

Understanding the “PUFA (Polyunsaturated Fatty Acid) Theory of Schizophrenia”

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Theory and presentation based on “Rappoport, A. (2024). A Polyunsaturated Fatty Acid (PUFA) Theory of Schizophrenia. arXiv preprint arXiv:2408.06794.”

Precursors to Ari's "PUFA Theory of Schizophrenia"

Horrobin et. al's "Phospholipid Spectrum Disorders in Psychiatry and Neurology"

Phospholipase A₂-Associated Processes in the Human Brain and Their Role in Neuropathology and Psychopathology

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Ross BM, Hudson C, Erlich J, Warsh JJ, Kish SJ. Increased phospholipid breakdown in schizophrenia – evidence for the involvement of a calcium-independent phospholipase A₂. *Arch Gen Psychiatry* 1997; 54: 487–494.

PLA₂ in schizophrenia

The observations described in the preceding section suggest that schizophrenia may be associated with a systemic abnormality in phospholipid metabolism, though it remains unclear what the underlying molecular cause(s) of such a deficiency may be. One candidate mechanism is abnormally high activity of PLA₂. With this in mind, it is apparent that increased PLA₂ activity could result in reduced levels of the enzyme's phospholipid/fatty acid substrate, with concomitant increases in the abundance of PLA₂-derived metabolites, lysophospholipids and glycerophosphodiester, changes consistent with that which occurs in schizophrenia.

Furthermore, the major calcium-stimulated PLA₂ type in human brain, assayed under the conditions used in the autopsied brain study (Ross et al., 1999), is a membrane-associated form of the enzyme, the characteristics of which are very different from that of cPLA₂ (Ross et al., 1995a). The pattern of fatty acid loss during storage in schizophrenia (Fox et al., in press), which indicates a preference for C20 fatty acids, does suggest, however, that this enzyme is activated in schizophrenia. Investigation of this PLA₂ subtype therefore awaits the use in schizophrenia of either cPLA₂-specific activity assays (Yang et al., 1999) or immunological procedures (Stephenson et al., 1996; MacDonell et al., 2000).

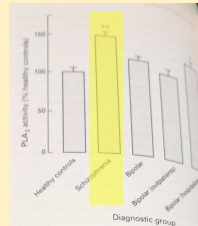
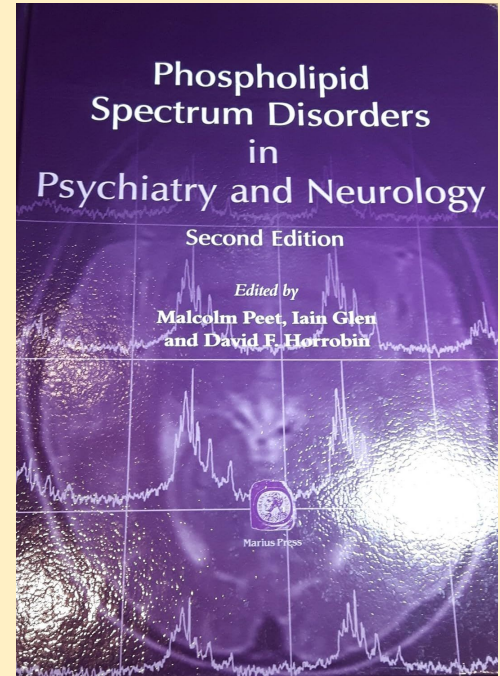


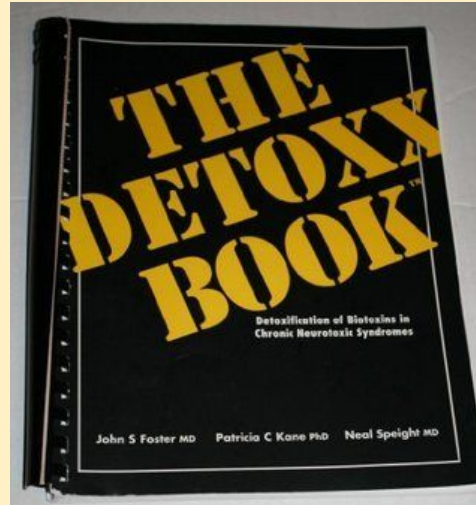
Figure 8.6. Calcium-independent phospholipase A₂ (PLA₂) activity in serum of patients with schizophrenia (n = 37) and bipolar disorder (n = 37) compared to healthy controls (n = 38). The bipolar group is shown in total, and separated into patients hospitalized for acute episodes (n = 13) and stabilized outpatients (n = 24). Values are mean activity relative to healthy controls; bars indicate SEM. Groups were significantly different by one-way ANOVA ($F_{4,131} = 6.86$, $p < 0.0001$). In comparison with controls, $p < .01$, $^{**}0.0001$ (post-hoc test: least significant difference). After Ross et al. (1997a).



Patricia Kane et. al's "The Detox Book: Detoxification of Biotoxins in Chronic Neurotoxic Syndromes" and Kennedy Krieger lab "Red Cell Lipid Biomarkers" used to inform book

Increases in Phospholipase A2 (PLA2) activity result in premature uncoupling of the essential fatty acids (EFAs) from phospholipids in the cell membrane. Accelerated loss of EFA places the patient in a severely compromised position as that of inflammation which results from the promiscuous release of AA in the presence of an over expression of PLA2. Carbohydrate consumption must be restricted to control the insulin response and the subsequent loss of EFAs.

Enzymes arrive on the metabolic scene with varying degrees of importance. The PLA2 superfamily including PLA1, PLC, PLB, and PLD is of major significance in our appreciation of lipid biochemistry. Of particular concern is the over expression of PLA2, since the concentration of Arachidonic acid (AA) in erythrocytes is 10 times the concentration of Dihomo-gamma linolenic Acid (DGLA) and 45 times Eicosapentaenoic Acid (EPA). AA and its metabolites will subsequently be over expressed with any excitation of PLA2. It's a simple matter of substrate quantity. If AA is over stimulated, inflammation becomes endemic. DGLA's offspring is the delightful PGE1, which is anti-constricting and anticoagulating. However, DGLA doesn't stand a chance. DGLA doesn't have the pull, nor does EPA, and its offspring PGE3. Both PG1 and PG3 can and do modulate AA very effectively, if PLA2 is controlled. Research has been emerging that clearly reveals insulin stimulates PLA2 (Furuya 1999; Simonsson 2000), reinforcing the premise that an over expression of PLA2 is a prerequisite to an inflammatory condition.



Cognition

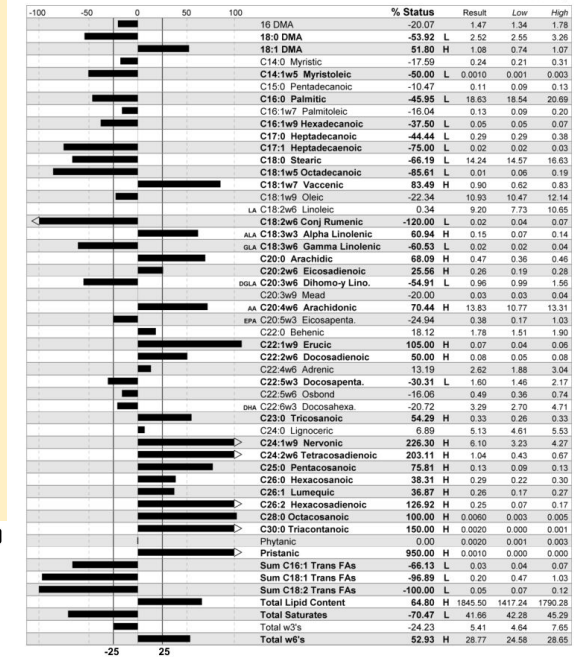


Cognition is a combination of learning and mental performance which are highly lipid dependent with particular focus on DHA (docosahexaenoic acid) and AA (arachidonic acid). Both are ultra polyunsaturated FAs (PUFA) found predominantly within the membranes of brain cells. It has been demonstrated that alterations in the fatty acid (FA) composition of brain cells and subcellular fractions of myelin, microtubular and synaptosomal plasma membranes could be induced through changes in dietary fat intake (88-91). Maintaining the optimal w6/w3 ratio enhances learning capacity and performance factors, which include sensory and motor function, motivation, arousal, attention and reactivity (92) as well as more efficient thermoregulation, pain tolerance, and facilitation of sleep (93).

Comments: Brain performance can be controlled by adjusting the diet to include a balance of w6 and w3 FA. This is a rather dramatic change in how we view mental health. The extensive biochemical regulation of these Essential FAs are only now being unlocked through lipid research. The regenerative impact that EFAs and their congeners (vitamins and minerals) have on brain function and performance could be one of the most important medical events of our times.

* AA -- Major w6 FA Elevated * Consume less Animal Fat * Add Marine Oil, Sesame, EPO, OA * Restet in 1 yr
w6 FA -- Excess * Use Marine Oil, Low Carbs * Restet 1 year

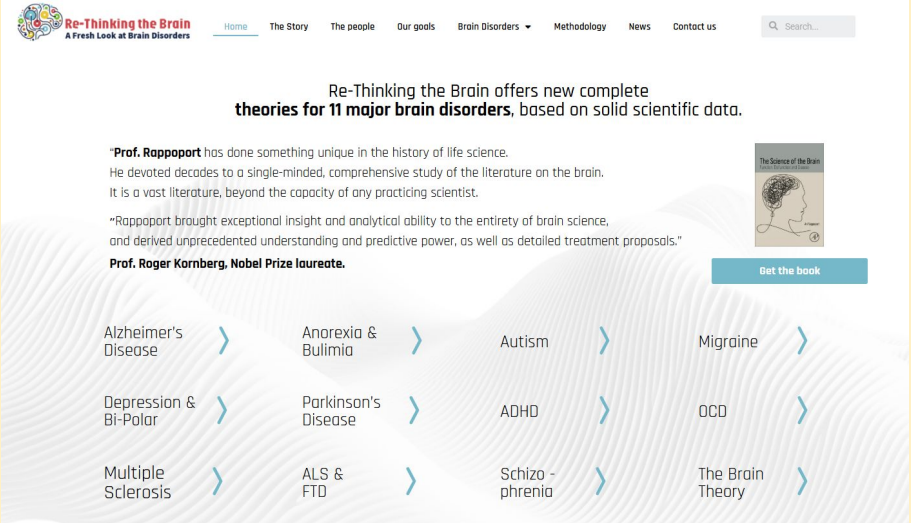
	% Status	Result	Low	High
C20:4w6 Arachidonic	70.44	13.83	10.77	13.31
C22:5w6 Docosahexa.	20.72	3.29	2.70	4.71
Total w6's	52.93	28.77	24.58	28.65
Total w3's	24.23	5.41	4.64	7.65
Fluidity Index	35.00	0.93	0.90	1.10
EFA Index	33.48	4.92	3.00	5.30



Introduction to “PUFA Theory of Schizophrenia”

Why does this matter?

- **Ari Rappoport**, a computer scientist turned neurologist/psychologist by hobby, has had his theories (including the PUFA theory) recognized by the Nobel Laureate Roger Kornberg, who described Rappoport's work as bringing "exceptional insight and analytical ability to the entirety of brain science, and derived unprecedented understanding and predictive power, as well as detailed treatment proposals."
- Ari studied close to **half a million research articles** to develop his theories suggesting thorough coverage of the literature
- Ari aimed to have his theories be as **mechanistically complete** as possible but also suggest potential **treatments** for which clinical trials may be beginning
- **Medications for schizophrenia, in particular, have serious side effects for many, and often don't address the root-cause nor adequately address cognition**



The screenshot shows the homepage of the website "Re-Thinking the Brain: A Fresh Look at Brain Disorders". The navigation menu includes Home, The Story, The people, Our goals, Brain Disorders, Methodology, News, and Contact us. The main heading states: "Re-Thinking the Brain offers new complete theories for 11 major brain disorders, based on solid scientific data." Below this, there are quotes from Prof. Rappoport and Prof. Roger Kornberg. A "Get the book" button is visible. A grid of 11 brain disorders is listed, each with a right-pointing arrow:

Alzheimer's Disease	Anorexia & Bulimia	Autism	Migraine
Depression & Bi-Polar	Parkinson's Disease	ADHD	OCD
Multiple Sclerosis	ALS & FTD	Schizo-phrenia	The Brain Theory

<https://www.brainrethink.org/>

Most important terms - PUFAs and Endocannabinoids

1. **Polyunsaturated fatty acids (PUFAs)** - fatty acids that are embedded in every cell's membranes and are vital for structure and function. "Unsaturated" refers to the fact that there are at least two double bonds in the structure. ***The biggest PUFA of interest in this paper will be arachidonic acid (ARA).***
2. **Endocannabinoids (ECBs)** - fat-loving molecules (identified and named due to similarity in signaling to compounds in cannabis). Endocannabinoids have ***widespread brain activity*** and ***help neurons communicate, especially during states of emotional or cognitive significance.***

Introduction to PUFA Theory of Schizophrenia (P*SZ)

1. An attempt by a computer scientist and neuroscience hobbyist, to **unify symptom dimensions into an original mechanistic explanation** that integrates as much of the existing evidence as possible (lots of existing literature on ECBs and lipid abnormalities)
2. Explain **origin and maintenance of symptoms in chronic psychosis** (schizophrenia spectrum conditions)
3. Potentially explain **why long-term use of traditional antipsychotics (those which tend to block D2 dopamine receptors) may worsen cognition for some**
4. Suggest **new treatment targets** to explore—namely to **inhibit collapse of cell membranes** due to (mainly) an **excessive release of** a type of PUFA, **arachidonic acid**

1. P*SZ's claims on symptom dimensions

- *Positive symptoms* are due mainly to **hyperexcitability** of neurons representing sensory experience. These neurons tend to be in areas that are heavily signaled by **ECBs** like **AEA** and **2-AG**. These neurons may also be rich in **D2** (a type of dopamine receptor) and **SER2a** (a type of serotonin receptor) receptors, explaining the relative efficacy of second generation D2-blocker type antipsychotics in reducing positive symptoms
- *Negative symptoms* are due mainly to **disconnection of neurons from inputs from other neurons**. These neurons also tend to be in the same regions as those implicated in positive symptoms, but may additionally include those relating to movement
- *Cognitive symptoms* are due mainly to **lack of coordinated network activity**—coordinated network activity is mediated by delicate GABA interneuron inhibitory circuits, and disruption of these circuits by excessive ECB release

Bottom line: ECBs are the “upstream disconnecting switches” regardless of the symptom domain in consideration. These disconnecting switches can increase random firing of neurons and reduce coordinated brain activity. Upstream of all this is excessive release from cell membranes in brain and body, of a precursor to ECBs, namely Arachidonic Acid (AA). P*SZ claims chronic, excessive ARA release is at the heart of symptoms and their maintenance.

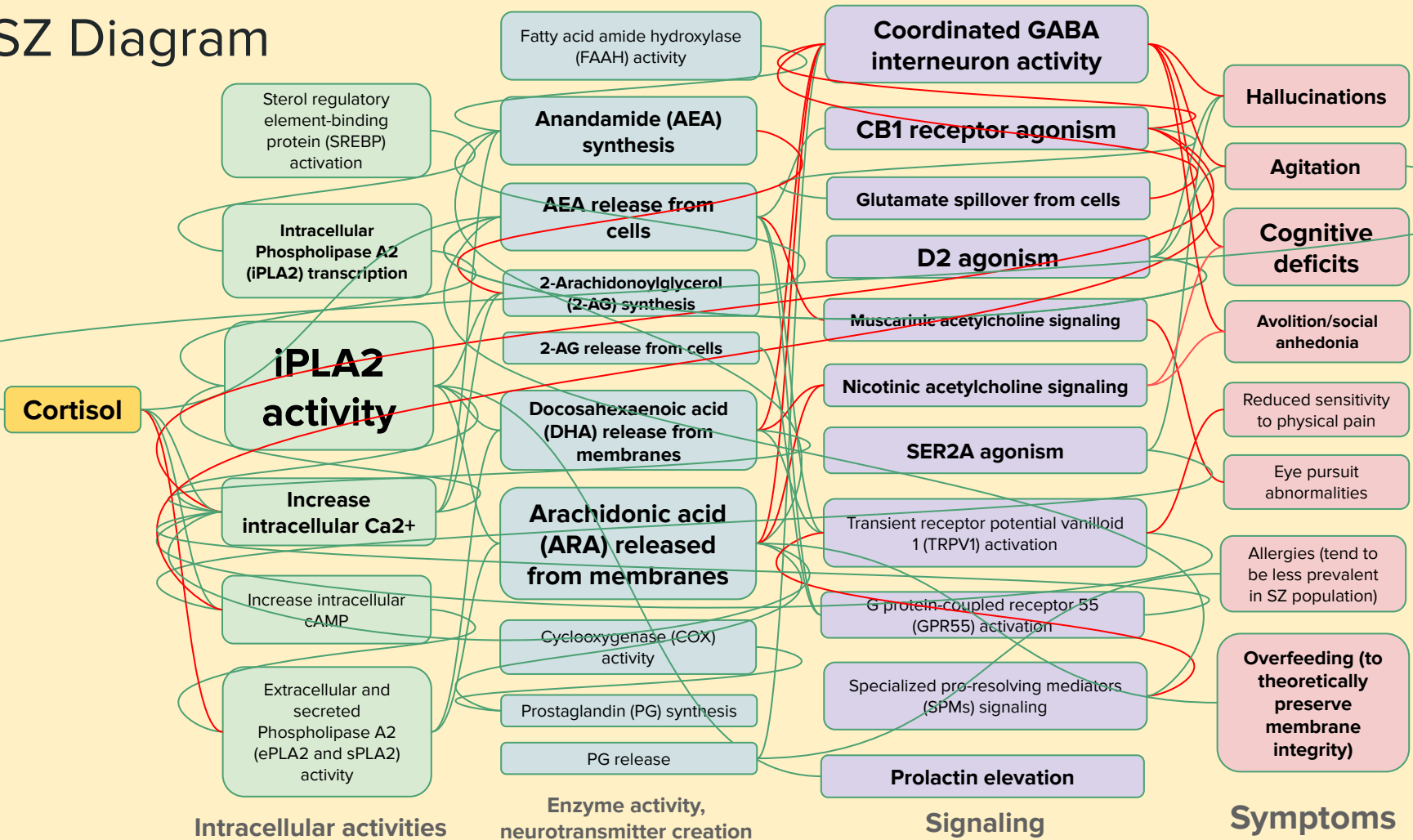
2. P*SZ's claims on symptom origins and maintenance

- **Chronic stress and/or genetic susceptibility**, especially during sensitive developmental periods, can **upregulate an enzyme (iPLA2) that liberates arachidonic acid (ARA) and docosahexaenoic acid (DHA) from the membrane**, starting a vicious feedback membrane degradation and lack of coordinated network activity
- **Compensations to reduce ECB signaling** (like reduction in CB1 receptor density commonly found in schizophrenic brains) are **overwhelmed** with the “root cause”: **excessive release of PUFAs** from the cell membranes

Disclaimer for following diagram

- The following slide features my attempt to diagram the connections *made within the paper* and used to evidence P*SZ. An arrow entering a box from the left, right is *influence of, that influence* that node, resp. **Green** arrows are positive flow, **Red** are inhibitory flow
- Many more connections may exist between these nodes in other papers that are not shown
- I am uncertain about how the dependencies distribute throughout different regions of the brain, layers of the brain, cell types, etc
- I am uncertain how well the dependencies match what is happening outside of the brain with the same types of receptors, hormones, neurotransmitters, etc
- Sometimes it's unclear how many nodes a connection should go through—as in, if there is a statement made that “ARA interferes with nACh function”, is that through increasing ECBs that interfere with acetylcholine binding to the nACh receptor *or* through ECB binding to CB1 etc. So some arrows may be redundant
- ***I would like feedback on how to more accurately study such a paper as that which features things like P*SZ. ChatGPT's “Reason” feature is at times inaccurate but may help gain foundation and verify understanding once the paper has been hand-read. Ideas?***

P*SZ Diagram



Intracellular activities

Enzyme activity, neurotransmitter creation

Signaling

Symptoms

3. P*SZ's claims on long term effects of antipsychotics on the market (excluding Cobenfy)

- Mixed results on 1) whether antipsychotics (AP) (with or without **SER2a** antagonism) administered to **FEP** patients normalize excessive ARA release from membranes, 2) conversion of **ARA** away from **ECBs** to prostaglandins (PG tend to increase coordinated brain activity)
- Some data on some AP activating genes which transcribe **iPLA2** (the enzyme that releases ARA from cell membranes)
- Lots of data on chronic AP disrupting cholinergic signaling leading to tardive dyskinesia
- ***P*SZ accords the common clinical observation of reduced efficacy of AP for non-positive symptoms, based on the fact that many other neurotransmitter systems beyond dopamine are involved in schizophrenia–this is not unique to this theory, however***

4. P*SZ's claims on potential treatment targets

- **iPLA2 inhibitors:** To reduce release of ARA from cell membranes). Also, there is data suggesting lower schizophrenia rates in parts of the world where iPLA2 is inadvertently being administered for non-SZ purposes (malaria and Sub-Saharan Africa) as well as some genetic data on increased linkage of iPLA2 genetics to SZ incidence
- **Drugs that co-stimulate of D2 and CB1 receptor (agonism of D2 and non-agonism of CB1):** To reduce CB1's constitutive activation-based decrease of cAMP/dysplasticity in schizophrenia – costimulation of these receptors apparently should rescue lowered cAMP and renew plasticity
- **NAC:** To help to increase ARA utilization for PG instead of AEA

Open questions - Asking is easier than answering!

Open questions - Related to P*SZ specifically

- How does P*SZ distinguish mechanistically between **positive symptoms** and **mood symptoms**? I felt this section could use more explaining.
- How does P*SZ distinguish mechanistically between **positive symptoms** and **disorganized symptoms**?
- How does P*SZ explain **stress-independent causes of chronic psychosis**, like 22q deletion syndrome, autoimmune related conditions, or infectious etiologies (Lyme brain)? Similarly, what of chronic psychosis in relation to **frontotemporal dementia** etc? *Is the syndrome described in P*SZ indexing “classic Bleulerian schizophrenia” itself?*
- Is the sort of **disconnected, hyperexcitability of neurons, mediated through CB1 overactivation, as P*SZ mentions, “neurotoxic in its own right”**? Or is it more neurotoxic because of inevitable atrophy of visuospatial and executive function systems due to disuse? Or is there no connection of disconnectivity to neurotoxicity, and there is a separate mechanism for neurotoxicity?

Open questions - Related to P*SZ specifically

- How does theory of **plasmalogens**, another important component of **cholinergic transmission** through **myelin** and **cell membrane integrity**, interface with P*SZ?
- How regionally specific is P*SZ in explaining all the feedback loops proposed in the paper? Do **region-specific iPLA2** inhibitors need consideration?
- ***How strong is the evidence supporting each biological connection in the P*SZ model? The model draws on a wide range of studies — from cell cultures to human research — to back up each link. How would adjusting the model to weight these connections based on the strength of their supporting evidence affect its overall structure or predictions?***

Open questions - Related to P*SZ specifically

- **How could Ari's theories explain comorbidities of psychiatric conditions? (He has many other theories for other psychiatric and neurological conditions like OCD, Alzheimer's, Bipolar Disorder, ADHD, Autism, etc).** Do his theories represent disassociable cognitive deficits whose treatments could be effectively 'stacked'?
- It appears that Ari didn't take a symptom-specific approach to develop his theory, but more tried to find the general biological patterns amongst all the variability subsumed under the label 'schizophrenia'. **How does this approach compare to researchers who take increasingly granular focus onto different symptom domains to find differing mechanisms?**
- How do we bridge discussion between folks who seem to have the incompatible aims of 1) needing to precisely define what is pathology and study/treat it like an illness against 2) increasing societal acceptance (not just to consider as an illness) and *normalization* of certain conditions? **Must these two camps be necessarily silo'd to each be able to maximally pursue their agendas?**

Open questions - **Caffeine** and **CB1** - Looking beyond cannabis

- Could **over-sensitization of CB1 receptors** in schizophrenia be explained not just by **cannabis** but **caffeine** too?
 - “Notably, due to changes in adenosine A1R:A2AR heteromers, chronic caffeine stimulates glutamate release (not shown; see Fig. 2). (B) In striato-pallidal GABAergic spiny projection neurons, the caffeine-mediated inhibition of presynaptic adenosine A2ARs facilitates CB1R-induced blockage of GABA release. Interestingly, chronic caffeine ingestion also sensitises CB1Rs to ECBs. The underlying mechanism remains to be investigated, but could be a consequence of decreased adenosine A2AR density in response to regular caffeine consumption.” (1)
- Related to the previous question, could this explain why **for some people with schizophrenia, caffeine can transiently worsen mental noise (if not psychosis)**, whereas **for others**, perhaps those with primarily negative symptoms, **caffeine can help potentiate CB1 and reward system**?
 - “This collectively suggests that caffeine-mediated upregulation of striatal dopamine D2R-signalling improves both wakefulness and flow proneness. Indeed, it has been suggested that caffeine ingestion may amplify other dopamine-associated behaviours besides flow, such as drug addiction or psychosis (Ferre, 2016, Simola, 2010).” (1)

1. Reich, N., Mannino, M., & Kotler, S. (2024). Using caffeine as a chemical means to induce flow states. *Neuroscience & Biobehavioral Reviews*, 159, 105577.

Open questions - General

- **CBD**, with many actions on diverse receptors, including a **partial NAM of the CB1 receptor**, has some promise for reducing psychotic symptoms. However, can CBD, through increased **TRPV1 overactivation**, **worsen hyperexcitability** of the glutamate system and cause disinhibition?
- Related to the first question, can **CB1 receptor downregulation** be then overly **inhibited** in action through **CBD**, producing symptoms similar to **drug withdrawal** (cold sweat, shakes, sensory hypersensitivity)?
- How much of **network disconnection** has treatment target overlaps with **chronic fatigue syndrome**?
- Is “**moodiness**” indicative of more **cognitive oversight** (relative to “impoverished” or “deficit schizophrenia” subtypes)? Or is moodiness just a **separate dimension** that may worsen cortisol mediated degeneration of membranes?

What would you like to know
more on?
