Original Paper

2026/3/24

Integrated Verification Plan for the Varicose Projection Astrocytes (VPA) Hypothesis, Syntelic Hypothesis, and Physiological Warburg Hypothesis: VPA as the Metabolic and Integrative Basis for Antecedent State Setting that Enables Challenging Cooperation

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Keywords: Challenging Cooperation, Antecedent State Setting, Constitutive Reactivity, Syntelic AI, VPA Loop Hypothesis

Summary

This paper aims to reorganize the theoretical framework previously proposed by the author into a falsifiable research program. This framework posits "Challenge Propensity" as the fundamental driver of the human lineage, which evolved into high-cost "Challenging Cooperation" with others, and locates its cell-biological basis in the "Constitutive Reactivity" of Varicose Projection Astrocytes (VPAs). The central hypothesis of this paper is that human-specific VPAs, supported by high basal glycolysis and global integration capabilities, serve as the metabolic and integrative basis for the "Antecedent State Setting" that enables challenging cooperation.

In our previous series of studies, it has been argued that challenge propensity may be the fundamental driver preceding shared intentionality and culture formation [Kikuchi 26a]; that VPAs may be involved in self-consciousness and the sense of agency [Kikuchi 26b]; that dysfunctions in the VPA loop may connect to psychopathology via evolutionary mismatch [Kikuchi 26c]; and that the constitutive reactivity of VPAs and the physiological Warburg effect might serve as the metabolic basis for high-cost exploration and cooperation [Kikuchi 26d, Kikuchi 26e]. However, logical leaps remain at each stage: cellular, computational/behavioral, and social/engineering.

Therefore, this paper narrows the main axis of the entire theory to "the antecedent state setting that connects VPAs and challenging cooperation." First, it strengthens the definition of challenge propensity. Second, it carefully steps away from the broad term "free will," restricting the focus to the level of the sense of agency, self-causation, and antecedent state setting. Third, it reinforces the psychological intermediate layer connecting the Body Budget to Human-Robot Interaction (HRI), before proposing five minimum core experimental groups. Specifically, these are: (1) comparative omics and morphological experiments to define VPAs as an independent cell type, (2) optogenetic manipulation experiments to establish causality between VPA activity, readiness potentials, and spontaneous behavior, (3) avalanche analysis linking VPA glycolysis to neural network criticality, (4) verification of region-specific VPA changes and functional connectivity alterations through environmental manipulation, and (5) engineering verification of the effects of Artificial Intelligence (AI) support on affective load, body budget, and relationship maintenance capacity. The goal of this paper is to transform the conventional theoretical framework from a "fascinating but speculative integrated hypothesis" into a "step-by-step falsifiable and modifiable research program," providing a robust scaffold for interdisciplinary verification in future evolutionary anthropology and cognitive science.

1. Introduction

To the question of what makes humans human, evolutionary anthropology has provided numerous explanations, including shared intentionality, language, cooking, and the social brain. For instance, Tomasello argued that shared intentionality, which forms joint intentions, is the foundation of cumulative culture and advanced cooperation [Tomasello 14, Laland 17], while Wrangham and Aiello et al. asserted that behavioral changes such as cooking established the energy basis for a massive brain [Aiello 95, Wrangham 09]. However, these theories excel at explaining adaptations that manifested after the emergence of the genus Homo, but insufficiently explain the prior behavioral drivers that generated those adaptations.

In our previous studies, we proposed the concept of "Challenge Propensity" to address this point [Kikuchi 26a]. Challenge propensity here does not merely reduce to novelty-seeking, curiosity, impulsivity, risk preference, or achievement motivation. It refers to a tendency to actively choose engagement and continue trial and error, rather than avoidance, in tasks involving uncertainty, the possibility of failure, and

effort costs. Furthermore, the extension of this propensity through shared goals and role division with others is termed "Challenging Cooperation." From this perspective, shared intentionality and cooking can be reinterpreted not as causes, but as results developed to adapt to the behavioral strategy of challenging cooperation [Burkart 14, Hare 17, Kikuchi 26a].

Subsequent studies proposed cell-biological, neurocomputational, and socio-evolutionary foundations for this behavioral hypothesis [Kikuchi 26b, Kikuchi 26c, Kikuchi 26d, Kikuchi 26e, Kikuchi 26f]. For example, it was suggested that VPAs, giant astrocytes unique to humans, might be involved in the formation of self-consciousness and the sense of agency by integrating neuronal activity and bodily energy states [Kikuchi 26b]. It was also argued that VPAs form a four-stage loop spanning the Salience Network (SN), Default Mode Network (DMN), and Central Executive Network (CEN) [Menon 11], and that its dysfunction could connect to psychopathology via evolutionary mismatch [Palaniyappan 12, Leech 14, Van de Cruys 14, Kikuchi 26c]. Furthermore, it was proposed that humans physiologically normalized (constituted) the state of reactive astrocytes, which appears only under stressful conditions in other species [Falcone 25, Kondev 26], securing the output basis necessary for high-cost exploration and cooperation through high basal glycolysis, namely the physiological Warburg effect [Pellerin 94, Magistretti 15, Kikuchi 26d, Kikuchi 26e]. Connecting these theories to modern society, it was suggested that "Vainglory" in Social Networking Services (SNS) depletes the Body Budget [Barrett 17] and pressures relationship maintenance capacity [Dunbar 92], while AI could revitalize challenging cooperation by providing affective and cognitive offloading [Kikuchi 26a, Kikuchi 26d].

However, this theoretical system still contains multiple leaps. First, VPAs are not yet sufficiently defined as an independent cell type. Second, the relationship between VPA activity and readiness potentials, spontaneous behavior, and the sense of agency still relies heavily on the proximity of their time scales. Third, the connection between high VPA glycolysis and network criticality is mathematically and causally insufficient. Fourth, the claim that evolutionary mismatch selectively affects VPAs in specific regions remains heuristic. Fifth, the psychological intermediate layer from the body budget to the extension of relationship maintenance capacity via AI support is thin.

Therefore, this paper narrows the central hypothesis of the entire theory to one point: "VPAs serve as the metabolic and integrative basis for the antecedent state setting that enables challenging cooperation." In the framework of Active Inference [Friston 15], this focuses the theory on a verifiable question: rather than treating VPAs as an omnipotent explanatory device, what exactly prepares the state that allows humans to enter uncertain and high-cost cooperative tasks, and how? This paper does not present a plan to be completed by a single laboratory in a short period, but rather proposes a multi-layered research framework (Perspective / Hypothesis and Theory) to specify verifiable research questions and encourage cross-disciplinary connections.

2. Related Work

2.1 Conceptual Positioning of Challenge Propensity

Challenge propensity overlaps with curiosity and exploratory tendencies but is distinct. Curiosity generally refers to the desire for information acquisition, and exploratory tendencies involve approaching unknown elements, whereas challenge propensity strictly requires sustained engagement in tasks involving the possibility of failure, effort costs, and evaluation risks. While impulsivity involves immediate reactions to short-term rewards, challenge propensity includes the characteristic of enduring delays and failures while continuing. Unlike risk preference, challenge propensity is not a mere gamble but involves the formation of skills, relationships, and goals through trial and error. Furthermore, while achievement motivation focuses on intrapersonal desire for attainment [Csikszentmihalyi 90], challenging cooperation is distinguished by incorporating goal sharing and role division with others [Tomasello 14, Burkart 14].

2.2 VPA, Sense of Agency, and Antecedent State Setting

Regarding human-specific astrocyte morphologies, unique interlaminar and varicose projection astrocytes have been reported in humans and great apes [Oberheim 09, Sosunov 14]. Additionally, transplanting human-derived glial progenitor cells has been shown to enhance learning and plasticity in mice [Han 13]. This suggests that glia are not mere support cells but can contribute to species differences in brain function. However, the term "free will" is currently too broad. Readiness potentials are neurophysiological phenomena, the sense of agency is the subjective experience of self-attribution [Caspar 16], and free will encompasses further philosophical concepts. Thus, in this paper, the discussion is limited to the level that "VPAs are involved in the state setting antecedent to readiness potentials and spontaneous behavior, contributing to the sense of agency and self-causation as part of that process."

2.3 The VPA Loop Hypothesis and Evolutionary Mismatch

The VPA loop hypothesis in our previous work [Kikuchi 26c] is highly original in that it reinterprets the connections

among the SN, DMN, and CEN [Menon 11] not merely as neural network interactions but as spatiotemporal integration mediated by VPAs. However, the strong assertion that environmental factors impair specific networks on a one-to-one basis lacks support. What is necessary is not proof of one-to-one correspondence, but rather a quantification of "which environmental factors act with a stronger susceptibility gradient on the VPAs of which regions" [Torres-Platas 11, Uhlhaas 10].

2.4 Constitutive Reactivity, High Glycolysis, and Criticality

It has long been shown that astrocytes support neuronal activity through blood flow regulation [Attwell 10] and aerobic glycolysis [Pellerin 94, Magistretti 15]. It has also been reported that aerobic glycolysis is prevalent in development- and neoteny-related regions in the human brain [Goyal 14, Herculano-Houzel 12]. Our previous studies proposed the possibility that human VPAs physiologically normalized ("constituted") pathological reactivity, supporting high output and high flexibility of networks through high basal glycolysis [Poskanzer 16, Zhou 24, Kikuchi 26d, Kikuchi 26e]. In this paper, we refine this claim to state that "the high glycolysis of VPAs contributes to maintaining the metastability that supports the antecedent state setting necessary for challenging cooperation."

2.5 The Psychological Intermediate Layer from Body Budget to AI Support

While the concept of AI support we proposed is theoretically intriguing [Kikuchi 26a, Kikuchi 26d], the bridge from VPAs and the body budget to HRI remains thin. Therefore, this paper establishes a chain as an intermediate layer: Body Budget [Barrett 17] leads to Affective Threat Appraisal [Russell 80], which generates Cognitive Overload, increases Misunderstanding Repair Costs, and ultimately pressures Relationship Maintenance Capacity [Dunbar 92]. "Vainglory" in SNS environments is thought to elevate affective threat appraisal, increase cognitive overload, and raise repair costs, thereby decreasing relationship maintenance capacity. The position of this paper is that AI support can mitigate body budget depletion and enhance the sustainability of challenging cooperation by providing affective visualization and cognitive offloading to this intermediate layer.

3. Research Objectives

The purpose of the multi-layered framework proposed in this paper is to present the following five verification tasks:

First, to verify whether VPAs can be defined as an independent cell type rather than a transient state of reactive astrocytes.

Second, to clarify whether the calcium and metabolic dynamics of VPAs are causally involved in the antecedent state setting for readiness potentials, spontaneous behavior, and the sense of agency.

Third, to verify whether the high basal glycolysis of VPAs is a tuning factor that supports the criticality of neural networks.

Fourth, to clarify whether environmental factors associated with evolutionary mismatch manifest not uniformly across the brain, but as a "gradient" causing stronger alterations in the VPAs of specific networks.

Fifth, to verify from an engineering standpoint whether AI support saves the human body budget and extends practical relationship maintenance capacity, or the effective Dunbar's number.

4. Methods (Research Framework for Verification)

4.1 Core Hypotheses

This research framework centers on the following five hypotheses. The experimental groups based on these hypotheses are not strictly dependent on each other in series (i.e., they are not a single point of failure). For instance, even before the strict definition of cells (Experiment 1) is completed, environmental manipulation of macroscopic networks (Experiment 4) and measurement of body budget saving effects by AI support (Experiment 5) possess independent academic and engineering value for verification. They are mutually complementary and can be advanced in parallel.

Hypothesis 1: VPA Independent Cell Type Hypothesis

VPAs are a steady-state cell type possessing unique molecular signatures related to long-range projection, high glycolysis, vascular contact, and global synchronization support.

Hypothesis 2: VPA Antecedent State Setting Hypothesis

Spontaneous calcium activity in VPAs contributes to the antecedent state setting of readiness potentials and spontaneous behavior. This is a verifiable hypothesis that slightly weakens the strong proposition that "VPA equals free will itself."

Hypothesis 3: VPA Criticality Tuning Hypothesis

The high basal glycolysis of VPAs is a tuning parameter supporting the power-law nature, branching ratio, and metastability of neural avalanches.

Hypothesis 4: Mismatch as a Gradient Hypothesis

Various deficiencies in modern environments do not impair specific regions one-to-one but manifest as a gradient causing

stronger alterations to the VPAs of a particular network.

Hypothesis 5: Syntelic AI Assistance Hypothesis

AI support equipped with affective visualization and cognitive offloading mitigates body budget consumption and pushes up the effective upper limit of maintaining cooperative relationships.

4.2 Experiment 1: Establishment and Definition of the VPA Cell Type

[Hypothesis] VPAs are not transient responses during inflammation but an independent cell type steadily maintained in humans and some great apes [Falcone 25].

[Model] Postmortem brain tissues from humans, chimpanzees, macaques, and marmosets, as well as induced Pluripotent Stem (iPS) cell-derived astrocytes.

[Method] Extract molecular signatures involved in long-range process formation, glycolysis, calcium waves, vascular contact, and near-synaptic transport using a combination of spatial transcriptomics, single-cell Ribonucleic Acid (RNA) sequencing, multiplex Immunofluorescence (IF), and 3-Dimensional (3D) morphological reconstruction [Cáceres 03, Oberheim 09].

[Primary Endpoints] Gene expression profiles including species differences, VPA-specific marker groups, interlaminar projection length, varicosity density, and vascular contact rate.

[Expected Results] Cell populations possessing steady molecular modules supporting high glycolysis and long-range projections may be detected only in humans or great apes. If confirmed, the primary premise of the VPA hypothesis will acquire an empirical basis as a cell type for the first time.

[Falsification Condition] VPA candidate cells are indistinguishable from the inflammatory state of protoplasmic astrocytes in other species, and no steady unique signature is found.

4.3 Experiment 2: Causal Verification of Readiness Potentials and Spontaneous Behavior via Optical Manipulation of VPAs

[Hypothesis] VPA calcium waves set the antecedent state of spontaneous behavior, consequently affecting the onset of readiness potentials.

[Model] Chimeric mice transplanted with humanized glial progenitor cells as the first stage [Han 13, Windrem 17], to be expanded to genetically modified marmosets in the future.

[Method] Conduct free-timing lever-pull tasks, action-cancellation tasks, and choice-withholding tasks. Suppress or delay calcium waves in VPA-like cells using optogenetics or chemogenetics, while simultaneously recording Electroencephalograms (EEG), local field potentials, and action timing [Caspar 16, Javadi 17]. If necessary, add lactate transport inhibition or gap junction blockade to separate the contribution of calcium waves themselves from metabolic support.

[Primary Endpoints] Readiness potential onset time, amplitude, action initiation latency, timing variance, cancellation rate, and choice alteration rate.

[Expected Results] Suppressing VPA activity may destabilize or delay the onset timing of spontaneous behavior and readiness potentials, rather than affecting motor ability itself. This result would not prove that "VPA equals free will," but it would at least support its contribution to "antecedent state setting" and the formation of the sense of agency.

[Falsification Condition] No significant changes occur in readiness potentials, action initiation, or spontaneous action frequency despite VPA activity suppression.

4.4 Experiment 3: Avalanche Analysis under VPA Glycolysis Inhibition

[Hypothesis] The high basal glycolysis of VPAs is a tuning factor that maintains neural networks in a state of criticality.

[Model] Human iPS cell-derived cortical assembloids, or neural-glial assembloids containing VPA-like cells connected to high-density Microelectrode Arrays (MEA).

[Method] Apply stepwise inhibitions such as Pyruvate Kinase M2 (PKM2) inhibition, lactate transport inhibition, and gap junction inhibition, calculating neural avalanches, branching parameters, complexity, and metastability. Simultaneously measure the Extracellular Acidification Rate (ECAR) / Oxygen Consumption Rate (OCR) to correlate metabolic changes with network phase transitions [Prigogine 77, Swenson 89].

[Primary Endpoints] Power-law fit of avalanche size distribution, branching parameter, burst index, metastability, and ECAR/OCR ratio.

[Expected Results] Weakening glycolysis may cause the network to phase-transition into a hypersynchronous or silent state, deviating from criticality. This would make the massive bridge from the "Physiological Warburg Effect to Criticality" experimentally evaluable for the first time.

[Falsification Condition] Power laws, branching ratios, and network complexity are maintained even under glycolysis inhibition, with no deviation from criticality.

4.5 Experiment 4: Changes in Region-Specific VPA Morphology and Functional Connectivity via Environmental Manipulation

[Hypothesis] Evolutionary mismatch factors do not affect the whole brain uniformly but exert stronger influences on the VPAs of specific networks.

[Model] Common marmosets.

[Method] Long-term breeding divided into groups: normal

group, social isolation group, social isolation + excessive digital visual stimulation group, and social contact + excessive digital stimulation group. Conduct resting-state functional Magnetic Resonance Imaging (fMRI) and task-based functional connectivity analysis. Finally, quantify VPA morphology in the insular cortex, precuneus, Posterior Cingulate Cortex (PCC), Anterior Cingulate Cortex (ACC) / dorsolateral Prefrontal Cortex (dlPFC), and Posterior Parietal Cortex (PPC) [Lee 13, Leech 14]. Also, acquire general stress markers such as sleep, cortisol, and locomotor activity to differentiate from simple chronic stress effects.

[Primary Endpoints] Regional functional connectivity, VPA volume, process length, varicosity density, vascular contact rate, sleep rhythm, and autonomic nervous system indicators.

[Expected Results] For example, lack of interaction might show a stronger abnormal tendency in the PCC/DMN system, disruption of focus in the precuneus, and lack of challenge in the ACC/dlPFC system. Consequently, the "Six Deficiencies" model would be reformulated not as one-to-one assertions but as a map of vulnerability.

[Falsification Condition] Under any environmental manipulation, the entire brain changes uniformly, or conversely, VPAs remain completely unchanged and only the neuron side changes.

4.6 Experiment 5: Savings in Body Budget and Extension of Effective Dunbar's Number via AI Support

[Hypothesis] AI support combining affective visualization and cognitive offloading mitigates body budget depletion and pushes up the effective upper limit of relationship maintenance.

[Model] Human subjects engaged in multi-person online collaborative tasks.

[Method] Conduct collaborative tasks for 4-8 weeks, divided into a standard SNS group, a simple organizing AI group, and an affective visualization + cognitive offload AI group. Measure Heart Rate Variability (HRV), pupil diameter, sleep fragmentation, subjective fatigue, misunderstanding repair time, and the number of sustainable meaningful mutual relationships [Keeler 15]. If necessary, incorporate face-to-face interaction conditions to compare the complementary effects of digital support and real interactions.

[Primary Endpoints] Allostatic load indicators, relationship maintenance error rates, number of concurrent mutual relationships manageable, task completion rates, and subjective psychological safety.

[Expected Results] In the AI support group, body budget indicators may stabilize more than in the standard group, relationship maintenance failures may decrease, and the effective Dunbar's number may increase beyond individual baselines. If demonstrated, AI would be positioned not merely as an efficiency tool, but as an affective and cognitive facilitator that revitalizes "Challenging Cooperation."

[Falsification Condition] After introducing AI support, neither physiological indicators nor the number of maintained relationships improve, or they instead deteriorate.

5. Expected Results

If this plan progresses successfully, the conventional theoretical framework is expected to be repositioned as follows:

First, VPAs may be defined as a cell type candidate with molecular signatures and morphology, rather than a "poetic metaphor for consciousness."

Second, the free will hypothesis will be refined from the strong proposition that "VPA equals free will itself" to a more limited, verifiable form as "a factor contributing to the antecedent state setting of spontaneous behavior and the formation of the sense of agency."

Third, the physiological Warburg effect can be evaluated as a concrete tuning hypothesis supporting neural criticality, rather than a broad metabolic metaphor.

Fourth, the evolutionary mismatch hypothesis could be quantified as a "gradient" of vulnerability in specific networks, rather than a one-to-one correspondence.

Fifth, Syntelic AI will move beyond an ideological proposal and connect to HRI research measuring body budget protection and the extension of the radius of cooperation.

Additionally, dimensional models of metabolism, calcium, and synchronization abnormalities using patient-derived iPS cells could open a path to reorganize psychopathology not by disease names themselves, but by computational axes such as temporal update capacity, metabolic burst power, and synchronization instability [Mosconi 08, Naqvi 07]. Furthermore, regarding the cultural sublimation hypothesis, introducing intermediate variables such as "high-arousal cooperative states," "flow," and "abstract goal sharing" could allow the transition from war to culture to be reconstructed into a verifiable hypothesis as a collective experiment, rather than jumping straight from cells to cultural history [Kikuchi 26f].

6. Discussion

The greatest appeal of this theoretical system lies in its attempt to accommodate themes usually discussed in disparate fields—such as challenge propensity, self-consciousness, free will, body budget, cooperation, psychopathology, and cultural evolution—within a single biological and computational framework [Klein 09]. However, its greatest weakness also lies in the overly broad scope of integration. In particular, assertive claims like "VPA is free will itself," "lack of interaction only

breaks the PCC," or "the sublimation from war to culture can be explained solely by VPAs" are weakly supported at the current stage.

Therefore, without compromising the theory's appeal, this paper temporarily decomposed it into "weak but verifiable propositions." For instance, free will is rephrased as "antecedent state setting" rather than an "entity"; evolutionary mismatch is rephrased as a "gradient" rather than "one-to-one correspondence"; and cultural sublimation is rephrased into an intermediate variable of "rewiring high-arousal cooperative states" rather than a "direct explanation" [Bowles 09, James 10, Huizinga 38]. Such weakening is not a retreat, but a necessary condition to elevate the theory into a falsifiable science.

Moreover, this research plan is not intended to negate the author's previous series of hypotheses. Rather, it is an attempt to preserve its original perspective in a more rigorous form: the idea of "reinterpreting astrocyte reactivity, previously seen as pathological, as an exaptation of a highly functional infrastructure in human evolution," and the perspective of "understanding culture as a transformation of the energy dissipation destination of VPAs." In this sense, this paper is not a defense of the theory, but a blueprint for a durability test to measure how much the theory can withstand, guiding the field to the next stage.

7. Conclusion

This paper presented an integrated program designed to verify a series of hypotheses—"Challenge Propensity," "VPAs," "Constitutive Reactivity," "Physiological Warburg Effect," "Evolutionary Mismatch," "Syntelic AI," and "Cultural Sublimation"—across the cellular, circuit, behavioral, and social levels. The appeal of the author's previous papers lies in their bold integration. Conversely, their weakness lies in the integration being too massive. The significance of this paper lies in transforming the theory into a step-by-step and parallel-verifiable research framework without losing its grandeur. Ultimately, this paper goes beyond a mere defense of hypotheses, proposing a robust scaffold for interdisciplinary verification across evolutionary anthropology, neuroscience, and artificial intelligence engineering.

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