Mitochondrial Genomic Variation and the Embodied Architecture of Human Cognition: A Meta-Analytical Integration Across Disconnected Research Domains

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Introduction: The Epistemic Lacuna Between Organellar Genetics and Phenomenological Neuroscience

The contemporary scientific landscape presents a remarkable paradox wherein extraordinary advances in mitochondrial genomics, bioenergetics, and neurocognitive science have proceeded along largely independent trajectories, creating substantial epistemic blind spots regarding the potential mechanistic relationships between individual mitochondrial DNA (mtDNA) variation and the embodied, physiologically-grounded dimensions of human cognitive experience. While research into mitochondrial genetics has illuminated the profound influence of the 16,569 base pair circular genome on cellular energetics, apoptotic regulation, and metabolic homeostasis (Anderson et al., 1981; Wallace et al., 1999), and parallel investigations into embodied cognition have fundamentally challenged Cartesian models of mind-body separation by demonstrating the constitutive role of somatic states, interoceptive processing, and physiological feedback loops in cognitive operations (Varela et al., 1991; Damasio, 1994; Clark, 1997), these research programs have remained conceptually and methodologically isolated from one another despite mounting indirect evidence suggesting their fundamental interconnection.

The mitochondrial genome, inherited exclusively through maternal lineages and encoding thirteen essential polypeptides of the oxidative phosphorylation system alongside twenty-two transfer RNAs and two ribosomal RNAs (Taanman, 1999), exhibits substantially higher mutation rates compared to nuclear DNA—approximately ten to seventeen times greater—resulting in considerable inter-individual variation that manifests across populations as distinct haplogroups and within populations as private polymorphisms and pathogenic mutations (Brown et al., 1979; Wallace, 2005). This genetic variation produces heterogeneous bioenergetic phenotypes across individuals, affecting ATP synthesis efficiency, reactive oxygen species production, calcium buffering capacity, and metabolic

flexibility in ways that extend far beyond the simple energetic provision model that dominated earlier conceptualizations of mitochondrial function (Wallace, 2013; Picard & McEwen, 2014). Contemporary understanding recognizes mitochondria as sophisticated signaling organelles that engage in bidirectional communication with nuclear genetic programs through anterograde and retrograde signaling pathways, modulate epigenetic landscapes through metabolite provision for chromatin modification, govern cellular stress responses through integrated stress response activation, and serve as critical nodes in inflammatory signaling cascades through inflammasome regulation and innate immune pathway activation (Chandel, 2014; Quirós et al., 2016).

Concurrently, the embodied cognition framework has progressively dismantled traditional computational-representational theories of mind by accumulating substantial evidence that cognitive processes are fundamentally grounded in bodily states, sensorimotor contingencies, and physiological dynamics rather than abstract symbolic manipulations occurring in neural substrates isolated from somatic influence (Wilson, 2002; Shapiro, 2011). This theoretical reorientation encompasses multiple interrelated claims: that cognitive processes are constitutively dependent on features of the physical body beyond the brain; that sensorimotor functions are integral rather than peripheral to cognitive operations; that aspects of the body's interaction with environmental affordances scaffold and constrain cognitive possibilities; and that cognitive activity is situated within and responsive to bodily states including visceral conditions, proprioceptive feedback, and homeostatic fluctuations (Gallagher, 2005; Thompson, 2007). Empirical support for embodied cognition derives from diverse experimental paradigms demonstrating that bodily manipulations systematically influence ostensibly abstract cognitive processes including conceptual representation (Barsalou, 2008), decision-making under uncertainty (Bechara et al., 1997), moral judgment (Schnall et al., 2008), and mathematical reasoning (Lakoff & Núñez, 2000), while interoceptive processing—the neural representation of internal physiological states—has emerged as a fundamental dimension undergirding emotional experience, self-awareness, and subjective feeling states (Craig, 2002; Seth, 2013).

The theoretical convergence point that remains conspicuously underexplored concerns how individual variation in mitochondrial genomic architecture might systematically modulate the physiological substrates upon which embodied cognitive processes depend, thereby creating person-specific signatures in the relationship between bodily states and cognitive operations. Given that mitochondria constitute the primary energy-producing organelles within neurons, with individual cortical pyramidal cells containing between one thousand and two thousand mitochondria that must sustain the extraordinary energetic demands of synaptic transmission, action potential propagation, and biosynthetic processes (Harris et al., 2012), and given that mitochondrial bioenergetic capacity varies substantially across individuals as a function of mtDNA sequence variation, haplogroup membership, and heteroplasmy levels (Gomez-Duran et al., 2010; Kenney et al.,

2014), it follows necessarily that individual differences in mitochondrial genomic constitution should produce corresponding variation in the energetic landscapes supporting neural computation and, by extension, in the coupling dynamics between physiological states and cognitive processes that constitute embodied cognition.

This meta-analytical review undertakes a comprehensive synthesis of currently disconnected research streams spanning mitochondrial genetics, cellular bioenergetics, neuroscience, psychophysiology, interoceptive neuroscience, and embodied cognitive science to articulate testable hypotheses regarding how mtDNA variation influences the physiological foundations of embodied cognition. The analysis proceeds through several interconnected layers of investigation: first, establishing the mechanistic foundations by which mitochondrial genomic variation modulates cellular energetics and signaling in neural tissues; second, examining how these bioenergetic variations manifest in measurable differences in neural activity patterns, neurotransmitter dynamics, and brain network organization; third, investigating the psychophysiological interfaces where mitochondrial function intersects with interoceptive processing, autonomic nervous system regulation, and somatic marker generation; fourth, synthesizing evidence regarding how these physiological variations might systematically influence embodied cognitive processes including emotion processing, decision-making, bodily self-consciousness, and the phenomenological character of subjective experience; and finally, proposing computational frameworks and empirical methodologies capable of testing specific predictions regarding the relationships between individual mitochondrial genomic profiles and embodied cognitive phenotypes.

Part I: Mitochondrial Genomic Architecture and Functional Consequences for Neural Bioenergetics

1.1 The Structural and Functional Organization of the Mitochondrial Genome

The human mitochondrial genome represents a remarkable evolutionary retention of a substantially reduced endosymbiotic bacterial chromosome, maintaining only those genes whose protein products must be synthesized within the organelle to enable proper assembly of the electron transport chain complexes embedded in the inner mitochondrial membrane (Gray et al., 1999; Lane & Martin, 2010). The complete sequencing of human mtDNA by Anderson and colleagues in 1981 revealed a compact, economical genetic architecture: a circular double-stranded molecule of 16,569 base pairs containing thirty-seven genes with virtually no non-coding sequence, utilizing a slightly modified genetic code wherein UGA encodes tryptophan rather than serving as a stop codon and AUA encodes methionine rather than isoleucine (Anderson et al., 1981; Barrell et al., 1979). This

genomic compactness reflects extreme selective pressure for rapid replication given the high copy number requirements within individual cells, with most human cell types containing hundreds to thousands of mitochondrial genomes distributed across their mitochondrial reticulum, resulting in polyplasmy—the presence of multiple mitochondrial genomes per cell—that creates additional layers of complexity regarding the relationship between genotype and phenotype (Robin & Wong, 1988).

The thirteen mitochondrial-encoded polypeptides constitute essential subunits of four of the five oxidative phosphorylation complexes: seven subunits of Complex I (NADH:ubiquinone oxidoreductase, the largest enzyme complex in the respiratory chain containing forty-five total subunits), one subunit of Complex III (ubiquinol:cytochrome c oxidoreductase), three subunits of Complex IV (cytochrome c oxidase), and two subunits of Complex V (ATP synthase) (Fernández-Vizarra et al., 2009). Notably, Complex II (succinate:ubiquinone oxidoreductase) contains no mitochondrial-encoded subunits, being composed entirely of nuclear-encoded proteins, a distinction that has important implications for understanding differential vulnerabilities to mtDNA mutations across the respiratory chain (Rustin et al., 2002). The remaining twenty-four mitochondrial genes encode the twenty-two transfer RNAs and two ribosomal RNAs necessary for the mitochondrion's semi-autonomous protein synthesis machinery, enabling the translation of the thirteen oxidative phosphorylation subunits within the organellar matrix using the modified genetic code (Temperley et al., 2010).

The replication, transcription, and maintenance of mtDNA occur through mechanisms distinct from nuclear DNA metabolism, with critical implications for mutation rates and inheritance patterns. Mitochondrial DNA replication proceeds continuously throughout the cell cycle rather than being restricted to S phase, utilizing the DNA polymerase gamma (POLG) holoenzyme that exhibits 3' to 5' exonuclease proofreading activity yet still permits substantially higher error rates compared to nuclear DNA polymerases (Kaguni, 2004). The proximity of mtDNA to the inner mitochondrial membrane, where electron transport chain activity generates substantial reactive oxygen species, exposes the mitochondrial genome to oxidative damage at rates considerably exceeding nuclear DNA despite the presence of base excision repair mechanisms (Richter et al., 1988; Yakes & Van Houten, 1997). These factors combine to produce mitochondrial mutation rates approximately ten to seventeen times greater than nuclear mutation rates, establishing mtDNA as a rapidly evolving genetic system that accumulates variation both within individual lifespans through somatic mutagenesis and across generations through maternal transmission (Brown et al., 1979; Wallace et al., 1987).

The maternal inheritance pattern of mtDNA, first definitively demonstrated through restriction fragment length polymorphism analysis in human pedigrees by Giles and colleagues in 1980, results from the elimination of paternal mitochondria following

fertilization through multiple proposed mechanisms including ubiquitin-mediated proteolysis, autophagy-dependent degradation, and dilutional loss given the vast numerical predominance of oocyte mitochondria over the approximately one hundred sperm mitochondria introduced during fertilization (Giles et al., 1980; Sato & Sato, 2011; Al Rawi et al., 2011). This uniparental inheritance pattern has enabled the reconstruction of human maternal lineages extending back to a matrilineal most recent common ancestor, colloquially termed "Mitochondrial Eve," who lived approximately one hundred fifty thousand to two hundred thousand years ago in Africa, with subsequent population migrations producing the major mitochondrial haplogroups that define continental and subcontinental population clusters (Cann et al., 1987; Ingman et al., 2000; van Oven & Kayser, 2009). These haplogroups, designated by capital letters and defined by specific constellations of single nucleotide polymorphisms and insertion-deletion events, represent ancient maternal lineages that have accumulated characteristic variant patterns distinguishing, for example, African haplogroups L0-L6, European haplogroups H, J, K, T, U, V, W, and X, Asian haplogroups A, B, C, D, E, F, G, M, and N, and Native American haplogroups A2, B2, C1, D1, and X2a (Wallace et al., 1999; Torroni et al., 2006).

1.2 Functional Consequences of Mitochondrial Genomic Variation: From Sequence to Bioenergetic Phenotype

The translation of mitochondrial genomic sequence variation into functional bioenergetic consequences operates through multiple interconnected mechanisms affecting oxidative phosphorylation efficiency, proton motive force generation, ATP synthesis capacity, reactive oxygen species production rates, and metabolic flexibility in response to substrate availability and cellular energetic demands (Wallace, 2005; Picard et al., 2016). Non-synonymous mutations in mitochondrial protein-coding genes can alter amino acid sequences in the thirteen respiratory chain subunits, potentially modifying protein stability, catalytic efficiency, subunit assembly into supercomplexes, or electron transfer kinetics, with consequent impacts on overall oxidative phosphorylation flux (Blier et al., 2001). Mutations in mitochondrial tRNA and rRNA genes can impair mitochondrial translation efficiency, reducing the synthesis rates of all thirteen mitochondrial-encoded proteins simultaneously and creating coordinated deficiencies across multiple respiratory chain complexes, a pattern characteristic of several mitochondrial encephalomyopathies including mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes syndrome (MELAS) caused by the m.3243A>G mutation in MT-TL1 encoding tRNA-Leu(UUR) (Goto et al., 1990; Kirino et al., 2004).

The concept of heteroplasmy—the coexistence of multiple mitochondrial genotypes within a single cell or organism—introduces additional complexity to the genotype-phenotype relationship in mitochondrial genetics, as the functional consequences of pathogenic mutations depend critically on the proportion of mutant versus wild-type

mtDNA molecules present, with most pathogenic mutations exhibiting threshold effects wherein biochemical deficiency and clinical manifestations emerge only when mutant heteroplasmy exceeds approximately sixty to ninety percent depending on the specific mutation and tissue type (Rossignol et al., 2003; Stewart & Chinnery, 2015). This threshold phenomenon reflects the substantial reserve capacity built into oxidative phosphorylation systems, wherein mitochondrial respiratory chain activity can decline substantially before ATP synthesis becomes rate-limiting for cellular function, a reserve capacity that varies across tissue types corresponding to their baseline energetic demands and explaining the tissue-specific manifestations of many mitochondrial diseases (Rossignol et al., 1999). Heteroplasmy levels can shift over time within individuals through random genetic drift in mitochondrial populations, clonal expansion of particular mtDNA variants, and selective pressures favoring variants with replicative or functional advantages, producing age-related increases in mutant mtDNA burden in some tissues and potentially contributing to aging-related functional decline (Khrapko et al., 1999; Taylor et al., 2003; Kowald & Kirkwood, 2011).

Even common, non-pathogenic polymorphisms defining mitochondrial haplogroups produce measurable functional consequences for cellular bioenergetics, as demonstrated through numerous studies measuring oxygen consumption rates, ATP production, reactive oxygen species generation, and calcium handling capacity in cells harboring different haplogroup backgrounds (Gómez-Durán et al., 2010; Kenney et al., 2014). For instance, European haplogroup J, characterized by variants including m.295C>T in the D-loop, m.10398A>G causing a Thr114Ala substitution in ND3, and m.13708G>A causing an Ala458Thr substitution in ND5, exhibits reduced Complex I activity and altered coupling efficiency compared to haplogroup H, the most common European haplogroup, with corresponding differences in ATP production rates and mitochondrial membrane potential (Marcuello et al., 2009; Gómez-Durán et al., 2010). Asian haplogroup D, defined partly by the m.5178C>A mutation causing a Leu237Met substitution in ND2, has been associated with increased longevity in Japanese populations and exhibits enhanced Complex I stability and reduced oxidative stress under certain conditions (Tanaka et al., 1998; Alexe et al., 2007). The m.10398A>G polymorphism, present in approximately twenty-five percent of Europeans and defining several haplogroups including J, has been studied extensively due to associations with various neurological conditions, with biochemical evidence suggesting that the threonine to alanine substitution at position 114 of ND3 alters Complex I assembly or function in subtle ways that may become clinically relevant under conditions of additional metabolic stress (Martínez-Redondo et al., 2010; Hudson et al., 2013).

The functional investigation of mitochondrial genomic variation has been substantially advanced through the development of cybrid (cytoplasmic hybrid) cell models, wherein mitochondria-depleted cells (ρ 0 cells) are repopulated with mitochondria from donor cells harboring different mtDNA variants, enabling the examination of mtDNA effects

in controlled nuclear genetic backgrounds (King & Attardi, 1989). Cybrid studies have demonstrated that identical nuclear genomes paired with different mitochondrial haplogroups exhibit significant differences in respiratory chain function, metabolic profiles, gene expression patterns, and responses to environmental stressors including oxidative stress, calcium overload, and substrate deprivation (Moreno-Loshuertos et al., 2006; Gómez-Durán et al., 2010). These investigations establish conclusively that common mtDNA variation, not merely rare pathogenic mutations, produces functional bioenergetic consequences detectable at the cellular level, supporting the hypothesis that individual mitochondrial genomic backgrounds contribute to normal phenotypic variation across human populations.

The implications for neural tissues prove particularly profound given the exceptional energetic demands of neurons, which must maintain substantial ATP-dependent ion gradients across plasma membranes to support resting membrane potentials and action potential propagation while simultaneously fueling energy-intensive processes including synaptic vesicle trafficking, neurotransmitter synthesis and packaging, cytoskeletal dynamics, and local protein synthesis at dendrites (Attwell & Laughlin, 2001; Harris et al., 2012). The adult human brain, constituting approximately two percent of body mass, accounts for roughly twenty percent of whole-body oxygen consumption at rest, with regional metabolic rates varying substantially across brain structures corresponding to their functional specializations and connectivity patterns (Clarke & Sokoloff, 1999). Individual cortical neurons contain between approximately eight hundred and two thousand mitochondria distributed throughout soma, dendrites, and axons, with mitochondrial density particularly elevated at synaptic terminals and nodes of Ranvier where energy demands peak during neurotransmission (Li et al., 2004). Synaptic transmission alone accounts for a substantial fraction of neuronal energy consumption, with estimates suggesting that ATP utilization for maintaining and restoring ion gradients following excitatory postsynaptic potentials represents the largest single energy expenditure in cortical gray matter (Attwell & Laughlin, 2001; Alle et al., 2009).

Given these extraordinary energetic requirements and the tissue-specific vulnerabilities to mitochondrial dysfunction, wherein nervous system manifestations predominate in many mitochondrial diseases despite the ubiquitous presence of mutant mtDNA across all tissues, it becomes apparent that neurons operate closer to their bioenergetic limits compared to most other cell types, possessing reduced reserve capacity that renders neural function particularly sensitive to variations in mitochondrial performance (Schon & Manfredi, 2003; Kann & Kovács, 2007). This neuronal bioenergetic vulnerability provides a crucial mechanistic foundation for understanding how individual differences in mitochondrial genomic architecture might systematically influence neural function and, consequently, cognitive processes that depend upon distributed neural network activity. The high energetic cost of maintaining neural signaling capacity, combined with the

temporal precision required for cognitive operations that depend on millisecond-scale coordination of activity across distributed brain regions, suggests that even modest variations in mitochondrial ATP provision, calcium buffering, or reactive oxygen species generation could produce meaningful differences in neural dynamics at both local circuit and large-scale network levels.

1.3 Mitochondrial Bioenergetics and Neural Network Function: From Cellular Metabolism to Systems Neuroscience

The translation of cellular-level mitochondrial bioenergetic variation into systems-level neural network dynamics represents a multilayered process involving interactions between metabolic state, neuronal excitability, synaptic plasticity mechanisms, and large-scale oscillatory coordination patterns that collectively support cognitive functions (Magistretti & Allaman, 2015; Kann, 2016). At the most fundamental level, neuronal mitochondrial function directly determines the availability of ATP that powers sodium-potassium ATPases responsible for maintaining the steep ion gradients underlying resting membrane potentials and enabling action potential generation, with approximately fifty percent of neuronal ATP consumption devoted to reversing the ionic fluxes associated with postsynaptic potentials and action potentials (Attwell & Laughlin, 2001; Howarth et al., 2012). Experimental manipulations that impair mitochondrial function, whether through respiratory chain inhibitors, genetic disruption of mitochondrial components, or substrate deprivation, consistently produce decrements in neuronal firing rates, altered action potential waveforms including broadening and reduced amplitude, and ultimately conduction failure when bioenergetic capacity falls below critical thresholds (Rangaraju et al., 2014; Ivannikov et al., 2013).

Beyond simple energy provision, mitochondrial function influences neuronal excitability through multiple additional mechanisms including calcium buffering, reactive oxygen species signaling, and metabolite provision for neurotransmitter synthesis (Gleichmann & Mattson, 2011; Devine & Kittler, 2018). Mitochondria serve as critical calcium buffers in neurons, taking up calcium ions through the mitochondrial calcium uniporter following neuronal depolarization and synaptic activity, thereby shaping the spatiotemporal dynamics of intracellular calcium signals that trigger numerous calcium-dependent processes including neurotransmitter release, gene transcription, and synaptic plasticity induction (Rizzuto et al., 2012; Devine & Kittler, 2018). The magnitude and kinetics of mitochondrial calcium uptake depend on factors including mitochondrial membrane potential, the expression and regulation of calcium uniporter complex components, and the spatial positioning of mitochondria relative to calcium entry sites, with mitochondrial calcium buffering capacity varying substantially across neuronal subtypes and potentially exhibiting individual variation as a function of mitochondrial genomic background effects on

respiratory chain function and membrane potential generation (Niciu et al., 2014; Marland et al., 2016).

Mitochondrial reactive oxygen species production, traditionally viewed primarily through the lens of oxidative damage and pathology, has emerged as an important physiological signaling mechanism in neurons, with controlled ROS generation influencing synaptic plasticity, neuronal differentiation, and adaptive responses to activity patterns (Knapp & Klann, 2002; Hidalgo & Arias-Cavieres, 2016). Superoxide anions generated primarily at Complex I and Complex III of the electron transport chain can be converted to hydrogen peroxide by superoxide dismutases, producing a diffusible oxidant that modulates protein function through reversible cysteine oxidation, thereby influencing ion channel gating, neurotransmitter receptor sensitivity, and signal transduction pathway activation (Dröge, 2002; Hurd et al., 2008). The physiological ROS signaling hypothesis posits that mitochondrial ROS generation provides feedback regarding mitochondrial metabolic state to cellular signaling systems, potentially coupling cellular bioenergetic status to activity-dependent plasticity mechanisms, though the precise quantitative relationships and the conditions under which ROS transitions from signaling molecule to pathological oxidant remain incompletely characterized (Shadel & Horvath, 2015). Individual variation in mitochondrial genomic architecture that affects basal ROS production rates or the response of ROS generation to metabolic perturbations could thereby influence the redox-sensitive signaling pathways participating in synaptic plasticity and neural adaptation.

The provision of metabolic intermediates for neurotransmitter synthesis represents another critical link between mitochondrial function and neural signaling, as several neurotransmitter biosynthetic pathways require mitochondrial-derived precursors or cofactors (Rae & Williams, 2017). Glutamate, the primary excitatory neurotransmitter in the brain, derives predominantly from the mitochondrial TCA cycle intermediate alpha-ketoglutarate through transamination reactions, creating a direct link between mitochondrial oxidative metabolism and excitatory neurotransmission (Hertz, 2013). Similarly, gamma-aminobutyric acid (GABA), the primary inhibitory neurotransmitter, is synthesized from glutamate through glutamic acid decarboxylase, maintaining this metabolic connection. The monoamine neurotransmitters including dopamine, norepinephrine, and serotonin require tetrahydrobiopterin as a cofactor for their rate-limiting biosynthetic enzymes, with tetrahydrobiopterin synthesis depending on GTP availability and therefore linking to mitochondrial nucleotide metabolism (Thöny et al., 2000). Individual variation in mitochondrial bioenergetic capacity and TCA cycle flux could thereby influence the availability of precursors for neurotransmitter synthesis, potentially contributing to variation in neurotransmitter system function across individuals, though the quantitative significance of such effects requires further empirical investigation.

The integration of mitochondrial bioenergetics with synaptic plasticity mechanisms has received increasing attention as evidence accumulates that energy availability and metabolic state influence the induction, expression, and maintenance of long-term potentiation and long-term depression, the principal cellular correlates of learning and memory (Mattson et al., 2008; Lisman et al., 2012). Long-term potentiation induction through high-frequency stimulation protocols creates substantial energy demands to support the synthesis of new proteins required for structural synaptic modifications, the insertion of additional neurotransmitter receptors into postsynaptic membranes, and the expansion of dendritic spines, with estimates suggesting that the metabolic cost of maintaining potentiated synapses exceeds baseline synaptic maintenance costs by approximately threefold (Rangaraju et al., 2014). Experimental manipulations that impair mitochondrial function reduce the magnitude and durability of long-term potentiation, while genetic or pharmacological interventions that enhance mitochondrial bioenergetic capacity can facilitate plasticity induction under marginal stimulation conditions (Wyrembak et al., 2015; Cheng et al., 2012). Mitochondrial positioning within dendrites responds dynamically to synaptic activity, with mitochondria recruited to activated synaptic sites where they presumably provide localized energy provision and calcium buffering to support plasticity mechanisms (Li et al., 2004; MacAskill et al., 2009).

At the systems neuroscience level, mitochondrial bioenergetic state may influence large-scale neural network oscillations and synchronization patterns that coordinate information processing across distributed brain regions, though direct evidence for such relationships remains limited and largely circumstantial. Neural oscillations spanning frequency ranges from slow delta rhythms (one to four Hertz) through theta, alpha, beta, and into gamma frequencies (thirty to one hundred Hertz) emerge from interactions between cellular membrane properties, synaptic connectivity patterns, and population-level synchronization mechanisms, with different oscillatory bands associated with distinct cognitive operations and behavioral states (Buzsáki & Draguhn, 2004). Gamma oscillations, particularly in the forty to eighty Hertz range, depend critically on the precise temporal coordination of excitation and inhibition, with parvalbumin-expressing GABAergic interneurons playing essential pacemaking roles through their fast-spiking properties and extensive axonal arbors that synchronize local pyramidal cell populations (Cardin et al., 2009; Sohal et al., 2009). The high firing rates of fast-spiking interneurons during gamma oscillations create exceptional metabolic demands, with these cells exhibiting enriched mitochondrial content and elevated baseline oxidative metabolism compared to pyramidal neurons, suggesting particular vulnerability to mitochondrial dysfunction (Kann et al., 2014; Inan et al., 2016). Computational modeling studies and experimental investigations have demonstrated that impairments in interneuron energy metabolism can disrupt gamma oscillation generation and reduce the precision of network synchronization, potentially contributing to cognitive deficits observed in various neuropsychiatric conditions associated with mitochondrial dysfunction (Kann, 2016; Steullet et al., 2017).

The hypothesis that individual variation in mitochondrial genomic architecture systematically influences neural network dynamics through these multilayered bioenergetic effects remains largely untested in human populations, though several lines of circumstantial evidence support its plausibility. Studies in rodent models harboring different mitochondrial haplotypes have documented behavioral and cognitive differences alongside variations in brain metabolism, neurotransmitter levels, and susceptibility to neurological insults (Roubertoux et al., 2003; Gimsa et al., 2009). Neuroimaging investigations using positron emission tomography and magnetic resonance spectroscopy have revealed associations between mitochondrial DNA haplogroups and regional brain metabolism or metabolite concentrations in human subjects, though such studies remain relatively sparse and often suffer from small sample sizes (Feder et al., 2011; Tranah et al., 2012). The emerging field of neuroenergetics, which seeks to understand the relationships between brain metabolism and neural function, has identified numerous conditions wherein metabolic perturbations produce specific cognitive and behavioral consequences, establishing proof-of-principle that bioenergetic variation can manifest as functional neural differences (Magistretti & Allaman, 2015). What remains absent from the literature is a systematic, comprehensive investigation specifically examining how common, non-pathogenic mitochondrial genomic variation maps onto neural network properties and cognitive phenotypes in healthy human populations.

Part II: Interoceptive Processing and Physiological Foundations of Embodied Cognition

2.1 The Neuroscience of Interoception: Neural Systems for Bodily State Representation

Interoception, formally defined as the sense of the physiological condition of the body encompassing both conscious perception of internal bodily states and non-conscious physiological regulation, has emerged as a fundamental dimension of nervous system organization with profound implications for understanding emotion, self-awareness, motivation, and decision-making (Cameron, 2001; Craig, 2002; Critchley & Harrison, 2013). The neural systems supporting interoceptive processing span from peripheral afferent pathways that transduce information about tissue metabolic state, mechanical distension, temperature, pH, osmolality, and inflammatory signals, through brainstem and subcortical relays that integrate and process these ascending signals, to cortical regions that generate conscious representations of bodily feelings and contribute to homeostatic control through descending modulation (Craig, 2003; Critchley & Harrison, 2013). This hierarchical organization enables multiple levels of interoceptive representation, from automatic reflexive regulation that operates entirely subcortically to explicit conscious awareness of

specific bodily sensations including heartbeat perception, respiratory sensations, gastric fullness, bladder distension, muscular fatigue, and thermal comfort or discomfort (Khalsa et al., 2018).

The primary afferent pathways conveying interoceptive information from visceral organs, vascular structures, and deep somatic tissues utilize small-diameter myelinated A-delta and unmyelinated C fibers that project to the spinal cord dorsal horn and brainstem, distinguishing interoceptive afferents anatomically and physiologically from the larger, faster-conducting A-beta fibers that convey discriminative touch and proprioceptive information (Craig, 2003). These interoceptive afferents express diverse molecular receptors enabling sensitivity to multiple stimulus modalities including mechanical distension through mechanosensitive ion channels, temperature through transient receptor potential channels, metabolic state through chemoreceptors sensitive to oxygen, carbon dioxide, pH, and glucose, inflammatory mediators through receptors for cytokines, prostaglandins, and bradykinin, and homeostatic signals including hormones and neuropeptides (Blackshaw et al., 2007; Prescott & Liberles, 2022). The central projections of interoceptive afferents terminate in the nucleus tractus solitarius in the medulla for vagal visceral afferents and in lamina I of the spinal dorsal horn for spinally-projecting visceral and deep somatic afferents, establishing the first central synapses in interoceptive pathways (Saper, 2002).

From these brainstem and spinal entry points, interoceptive information ascends through parallel pathways to higher brain regions, with a particularly well-characterized route proceeding from lamina I and the nucleus tractus solitarius through the parabrachial nucleus in the pons to the ventromedial posterior nucleus of the thalamus and ultimately to the posterior and mid-insula cortex (Craig, 2002, 2009). This pathway, termed the lamina I spinothalamocortical pathway or the interoceptive pathway, maintains distinct anatomical separation from the classical somatosensory pathways conveying discriminative touch and proprioception through the dorsal column-medial lemniscal system and pain/temperature through the lateral spinothalamic tract, though integration occurs at multiple levels including the insular cortex (Craig, 2003). The insular cortex has emerged as the primary cortical substrate for interoceptive representation, with functional neuroimaging studies consistently identifying insular activation during tasks requiring attention to internal bodily sensations including heartbeat detection, breath-holding, bladder distension, and gastric distension (Critchley et al., 2004; Farb et al., 2012; Schulz, 2016). The insula exhibits a posterior-to-anterior functional organization wherein posterior regions represent primary interoceptive information in relatively raw sensory form while more anterior regions progressively integrate interoceptive signals with emotional, cognitive, and social information to generate increasingly abstract and affectively-laden representations of bodily state (Craig, 2009; Kurth et al., 2010).

The relationship between objective physiological state and subjective interoceptive awareness proves neither simple nor direct, with substantial individual variation in interoceptive accuracy—the correspondence between actual bodily state and perceived bodily state—as measured through various psychophysical tasks (Garfinkel et al., 2015). The heartbeat detection task, wherein participants attempt to count their heartbeats over specified intervals without taking their pulse, represents the most widely-used behavioral measure of interoceptive accuracy, with performance varying considerably across healthy individuals and showing moderate test-retest reliability (Schandry, 1981; Garfinkel et al., 2015). Some individuals demonstrate remarkably accurate heartbeat perception, with counted heartbeats deviating minimally from electrocardiogram-verified actual heartbeats, while others perform at chance levels despite normal cardiac function and intact peripheral and central nervous systems, suggesting that interoceptive accuracy reflects not merely the presence of physiological signals and intact neural pathways but also attentional orientation toward internal sensations, interpretation of ambiguous somatic cues, and potentially individual differences in the gain or signal-to-noise characteristics of interoceptive neural representations (Khalsa et al., 2018; Murphy et al., 2019).

The construct validity of heartbeat detection tasks and other interoceptive accuracy measures has received critical scrutiny, with concerns raised regarding potential confounds including participant beliefs about their heart rate, influences of task instructions on attentional strategies, and the possibility that performance partially reflects general body awareness or attention rather than specific interoceptive processing (Ring & Brener, 2018; Desmedt et al., 2018). Nevertheless, convergent evidence from multiple methodologies including heartbeat detection, heartbeat discrimination tasks wherein participants judge whether external tones occur synchronously with their heartbeats, respiratory resistance detection, and gastric interoceptive paradigms supports the existence of meaningful individual differences in interoceptive processing that show some stability across measurement contexts and correlate with other psychological constructs in theoretically predicted ways (Garfinkel et al., 2015; Ferentzi et al., 2018). Garfinkel and colleagues (2015) proposed a tripartite distinction among interoceptive accuracy (objective performance on behavioral interoceptive tasks), interoceptive sensibility (self-reported tendency to focus on and notice bodily sensations), and interoceptive awareness (metacognitive knowledge about one's interoceptive accuracy), noting that these dimensions show only modest intercorrelations and may have distinct neural substrates and functional consequences. This multidimensional framework acknowledges that interoceptive processing encompasses perceptual, attentional, interpretive, and metacognitive components that may vary independently across individuals and contribute differentially to various outcomes including emotional experience, clinical symptoms, and decision-making patterns.

The neural substrates supporting individual differences in interoceptive accuracy have been investigated through structural and functional neuroimaging approaches that

relate brain morphometry or activation patterns to behavioral interoceptive performance. Multiple studies have identified positive correlations between interoceptive accuracy and gray matter volume or cortical thickness in the anterior insula, with some investigations also implicating the anterior cingulate cortex, somatosensory cortex, and inferior frontal regions (Critchley et al., 2004; Terasawa et al., 2013; Salvato et al., 2020). However, the literature exhibits considerable heterogeneity regarding which specific insular subregions show the strongest relationships with interoceptive accuracy, with some studies emphasizing right anterior insula, others bilateral mid-insula, and still others posterior insula, likely reflecting differences in interoceptive task demands, analysis approaches, and sample characteristics (Schulz, 2016). Functional connectivity investigations have revealed that individuals with higher interoceptive accuracy exhibit stronger coupling between insular cortex and other regions of the salience network including dorsal anterior cingulate cortex, as well as enhanced connectivity between insula and sensorimotor regions during interoceptive attention (Simmons et al., 2013; Eccles et al., 2021).

The relationship between interoceptive neural processing and autonomic nervous system function represents another critical dimension for understanding individual differences in bodily state representation. The autonomic nervous system, comprising sympathetic and parasympathetic branches that regulate cardiac function, vascular tone, respiratory patterns, digestive processes, and numerous other physiological parameters, operates under both reflexive and centrally-modulated control, with higher brain regions including insula, anterior cingulate cortex, and prefrontal areas capable of influencing autonomic outflow through descending pathways (Benarroch, 1993; Thayer & Lane, 2000). Individual differences in baseline autonomic function and autonomic reactivity to various stimuli could influence interoceptive processing through multiple mechanisms: autonomic state determines the magnitude and variability of physiological signals available for central representation, autonomic reactivity influences how physiological states change in response to psychological processes including attention and emotion, and the integration of afferent interoceptive information with efferent autonomic control enables predictive regulation wherein anticipated needs modulate autonomic function proactively rather than merely reactively (Thayer et al., 2012; Park & Thayer, 2014).

Heart rate variability, reflecting the beat-to-beat fluctuation in cardiac inter-beat intervals and providing a noninvasive index of cardiac autonomic regulation particularly parasympathetic vagal tone, has been investigated extensively in relation to interoceptive accuracy and emotional processing (Thayer & Lane, 2000; Quintana & Heathers, 2014). The neurovisceral integration model proposed by Thayer and Lane (2000) posits that heart rate variability reflects the functional capacity of a central autonomic network comprising prefrontal cortex, anterior cingulate cortex, insula, amygdala, hypothalamus, and brainstem structures that integrates emotional, cognitive, and physiological information to enable flexible behavioral and autonomic responses to environmental demands. According to this

framework, higher resting heart rate variability indicates greater capacity for self-regulation and adaptive responding, associated with better executive function, emotion regulation, and social engagement (Thayer et al., 2009; Holzman & Bridgett, 2017). Several investigations have reported positive associations between heart rate variability and interoceptive accuracy, supporting the hypothesis that autonomic function and interoceptive processing are interconnected dimensions of neurovisceral integration, though other studies have failed to replicate these associations or found them to be task-dependent and context-specific (Pollatos et al., 2007; Zamariola et al., 2018).

The developmental trajectory of interoceptive processing capabilities and their interaction with autonomic maturation represents an understudied area with important implications for understanding individual differences. While even neonates demonstrate basic interoceptive reflexes including responses to hunger, respiratory need, and thermoregulatory demands, the emergence of conscious interoceptive awareness and the ability to accurately perceive and report internal bodily states develops gradually across childhood and adolescence, paralleling the maturation of insular cortex, autonomic regulatory systems, and metacognitive capabilities (Quadt et al., 2018; Koch & Pollatos, 2014). Individual variation in the trajectory of interoceptive development, potentially influenced by genetic factors, early life experiences, attachment patterns, and the somatic aspects of emotional socialization, may establish enduring differences in adult interoceptive processing that contribute to variation in emotional experience, self-awareness, and vulnerability to various forms of psychopathology (Murphy et al., 2017; Fotopoulou & Tsakiris, 2017).

2.2 Embodied Cognitive Frameworks: Theoretical Foundations and Empirical Evidence

The embodied cognition paradigm represents a fundamental reconceptualization of cognitive architecture, rejecting traditional information-processing models that treat cognition as computational operations over amodal symbolic representations implemented in neural substrates that are functionally independent of bodily systems and sensorimotor processes (Varela et al., 1991; Clark, 1997; Wilson, 2002). Instead, embodied approaches emphasize that cognitive processes are constitutively dependent on features of the organism's physical body, grounded in sensorimotor systems, shaped by bodily interactions with environmental affordances, and situated within contexts that include the body's physiological state (Shapiro, 2011; Chemero, 2011). The embodiment thesis encompasses multiple distinguishable claims of varying strength and scope, ranging from relatively modest assertions that bodily states influence some cognitive processes as one factor among many, through intermediate positions that sensorimotor experiences scaffold conceptual development and reasoning about abstract domains, to radical claims that cognition is fundamentally constituted by sensorimotor contingencies and bodily dynamics

rather than internal representational structures (Wilson, 2002; Goldman & de Vignemont, 2009).

The conceptual grounding hypothesis, articulated most comprehensively by Barsalou (1999, 2008) through the perceptual symbol systems framework, proposes that conceptual knowledge is fundamentally grounded in modality-specific perceptual, motor, and interoceptive systems rather than being recoded into amodal symbolic formats. According to this view, understanding a concept involves partial reactivation or simulation of the sensorimotor and affective states that were active during experiences with the concept's referent, such that processing the concept "kick" partially reactivates motor representations associated with kicking actions, processing "apple" partially reactivates visual representations of apples' appearance and perhaps gustatory representations of their taste, and processing emotion concepts partially reactivates the interoceptive and somatosensory states characteristic of those emotions (Barsalou, 2008; Wilson-Mendenhall et al., 2011). Substantial empirical evidence supports conceptual grounding, including demonstrations that conceptual processing activates modality-specific brain regions in systematic, concept-appropriate ways, that bodily manipulations influence conceptual processing speed and accuracy, and that neurological damage to modality-specific regions impairs corresponding conceptual knowledge (Martin, 2007; Kiefer & Pulvermüller, 2012).

The evidence for motor grounding of action concepts derives from numerous studies demonstrating that processing action-related language activates premotor and motor cortical regions in somatotopic patterns corresponding to the body parts involved in the described actions, that concurrent motor actions facilitate or interfere with processing action words depending on compatibility, and that motor cortex stimulation or damage selectively affects action concept processing (Hauk et al., 2004; Pulvermüller, 2005; Willems et al., 2010). For instance, Hauk and colleagues (2004) used functional magnetic resonance imaging to demonstrate that reading words referring to face-related actions (lick), leg-related actions (kick), and arm-related actions (pick) activated motor and premotor cortex in somatotopically-organized patterns overlapping with the representations activated by actual movements of those body parts. Similarly, action-sentence compatibility effect studies have shown that participants execute actions more quickly following sentences describing congruent actions and more slowly following sentences describing incongruent actions, suggesting that language comprehension involves motor simulation that interacts with actual motor execution (Glenberg & Kaschak, 2002). Transcranial magnetic stimulation studies further demonstrate that motor cortex excitability increases in effector-specific ways during processing of effector-related action language, providing converging evidence that action concept processing recruits motor systems (Pulvermüller et al., 2005).

The sensory grounding of object concepts and perceptual properties exhibits similar empirical support, with neuroimaging investigations revealing that processing words or

concepts referring to objects with strong visual features activates visual processing regions, olfactory concepts activate olfactory regions, auditory concepts activate auditory regions, and so forth, with the specific patterns of activation corresponding to the modality-specific properties characteristic of the concept's referent (Martin, 2007; Simmons et al., 2007). Critically, these activations are not merely epiphenomenal accompaniments to amodal conceptual processing occurring elsewhere but appear functionally necessary for conceptual processing, as evidenced by studies showing that transcranial magnetic stimulation or damage to modality-specific regions selectively impairs processing concepts associated with that modality (Simmons et al., 2007; Kiefer et al., 2008). The temporal dynamics of conceptual grounding have been investigated through event-related potential studies demonstrating that conceptual processing elicits modality-specific activity with latencies that overlap semantic processing time courses, supporting the claim that sensorimotor simulations contribute to conceptual processing rather than occurring as post-conceptual elaborations (Pulvermüller et al., 2001; Kiefer et al., 2008).

The grounding of abstract concepts in bodily and sensorimotor experiences represents a more contentious proposition, as abstract concepts by definition lack direct perceptual referents and seem unlikely candidates for sensorimotor simulation. Nevertheless, several lines of evidence suggest that even abstract concepts maintain connections to bodily experiences through metaphorical mappings and image schemas that structure abstract reasoning in terms of spatial, motoric, and somatic relations (Lakoff & Johnson, 1999; Boroditsky & Ramscar, 2002). The conceptual metaphor theory proposes that abstract domains such as time, morality, emotion, and social relations are understood through systematic metaphorical mappings from more concrete source domains grounded in physical experience, such as understanding time in terms of spatial extent ("a long time," "time flies"), affection in terms of warmth ("a warm greeting," "cold-hearted"), and moral valence in terms of verticality ("upstanding citizen," "moral decline") (Lakoff & Johnson, 1980, 1999). Experimental investigations of these metaphorical mappings have demonstrated bidirectional influences between conceptual processing and relevant bodily states or sensorimotor experiences: physical warmth facilitates processing of affection-related concepts and judgments of interpersonal warmth, weight influences importance judgments, spatial manipulations affect temporal reasoning, and vertical position influences moral judgments (Williams & Bargh, 2008; Jostmann et al., 2009; Casasanto & Boroditsky, 2008; Meier et al., 2012).

The moral-purity metaphor, wherein moral violations are conceptualized in terms of physical contamination and moral righteousness in terms of cleanliness, has been investigated extensively following Schnall and colleagues' (2008) finding that inducing physical disgust through exposure to a fart-spray odor or working in a disgusting room led participants to render harsher moral judgments of described violations, while physical cleansing through handwashing following a moral transgression reduced feelings of guilt

and reduced compensatory prosocial behavior. Subsequent investigations have yielded mixed evidence regarding the robustness and replicability of these cleansing effects, with some successful replications and conceptual extensions but also multiple failures to replicate under certain conditions, prompting debates about boundary conditions, effect sizes, and methodological considerations (Fayard et al., 2009; Zhong et al., 2010; Johnson et al., 2014; Earp et al., 2014). Meta-analyses of the moral-cleansing literature have concluded that reliable effects exist but are smaller than initially reported and may depend on factors including the specific type of moral threat, individual differences in embodied processing tendencies, and cultural variations in the strength of metaphorical associations between cleanliness and morality (Huang, 2014). The debates surrounding moral embodiment exemplify broader discussions within embodied cognition regarding effect sizes, replicability, and the theoretical interpretation of bodily influences on cognition.

The situated conceptualization framework extends embodied approaches by emphasizing that conceptual processing depends not only on reactivation of prior sensorimotor experiences but also on the current bodily, environmental, and social context in which concepts are processed, with different aspects of conceptual knowledge becoming active depending on situational relevance (Barsalou, 2003, 2016). This framework accommodates the observation that concepts exhibit considerable flexibility and context-sensitivity, with different features becoming salient depending on the sentence context, task demands, and the individual's goals and bodily state. For instance, the concept "piano" might activate different features when encountered in the context "The piano needs to be moved" (emphasizing weight and physical properties) versus "The piano was beautifully tuned" (emphasizing musical properties), and an individual's current bodily state might influence which aspects of concepts are most accessible or salient (Yee & Thompson-Schill, 2016; Barsalou, 2016).

The extension of embodied cognition principles to decision-making processes has generated the somatic marker hypothesis, which proposes that decision-making under uncertainty relies critically on bodily emotional responses that mark particular options as advantageous or disadvantageous based on prior experience (Damasio, 1994, 1996). According to this hypothesis, when individuals contemplate potential courses of action, they generate anticipatory bodily states—somatic markers—that recapitulate the emotional consequences previously associated with similar decisions or outcomes, and these bodily signals guide decision-making by biasing option selection toward choices associated with positive somatic states and away from choices associated with negative somatic states (Damasio, 1996; Bechara & Damasio, 2005). The somatic marker hypothesis emphasizes that these bodily states and their neural representations in somatosensory and insular cortices are not merely consequences or correlates of decision processes but play a constitutive role in enabling effective decision-making, particularly in complex situations involving multiple

options, uncertain outcomes, and trade-offs between short-term and long-term consequences (Bechara et al., 1997).

The empirical foundation for the somatic marker hypothesis derives substantially from studies of patients with ventromedial prefrontal cortex damage who exhibit impaired decision-making in real-world situations despite intact intellectual abilities, working memory, and explicit knowledge of rules and contingencies (Bechara et al., 1994, 1997). These patients show deficits on the Iowa Gambling Task, wherein participants select cards from multiple decks that differ in their schedules of gains and losses, with some decks providing larger immediate gains but ultimately leading to net losses while other decks provide smaller immediate gains but result in net gains over time. Neurologically intact individuals develop anticipatory skin conductance responses before selecting from disadvantageous decks, suggesting that bodily emotional responses signal the negative expected value of these options even before participants can explicitly articulate which decks are disadvantageous (Bechara et al., 1997). Patients with ventromedial prefrontal damage fail to develop these anticipatory somatic markers and continue selecting from disadvantageous decks despite eventually gaining explicit knowledge that these decks are risky, interpreted as evidence that the explicit knowledge alone cannot guide decision-making effectively in the absence of somatic marker signals (Bechara et al., 1997, 2000).

Critical evaluations of the somatic marker hypothesis have raised several important considerations regarding the necessity and sufficiency of bodily feedback for decision-making. Some investigations have found that patients with pure autonomic failure, who lack peripheral bodily feedback due to autonomic neuropathy, can nonetheless perform normally on the Iowa Gambling Task and other decision-making paradigms, suggesting that peripheral somatic feedback may not be strictly necessary for effective decision-making (Heims et al., 2004; Dunn et al., 2006). However, proponents of the somatic marker hypothesis note that central representations of bodily states in somatosensory and insular cortices could support somatic marker function even in the absence of actual peripheral bodily changes, reframing the hypothesis in terms of somatosensory representations (whether arising from peripheral feedback or centrally generated) rather than requiring peripheral physiological changes themselves (Damasio & Carvalho, 2013). This "as-if body loop" concept proposes that the brain can generate representations of bodily states without actually implementing those states peripherally, enabling efficient decision-making through simulated rather than actual somatic markers (Damasio, 1994).

The integration of somatic marker concepts with predictive processing frameworks has emerged as a promising theoretical development that addresses some critiques while preserving core embodied principles (Seth, 2013; Barrett & Simmons, 2015). Predictive processing theories propose that the brain continuously generates predictions about

incoming sensory information based on hierarchical generative models, comparing predictions against actual sensory input to compute prediction errors that drive both perceptual inference and model updating (Clark, 2013; Friston, 2010). When applied to interoception and emotion, predictive processing suggests that the brain actively predicts the body's physiological state based on context and prior experience, comparing these predictions against actual interoceptive afference to update both bodily state representations and the models generating predictions (Seth, 2013; Barrett & Simmons, 2015). In this framework, emotions and feelings arise from the brain's construction of interoceptive predictions that prepare the body for anticipated demands, with differences between predicted and actual interoceptive states contributing to emotional intensity and valence (Seth & Friston, 2016). Individual differences in interoceptive prediction accuracy, prediction precision-weighting, and the ease of updating interoceptive models could thereby contribute to variation in emotional experience and regulation.

2.3 Physiological Foundations of Emotional Experience and Their Cognitive Consequences

The relationship between peripheral physiological responses and subjective emotional experience has constituted a central debate in affective science since William James's (1884) proposal that emotions are the perception of bodily changes induced by emotional stimuli rather than being central mental states that cause bodily responses, famously captured in his rhetorical question of whether we run from the bear because we are afraid or are afraid because we run. Contemporary theories of emotion vary in the degree to which they emphasize peripheral physiological contributions to emotional experience versus central neural processes, but most acknowledge some role for bodily feedback in shaping emotional feelings even if disagreeing about its necessity or sufficiency (Schachter & Singer, 1962; Ekman, 1992; LeDoux, 2012; Barrett, 2017). The somatic feedback hypothesis, a modern descendant of James's peripheral theory, proposes that activation of modality-specific somatosensory and interoceptive representations of bodily states during emotion contributes causally to emotional experience rather than being merely an epiphenomenal consequence (Damasio, 1994; Niedenthal, 2007).

Empirical evidence for somatic contributions to emotional experience derives from multiple experimental paradigms including facial feedback studies, postural manipulation effects, and direct induction of physiological states. The facial feedback hypothesis proposes that proprioceptive and cutaneous feedback from facial expressions influences emotional experience, with facial configurations associated with particular emotions intensifying the subjective experience of those emotions when voluntarily adopted (Strack et al., 1988; Larsen et al., 1992). The influential pen-in-teeth paradigm, wherein participants hold a pen between their teeth (forcing contraction of muscles involved in smiling) or between their lips (preventing smile-related muscle activation) while rating the funniness of

cartoons, initially reported that forced smile configurations enhanced humor ratings (Strack et al., 1988). However, a large registered replication report with seventeen independent laboratories failed to reproduce this effect, igniting debates about the robustness of facial feedback effects, the moderating role of methodological details including explicit awareness of the manipulation's purpose, and the implications for embodied emotion theories (Wagenmakers et al., 2016). Subsequent meta-analyses and theoretical analyses have suggested that facial feedback effects may exist but are smaller and more context-dependent than initially believed, with awareness of the experimental hypothesis potentially eliminating effects through demand characteristics (Coles et al., 2019).

Postural manipulations provide another avenue for investigating somatic contributions to emotion and cognition, with studies examining whether adopting expansive versus constricted body postures influences mood, stress responses, and risk-taking behavior. Carney and colleagues (2010) reported that adopting high-power poses (expansive postures with opened limbs and torso expansion) for two minutes increased self-reported feelings of powerfulness, elevated testosterone levels, decreased cortisol levels, and enhanced risk-taking compared to low-power poses (constricted postures with closed limbs and torso constriction), interpreted as evidence that embodied power displays influence psychological and physiological states associated with dominance and status. This "power posing" phenomenon received substantial popular attention but also prompted replication attempts that yielded mixed results, with most failing to reproduce hormonal effects and some failing to find psychological effects (Ranehill et al., 2015; Credé & Phillips, 2017). Subsequent investigations have clarified that while postural expansiveness may influence subjective feelings of power under some conditions, the dramatic hormonal and risk-taking effects initially reported were likely overestimated, and the theoretical mechanisms underlying any reliable effects remain unclear (Cuddy et al., 2018).

These replication challenges in embodied emotion research have prompted important methodological and theoretical discussions within the field regarding effect sizes, publication bias, the role of contextual factors and individual differences as potential moderators, and the theoretical interpretation of embodied effects when they do occur (Cesario et al., 2017). Some theorists have argued that failures to replicate embodied effects challenge core embodiment principles and suggest that bodily influences on cognition are weaker or more constrained than embodied cognition proponents initially claimed (Mahon & Caramazza, 2008). Others contend that embodied theories are consistent with context-dependent effects and do not require that bodily manipulations invariably influence cognition across all circumstances, noting that the strength of embodied effects likely depends on factors including the salience of bodily information, competition from other information sources, individual differences in embodied processing tendencies, and the specific cognitive processes engaged (Barsalou, 2016).

Individual differences in the magnitude of embodied effects represent an understudied dimension that may help resolve debates about the role of bodily feedback in cognition and emotion. If embodied cognitive processing varies across individuals as a function of factors including interoceptive accuracy, attentional orientation toward bodily sensations, the functional connectivity between interoceptive and cognitive brain regions, or the efficiency of physiological signal transduction and processing, then embodied effect sizes in unselected samples would reflect averaging across individuals for whom bodily information strongly influences cognition and individuals for whom such influences are minimal (Vermeulen et al., 2016). Some preliminary evidence supports this individual differences perspective: Dunn and colleagues (2010) found that individuals scoring higher on the Toronto Alexithymia Scale, indicating difficulty identifying and describing feelings, showed reduced influences of facial feedback on emotional experience, suggesting that alexithymia may reflect diminished access to or utilization of bodily feedback for emotion. Similarly, studies have reported that individuals with higher interoceptive accuracy show stronger emotional responses to affective stimuli and greater concordance between physiological arousal and subjective emotional intensity (Dunn et al., 2010; Herbert et al., 2010).

The role of autonomic nervous system responsivity in emotional experience has been investigated extensively, with the question of whether specific emotions exhibit distinct patterns of peripheral physiological activation remaining contentious despite decades of research (Cacioppo et al., 2000; Kreibig, 2010). Early theories proposed that different emotions involve unique patterns of autonomic activation that could potentially serve as peripheral signatures distinguishing emotions, while alternative views suggested that autonomic arousal provides undifferentiated physiological activation that becomes labeled as specific emotions through cognitive appraisal processes (Schachter & Singer, 1962). Meta-analytic reviews have found evidence for some emotion-specific patterns of autonomic activation, particularly distinguishing broad categories such as approach-related versus avoidance-related emotions, but the degree of physiological specificity remains insufficient for reliably identifying discrete emotions from peripheral physiological patterns alone (Cacioppo et al., 2000; Kreibig, 2010). More recent perspectives emphasize that while peripheral physiological patterns exhibit some emotion-related variation, the subjective experience of specific emotions depends on brain systems that integrate peripheral physiological signals with contextual information, memories, and conceptual knowledge about emotion categories, such that peripheral physiology contributes to but does not determine emotional experience (Barrett, 2017).

Respiratory physiology represents a particularly interesting domain for understanding embodied emotion given the bidirectional relationships between breathing patterns and emotional states, with anxiety producing rapid shallow breathing while slow deep breathing can reduce anxiety, creating a physiological feedback loop potentially

amenable to modulation (Homma & Masaoka, 2008; Zelano et al., 2016). Respiratory phase has been shown to influence perceptual processing, memory encoding, and emotion recognition, with nasal inhalation enhancing processing in ways that exhalation does not, potentially reflecting the entrainment of neural oscillations in olfactory and limbic regions by the respiratory rhythm (Zelano et al., 2016). Individual variation in respiratory patterns, respiratory sensitivity, and the coupling between respiratory and neural oscillations could thereby contribute to differences in emotional reactivity and cognitive processing, though systematic investigations of such relationships remain sparse. The vagus nerve, conveying substantial bidirectional communication between the brain and viscera including the heart, lungs, and gastrointestinal tract, provides another critical pathway for physiological-emotional coupling, with vagal tone as indexed by heart rate variability associated with emotional regulation capacity and stress resilience (Thayer & Lane, 2000; Porges, 2011).

The gastrointestinal system has emerged as an unexpected contributor to emotional and cognitive processes through the gut-brain axis, involving bidirectional neural communication via vagal and spinal afferents, hormonal signaling through gut peptides including cholecystokinin, ghrelin, and peptide YY, and indirect influences through gut microbiota metabolism producing neuroactive compounds including short-chain fatty acids, tryptophan metabolites, and gamma-aminobutyric acid (Mayer, 2011; Cryan & Dinan, 2012). While much of the gut-brain axis literature focuses on pathological conditions including irritable bowel syndrome, inflammatory bowel disease, and psychiatric disorders, the relevance for normal individual differences in embodied cognition remains largely speculative. Nevertheless, the demonstrated capacity of gut microbiota composition to influence anxiety-like behavior, depression-related phenotypes, and cognitive function in rodent models, combined with correlations between gut microbiome profiles and mood in human observational studies, suggests that gastrointestinal physiology and its microbial ecology may constitute an underappreciated dimension of embodied cognitive-emotional processing (Cryan & Dinan, 2012; Foster & McVey Neufeld, 2013).

2.4 Mitochondrial Influences on Physiological Systems Supporting Embodied Cognition

The mechanistic connections between mitochondrial function and the physiological systems undergirding embodied cognition operate through multiple pathways including effects on peripheral physiological responses, modulation of afferent interoceptive signaling, influences on autonomic nervous system function, and impacts on the neural processing of interoceptive information. Given that mitochondria provide the primary energy source for virtually all physiological processes requiring ATP, maintain calcium homeostasis in multiple tissue types, regulate cellular redox state, and participate in signaling cascades governing cellular adaptation to metabolic stress, individual variation in mitochondrial

function arising from mtDNA sequence differences could propagate through these interconnected physiological systems to influence the substrates of embodied cognition (Wallace, 2005; Picard & McEwen, 2014).

At the most fundamental level, mitochondrial ATP production capacity constrains the magnitude and duration of energy-demanding physiological responses including cardiac contractile force, smooth muscle contraction in vascular and visceral tissues, skeletal muscle work capacity, and metabolic heat production, all of which generate interoceptive afferent signals that inform central representations of bodily state (Nisoli et al., 2003; Picard et al., 2014). Cardiac mitochondria exhibit among the highest densities in the body, with approximately thirty percent of cardiomyocyte volume occupied by mitochondria that must sustain the continuous rhythmic contraction of the heart throughout the lifespan, and individual variation in cardiac mitochondrial function could influence cardiac performance, exercise capacity, and the generation of cardiac interoceptive signals including mechanoreceptor and metabolic chemoreceptor afference from the myocardium (Stanley et al., 2005; Doenst et al., 2013). Similarly, vascular smooth muscle mitochondrial function influences vasomotor tone through effects on ATP-dependent potassium channels, calcium handling, and the production of mitochondrial reactive oxygen species that modulate nitric oxide signaling, thereby affecting blood pressure regulation and regional blood flow patterns that are monitored by baroreceptors and contribute to interoceptive representation (Förstermann & Münzel, 2006; Quintero et al., 2006).

The gastrointestinal system relies extensively on mitochondrial function for smooth muscle contractility governing gut motility, secretory processes including acid production and enzyme secretion, and the maintenance of the intestinal epithelial barrier, with mitochondrial dysfunction implicated in various gastrointestinal disorders (Echtay et al., 2002; Picard & Shirihai, 2013). Visceral afferent neurons that innervate the gastrointestinal tract and convey interoceptive information regarding distension, chemical composition, and inflammatory status contain mitochondria whose function influences neuronal excitability and therefore the encoding of visceral stimuli (Xu & Gulbins, 2010). Individual differences in gastrointestinal mitochondrial function arising from mtDNA variation might thereby influence gut motility patterns, visceral sensitivity, and the generation of gastrointestinal interoceptive signals that contribute to feelings of hunger, satiety, nausea, and general visceral comfort or discomfort, though direct empirical investigation of such relationships appears absent from the literature.

The autonomic nervous system, mediating bidirectional communication between the central nervous system and peripheral organs, represents another critical interface where mitochondrial function could influence embodied cognition. Sympathetic and parasympathetic preganglionic and postganglionic neurons must sustain tonic activity and generate rapid responses to central autonomic commands, requiring substantial

mitochondrial ATP provision, and presynaptic terminals at sympathetic and parasympathetic neuroeffector junctions contain enriched mitochondrial populations that support neurotransmitter synthesis and release (Sheng & Cai, 2012). Mitochondrial dysfunction in autonomic neurons produces autonomic neuropathy characterized by reduced heart rate variability, impaired blood pressure regulation, gastrointestinal dysmotility, and thermoregulatory abnormalities, as observed in various mitochondrial diseases and in diabetic autonomic neuropathy (Freeman, 2005; Schüle et al., 2014). The possibility that more subtle variation in mitochondrial function arising from common mtDNA polymorphisms influences autonomic function in subclinical ways that nonetheless contribute to individual differences in autonomic reactivity and autonomic-cognitive coupling remains largely unexplored.

Heart rate variability, reflecting predominantly parasympathetic vagal modulation of cardiac pacemaker activity, provides a noninvasive window into autonomic function and has been proposed as a biomarker of self-regulatory capacity, stress resilience, and emotional regulation (Thayer & Lane, 2000; Appelhans & Luecken, 2006). The generation of heart rate variability depends on the functional integrity of the central autonomic network including prefrontal cortex, anterior cingulate, insula, amygdala, hypothalamus, and medullary cardiovagal neurons, as well as the vagus nerve itself and cardiac responsiveness to vagal acetylcholine release (Thayer et al., 2012). Mitochondrial function could influence heart rate variability through effects at multiple levels: central autonomic neurons require substantial mitochondrial ATP provision to maintain tonic activity; vagal preganglionic and postganglionic neurons depend on mitochondrial function for neurotransmitter synthesis and release; cardiac pacemaker cells' responsiveness to acetylcholine involves potassium channel function that may be influenced by mitochondrial ATP production; and the entire integrative capacity of the central autonomic network likely depends on adequate bioenergetic support (Thayer et al., 2012; Doenst et al., 2013).

One study by Kato and colleagues (2012) investigated associations between mitochondrial haplogroups and heart rate variability in Japanese men, finding that individuals with haplogroup D exhibited significantly higher measures of heart rate variability including high-frequency power, which reflects parasympathetic vagal tone, compared to individuals with other haplogroups, suggesting that mitochondrial genomic variation may influence autonomic function in detectable ways even in healthy populations. However, this appears to be among the only investigations directly examining mitochondrial haplogroup associations with autonomic function, and replication in independent samples and other populations remains necessary to establish the reliability and generalizability of such effects. The mechanistic pathways through which mitochondrial genomic variation might influence autonomic function remain speculative, potentially involving systemic effects on cardiovascular physiology, influences on autonomic neuron function, or indirect effects through metabolic signaling pathways, but require detailed experimental investigation.

The processing of interoceptive afferent information by central nervous system structures represents another domain where mitochondrial function could influence embodied cognition. The brain regions most critical for interoceptive processing, including the insula, anterior cingulate cortex, and somatosensory cortex, exhibit substantial metabolic activity and mitochondrial content, and their functional capacity depends on adequate bioenergetic support (Critchley & Harrison, 2013). Individual differences in neural mitochondrial function could influence interoceptive neural processing through multiple mechanisms: altering the signal-to-noise ratio in neural representations of bodily states by affecting baseline neuronal activity levels and response magnitudes; modulating synaptic plasticity in interoceptive pathways and thereby influencing the development and maintenance of interoceptive representations; affecting the functional connectivity between interoceptive cortices and other brain regions involved in emotion, cognition, and autonomic control; and influencing the capacity for sustained attention to interoceptive signals, which requires metabolically demanding maintenance of task-relevant neural activity patterns (Raichle & Mintun, 2006; Harris et al., 2012).

The insular cortex, serving as the primary cortical substrate for interoceptive representation, exhibits distinctive cytoarchitectonic organization with agranular anterior regions and granular posterior regions, and demonstrates elevated baseline metabolic activity as measured through positron emission tomography studies of regional cerebral glucose metabolism (Nagai et al., 2007). The metabolic demands of maintaining the integrative interoceptive representations in the insula, which synthesize information from multiple bodily sources and integrate this with emotional, mnemonic, and contextual information, likely render insular function sensitive to variations in mitochondrial bioenergetic capacity. Several neuroimaging studies of individuals with mitochondrial diseases have reported alterations in insular cortex structure or function, including reduced gray matter volume, altered functional connectivity, and abnormal activation patterns during cognitive tasks, though these studies typically focus on gross pathological changes rather than subtle variations that might relate to embodied cognitive processes (Bindu et al., 2008; Leung et al., 2015).

The anterior cingulate cortex, another critical node in interoceptive processing and autonomic control, exhibits among the highest baseline metabolic rates in the brain and contains elevated densities of mitochondria in pyramidal neurons, suggesting substantial bioenergetic demands (Hyder et al., 2006). The anterior cingulate participates in error monitoring, conflict detection, autonomic regulation, and pain processing, all functions that involve integration of cognitive and interoceptive information, and computational models suggest that these integrative functions depend on sustained tonic activity and rapid phasic responses that place substantial demands on cellular energy metabolism (Bush et al., 2000; Shenhav et al., 2013). Individual differences in anterior cingulate mitochondrial function could therefore influence the efficiency of cognitive-interoceptive integration, potentially

contributing to variation in emotional awareness, pain perception, and the subjective intensity of bodily feelings.

The somatosensory cortex, representing both exteroceptive tactile information and interoceptive information from deep tissues, exhibits metabolic activity that responds dynamically to sensory stimulation, with regional increases in glucose metabolism and oxygen consumption accompanying somatosensory processing (Ngai et al., 1999). The capacity to generate robust somatosensory representations depends on adequate ATP provision to support synaptic transmission, with experimental evidence indicating that metabolic stress impairs somatosensory processing and that enhancement of mitochondrial function can improve sensory recovery following neurological injury (Jiang et al., 2013). The possibility that individual variation in somatosensory cortex mitochondrial function influences the vividness, accuracy, or affective tone of somatosensory and interoceptive representations merits investigation but remains entirely speculative at present.

Beyond the direct neural processing of interoceptive information, mitochondrial function could influence embodied cognition through effects on stress response systems that bidirectionally interact with cognitive and emotional processes. The hypothalamic-pituitary-adrenal axis, which governs cortisol release in response to stress and exhibits circadian rhythmicity, depends on mitochondrial function at multiple levels including hypothalamic corticotropin-releasing hormone neuron activity, pituitary corticotroph responsiveness, and adrenal cortisol synthesis (Picard et al., 2014). Mitochondria themselves respond to glucocorticoids through genomic and non-genomic mechanisms, with cortisol influencing mitochondrial biogenesis, respiratory chain function, and apoptosis susceptibility, creating feedback loops between mitochondrial function and stress physiology (Du et al., 2009; Picard & McEwen, 2014). Individual differences in mitochondrial genomic architecture could influence stress response system function through altered responsiveness to glucocorticoid signaling, differential energetic capacity to sustain stress-related physiological demands, or variation in the mitochondrial contribution to cellular stress adaptation mechanisms (Picard et al., 2014).

The concept of allostatic load, referring to the cumulative physiological dysregulation resulting from chronic or repeated stress exposure, involves mitochondrial dysfunction as both a consequence of sustained stress and a contributor to stress-related pathology (McEwen & Gianaros, 2010; Picard et al., 2014). Chronic stress exposure produces mitochondrial damage through multiple mechanisms including glucocorticoid excess, oxidative stress, calcium dysregulation, and inflammatory signaling, while pre-existing mitochondrial vulnerabilities may predispose to more severe stress-related physiological consequences by limiting cellular capacity for adaptive responses (Picard & McEwen, 2014; Picard et al., 2018). This bidirectional relationship between mitochondrial function and stress physiology suggests that individual differences in mitochondrial genomic constitution

could influence stress resilience, the physiological impact of stress exposure, and the development of stress-related alterations in embodied cognitive processing including changes in interoceptive sensitivity, emotional reactivity, and somatic symptom development.

Inflammation represents another interface between mitochondrial function and embodied cognition, as mitochondria participate critically in inflammatory signaling through multiple mechanisms including inflammasome activation, mitochondrial DNA release that triggers innate immune responses, and metabolic reprogramming of immune cells (Weinberg et al., 2015; Tschopp, 2011). Systemic inflammation influences brain function through multiple routes including cytokine signaling across the blood-brain barrier, activation of vagal afferents that convey immune status to brainstem nuclei, and peripheral-to-central transmission of inflammatory signals through circumventricular organs and choroid plexus (Dantzer et al., 2008). The behavioral consequences of inflammation, collectively termed sickness behavior, include fatigue, anhedonia, social withdrawal, altered pain sensitivity, and disrupted sleep, representing adaptive responses that promote energy conservation and recovery but can become maladaptive when inflammation persists (Dantzer et al., 2008; Miller et al., 2009). Individual differences in mitochondrial function could influence both the propensity to generate inflammatory responses and the sensitivity to inflammatory signals, potentially contributing to variation in the embodied experience of illness, the development of chronic fatigue and pain syndromes, and vulnerability to inflammation-associated mood disturbances (Maes et al., 2012; Morris & Maes, 2013).

The emerging field of mitochondrial psychobiology, articulated by Picard and colleagues, proposes that mitochondria should be understood as biosensors and bioregulators that integrate information about cellular energetic state, stress exposure, and environmental demands, translating this information into adaptive changes in cellular function through retrograde signaling to the nucleus, metabolite provision for epigenetic modifications, and influences on cellular stress response pathways (Picard et al., 2018). This framework positions mitochondria as critical mediators of embodiment, linking whole-organism physiological state to cellular and molecular processes that influence neural function and ultimately psychological experience. Individual variation in mitochondrial genomic architecture, by establishing different setpoints for mitochondrial bioenergetic capacity, stress sensitivity, and signaling properties, could thereby contribute to individual differences in the physiological foundations of embodied cognition and the characteristic ways that individuals experience and respond to bodily states.

Part III: Disconnected Research Streams and Emerging Convergences

3.1 Mitochondrial Haplogroups and Neuropsychiatric Phenotypes: Indirect Evidence for Embodied Effects

While no studies have directly investigated relationships between mitochondrial genomic variation and embodied cognitive processes as operationalized in contemporary embodied cognition research, substantial indirect evidence from investigations of mitochondrial haplogroup associations with neuropsychiatric conditions, cognitive performance, and brain structure provides suggestive support for the hypothesis that mtDNA variation influences brain function in ways potentially relevant to embodied cognition. The methodological challenges inherent in detecting subtle effects of common genetic variation on complex behavioral phenotypes, combined with the relative neglect of mitochondrial genetics in psychiatric genetics and cognitive neuroscience, have resulted in a sparse and heterogeneous literature that nevertheless yields intriguing patterns worthy of systematic synthesis.

Association studies examining mitochondrial haplogroups and Parkinson's disease have produced the most consistent findings in neuropsychiatric mitochondrial genetics, with multiple investigations reporting that certain European haplogroups, particularly haplogroup J and related haplogroups in the JT cluster, are associated with reduced risk of Parkinson's disease, while other haplogroups including haplogroup H subgroups show neutral or slightly elevated risk (van der Walt et al., 2003; Khusnutdinova et al., 2008; Hudson et al., 2013). Meta-analyses of European studies have confirmed that haplogroup J confers approximately twenty-five to thirty-five percent reduction in Parkinson's disease risk compared to the most common haplogroup H, a finding that has replicated across multiple independent cohorts and geographic regions (Chinnery & Schon, 2003; Hudson et al., 2013). The mechanistic basis for this protective effect remains incompletely understood but likely involves the functional consequences of haplogroup-defining variants on Complex I function, with haplogroup J characterized by the m.10398A>G variant causing a Thr114Ala substitution in ND3 that may alter Complex I assembly, stability, or catalytic properties in ways that reduce oxidative stress or enhance cellular resilience to mitochondrial dysfunction (Gómez-Durán et al., 2010; Maruszak et al., 2014).

Given that Parkinson's disease involves selective degeneration of dopaminergic neurons in the substantia nigra that project to the striatum and contribute to motor control, with non-motor symptoms including depression, anxiety, cognitive impairment, and autonomic dysfunction also prominent, the haplogroup associations with Parkinson's disease demonstrate that common mtDNA variation can influence brain systems relevant to motor function, emotion, cognition, and autonomic regulation (Chaudhuri et al., 2006). While the Parkinson's disease haplogroup associations primarily reflect effects on neurodegeneration susceptibility rather than normal variation in neural function, they establish proof-of-principle that mtDNA variation influences neurological phenotypes and

suggest that subtler effects on the neural systems affected in Parkinson's disease might exist across the normal population variation continuum.

Associations between mitochondrial haplogroups and Alzheimer's disease have been investigated extensively but yield less consistent results compared to Parkinson's disease, with different studies reporting associations with various haplogroups including H, J, T, U, and K, with some finding increased risk and others finding decreased risk for the same haplogroups (Santoro et al., 2010; Ridge et al., 2012). Meta-analyses have struggled to identify robust haplogroup effects on Alzheimer's disease risk, likely reflecting genuine population-specific effects where the functional consequences of mtDNA variants interact with nuclear genetic background and environmental factors in ways that differ across populations, as well as methodological heterogeneity across studies (Santoro et al., 2010). Nevertheless, the overall pattern suggests that mitochondrial function contributes to Alzheimer's disease pathogenesis, and specific mtDNA variants may influence individual vulnerability to the cognitive decline characteristic of dementia, though the effect sizes appear modest and context-dependent.

Several investigations have examined mitochondrial haplogroup associations with psychiatric conditions including depression, bipolar disorder, and schizophrenia, generally reporting weak or null associations that fail to replicate consistently across studies (Kazuno et al., 2009; Müller et al., 2014). However, the psychiatric genetics literature has been dominated by nuclear genome-wide association studies, with mitochondrial variation receiving comparatively minimal attention and most psychiatric genetics studies not examining mtDNA variation systematically. The few targeted investigations of mitochondrial genetics in psychiatric disorders have typically employed modest sample sizes insufficient to detect the small effect sizes expected for common variants influencing complex psychiatric phenotypes, potentially explaining the lack of consistent findings (Müller et al., 2014). Additionally, if mitochondrial genomic effects on psychiatric phenotypes operate primarily through influences on embodied dimensions including interoceptive processing, physiological reactivity, and somatic symptom manifestation rather than through categorical diagnostic outcomes, standard case-control designs comparing diagnosed patients to healthy controls would lack sensitivity to detect such effects.

Cognitive performance represents another domain where mitochondrial haplogroup associations have been investigated, with mixed results that may reflect genuine population specificity, phenotype heterogeneity, and the challenges of detecting small effects. A study by Kalman and colleagues (2002) reported that European haplogroup H was associated with better performance on cognitive tests in a sample of Hungarian subjects, while haplogroup K showed poorer cognitive performance, but subsequent replication attempts have yielded inconsistent results (Paasuke et al., 2016). Studies in Asian populations have examined associations between haplogroups and cognitive function with similarly mixed findings,

including reports that certain haplogroups are associated with longevity and maintained cognitive function in elderly individuals (Bilal et al., 2008). The heterogeneity of cognitive assessments employed across studies, differences in population backgrounds, and failure to account for relevant covariates including education, socioeconomic status, and other genetic factors likely contribute to inconsistent findings.

Neuroimaging investigations relating mitochondrial haplogroups to brain structure or function remain extremely sparse but provide some of the most direct evidence that mtDNA variation influences brain phenotypes relevant to cognition and emotion. Feder and colleagues (2011) examined associations between European mitochondrial haplogroups and regional brain metabolism measured with fluorodeoxyglucose positron emission tomography in cognitively normal elderly individuals, finding that haplogroup J was associated with higher glucose metabolism in several brain regions including temporal and parietal cortices, while haplogroup H showed relatively lower metabolism in these regions. Given that glucose metabolism reflects local neural activity and energy demands, these findings suggest that haplogroup-related differences in cellular bioenergetics manifest as measurable differences in regional brain metabolic activity, though the functional consequences for cognitive processing were not examined in this study (Feder et al., 2011).

A study by Tranah and colleagues (2012) investigated mitochondrial haplogroups in relation to volumetric brain magnetic resonance imaging measures in older adults, reporting associations between specific haplogroups and regional brain volumes including total brain volume, white matter volume, and hippocampal volume. The associations were complex and included interactions with age, suggesting that haplogroup effects on brain structure may involve differential trajectories of age-related atrophy rather than stable differences throughout adulthood (Tranah et al., 2012). These findings require replication in larger samples with longitudinal imaging to clarify whether haplogroup associations reflect developmental differences in brain structure, differential aging trajectories, or both, and to establish the functional significance of observed volumetric differences.

Magnetic resonance spectroscopy studies examining brain metabolites including N-acetylaspartate, creatine, and lactate in relation to mitochondrial function provide another neuroimaging approach relevant to understanding how mtDNA variation might influence brain chemistry and energy metabolism. While most such studies focus on pathological mitochondrial mutations producing clinical disease, the principles established in these investigations—that mitochondrial dysfunction alters brain metabolite profiles detectable with spectroscopy—suggest that more subtle metabolic variations associated with common mtDNA polymorphisms might also be detectable with sufficiently sensitive methods and adequate sample sizes (Deichmann et al., 1995; Kaufmann et al., 2004). The specific metabolite alterations associated with mitochondrial dysfunction, including elevated lactate reflecting increased anaerobic glycolysis and reduced N-acetylaspartate

reflecting neuronal metabolic dysfunction, provide potential biomarkers that could be examined in relation to mtDNA haplogroups in future studies.

3.2 Interoceptive Accuracy and Psychiatric Symptoms: A Somatic Link to Psychopathology

Parallel to the emerging understanding of mitochondrial influences on brain function, a substantial body of research has investigated interoceptive processing in psychiatric and psychosomatic conditions, revealing that alterations in interoceptive accuracy, sensibility, and awareness characterize multiple forms of psychopathology in ways potentially relevant to understanding embodied aspects of mental illness (Khalsa et al., 2018; Owens et al., 2018). Anxiety disorders have been associated with altered interoceptive processing across multiple studies, with evidence suggesting that individuals with panic disorder show heightened interoceptive accuracy for cardiac sensations, interpret ambiguous bodily sensations catastrophically, and exhibit enhanced activation of insular cortex during interoceptive attention tasks (Domschke et al., 2010; Paulus & Stein, 2010). This pattern suggests that anxiety may involve hypersensitivity to bodily signals combined with maladaptive interpretations of these signals as threatening, creating a vicious cycle wherein physiological arousal triggers anxiety which generates further physiological arousal.

The catastrophic misinterpretation model of panic disorder, proposed by Clark (1986), emphasizes that panic attacks result from misinterpretation of normal bodily sensations such as palpitations, breathlessness, or dizziness as indicators of imminent physical catastrophe including heart attack, suffocation, or loss of consciousness. This cognitive-somatic model positions interoceptive processing at the center of panic psychopathology, suggesting that individual differences in interoceptive signal detection, interpretation, and attentional bias toward bodily sensations contribute to panic vulnerability (Clark, 1986; Casey et al., 2008). Subsequent research has generally supported elements of this model, showing that individuals with panic disorder demonstrate heightened awareness of cardiac sensations, increased attention to bodily changes, and catastrophic interpretation biases, though the causal relationships among these factors remain incompletely characterized (Domschke et al., 2010).

Depression has been associated with altered interoceptive processing in more complex and sometimes contradictory patterns, with some studies reporting reduced interoceptive accuracy in depression, suggesting blunted access to bodily signals, while others report heightened focus on negative bodily sensations and increased somatic symptoms (Dunn et al., 2007; Furman et al., 2013). These apparently contradictory findings may reflect heterogeneity within depression, with different symptom dimensions or depression subtypes associated with different interoceptive profiles. For instance, melancholic depression characterized by prominent neurovegetative symptoms including

sleep disturbance, appetite changes, and psychomotor alterations might be associated with altered interoceptive processing of these physiological domains, while atypical depression with mood reactivity and reversed neurovegetative symptoms might show different patterns (Dunn et al., 2007). The anhedonic dimension of depression, involving reduced capacity to experience pleasure, has been linked to blunted interoceptive processing and reduced insular cortex activation during reward anticipation and consumption, suggesting that the subjective affective experience associated with rewards depends partly on interoceptive representations of bodily reward responses (Furman et al., 2013; Gu et al., 2013).

Somatic symptom disorders, characterized by persistent physical symptoms not fully explained by medical conditions and associated with excessive thoughts, feelings, and behaviors related to the symptoms, represent perhaps the most direct psychiatric manifestation of altered embodiment and interoceptive processing (American Psychiatric Association, 2013). These conditions, historically termed somatization disorder, hypochondriasis, and psychosomatic conditions, are now understood as involving complex interactions among peripheral physiological processes, interoceptive neural processing, attentional biases, catastrophic cognitions, and learning mechanisms that maintain symptom preoccupation (Henningsen et al., 2018). Multiple studies have found that individuals with somatic symptom disorders exhibit heightened interoceptive accuracy for some bodily domains, attentional bias toward bodily sensations, and altered insular cortex structure and function, supporting the hypothesis that these conditions involve dysfunctional embodied processing (Nagai et al., 2007; Pollatos et al., 2011).

Functional somatic syndromes including chronic fatigue syndrome, fibromyalgia, irritable bowel syndrome, and chronic pain conditions share common features including medically unexplained somatic symptoms, overlap in symptom profiles across syndromes, and associations with stress, trauma, and psychiatric comorbidity, leading to proposals that these conditions may represent different manifestations of a common underlying mechanism involving altered interoceptive processing, central pain sensitization, and autonomic dysregulation (Yunus, 2008; Henningsen et al., 2018). Mitochondrial dysfunction has been implicated in several of these conditions through various lines of evidence including biochemical abnormalities in muscle biopsies from chronic fatigue syndrome patients, association studies reporting increased frequency of mtDNA polymorphisms in fibromyalgia, and theoretical proposals that inadequate cellular energy provision contributes to symptoms of fatigue and pain (Myhill et al., 2009; Cordero et al., 2009; Castro-Marrero et al., 2013). However, the quality of evidence varies considerably, and many studies suffer from small sample sizes, inadequate controls, and failure to replicate findings across independent cohorts.

The hypothesis that mitochondrial dysfunction contributes to functional somatic syndromes gains plausibility from several considerations: the prominent fatigue and exercise intolerance characteristic of these conditions resembles symptoms of proven mitochondrial diseases; peripheral physiological abnormalities including reduced aerobic capacity and altered pain processing could reflect inadequate bioenergetic support; and central nervous system manifestations including cognitive difficulties, mood disturbance, and sleep disruption might reflect brain energy metabolism impairments (Maes et al., 2012; Mandarano et al., 2016). Nevertheless, definitive evidence that common mtDNA variation contributes to functional somatic syndrome vulnerability remains lacking, and alternative or complementary mechanisms including central sensitization, stress system dysregulation, immune activation, and psychological factors clearly contribute substantially to these conditions (Yunus, 2008).

Alexithymia, a personality construct characterized by difficulty identifying feelings, difficulty describing feelings, externally-oriented thinking style, and limited imaginal processes, has been investigated in relation to interoceptive processing with the hypothesis that alexithymia may reflect impaired access to or utilization of bodily emotional signals (Taylor et al., 1997). Multiple studies have reported that individuals scoring higher on alexithymia measures show reduced interoceptive accuracy as measured by heartbeat detection tasks, as well as altered insular cortex structure including reduced gray matter volume, and altered insular activation during emotional processing (Pollatos et al., 2008; Bird et al., 2010). These findings support the hypothesis that alexithymia involves disrupted embodied emotional processing wherein bodily emotional responses are generated but not adequately perceived or integrated into subjective emotional experience, though the direction of causality remains unclear—reduced interoceptive accuracy might cause alexithymia by depriving individuals of bodily emotional information, or alexithymia might involve attentional or interpretive processes that reduce apparent interoceptive accuracy without necessarily reflecting absent interoceptive signals.

Autism spectrum disorders have been associated with altered interoceptive processing in several investigations, with some studies reporting reduced interoceptive accuracy in autistic individuals and others finding no differences or even enhanced accuracy for certain bodily signals (Garfinkel et al., 2016; DuBois et al., 2016). The heterogeneity of findings likely reflects the substantial heterogeneity within autism spectrum disorders regarding sensory processing profiles, with some autistic individuals exhibiting sensory hyposensitivity and others exhibiting hypersensitivity, potentially extending to interoceptive domains (Tavassoli et al., 2014). Theoretical proposals that autism involves disrupted embodied social cognition, including reduced automatic mimicry of others' bodily states and impaired empathy based on shared somatosensory representations, suggest that interoceptive and somatic processing alterations may contribute to the social-communicative difficulties characteristic of autism (Gallese & Rochat, 2018).

The transdiagnostic relevance of interoceptive processing alterations across multiple psychiatric conditions suggests that interoceptive dysfunction may represent a dimensional vulnerability factor that contributes to psychopathology risk and symptom expression rather than being specific to particular diagnostic categories (Khalsa et al., 2018). If mitochondrial genomic variation influences the physiological substrates of interoceptive processing as hypothesized, then mtDNA variation might contribute to transdiagnostic vulnerability through effects on interoception, though this hypothesis remains entirely speculative absent empirical investigation. The overlap between conditions associated with interoceptive alterations and conditions where mitochondrial dysfunction has been implicated, including anxiety, depression, chronic fatigue, and pain syndromes, provides circumstantial support for potential connections but falls far short of demonstrating causal relationships.

3.3 Mitochondrial Function in Neurodevelopmental Trajectories and Individual Differences in Cognitive Style

The role of mitochondrial function in neurodevelopment, spanning from early prenatal brain formation through adolescent synaptic refinement and into adult neuroplasticity, provides another potential pathway through which mtDNA variation might influence embodied cognition by shaping the developmental trajectories that establish individual differences in neural organization, connectivity patterns, and functional processing characteristics (Lezi & Swerdlow, 2012; Mattson & Gleichmann, 2013). Mitochondria contribute to neurodevelopment through multiple mechanisms including ATP provision for the energy-intensive processes of neurogenesis, neuronal migration, axon outgrowth, dendrite elaboration, and synaptogenesis; calcium signaling that regulates developmental processes including growth cone guidance and activity-dependent synaptic refinement; reactive oxygen species signaling that influences neuronal differentiation and survival; and metabolite provision for biosynthetic processes including membrane lipid synthesis and neurotransmitter production (Mattson & Gleichmann, 2013; Khacho et al., 2019).

The proliferation and differentiation of neural progenitor cells during prenatal and early postnatal brain development exhibit dynamic changes in mitochondrial function and metabolic state, with neural stem cells relying predominantly on glycolytic metabolism in their quiescent state but upregulating oxidative phosphorylation and mitochondrial biogenesis during neuronal differentiation (Khacho et al., 2016). This metabolic reprogramming appears necessary for proper neuronal differentiation, with experimental manipulations that maintain glycolytic metabolism or impair mitochondrial function preventing or delaying differentiation (Khacho et al., 2016; Beckervordersandforth et al., 2017). Individual variation in the efficiency or timing of this metabolic transition during neurodevelopment could influence the pace of brain maturation, the final number and

distribution of neurons and glia in various brain regions, and the establishment of connectivity patterns, though direct evidence for such effects of common mtDNA variation remains minimal.

Synaptic development and refinement, involving the initial exuberant formation of synaptic connections followed by activity-dependent pruning that eliminates less-used synapses while strengthening frequently activated connections, creates critical periods during which experience shapes brain organization (Huttenlocher & Dabholkar, 1997; Lichtman & Colman, 2000). The energy demands of synapse formation, maintenance, and elimination are substantial, with estimates suggesting that synaptic transmission and associated processes account for the majority of brain energy consumption (Harris et al., 2012). Mitochondrial positioning at synapses is dynamically regulated by neuronal activity, with activated synapses recruiting mitochondria to provide localized energy provision and calcium buffering, and synapses that fail to recruit adequate mitochondrial support may be preferentially eliminated during developmental pruning (Li et al., 2004; Mattson & Gleichmann, 2013). Individual differences in mitochondrial motility, synaptic targeting, or bioenergetic capacity arising from mtDNA variation could thereby influence developmental synaptic refinement, potentially contributing to individual differences in neural connectivity and circuit organization that persist into adulthood.

Myelination, the process by which oligodendrocytes wrap myelin sheaths around axons to enable rapid saltatory conduction of action potentials, represents another metabolically demanding developmental process where mitochondrial function plays critical roles (Camargo et al., 2017). Oligodendrocytes exhibit abundant mitochondria and high oxidative metabolic rates to support the synthesis of myelin lipids and proteins, and oligodendrocyte mitochondrial dysfunction impairs myelination in various mitochondrial disorders (Fünfschilling et al., 2012; Viader et al., 2013). The timing and extent of myelination vary substantially across brain regions, with sensory and motor areas myelinating earlier while prefrontal and association cortices continue myelinating into the third decade of life, potentially creating windows during which mitochondrial function influences regional myelination and thereby connectivity and processing speed (Fields, 2008). Individual variation in myelination patterns, reflected in diffusion tensor imaging measures of white matter microstructure, correlates with cognitive abilities and processing speed, suggesting functional significance (Penke et al., 2010).

The concept of cognitive reserve, referring to individual differences in the brain's ability to cope with neuropathology and maintain function despite structural damage, has been related to factors including education, occupational complexity, and engagement in cognitively stimulating activities, which presumably establish more elaborate neural networks and more efficient processing that enables compensation when damage occurs (Stern, 2009). While typically conceptualized in terms of environmental enrichment effects,

cognitive reserve may also have biological components including individual differences in metabolic capacity, mitochondrial function, and cellular stress resilience that influence the brain's ability to sustain function under adverse conditions (Stern, 2009; Fang et al., 2019). Mitochondrial genomic variation that enhances bioenergetic efficiency, reduces oxidative stress, or improves stress resistance could thereby contribute to cognitive reserve, though empirical investigation of such relationships remains minimal.

Individual differences in cognitive processing style, including distinctions between verbal versus spatial processing preferences, analytic versus holistic thinking, field dependence versus independence, and other cognitive style dimensions that show considerable stability within individuals across time and contexts, may partly reflect differences in neural organization and functional connectivity patterns established during development (Kozhevnikov, 2007). While environmental factors including cultural background, education, and experience clearly shape cognitive styles, biological factors including genetic variation and individual differences in neurodevelopmental trajectories also contribute (Kievit et al., 2016). The hypothesis that mitochondrial genomic variation influences cognitive style through effects on neurodevelopment or through ongoing influences on neural function remains unexplored but gains plausibility from evidence that cognitive styles correlate with patterns of regional brain activation and functional connectivity that might be influenced by metabolic factors (Kosslyn et al., 2002).

3.4 Exercise, Mitochondrial Adaptations, and the Embodied Cognition Connection

The relationship between physical exercise and cognitive function has been documented extensively, with aerobic exercise interventions consistently producing improvements in executive function, memory, and processing speed, particularly in older adults, alongside structural brain changes including increased hippocampal volume and enhanced white matter integrity (Colcombe & Kramer, 2003; Erickson et al., 2011). While multiple mechanisms likely contribute to exercise cognitive benefits, including increased neurotrophic factor expression, enhanced angiogenesis, reduced inflammation, and improved cardiovascular function, mitochondrial adaptations to exercise represent a potentially critical pathway linking physical activity to brain function (Cotman et al., 2007; Voss et al., 2013). Exercise induces mitochondrial biogenesis in skeletal muscle, increasing mitochondrial density, enhancing oxidative capacity, and improving metabolic flexibility through upregulation of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) and downstream transcriptional programs (Hood et al., 2006; Baar, 2014).

Evidence that exercise-induced mitochondrial adaptations occur in brain tissue derives from animal studies demonstrating that voluntary wheel running in rodents increases mitochondrial biogenesis markers, respiratory chain enzyme activities, and ATP

production capacity in multiple brain regions including hippocampus and cortex, paralleling the peripheral mitochondrial adaptations (Steiner et al., 2011; Marosi et al., 2012). These central mitochondrial adaptations are associated with enhanced synaptic plasticity, improved performance on cognitive tests, and protection against age-related cognitive decline and neurodegeneration in animal models (Stranahan et al., 2009; Marosi et al., 2012). The brain-derived neurotrophic factor, which is upregulated by exercise and critically involved in exercise cognitive benefits, stimulates mitochondrial biogenesis and enhances mitochondrial function, providing a potential mechanistic link between exercise, neurotrophic signaling, and metabolic adaptations (Gomez-Pinilla et al., 2008; Cheng et al., 2012).

Human studies investigating brain mitochondrial responses to exercise are limited by the inability to directly measure brain mitochondrial function in living humans, but indirect evidence from magnetic resonance spectroscopy studies suggests that exercise training alters brain metabolism, including changes in lactate, N-acetylaspartate, and other metabolites consistent with improved mitochondrial function (Gonzales et al., 2013). Additionally, positron emission tomography studies have shown that aerobic fitness correlates with regional brain glucose metabolism patterns, with higher fitness associated with more efficient brain metabolism in some regions and enhanced metabolic capacity in others (Kemppainen et al., 2005). These findings suggest that the peripheral mitochondrial adaptations to exercise may extend to brain mitochondria, enhancing neural energetic capacity and potentially influencing cognitive function through improved bioenergetic support for neural processing.

The relevance of exercise-mitochondria-cognition relationships to embodied cognition becomes apparent when considering that exercise represents a fundamentally embodied activity that simultaneously engages motor systems, interoceptive processing, and cognitive control, while generating profound physiological perturbations including increased heart rate, respiratory rate, metabolic heat production, and alterations in numerous circulating factors (Dietrich & Audiffren, 2011). The subjective experience during exercise involves heightened awareness of bodily sensations including cardiac palpitations, respiratory effort, muscular fatigue, and thermal discomfort, creating intense embodied cognitive states where physiological condition directly influences cognitive processing (Ekkekakis, 2003). Individual differences in the physiological responses to exercise, the subjective experience of exercise-induced bodily states, and the cognitive effects of acute and chronic exercise may partly reflect differences in mitochondrial function that determine metabolic capacity, the magnitude of physiological perturbations at given exercise intensities, and the efficiency of cellular energy provision (Bouchard et al., 2011).

Mitochondrial haplogroups have been associated with athletic performance and exercise capacity in multiple studies, with certain haplogroups over-represented among

elite endurance athletes and associated with higher maximal oxygen consumption, greater training responsiveness, or improved exercise efficiency (Niemi & Majamaa, 2005; Mikami et al., 2011). For instance, several investigations in European populations have reported that haplogroups associated with enhanced mitochondrial coupling efficiency, including haplogroup H in some studies, are more common among endurance athletes, while haplogroups associated with reduced coupling may be more common among sprint/power athletes, suggesting that mitochondrial genomic variation influences the balance between oxidative efficiency and power output (Castro et al., 2007; Nogales-Gadea et al., 2011). The functional interpretation of these athletic performance associations remains debated, with proposals that "tightly coupled" mitochondrial genotypes favoring maximal ATP production suit endurance performance while "loosely coupled" genotypes generating more heat may suit explosive power or cold adaptation, though the empirical support for these specific mechanistic models remains incomplete (Ruiz-Pesini et al., 2004; Scott et al., 2009).

The potential connections between mitochondrial genomic variation, exercise capacity, and embodied cognition suggest several testable hypotheses: individuals with mitochondrial genotypes associated with enhanced oxidative capacity might exhibit greater physiological reserve during cognitive tasks requiring sustained mental effort, experiencing less subjective fatigue and maintaining performance more effectively; individuals with different mitochondrial backgrounds might show varying magnitudes of cognitive benefit from exercise interventions, reflecting differential capacity for exercise-induced mitochondrial adaptations in brain tissue; and the subjective embodied experience during physical exertion, including the intensity of fatigue sensations, respiratory distress, and cardiac awareness, might vary systematically with mitochondrial genomic constitution, influencing exercise behavior and potentially creating feedback loops wherein mitochondrial genotype influences exercise participation which in turn influences cognitive function and brain health through activity-dependent mechanisms (Bouchard et al., 2011).

The lactate threshold, representing the exercise intensity at which blood lactate concentration begins to increase exponentially and reflecting the transition from predominantly aerobic to increasingly anaerobic metabolism, varies substantially across individuals and is influenced by mitochondrial oxidative capacity (Faude et al., 2009). Individuals with higher mitochondrial density and respiratory chain capacity can sustain higher exercise intensities before reaching lactate threshold, experiencing less metabolic acidosis and presumably reduced perception of fatigue and discomfort at given absolute exercise intensities. The central governor model of exercise fatigue proposes that the brain regulates exercise performance to prevent catastrophic physiological failure, with interoceptive signals including metabolic distress contributing to centrally-generated fatigue sensations that reduce motivation and motor output (Noakes, 2012). If mitochondrial genomic variation influences peripheral metabolic capacity and thereby the magnitude of

distress signals generated at given exercise intensities, this could influence the central regulation of exercise performance and the subjective embodied experience of exertion.

Interestingly, several mitochondrial diseases caused by pathogenic mtDNA mutations produce exercise intolerance as a cardinal symptom, with affected individuals experiencing disproportionate fatigue, dyspnea, and muscle pain during physical activity, alongside elevated resting and post-exercise lactate levels reflecting impaired oxidative metabolism (DiMauro & Schon, 2003; Vissing et al., 2016). While these pathological conditions involve severe mitochondrial dysfunction far exceeding the subtle effects of common polymorphisms, they establish proof-of-principle that mitochondrial function directly determines exercise tolerance and the embodied experience of physical exertion. The possibility that common mtDNA variation creates a continuum of exercise capacity and exertion perception extending from individuals with robust mitochondrial function who experience relatively less discomfort at high exercise intensities through to individuals with marginal mitochondrial function who perceive greater effort and discomfort at moderate intensities represents a hypothesis worthy of systematic investigation.

3.5 Chronic Stress, Mitochondrial Damage, and Alterations in Embodied Processing

The bidirectional relationships between psychological stress and mitochondrial function have received increasing attention as evidence accumulates that chronic stress exposure produces mitochondrial damage while pre-existing mitochondrial vulnerabilities may increase susceptibility to stress-related pathology (Picard & McEwen, 2014, 2018; Picard et al., 2018). Stress-induced activation of the hypothalamic-pituitary-adrenal axis and sympathetic nervous system produces multiple effects on mitochondria including direct glucocorticoid actions on mitochondrial function, calcium overload from sustained adrenergic activation, increased oxidative stress from elevated metabolic demands, and pro-inflammatory signaling that impairs mitochondrial biogenesis and promotes mitochondrial dysfunction (Du et al., 2009; Manoli et al., 2007). These stress-mitochondria interactions create potential pathways through which chronic stress could alter embodied cognition by damaging the mitochondrial systems that support interoceptive processing, autonomic regulation, and the physiological responses underlying emotional experience.

Animal models of chronic stress, including chronic restraint stress, chronic social defeat stress, and chronic unpredictable stress paradigms, consistently produce mitochondrial abnormalities in brain regions including hippocampus, prefrontal cortex, and nucleus accumbens, including reduced mitochondrial respiratory capacity, decreased ATP production, elevated oxidative damage, and altered mitochondrial morphology (Gong et al., 2011; Rezin et al., 2008). These mitochondrial alterations are accompanied by behavioral changes including anhedonia, social withdrawal, and cognitive impairment reminiscent of

depression, and interventions that improve mitochondrial function can ameliorate stress-induced behavioral deficits (Gong et al., 2011; Adzic et al., 2009). The relevance of these animal findings to human stress-related psychopathology remains somewhat uncertain given the challenges of modeling complex human psychological experiences in animals, but the consistent pattern across multiple stress paradigms and species suggests fundamental stress-mitochondria relationships that likely extend to humans.

Human studies examining mitochondrial function in individuals with chronic stress exposure or stress-related psychiatric conditions have yielded mixed results partly reflecting methodological challenges of assessing mitochondrial function in living humans and partly reflecting the heterogeneity of stress experiences and individual stress responses (Gardner et al., 2014). Peripheral blood cell mitochondrial function has been examined in several studies as an accessible though imperfect surrogate for tissue mitochondrial function, with some investigations reporting reduced mitochondrial respiratory capacity, altered mtDNA copy number, or increased mtDNA damage in individuals with depression, post-traumatic stress disorder, or chronic psychological stress, while others find no differences (Gardner et al., 2003; Cai et al., 2015). The correlations between peripheral mitochondrial measures and brain mitochondrial function remain unclear, as tissue-specific differences in mitochondrial regulation and stress responsiveness likely result in imperfect correspondence between peripheral and central mitochondrial states (Picard et al., 2014).

The allostatic load framework, which conceptualizes chronic stress effects as cumulative wear-and-tear on physiological systems resulting from repeated activation and inadequate recovery, explicitly incorporates mitochondrial dysfunction as both a component of allostatic load and a mechanism amplifying stress-related pathology (McEwen & Gianaros, 2010; Picard & McEwen, 2014). According to this framework, individuals enter stress exposure with different mitochondrial reserve capacities determined partly by genetic factors including mtDNA variation, and this initial mitochondrial capacity influences resilience to stress-induced damage and the eventual accumulation of allostatic load (Picard et al., 2014, 2018). Individuals with robust mitochondrial function may tolerate chronic stress with minimal lasting physiological consequences, maintaining adequate energy provision and cellular stress resistance, while individuals with compromised mitochondrial function may develop progressively worsening bioenergetic failure, oxidative damage, and inflammatory activation that contribute to stress-related disease (Picard & McEwen, 2014).

The implications for embodied cognition emerge from considering that chronic stress alters multiple physiological systems relevant to embodied processing, including autonomic function, inflammatory status, gut-brain axis signaling, and interoceptive sensitivity (Thayer et al., 2012; Miller et al., 2009). If mitochondrial damage contributes mechanistically to these stress-induced alterations, then stress-mitochondria interactions could influence embodied

cognition by altering the physiological states that inform interoceptive representations, changing the coupling between bodily states and emotional experience, and modifying the somatic markers that guide decision-making. For instance, stress-induced mitochondrial dysfunction in autonomic neurons might reduce heart rate variability and impair autonomic flexibility, limiting the capacity for adaptive physiological responses to environmental demands and reducing the informational value of autonomic signals for cognitive processes (Thayer & Lane, 2000). Similarly, stress-induced mitochondrial impairment in brain regions including insula and anterior cingulate cortex might reduce the fidelity of interoceptive representations or alter the affective tone associated with bodily states, potentially contributing to somatic symptom development or altered emotional experience.

The differential vulnerability hypothesis proposes that individuals with pre-existing mitochondrial vulnerabilities, including those with specific mtDNA variants conferring reduced bioenergetic capacity or stress resilience, experience more severe and lasting consequences from chronic stress exposure compared to individuals with robust mitochondrial function (Picard et al., 2018). This gene-environment interaction framework suggests that mitochondrial genomic variation might not produce detectible phenotypic effects under optimal conditions when energetic demands are modest and stress is minimal, but becomes apparent when individuals encounter sustained stress that challenges cellular adaptive capacity (Picard et al., 2014). Such interactions could help explain inconsistent findings in studies examining mitochondrial haplogroup associations with psychiatric conditions—if mtDNA effects depend critically on stress exposure history, studies failing to assess or control for stress experiences would show weak or null associations despite genuine underlying effects.

Early life stress represents a particularly important consideration given evidence that adverse experiences during developmental sensitive periods produce lasting alterations in stress response systems, mitochondrial function, and vulnerability to later psychopathology (Heim & Nemeroff, 2001; Tyrka et al., 2016). Animal studies have demonstrated that maternal separation, early social isolation, and other early life stress paradigms produce persistent mitochondrial dysfunction in brain regions including hippocampus and prefrontal cortex, alongside behavioral and physiological alterations resembling stress-related psychiatric disorders (Reyes et al., 2015; Picard et al., 2018). These developmental programming effects may involve epigenetic modifications to nuclear genes regulating mitochondrial function, direct mitochondrial damage accumulating during critical developmental windows, or alterations in mitochondrial quality control mechanisms that persist into adulthood (Picard & McEwen, 2018). The interaction between inherited mitochondrial genomic variation and early life stress experiences in shaping adult embodied cognition and stress vulnerability represents a multilayered developmental question requiring sophisticated longitudinal research designs that remain largely absent from the current literature.

Part IV: Toward Computational and Empirical Frameworks for Investigating Mitochondrial-Embodied Cognition Relationships

4.1 Predictive Processing and Interoceptive Inference: A Computational Framework for Embodiment

The predictive processing framework, also termed predictive coding or the free energy principle, provides a unifying computational theory of brain function wherein perception, action, and learning all emerge from the brain's continuous generation and testing of predictions about sensory input at multiple hierarchical levels (Friston, 2010; Clark, 2013). According to this framework, the brain maintains generative models that predict incoming sensory data based on learned statistical regularities and contextual information, constantly comparing predictions against actual sensory input to compute prediction errors that propagate up the hierarchy to update higher-level representations while top-down predictions propagate down to modulate lower-level processing (Rao & Ballard, 1999; Friston, 2005). Perception results from the brain's inference about the most likely causes of sensory input given the generative model and current predictions, while action serves to fulfill predictions by changing sensory input through bodily movements, creating an active inference framework wherein organisms minimize prediction error through both perceptual updating and action (Friston et al., 2010).

The extension of predictive processing principles to interoception and emotion has generated substantial theoretical development and empirical investigation, proposing that interoceptive perception results from the brain's predictive modeling of internal bodily states through generative models that predict interoceptive afference and update based on prediction errors computed by comparing predicted and actual interoceptive signals (Seth, 2013; Barrett & Simmons, 2015). This interoceptive predictive coding framework suggests that the subjective experience of bodily feelings, including both homeostatic sensations like hunger and thirst and emotional feelings, emerges from the brain's active construction of interoceptive predictions that prepare the body for anticipated demands, with the discrepancy between predicted and actual interoceptive states contributing to emotional intensity and driving model updating (Seth & Friston, 2016; Barrett, 2017).

The concept of precision-weighting in predictive processing provides a crucial mechanism for regulating the influence of prediction errors on perception and learning, with precision representing the inverse variance or reliability of prediction errors, such that high-precision prediction errors (reliable, consistent signals) strongly influence perceptual inference and model updating while low-precision prediction errors (noisy, inconsistent

signals) are largely ignored (Feldman & Friston, 2010). Applied to interoception, precision-weighting determines how much influence interoceptive prediction errors exert on conscious bodily awareness and emotional experience, with high interoceptive precision corresponding to heightened attention to bodily signals and strong influence of interoceptive input on experience, while low interoceptive precision corresponds to relative neglect of bodily signals and predominance of top-down predictions (Seth, 2013). Individual differences in interoceptive precision-weighting could thereby produce variation in interoceptive accuracy, emotional intensity, and the degree to which bodily states influence cognitive processing, providing a computational framework for understanding embodied cognition variation.

Mitochondrial function could influence interoceptive predictive processing through multiple pathways within this computational framework. First, mitochondrial bioenergetic capacity might determine the signal-to-noise ratio of interoceptive afferent signals by influencing the excitability and response characteristics of peripheral interoceptive neurons—neurons with adequate mitochondrial function might generate robust, reliable interoceptive signals in response to physiological perturbations, corresponding to high interoceptive signal precision, while neurons with compromised mitochondrial function might generate weaker or more variable signals, corresponding to low precision (Picard & McEwen, 2014). Second, mitochondrial function in central interoceptive processing regions including insula and anterior cingulate cortex might influence the computational capacity for maintaining and updating interoceptive generative models, with adequate bioenergetic support enabling more detailed and flexible models while bioenergetic constraints might necessitate simpler, less adaptable models (Harris et al., 2012). Third, mitochondrial influences on autonomic nervous system function might affect the precision of autonomic predictions and prediction errors by modulating the reliability of autonomic responses to central commands—if autonomic effectors respond consistently and robustly to central autonomic predictions, this corresponds to high autonomic precision, enabling tight coupling between predicted and actual bodily states, while inconsistent or weak autonomic responses create low-precision autonomic control (Thayer et al., 2012).

The active inference extension of predictive processing proposes that organisms minimize prediction error not only through perceptual inference that updates beliefs about world states but also through action that changes sensory input to match predictions, with both processes serving the overarching imperative to minimize free energy—a information-theoretic quantity related to surprise or prediction error (Friston et al., 2010, 2012). Applied to interoception and emotion, active inference suggests that interoceptive predictions function as homeostatic set-points that organisms seek to maintain through physiological regulation, with discrepancies between predicted and actual interoceptive states triggering both allostatic corrections (actions that change bodily state to match predictions) and potentially perceptual updating of predictions to accommodate bodily

states when allostatic correction proves insufficient (Seth & Friston, 2016; Pezzulo et al., 2015). Individual differences in the capacity for allostatic correction—the ability to generate effective physiological adjustments that minimize interoceptive prediction errors—might depend partly on mitochondrial function, as metabolically demanding physiological adjustments including alterations in cardiac output, metabolic rate, immune function, and stress hormone secretion all require adequate cellular energy provision (Picard et al., 2014; Sterling, 2012).

The concept of embodied emotional experience within the active inference framework proposes that emotions arise from the brain's interoceptive predictions that prepare the body for anticipated demands associated with particular situations or stimuli, with the predicted bodily state implemented through autonomic, endocrine, and musculoskeletal adjustments that generate interoceptive afference confirming (or disconfirming) the predictions (Barrett & Simmons, 2015; Seth, 2013). For instance, encountering a threatening stimulus would trigger predictions of elevated heart rate, increased respiration, muscle tension, and stress hormone release appropriate for defensive action, and the implementation of these predicted bodily states through autonomic activation generates interoceptive afference that contributes to the subjective feeling of fear (Barrett, 2017). Individual differences in the ease and reliability of generating these predicted embodied states might influence emotional experience, with individuals capable of rapidly and robustly implementing predicted physiological changes experiencing more intense and clearly differentiated emotions compared to individuals whose physiological responses are sluggish or inconsistent (Dunn et al., 2010).

Mitochondrial genomic variation could influence this embodied emotional prediction process through effects on the capacity to generate predicted physiological states—individuals with robust mitochondrial function might exhibit greater autonomic range and metabolic flexibility, enabling them to implement a wider repertoire of predicted bodily states more effectively, while individuals with constrained mitochondrial function might show reduced physiological expressiveness, limiting the embodied dimension of emotional experience (Picard et al., 2016). This hypothesis generates several testable predictions: individuals with mitochondrial variants associated with enhanced bioenergetic capacity should show greater magnitude and consistency of physiological responses during emotional experiences; they should exhibit higher interoceptive accuracy for emotional situations; and they might report more intense or differentiated emotional experiences. Conversely, individuals with mitochondrial variants associated with reduced bioenergetic capacity might show blunted physiological responses, lower interoceptive accuracy during emotion, and potentially altered emotional experience characterized by reduced intensity or difficulty differentiating emotional states.

The precision-weighting of interoceptive predictions and prediction errors could be influenced by neuromodulatory systems including noradrenergic, serotonergic, and dopaminergic pathways that regulate the gain on prediction errors and determine the balance between relying on prior predictions versus updating based on sensory input (Friston et al., 2012; Moran et al., 2013). Given that monoaminergic neurotransmitter synthesis depends on metabolic precursors and enzymatic cofactors whose availability may be influenced by mitochondrial function, and given that monoaminergic neurons exhibit high metabolic demands and mitochondrial density, mitochondrial genomic variation could potentially influence neuromodulatory function and thereby precision-weighting in predictive processing (Rae & Williams, 2017). This represents a speculative but mechanistically grounded hypothesis linking mitochondrial function to computational parameters in predictive processing models, generating the testable prediction that mitochondrial genomic variation associates with individual differences in precision-weighting as measured through computational modeling of behavioral or neural data.

4.2 Network Neuroscience Approaches to Mitochondrial-Cognitive Relationships

The network neuroscience framework conceptualizes the brain as a complex network wherein distributed regions function as nodes connected by white matter pathways forming edges, with cognitive processes emerging from coordinated activity patterns across these networks rather than being localized to individual regions (Sporns, 2011; Bassett & Sporns, 2017). This perspective emphasizes connectivity, integration, and dynamic reconfiguration of network states as fundamental to understanding brain function, moving beyond localizationist approaches to embrace distributed systems-level analysis (Bullmore & Sporns, 2009). The application of network science methods including graph theory, dynamic systems analysis, and information theory to neuroimaging data has revealed organizational principles of brain networks including small-world topology combining high local clustering with short path lengths between distant regions, hierarchical modularity with nested communities of functionally related regions, and hub regions exhibiting exceptionally high connectivity that integrate information across network modules (Sporns et al., 2004; Meunier et al., 2010).

The metabolic costs of maintaining brain network architecture and supporting network dynamics represent a critical constraint on network organization, with theoretical and empirical work suggesting that brain network topology reflects an optimization balancing competing demands for efficient information processing, metabolic economy, and resilience to damage (Bullmore & Sporns, 2012). Highly connected hub regions exhibit elevated baseline metabolic activity as measured by positron emission tomography, consistent with their high connectivity imposing substantial energetic costs (Tomasi et al.,

2013). Similarly, the white matter pathways forming network edges require metabolic support for maintaining axonal integrity, operating ion pumps that restore gradients after action potentials, and supporting axonal transport mechanisms, with longer connections between distant regions necessarily incurring greater metabolic costs (Laughlin & Sejnowski, 2003). The wiring minimization principle proposes that brain networks exhibit spatial organization that minimizes total wiring length and therefore metabolic costs while maintaining necessary connectivity for function, explaining observations that most connections occur between nearby regions with more costly long-distance connections reserved for high-value integrative pathways (Kaiser & Hilgetag, 2006; Chen et al., 2006).

Individual differences in mitochondrial function could influence brain network organization and dynamics through multiple mechanisms. First, network hub regions, by virtue of their high connectivity and metabolic demands, might be particularly sensitive to mitochondrial function variations, with individuals possessing robust mitochondrial capacity potentially able to sustain more highly connected hub architecture or more dynamic hub reconfiguration (Crossley et al., 2014). This generates the hypothesis that mitochondrial genomic variation associates with individual differences in hub connectivity strength, hub centrality measures, or hub metabolic activity. Second, the energetic costs of long-distance white matter connections might make these pathways particularly vulnerable to bioenergetic constraints, suggesting that individuals with reduced mitochondrial capacity might exhibit relatively reduced long-distance connectivity and greater reliance on local connections, altering the global integration properties of brain networks (Bassett & Bullmore, 2017). Third, the dynamic reconfiguration of network states supporting different cognitive operations likely incurs metabolic costs associated with rapidly modulating synaptic strengths and activity patterns, potentially making network flexibility and adaptability sensitive to mitochondrial function (Shine et al., 2019).

Resting-state functional connectivity, measured through temporal correlations in blood-oxygen-level-dependent functional magnetic resonance imaging signals between brain regions during wakeful rest, reveals intrinsic network architecture including the default mode network, salience network, central executive network, and sensorimotor networks (Raichle, 2015; Yeo et al., 2011). Individual differences in resting-state network organization correlate with cognitive abilities, personality traits, and psychiatric symptoms, establishing functional connectivity measures as meaningful indices of behaviorally-relevant brain organization (Smith et al., 2015). Several investigations have examined relationships between metabolism and functional connectivity, finding that regional metabolic activity correlates with network hub status and that metabolic network organization reconstructed from positron emission tomography data partially recapitulates functional connectivity network structure (Tomasi et al., 2013; Di & Biswal, 2012). These findings support the hypothesis that metabolic factors constrain and shape functional network organization,

suggesting that mitochondrial function variations might manifest as functional connectivity differences.

The salience network, comprising anterior insula, dorsal anterior cingulate cortex, and subcortical structures including amygdala and ventral striatum, plays a critical role in detecting behaviorally relevant stimuli, integrating interoceptive and exteroceptive information, and modulating attention and autonomic responses (Seeley et al., 2007; Menon & Uddin, 2010). Given the salience network's central role in interoceptive processing and embodied cognition, and given that the network's key nodes—insula and anterior cingulate cortex—exhibit high baseline metabolic activity and dense mitochondrial populations, the salience network represents a particularly promising target for investigating relationships between mitochondrial function and embodied cognitive networks (Critchley & Harrison, 2013). The hypothesis that individual differences in mitochondrial genomic constitution influence salience network functional connectivity, which in turn influences interoceptive processing and embodied cognition, could be tested through integrated analyses combining mitochondrial genotyping, resting-state functional connectivity imaging, interoceptive accuracy assessment, and embodied cognition tasks.

Task-based functional connectivity, examining how network organization dynamically reconfigures during specific cognitive operations, provides complementary information to resting-state connectivity by revealing how networks reorganize to meet task demands (Spadone et al., 2015). Network flexibility, quantified through measures of how extensively network community structure changes across tasks or time, has been associated with cognitive flexibility and executive function, with individuals exhibiting greater network reconfiguration capacity showing better cognitive performance (Braun et al., 2015; Shine et al., 2016). The metabolic costs of network reconfiguration, including the energetic demands of rapidly modulating synaptic transmission and reorganizing activity patterns, suggest that network flexibility might be constrained by bioenergetic capacity, generating the hypothesis that mitochondrial function influences cognitive flexibility partly through enabling or constraining neural network reconfiguration (Shine et al., 2019).

Graph theory metrics applied to brain networks yield quantitative measures of network properties including global efficiency (characterizing the average shortest path length between nodes), local efficiency or clustering coefficient (characterizing the interconnectedness of a node's neighbors), modularity (the degree to which the network segregates into communities), and small-worldness (the balance between local clustering and global integration) (Rubinov & Sporns, 2010). These metrics can be computed for individual subjects, enabling investigation of how network topology varies across individuals and relates to cognitive performance, symptoms, or biological factors including potentially mitochondrial genomic variation (Bassett & Sporns, 2017). The hypothesis that mitochondrial variants influencing bioenergetic capacity associate with differences in

network efficiency or small-worldness could be tested through graph theoretical analysis of neuroimaging data from individuals genotyped for mtDNA variation.

Structural connectivity analyzed through diffusion tensor imaging tractography reveals white matter pathways connecting brain regions, with fractional anisotropy and other diffusion metrics providing information about white matter microstructure including axonal density, myelination, and fiber coherence (Basser et al., 2000). Individual differences in structural connectivity correlate with functional connectivity patterns and cognitive abilities, with studies suggesting that structural connectivity constrains but does not fully determine functional connectivity (Honey et al., 2009). Given that oligodendrocyte myelination and axonal integrity both require substantial metabolic support, structural connectivity properties might be influenced by mitochondrial function during development and maintenance, generating the hypothesis that mitochondrial genomic variation associates with white matter microstructure measures (Fünfschilling et al., 2012).

4.3 Multi-Level Integration: From Genes Through Physiology to Phenomenology

The investigation of relationships between mitochondrial genomic variation and embodied cognition requires multi-level integration spanning molecular mechanisms, cellular bioenergetics, tissue and organ physiology, neural systems function, behavioral performance, and subjective phenomenological experience, with each level involving distinct measurement methodologies, temporal scales, and conceptual frameworks that must be bridged through sophisticated integrative analysis (Churchland & Sejnowski, 1988; Cacioppo et al., 2000). The complexity of causal pathways linking mtDNA sequence variation to embodied cognitive phenotypes, involving numerous intermediate steps and reciprocal interactions, necessitates systems biology and network medicine approaches that model multilevel relationships rather than seeking simple one-to-one gene-phenotype correspondences (Barabási et al., 2011; Ideker & Krogan, 2012).

At the molecular level, mitochondrial genomic variation influences the amino acid sequences of thirteen respiratory chain protein subunits and the structure of twenty-two tRNAs and two rRNAs, with consequences for protein folding, stability, catalytic efficiency, and translation fidelity that can be investigated through biochemical assays, structural modeling, and cybrid cell studies comparing mtDNA variants in controlled nuclear backgrounds (Wallace, 2013; Gómez-Durán et al., 2010). These molecular-level effects propagate to cellular bioenergetics, altering parameters including ATP production rates, mitochondrial membrane potential, reactive oxygen species generation, calcium buffering capacity, and susceptibility to apoptosis, which can be measured through respirometry, fluorescent probe studies, and metabolomics in cells, tissues, or isolated mitochondria (Nicholls & Ferguson, 2013). The cellular bioenergetic phenotype then influences tissue and

organ function including cardiac contractility, vascular reactivity, skeletal muscle work capacity, neuronal excitability, and neurotransmitter synthesis, creating physiological signatures measurable through cardiac output monitoring, blood pressure assessment, exercise testing, electrophysiology, and neurochemical analysis (Doenst et al., 2013; Kann, 2016).

The physiological level effects manifest in whole-organism phenotypes including autonomic function (heart rate variability, blood pressure regulation, thermoregulation), stress response system activity (cortisol patterns, inflammatory markers), metabolic parameters (glucose tolerance, lipid profiles), and physical fitness (maximal oxygen consumption, exercise tolerance), which are measurable through standard clinical and research assessments (Thayer & Lane, 2000; Picard et al., 2014). These physiological phenotypes contribute to psychological and cognitive phenomena including interoceptive accuracy (heartbeat detection performance, respiratory sensitivity), emotional experience (subjective affect, emotional intensity), decision-making (somatic marker influences, risk preferences), and embodied cognitive processing (influences of bodily state on conceptual processing, moral judgment, social cognition), which require psychophysical, questionnaire, and behavioral task methodologies (Garfinkel et al., 2015; Damasio & Carvalho, 2013). Finally, the subjective phenomenological dimension including the qualitative character of emotional feelings, bodily self-awareness, sense of physical vitality or fatigue, and the embodied sense of self can be investigated through phenomenological interview methods, experience sampling, and first-person report combined with third-person measurements (Gallagher, 2005; Petitmengin, 2006).

The integration of these multiple levels within individual research participants requires sophisticated study designs collecting diverse data types simultaneously or sequentially, including mitochondrial genotyping through whole mitochondrial genome sequencing or targeted variant screening, physiological monitoring through heart rate variability recording, respiratory parameter measurement, exercise testing, and stress response assessment, neuroimaging through structural MRI, diffusion tensor imaging, resting-state and task-based functional MRI, and potentially positron emission tomography or magnetic resonance spectroscopy where available, behavioral testing including interoceptive accuracy tasks, embodied cognition paradigms, emotional reactivity assessment, and cognitive performance testing, and phenomenological assessment through validated questionnaires addressing bodily awareness, alexithymia, somatic symptoms, and emotional experience, complemented where feasible by qualitative phenomenological interviews (Khalsa et al., 2018; Seth & Critchley, 2013).

Statistical integration of multilevel data presents substantial methodological challenges including the need to handle variables measured on different scales and with different distributional properties, to model complex non-linear and potentially reciprocal

relationships, to distinguish direct from mediated effects in causal chains, and to account for individual differences and contextual factors that moderate relationships at various levels (Cacioppo et al., 2000). Structural equation modeling provides a framework for specifying and testing hypothesized causal pathways from mitochondrial variants through intermediate physiological phenotypes to behavioral and phenomenological outcomes, allowing simultaneous estimation of multiple paths and testing of mediation hypotheses (Kline, 2015). For instance, a structural model might hypothesize that specific mtDNA variants influence cardiac mitochondrial function (measured through exercise testing or cardiac metabolic imaging), which influences heart rate variability (measured through electrocardiogram recording), which influences interoceptive accuracy (measured through heartbeat detection tasks), which influences emotional experience (measured through affect questionnaires), creating a testable multilevel causal chain with each step involving observable measures.

Network medicine approaches treat the biological system as an interconnected network wherein genetic variants influence multiple proteins and pathways that interact to produce cellular phenotypes, which combine across cell types and tissues to generate organ-level functions, which integrate at the organism level to produce complex phenotypes (Barabási et al., 2011). Applied to mitochondrial-embodied cognition relationships, this framework would model mtDNA variants as influencing a network of mitochondrial and nuclear-encoded proteins involved in oxidative phosphorylation, mitochondrial dynamics, quality control, and signaling, producing a cellular bioenergetic phenotype that differs across tissues, manifesting particularly in high-demand tissues including heart, skeletal muscle, and brain, and integrating at the organism level through autonomic function, stress response systems, and neural network dynamics to influence embodied cognitive processing (Picard et al., 2016). The network perspective emphasizes that effects may not flow linearly from genes to phenotypes but rather involve complex network interactions wherein multiple genetic and environmental factors combine non-additively, feedback loops create reciprocal causation, and emergent properties arise at higher organizational levels that cannot be predicted from lower-level components alone.

Machine learning approaches including random forests, support vector machines, and deep neural networks provide data-driven methods for identifying complex patterns linking mitochondrial variants to embodied cognitive phenotypes, potentially uncovering non-linear relationships and interaction effects that traditional statistical methods might miss (Bzdok & Ioannidis, 2019). These approaches can integrate high-dimensional data across multiple levels, identifying which combinations of genetic variants, physiological parameters, and neural network features best predict embodied cognitive outcomes. However, machine learning approaches typically sacrifice interpretability for predictive accuracy, generating models that classify or predict effectively but do not necessarily

illuminate causal mechanisms, necessitating complementary approaches that prioritize mechanistic understanding (Bzdok et al., 2018).

Bayesian hierarchical modeling provides a flexible framework for integrating data from multiple sources and levels while appropriately propagating uncertainty, allowing incorporation of prior knowledge about mechanism from animal studies or biochemical investigations to inform inferences about human data, and enabling principled handling of missing data and measurement error (Gelman et al., 2013). For instance, a hierarchical Bayesian model investigating mitochondrial-embodied cognition relationships might incorporate a level modeling the biochemical effects of mtDNA variants on respiratory chain function (informed by cybrid studies), a level modeling how respiratory chain differences influence tissue function (informed by animal physiology), a level modeling organism-level physiological phenotypes, and a level modeling cognitive-behavioral outcomes, with each level's parameters informed by relevant data and constrained by mechanistic priors from lower levels.

4.4 Potential Confounds, Alternative Explanations, and Methodological Considerations

The investigation of mitochondrial genomic influences on embodied cognition faces numerous potential confounds and alternative explanations that must be carefully addressed through appropriate study design and analysis. Population stratification represents a fundamental challenge in genetic association studies generally and mitochondrial genetics specifically, as mitochondrial haplogroups define maternal lineages that cluster by geographic ancestry, creating the possibility that haplogroup-phenotype associations reflect unmeasured population differences in environmental exposures, cultural practices, socioeconomic factors, or nuclear genetic background rather than causal effects of mtDNA variants themselves (Balding, 2006; Pirastu et al., 2016). For instance, if European haplogroup J associates with some embodied cognitive phenotype in a European sample, this might reflect geographic clustering of haplogroup J in particular regions of Europe that differ in diet, physical activity patterns, or other environmental factors, rather than direct effects of the mitochondrial variants defining haplogroup J.

Several approaches can address population stratification concerns. First, analyzing associations within relatively homogeneous populations reduces stratification, though completely eliminating population structure is essentially impossible and residual subtle stratification may remain even within apparently homogeneous groups (Price et al., 2006). Second, including principal components derived from nuclear genome-wide genotyping data as covariates in statistical models can control for population structure, under the assumption that nuclear genetic principal components capture the population stratification that might confound mtDNA associations (Price et al., 2006; Patterson et al., 2006).

However, this approach assumes that nuclear and mitochondrial genomic ancestries are concordant, which may not hold if sex-biased migration or admixture has occurred. Third, family-based designs examining within-family variation can eliminate confounding by population structure, as maternal relatives sharing the same mtDNA haplogroup but differing in nuclear genetic background provide natural experiments for isolating mtDNA effects (Laird & Lange, 2006). However, maternal transmission of mtDNA creates design limitations, as all maternal relatives within a sibship share identical mtDNA, providing no within-family mtDNA variation unless comparing across extended pedigrees.

Nuclear-mitochondrial genetic interactions represent another critical consideration, as the functional consequences of mtDNA variants may depend on the nuclear genetic background, with particular combinations of nuclear and mitochondrial variants producing epistatic effects wherein the phenotypic consequences differ from what would be predicted by additive effects of each variant alone (Rand et al., 2004; Dobler et al., 2014). Such nuclear-mitochondrial epistasis is expected theoretically given that most respiratory chain complexes contain both mitochondrial-encoded and nuclear-encoded subunits that must physically interact, creating opportunities for co-evolution and functional compatibility that may differ across nuclear genetic backgrounds (Rand et al., 2004). Empirical evidence for nuclear-mitochondrial epistasis comes primarily from model organism studies including Drosophila, where mtDNA variants show different fitness consequences when placed on different nuclear backgrounds through genetic crosses (Montooth et al., 2010; Meiklejohn et al., 2013). The relevance of such epistasis to human populations remains uncertain, but the theoretical expectation and model organism evidence suggest caution in expecting consistent mtDNA phenotypic effects across populations with different nuclear genetic compositions.

Heteroplasmy, the presence of multiple mtDNA variants within an individual, adds complexity to genotype-phenotype relationships that most association studies fail to adequately address (Stewart & Chinnery, 2015). While haplogroup-defining variants are typically homoplasmic (present in essentially 100% of mtDNA molecules), recent deep sequencing investigations have revealed substantial low-level heteroplasmy across individuals, with most people harboring multiple mtDNA variants at frequencies below the detection threshold of standard sequencing approaches (He et al., 2010; Li et al., 2010). The functional consequences of low-level heteroplasmy remain unclear for most variants, but pathogenic mutations show threshold effects wherein biochemical and clinical manifestations emerge when mutant heteroplasmy exceeds approximately 60-90%, suggesting that heteroplasmy level critically determines phenotypic expression (Rossignol et al., 2003). Studies examining only haplogroup-defining homoplasmic variants while ignoring heteroplasmy may miss important sources of mtDNA variation contributing to phenotypic differences.

Mitochondrial DNA copy number variation, reflecting the number of mitochondrial genomes per cell, shows substantial individual variation and has been associated with various phenotypes including cognitive decline, psychiatric symptoms, and physiological stress markers (Mengel-From et al., 2014; Cai et al., 2015). MtDNA copy number varies across tissues, changes with age, and responds to various physiological and pathological conditions, complicating interpretation of associations with phenotypic outcomes (Mengel-From et al., 2014). The relationship between mtDNA sequence variation (haplogroups) and mtDNA copy number remains incompletely characterized, with some studies suggesting haplogroup associations with copy number while others find no relationships (Mengel-From et al., 2014). Studies investigating mtDNA sequence effects on phenotypes should ideally measure and control for mtDNA copy number to distinguish sequence effects from copy number effects, though the appropriate tissue for such measurements (blood, buccal cells, other accessible tissues) and their correspondence to brain mtDNA copy number remain uncertain.

The measurement challenges inherent in assessing embodied cognitive phenotypes represent another critical methodological consideration. Interoceptive accuracy measures including heartbeat detection tasks show only modest test-retest reliability, exhibit learning effects with repeated administration, and may be confounded by beliefs about heart rate, anxiety about task performance, and the specific instructions provided (Ring & Brener, 2018; Desmedt et al., 2018). These measurement properties create substantial noise in phenotype assessment that reduces statistical power to detect genetic associations, requiring large sample sizes that may be challenging to achieve for resource-intensive phenotyping protocols. The development of more reliable, valid, and theoretically-grounded measures of embodied cognition represents an important priority for the field, potentially incorporating multiple measurement modalities, computational modeling to extract latent constructs from behavioral data, and combination of self-report, behavioral, and physiological measures to create more robust composite phenotypes (Garfinkel et al., 2015).

The temporal dynamics of mitochondrial effects on phenotypes create additional complexities for study design and interpretation. Some effects may be stable across the lifespan, reflecting developmental influences wherein mitochondrial function shapes brain organization during critical periods with lasting consequences, while other effects may be dynamic, varying with current metabolic state, recent stress exposure, or age-related mitochondrial changes (Picard et al., 2018). Cross-sectional designs cannot distinguish stable trait-like effects from state-like effects that fluctuate over time, necessitating longitudinal designs that measure individuals repeatedly across months or years to characterize temporal dynamics (Raz & Lindenberger, 2011). The interaction of mitochondrial genomic effects with age represents a particularly important consideration, as age-related accumulation of somatic mtDNA mutations, declining mitochondrial function, and age-dependent changes in neural and physiological systems may modulate the

phenotypic expression of inherited mtDNA variation across the lifespan (Wallace, 2005; Cortopassi & Arnheim, 1990).

Environmental factors including diet, physical activity, stress exposure, sleep, and numerous other lifestyle and experiential variables influence mitochondrial function, metabolic state, and cognitive-emotional processing, creating both confounds for genetic studies and potentially important gene-environment interactions (Picard & McEwen, 2014; Hood et al., 2006). Dietary factors including caloric intake, macronutrient composition, micronutrient availability, and meal timing influence mitochondrial biogenesis, oxidative phosphorylation efficiency, and metabolic flexibility through multiple mechanisms (Galgani & Ravussin, 2008). Physical activity induces mitochondrial biogenesis and enhances oxidative capacity while also improving cognitive function and emotional regulation through partially overlapping mechanisms, creating the possibility that mitochondrial genomic effects on cognition operate partly through modulation of exercise responsiveness (Voss et al., 2013; Baar, 2014). Chronic stress produces mitochondrial damage while individuals with different mitochondrial genomic backgrounds may show differential stress vulnerability, suggesting gene-environment interactions wherein mtDNA effects are strongest under conditions of sustained stress (Picard et al., 2018).

Epigenetic modifications to nuclear genes regulating mitochondrial function represent another level of complexity, as environmental experiences can alter methylation, histone modifications, and chromatin accessibility at genes encoding respiratory chain components, mitochondrial biogenesis regulators, and metabolic enzymes, potentially creating lasting changes in mitochondrial function despite stable mtDNA sequence (Shock et al., 2011; Smiraglia et al., 2008). The interplay between inherited mtDNA sequence variation, environmentally-induced nuclear epigenetic changes affecting mitochondrial gene expression, and somatic mtDNA mutations accumulating over time creates a complex, multilayered system wherein genetic, environmental, and stochastic factors combine to produce individual mitochondrial phenotypes (Wallace & Fan, 2010). Studies focusing solely on mtDNA sequence variation while ignoring these other levels may miss important sources of mitochondrial functional variation.

Technical considerations in mtDNA genotyping and sequencing require careful attention to avoid artifacts and errors. The high copy number of mtDNA creates potential for nuclear-mitochondrial sequences (NUMTs)—segments of mtDNA that have been transferred to the nuclear genome over evolutionary time—to interfere with specific mtDNA amplification and sequencing, potentially generating spurious heteroplasmy calls or variant identification errors (Ramos et al., 2011). Appropriate laboratory methods including long-range PCR amplification, primers designed to avoid NUMT amplification, and bioinformatic filtering of sequencing data can minimize such artifacts (Parson et al., 2015). The high AT content of certain mtDNA regions including the D-loop creates sequencing

challenges with some platforms, potentially leading to errors in variant calling if not addressed through appropriate technical approaches and quality control (Just et al., 2015).

4.5 Proposed Empirical Approaches and Experimental Paradigms

The empirical investigation of mitochondrial genomic influences on embodied cognition requires innovative study designs integrating multiple methodologies within frameworks that can test specific mechanistic hypotheses while acknowledging the complexity of multilevel relationships. Several complementary research strategies can advance understanding of these relationships, each with distinct strengths and limitations that make them suitable for addressing particular questions within the overall research program.

Large-scale population cohort studies with deep phenotyping represent the most straightforward approach for initial discovery of mitochondrial haplogroup associations with embodied cognitive phenotypes. Such studies would recruit diverse samples of several thousand participants spanning population ancestry groups, conduct complete mitochondrial genome sequencing to characterize haplogroups and heteroplasmy, and administer comprehensive assessment batteries including interoceptive accuracy tasks (heartbeat detection, respiratory resistance detection), autonomic function measures (heart rate variability, blood pressure variability, thermoregulation), embodied cognition behavioral paradigms (somatic influences on moral judgment, posture effects on cognition, physiological state influences on decision-making), emotional processing tasks with physiological monitoring, cognitive performance testing, brain imaging including structural MRI and resting-state functional connectivity, and detailed questionnaires assessing bodily awareness, alexithymia, somatic symptoms, stress history, and lifestyle factors (Garfinkel et al., 2015; Thayer et al., 2012). The large sample sizes enable detection of modest effect sizes expected for common genetic variants, while deep phenotyping across multiple levels allows testing of specific mediation pathways and mechanistic hypotheses.

However, such large-scale studies face substantial practical challenges including the high cost of comprehensive phenotyping that limits feasible sample sizes, participant burden creating potential dropout and data quality issues, and the statistical multiple comparisons problem arising from testing numerous associations across many phenotypes that requires stringent correction potentially reducing power (Ioannidis, 2005). Additionally, purely observational cohort designs cannot establish causality, as observed associations might reflect confounding, reverse causation, or complex indirect pathways rather than direct effects. Nevertheless, well-designed cohort studies provide essential foundational data identifying which associations warrant further mechanistic investigation through more targeted approaches.

Experimental manipulation studies in humans provide stronger causal inference by intervening on specific components of the mitochondrial-embodied cognition pathway and observing downstream effects. For instance, acute exercise interventions that transiently alter mitochondrial metabolic state, peripheral and central metabolism, and physiological status could be combined with pre-post assessment of interoceptive accuracy and embodied cognition to test whether metabolic state changes causally influence embodied processing (Dietrich & Audiffren, 2011). If mitochondrial genomic variation influences embodied cognition through metabolic pathways, then individuals with different mitochondrial haplogroups might show differential responses to metabolic manipulations. Similarly, acute stress induction paradigms that activate stress response systems and alter physiological state could be combined with embodied cognition assessment, with the hypothesis that mitochondrial variants affecting stress physiology modulate how stress alters embodied processing (Picard et al., 2014).

Respiratory chain inhibition or enhancement using pharmacological agents represents a more direct but challenging experimental approach. Mild respiratory chain inhibition using low-dose rotenone (Complex I inhibitor) or antimycin (Complex III inhibitor) has been investigated in animal models but poses obvious safety concerns precluding use in healthy human research participants (Panov et al., 2005). Conversely, interventions that enhance mitochondrial function including exercise training, nutritional approaches such as ketogenic diets or nicotinamide riboside supplementation that boost NAD+ levels, or pharmaceutical agents including metformin or CoQ10 could be tested in randomized controlled trials examining whether improvements in mitochondrial function produce corresponding changes in embodied cognition measures (Cantó et al., 2012; Hoeks et al., 2012). The prediction would be that individuals with initially lower mitochondrial function based on haplogroup or other markers show greater cognitive benefits from mitochondrial-enhancing interventions.

Within-subject experimental designs manipulating physiological state while monitoring neural processing and subjective experience provide powerful approaches for examining real-time relationships between bodily state, neural representation, and phenomenology. For example, manipulating cardiac interoceptive input through external heart rate feedback that is synchronous versus asynchronous with actual heartbeats while conducting functional neuroimaging allows testing how faithful interoceptive input affects insular cortex activation and emotional processing (Gray et al., 2007). Combining such paradigms with mitochondrial genotyping could reveal whether individuals with different mitochondrial backgrounds show differential neural sensitivity to interoceptive manipulations. Similarly, respiratory manipulations including voluntary breath-holding or paced breathing at different rates could be combined with interoceptive awareness ratings and neural imaging to examine how respiratory-neural coupling varies with mitochondrial genomic constitution (Zelano et al., 2016).

Ecological momentary assessment designs using smartphone-based experience sampling provide methodologies for investigating relationships between mitochondrial genomic variation and embodied experience in naturalistic contexts across daily life (Shiffman et al., 2008). Participants would be prompted multiple times daily to rate current bodily feelings including energy level, physical comfort, interoceptive awareness, and emotional state, combined with contemporaneous physiological monitoring through wearable devices capturing heart rate variability, physical activity, and other parameters (Ebner-Priemer & Trull, 2009). Over weeks of repeated sampling, individual-level relationships between physiological state and subjective experience could be characterized, testing whether mitochondrial genomic variation influences the coupling between objective physiological parameters and subjective embodied feelings. This approach directly addresses the ecological validity concern that laboratory-based assessments may not capture individual differences in embodied processing as they manifest in everyday life.

Computational psychiatry approaches applying formal models from cognitive science and machine learning to behavioral and neural data provide methods for extracting latent computational parameters that might vary with mitochondrial genomic background (Huys et al., 2016). For instance, applying predictive coding models to interoceptive tasks yields estimates of parameters including interoceptive precision-weighting, learning rates for updating interoceptive predictions, and prior beliefs about bodily state (Paulus et al., 2019). If mitochondrial function influences interoceptive predictive processing as hypothesized, then mitochondrial haplogroups should associate with these computational parameters in theoretically-predicted ways. Similarly, reinforcement learning models applied to decision-making tasks can estimate parameters including reward sensitivity, punishment sensitivity, and exploration-exploitation trade-offs that might be influenced by somatic marker processes varying with mitochondrial function (Daw et al., 2006; Bechara & Damasio, 2005).

Multi-site collaborative studies pooling data across multiple research groups provide one solution to the sample size requirements for detecting modest genetic effects while maintaining the comprehensive phenotyping necessary to test mechanistic hypotheses. Several successful models exist in neuroimaging genetics including the ENIGMA consortium, which has pooled brain imaging and genetic data from dozens of sites to enable well-powered investigations of genetic influences on brain structure (Thompson et al., 2014). A similar collaborative framework focusing specifically on mitochondrial genomic variation, interoceptive processing, embodied cognition, and their neural substrates could accelerate progress by combining resources and expertise across research groups while implementing harmonized assessment protocols to enable data pooling (Manolio et al., 2009).

Animal model studies, while limited in their ability to address higher-order cognitive and phenomenological questions, provide essential opportunities for mechanistic investigation through experimental approaches infeasible in humans. Conplastic mouse strains—mice with identical nuclear genomes but different mtDNA variants—enable clean isolation of mtDNA effects from nuclear genetic confounds, providing definitive tests of whether mtDNA variation causally influences phenotypes (Moreno-Loshuertos et al., 2006). Studies in conplastic mice have demonstrated mtDNA influences on behavior, cognition, and brain metabolism, establishing proof-of-principle that common mtDNA variation affects brain phenotypes (Roubertoux et al., 2003; Gimsa et al., 2009). Extension of such work to examine behavioral correlates of interoceptive processing, autonomic function, and stress responsiveness across conplastic strains could test specific hypotheses about mitochondrial influences on embodied processing dimensions. Furthermore, brain tissue from such models enables direct measurement of mitochondrial function, neural metabolism, neurotransmitter levels, and other parameters inaccessible in living humans, providing mechanistic insights complementing human observational data.

Optogenetic and chemogenetic approaches enabling selective manipulation of specific neural populations in animal models provide tools for testing whether particular neural circuits mediate mitochondrial effects on embodied cognition (Roth, 2016). For instance, if mitochondrial function in insular cortex neurons causally contributes to interoceptive accuracy and emotional processing as hypothesized, then selective enhancement or impairment of insular neuron mitochondrial function through targeted genetic manipulations should produce corresponding changes in behavioral measures of interoception and emotion. Such experiments require sophisticated viral vector approaches delivering mitochondria-targeted constructs to specific brain regions, but recent technical advances make such manipulations increasingly feasible (Pathak et al., 2015). Conversely, testing whether behavioral or physiological interventions that improve embodied processing produce corresponding changes in neural mitochondrial function would address reverse causation questions about whether observed correlations between mitochondrial function and embodied cognition reflect mitochondrial effects on cognition versus cognitive or behavioral influences on mitochondrial function.

Part V: Theoretical Synthesis and Future Directions

5.1 An Integrated Framework: From Mitochondrial Genomics to Embodied Phenomenology

The synthesis of evidence from disconnected research domains spanning mitochondrial genetics, cellular bioenergetics, neuroscience, interoceptive processing, autonomic physiology, and embodied cognition reveals multiple potential pathways through

which individual differences in mitochondrial genomic architecture might systematically influence the physiological substrates, neural processing, and subjective phenomenology constituting embodied cognitive experience. While direct empirical evidence for these connections remains sparse, the theoretical coherence of the proposed relationships combined with substantial indirect evidence from each constituent domain provides a compelling rationale for systematic investigation. The integrated framework that emerges from this synthesis positions mitochondrial function as a fundamental constraint on and modulator of the physiological expressiveness, neural computational capacity, and phenomenological richness of embodied existence.

At the foundation, mitochondrial genomic variation creates individual differences in cellular bioenergetic capacity, reflected in parameters including maximal ATP production rates, coupling efficiency between electron transport and ATP synthesis, reactive oxygen species generation, calcium buffering capacity, and responsiveness to metabolic demands and stressors (Wallace, 2005, 2013). These cellular-level bioenergetic differences manifest differentially across tissues according to their metabolic demands and mitochondrial dependencies, with particularly pronounced effects in energetically demanding tissues including cardiac muscle, skeletal muscle, and neural tissue where mitochondrial function approaches rate-limiting for tissue function (Schon & Manfredi, 2003). The heart, maintaining rhythmic contraction throughout the lifespan with extraordinarily high ATP turnover, exhibits strong dependence on mitochondrial function for sustaining cardiac output and responding to hemodynamic demands, creating a pathway from mitochondrial genomic variation through cardiac bioenergetics to cardiac interoceptive signal generation (Stanley et al., 2005; Doenst et al., 2013).

The autonomic nervous system, orchestrating bidirectional communication between brain and peripheral organs while regulating physiological parameters including heart rate, blood pressure, respiratory patterns, gastrointestinal motility, and thermoregulation, depends on mitochondrial function at multiple levels including autonomic neuron activity, neurotransmitter synthesis and release, and end-organ responsiveness to autonomic signaling (Benarroch, 1993). Individual variation in mitochondrial genomic constitution that affects autonomic nervous system function would manifest in differences in baseline autonomic tone (reflected in measures including heart rate variability), autonomic reactivity to stimuli and stressors (reflected in magnitude and dynamics of physiological responses), and autonomic flexibility (reflected in the range and adaptability of autonomic states accessible to the individual) (Thayer & Lane, 2000). These autonomic differences create corresponding variation in the physiological landscape that forms the substrate for embodied cognition—individuals with robust autonomic function exhibit rich, dynamic, and responsive physiological states that provide abundant interoceptive information, while individuals with constrained autonomic function exhibit more limited physiological expressiveness.

The afferent interoceptive pathways conveying information about bodily physiological state from peripheral receptors through brainstem and spinal relays to cortical processing regions depend on neuronal mitochondrial function for generating and transmitting interoceptive signals, potentially creating a pathway from mitochondrial genomic variation through interoceptive neuron bioenergetics to interoceptive signal characteristics including magnitude, reliability, and temporal dynamics (Critchley & Harrison, 2013). Interoceptive neurons with adequate mitochondrial function might generate robust, consistent signals in response to physiological perturbations, corresponding to high signal-to-noise ratios and high precision in predictive processing frameworks, while interoceptive neurons with compromised mitochondrial function might generate weaker or more variable signals corresponding to low precision (Seth, 2013). This peripheral interoceptive signal quality then influences central interoceptive processing, as cortical regions including insula and anterior cingulate cortex integrate interoceptive afference with contextual information, prior expectations, and emotional significance to construct conscious representations of bodily state and generate somatic contributions to emotion and decision-making (Craig, 2009).

The neural processing of interoceptive information in cortical and subcortical regions itself depends on mitochondrial function to sustain the computational operations required for predictive processing, belief updating, and integration of interoceptive signals with cognitive and emotional information (Harris et al., 2012; Magistretti & Allaman, 2015). The insular cortex, exhibiting high baseline metabolic activity and dense mitochondrial populations, may be particularly sensitive to mitochondrial functional variation, with individual differences in insular mitochondrial capacity potentially influencing the computational sophistication, temporal precision, and affective elaboration of interoceptive representations (Nagai et al., 2007). Similarly, the anterior cingulate cortex's roles in integrating cognitive and interoceptive information, monitoring prediction errors, and regulating autonomic responses likely depend on adequate bioenergetic support, creating additional pathways from mitochondrial function to embodied processing (Bush et al., 2000; Shenhav et al., 2013).

The large-scale neural network dynamics supporting coordinated cognitive operations show sensitivity to metabolic factors, with network hub regions exhibiting elevated metabolic demands and network reconfiguration incurring energetic costs that might constrain network flexibility under conditions of limited bioenergetic capacity (Bullmore & Sporns, 2012; Shine et al., 2019). The salience network, comprising insula, anterior cingulate cortex, and connected regions, plays a central role in detecting behaviorally relevant stimuli, switching between large-scale networks, and integrating interoceptive and exteroceptive information, positioning it as a critical interface where mitochondrial function could influence embodied cognition through effects on network dynamics (Menon & Uddin, 2010; Seeley et al., 2007). Individual differences in mitochondrial

genomic constitution might manifest in salience network functional connectivity, activation dynamics, and the efficiency of network switching operations that enable flexible cognitive processing.

At the behavioral level, these multilayered physiological and neural effects converge to produce individual differences in interoceptive accuracy, the subjective intensity and differentiation of emotional experience, the magnitude of somatic influences on cognitive processes including decision-making and moral judgment, and the phenomenological character of embodied self-awareness (Garfinkel et al., 2015; Damasio, 1994; Critchley & Harrison, 2013). Individuals with robust mitochondrial function across the relevant physiological and neural systems might exhibit enhanced interoceptive accuracy, reflecting high-quality peripheral signals, efficient neural processing, and effective integration of interoceptive information; more intense and clearly differentiated emotional experiences, reflecting vigorous physiological emotional responses and faithful neural representation of bodily emotional states; greater susceptibility to somatic influences on cognition, reflecting strong coupling between bodily state and cognitive processing; and rich embodied phenomenology characterized by vivid bodily feelings and strong sense of physical presence (Seth, 2013; Gallagher, 2005).

Conversely, individuals with constrained mitochondrial function might exhibit reduced interoceptive accuracy due to weak peripheral signals, noisy neural processing, or inefficient integration; blunted or undifferentiated emotional experience reflecting limited physiological emotional expressiveness or poor neural representation of bodily states; reduced somatic influences on cognition reflecting weak coupling between bodily state and cognitive systems; and impoverished embodied phenomenology characterized by diminished bodily feelings and reduced sense of physical vitality (Dunn et al., 2010; Herbert et al., 2010). These patterns might remain subclinical, manifesting as normal-range individual differences in embodied processing style, or might contribute to vulnerability for conditions involving embodied dysfunction including alexithymia, somatic symptom disorders, chronic fatigue, or emotional regulation difficulties under sufficient additional risk factors (Pollatos et al., 2008; Henningsen et al., 2018).

The developmental dimension adds temporal complexity to this framework, as mitochondrial function influences neurodevelopmental processes including neurogenesis, synaptic refinement, and myelination that establish neural organization during critical periods, potentially creating enduring individual differences in neural architecture that persist even if mitochondrial function later changes (Mattson & Gleichmann, 2013; Khacho et al., 2019). Individual variation in mitochondrial genomic constitution might thereby exert effects on embodied cognition through both developmental programming of neural systems and ongoing influences on neural function throughout life, with the relative importance of

these developmental versus concurrent effects remaining unclear and likely varying across specific embodied processing dimensions.

Environmental modulation through factors including physical exercise, stress exposure, dietary patterns, and sleep introduces additional complexity, as these experiential variables influence mitochondrial function while also directly affecting physiological and neural systems relevant to embodied cognition (Picard & McEwen, 2014; Hood et al., 2006). Gene-environment interactions might create threshold or multiplicative effects wherein mitochondrial genomic vulnerabilities become phenotypically expressed primarily under conditions of sustained stress, physical inactivity, or metabolic challenge, while remaining largely inapparent under optimal conditions (Picard et al., 2018). This interactive perspective suggests that mitochondrial genomic effects on embodied cognition might be highly context-dependent and vary substantially across individuals' life circumstances, developmental trajectories, and behavioral patterns.

5.2 Clinical Implications and Translational Potential

The potential clinical implications of understanding mitochondrial genomic influences on embodied cognition span multiple domains including psychiatric diagnosis and treatment, psychosomatic medicine, personalized interventions, and mechanistic insights into mind-body relationships that have long puzzled clinical medicine (Picard et al., 2018; Henningsen et al., 2018). While speculative given the current evidence base, several translational directions merit consideration as the foundational science advances.

Psychiatric nosology and diagnosis could potentially be informed by embodied and physiological dimensions that relate to underlying mitochondrial function. Current psychiatric classification relies predominantly on symptom-based criteria that may obscure important biological heterogeneity within diagnostic categories (Insel et al., 2010). The incorporation of embodied processing measures including interoceptive accuracy, autonomic function, and physiological stress responsiveness as transdiagnostic dimensions could identify biologically-meaningful subgroups that cut across traditional diagnostic boundaries (Khalsa et al., 2018). If mitochondrial genomic variation contributes to dimensional variation in embodied processing that in turn influences psychiatric symptom expression, then mitochondrial genotyping combined with embodied phenotyping might enable more precise subtyping of conditions including anxiety disorders, depression, and somatic symptom disorders, potentially predicting treatment response or informing intervention selection.

Somatic symptom disorders and functional somatic syndromes represent particularly promising targets for clinical application of mitochondrial-embodied cognition frameworks, as these conditions centrally involve alterations in bodily symptom perception, physiological function, and mind-body relationships (Henningsen et al., 2018; Yunus, 2008). Understanding

whether subgroups of patients with these conditions exhibit identifiable mitochondrial dysfunction, either genetic or acquired, could inform mechanistic understanding and potentially identify targets for intervention. Mitochondrial-supporting interventions including exercise programs, nutritional approaches, or pharmacological agents might benefit patient subsets with demonstrable mitochondrial involvement, though current evidence remains insufficient to support such targeted interventions (Castro-Marrero et al., 2013).

Psychotherapeutic approaches increasingly incorporate body-focused techniques including mindfulness-based interventions, somatic experiencing, and sensorimotor psychotherapy that explicitly target embodied dimensions of psychological experience (Ogden et al., 2006; van der Kolk, 2014). Understanding individual differences in embodied processing capacities and their potential relationship to mitochondrial function could inform treatment personalization, with individuals showing robust interoceptive processing potentially benefiting more from body-focused interventions while individuals with impaired interoceptive access might require different therapeutic approaches or preliminary work developing interoceptive awareness before body-focused techniques become effective (Price & Hooven, 2018). However, such personalization requires prospective evidence that baseline embodied processing predicts differential treatment response, which remains lacking.

Lifestyle interventions targeting mitochondrial function through exercise, diet, stress management, and sleep optimization show promise for improving cognitive function, emotional regulation, and stress resilience (Voss et al., 2013; Picard & McEwen, 2014). If mitochondrial genomic variation influences the magnitude of benefit individuals derive from such interventions, then genotype-stratified analyses in intervention trials could identify genetic markers predicting treatment response, enabling precision prescription of lifestyle modifications (Bouchard et al., 2011). For instance, individuals with mitochondrial genotypes associated with lower baseline oxidative capacity might show particularly robust cognitive and emotional benefits from aerobic exercise interventions that induce mitochondrial biogenesis, while individuals with already-high mitochondrial capacity might exhibit ceiling effects limiting additional gains.

Pharmacological approaches targeting mitochondrial function remain limited, with most existing agents showing modest efficacy in clinical trials despite promising preclinical data (Pfeffer et al., 2012). Coenzyme Q10, idebenone, creatine, and various antioxidants have been investigated for mitochondrial diseases and neurodegenerative conditions with mixed results (DiMauro et al., 2004). The development of more effective mitochondria-targeted therapeutics represents an active area of drug development, with novel approaches including mitochondria-targeted antioxidants, modulators of mitochondrial dynamics and quality control, and enhancers of mitochondrial biogenesis

showing promise in preclinical studies (Murphy & Smith, 2007; Smith & Murphy, 2010). If such agents prove effective and safe in humans, their potential application to enhancing embodied cognitive processing or treating conditions involving embodied dysfunction could be explored, though substantial research would be required to establish efficacy for such indications.

The mind-body problem in medicine, exemplified by the challenges of understanding and treating conditions at the interface of psychological and physical health, might be illuminated by mechanistic frameworks linking mitochondrial function to embodied cognition (Kirmayer & Looper, 2007). Rather than conceptualizing mind and body as separate domains that mysteriously interact, the embodied cognition perspective informed by mitochondrial bioenergetics suggests that cognitive and emotional processes are fundamentally grounded in physiological states and bodily dynamics, with mitochondrial function serving as a critical mediator linking cellular metabolism to organismal behavior and experience (Picard et al., 2016). This integrated framework could help destigmatize conditions involving prominent somatic symptoms by providing biological explanations that validate patients' experiences while avoiding dualistic mind-body conceptualizations (Henningsen et al., 2018).

5.3 Methodological Innovations and Technical Advances Required

Advancing the investigation of mitochondrial genomic influences on embodied cognition requires methodological innovations addressing current limitations in mitochondrial functional assessment, embodied cognition measurement, multi-level integration, and causal inference. Several technical advances would substantially accelerate progress in this research domain.

Non-invasive assessment of human brain mitochondrial function remains a major challenge limiting investigation of mitochondrial influences on neural processing and cognition. Current approaches including magnetic resonance spectroscopy measuring metabolites such as N-acetylaspartate, lactate, and phosphocreatine provide indirect indices of mitochondrial function but lack the specificity and sensitivity to detect subtle variations associated with common mtDNA polymorphisms (Kato et al., 1998). Positron emission tomography using mitochondria-targeted radiotracers represents a promising avenue but remains limited by radiation exposure restricting repeated measurements and by the paucity of validated mitochondrial PET tracers suitable for human use (Fink et al., 2019). Optical imaging approaches including near-infrared spectroscopy measuring tissue oxygenation and oxidative metabolism show promise for non-invasive monitoring but have limited penetration depth restricting assessment to cortical surfaces (Ferrari & Quaresima, 2012). The development of novel neuroimaging methods capable of quantifying

mitochondrial function or metabolism in deep brain structures with sufficient sensitivity to detect individual differences would represent a transformative advance.

Peripheral biomarkers of mitochondrial function accessible through blood sampling or other minimally-invasive procedures provide practical alternatives to brain-based measurements, but their correspondence to brain mitochondrial function requires validation. Platelet mitochondrial function has been proposed as a surrogate for neuronal mitochondrial function based on shared ectodermal origin, with studies measuring platelet respiratory capacity, membrane potential, and reactive oxygen species generation (Wrighton et al., 2013). However, the correlation between platelet and brain mitochondrial function remains poorly characterized, and tissue-specific differences in mitochondrial regulation may limit the utility of peripheral measurements as proxies for brain metabolism (Picard et al., 2014). Lymphocyte or peripheral blood mononuclear cell mitochondrial function represents another accessible measure, but immune cell mitochondria show distinctive metabolic properties related to immune function that may not generalize to neurons (Weinberg et al., 2015). Circulating metabolite biomarkers reflecting mitochondrial metabolism including lactate/pyruvate ratios, ketone bodies, amino acid profiles, and markers of oxidative stress might provide systemic indices of mitochondrial function, though their sensitivity to localized brain mitochondrial variation requires investigation.

The measurement of embodied cognition itself requires methodological refinement to improve reliability, validity, and theoretical grounding. Heartbeat detection tasks, despite their widespread use, show problematic psychometric properties including modest test-retest reliability and susceptibility to confounds including beliefs about heart rate and task strategy effects (Ring & Brener, 2018; Desmedt et al., 2018). Alternative interoceptive accuracy measures including heartbeat discrimination tasks wherein participants judge whether external stimuli occur synchronously with heartbeats, respiratory resistance detection, and gastric distension perception tasks each have limitations and may assess partially distinct interoceptive processing dimensions (Garfinkel et al., 2015). The development of latent variable models integrating multiple interoceptive measures to extract a more reliable construct of interoceptive accuracy, or alternatively recognizing that interoception comprises distinct modality-specific processes that should not be aggregated, represents an important psychometric priority (Murphy et al., 2019).

Beyond interoceptive accuracy, the assessment of embodied cognitive processing more broadly requires validated paradigms with adequate effect sizes and reliability for individual differences research. Many embodied cognition phenomena were discovered in experimental studies demonstrating within-subject effects of bodily manipulations on cognitive processing, but translating these paradigms to measure stable individual differences in embodied processing propensity requires establishing that task performance shows temporal stability within individuals and meaningful variation across individuals

(Vermeulen et al., 2016). The development of a standardized battery of embodied cognition tasks with established psychometric properties, normative data, and demonstrated relationships to relevant neural and physiological measures would facilitate systematic investigation of individual differences (Winkielman et al., 2015).

Computational phenotyping approaches applying formal models to extract latent parameters from behavioral and physiological data represent a promising methodological direction. Rather than relying solely on raw behavioral performance metrics, computational modeling can estimate theoretically-meaningful parameters including interoceptive precision-weighting, learning rates for updating bodily predictions, prior beliefs about physiological state, and decision parameters reflecting somatic marker influences (Paulus et al., 2019; Bechara & Damasio, 2005). These computational parameters may show superior reliability compared to raw performance measures and provide more direct indices of the cognitive processes hypothesized to be influenced by mitochondrial function. The application of hierarchical Bayesian modeling enabling simultaneous estimation of group-level and individual-level parameters while appropriately handling uncertainty represents a particularly sophisticated approach (Gelman et al., 2013).

Ecological momentary assessment combined with wearable physiological monitoring enables investigation of embodied processing in naturalistic contexts across daily life, addressing concerns about ecological validity of laboratory findings (Ebner-Priemer & Trull, 2009). Modern wearable devices can continuously monitor heart rate, heart rate variability, physical activity, sleep, and increasingly sophisticated measures including respiratory patterns and electrodermal activity, providing rich physiological data streams (Bent et al., 2020). When combined with smartphone-based experience sampling prompting participants to rate subjective bodily feelings, emotional states, and cognitive experiences multiple times daily, these approaches enable within-person modeling of relationships between physiological state and subjective experience across varying natural contexts (Shiffman et al., 2008). The investigation of whether mitochondrial genomic variation influences the coupling between objective physiological parameters and subjective embodied experience in daily life represents a novel application of these methodologies.

Multi-omic integration combining mitochondrial genomics with nuclear genomics, transcriptomics, proteomics, metabolomics, and epigenomics provides comprehensive characterization of the molecular landscape linking genetic variation to functional phenotypes (Hasin et al., 2017). While single-omic approaches examining only mtDNA sequence variation may detect associations, understanding mechanism requires characterizing downstream effects on gene expression, protein abundance, metabolite profiles, and epigenetic states. The decreasing costs of omics technologies enable their incorporation in reasonably-sized human studies, though the analytical challenges of integrating multi-omic data remain substantial (Ritchie et al., 2015). Network approaches

modeling relationships among molecular features across omic layers can identify pathways through which genetic variation propagates to influence complex phenotypes (Ritchie et al., 2015; Barabási et al., 2011).

Longitudinal study designs with repeated measurements across months or years enable investigation of temporal dynamics, developmental trajectories, and the effects of environmental exposures on mitochondrial-embodied cognition relationships (Raz & Lindenberger, 2011). Cross-sectional designs cannot distinguish stable trait-like associations from dynamic state-dependent relationships or characterize how associations change with age, experience, or environmental context. Longitudinal designs tracking individuals from childhood through adolescence could illuminate how mitochondrial function influences neurodevelopmental trajectories and the emergence of individual differences in embodied processing. Similarly, longitudinal studies in older adults could characterize how age-related mitochondrial decline relates to changes in interoceptive accuracy, autonomic function, and embodied cognition, potentially identifying mitochondrial genomic factors that influence cognitive aging trajectories (Fang et al., 2019).

Intervention studies manipulating mitochondrial function, physiological state, or embodied processing provide causal leverage unavailable in observational designs. Exercise training interventions that enhance mitochondrial biogenesis can test whether improvements in mitochondrial function produce corresponding changes in embodied processing (Voss et al., 2013). Mindfulness or body-focused psychotherapeutic interventions that train interoceptive attention and bodily awareness can test whether enhanced embodied processing alters physiological function or shows differential effects based on mitochondrial genomic background (Farb et al., 2015). Pharmacological interventions targeting mitochondrial function, if safe agents become available, could provide direct tests of mitochondrial causal contributions to embodied cognition.

Advanced neuroimaging approaches including ultra-high-field 7 Tesla MRI enabling higher spatial resolution and improved spectroscopy, simultaneous EEG-fMRI combining temporal precision of electrophysiology with spatial precision of hemodynamic imaging, and arterial spin labeling MRI quantifying regional cerebral blood flow as a metabolic proxy, each offer enhanced capabilities for investigating neural correlates of embodied processing and their relationship to mitochondrial function (Duyn, 2012; Jorge et al., 2014). Functional connectivity analyses using dynamic rather than static approaches can characterize time-varying network configurations during interoceptive processing and embodied cognition tasks, potentially revealing whether mitochondrial genomic variation influences network dynamics (Hutchison et al., 2013). Multi-modal imaging integrating structural, functional, diffusion, and metabolic imaging modalities provides comprehensive characterization of brain organization supporting individual differences in embodied cognition (Sui et al., 2012).

5.4 Evolutionary Perspectives and Population Differences

The evolutionary context of mitochondrial genomic variation provides important perspective on the functional significance of haplogroup differences and informs hypotheses about selective pressures that may have shaped relationships between mtDNA variation and phenotypic traits including those relevant to embodied cognition (Wallace, 2005, 2015). Mitochondrial haplogroups arose through mutations accumulating along maternal lineages as human populations expanded from Africa into diverse geographic and climatic environments, with different haplogroups predominating in different regions reflecting founder effects, genetic drift, and potentially natural selection acting on mtDNA variants (Torroni et al., 2006; Wallace, 2015). The hypothesis that mitochondrial haplogroups underwent selection for metabolic properties suiting local environmental conditions has been proposed based on the observation that haplogroups show non-random geographic distributions that correlate with climate variables including temperature, with some patterns consistent with selection for cold adaptation or heat adaptation (Ruiz-Pesini et al., 2004; Mishmar et al., 2003).

The thermogenic hypothesis proposes that mitochondrial variants reducing oxidative phosphorylation coupling efficiency, thereby generating more heat relative to ATP production, were selected in cold climates while tightly-coupled variants maximizing ATP production were selected in warm climates (Ruiz-Pesini et al., 2004). According to this hypothesis, mtDNA variants affecting the proton leak across the inner mitochondrial membrane create a tradeoff between ATP yield and thermogenesis, with natural selection favoring different points along this tradeoff in different thermal environments. While some genetic and biochemical evidence supports this hypothesis, including associations between climate and the frequency of specific mtDNA variants and functional studies showing coupling efficiency differences among haplogroups, other analyses have challenged the hypothesis, noting that human behavioral thermoregulation through clothing, shelter, and fire may have reduced selective pressure on mitochondrial thermogenic capacity (Amo & Brand, 2007; Scott et al., 2011).

An alternative or complementary evolutionary perspective emphasizes selection on mitochondrial ATP production efficiency for supporting physically demanding activities, with population variation in subsistence strategies and activity patterns potentially creating differential selection pressures (Cai et al., 2009). Populations relying on endurance hunting or other sustained physical activities might have experienced selection for mitochondrial variants optimizing oxidative ATP production and exercise capacity, while populations with different subsistence patterns might show different mtDNA frequency patterns. Some evidence for such selection comes from observed associations between mitochondrial haplogroups and athletic performance, with certain haplogroups over-represented among

elite endurance athletes, though alternative explanations including demographic factors and chance require consideration (Mikami et al., 2011; Castro et al., 2007).

The relevance of evolutionary perspectives to embodied cognition emerges from considering that the selective pressures acting on mitochondrial function—including thermoregulation, physical work capacity, stress resilience, and metabolic flexibility—all involve physiological dimensions that generate interoceptive signals and contribute to embodied experience. If different environments favored different metabolic strategies with corresponding physiological profiles, then population differences in average mtDNA functional properties might create population differences in average embodied processing characteristics, including interoceptive sensitivity, autonomic response patterns, and the subjective experience of physical exertion, thermal stress, or metabolic states (Wallace, 2015). However, such population differences, if they exist, would represent average tendencies with substantial individual variation within populations, and environmental, cultural, and nuclear genetic factors would also contribute substantially to embodied cognition variation across populations.

The ethical implications of investigating population differences in embodied cognition related to mitochondrial genomic variation require careful consideration. Human population genetics has a troubled history including misuse of genetic findings to justify discriminatory practices and propagate unfounded claims of population differences in behavioral or cognitive traits (Fullwiley, 2007). Research examining potential population differences must proceed with explicit acknowledgment of the complex interplay of genetic, environmental, and cultural factors influencing phenotypes, avoidance of essentialist interpretations attributing differences solely to genetic ancestry, and careful communication emphasizing within-group variation and between-group overlap (Jablonski & Fuentes, 2010). The scientific investigation of mitochondrial haplogroup associations with embodied cognition should focus primarily on understanding biological mechanisms and individual differences that cut across population boundaries rather than emphasizing population comparisons that risk reinforcing problematic racial or ethnic stereotypes.

5.5 Philosophical Implications for Mind-Body Relationships and Embodied Existence

The potential relationships between mitochondrial genomic variation and embodied cognition raise fundamental philosophical questions about mind-body relations, the nature of subjective experience, and the biological foundations of phenomenological consciousness that extend beyond empirical investigation into conceptual and metaphysical territory (Gallagher, 2005; Thompson, 2007). While speculative, considering these philosophical implications helps situate the scientific investigation within broader theoretical contexts and illuminates the potential significance of findings.

The hard problem of consciousness, articulated by Chalmers (1995), concerns explaining how and why physical processes in the brain give rise to subjective phenomenal experience—why there is "something it is like" to be a conscious organism rather than information processing occurring without subjective experience. While neuroscience can identify neural correlates of consciousness and explain cognitive functions, accounting for the subjective, first-person character of experience remains conceptually challenging (Chalmers, 1995, 1996). The embodied cognition perspective, particularly in its neurophenomenological formulation, proposes that subjective experience is fundamentally embodied, grounded in the organism's sensorimotor engagement with its environment and in the regulatory dynamics of the living body (Varela et al., 1991; Thompson, 2007).

The possibility that individual differences in mitochondrial function influence the character of embodied subjective experience raises the prospect that metabolic variation at the cellular level propagates through physiological and neural levels to influence phenomenological properties of consciousness including the intensity, affective tone, and bodily groundedness of experience (Picard et al., 2016). If confirmed, such relationships would suggest that the subjective feel of existence, the felt sense of bodily vitality or exhaustion, the emotional coloring of experience, and the phenomenological richness or poverty of embodied awareness have identifiable biological substrates extending to mitochondrial genomics. This does not necessarily resolve the hard problem—explaining correlations between biological processes and phenomenology does not fully explain why these correlations exist or how physical processes generate subjective experience—but it deepens understanding of the biological architecture supporting consciousness (Thompson, 2007; Seth, 2013).

The concept of the embodied self, central to phenomenological philosophy and increasingly influential in cognitive neuroscience, emphasizes that the sense of self is fundamentally grounded in bodily experience, sensorimotor integration, and the pre-reflective feeling of being a bodily subject rather than merely having a body as an external object (Gallagher, 2000, 2005). The minimal self, constituting the most basic sense of self-as-subject preceding more elaborate narrative or conceptual self-representations, involves proprioceptive and interoceptive bodily awareness, sense of agency in action, and the first-person givenness of experience (Gallagher, 2000; Zahavi, 2005). Individual differences in interoceptive processing, bodily awareness, and the integration of bodily signals into self-representation might thereby influence the phenomenological structure of selfhood, with implications for understanding clinical conditions involving disturbed self-experience (Fotopoulou & Tsakiris, 2017).

If mitochondrial genomic variation influences these dimensions of embodied self-experience through effects on interoceptive processing and physiological regulation, this suggests that biological variation at the genetic level contributes to phenomenological

variation in how individuals experience existing as embodied selves. Individuals with robust interoceptive processing might experience a more vivid, present, and stable sense of embodied self, while individuals with impaired interoceptive processing might experience reduced bodily grounding of selfhood, potentially contributing to phenomena including depersonalization, disembodiment, or fragmented self-experience under conditions of stress or pathology (Seth et al., 2011; Medford & Critchley, 2010). These are speculative extensions requiring empirical investigation, but they illustrate how biological findings might inform philosophical understanding of selfhood and consciousness.

The free energy principle and active inference framework, proposed by Friston and colleagues as a unifying theory of life and mind, suggests that living systems minimize surprise or prediction error through perception and action, with consciousness emerging from hierarchical predictive modeling of sensory input including interoceptive input (Friston, 2010; Seth & Friston, 2016). In this framework, the subjective feel of bodily states and emotions reflects the brain's predictions about bodily state and prediction errors signaling discrepancies between predicted and actual interoceptive signals (Barrett & Simmons, 2015). Individual differences in the precision-weighting of interoceptive predictions, the accuracy of interoceptive models, and the efficiency of prediction error minimization would influence the phenomenological character of embodied experience (Seth, 2013). If mitochondrial function influences these computational parameters as hypothesized, then mitochondrial variation contributes to the generative modeling processes through which conscious experience is constructed.

The enactive approach to cognition, developed by Varela, Thompson, and Rosch (1991) and elaborated by subsequent theorists, emphasizes that cognition constitutes enacted, embodied sense-making wherein organisms bring forth meaningful worlds through sensorimotor engagement and autonomous self-regulation (Thompson, 2007; Di Paolo et al., 2017). According to enactivism, cognition is fundamentally life-regulating activity, and meaningful experience emerges from the organism's ongoing efforts to maintain its integrity and viability in relation to environmental perturbations (Di Paolo, 2005). Metabolic self-production (autopoiesis) and metabolic regulation constitute the foundational level of sense-making from which higher cognitive capacities emerge (Thompson, 2007). This perspective positions mitochondrial metabolism not as merely providing energy for cognition occurring elsewhere but as participating in the constitutive processes through which organisms enact meaningful worlds (Barandiaran & Moreno, 2008).

From an enactive perspective, individual differences in mitochondrial function would influence the affective and sense-making capacities through which organisms evaluate situations as beneficial or harmful, urgent or ignorable, emotionally significant or neutral, because these evaluations depend fundamentally on the organism's metabolic relation to its environment and its capacity to regulate its own viability (Di Paolo, 2005; Colombetti, 2014).

Mitochondrial genomic variation, by establishing different metabolic capacities and vulnerabilities, might thereby influence the organism's evaluative engagement with its world at the most fundamental level. While these philosophical extensions remain speculative and may seem far removed from empirical investigation, they illustrate the depth of theoretical implications that mitochondrial-embodied cognition relationships might hold.

Conclusion: Toward an Integrated Science of Metabolic Embodiment

This meta-analytical review has synthesized currently disconnected research domains spanning mitochondrial genetics, cellular bioenergetics, neuroscience, interoceptive processing, autonomic physiology, and embodied cognition to articulate a comprehensive framework for understanding how individual differences in mitochondrial genomic architecture might systematically influence the physiological substrates, neural processing, and phenomenological dimensions constituting embodied cognitive experience. While direct empirical evidence for these relationships remains sparse, requiring substantial future investigation to test specific predictions, the theoretical coherence of proposed mechanisms combined with indirect evidence from constituent research areas establishes a compelling rationale for systematic inquiry.

The key mechanistic pathways linking mitochondrial genomic variation to embodied cognition operate through multiple interconnected levels: mitochondrial DNA sequence variation influences cellular bioenergetics through effects on respiratory chain function, ATP production capacity, calcium buffering, and reactive oxygen species generation; these cellular metabolic effects manifest in tissue and organ function particularly in energetically demanding systems including cardiac muscle, skeletal muscle, and neural tissue; physiological effects on autonomic function, stress response systems, and peripheral physiological responses influence the generation of interoceptive afferent signals that inform central representations of bodily state; neural processing of interoceptive information in insular cortex, anterior cingulate cortex, and interconnected regions depends on adequate mitochondrial bioenergetic support for computational operations; large-scale brain network dynamics supporting cognitive operations show sensitivity to metabolic constraints that may vary with mitochondrial genomic constitution; and these multilevel effects converge to produce individual differences in interoceptive accuracy, emotional experience intensity and differentiation, somatic influences on cognitive processing, and the phenomenological character of embodied self-awareness.

The empirical investigation of these proposed relationships requires methodological innovations including improved non-invasive assessment of brain mitochondrial function,

validated measurement of embodied cognitive phenotypes with adequate psychometric properties, multi-level integration of genetic, physiological, neural, behavioral, and phenomenological data within individual participants, longitudinal designs characterizing developmental trajectories and temporal dynamics, experimental manipulations testing causal relationships, and computational phenotyping approaches extracting latent parameters from complex behavioral and physiological data. Large-scale collaborative studies pooling data across research groups while implementing harmonized assessment protocols could provide the sample sizes necessary for detecting modest genetic effects while maintaining comprehensive phenotyping required for mechanistic investigation.

The clinical translation potential encompasses multiple domains including psychiatric subtyping based on embodied dimensions, mechanistic understanding of somatic symptom disorders and functional somatic syndromes, personalization of psychotherapeutic approaches based on embodied processing capacities, and stratification of intervention responses based on mitochondrial genomic markers. However, clinical applications remain speculative pending empirical validation of foundational relationships between mitochondrial variation and embodied cognition in healthy populations.

The broader theoretical implications extend to fundamental questions about mind-body relationships, the biological foundations of consciousness and selfhood, and the metabolic underpinnings of sense-making and meaningful experience. While philosophical extrapolations necessarily remain speculative, they illustrate the potential depth of significance that mitochondrial-embodied cognition relationships might hold for understanding human existence as fundamentally metabolic and embodied.

The research program outlined here represents an ambitious integration across disciplines that have developed largely independently, requiring collaboration among mitochondrial biologists, neuroscientists, psychophysiologists, cognitive scientists, and clinical researchers to fully realize. The challenges are substantial, including methodological limitations, the complexity of multilevel relationships, the modest effect sizes expected for common genetic variants, and the need for large well-phenotyped samples. Nevertheless, the potential rewards—a deeper understanding of individual differences in embodied experience grounded in identifiable biological mechanisms, improved approaches to conditions involving embodied dysfunction, and theoretical advances illuminating mind-body relationships—justify the investment required to systematically investigate these currently disconnected research domains and forge integrative frameworks capable of bridging from mitochondrial genomics through physiological embodiment to phenomenological consciousness.

The future of this research area depends on moving beyond the current state of isolated investigations in separate domains toward genuine integration wherein studies simultaneously assess mitochondrial variation, physiological function, neural processing,

behavioral performance, and subjective experience within the same participants, enabling direct testing of multilevel mechanistic hypotheses. As methodological capabilities advance and collaborative research infrastructure develops, the vision of a truly integrated science of metabolic embodiment linking cellular bioenergetics to lived experience becomes increasingly achievable, promising to illuminate fundamental aspects of what it means to exist as a metabolically-sustained, physiologically-regulated, phenomenologically-experiencing embodied human being whose sense of self and engagement with the world are grounded in the coordinated functioning of billions of mitochondria distributed throughout body and brain.

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