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Extension of the Syntelic Ape Hypothesis via the Free Energy Principle: The Constitutive Reactivity of VPAs as the Brain's Dark Energy and the Metabolic Origins of Psychopathology

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Summary

This paper discusses the biological basis for the fundamental driving force separating the human lineage, positing it as a "Syntelic" challenge—a term coined by the author to describe a "Challenging Cooperation Propensity" that shares goals with others to overcome risks.

In Karl Friston's Active Inference framework, organisms engage in exploratory behavior to minimize "Expected Free Energy" [Friston 15]. However, exploration in complex social environments demands enormous computational loads and metabolic costs from the brain. This paper proposes that humans may have evolved "Varicose Projection Astrocytes (VPAs)," a type of giant astrocyte unique to primates, and established a wide-area metabolic network centered on their "Constitutive Reactivity" to make this high-cost strategy feasible.

Human VPAs are thought to maintain neuronal networks in a constant state of "Criticality" through high basal metabolism, physically enabling (permissive role) the maintenance of higher-order cognitive functions. Furthermore, this system is redefined as a "Physiological Warburg Effect," and the paper discusses the biochemical necessity of selecting the glycolytic system and the psychopathology resulting from its failure.

1. Introduction: The Implementation Problem of High-Cost "Exploration"

What drives humans toward "Challenging Cooperation"? In the framework of Active Inference, the human expansion into the savannah and the establishment of complex societies can be explained as exploratory behaviors (information acquisition) to minimize long-term Expected Free Energy (G).

However, a problem of physical implementation remains. To constantly update a world model in an uncertain environment, enormous energy is required to resist the brain's thermodynamic entropy increase. Rather than a low-cost strategy of remaining in a "dark room" (a safe place), why can humans sustain such high-cost "exploration"?

This paper proposes the hypothesis that the "Constitutive Reactivity" acquired by human VPAs is the energy foundation that physically satisfies this computational requirement (exploration).

2. Theoretical Framework: From Homeostasis to Allostasis

2.1 Definition of Constitutive Reactivity and Molecular Biological Evidence

While astrocytes in other species are "on-demand," human VPAs are inferred to have acquired "Constitutive Reactivity."

This refers to a state where the network maintains a "High Basal Level" and sustains autonomous oscillations even in the absence of input. This reversal of causality (where astrocyte activity leads rather than neuronal activity) aligns with research by Poskanzer et al., which showed that astrocytes generate spontaneous calcium oscillations independent of neuronal activity, inducing switching of cortical states [Poskanzer 16].

Biologically, this state of continuously running the glycolytic system in an oxygen-rich environment closely resembles the "Warburg Effect" seen in cancer cells. In human VPAs, it is possible that this functions not as pathology but as a "Physiological Warburg Effect."

Evidence for this includes comparative transcriptome analysis by Cáceres et al. They reported that in the human brain, compared to chimpanzees and macaques, the expression levels

of gene groups involved in the electron transport chain and glycolysis (e.g., COX5A, NDUFA4) are specifically elevated [Cáceres 03]. This could serve as evidence that the human brain is not merely larger, but that metabolic flux per unit volume is constitutively enhanced.

2.2 Morphological Necessity of VPAs: Why Protoplasmic Astrocytes Are Insufficient

Why did it have to be VPAs and not typical Protoplasmic Astrocytes?

Protoplasmic astrocytes have spherical domains and are suitable for managing local synapse groups, but are considered unsuitable for synchronization between distant regions. In contrast, VPAs possess long processes unique to primates, extending up to 1 mm, and are said to penetrate the cortical layer structure (layers I to VI) vertically, accessing millions of synapses [Oberheim 09, Sosunov 14].

This "Interlaminar" morphological feature may physically enable Global Synchronization beyond local modules. It is suggested that VPAs function as an essential hub, propagating metabolic energy and information to remote areas like "optical fibers" within the brain, leading the entire brain to a unified state of the Physiological Warburg Effect.

2.3 Evolutionary Trade-off: Toxicity Avoidance and Mitophagy

While continuous glycolysis provides the benefit of computational speed, it carries the extremely high risk of accumulating lactic acidosis and Reactive Oxygen Species (ROS). Humans are thought to counter this through waste removal by the Glymphatic System during sleep [Iliff 12] and the enhancement of antioxidant systems via the Pentose Phosphate Pathway (PPP) [Herrero-Mendez 09].

Furthermore, strict quality control of "Mitophagy," which selectively removes damaged mitochondria, is a crucial intracellular defense mechanism [Youle 11]. VPAs may prevent self-destruction (apoptosis) due to oxidative stress associated with high metabolism by keeping this mitophagy highly functional.

However, maintaining the Physiological Warburg Effect over long periods can promote the accumulation of amyloid-beta and tau proteins, potentially increasing the risk of neurodegenerative diseases like Alzheimer's disease. Indeed, Alzheimer's disease is known to begin with a decline in brain glucose metabolism (breakdown of glycolysis) [Mosconi 08].

2.4 Function of Dark Energy: Tuning of Criticality

The immense dark energy (resting-state activity) supplied by VPAs provides the physical foundation (permissive role) for the emergence of higher-order cognitive functions. Specifically, it is thought to be used to maintain the following large-scale networks in a state of "Criticality."

• Information Integration: By supplying energy to the Salience Network (SN), it enhances the degree of integration of interoception.

• Counterfactual Simulation: By keeping the Default Mode Network (DMN) active, it reconstructs memory traces even in the absence of external input.

• Neural Basis of Agency: It not only lowers the energy threshold required for "Ignition" of the Global Workspace but also controls stochastic firing fluctuations (Stochastic Resonance).

Crucially, the reason why this high-energy state does not lead to mere "runaway" (epileptic seizures) is that VPAs are inferred to constitutively enhance not only the supply of excitatory Glutamate but also energy supply to inhibitory GABAergic Interneurons and the recycling of Gamma-Aminobutyric Acid (GABA). This strict tuning of the Excitation/Inhibition (E/I) balance by VPAs may function as a safety mechanism keeping the brain at the "edge of chaos," or Criticality [Rubenstein 03].

2.5 Allostasis and "Pre-supply" of Energy

Why bear such risks and costs? Lisa Feldman Barrett posited that the brain's primary job is "Body Budget management" [Barrett 17].

Predicting "betrayal by others" or "sudden crises" in a complex social environment requires the instantaneous mobilization of computational resources. If energy supply were "reactive" (on-demand), supply might not keep up, leading to computational failure (freezing).

It is thought that by normalizing "pre-supply (Allostasis)" via VPAs, humans pay a "premium" in metabolic costs to avoid fatal "computational latency" related to survival.

2.6 Syntelic Necessity: Connection to Joint Active Inference

If simply having a high-energy brain were the goal, oxidative phosphorylation in mitochondria, which has high Adenosine Triphosphate (ATP) production efficiency, should suffice. Why did the human brain choose the inefficient glycolytic system (Warburg Effect)?

The first reason lies in "speed." According to research by Pfeiffer et al., the rate of ATP production in glycolysis is approximately 100 times faster than oxidative phosphorylation [Pfeiffer 01]. Additionally, "On-board fueling" by glycolytic enzymes to synapses [Jang 16] is inferred to have been

essential for responding immediately to the "combinatorial explosion" associated with recursive social prediction.

However, this "living fast" high-metabolism system generates constant high entropy (metabolic instability) within the individual. To resolve this internal instability, humans may have been compelled to use others as an "external scaffold."

According to "Joint Active Inference" proposed by Friston and Frith, sharing prediction models with others and mutually minimizing prediction errors can mitigate uncertainty that an individual alone cannot handle [Friston 15b].

Thus, "Syntelic (Challenging Cooperation)" might be defined as a homeostatic behavior attempting to quell the internal "metabolic urgency" generated by VPA high metabolism through synchronization (cooperation) with others.

2.7 Neurochemical Evolution: Contrast with Neanderthals

Neurochemical evidence offers hints as to how this VPA system promoted Sapiens-specific evolution.

Pereira-Sanchez et al. showed that modern humans with Neanderthal genes have lower dopamine synthesis capacity [Pereira-Sanchez 21], suggesting their exploratory impulse (challenge) might not have been as excessive as in Sapiens.

Meanwhile, Sardar et al. discovered that serotonin directly controls gene expression in astrocytes and other cells via histone modification (serotonylation) [Sardar 23]. This implies that Sapiens acquired scalability to update brain hardware epigenetically according to the social environment by balancing "high dopamine (challenge)" and "VPA-mediated serotonin control (cooperation)."

2.8 Pathological Implications: Failure of Temporal Resolution and Psychopathology

The hypothesis that VPAs tune neuronal networks to criticality allows for redefining mental illness as a "failure of temporal resolution."

• Schizophrenia: If the constitutive reactivity of VPAs declines and the burstiness of energy supply is lost, millisecond-level prediction model updates may fail to keep up. This could cause "Temporal Fragmentation," leading to hallucinations and delusions as desynchronization between self and the external world [Uhlhaas 10, Sullivan 19].

• Autism Spectrum Disorder (ASD): Conversely, if control by VPAs is excessive and the network is fixed in a "Super-Critical State (excessive order)," the E/I balance may tip too far toward excitation, disallowing flexible "fluctuations (temporal exploration)." This could manifest as maladaptation to change or excessive fixation on details (High Precision Priors) [Van de Cruys 14].

3. Experimental Plan: Verification of Hypothesis

To verify that the constitutive reactivity of VPAs is the physical basis supporting active inference, we propose the following experiments.

Experiment 1: Computational Model Incorporating Energy Supply Latency

• Objective:

To mathematically demonstrate the conditions under which high-cost "Constitutive Reactivity" becomes advantageous for survival in exploratory behavior.

• Method:

Introduce "Energy production latency parameter (tau)" and "Maintenance cost (C)" into Friston's Active Inference agent model.

• Agent A (Homeostatic type): Low maintenance cost (C_low), but has supply latency (tau > 0).

• Agent B (Constitutive VPA type): High maintenance cost (C_high), but supply latency is minimized (tau approx 0).

• Predicted Result:

In a simple physical environment, Agent A is advantageous. However, in a "recursive social environment" involving reading others' intentions, Agent A will fail to adapt due to computational latency, whereas Agent B is expected to show maximized survival rates in the long term by instantly updating models despite paying high costs.

Experiment 2: Functional Verification Using Human Brain Organoids (Assembloids)

• Objective:

To verify the influence of human VPAs on the activity mode (criticality) of neuronal networks.

• Method:

Create "Cortical Organoids" derived from human induced Pluripotent Stem cells (iPS cells). Create "Assembloids" by incorporating human astrocytes into one group and astrocytes from other species or modified astrocytes into another.

• Evaluation Metrics:

In addition to Lempel-Ziv Complexity, measure flux to the PPP and Glutathione (GSH) metabolic dynamics to quantify the balance between high metabolism and antioxidant capacity.

• Predicted Result:

In organoids containing normal human VPAs, it is expected that neuronal networks will show more robust criticality, and simultaneously, a significant increase in PPP activity will be observed, suggesting the existence of metabolic infrastructure supporting constitutive reactivity.

Experiment 3: Verification via Local Control of Constitutive Reactivity

• Objective:

To verify that only human-specific "excessive aerobic glycolysis" is essential for allostasis.

• Method:

Since complete inhibition of PKM2 risks cytotoxicity, create a model that "partially and reversibly" suppresses glycolytic activity in VPAs in the Anterior Cingulate Cortex (ACC) etc., using DREADDs (Designer Receptors Exclusively Activated by Designer Drugs) or optogenetics. Alternatively, consider methods to induce splicing from PKM2 to the basal metabolism type PKM1 [Christofk 08].

• Predicted Result:

It is predicted that the operation group will show no effect on basic motor functions, but will show significant performance decline and increased reaction latency only in highly uncertain exploration tasks or complex social tasks.

Experiment 4: Metabolic Comparison of Astrocytes Derived from Psychiatric Patients

• Objective:

To directly verify whether a failure of "Constitutive Reactivity" occurs in astrocytes derived from psychiatric patients as hypothesized.

• Method:

Use astrocytes differentiated from iPS cells derived from patients with Schizophrenia (SZ) and Bipolar Disorder (BD). Use an Extracellular Flux Analyzer to measure Extracellular Acidification Rate (ECAR) and Oxygen Consumption Rate (OCR), comparing glycolytic capacity (constitutive reactivity) at rest with a healthy control group.

• Predicted Result:

Astrocytes derived from schizophrenia patients are predicted to have significantly lower ECAR in the basal state compared to the healthy group [Windrem 17]. This could strongly suggest that the lack of VPA "Constitutive Reactivity" underlies clinical psychopathology.

4. Conclusion: Integration of Thermodynamic Antinomies

The brain is a chemical reactor before it is a computer.

At first glance, the "Free Energy Principle (FEP)," which seeks to minimize energy consumption, and the "Maximum Entropy Production Principle (MEPP)," which seeks to maximize energy dissipation, appear contradictory.

However, according to Ilya Prigogine's theory of Dissipative Structures, these two are considered two sides of the same coin [Prigogine 77, Swenson 89]. The human brain may maintain an internal state of low entropy (high order and low free energy) only by maximizing entropy production (dissipation of heat and waste) to the outside through the "Constitutive Reactivity" of VPAs.

It is inferred that this "living fast" physiology brought about by VPAs is the ultimate driving force that evolved humans not into solitary predators but into Syntelic cooperators, maintaining intelligence amidst the turbulent waves of entropy.

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