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Mitochondrial psychobiology

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ABSTRACT

A field that uses mitochondria to unify biological and psychological sciences and to better understand the basis of health has emerged—*Mitochondrial Psychobiology*. Mitochondria are the body's cellular hubs for energy transformation and signaling. Mitochondria regulate functions as diverse as metabolism, gene expression, and stress adaptation; consequently, their dysregulation is linked to most chronic illnesses and aging. Here, we propose that mitochondria provide a mechanistic bridge between body and the measurable functions of the mind, including perception, cognition, emotion, and behavior. From this perspective, mitochondria provide a scientifically tractable interface through which bioenergetic processes relate to subjective experiences and behaviors. We outline foundational principles for Mitochondrial Psychobiology, discuss the key gaps that the field needs to address to advance our understanding of mind-mitochondria relationships across the lifecourse, and review emerging approaches to probe the mind-mitochondria connection across levels. This stimulating scientific challenge is a unique opportunity to train the next generation of interdisciplinary scientists, resolve conceptual and technical challenges spanning temporal and spatial scales, and develop a more accurate, holistic model of health. Rooted in general energetic principles, Mitochondrial Psychobiology is poised to productively steer biomedicine over the coming decades.

Mitochondrial Psychobiology has emerged at the intersection of biological and psychological sciences. This new field aims to explain how the biology of cellular energy and cellular signaling supports and shapes variation in psychological functions and behavior.

Biomedicine, neuroscience, and related disciplines have addressed this challenge using cutting-edge mechanistic approaches from neuroscience and psychopharmacology, predominantly in pre-clinical *in vivo* and *in vitro* models. This has yielded remarkable precision, but leaves an explanatory gap between physiology, mind, and subjective experience (Picard, 2022; Dossett et al., 2020). Simultaneously, the same overarching challenge has been addressed by the humanities, psychological, and social sciences from the viewpoint of behavior, psychosocial factors, and environmental forces (Marmot et al., 2008; Carey and Crammond, 2015; O'Connor et al., 2021). However, these insights are less often anchored in the biological processes that implement them. Guided by distinct traditions, methods, and approaches, outside of a few exceptions, these two scientific worlds have often operated disconnected from each other. As a result, we lack a shared framework that naturally and rigorously links biology to the mind and its measurable expressions across perception, cognition, emotion and behavior. Bridging this scientific divide is essential to resolving the most pressing questions around human health and flourishing.

Decades of research into mind-body mechanisms have revealed that the biological and psychological dimensions of life are deeply intertwined (Kelly et al., 2024; Cohen et al., 2019; Thaker et al., 2006; Gianaros and Wager, 2015; Cole, 2014). Yet, a general unifying point of convergence that can be interrogated across this spectrum is still missing. For example, in humans, breathing in-and-out patterns shape the neural dynamics of memory (Tarrasó et al., 2026), and systemic immune activity is now recognized to regulate diverse cognitive functions—including the inflammatory pathways that may underpin the pathophysiology of depression (Miller and Raison, 2016; Miller, 2025; Nuber-Champier et al., 2026). Neural and physiological systems interact widely with one another.

The present article is the result of a search for a point of consilience (Wilson, 1999) where these disparate observations meet. We propose that mitochondria are such a point of consilience. This proposal is justified by the role of mitochondria as dynamic hubs of energy transformation and signaling, which integrate internal physiological states with environmental demands and thereby shape neural and systemic functions that implement perception, cognition, emotion, and behavior.

The central idea of Mitochondrial Psychobiology is this bidirectional relationship; mitochondrial energy transformation and signaling can influence the biological processes that support psychological function and behavior, while on the other hand psychological states and behavior can as well regulate different aspects of mitochondrial biology at different body levels. Rigorously examining this psychobiological intersection holds the promise of revealing a unifying framework—Mitochondrial Psychobiology—that links mitochondrial bioenergetics to the mind-body adaptations sustaining psychological function.

1. Mitochondria as the consilience point

To define this fundamental psychobiological regime, we argue for first-principles reasoning: *What is the most fundamental level(s) of regulation that operate across psychobiological (mind and body) processes? Where do the biophysical constraints and possibilities of our biology intersect with human experiences and behaviors?* Asking these questions can help free us from the assumptions that define the discipline(s) that shaped each of our scientific upbringing. Conceptually, they also direct inquiry towards a fundamental common denominator that crosses levels of explanation.

Given the bioenergetic demands imposed by psychological function and all adaptive responses (Fig. 1**A**), following this thread brings us to *energy*. Given that Mitochondrial Psychobiology is poised at bridging disciplines that have traditionally not incorporated concepts and facts from mitochondrial biology, we briefly outline below the mitochondrial properties needed to grasp this framework. For a more comprehensive account of other aspects related to mitochondrial metabolism, signaling and brain-related functions, we refer the reader to relevant reviews (Spinelli and Haigis, 2018; Picard and Shirihai, 2022; Li and Sheng, 2022; Shen et al., 2022; López-Doménech and Kittler, 2023; Suomalainen and Nunnari, 2024; Sandi et al., 2026).

In its broadest sense, *energy is the potential for change* (Picard and Murugan, 2025). In this framework, the term "energy" is used across multiple levels of analysis, from cellular bioenergetic processes that transform substrates into usable energy (e.g., adenosine triphosphate, ATP), to organism-level energetic and metabolic states reflected in variables such as mitochondrial membrane potential and heat, together with metabolic substrates and intermediates such as glucose and lactate, that can influence motivation, behavior, and subjective experiences (Picard and Kempes, 2026). Energy is the fundamental resource that living organisms transform and use to sustain their entropy-defying existences filled with rich experiences, challenges, and opportunities for growth and development, as well as disease and death (Picard and Kempes, 2026). Nothing in biology is free. Everything from turning on a gene (Lynch and Marinov, 2015), a neuronal action potential (Chintaluri and Vogels, 2023), cellular life transitions (Monzel et al., 2024), digesting a meal (Calcagno et al., 2019), fighting an infection (Ganeshan et al., 2019), having feelings and thoughts (Jamadar et al., 2025), interoception (Quigley et al., 2021) to aging (Shaulson et al., 2024)—requires energy transformation.

As breathing animals, much of the energy that feeds us flows through our mitochondria. This is because mitochondria are the nexus where food-derived electrons converge with oxygen (Picard and Murugan,

2025), and their flow is transformed into a membrane potential that fuels the multiple mitochondrial functions (Monzel et al., 2023). Given that oxygen is the terminal electron acceptor of the respiratory chain, hypoxic conditions deter mitochondrial oxidative phosphorylation and, thus, when the delivery of oxygen to the brain drastically decays, ATP-dependent neuronal function fails and consciousness is compromised. Sustaining the flow of energy towards oxygen, mitochondria are small endosymbiotic organelles that sense, integrate, and signal energy and information to power our cells, and, hence, our behaviors, and our mind (Suomalainen and Nunnari, 2024; Picard, 2022). In this framework, mitochondrial bioenergetics provide a mechanistic substrate through which environmental demands, physiological states, and psychological processes are integrated to regulate behavior and health. Mitochondria do not only transform energy. They also synthesize steroid hormones and DNA precursors, metabolize neurotransmitters, transduce signals that coordinate cellular responses, can travel within and between cells and organs, and drive cellular and organismal behaviors (Picard and Shirihai, 2022; Spinelli and Haigis, 2018; Shen et al., 2022).

Decades of work show how impaired mitochondrial energy transformation and signaling leads to metabolic and neurodegenerative disorders, cancer, psychiatric disorders, and other developmental and age-related disorders (Suomalainen and Nunnari, 2024; Picard et al., 2016). Dozens of animal and human studies further indicate that psychosocial factors, including chronic and traumatic stress, early-life experiences, and variations in affective states, are associated with molecular and functional changes in mitochondria (Lambertini et al., 2015; Gyllenhammer et al., 2022; Morató et al., 2022; Trumpff et al., 2024) and alterations in circulating energy-related biomarkers (Hunter et al., 2025). Further, recent discoveries in humans also link mitochondria to mental health, social stress, and broader mind-body processes (Gumpp et al., 2020, 2023; Duchowny et al., 2024; Trumpff et al., 2024). These data point to a tight interplay of experiences and mitochondrial biology across bodily systems.

Based on this rapidly evolving body of research, an emerging hypothesis posits that *mitochondria may operate as a functional linchpin bridging the subjective experiences that are the domain of the psyche ("psycho") and the molecular events that are the domain of biology ("bio")*, thereby linking these domains to development, resilience, and health trajectories (Fig. 1**B**).

2. Defining mitochondrial psychobiology

Mitochondrial Psychobiology is an emerging field that builds on the foundations of psychobiology (Dewsbury, 1991). Psychobiology is the interdisciplinary science at the crossover between psychology and biology—which preceded neuroscience—that aims to explain behavior and mental processes as outcomes of peripheral and central biological mechanisms. While psychobiology seeks to link biology to behavior, its mechanistic focus has traditionally centered on neural, neuroendocrine and neuroimmune regulation, not on mitochondria. This is in part because mitochondria were considered as organelles mainly involved in energy transformation and housekeeping functions (i.e., "mitochondria are the powerhouse of the cell"). This limited understanding also resulted from the fact that the tools required to investigate mitochondria in relation to brain function and behavior *in vivo,* and with cell type and circuit resolution, only recently became available. Mitochondrial Psychobiology introduces a novel perspective in which mitochondria play a central role in linking cellular and systemic physiology to brain function and psychological processes (Filiou and Sandi, 2019; Daniels et al., 2020; Gumpp et al., 2020; Morava and Kozicz, 2013; Picard et al., 2019), including the measurable expressions of mind across perception, cognition, emotion, behavior, and (in humans) subjective experiences.

Yet, while the brain is the organ believed to produce the mind and behaviors, its performance is deeply influenced by whole-body bioenergetics. The brain's ability to support perceptual, cognitive, emotional, and behavioral processes depends not only on neural circuit function, but also on the energetic and metabolic context provided by the rest of the organism, as conveyed to, and sensed by, the nervous system through circulating substrates and signals (Andreazza et al., 2025; Barros et al., 2025) and afferent signals propagated to the brain by the vagus nerve, among other neural routes (Kleckner et al., 2017). These interoceptive signals conveying information about the energetic state of the body may play a critical role in driving affective states that regulate whole-organism behavior (Barrett et al., 2016; Seth and Friston, 2016; Kleckner et al., 2017). Moreover, every cognitive or behavioral process carries an energetic cost, and mitochondria are key determinants of whether that cost can be met (Kelley et al., 2025). Thus, cognitive performance, motivation, resilience/adaptability, and even consciousness must ultimately be rooted in the capacity to "pay their part of the brain's energy bill" (Padamsey and Rochefort, 2023; Barrett, 2017; Vishwanath et al., 2026)—in the mitochondria's capacity to manage energy efficiently and flexibly (Theriault et al., 2023).

Mitochondria comprise distributed information-processing networks that function as integrative hubs or intracellular processors both within cells and between cells. They sense oxygen, nutrients, hormones, and stress signals, translating these cues into adaptive responses and

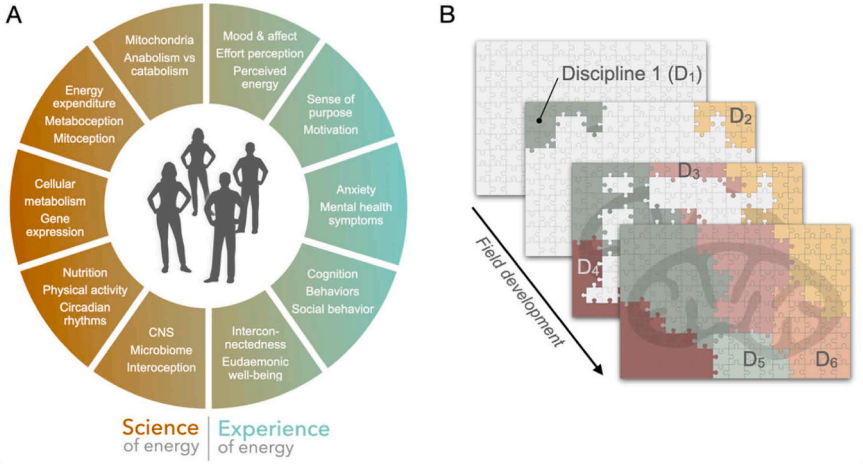


Fig. 1. The mitochondrial psychobiology puzzle. (**A**) Scientific concepts and measurements related to energy (*left*), and psychological function, including subjective experiences, cognition and behaviors (*right*), coalesce to form the basis of health and well-being. (**B**) The structured assembly of concepts, approaches, and technologies from distinct disciplines constitutes the full spectrum of possibilities to develop and address the most pressing questions in mitochondrial psychobiology. *Abbreviations*: *CNS*, central nervous system.

intracellular and systemic signals to coordinate their activities between cells and tissues (Picard and Shirihai, 2022; Shen et al., 2022). Mitochondria regulate cellular and systemic function by physically moving within and between cells to ensure energy availability to high-demand cellular compartments and tissues as environmental demands change over time. Within the brain, mitochondrial bioenergetic and signaling states in neurons and glia regulate cellular and circuit structure and function and thus contribute to establishing and regulating the circuit operations that support cognition, emotion, and behavior (Rae et al., 2025; Sandi et al., 2026). In addition, through their signaling taking place alongside energy transformation, mitochondria participate in the communication between the peripheral body and brain, and vice versa (Kelly et al., 2024). Peripheral energetic states influence neural activity and mood (Quigley et al., 2021), as evidenced, for example, by the effects of blood ketones and lactate on the brain and on neuroendocrine regulation (Bolaños and Magistretti, 2025; Rae et al., 2025; Jimenez-Blasco et al., 2026), and these actions can in part be mediated via effects on brain mitochondria.

Conversely, psychological states can also rapidly reshape peripheral metabolism, notably including mitochondrial contributions that within minutes alter peripheral levels of metabolites such as lactate, glucose, and amino acids (Picard et al., 2015; Lee et al., 2023), metabolism-regulated metabokines (Huang et al., 2024; Kurade et al., 2025), and other mitochondria-related biomarkers including cell-free mitochondrial DNA (Trumpff et al., 2025a, 2025b; Hunter et al., 2025). These peripheral metabolic signatures directly or indirectly reflect shifts in mitochondrial physiology that convey signals of adaptation across body tissues.

In this view, mitochondria are not passive energy transformers, but dynamic regulators of body-brain axes. Within this framework, Mitochondrial Psychobiology considers mitochondria as primary regulators of physiological integration of internal and environmental cues (Picard and Shirihai, 2022), functioning at every level of biological organization, from molecular signaling to inter-organ communication and the neural circuit dynamics that support cognition, emotion, and behavior.

It should be noted that the mitochondrial focus in this perspective does not imply that every metabolic or physiological variable considered in Mitochondrial Psychobiology is mitochondria-specific. There are several measures relevant to this emerging field, such as circulating glucose, lactate, or GDF15 that are intimately interlinked with mitochondrial functions while also reflecting broader metabolic or systemic states. Thus, our focus on mitochondria allows us to anchor the field in a measurable organellar system amenable to experimental enquiry (Picard and Shirihai, 2022; Shen et al., 2022; Sandi et al., 2026), while our framework combines direct mitochondrial measurements and broader metabolic and physiological readouts and keeps these levels conceptually distinct.

Thus, we define Mitochondrial Psychobiology as *the study of the bidirectional interactions between mitochondrial biological processes and the mind, in which mental and metabolic states mutually emerge to influence mitochondrial functions across bodily systems, while mitochondrial processes in turn influence the biological substrates of mental states, resilience, and health outcomes*.

3. Approach to Mitochondrial Psychobiology thinking

Two simple analogies illustrate how Mitochondrial Psychobiology bridges *psychological and biological sciences*, serving as a fertile point of integration for discipline- and field-specific knowledge. They help identifying the level of explanation at which mitochondrial mechanisms and energetic principles can be meaningfully connected to psychological functions at the level of the whole organism.

The first is the *tree of knowledge* (Fig. 2). In the mitochondrial psychobiology tree of knowledge, each branch represents a discipline or subdiscipline, branching outward towards specialization. The trunk represents our *shared foundation*. In this model, each scientific discovery

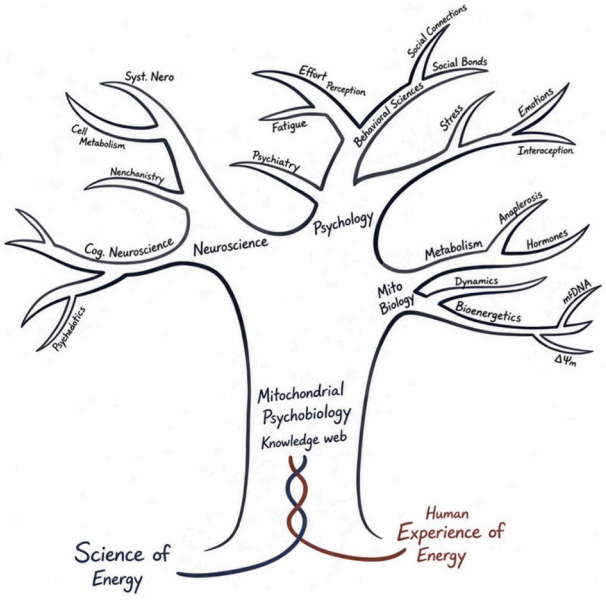


Fig. 2. The tree of knowledge for mitochondrial psychobiology. Tree analogy to visualize the point of consilience and integration for psychological and biological disciplines. Finer branches reflect more specific fields and disciplines broadly related to psychology, neuroscience, and mitochondrial biology.

is a new leaf on a distal branch, whereas unusually broad concepts and principles exist near the trunk. Seeking the most fundamental framework common to all branches moves us closer to the trunk. Major branches/disciplines connect at *interdisciplinary* junctions, where teams of scientists (Yanai and Lercher, 2024) can together produce some of the most radical innovation and actionable discoveries (Disis and Slattery, 2010). Reasoning at this level requires abstraction from disciplinary details, far from empirically tractable problems. As a result, to most scientists, this practice feels intellectually unproductive and uncomfortable. However, it is a necessary state for capturing what is most universally true across branches—i.e., to capture core principles. For Mitochondrial Psychobiology, this movement toward a shared foundation is anchored in energy transformation and in mitochondrial biology as a measurable system through which energetic principles can be related to psychological function.

The second analogy is that of the *computer*. Like our biological bodies, computers contain a layered architecture ranging from nanometer-scale silicon semiconductor gates, to processors, operating systems and command line logic, to the user interface composed of icons on the desktop. One's ability to produce stunning programming feats typically relies on an intermediate level of resolution. To program effectively, the programmer gains little from solving the physics of semiconductors (too fine-grained). The effective programmer must also go beyond the simplified icon-based desktop interface (too coarse-grained). Neither the too granular (tip of branches in the tree analogy) nor the too abstract (deep in the trunk) levels are productive. For Mitochondrial Psychobiology, the useful explanatory level is therefore intermediate; i.e., sufficiently mechanistic to interrogate mitochondrial processes, while sufficiently integrative to relate them to cellular, circuit, whole-body and psychological states.

To solve the energetic and mitochondrial basis of psychobiological processes—our *psychobiological puzzle* (see Fig. 1)—we may not gain much from enumerating the atomic- and molecular-level operations at play, nor perhaps the genes involved in a function of interest. At the other extreme, the general laws of thermodynamics or the mass-energy equivalence principle ($E = mc^2$), although true, are not directly informative nor actionable at the scale of psychobiological systems.

Somewhere between the granular layers of genes and general fundamental physical laws lies the explanatory sweet spot: *energetic principles* grounded in generalizable biophysical constraints and linked to measurable mitochondrial and psychobiological processes (Fig. 3).

The following sections introduce key principles we propose can help us understand the interplay of mind and mitochondria, and the basis of health. We discuss how energy constraints and systemic demands shape mitochondrial biology and psychological function, and emphasize the principles of energy budgeting and trade-offs in psychobiological adaptation, and how energy constraints interface with human experiences.

4. Principles of Mitochondrial Psychobiology

Mitochondrial Psychobiology is built on seven foundational principles that are relevant broadly to psychobiology. These principles serve as a lens to examine the intersection of energetic processes within mitochondria and psychological function, including perception, cognition, emotion, behavior, and subjective experience. They provide the theoretical framework guiding how this organelle-to-organism relationship can be conceptualized and tested and, thus, for developing hypotheses, experiments, and technologies in mitochondrial psychobiology. We punctuate each principle with a *brief statement* (*) to make it experimentally tractable.

1. **Forms of energy are interchangeable**. Within living systems, energy is continually transformed between chemical, electrical, thermal, electromagnetic, mechanical, and other forms (Demirel, 2002; Picard and Murugan, 2025). By probing metabolite concentrations, membrane potential, oxygen consumption, CO_2 and heat production, electrical activity, redox state, circulating energetic state signals (e.g., cytokines, mitokines), we measure energy transformation and bioenergetic states across multiple modalities. Psychological and behavioral measurements can then be related to these energetic processes. Mitochondria lie at the center of these exchanges, transforming food and macronutrients into ATP, heat, and dozens of intra- and inter-cellular metabolic and signaling outputs, including those that underlie psychological phenomena. * *A full view of mitochondrial energy transformation requires multi-modal assessments.* For example, regional neurometabolic states have been associated with the willingness and capacity to exert cognitive and physical effort (Strasser et al., 2020; Wiehler et al., 2022; Barakat et al., 2025; Clairis et al., 2025). Complementing these associations, selective disruption of mitochondrial integrity through mitofusin-2 (Mfn2) loss in ventral striatal dopamine D1 receptor-expressing neurons reduces effort-based motivation (Chioino et al., 2026). From this principle, we predict that constraining mitochondrial energy-transformation capacity should limit the intensity or duration of effort that can be sustained, particularly as task demands increase.
2. **Phase transitions drive behavior.** Organisms operate across an energy landscape that involves gradual or rapid transitions between distinct states. These transitions occur across scales, ranging from energetic states (e.g., changes in NADH/NAD^+ ratio) and cellular states (activated or quiescent) to physiological states (anabolic or catabolic) and psychological states, including cognitive (attentive or disengaged) and emotional (calm or distressed) modes, with downstream consequences for behavioral output (e.g., active or sedentary). Although some variables operate across fairly constrained scalar values, many operate within narrow windows with sharp functional thresholds (Csordás et al., 2013). All such transitions cost

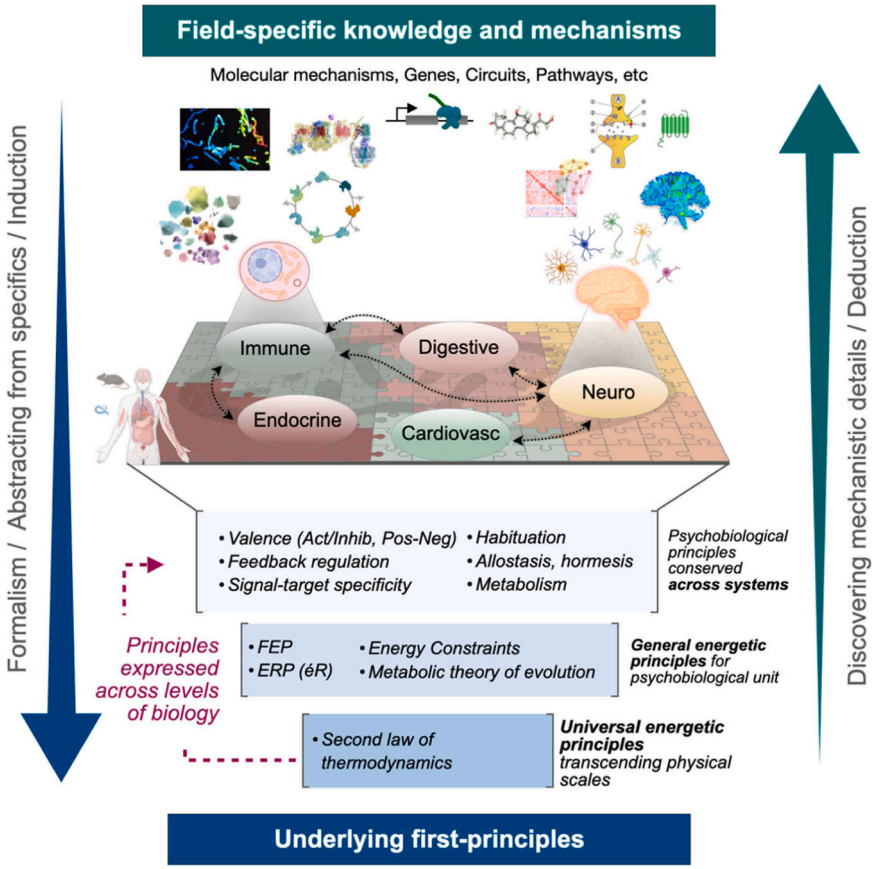


Fig. 3. Whereas discovering field-specific knowledge and mechanisms (*right*) is the traditional direction for biomedical research, the movement towards uncovering underlying first-principles (*left*) is required to perceive interdisciplinary connections that form the basis for new, general questions and principles including organism-level psychological states (e.g., vitality, fatigue, effort perception) that reflect underlying energetic conditions.

energy (Monzel et al., 2024; Gu et al., 2018), and mitochondria influence the timing, probability and thresholds of these transitions through both energy availability and signaling (Chakrabarty and Chandel, 2021; Picard and Shirihai, 2022; López-Doménech and Kittler, 2023). * *Non-linear modeling is key to understanding these state-dependent transitions in living, non-linear systems.* For example, mitochondrial Ca^{2+} uptake exhibits threshold-dependent activation (Csordás et al., 2013), and experimentally increasing mitochondrial Ca^{2+} retention and metabolism in neuronal memory circuits can enable long-term memory under training conditions in which control animals fail to form it (Vishwanath et al., 2026). These observations suggest that mitochondrial state may influence functional thresholds across levels. Accordingly, we predict that reducing mitochondrial energy-transformation capacity would shift the transition from sustained engagement to disengagement during an escalating effort task toward lower levels of task demand.

3. **Energy constraints shape function**. No living system operates with unlimited energy. The body has a limited, relatively fixed energy budget, even in the presence of increased energy input from unlimited feeding (Behnke et al., 2026). Importantly the energy budget is defined by the rate of transformation of energy substrates (e.g., glucose, ketones) into the cellular energy currency, ATP per unit of time, which largely takes place within mitochondria. Therefore, organisms negotiate trade-offs (for example between repair, reproduction, cognition, or social engagement) within these finite energy budgets (Ganeshan et al., 2019; Yang et al., 2021; Ülgen et al., 2023; Behnke et al., 2026). Like reducing valves, mitochondria both impose and sense these limits, influencing signaling and behaviors that balance energy expenditure with survival. The brain-body energy conservation (BEC) model of aging (Shaulson et al., 2024) integrates animal, cellular, and clinical studies illustrating that the biology of aging is accelerated by mitochondrial (Sturm et al., 2023) and stress-related (Bobba-Alves et al., 2023) perturbations. * *Even in a molecularly intact system, energy constraints can drive trade-offs that shape behavior, psychological functions, and symptoms of disease.* For example, under food shortage, energetically costly long-term memory formation can be suppressed in favor of survival in drosophila (Plaçais and Preat, 2013) and, similarly, negative energy balance can reduce prosocial helping behavior in mice (Pozo et al., 2023). Thus, from this principle, we predict that, under comparable energetic demands, organisms with lower mitochondrial bioenergetic reserve will exhibit earlier or stronger trade-offs away from energetically costly cognitive, social, or other non-essential functions.
4. ***Energy patterning encodes information***. Energy is not merely a high or low quantity, but is patterned in space and time (Picard and Murugan, 2025). In biological systems, variations in the amplitude, frequency, duration and timing of signals can encode information, as illustrated by oscillatory electrical activity in the brain (Buzsáki and Draguhn, 2004). Oscillations and other types of organized energy patterns encode the information that underlies cell-cell, organ--to-organ, and person-to-person communication (Sonnen and Aulehla, 2014). Similarly, animals communicate with each other by the modulation of energy patterns in time—spoken words as pressure waves interspersed by silences: information-rich, patterned energy. Analogously, mitochondria are not simply present or absent across the body. They exist as a diverse family of organelles heterogeneously distributed (i.e., patterned) across cell types and organs (Monzel et al., 2025; Fecher et al., 2019). * *Capturing dynamic patterns, rather than single-variable phenotypes, is key to grasping information content and transmission*. For example, brief openings of the mitochondrial permeability transition pore in astrocyte processes generate spatially localized Ca^{2+} transients, coupling mitochondrial activity to local cellular signaling (Agarwal et al., 2017). From this principle, we predict that the frequency, duration and spatial localization of mitochondrial bioenergetic and signaling events will provide information about downstream responses that is not captured by their average magnitude alone.
5. **Energy is dynamic**. A natural property of energy in different forms is that it naturally flows and transforms *over time*. An expression of this principle is the reliance of living systems on continuous energy flow, where the absence of flow (i.e., units of energy per minute) is synonymous with death (Kempes et al., 2026; Picard and Kempes, 2026). Beyond life-death polarity, biological systems continuously recalibrate their energetic state in response to changing conditions (both internal and external). Thus, all stress responses and forms of adaptation involve dynamic shifts in energy and mitochondrial functions, unfolding dynamically over milliseconds to weeks or years (Picard et al., 2018), depending on the outcome of interest. * *We always learn more about any system from time courses than from single time point snapshots.* Indeed, time-resolved measurements can reveal rich information that is frequently missed by single-time-point snapshot measurements. For example, acute psychosocial stress induces distinct temporal trajectories of the metabolic hormone fibroblast growth factor-21(FGF-21) depending on individual's mitochondrial oxidative phosphorylation (OxPhos) capacity (Kurade et al., 2025). From this principle, we predict that the onset, peak and recovery kinetics of mitochondrial and metabolic responses to challenge will provide information about psychobiological adaptation that cannot be captured from single-time-point measurements.
6. **Individual differences matter**. The same genetic mitochondrial defects cause vastly different bioenergetic phenotypes in different people (Liu et al., 2026b). Likewise, even animals raised under highly standardized laboratory conditions can diverge in mitochondrial energy transformation capacity, anxiety-related behaviors, and resilience profiles (Hollis et al., 2015; Rosenberg et al., 2023; Larrieu et al., 2017; Cherix et al., 2020). These bioenergetic idiosyncrasies likely arise from differences in mitochondrial biogenesis, distribution, and regulation across tissues in organ-specific ways (Devine et al., 2025), which can emerge from stochastic processes as well as from subtle differences in developmental context and lifetime experience. In this way, mitochondria may contribute individuality (both inter- and intra-individual differences) by modulating how each organism processes stress and allocates energy over time (Liu et al., 2026b; Gebara et al., 2021; Ghosal et al., 2023). Similarly, all hairs on an individual's head share the same genome and broadly similar endocrine exposure, yet they grey at different moments across the lifespan—a process related to changes in mitochondrial phenotypes (Rosenberg et al., 2021). * *Group averages obscure important individual level psychobiological processes, calling for designs that integrate both within-individual dynamics and between-individual variability.* For example, brain-wide mitochondrial phenotypes can account for a substantial fraction of animal-to-animal differences in anxiety-related behavior (Rosenberg et al., 2023). From this principle, we predict that individual mitotypes measured before a common challenge will explain part of the variability in subsequent physiological and behavioral responses beyond analyses based on group effects.
7. **Biological and developmental specificity is key.** Experimentally, depending on the anatomical location, cell type, biofluid, developmental stage, and timing of measurement, the same measurement or biological signal may reflect different psychobiological processes, and therefore entail different interpretations. Measuring dermal electrical activity captured with electrodes illustrates this principle: on the head, it reflects brain activity; on the chest, it reflects cardiac activity. Temporally, cortisol exemplifies this principle: the cortisol awakening response (CAR) reflects something quite different from the mental stress-induced cortisol spike (Stalder et al., 2016). In relation to mitochondria, cell-free mitochondrial DNA (cf-mtDNA) in saliva and blood are not correlated, and they exhibit unique stress reactivity dynamics (peaking within <10 min after acute stress in saliva, but at 60 min in blood (Trumpff et al., 2025b). Similarly, the

energetic stress marker growth differentiation factor 15 (GDF15) is not correlated between saliva and blood, and each biofluid follows distinct stress-induced dynamic trajectories (e.g., saliva GDF15 peaks at 5 min whereas blood GDF15 peaks 10 min after mental stress (Huang et al., 2025)). Different brain (Mosharov et al., 2025; Chandra et al., 2019; Mallet et al., 2025) and immune cells also contain distinct mitochondrial phenotypes with divergent associations with psychosocial, clinical, and other markers (Rausser et al., 2021). The biological and developmental context in which measurements are made is integral to their interpretation. Mitochondrial biology unfolds within the temporal architecture of development and aging and thus assessments must be interpreted in relation to both where and when they are made and the life stage at which they are obtained. Critical life stages, such as early life, puberty/adolescence, the peripartum period, menopause and aging have distinct physiological states (Sisk et al., 2016; Barth et al., 2023), plasticity rules (Sydnor et al., 2026) and energy demands (Pontzer et al., 2021) that interact with mitochondria, potentially altering susceptibility to environmental challenges (Gorman-Sandler et al., 2023a; Gorman-Sandler et al., 2023b; Huang et al., 2025; Lambertini et al., 2015; Morató et al., 2022; Papilloud et al., 2018; Amorim et al., 2022). * ***Measurement specificity is key, and generalization across biological compartments or developmental stages requires empirical validation.*** For example, the distinct stress-response trajectories of cf-mtDNA in saliva, serum and plasma illustrate that mitochondrial-related measures obtained from different biological compartments should not be treated as interchangeable (Trumpff et al., 2025b). From this principle, we predict that relationships between mitochondrial phenotypes and psychological states will depend on the biological compartment, cell type, sampling time and developmental stage in which they are measured; generalization across these contexts should therefore be tested rather than assumed.

Together, these seven foundational principles (Box 1) will guide how the field forms hypotheses, designs tools to test them, and evaluates the limitations of its models. By formalizing and adhering to these principles, those who contribute to this emerging field can remain grounded in the energetic nature of processes at play, and progress mindful of their assumptions.

5. Energy budgeting across the body-brain system

One overarching principle that integrates several of the specific principles above is the concept of *energy budgeting*. Owing to biologically set evolutionary constraints, organisms operate within finite energy limits (Yang et al., 2021). These constraints influence the scale and scope of our physiology and behaviors (Behnke et al., 2026). This includes, for example, why acute activation of the stress response shunts blood flow and energy substrates from the gastrointestinal tract to the brain, heart, and skeletal muscle to facilitate the fight or flight response. At longer timescales, excessive physical activity can cause amenorrhea (the loss of menses) in young women and reductions in testosterone in men, illustrating how spending too much energy on one function requires budgetary cuts elsewhere (Pontzer, 2018). Similarly, the competition for energetic resources between the immune system and somatic growth in childhood helps explain why chronic immune challenges can stunt growth (Urlacher et al., 2019). In addition, the social landscape an organism inhabits profoundly shapes resource allocation.

Thus, chronic exposure to structural and social adversity, including discrimination and socioeconomic disadvantage, can become biologically embedded across multiple physiological and molecular systems (Hertzman and Boyce, 2010; Martin et al., 2022). Such persistent psychosocial demands also carry energetic costs and may therefore contribute to trade-offs in resource allocation and long-term maintenance (Behnke et al., 2026). Mitochondria may represent one component of this biological embedding, as adverse social and early-life experiences have been associated with changes in mitochondrial biology in peripheral tissues and the human brain (Gumpp et al., 2020; Duchowny et al., 2024; Trumpff et al., 2024). Importantly, socioeconomic marginalization itself arises from social, structural and material conditions and cannot be reduced to energy metabolism or mitochondrial function. Here, we consider biological embedding only as one set of downstream pathways through which such exposures may influence health. Thus, regardless of the mechanism, the organism must always allocate finite energetic resources among competing demands.

Across single cells, tissues and organs, and the mind, the amount and balance of available energy and energetic demand determine the capacity for adaptation (Behnke et al., 2026; Plaçais and Preat, 2013). Mitochondria sit at the center of this process by determining, and dynamically adjusting, energy transformation capacity. Mitochondrial biogenesis increases whereas mitophagy decreases their abundance (Pickles et al., 2018; Youle and Narendra, 2011), while dynamic transcriptional and molecular processes modulate their oxidative, biosynthetic, and signaling functions (Monzel et al., 2023). Together, mitochondrial abundance and phenotype determine how much energy a tissue can transform and its ability to meet functional demands. Mitochondria therefore set the limit for what a system can achieve at a given moment and generate signals when the limit to energy flow is approached (Picard and Murugan, 2025). At the cellular level, such limits are experienced for example when cells produce lactate (Vander

Box 1
Mitochondrial Psychobiology's Specific Principles.

Principle	Involvement of mitochondria
1. Energy forms are interchangeable	Act as the consilience point where food energy is transformed into other forms
2. Phase transitions drive behaviors	Regulate phase transitions by modulating energy availability and through signaling
3. Energy constraints shape functions	Decreases and increases in mitochondrial energy transformation capacity influence energy budgets
4. Energy patterning encodes information	Like morse-code devices, mitochondria pattern raw biochemical energy into meaningful signals
5. Energy is dynamic	Sustain the uninterrupted process of energy transformation, fueled by continuous fission, fusion, turnover matching changing energy demand/availability
6. Individual differences matter	Exist as unique mitotypes that influence individuality and behaviors at the whole organism level
7. Biological and developmental specificity is key	Express cell-, tissue- and biofluid-specific features with unique functional relations to the psychobiological state

Heiden et al., 2009) or enter growth arrest as energetic capacity is overwhelmed (Sturm et al., 2023; Han et al., 2023). At the experiential level, they may be reflected in effort-reward tradeoffs, fatigue, or motivational withdrawal when behavior is perceived to be too energy costly (Clairis et al., 2025; Barakat et al., 2025).

Therefore, psychological and behavioral outputs can be understood, in part, as downstream expressions of how organisms allocate limited energetic resources; i.e., expressions of energetic budgeting. From this perspective, stress responses may arise when the brain predicts that environmental demands will exceed available energetic resources, thereby recruiting physiological systems that mobilize energy and reprioritize biological processes (Picard et al., 2018). Conversely, vitality may reflect states in which energetic capacity is sufficient to meet anticipated demands, promoting engagement, exploration and action (Ryan and Frederick, 1997, Ryan and Deci, 2000; Ryan and Deci, 2008) when energetic reserves are sufficient, whereas constrained energetic capacity may be experienced as fatigue, effort aversion, or motivational withdrawal. Importantly, vitality and fatigue may not represent opposite ends of a single continuum but instead partially distinct experiential states that reflect different energetic conditions and regulatory processes (e.g., Loy et al., 2018, Lerdal and Kottorp, 2011).

The brain is a particularly stringent case of energy budget. Although it only accounts for ~2% of total body mass, the human brain consumes approximately 20% of resting metabolic energy (Padamsey and Rochefort, 2023; Bobba-Alves et al., 2022). Most of this cost supports ongoing neural function, including synaptic transmission and maintenance of resting membrane potentials (Jamadar et al., 2025; Tomasi et al., 2013), whereas explicit cognitive tasks require relatively little on top of baseline (Jamadar et al., 2025; Theriault et al., 2023). This large and continuous energy demand is essentially met by mitochondrial OxPhos (Astori et al., 2026). Brain regions involved in high-order cognition, such as the frontoparietal cortex, exhibit particularly high synaptic densities and are enriched in metabotropic neuromodulatory receptor systems (Castrillon et al., 2023), resulting in high metabolic rates (Castrillon et al., 2023; Yu et al., 2023) and matched by high content of mitochondria specialized for energy transformation (Mosharov et al., 2025). In addition to providing ATP, mitochondria contribute to a range of processes critical for brain function, including calcium buffering, redox regulation, neuroplasticity, cell activation, and neurotransmitter synthesis and degradation (Picard and Shirihai, 2022; Graves et al., 2020; Mattson et al., 2008), all of them essential to understand how mitochondrial states influence cognition and behavior.

The brain also generates an internal model of the organism's energetic state from interoceptive information, vagal and other afferent inputs and systemic signaling molecules, and uses this model to regulate energy expenditure and behavior (Seth and Friston, 2016; Kleckner et al., 2017). This internal model was proposed to be represented as affective states defined by valence and intensity. According to constructivist models, such affective states are then interpreted in context and shaped by prior learning and socio-cultural meaning into emotions, linking bodily energetic conditions to emotional experiences (Barrett, 2017). Whether this mobilization is experienced predominantly as a challenge or as a distress depends in part on whether available coping resources are appraised as sufficient or insufficient relative to those demands. When resources are considered sufficient, arousal can be motivating, enabling adaptive engagement and action. On the contrary, when demands are considered as higher than resources, stress responses may promote threat-related emotions and defensive actions (for example, a negative high arousal state emerging after a physical assault may be experienced as anger, guiding future behavior). Critically, the experience of affect and emotions are not necessarily veridical; under prolonged or extreme stress, the constructive mapping can become distorted (i.e., disrupting the brain's ability to accurately represent the organism's energetic state), potentially leading to affective signals that no longer reliably reflect underlying bioenergetic conditions (Barrett et al., 2016). We experience generative energy states.

Applied to chronic stress and mental illness, the concept of energy constraints yields new ideas. For example, the recently proposed Allostatic Triage model of Psychopathology (ATP Model) (Kelley et al., 2025) emphasizes that when stressors chronically increase metabolic demand, the brain reprioritizes activity away from metabolically expensive networks and processes that promote long-term optimization and flexible adaptation, such as executive control, and towards less expensive networks and processes that can ensure short-term survival, including salience, threat detection, and habitual responding (Kelley et al., 2025). In parallel, these shifts in brain activity may underlie a shift from goal-directed behavior and executive function to fear and habitual and compulsive behaviors, which in turn underlie many symptoms of mental disorders (Kelley et al., 2025). In general, stress triggers changes at all levels of functioning—e.g., heightened arousal and vigilance, increased heart rate and blood pressure, hormone synthesis, and immune activation, etc—that necessarily increase energy expenditure. The recently proposed Energetic Model of Allostatic Load (EMAL) in turn highlights how these costs come at the expense of growth, maintenance, and repair processes required for development, well-being, and optimal aging (Bobba-Alves et al., 2022). We present these models as emerging frameworks that generate testable hypotheses about energetic contributions to psychopathology and allostatic load.

Thus, prolonged stress may force energetic tradeoffs and thereby beget energy deficiency. In turn, signals induced by energetic challenge (including the energetic stress-related hormone GDF15 and others) may translate peripheral mitochondrial states into psychological states (i.e., states of mind), including mood, and more complex experiences such as fatigue, irritability, or depressive symptoms (Mac Giollabhui et al., 2026; Liu et al., 2026a). Conversely, restorative interventions or experiences that optimize mitochondrial energy transformation capacity or reduce energetic load, such as sleep, nutritional interventions, exercise, oxygen therapy, and contemplative practices, supportive social environments and reductions in chronic social adversity, may act by reversing stress-related energy re-allocation and improving mitochondrial efficiency (Hollis et al., 2018; Seo et al., 2019; Karrasch et al., 2023).

An energetic framework for stressful and restorative interventions that integrates brain and body (Theriault et al., 2025) overcomes dualistic models. Moreover, it provides a first-principles framework to examine how exposures and interventions can either impose an energetic tax on the organism or relieve it, thus shaping tradeoffs between survival-oriented functions and longer term maintenance and repair.

6. The mind-mitochondria interface

The proposed energy-centric, mitochondrial perspective of psychobiology emphasizes that brain function and the mind are shaped by, and responsive to, systemic energetic and immunometabolic signals. The mind-mitochondria interface operates bidirectionally, and this reciprocal interface is the core concept underlying Mitochondrial Psychobiology.

On the one hand [*Mitochondria → Mind*], whole-body factors such as immune activation, nutrient availability, hormonal fluctuations, and psychological stress influence mitochondrial biology within and outside the brain (Picard and McEwen, 2018; Pozo et al., 2023; Mujica-Parodi et al., 2020; Weger et al., 2020; Morato et al., 2022; Santos-Silva et al., 2025). Converging evidence indicates that mitochondrial states, particularly within brain cells and circuits, can influence or relate to variation in anxiety, motivation and decision-making (Chandra et al., 2017; Gebara et al., 2021; Ghosal et al., 2023; Mallet et al., 2025; Clairis et al., 2025; Barakat et al., 2025; Chioino et al., 2026; Chioino and Sandi, 2025). Thus, heterogeneity in mitochondrial phenotypes and their plasticity—such as how well they adjust the OxPhos machinery (Lopez-Fabuel et al., 2016; Vicente-Gutierrez et al., 2019; Morant-Ferrando et al., 2023; Bonvento and Bolaños, 2021; Bolaños and Magistretti, 2025), fission, fusion or turnover/mitophagy (Mallet et al.,

2025)—may underlie the differences in our psychological responses and stress resilience. From a psychobiological perspective, psychological processes such as emotion, motivation, and stress appraisal may therefore function as regulatory systems that influence how organisms allocate limited energetic resources across competing behavioral demands. A key hypothesis that derives from this foundation is that a person with greater mitochondrial flexibility (i.e., the capacity to mount, calibrate and address energetic transitions relevant to context) may be better able to efficiently adapt to changing demands (e.g., from anabolism to catabolism), and therefore be more resilient in the face of stress. Conversely, someone with less plastic or dysregulated mitochondria, perhaps as a result of stress at an early age or repeated insults, may become more vulnerable and be, therefore, less resilient to psychological stress in the future. Accordingly, resilience is unlikely to depend only on plasticity, but on appropriateness according to context, timing and regulation of mitochondrial plastic responses.

In turn [*Mind → Mitochondria*], the central nervous system regulates energy (re)allocation across the body via neuroendocrine, neuroimmune, and autonomic pathways (Picard et al., 2015; Myers and Olson, 2012; Russell and Lightman, 2019). We propose that mitochondria act as sensors and signal transducers (Picard and Shirihai, 2022) by translating brain-derived, systemic hormonal, immune, and behavioral signals into cellular states. Environmental information and states of mind can be conveyed to cells through endocrine, immune, and autonomic outputs, and through behavior dependent inputs such as sleep, feeding and activity, which shape mitochondrial fluctuations in ATP production, redox potential, calcium signaling, reactive oxygen signaling (Vicente-Gutierrez et al., 2019), and the production of metabolites, many of which epigenetically regulate the expression of certain genes controlling short- and long-term cellular adaptation and function and, consequently, behaviors (Picard and Shirihai, 2022).

Importantly, these bidirectional links raise a central question for Mitochondrial Psychobiology: *When associations are observed between mental processes such as emotions, and mitochondrial measures, what is the direction and mechanisms of influence, or are both jointly driven by shared upstream factors?* For example, psychological stressors, or inversely, positive experiences of safety, reward, or success, could recalibrate and rewire mitochondrial phenotypes, potentially shaping future psychological states and influencing how individuals perceive themselves and the world. Consistent with this possibility, individuals reporting greater purpose in life, social connectedness, and well-being exhibited higher mitochondrial complex I protein abundance in the dorsolateral prefrontal cortex (Trumpff et al., 2024). Is this association due to positive psychological states remodeling brain mitochondria, or to brain mitochondrial biology influencing how individuals perceive and respond to life, or most likely to reciprocal dynamics unfolding over time? Distinguishing these possibilities will require experimental studies combining longitudinal cohorts, along with within-individual measurements with mechanistic perturbations in model systems.

Mitochondrial Psychobiology aims to formalize and make experimentally testable this mind-mitochondria interface, but doing so requires the right tools.

7. Experimental and analytical approaches

To bring Mitochondrial Psychobiology from a concept to a field where hypotheses about the mind-mitochondria connection can be empirically tested rests on a robust and diverse scientific toolbox. The capacity to test these hypotheses requires integrating multi-level technologies spanning the basic sciences of molecular, cellular, metabolism,

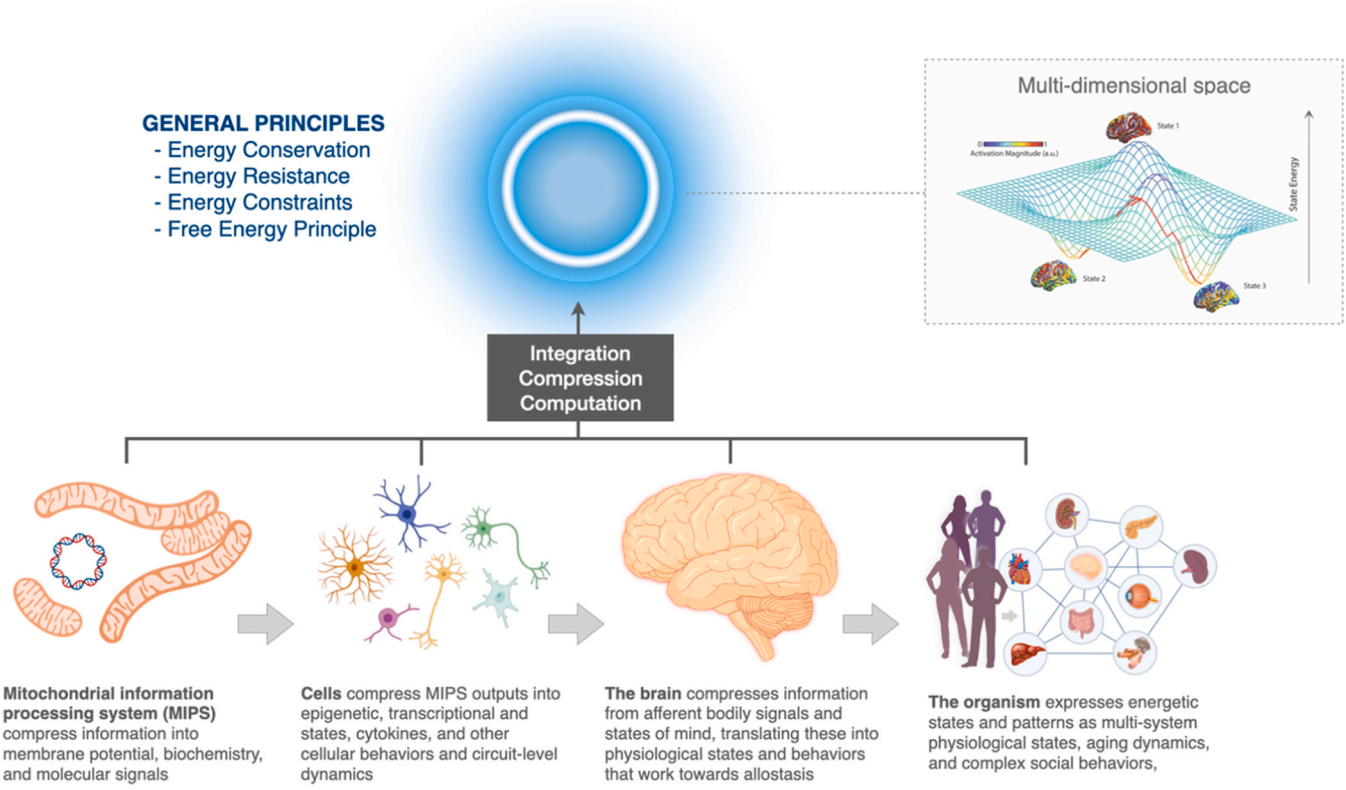


Fig. 4. Hierarchy of energy and information processing. Energy is patterned and processed across scales from subcellular and mitochondrial systems, to cells, organs, and whole-body states shared between individuals that can also be co-regulated in social contexts (bottom, from left to right). These multi-level states are governed by general principles that transcend and apply across levels of complexity, and are best conceptualized as state spaces with more (un)stable zones. Transitions between states are believed to drive the adoption of enduring cellular and anatomical characteristics (e.g., rapid or slow growth, final body/organ size) during development, behavioral dispositions (e.g., submissive or dominant) in fully developed organisms, and labile psychological states (e.g., anxiety, effort perception) that are dynamically shaped by environmental context.

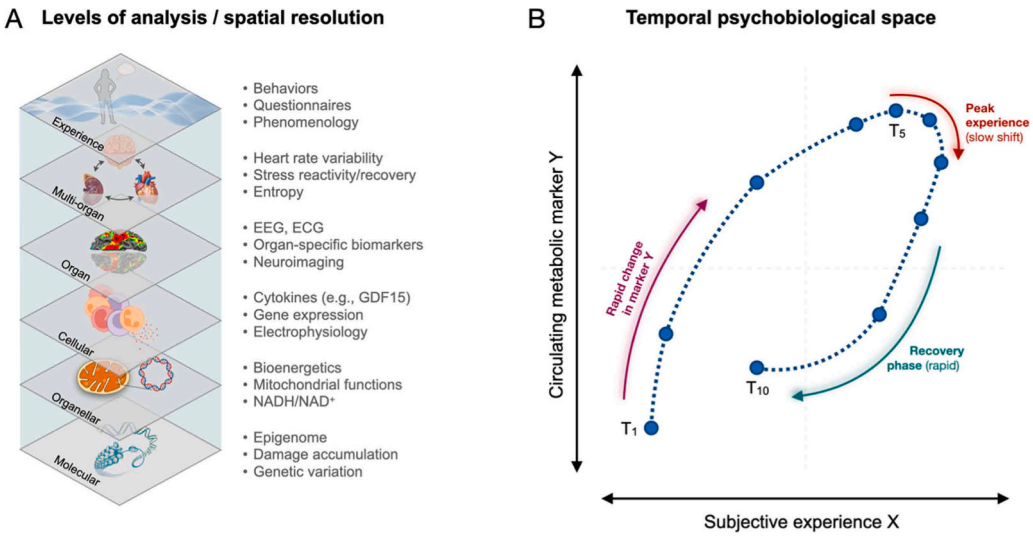


Fig. 5. Multi-level and time-resolved approaches to Mitochondrial Psychobiology. (**A**) Six main levels of analysis for Mitochondrial Psychobiology, including example outcome measures highlighted. (**B**) Example psychobiological trajectory of response combining changes in subjective experience (x-axis) and a quantitative blood-based parameter (y-axis). The hypothetical trajectory shows rapid upregulation of the biomarker prior to the change in subjective experience (purple $T_{1–3}$), slow phase where both systems stabilize around peak experience (red, $T_{4–7}$), followed by a trajectory to incomplete recovery (green, $T_{8–10}$).

and systems physiology and neuroscience with computational modeling and behavioral and subjective experiential readouts sampled over time (Fig. 4). Together, these tools will make it possible to move from conceptual models of energy and psychological function to a measurable, mechanistic science of vitality, emotion, and behavior.

8. Multi-level mitochondrial measurements

We envision that the Mitochondrial Psychobiology toolkit will be multi-tiered, integrating measurements across molecular, organellar, cellular, and peripheral levels alongside functional neural assessments and brain-based approaches (Fig. 5**A**). In the periphery, circulating indicators can be measured in mammalian models and humans with relative ease. Cytokines, cf-mtDNA, metabolites, and hormones, as well as mitochondrial stress-associated signaling proteins (e.g., GDF15 (Huang et al., 2024)) can serve as outputs that reflect mitochondrial function and energy conversion.

At the cellular level, technologies such as high-resolution respirometry and extracellular flux assays (e.g., Seahorse and Oroboros assays), imaging of mitochondrial membrane potential, redox and calcium-sensitive reporters, mitotyping to assess specialization and plasticity of mitochondria (Monzel et al., 2025), and single-cell oxygen consumption measurements enable direct assessment of mitochondrial recalibrations across cell-level mitochondrial parameters, molecular features, mitochondrial functions, and behaviors. Recalibrations can occur in response to either intrinsic or environmental inputs.

Longitudinal sampling across time and across tissues in the organism as a whole will allow researchers to track mitochondrial responses to life changes, including stress and periods of recovery (Fig. 5**B**). While sensitive measurements at the cellular and peripheral level are key, understanding how the brain integrates and responds to this peripheral information will be critical for moving the field forward.

8.1. *Brain-based methods*

Brain-based methods, particularly neuroimaging, can indirectly capture energetic processes *in vivo* (Tomasi et al., 2013, Theriault et al., 2023, Mosharov et al., 2025). Magnetic resonance Spectroscopy (MRS), including ^{1}H and ^{31}P-MRS, calibrated fMRI-based estimates of CMRO, and positron emission tomography (PET) can quantify cerebral metabolism, oxygen utilization, and changes in energy use in response to stimuli known to evoke behavioral responses (e.g., effort-based decision paradigms (Wiehler et al., 2022)). PET approaches can include glucose metabolism tracers (e.g., FDG-PET) and emerging probes targeting mitochondrial function (e.g., complex I ligands) in animals (Tsukada, 2014) and humans (Terada et al., 2020); they are already providing key information regarding mitochondrial engagement during task performance in humans (Shatalina et al., 2025) as well as regional complex I density in neurodegenerative disorders such as ALS (de Natale et al., 2025). MRS-based neurometabolic measures linked to energy metabolism and mitochondrial-related processes in defined brain regions could eventually provide non-invasive markers of interindividual differences in brain bioenergetic states relevant to different behavioral and cognitive processes (Strasser et al., 2019, 2020; Zalachoras et al., 2022) and within-person changes in mitochondrial biology over time (Thiebaut de Schotten and Forkel, 2022). Functional measurements such as fMRI-BOLD provide an indirect readout of brain activity, but a mixed picture of blood flow, cellular energy metabolism, and neurovascular coupling (Theriault et al., 2023; Epp et al., 2025), warranting caution in the interpretation of these signals. EEG, in turn, provides a fairly direct, medium-resolution, view of the electrical activity of the brain (one energy modality among several), but has considerably lower spatial resolution, especially for subcortical regions. Together, these multi-level (molecular, cellular, blood-based and neural) measurements can begin to reveal how individual mitochondrial phenotypes relate to broader brain changes.

8.2. *Psychological methods*

Psychological methods provide essential measurements of the experiential and behavioral manifestations of bioenergetic processes. While molecular and physiological measurements quantify energetic transformations within cells and tissues, psychological assessments capture how these energetic states are experienced and translated into motivation, emotion, and behavior. Integrating biological and psychological measurements is therefore essential for understanding how mitochondrial function relates to the lived experiences of vitality, fatigue, stress and behavioral engagement.

Subjective self-report measures provide standardized tools to quantify experiential correlates of energetic states. For example, subjective vitality, defined as the felt sense of aliveness and available energy for action, can be assessed using instruments such as the Subjective Vitality

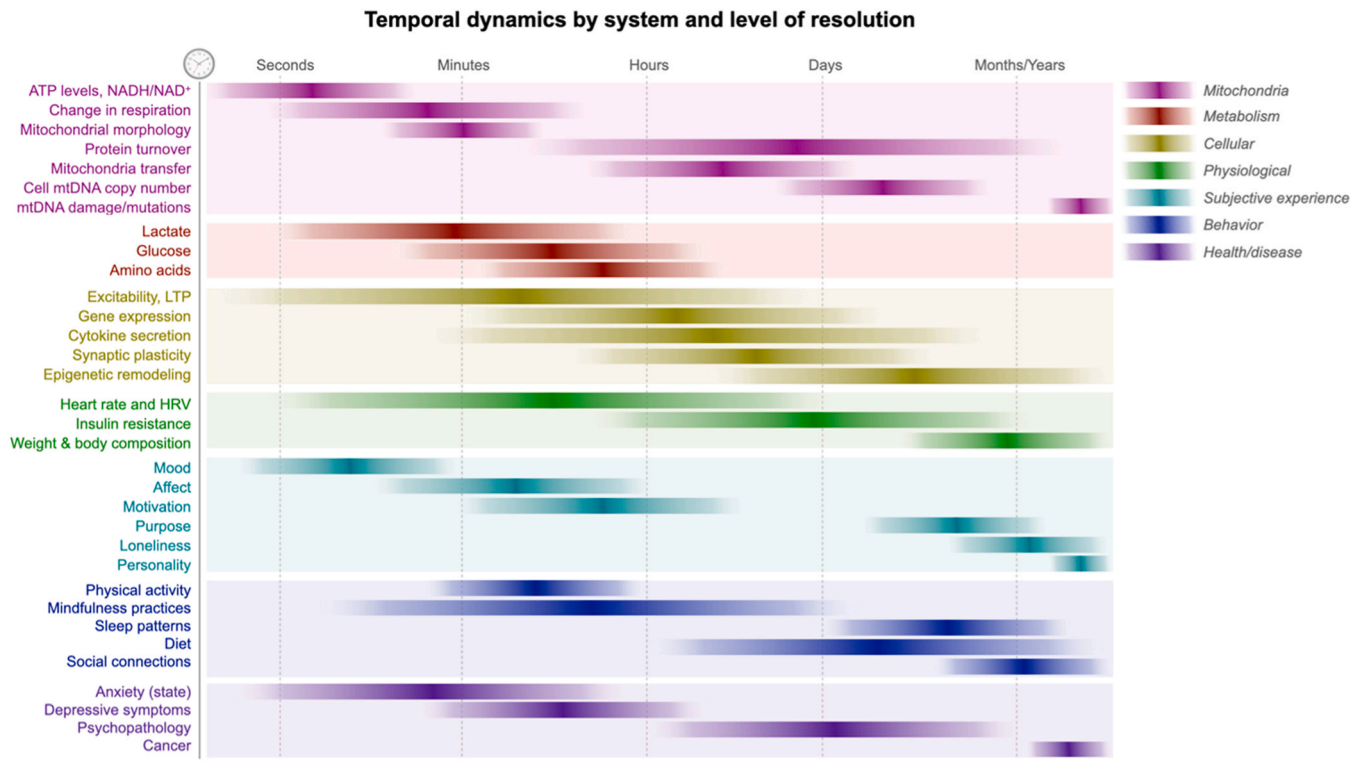


Fig. 6. Approximate, relative time frames for psychobiological processes and outcome variables. Shown are selected processes, systems, and experiences across seven domains of mitochondrial psychobiology.

Scale (Ryan and Frederick, 1997). Emotional tone and mood variation can be captured using measures such as the Positive and Negative Affect Schedule (PANAS; Watson et al., 1988) and the Perceived Stress Scale (Cohen et al., 1983), which index affective and cognitive responses to environmental demands. Measures of interoception, such as the Multidimensional Assessment of Interoceptive Awareness (MAIA; Mehling et al., 2018), assess individuals' awareness of internal bodily signals, including sensations associated with energetic states such as fatigue, arousal, and bodily readiness for action.

Behavioral paradigms such as effort-based decision-making tasks, cognitive persistence challenges, and exploration or avoidance behaviors provide experimentally tractable measures of how organisms allocate energy toward action under varying costs and rewards (Strasser et al., 2020; Rodrigues et al., 2020, 2021; Zalachoras et al., 2022). This is because effort essentially entails, and thus reflects, energy use or transformation. Thus, experimental paradigms such as effort-based decision-making tasks, cognitive control challenges, and exploration or avoidance behaviors allow researchers to examine how individuals weigh energetic costs against anticipated rewards when selecting actions. These paradigms provide objective indicators of motivational processes and effort/energy allocation that can be directly linked to underlying bioenergetic states.

Because energetic processes unfold dynamically over time, within-person measurements are particularly valuable for capturing fluctuations in energetic experience and behavior. Experience sampling and ecological momentary assessment (EMA) (Shiffman et al., 2008; Kamath et al., 2022) approaches enable repeated measurement of affect, vitality, stress, and behavior in naturalistic contexts, capturing the dynamic fluctuations in energetic states across time and context. Together, subjective reports, behavioral paradigms, and repeated measurements provide essential tools for linking mitochondrial biology and systemic energy dynamics to the psychological experiences and behaviors that shape everyday functioning.

An additional consideration is that perceived energy and fatigue are not simply opposite ends of a single continuum (Loy et al., 2018; Deng et al., 2015). Research in health psychology and behavioral medicine suggests that vitality and fatigue often arise from partially distinct biological and psychological processes. For example, approach-related energetic states associated with motivation and vigor may involve neural reward and dopaminergic pathways (van der Kooij et al., 2018; Ghosal et al., 2019; Strasser et al., 2020; Salamone and Correa, 2024), whereas fatigue is frequently linked to inflammatory signaling, metabolic stress, and illness-related processes (Bekhbat et al., 2022; Pessiglione and Wiehler, 2025). Distinguishing these experiential states may therefore help clarify how different mitochondrial signals and systemic energetic conditions manifest psychologically.

Only by bridging biomedical technologies with those of the psychology and social sciences can Mitochondrial Psychobiology empirically test how fluctuations in mitochondria or metabolic function correspond to how people feel, think, behave and experience their existence (Loy et al., 2018; Deng et al., 2015).

8.3. *Temporal approaches*

To fully characterize the mind-mitochondria interface, we must distinguish between an individual's stable bioenergetic trait (i.e., the dispositional set point that determines baseline vitality) and their dynamic reactivity to environmental demands. Cross-sectional assessments are vital for identifying this inherent capacity—explaining, for instance, why certain individuals consistently possess more energy than others. However, the true nature of energetic regulation is revealed through its flow over time. Consistent with this principle, we advocate for repeated measurements to track functional trajectories (e.g., onset, peak, recovery) rather than relying on isolated snapshots. Given the dynamic nature of energetic processes, we must also aim to measure relevant processes and outcomes across biological and psychological domains with adequate temporal resolution (Fig. 6).

Importantly, these processes do not necessarily unfold on the same timescale; different signals may differ substantially in their onset, peak, duration and recovery. They may also be coupled through temporal lags,

rather than rigid synchronous changes. Accordingly, a central challenge for Mitochondrial Psychobiology is to align measurements across levels of analysis and to match sampling schemes to the kinetics of the processes under study. Repeated measurements allow us to capture more of the potentially relevant signals, and to subsequently determine what is relevant, only once a trajectory has been described with sufficient resolution. In particular, using experimental challenges to elicit changes in either the mind or specific biological parameters will allow researchers to understand how mitochondria respond, adapt, resist, or recalibrate over different timescales.

For example, the MiSBIE study was specifically designed to examine the influence of mitochondrial biology on psychobiological processes in healthy adults and individuals with rare genetic defects affecting mitochondrial OxPhos capacity (Kelly et al., 2024). This enables testing whether mitochondrial measures predict baseline and reactive psychobiological states. Clinical, pre-clinical, and cellular studies where specific mitochondrial features, activities, functions, or behaviors (Monzel et al., 2023) are perturbed will enable researchers to dissect the mind-mitochondria connection with sufficient specificity. Time-resolved designs from which we can explore directionality and time-relevant relationships between mitochondrial changes and psychological and behavioral outcomes will be particularly valuable.

However, while causal inference is essential, the mind-mitochondria interface may not be fully captured just using simple linear cause-effect models. Clearly, mechanistic studies are crucial for establishing how mitochondrial and metabolic processes relate to psychological and behavioral outcomes (Critchley and Garfinkel, 2017), but subjective experiences should not be treated solely as passive readouts of underlying biology. We must keep in mind the possibility that subjective experiences arise as emergent phenomena that co-occur with, reflect, and potentially feed back onto biological processes across time (Barrett and Simmons, 2015; Seth and Friston, 2016; Feldman et al., 2024; Picard and Murugan, 2025).

Finally, these considerations around time and mitochondria also apply to the aging process. Aging is the progressive loss of physiological integrity, leading to impaired function and increased vulnerability to disease and death (López-Otín et al., 2023). Aging necessarily unfolds over time and is directly influenced by cellular energetics in general, and mitochondria in particular. In cultured human cells, perturbing mitochondrial energy transformation accelerated several biological aging indicators including telomere shortening, epigenetic againg, and secreted markers of cellular aging (Sturm et al., 2023). Like aging, the pace of embryonic development (which is faster in mice than humans, for example) is set by the rate of mitochondrial energy transformation (Diaz-Cuadros et al., 2023; Iwata et al., 2023). Therefore, the mechanism linking chronic stress exposure and accelerated aging (Lyons et al., 2023; 2025) could involve stress-driven hypermetabolism—the excess energy demand driven by the fact that all stress responses entail additional energy costs from a limited organismal budget (Bobba-Alves et al., 2022).

In brain-bearing animals, the link between energy demands and aging phenotypes is likely further complexified as cellular signals of energetic stress (i.e., energy resistance) affect function and behaviors by signaling onto the brain. Signals of cellular energetic stress include cytokines, such as GDF15 that signal mitoception (Liu et al., 2026a). GDF15, which increases with both mental stress (Huang et al., 2025) and aging (Conte et al., 2022), mobilizes complex energy conserving and energy mobilizing responses affecting the autonomic nervous system, endocrine, metabolic, and other systems (Liu et al., 2026a). When the brain perceives GDF15 and other cytokines, it may deploy a brain-body energy conservation program that forces systemic energy tradeoffs that accelerate the loss of physiological integrity, in service of longevity (Shaulson et al., 2024). The drive to conserve energy may become particularly salient given the age-related decline in oxygen consumption, or in the total energy budget, in humans after the sixth decade on average (Pontzer et al., 2021). Thus, mitochondrial psychobiology processes may impact function across wide ranging time scales from seconds to the entire lifespan.

8.4. Computational and modeling approaches

To understand Mitochondrial Psychobiology, one must understand the network underlying it—a network composed of molecular and cellular "hardware", tissues and organ systems, connected and responding to the flow of energy from the environment across temporal scales. How this biophysical network intersects with human experience and behavior is complex. The more complex a system, the more possible and diverse points of failure which can each then drive distinct psychopathological phenotypes (Kempes et al., 2019; Picard and Kempes, 2026). Therefore, powerful computational methods fed rich datasets will be essential for building testable models in this field. Dynamic systems models, and machine-learning pipelines that can integrate multimodal inputs—imaging, bioenergetics and subjective measures—to identify patterns of energy constraint and resilience will be essential.

One potential avenue is to computationally model bioenergetic systems. For example, large-scale neuroimaging analyses combined with metabolic biomarkers suggest that dysregulated glucose homeostasis drives nonlinear network aging dynamics (Antal et al., 2025). By simulating virtual mitochondria and *in silico* neural circuits, the field can begin generating testable hypotheses about how systemic energy flow shapes cognition and emotion. The technologies already exist to integrate experimental, computational and subjective approaches to build the infrastructure for Mitochondrial Psychobiology. The main challenges that remain involve integrating objective observation with subjective experience and training future scientists to work across these traditionally separate domains.

8.5. Multi-species and translational studies

Multispecies approaches are essential for Mitochondrial Psychobiology because they are key to allowing the establishment of robust conclusions across different levels of analyses. For example, clinical or phenomenological observations in humans can be followed up at the mechanistic level in appropriate animal models through invasive mechanistic interventions that can be coupled to *in vivo* invasive or *ex vivo* detailed analyses (Zalachoras et al., 2022). Specifically, for this emerging field, the main objective is to establish cross-species bridges by identifying i) representative and informative mitochondrial features; ii) homologous circuits and physiological systems; and iii) well-matched behavioral and psychological readouts. Such an approach benefits by iterative translation and back-translation, in which human correlational data inform mechanistic interrogation in animals, while in turn animal mechanistic observations translate into specific measurements or even interventions in humans.

One opportunity to examine the lived experience of mitochondrial defects are primary mitochondrial diseases (MitoD) (Kelly et al., 2024). This heterogeneous group of clinical disorders is caused by pathogenic variants in mitochondrial DNA (mtDNA) or in nuclearly encoded mitochondrial genes, both of which frequently impair oxidative phosphorylation (Gorman et al., 2016). Interestingly, MitoD do not necessarily cause a decrease in overall metabolic rate, they can instead be accompanied by systemic hypermetabolism and energetically costly compensatory responses (Sturm et al., 2023; Sercel et al., 2024). Affected individuals typically experience severe fatigue and suffer from multiple comorbid conditions, including cognitive, mood and other psychiatric manifestations (Anglin et al., 2012), providing causal evidence that mitochondria contribute to shaping brain function, cognition and behaviour in humans, while their multisystem nature cautions against attributing individual symptoms to a single mitochondrial mechanism. Moreover, most individuals with MitoD report that the severity of some, albeit not all symptoms, is linked to their states of mind (Kelly et al.,

2025), providing a basis for exploring the bidirectional mind-mitochondria connection in laboratory and observational research.

One example of this work in people with MitoD is the MiSBIE study (Kelly et al., 2024), which developed as the human translation of pre-clinical studies in mouse models with distinct mitochondrial defects (Picard et al., 2015). In its multi-day design, MiSBIE[1] leveraged baseline, stress reactivity, and home-base data collection protocols to characterize how mitochondrial OxPhos capacity relates to stable psychobiological traits, acute responses to challenges, and everyday functioning in real life contexts. More broadly, translational approaches can combine i) behavioral and self-report measures captured either through lab experiments or actual life measurements; ii) repeated and well-timed sampling and measurements of circulating and cellular mitochondrial markers; and iii) experimental challenges.

8.6. *Relating pre- and post-mortem human tissues*

Studies in post-mortem tissues allow us to examine questions about Mitochondrial Psychobiology directly in otherwise inaccessible tissues, such as the brain. A key strength of this approach is the collection of samples in the context of prior psychological, and ideally also environmental, measurements, that allow connections between premortem phenotyping and cellular, molecular and biochemical measures in specific brain regions and, ideally, cell types. Self-reported outcomes, including positive (e.g., sense of purpose, connections, well-being) and negative (loneliness, depressive symptoms, perceived stress) psychosocial factors can be collected using sensitive instruments (see above), and related to molecular features (e.g., respiratory complex subunits abundance and activities, mtDNA, redox measurements) and broader cellular parameters in post-mortem tissue.

Potential limitations with this design include confounders due to the cause of death, comorbidities, medication, and also the post-mortem to tissue collection interval, as well as the differential instability of molecular markers assessed. In addition, changes in cellular composition, including neuronal loss, gliosis, immune infiltration, or shifts in cell subtype proportions, can substantially influence apparent mitochondrial measures in bulk tissue. Accordingly, cell-type-specific profiling approaches are critical for accurate interpretation (Fecher et al., 2019; Ulgen et al., 2025). Although proteins and some enzyme activities can exhibit substantial stability (Stan et al., 2006; White et al., 2018), RNA levels may change rapidly during the agonal phase and degrade post-mortem (Tomita et al., 2004; Birdsill et al., 2011), warranting caution in interpreting data from such studies. Accordingly, experimental designs should follow strictly controlled conditions taking into account all relevant tissue quality variables, and aim to implement rapid autopsy protocols when possible, while also importantly include several complementary and convergent mitochondrial readouts, instead of relying on single measurements. However, until scalable, non-invasive approaches enable probing mitochondrial biology in the living human body with sufficient cellular and regional resolution, post-mortem studies remain unmatched for testing mind-mitochondria connections and linking *in vivo* mental states to mitochondrial biology.

9. Unresolved questions and knowledge gaps

Despite these expanding methodological capabilities, several conceptual and technical gaps still limit our ability to fully characterize mind-mitochondria interactions.

The first gap concerns the *spatial and temporal resolution* required to profile meaningful bioenergetic signals, states, and recalibrations. How quickly do mitochondria within a given cell type recalibrate? To examine the relevance of brain mitochondria to human experiences, do we need single-cell resolution, or are brain region bulk measures including a mixture of different cell types (e.g., tissue homogenates) sufficient? When measuring a blood-based biomarker in immune cells, do we need to isolate specific subsets of cells? Evidence indicates that immune, brain, muscle, and other organ-specific cell types have unique mitochondrial phenotypes (Monzel et al., 2023; Mosharov et al., 2025; Pekkurnaz and Wang, 2022; Willingham et al., 2021) and that mitochondrial recalibration can occur on the scale of days to weeks (Cai et al., 2015; Rausser et al., 2021; Amar et al., 2024; Monzel et al., 2025). Differences in cell type proportions can also drive apparent differences independent of any actual variation in mitochondrial biology (Rausser et al., 2021; Picard, 2021). Furthermore, the distribution of mitotypes within each cell represents another layer of complexity (Monzel et al., 2025). Thus, both spatial and temporal resolution are relevant parameters to mitochondrial studies.

The second gap relates to *the energetic cost of biological and psychological functions*. Nothing in biology is free. What, then, is the absolute cost (or the proportion of a cell's resting energy budget) required to activate a gene during stress, recycle half a cell's mitochondrial population, or hyperactivate a particular brain circuit, or a neuroendocrine axis? In the face of stressors, what is the cost of sustaining an anxious or depressed state versus an active coping state? Alternatively, could depressive low activity states provide an acute benefit to the energy budget?

All aspects of the stress response involve energetic costs (Bobba-Alves et al., 2022). "Stress" hormones, examined based on their physiological effects, are in fact "energy mobilizing" hormones harnessed by the brain to fuel adaptation. Human cells exposed to glucocorticoid signaling consume ~60% more energy than non-stressed cells (Bobba-Alves et al., 2023) and animal models exhibit elevated basal metabolic rates (heart rate, breathing rate, hypermetabolism-promoting hormones) when exposed to acute psychogenic stressors (Cordero et al., 1998; Huzard et al., 2019). Yet, the energetic cost of most psychobiological states has not been quantified, and we still lack the conceptual and empirical resolution to determine whether distinct psychological experiences and dimensions (e.g., chronic loneliness, acute shame, vitality, fatigue, etc.) impose different bioenergetic demands or map onto distinct mitochondrial phenotypes.

The third gap relates to *what can be measured and what those measurements mean*. In human and animal studies, direct mitochondrial measurements are often limited or inaccessible, requiring reliance on proxy measures, or measurements in convenient samples such as circulating immune cells. What does it mean, conceptually and mechanistically, to measure immune cell *respiration* versus OxPhos *enzyme activities*, circulating mitochondrial *proteins*, mtDNA abundance, or brain metabolic indices via neuroimaging? When do these measures reflect shared versus compartment-specific mitochondrial processes that do not generalize over tissues? Advancing knowledge as to whether any peripheral measurements, acquired with minimal disturbance to the experimental subject, do or do not reflect relevant aspects of mitochondrial biology in less accessible tissues (notably the brain) in living humans, and, where relevant, in animal models, remains a key challenge.

The fourth gap relates to *how we identify meaningful patterns and signatures*. Single modalities or channels are easily quantified over time, yet mitochondrial populations and mitochondria-mind interactions are inherently multimodal. Mitochondria have over a hundred categorized activities, functions and behaviors (Monzel et al., 2023). Multiple dimensions of mitochondrial biology are differentially co-regulated, interrelated or not, across contexts. Biochemical processes within mitochondria may also lead to field effects, including local electromagnetic fields that may tie into cellular sensing and information processing (Lane and Rodriguez, 2025). In the same way that we can capture distributed patterns of electrical brain activity across hundreds of sites on the scalp to decode brain states, how can we capture coherent,

[1] Open resources and a summary of all findings from the MiSBIE study is available at www.picardlab.org/MiSBIE

biologically informative energy patterns across molecular, physiological, neural, and experiential domains? What combinations of variables best represent energetic states or energy patterns relevant to human behavior and subjective experiences?

The fifth gap is about *how to construct informative models*. Integrating relevant, time-resolved multi-modal data across molecular, organ-system, and psychological levels requires computational models capable of representing energy flow and constraint across scales and time. Which modeling technologies are best to capture these? How do we validate models against measurable biological outcomes and subjective experience? Progress in this front is expected to require iterative model building with synergistic coupling from longitudinal and perturbation studies.

10. Future directions and opportunities

In the next decade, Mitochondrial Psychobiology can evolve into a coherent scientific discipline. While challenges include integrating principles from molecular biology, neuroscience, psychology, physics and computational biology to understand how mitochondrial and energetic processes relate to psychological function and experience, these challenges also create an exciting opportunity. They invite different fields to learn from each other, coordinate, and to build a shared scientific vision anchored in standardized terminology, principles and testable frameworks. Although this article provides examples of such a framework, the field will evolve organically, shaped by diverse perspectives beyond those of the authors, and not constrained by rigid rules.

11. Nomenclatures

A key objective in building the field will be to develop and agree upon a common nomenclature that bridges the many disciplines underlying Mitochondrial Psychobiology. Terms will span classic disciplinary boundaries, so their underlying concepts must be defined in ways that are understandable and operationalizable for biochemists, psychologists and computational scientists alike. Words such as “energy” “energy flow”, “energy transformation” “vitality”, “energetic efficiency”, and “energy budgeting” must be defined carefully. A useful goal for the field would be to develop a structured cross-level framework that maps such terms onto levels of analysis (whether at the cellular, tissue or organism levels), timescales, and measurement domain/s to which they refer (biological, behavioral, subjective) in order to enable more precise communication and comparison across studies.

11.1. Training scientists for the future

Building the field, defining the nomenclature, and developing interdisciplinary hypotheses cannot happen in isolation. An impactful next step requires bringing colleagues together through cross-disciplinary conferences, workshops and training programs aimed at broadening the perspectives. This involves training future scientists to be fluent in biological, physical, and psychological concepts—focusing on their intersection principles. We need opportunities that enable scientists across career stages to share emerging ideas and hypotheses around Mitochondrial Psychobiology; and workshops and graduate curricula to train future scientists to move fluidly between molecular assays, computational models, behavioral paradigms, and rigorous assessments of subjective states. In these efforts, we suspect that the concepts energy flow and energy resistance will be valuable substrate upon which to build common language bridging concepts from physics to the ecological validity required for psychological studies.

11.2. Future opportunities and goals

Looking ahead, the promise of Mitochondrial Psychobiology lies in its potential to help inform (and hopefully revolutionize!) how health is defined, measured, optimized, and restored throughout the lifecourse (Halfon et al., 2014). For example, a predictive, energy-based model of health (see for example (Behnke et al., 2026)) could simulate how biological systems respond to stress, estimate energetic trade-offs, and model the consequences of limited energy supply, excessive demand, or energy re-routing. Such a framework might allow us to anticipate what happens next after a stressor or environmental insult, allowing early identification of markers of energetic dysregulation before symptoms emerge.

This calls for a shift from reactive to preventive and mechanism-guided care, and from a disease-centric to a health-centric framework (Picard, 2022). This shift could be particularly transformative for medicine, particularly mental health. In addition to individualized care, this framework could also help explain, prevent and ameliorate health disparities arising from chronic exposure to social and environmental adversity, including the social determinants of health (Hertzman and Boyce, 2010; Jones et al., 2019). Specifically, the impact of Mitochondrial Psychobiology on clarifying how such exposure becomes biologically embedded as enduring bioenergetic characteristics can help identify mechanisms through which structural disadvantage shapes vulnerability to disease across life. In the clinic, energetic diagnostics could guide personalized interventions designed to restore vitality. Relaxation, for instance, may feel good because it rebalances energy flow (Karrasch et al., 2023); Mitochondrial Psychobiology could help explain how restoration and recovery engage biochemical and psychological processes that reverse maladaptive “energy resistance” and reduce pain.

Beyond the mitigation of disease, this field also provides a framework to redefine health not as a static absence of pathology, but as adaptive energetic flexibility (Cohen et al., 2025). In this view, health is the capacity to dynamically allocate energy toward growth, repair, and meaningful experience even under challenge. Such a model may also help determine whether high-order psychological states, such as eudaimonic well-being and a sense of purpose, become biologically embedded in ways that support mitochondrial architecture and functioning, and whether different mitotypes predict differential responsiveness to pharmacological, behavioral or lifestyle interventions.

The MiSBIE study was the first interdisciplinary step toward this vision (Kelly et al., 2024). By mapping the mind-mitochondria interface using deeply-phenotyped, multimodal datasets, similar studies will establish a foundational resource for the field. Coordinated efforts like these will lay the groundwork for a truly interdisciplinary, holistic and personalized science of life.

12. Conclusion

The emerging field of Mitochondrial Psychobiology is analogous to an evolving tree of knowledge building on a rich scientific history and collective body of work (see Fig. 2). Historical roots anchor the trunk, which gives rise and feeds the rich disciplinary foliage where most of our scientific activities operate. The trunk represents the most central principle that connects all branches and leaves: *energy*. Energy transformation through mitochondria supports all processes within cells, organs, organisms, and also between organisms, and also regulates and facilitates interactions between organisms and their environments (Picard and Kempes, 2026). Thus, the rich science of mitochondria provides a foundation for addressing the stimulating challenge of linking mitochondrial biology to psychological functions and experience. More broadly, it offers a framework for understanding human health as emerging from dynamic interactions among biological, social, and environmental processes.

To move toward this goal, we have outlined foundational principles and key concepts, together with both existing and emerging approaches, techniques, and methods. For this and the next generation of scientists, these represent a broad and empowering scientific toolkit. Each discipline holds only a piece, albeit possibly a critical one, of the puzzle.

Moving with humility, our scientific progress will depend on successful integration across levels, from molecules and cells to circuits, behavior, and subjective experiences. Our hope is that the emerging concepts in Mitochondrial Psychobiology, together with the tools it assembles, contribute to an increasingly accurate and actionable model of human health across the life course. This framework offers a first-principles approach to understand vulnerability and resilience, guide mechanism-informed interventions, and help sustain health by supporting what keeps us healthy in the first place.

Box|Definitions of terms

Energy: the potential for change. It takes many forms, including chemical, electrical, thermal, magnetic, and others. In this framework, physical energy and its transformations are distinguished from related metabolic substrates or intermediates (e.g., glucose, lactate) and from subjective experiences such as vitality or fatigue.

Mitochondria: small intracellular organelles, present in 100's to a few thousands in the cytoplasm of every nucleated cell in the body. Mitochondria contain their own circular genome and coexist as a social collective (Picard and Sandi, 2021) operating as the Mitochondrial Information Processing System (MIPS) that senses, integrates, and signals information within and between cells (Picard and Shirihai, 2022).

Cytokines: small messengers that mediate communication between cells, particularly within the immune system, but also across different systems such as metabolic, endocrine and neural, with functions related to inflammation, cellular activation, tissue repair and, more broadly, adaptation to challenges.

Energy resistance (éR): a recently proposed concept describing the intrinsic resistance to the flow of energy (electrons) enabling biological systems to convert energy potential (food) into useful work. In this framework, éR is a fundamental property of living matter that governs energy transformation across biological constraints (Picard and Murugan, 2025).

Energy constraint: the limitation imposed by finite energetic resources on the range, magnitude, timing or duration of biological and psychological processes, pressing organisms to prioritize among competing demands (Pontzer, 2018, Pontzer and McGrosky, 2022).

Phase transition: a shift from one functional state to another, which can occur abruptly once critical thresholds are achieved or more gradually as key parameters change (Scheffer et al., 2009).

Mitotype: the specific mitochondrial phenotype across parameters that can represent from a single cell, to a tissue or an organism.

Bioenergetic reserve: the capacity of a cell, tissue or organism to generate additional energy above basal requirements when there are increases in energetic demands, reflecting the fraction of total bioenergetic capacity that remains available to support additional responses to stress or workload.

Allostatic load: the cumulative physiological cost to the organism of repeated or chronic activation of adaptive regulatory systems, particularly when demands are prolonged or dysregulated (McEwen and Stellar, 1993)

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