining neural network balance and function in both physiological and pathological conditions.

	These results represent a fundamental shift in the understanding of GABA: it has an excitatory action on sensory axons and regulates which axon branches conduct signals and which fail to conduct, acting like a router in a network. https://www.nature.com/articles/s41593-022-01162-x Gaba has a large role in regulating axons. Also axon development, so we are learning more about the actual mechanisms of this disruption. And again, the solution is not just giving gaba. NMDA is a viable one Boost GABAergic Differentiation from Endogenous Neural Stem Cells: ● Wnt pathway modulators (e.g., CHIR99021) could push stem cells toward GABAergic fate. ● Sonic Hedgehog (Shh) pathway activators (e.g., SAG) might stimulate interneuron regeneration. ● BDNF & NGF mimetics (like 7,8-DHF or LM22A-4) could enhance interneuron survival and synaptogenesis. Stimulate Axon Growth & Synapse Formation: ● mTOR activators (like rapamycin in low doses or ISRIB) to promote axon sprouting. ● Semaphorin/Neuropilin inhibitors to remove inhibitory cues blocking regrowth.
January 28th, 2025	My exploratory analysis, normal ICA, found disruptions in visual and sensorimotor most profoundly. What are gabaergic interneurons? Currently, we are using GABA agonists as adjunct medication. Gaba agonists activate the GABA receptors. However, as we are finding through our results, GABAergic interneurons are functionally modulated, both through decreased activity AND increased activity. This suggests that agonists are non specific and therefore ineffective for targeting gabaergic interneuron dysfunction.

January 29th, 2025	Continued looking into RNA seq implications: Cortical networks in the brain are made up of two main types of neurons: glutamatergic excitatory projection neurons and GABAergic inhibitory interneurons. Excitatory projection neurons use glutamate as a neurotransmitter and send signals to other neurons, increasing activity in the network. In contrast, inhibitory interneurons use GABA as a neurotransmitter and regulate the activity of excitatory neurons by suppressing their signals. Gabaergic inter - inhibitory neurons, regulate excitatory neurons. Glutamate is the brain's most abundant excitatory neurotransmitter, meaning it stimulates other neurons and increases their activity. It plays a key role in learning, memory, So gabaergic regulates it using GABA. Gabaergic interneurons are highly heterogeneous - good next step is identifying what specific ones. Anatomically, cortical GABAergic INs show a variety of somatic, dendritic and axonal morphologies, including the specific subcellular domain of pyramidal cells (and INs) targeted by their axons “functional superiority of the human brain is intimately bound up with the prodigious abundance and the unusual wealth of forms of the so called neurons with short axons” it has been difficult to study cortical INs in the neocortex due to their large diversity and small representation of the total neuronal population. axon activity is fundamental to the function of GABAergic interneurons. Their inhibitory impact is largely defined by axonal projections, firing properties, and synaptic targeting The reason is that interneurons are all about control and timing rather than just transmitting information forward. Unlike pyramidal neurons, where dendrites do a ton of integration before a spike even happens, interneurons rely heavily on their axons to determine when, where, and how inhibition happens. The way their axons branch, how fast they conduct signals, and where

	they make synapses basically define what kind of role they play in a circuit. Axons - Dendrites receive information, has receptors - picks up neurotransmitters and these changes are interpreted in soma. All this signal is put in the axon pillar. If strong enough, it is sent to the axon. The signal is now an axon potential. It travels down axon which is coated in myelin, which prevents the signal from deteriorating. Lastly, the axon terminals/synaptic buttons
February 6th, 2025	Looked into neurogenesis and also started developing treatment ideas. Neurogenesis https://pubmed.ncbi.nlm.nih.gov/17468935/ Protein involved in neurogenesis, which involves the differentiation and development of the nervous system - essentially creation of neurons, so we should also be supporting developing. Known to contribute to schizophrenia - again supports differentiation and development hypothesis, especially since it is with neural progenitor cells… Neuroneogenesis only takes place in few, well-defined brain areas: the subventricular zone (SVZ), i.e. the boundary between the striatum and the lateral ventricle, from where newborn cells migrate along the rostral migratory stream to the olfactory bulb (OB); and the dentate gyrus (DG), where neural stem cells are aligned along the subgranular zone (SGZ) These are areas in the previously noted gabaergic rich ones.

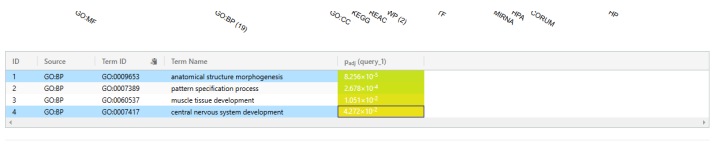
Differentiation

Same old, issues w differentiation - supports neurodevelopmental and core issue with neurons must be targetted.

DOWN REG - Retinoic acid (RA)

is essential for the generation of GABAergic inhibitory neurons

So.. retinoic acid is consistently downregulated and altered. Could be a good target for neuroinflammation. Impaired retinoic acid signaling results in neuroinflammation, oxidative stress, mitochondrial malfunction, and neurodegeneration - also supports neurodegenerative hypothesis. So, target is uplifting retinoic acid! Or,,, maybe not. Revert to gabaergic, find therapeutics that have a binding affinity ot both gabaergic interneurons AND retinoic acid receptors?
https://www.nature.com/articles/nrn2212



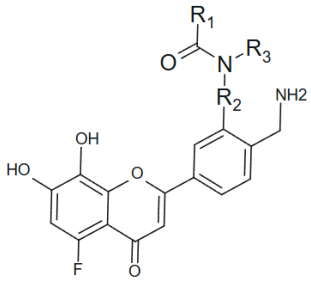
We are again seeing issues with development, growth, genesis, differentiation.

UP REG - OVERGROWTH

- abnormal increase in the size or number of cells in a particular tissue or organ, often due to dysregulated cell growth, proliferation, or differentiation.
- Suggests that the issue is also too much growth..
- Strange finding - literature finds that there is less proliferation, will still report it. - https://scheid.blog.yorku.ca/files/2014/01/DISC1-and-Schizophrenia.pdf

	Not statistically significant ones: Diseases - downreg chance of albumineria - so less chance to get too much albumin - decreased albumin essentially which is found in schizophrenia for sure - Albumin also has to do with neuroinflammation Non disease- - Bone morphegenesis, nervous system development, etc Treatment ideas: - Target issues with development of gabaergic interneurons by healing specific pathways (how would we figure out binding affinity) - Cells receive signals that tell them where they are located in relation to other cells. These signals can be chemical - the cells need to migrate to their correct location in the cortex and then differentiate to carry out inhibitory signaling. - heal this process too :) - Heal/encourage neural cell generation. - Lets also see correlation between inflammation and those growth/differentiation related stuff - do now - Cus our mainstuff is of course helping gabaergic interneurons but if that can help the inflammation and all but thats also lower priority since not stat significant. - But that is important cus the inflammatory ones have roles in growth and differentiation/immune responses, so we will look into that fs.
February 10th, 2025	I worked to read a lot of literature when doing this - next step: Targets BDNF/Wnt for GABAergic interneuron support. ● Enhances neurogenesis via serotonin receptor pathways. Alternative medication (immune-inflammatory focus) ● Targets IL-6, TNF-α, and related inflammatory pathways. ● Ensures proper differentiation and neurodevelopment.

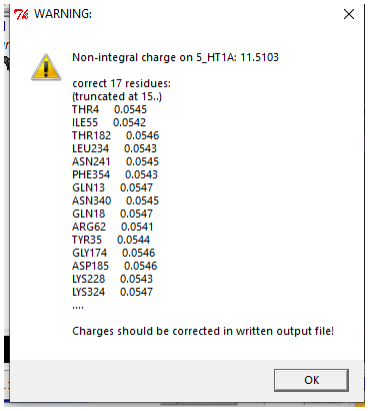
	• A neuroinflammation-modulating drug that supports neurogenesis indirectly.
February 15th, 2025	Started designing drug and decided to have a TRKB agonist but wanted to incorporate ideas - want this to increase BDNF as promotes neuroplasticity - parvalabumin GABAergic interneurons require TRKB a lot due to assistance in balancing the excitatory regions. Would need a mild serotonin modulator and an agonist specifically for HT3 Flavones have a three-ring structure (C6-C3-C6 system): O / \ | | (Ring A) \ / | / \ | | (Ring B) \ / Key modifications can be made at positions 7 and 8 (where hydroxyl groups enhance activity). Final Hybrid Structure Idea Core: 7,8-Dihydroxyflavone (TrkB activation) C5 Modification: Fluorine (-F) or methoxy (-OCH3) → Enhances 5-HT1A partial agonism. C4' Modification: Ethylamine (-CH2CH2NH2) → Mimics serotonin, interacts with 5-HT3. C3 or C4 Side Chain: Amide (-CONH2) or ether (-OCH3) → Fine-tunes 5-HT3 binding.
March 9th, 2025	Started working in CHEM DRAW to design prototype 2-[4-(aminomethyl)-3-{[substituted (substituted carbonyl)amino]substituted }phenyl]- 5-fluoro-7,8-dihydroxy-4H-chromen-4-one



Docking scores were okay but not great - beat many drugs but not by much so I tried again -

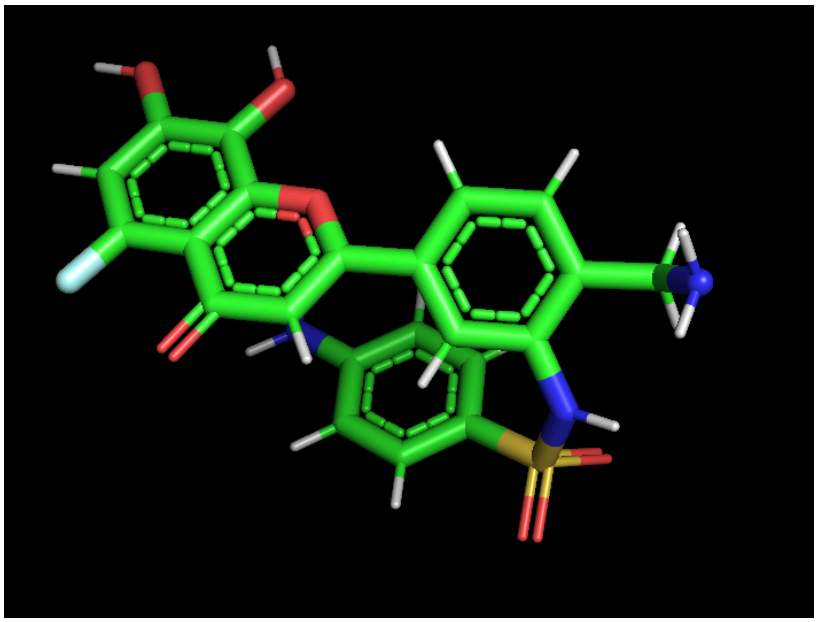
Method - download ligand and protein

- Delete water - interfere w docking - does not sit well
- Add polar hydrogens



- Add kollman charges

https://www.rcsb.org/structure/4at4
https://www.rcsb.org/structure/7e2y
https://www.rcsb.org/structure/8AXD

	 🔹 C5 Modification: Fluorine (-F) → Enhances 5-HT1A partial agonism. 🔹 C4' Modification: Ethylamine (-CH2CH2NH2) (LOOKS LIKE NH2)→ Mimics serotonin, interacts with 5-HT3. 🔹 C3 Side Chain: sulfanimide (https://pubchem.ncbi.nlm.nih.gov/compound/Sulfanilamide) the NH and O-S-O group → Fine-tunes 5-HT3 binding. "4-amino-N-[2-(aminomethyl)-5-(5-fluoro-7,8-dihydroxy-4-oxo-4H-chromen-2-yl)phenyl]benzene-" "1-sulfonamide"
March 10th, 2025	Modified my structure again to further improve docking by changing C3 ring with amide: amino-N-[2-(aminomethyl)-5-(5-fluoro-7,8-dihydroxy-4-oxo-4H-chromen-2-yl)phenyl]benzene-1-sulfonamide
March 11th, 2025	Tested docking for my drug and planned other drugs to do: TKRB: mode | affinity | dist from best mode | (kcal/mol) | rmsd l.b.| rmsd u.b. -----+------------+----------+---------- 1 -6.3 0.000 0.000 2 -6.3 4.768 7.920

	3 -5.7 6.238 8.378 4 -5.7 7.116 8.289 5 -5.7 1.445 3.199 6 -5.7 6.163 8.263 7 -5.5 6.824 8.689 8 -5.5 8.671 9.721 9 -5.4 6.416 9.510 Writing output ... done. 5_HT3A mode | affinity | dist from best mode | (kcal/mol) | rmsd l.b.| rmsd u.b. -----+------------+----------+---------- 1 -9.3 0.000 0.000 2 -9.3 16.993 18.615 3 -9.2 28.468 30.214 4 -9.2 16.967 18.557 5 -9.2 28.384 30.210 6 -9.1 17.179 18.718 7 -9.1 29.062 31.141 8 -9.1 18.113 19.846 9 -9.1 17.480 19.793 5_HT1A mode | affinity | dist from best mode | (kcal/mol) | rmsd l.b.| rmsd u.b. -----+------------+----------+---------- 1 -8.1 0.000 0.000 2 -7.9 28.909 30.245 3 -7.9 3.889 7.388 4 -7.9 1.434 2.093 5 -7.8 6.704 10.483 6 -7.8 2.073 2.374 7 -7.7 1.438 2.854 8 -7.7 3.876 7.170 9 -7.6 4.158 7.330 Writing output ... done. **Why flavones?**

	TrkB Activation – Some flavones (like **7,8-Dihydroxyflavone**) **directly activate TrkB**, mimicking BDNF. **Blood-Brain Barrier (BBB) Penetration** – Unlike BDNF itself (which is too large), flavones can cross the BB Anti Inflammatory Olazapine: - Comparable docking score for TRKB but less for our HT3A and HT1A (by around 2.3) Test three drugs Abilify: TRKB score was worse mode | affinity | dist from best mode | (kcal/mol) | rmsd l.b.| rmsd u.b. -----+------------+----------+---------- 1 -5.5 0.000 0.000 2 -5.4 7.407 9.728 3 -5.4 2.758 5.200 4 -5.3 2.975 5.552 5 -5.2 1.918 2.891 6 -5.1 3.336 6.027 7 -5.1 2.919 5.978 8 -5.0 5.222 7.131 9 -4.8 9.325 12.357 Writing output ... done. Have not tested others but def will!! And last drug we will do is clozapine ! So 3 for clozapine left, 2 for one, 1 for the others so 6 more tests….!
March 13th, 2025	Decided next steps for the project - reducing molecular weight, compiling results to see if there was a noticeable difference in affinity.
March 14th, 2025	Did some more research in structure and realized my ethlymanine group was incredibly large which may be contributing to low liphophicility. Wanted to increase it as drugs that permeate the BBB typically have higher liphophicility. I also realize this comes from

	having less hydrogen groups. Replaced ethylamine with piperazine ring which is found on some first generation antipsychotics.
March 15th, 2025	Started compiling parts of methodology and write up for CYSF to ensure I will be done before the 20th.

March 16th, 2025	Continued working on write up, finishing methodology and problem by highlighting the current scene of schizophrenia treatment. Also finalized locations for flavone modulation + next steps: A8: Replaced hydroxide with oxygen. C3: Attached Fluorine C4: Attached a Piperazine Ring Next steps: - Reducing molecular weight - Increasing lipophilicity - attempts led to inhibition of CYP groups and safety and efficacy are the first priority so need to gain a better understanding of pharmacokinetics to perfect the drug - Actually testing it
March 21st, 2025	Inputting all information into project board and preparing for fair.
