# 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.”

What are the neurotransmitters, brain circuits, etc that *you* think are involved in chronic psychosis, schizophrenia etc?

# Introduction to “PUFA Theory of Schizophrenia”

**Disclaimer: My “understanding” is based on mostly associative thinking that I used to read the paper, which is the schizotypy-laden person's forte.  I am really looking to deepen "gears type"/"mechanistic" thinking, but that may take new cognitive units and a new brain altogether, though I can try/aspire to that.

# 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.***

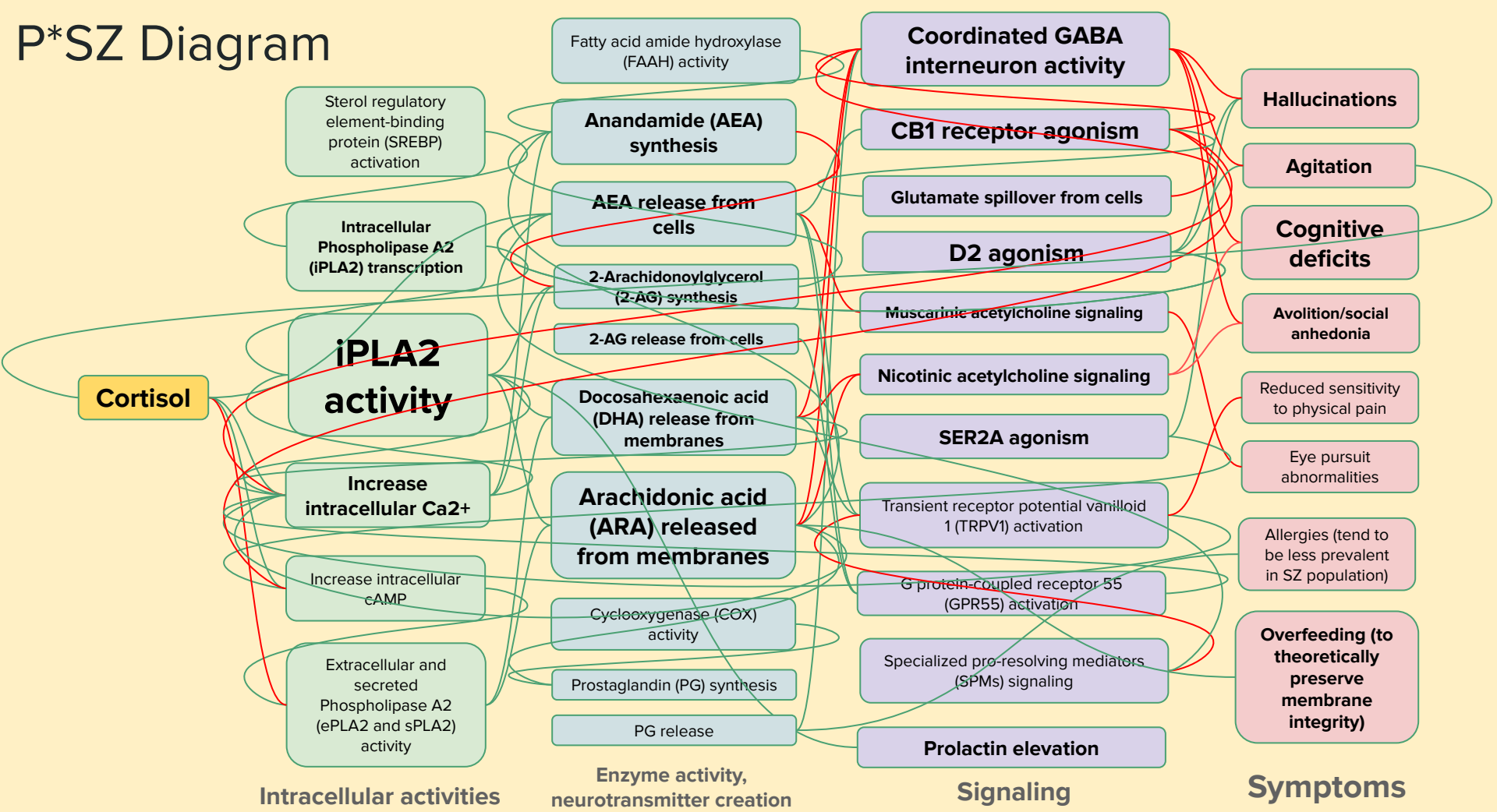
## 2. P*SZ's claims on symptom origins and maintenance

- **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


Cortisol
Sterol regulatory element-binding protein (SREBP) activation
Intracellular Phospholipase A2 (iPLA2) transcription
iPLA2 activity
Increase intracellular Ca2+
Increase intracellular cAMP
Extracellular and secreted Phospholipase A2 (ePLA2 and sPLA2) activity
Intracellular activities
Fatty acid amide hydroxylase (FAAH) activity
Anandamide (AEA) synthesis
AEA release from cells
2-Arachidonoylglycerol (2-AG) synthesis
2-AG release from cells
Docosahexaenoic acid (DHA) release from membranes
Arachidonic acid (ARA) released from membranes
Cyclooxygenase (COX) activity
Prostaglandin (PG) synthesis
PG release
Enzyme activity, neurotransmitter creation
Coordinated GABA interneuron activity
CB1 receptor agonism
Glutamate spillover from cells
D2 agonism
Muscarinic acetylcholine signaling
Nicotinic acetylcholine signaling
SER2A agonism
Transient receptor potential vanilloid 1 (TRPV1) activation
G protein-coupled receptor 55 (GPR55) activation
Specialized pro-resolving mediators (SPMs) signaling
Prolactin elevation
Signaling
Hallucinations
Agitation
Cognitive deficits
Avolition/social anhedonia
Reduced sensitivity to physical pain
Eye pursuit abnormalities
Allergies (tend to be less prevalent in SZ population)
Overfeeding (to theoretically preserve membrane integrity)
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 explain **stress-independent causes of psychosis**, like 22x deletion syndrome? Similarly, what of chronic psychosis in relation to **frontotemporal dementia** etc? ***Is the syndrome described in P*SZ indexing "classic 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 - Caffeine and CB1

- What leads to **over-sensitization of CB1 receptors** in schizophrenia, whereas in general, social stress (which people with schizophrenia tend to have much of in the prodrome at least) actually tends towards CB1 receptor desensitization, in the general population?
    - “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 worsen psychosis**, whereas **for others**, perhaps those with primarily negative symptoms, **caffeine can help potential 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?

# What would you like to know more on?