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ORIGINAL ARTICLE

Psychobiological and Metabolic Correlates of Time Perception in Humans: An Exploratory Study

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Received: 26 May 2026 | **Revised:** 29 July 2026 | **Accepted:** 13 August 2026

Keywords: mitochondrial disease | norepinephrine | resting energy expenditure | time perception

ABSTRACT

Time perception—the subjective sense of how quickly or consistently time passes—shows striking variability across individuals, yet its physiological basis remains poorly understood. We hypothesized that internal clock speed and trial-to-trial variability in time perception would be linked to physiological and behavioral states. In a cohort of healthy adults ($n = 59$) and individuals carrying rare mitochondrial DNA mutations affecting mitochondrial energy transformation ($n = 36$), we explored the associations between time perception (time estimation and production) with measures of immune mitochondrial bioenergetics, blood catecholamines, working memory, and structural and functional neuroimaging. We found weak evidence suggesting that internal clock speed and time perception variability correlated with age and physiological metrics including resting energy expenditure, serum and urine norepinephrine levels, mood and fatigue, working memory performance, and neuroimaging measures of brain structure and function. Individuals with mitochondrial disorders and those with healthy mitochondria exhibited no main difference in time perception. However, they exhibited differential relations with physiological and neural variables, suggesting that mitochondria may moderate how specific processes influence time perception. These results provide a foundation for future studies to examine how cellular bioenergetics relate to time perception in humans.

1 | Introduction

Although clock time flows uniformly, our subjective experience of its passage can vary (Lamotte et al. 2014). Moment-to-moment fluctuations in time perception, whether we think a lot or little has passed, influence decision making, emotional regulation, attention, and even long-term mental health (Ren et al. 2023; Wittmann et al. 2015; Wittmann and Paulus 2008). Classic cognitive models have proposed internal neural pacemakers, temporal accumulators, and attentional gate theories to explain the construction of subjective time (Treisman 1963; Zakay and Block 1995). Yet, these frameworks often isolate time perception from the broader physiological systems in which it operates. More recent accounts move away from a single dedicated timekeeper toward distributed and embodied mechanisms, in which subjective time emerges from activity across multiple brain regions (Merchant et al. 2013) and, from a hierarchy of coupled brain–body rhythms rather than a discrete neural clock (Buzsáki 2026). In parallel, a growing human literature situates duration perception in the brain's monitoring of bodily and interoceptive state, implicating the insula and supplementary motor area and signals such as heartbeat and arousal

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(Craig 2009; Teghil and Wittmann 2025; Wittmann 2013). Here, we focus on two dimensions of time perception: Clock Speed, the systematic rate at which subjective time flows, where a faster clock causes intervals to feel longer and Variation, trial-to-trial noise in duration estimates, reflecting imprecision independent of mean clock rate.

Comparative physiology suggests that metabolic rate may shape Clock Speed: animals with higher metabolic rates, such as mice, tend to have finer temporal resolution and shorter reaction times, whereas species with lower metabolic rates, such as tortoises, show lower temporal resolution and longer reaction times (Healy et al. 2013). A classic demonstration of this principle is critical flicker fusion frequency (CFF), the threshold at which flickering light is perceived as continuous, which increases with metabolic rate across species, indicating finer-grained temporal processing and faster internal clock speed, meaning more perceptual events are registered per unit of clock time, such that a given interval feels longer subjectively. In humans, mental fatigue, hypoxia, or reduced cerebral metabolism lower CFF threshold, indicating that decreases in energetic availability slow internal clock resolution and internal clock resolution depends on energetic availability (Lafère et al. 2010; Mankowska et al. 2021; Seki and Hugon 1976; Truszczyński et al. 2009). Consistent with this view, experimental manipulations of body temperature show that heating makes time feel longer (more is processed per second), while cooling makes time feel shorter, suggesting that internal clock dynamics are sensitive to metabolic state (Wearden and Penton-Voak 1995).

Sympathetic arousal provides another example of how energy-regulating systems may shape time perception. Norepinephrine release during acute stress and heightened arousal has long been associated with an overestimation of elapsed time and a subjective acceleration of its passage time (Ogden et al. 2019; Penney et al. 1996; Yuan et al. 2020). Neuroimaging studies implicate greater locus coeruleus activity, the brain's main norepinephrine source, in increased variation in time perception (Mather et al. 2016). Pharmacological studies also suggest a role for noradrenergic signaling, as administration of the reuptake inhibitor reboxetine selectively improved timing accuracy for second-range intervals but not for millisecond-range intervals, suggesting that elevated noradrenergic tone enhances precision specifically at longer timescales (Rammsayer et al. 2001). More broadly, the brain's continuous monitoring of bodily and autonomic signals, including cardiac activity and interoceptive state, has been shown to shape the perceived passage of time, linking duration judgments to visceral and energetic status (Meissner and Wittmann 2011; Pollatos et al. 2014; Teghil and Wittmann 2025). Together, comparative metabolic evidence and sympathetic arousal studies converge on the idea that time perception is not isolated to neural circuits alone but is bidirectionally influenced by peripheral and systemic energy metabolism, possibly also including mitochondria as cellular mediators of this relationship.

Building on this, we hypothesized that systemic energy metabolism itself may influence how time is experienced. Individuals carrying mitochondrial DNA (mtDNA) pathogenic variants that affect oxidative phosphorylation often exhibit both reduced energetic capacity and elevated norepinephrine levels at rest and during exertion (Jeppesen et al. 2013; Taivassalo et al. 2003). This pronounced metabolic imbalance offers a system to ask whether, and in what ways, time perception is modulated under conditions of chronic energetic imbalance. Previous research has primarily linked time perception to attention, arousal, and psychiatric status (Matthews and Meck 2014; Pouthas and Perbal 2004; Wittmann and Paulus 2008). Comparatively, very few studies have examined how these psychological dimensions interact with systemic and cellular energy capacity.

To address this gap, we leveraged data from the Mitochondrial Stress, Brain Imaging, and Epigenetics (MiSBIE) study (Kelly et al. 2024), a deeply phenotyped cohort of individuals with genetically confirmed mitochondrial oxidative phosphorylation mutations (mitoD) and matched healthy controls. We combined behavioral measures of time perception, Clock Speed (the subjective rate of time perception) and Variation (the stability of time perception), with a multimodal battery of physiological and psychological assessments. We tested four a priori hypotheses:

Hypothesis 1. *Greater bioenergetic capacity (resting energy expenditure) is associated with faster Clock Speed and more stable timing.*

Hypothesis 2. *Tonic norepinephrine is associated with Clock Speed and Variation.*

Hypothesis 3. *Mitochondrial OxPhos dysfunction disrupts these physiological couplings (group × predictor interactions).*

Hypothesis 4. *Working-memory capacity relates to Clock Speed and Variation. All other analyses were exploratory.*

By comparing mitoD participants to healthy controls, this study aimed to test whether energy constraints alter the integration of physiological and cognitive regulators that normally stabilize time perception.

2 | Methods

2.1 | Participants

Participant recruitment and eligibility criteria have been described in detail previously as part of the Mitochondrial Stress, Brain Imaging, and Epigenetics (MiSBIE) study (ClinicalTrials.gov: NCT04831424) (Kelly et al. 2024). In brief, 110 individuals aged 18–60 were recruited between April 2018 and May 2023 through Columbia University Irving Medical Center and national outreach efforts. Of these, 95 participants (59 healthy controls, 36 with genetically confirmed mitochondrial disease (mitoD)) were included in the present study based on availability of relevant samples. All participants provided written informed consent in accordance with IRB protocols at Columbia University Irving Medical Center and the New York State Psychiatric Institute.

Inclusion criteria for healthy controls included willingness to undergo venous catheterization and sample collection. MitoD participants carried a confirmed diagnosis of either the

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m.3243A > G mtDNA pathogenic variant ($n = 22$) or a single, large-scale mtDNA deletion ($n = 14$). General exclusion criteria across both groups included significant cognitive impairment, recent infection, and current enrollment in interventional trials. Additional exclusions for the MitoD group included use of systemic steroids.

2.2 | Time Perception Task

Prospective time perception was assessed using two complementary paradigms: a Verbal Time Estimation Task and a Verbal Time Production Task, each lasting approximately 10 min. Participants completed the tasks in a quiet, controlled setting. To eliminate external time cues, they removed and stored watches and any other devices capable of displaying the time. No secondary articulatory-suppression or verbal-distractor task was employed to prevent chronometric counting. This methodological limitation, given that someone's counting strategy and speed may act as a confounding variable, could similarly influence the observed temporal performance during the supra-second intervals used in this study (Hinton et al. 2004).

2.2.1 | Verbal Time Estimation Task

In the estimation task, participants were instructed to remain silent and mentally estimate the duration of time intervals of varying lengths. For each trial, the experimenter initiated a timer for a predetermined duration (randomized across 8, 11, 12, 13, 25, 28, 29, 32, 47, 50, 51, or 55 s). When the interval ended and an auditory cue was presented, participants verbally reported how much time they believed had elapsed. Trials were separated by brief pauses, during which the experimenter prepared the next interval. Participants were informed that the purpose of the task was to understand their internal sense of time. The experimenter avoided looking at the participant or the timer during trials and ensured that the data sheet remained hidden throughout.

2.2.2 | Verbal Time Production Task

In the production task, participants were asked to produce a target time interval by internally tracking time. For each trial, the experimenter verbally presented a target duration (10, 30, or 60 s) and started a timer. Participants were instructed to indicate when they believed the target interval had passed. The actual time elapsed was recorded by the experimenter. As with the estimation task, trials were separated by short pauses, and the same procedural controls were maintained to prevent visual or auditory cues.

2.2.3 | Scoring

For both tasks, individual trial scores were computed as the ratio of estimated or produced time to the actual interval. A ratio > 1 indicated overestimation (faster perceived time) or overproduction (slower perceived time), while a ratio < 1 indicated underestimation (slower perceived time) or underproduction (faster perceived time). Composite Clock Speed scores were derived by averaging normalized scores across both tasks to reflect directional bias in internal time perception. Variation was computed as the coefficient of variation across trials within individuals, representing temporal precision.

2.3 | Physiological Measures

Blood and urine samples were collected for quantification of mitochondrial DNA copy number (mtDNAcn), mitochondrial health index (MHI), serum and urinary catecholamines (e.g., norepinephrine). Norepinephrine, epinephrine, dopamine, and serotonin were quantified in human serum and urine using UPLC-MS/MS with deuterated internal standards, as previously described. Briefly, metabolites were extracted via protein precipitation, derivatized with dansyl chloride, and purified by liquid–liquid extraction. Chromatographic separation was performed on a Waters ACQUITY UPLC HHS C18 column, followed by detection in positive ESI mode using MRM transitions. Assays were conducted at Columbia University's Biomarkers Core Laboratory.

Resting energy expenditure (REE) was measured using Reevue Metabolic Rate Analysis System (Korr Medical Technologies, CPT#94690, Salt Lake City, Utah). Body composition including fat-free mass was assessed via Body Composition Scale, InnerScan PRO, Multi-Frequency, Segmental, Wireless, Body Composition Monitor (Tanita, SKU: MT05, Arlington Heights, IL).

2.4 | Mitochondrial Health Index in Immune Cell Types

MHI from immune cell types was calculated using measures of mitochondrial respiration and content that have been described in detail previously (Liu et al. 2025). Peripheral blood cell subtypes collected in a fasted state—including monocytes, lymphocytes, neutrophils, and PBMCs—as well as platelets—were isolated via density gradient centrifugation and magnetic bead separation. Each cell subtype was aliquoted and homogenized and used for downstream assays. Enzyme activities of mitochondrial respiratory chain complexes, Complex I (NADH:ubiquinone oxidoreductase), Complex II (succinate dehydrogenase, SDH), and Complex IV (cytochrome *c* oxidase, COX), as well as the mitochondrial matrix marker citrate synthase (CS), were quantified spectrophotometrically in triplicate following established protocols (Rausser et al. 2021). Reaction rates were recorded kinetically over several minutes, and enzymatic activity was calculated using the slope of absorbance change over time. All measurements were normalized to total protein content determined by bicinchoninic acid (BCA) assay for platelets, or to nuclear DNA (nDNA) content for all other cell types.

Mitochondrial and nuclear DNA content were quantified via qPCR (Rausser et al. 2021). Twenty microliters of the same homogenate used for enzymatic assays were lysed in Tween20/Tris–HCl buffer with Proteinase K for 16 h at 55°C, followed by heat inactivation. qPCR was performed using TaqMan chemistry with ND1/B2M and COX1/RNaseP primer pairs in triplicate across two 384-well plates on a QuantStudio 7 system.

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mtDNA copy number (mtDNAcn) was calculated as $2^{\Delta Ct} \times 2$ ($\Delta Ct = nDNA\ Ct - mtDNA\ Ct$) and averaged across both primer sets. For platelets lacking nDNA, mtDNA content was normalized to protein concentration by dividing linearized mtDNA Ct by sample protein concentration.

A composite Mitochondrial Health Index (MHI) was then calculated as the ratio of respiratory chain activity (CI, SDH, COX) to mitochondrial content (CS, mtDNA), using mean-centered, batch-corrected values (*z*-variable). The MHI was computed for each sample and cell type following outlier removal, yielding an index of respiratory chain efficiency relative to mitochondrial content:

$$MHI = \left(\frac{z - C1 + z - SDH + z - COX}{z - CS + z - mtDNAcn + 1} \right) * 100$$

2.5 | Neurological and Psychosocial Measures

Participants' psychosocial and neurological profiles were assessed using a battery of standardized instruments across the following domains.

2.5.1 | Stress and Affect

Perceived stress and stress exposure were evaluated using multiple validated scales: the Perceived Stress Scale (PSS) for perceived stress (Cohen et al. 1983), the Trier Inventory for Chronic Stress (TICS) for chronic stress (Schulz and Schlotz 1999), and the Daily Hassles Scale (DHS) for the frequency and impact of daily stressors (Kanner 1981).

2.5.2 | Physical Symptoms

A range of physical symptoms was assessed through various methods: (1) The Newcastle Mitochondrial Disease Adult Scale (NMDAS), a clinician-administered tool measuring symptom burden and functional limitations across life domains; (2) The Columbia Neurological Score (CNS), which evaluates central nervous system-related symptoms and is also clinician-administered; (3) The Composite Autonomic Symptom Score (COMPASS-31), assessing autonomic dysfunction across six domains; (4) The 30-s sit-to-stand test, used to assess functional capacity (Zheng et al. 2023); (5) The Modified Fatigue Impact Scale (MFIS) (Fisk 1994), measuring perceived fatigue and its physical, cognitive, and psychosocial impacts; (6) The SST energy score, derived from the 30-s sit-to-stand test, reflecting the estimated energy expenditure per movement as an index of neuromuscular efficiency (Alcazar et al. 2018); (7) The Memory complaints composite score, estimating memory decline; (8) The Pittsburgh Fatigue Score (PFS), a subjective self-report measure evaluating the frequency and severity of fatigue symptoms across physical, mental, and emotional domains (Glynn et al. 2015).

2.5.3 | Mental Health and Wellbeing

Mental health and wellbeing were assessed using several self-report measures: the State–Trait Anxiety Inventory (STAI-Y) for anxiety (Spielberger et al. 1970), the Beck Depression Inventory (BDI) (Beck and Steer 1987) for depressive symptoms, the Maslach Burnout Inventory (MBI) for burnout (Maslach et al. 1996), and the Self-Perceptions of Aging (SPA) scale for attitudes toward one's aging process.

2.5.4 | Working Memory and Cognitive Measures

Working memory was assessed using standardized scores from the Digit Span and N-back Letter (N&L) tasks. Composite scores were derived to quantify working memory capacity for correlation analyses with time perception metrics (Kelly et al. 2024).

2.6 | Neuroimaging

The neuroimaging data were organized in BIDS format and preprocessed using fMRIPrep (version 21.0.1; (Esteban et al. 2019)). Structural T1-weighted images were processed with FreeSurfer (version 6.0.1; (Fischl 2012)). In this study, cortical thickness and volume measures were extracted from FreeSurfer's surface-based anatomical parcellations using the aparc.a2009s atlas (Destrieux et al. 2010). Resting-state functional images were also preprocessed by fMRIPrep and underwent additional denoising procedures. These included regression of nuisance signals comprising 24 head motion parameters (including derivatives and quadratic terms), as well as cerebrospinal fluid (CSF) signals and their temporal derivatives. To further account for motion-related artifacts, spike regressors were created to identify volumes with significant deviations in image intensity. These spikes were detected using Mahalanobis distance outlier analysis, where a time point was marked as an outlier if its multivariate distance from the distribution of all time points exceeded the 95% confidence interval. Each spike was encoded as a binary regressor, with 1 indicating an outlier volume and 0 otherwise. The denoised data were linearly detrended and spatially smoothed using a Gaussian kernel of 4 mm full width at half maximum (FWHM). Subsequent analyses focused on the intrinsic functional metric Regional Homogeneity (ReHo), computed using the Data Processing & Analysis of Brain Imaging (DPABI) toolbox (Yan et al. 2016). A band-pass filter (0.01–0.08 Hz) was applied to isolate low-frequency fluctuations of interest. From the resulting whole-brain ReHo map, average ReHo values signifying intrinsic functional coherence were extracted within each of the seven large-scale resting-state networks defined before (Thomas Yeo et al. 2011), reflecting the degree of local synchronization of BOLD signals across neighboring voxels within each network.

Regional Homogeneity was selected as a targeted measure of local intrinsic functional coherence rather than as a comprehensive measure of distributed functional connectivity. ReHo quantifies the similarity of low-frequency BOLD fluctuations among neighboring voxels and therefore provides a seed-free, model-free index of local synchronization. This approach was well suited to the exploratory nature of the present multimodal study, in which the primary goal was to test whether individual differences in time perception were associated with regional coherence in intrinsic brain activity.

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We did not use seed-based connectivity or independent component analysis as the primary analysis because these approaches address different questions, namely long-range coupling between predefined regions or data-driven decomposition of large-scale networks, and require additional analytic choices such as seed selection, component number, and component labeling. Given the moderate sample size and the number of behavioral, physiological, and structural variables examined, we prioritized a lower dimensional functional metric. To retain network-level interpretability, whole-brain ReHo maps were summarized within the seven canonical Yeo resting-state networks. Thus, the ReHo results should be interpreted as reflecting local intrinsic coherence within large-scale systems, not between-network connectivity or dynamic functional connectivity.

The imaging metrics, including cortical thickness, gray matter volume, and intrinsic functional coherence, were subsequently used in analyses examining their correlation with time perception variables to assess brain–behavior relationships.

2.7 | Statistical Analysis

Correlations between continuous variables were assessed using Spearman's rank correlation coefficient to accommodate the modest sample sizes and non-normal distributions. Between-group comparisons (healthy controls vs. mitoD) were assessed using nonparametric tests, the Mann–Whitney U test for Clock Speed and the Kolmogorov–Smirnov test for Variation. Differences between groups in the association between time perception and a given predictor were tested as a group × predictor interaction, operationalized as the difference in linear-regression slopes between groups. An uncorrected threshold of $p < 0.05$ was used to denote statistical significance and $0.05 \leq p < 0.1$ to denote trends. Heatmaps display z-scored correlation coefficients to aid visual comparison across groups. Analyses were performed in GraphPad Prism (versions 10–11; GraphPad Software, San Diego, CA).

The analyses were guided by a priori hypotheses and restricted to a targeted set of physiological, cognitive, and psychological variables rather than derived from an exhaustive search across all available measures. To address multiple comparisons, we prespecified a confirmatory set of hypothesis-driven tests and controlled the false discovery rate (FDR) within this set using the Benjamini–Hochberg procedure. Because correlations, group comparisons, and interactions address distinct questions, corrections were applied separately within families defined jointly by test type and by time-perception dimension (Hypothesis 1–4) (Table S1).

Five confirmatory families were specified: (1) Spearman correlations of Clock Speed with the a priori physiological predictors (chronological age, fat-free-mass–adjusted REE, serum norepinephrine, and urinary norepinephrine); (2) the corresponding correlations for Variation; (3) group × predictor interactions for Clock Speed across age, adjusted REE, serum norepinephrine, urinary norepinephrine, and working memory (Digit Span Backward, T-score); (4) the corresponding interactions for Variation; and (5) between-group comparisons of Clock Speed and Variation. All a priori tests within a family were entered into the correction regardless of their nominal significance, and for each we report the uncorrected p-value together with the Benjamini–Hochberg FDR-adjusted q-value, treating $q < 0.05$ as significant after correction.

All other analyses were considered exploratory and were not included in the FDR correction. These comprised the full cell-type mitochondrial survey (mitochondrial health index and mtDNA copy number across all immune cell subtypes), the psychosocial, affective, and somatic-symptom battery, the seven-network regional homogeneity (ReHo) analysis, and the structural neuroimaging measures. Exploratory findings are reported with uncorrected p-values, are explicitly labeled as exploratory, and are interpreted as hypothesis-generating only.

3 | Results

3.1 | Quantifying Inter-Individual Variability in Subjective Time Perception Through Dual-Task Integration

To quantify individual differences in subjective time perception, we utilized a dual-task approach that captured both the direction and precision of internal clock dynamics. Participants performed time estimation (judging elapsed time) and time production (generating target intervals). These two tasks are theoretically reciprocal: a faster clock speed leads to shorter estimation and longer production intervals, while a slower clock leads to longer estimation and shorter production intervals (Figure 1A).

Across all participants ($N = 95$; 65% female), we observed significant inter-individual variation in time estimated or produced (Figure S1A–D). As expected, those who estimated longer intervals produced shorter intervals ($r = -0.83$, $p < 0.001$; Figure S1F). We therefore used factor analysis to capture the variance across both tasks and create a single score quantifying each participant's Clock Speed (Figure S2). Positive values reflect faster internal clock speed, while negative values reflect slower internal clock speed participants (Figure 1B).

Interestingly, there was a significant positive correlation between absolute Clock Speed and Variation ($r = 0.85$, $p < 0.001$; Figure 1D,G; Figure S1). This means that individuals with the most extreme clock speed deviations (faster or slower) were also those who showed the most inconsistency in their timing performance, suggesting a shared underlying factor driving both clock speed accuracy and trial-to-trial variation in time perception. For subsequent analyses we have used signed Clock speed, which captures directional bias, while Variation captures precision independent of direction. Together, these analyses establish two complementary dimensions of subjective time perception: Clock Speed and Variation, which can now be related to psychobiological features of interest, which have been compared in further analyses.

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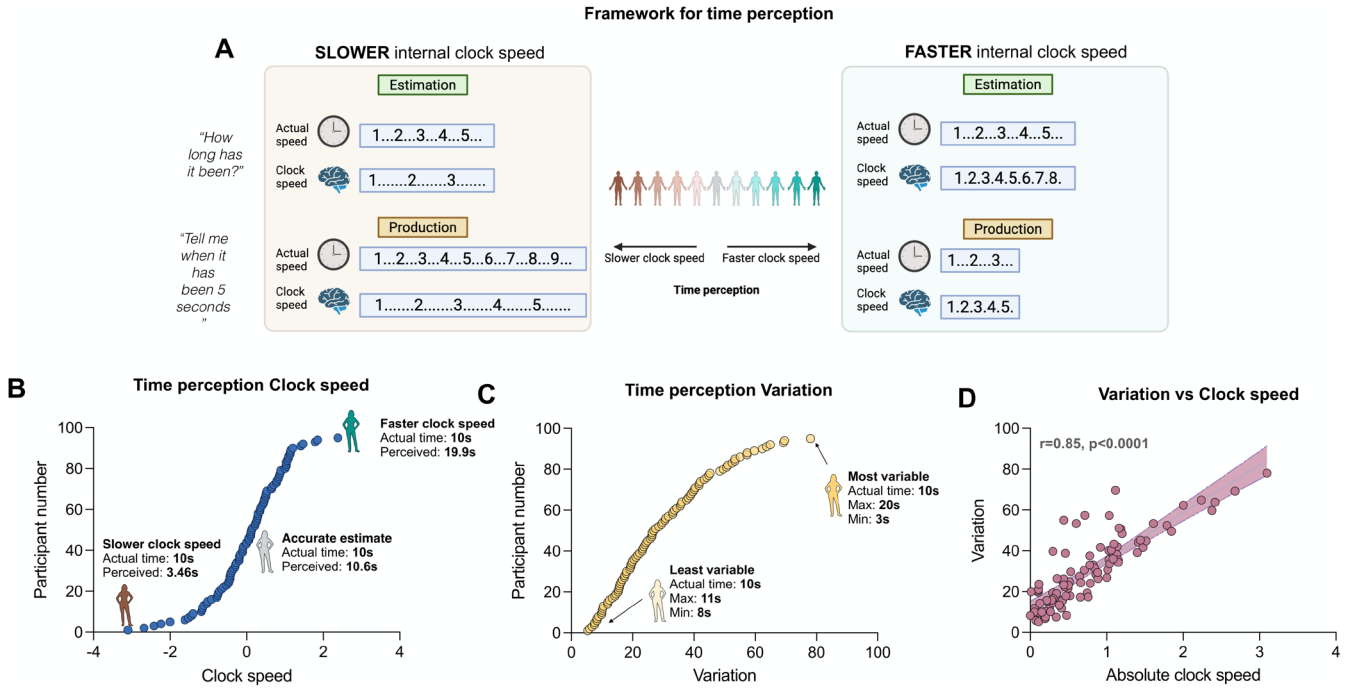

FIGURE 1 | Quantifying inter-individual variability in subjective time perception. (A) Conceptual model illustrating internal clock dynamics using a dual-task approach: Time estimation (judging a presented duration) and time production (producing a target duration). Because the tasks are reciprocal, faster internal clocks yield shorter estimates and longer productions, and slower clocks yield the opposite. Integrating both tasks enables inference of individual Clock Speed as a bias in time perception. (B) Participants ($N = 95$, 65% female) ranked by composite Clock Speed scores, derived from normalized time estimation and production data. Positive values indicate faster clocks, and negative values indicate slower clocks. (C) Participants ranked by Coefficient of Variation, capturing intra-individual variability in timing precision across trials. Higher values indicate greater inconsistency, independent of clock direction. (D) Positive association between absolute Clock Speed and Variation suggests that Clock Speed and Variation may arise from shared underlying mechanisms. Clock Speed and Variation provide complementary metrics to characterize individual differences in time perception.

3.2 | Biological Regulation of Internal Clock Speed and Variation

To examine the physiological foundations of subjective time perception, we examined associations between Clock Speed and Variation and a broad panel of physiological and metabolic markers, including mitochondrial health indices in immune cells, age, heart rate, resting energy expenditure (REE), and catecholamine levels (Figure 2).

Given that REE was strongly associated with fat-free mass across participants ($r = 0.47$, $p < 0.001$; Figure S3A), we used fat-free mass-adjusted REE as a normalized metric. Clock Speed was positively associated with adjusted REE ($r = 0.30$, $q = 0.12$), suggesting that individuals with greater energetic capacity tend to experience time as passing more quickly. Clock Speed was also positively associated with the MHI from blood monocytes ($r = 0.32$, $p = 0.028$). However, we did not observe a significant correlation with MHI in any other cell type and Clock speed. Conversely, higher serum norepinephrine (NE) levels were negatively correlated with Clock Speed ($r = -0.22$, $q = 0.12$), suggesting a potential association between heightened autonomic arousal and a deceleration of the internal clock. Variation showed no significant correlations with MHI, mitochondrial DNA content or heart rate. Adjusted REE was negatively correlated with Variation ($r = -0.28$, $q = 0.0.8$), suggesting that reduced energetic capacity may contribute to less stable time perception. Urinary NE levels were positively associated with Variation ($r = 0.23$, $q = 0.08$), raising the possibility that systemic catecholamine turnover serves as a factor in the disruption of stable time perception. Sex-stratified analyses revealed overlapping distributions of Clock Speed and Variation between males and females (Figure S4A,B), but partially distinct biological correlates (Figure S4C).

3.3 | Mitochondrial OxPhos Defects Alter Time Perception and Its Physiological Correlates

To determine whether mitochondrial oxidative phosphorylation (OxPhos) dysfunction affects internal timekeeping, we compared Clock Speed and Variation between healthy controls and individuals with genetically confirmed mitochondrial OxPhos disorders (mitoD), including the m.3243A > G mutation and large-scale mitochondrial DNA deletions (Figure 3A).

Substantial intra-individual variability was observed in both Clock Speed and Variation (Figures 3B and 4A). Group means did not differ significantly between controls and mitoD participants (Figures 3C and 4B). In healthy controls, Clock Speed was positively correlated with resting energy expenditure

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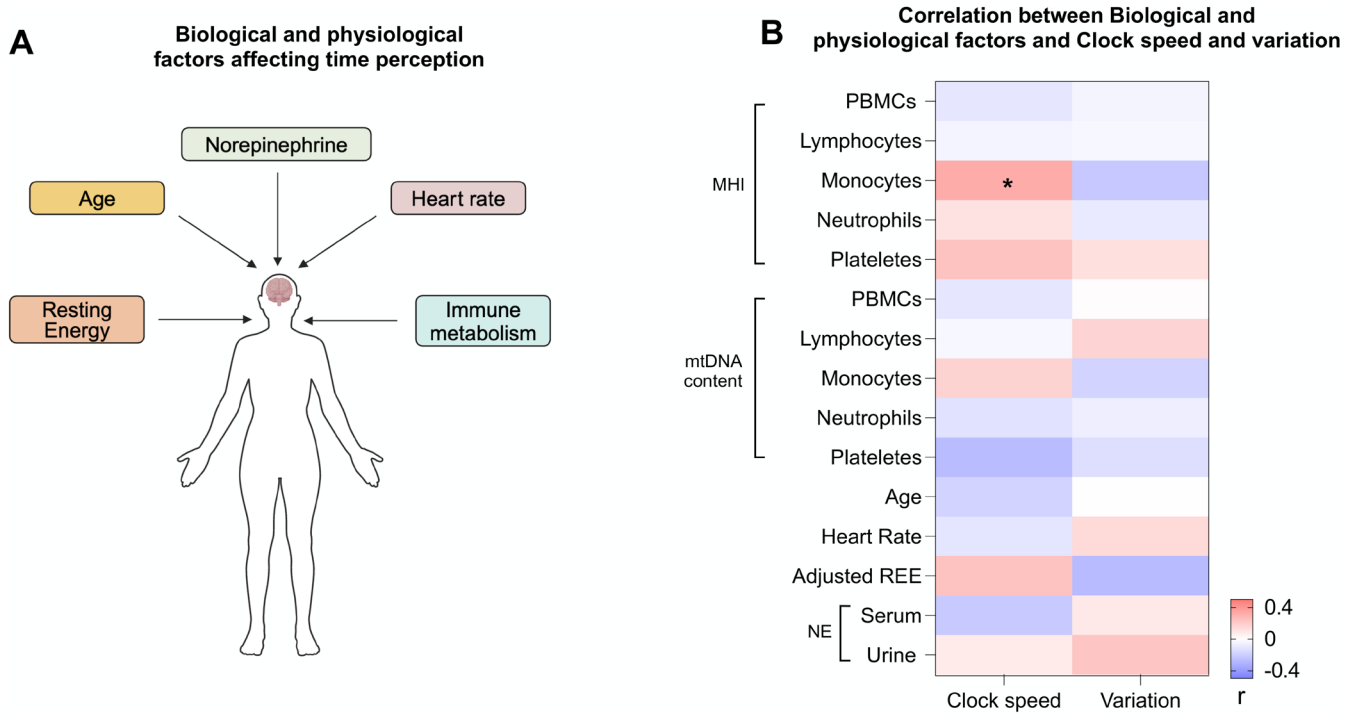

FIGURE 2 | Patterns of physiological regulation of Clock Speed and timing variability in subjective time perception. (A) Schematic overview of hypothesized physiological modulators of internal timing mechanisms, illustrating potential contributions from bioenergetic, neuroendocrine, autonomic, and demographic factors. These modulators are posited to influence both the speed and stability of internal clock dynamics. (B) Heatmap depicting correlations between individual differences in Clock Speed and Coefficient of Variation with a range of physiological measures, including mitochondrial health index (MHI) and mitochondrial DNA copy number (mtDNAcn) across immune cell subtypes, chronological age, resting heart rate, resting energy expenditure (REE), and norepinephrine (NE) levels in serum and urine. Positive correlations (red) indicate that higher values in the physiological measure are associated with faster Clock Speeds or greater timing variability, while negative correlations (blue) indicate associations with slower clocks or more stable timing. These results suggest that subjective time perception is not solely a cognitive construct but is systematically modulated by underlying physiological states. *$p < 0.05$.

adjusted for fat-free mass (adjusted REE) ($r = 0.31$, $p = 0.048$) and negatively with only serum NE levels ($r = -0.24$, $p = 0.082$) (Figure 3D–G), suggesting that faster internal timing in controls may be supported by higher energetic capacity and lower autonomic arousal. These relationships were absent in mitoD, suggesting that OxPhos dysfunction disrupts the normal physiological modulation of time perception. For Variation, controls exhibited a significant negative correlation with REE ($r = -0.42$, $p = 0.0052$) and positive associations with urine NE ($r = 0.35$, $p = 0.0077$). In contrast, mitoD participants showed either a reversed or absent pattern for these same physiological markers. Importantly, the direction of association significantly differed between groups (Age: $q = 0.11$; Adjusted REE: $q = 0.23$; Serum NE: $q = 0.11$), suggesting that mitochondrial OxPhos dysfunction may alter the normative physiological modulation of time perception.

In addition, neurotransmitter–time perception associations differed by group (Figure S6B). In controls, urinary serotonin ($r = 0.35$, $p = 0.0079$), dopamine ($r = 0.32$, $p = 0.017$), and epinephrine ($r = 0.27$, $p = 0.045$) were positively associated with Variation. These associations were diminished or absent in mitoD. Collectively, these findings indicate that while overall time perception may remain behaviorally intact in individuals with mitochondrial disease, the physiological framework supporting these processes, involving energy metabolism and neurochemical signaling, may be altered.

3.4 | Associations Between Peripheral Mitochondrial Function and Subjective Time Perception Differ by Disease Status

To investigate how cell-specific peripheral mitochondrial bioenergetics relate to time perception in control vs. mitoD participants, we assessed correlations between Clock Speed and Variation and cellular markers of mitochondrial function in peripheral blood (Figure 5). Notably, the direction of association differed significantly between groups for Clock Speed and MHI in fasted PBMCs ($p = 0.04$), as well as for mtDNAcn in neutrophils ($p = 0.04$).

Parallel analyses for Variation revealed that in healthy controls, higher MHI in monocytes was significantly associated with lower Variation ($r = -0.47$, $p = 0.013$), and mtDNAcn in platelets was also negatively associated ($r = -0.44$, $p = 0.029$) with Variation (Figure 5B,C). In mitoD participants, these relationships were either weakened or reversed; particularly, neutrophil mtDNAcn was strongly negatively correlated with Variation ($r = -0.54$, $p = 0.021$; Figure 5F). Statistical tests confirmed significant differences in the direction of association between

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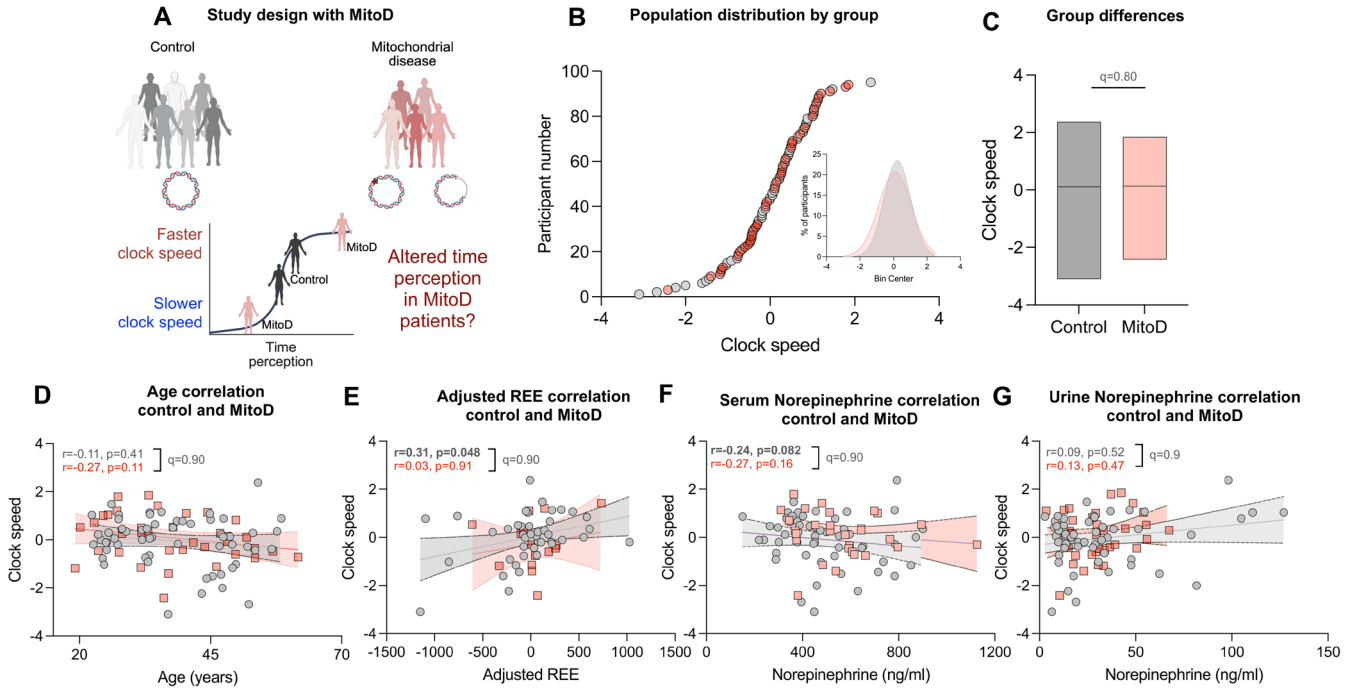

FIGURE 3 | Mitochondrial OxPhos dysfunction alters the physiological correlates of Clock Speed in prospective time perception. (A) Study design schematic, depicting the population stratification used to assess the impact of mitochondrial oxidative phosphorylation (OxPhos) dysfunction on time perception. Participants were grouped as follows: (i) individuals carrying the m.3243A > G mitochondrial DNA point mutation, with or without clinical manifestations of mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS); and (ii) individuals with large-scale mtDNA deletions, associated with chronic progressive external ophthalmoplegia (CPEO) or Kearns–Sayre syndrome (KSS). (B) Distribution of Clock Speed scores across all participants (controls and mitochondrial disease groups), illustrating inter-individual variability. (C) Group comparisons of Clock Speed scores reveal no significant differences in the spread or central tendency between control and MitoD groups ($p = 0.8$). (D–G) Correlations between Clock Speed and physiological variables across control and MitoD participants: (D) Age, (E) Adjusted resting energy expenditure (REE), (F) Serum norepinephrine (NE) levels, and (G) Urine NE levels. Data points below the minimum detectable dose (MDD) threshold were excluded from analyses and visualization. Observed correlations suggest that the relationship between internal clock speed and physiological state may be attenuated or disrupted in the context of mitochondrial OxPhos dysfunction.

control and mitoD groups for Variation and MHI in monocytes ($p = 0.03$; Figure 5E), mtDNAcn in neutrophils ($p = 0.0032$; Figure 5F), and platelets ($p = 0.01$; Figure 5G).

3.5 | Psychological and Autonomic Correlates of Subjective Time Differ by Health Status

To assess the impact of psychological state on time perception in the MiSBIE cohort, we correlated Clock Speed and Variation with a battery of stress, affective, well-being, and somatic symptom measures (Figure 6; Figure S6).

Across the full cohort, Clock Speed showed no robust, consistent associations with most psychological or autonomic variables. (r range = −0.18 to 0.17 across all measures). The strongest associations were with trait and state anxiety (STAI-Y; $r = 0.17$, $p = 0.081$) and self-reported work efficiency from the Maslach Burnout Inventory ($r = -0.18$, $p = 0.088$), both of which remained at trend level only. No Clock Speed associations reached statistical significance. In group-stratified analyses (Figure S7), these associations reversed direction in mitoD participants, though neither reached significance in either group.

Variation showed stronger and more consistent psychosocial associations (r range = −0.25 to 0.22 across all measures). The strongest associations were with burnout efficiency ($r = -0.25$, $p = 0.009$) and fatigue, chronic stress, and physical symptom burden, with burnout efficiency being the only association to reach statistical significance. Conversely, better performance on the sit-to-stand energy measure was associated with lower Variation ($r = -0.17$, $p = 0.091$). These associations were consistent in direction and magnitude across both controls and mitoD participants (Figure S7), with no significant group differences.

3.6 | Working Memory Performance Predicts Clock Speed in Health but Not in Mitochondrial Disease

To investigate the cognitive basis of internal timekeeping, we assessed how individual differences in working memory relate to time perception and whether these relationships differ in control and mitoD patients. Working memory was evaluated using the Digit Span and N-back & Letter (N&L) tasks, which together capture both capacity and updating components of working memory.

Across all participants, faster Clock Speed and lower Variation were associated with better working memory performance (Figure 7A). Group-specific divergence emerged for Clock Speed. In controls, higher working memory capacity (Digit Span Backward T-score ($r = 0.31$, $p = 0.05$) and raw score ($r = 0.31$, $p = 0.017$)) was associated with faster Clock Speed, suggesting

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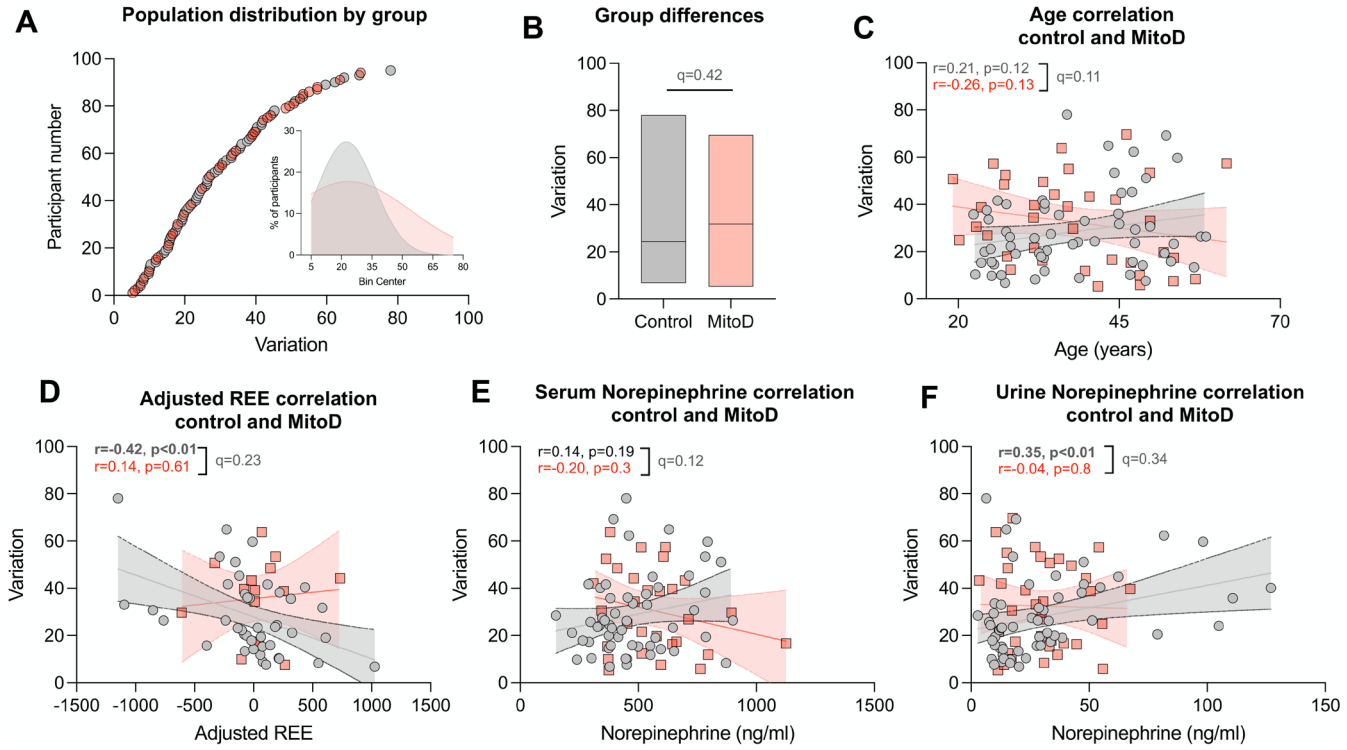

FIGURE 4 | Mitochondrial OxPhos dysfunction alters physiological correlates of Variation in time perception. (A) Scatter plot of individual variation in time perception across the full cohort. (B) No significant group differences in variability or associated factor scores between control participants and those with mitochondrial disease ($p = 0.21$ for variability). (C–F) Correlations between timing variability and physiological variables across all participants: (C) Age, (D) Adjusted resting energy expenditure (REE), (E) Serum norepinephrine (NE), and (F) Urine NE. Data points falling below the minimum detectable dose (MDD) for serum and urine NE were excluded from statistical analysis and visualization. Taken together, these findings suggest that while the degree of timing variability is broadly similar across mitochondrial disease and control groups, the underlying physiological correlates reflecting energetic demand and autonomic tone may be disrupted in the context of mitochondrial OxPhos defects.

that individuals with stronger working memory tend to experience time as passing more quickly (Figure 7B). This supports the idea that time perception is closely linked to executive functions such as attentional control and memory maintenance. In contrast, mitoD participants exhibited a reversed pattern, with higher working memory scores being weakly associated with slower Clock Speed (Digit Span Backward T-score: $r = -0.28$, $p = 0.1$; raw score: $r = -0.24$, $p = 0.16$). Notably, the direction of these associations differed significantly between groups (T-score: $q = 0.017$; raw score: $p = 0.021$), suggesting that mitochondrial OxPhos dysfunction may disrupt the normative link between cognitive control and internal timing. No such group differences were observed for Variation, which showed a consistent inverse correlation with working memory across both groups.

Together, these results point to a coupling between working memory and time perception in healthy individuals that appears uncoupled in individuals with mitochondrial disease.

3.7 | Brain–Behavior Correlates of Time Perception in Controls and MitoD Participants

To investigate how brain function and structure support time perception, we examined associations between Clock Speed and Variation and neural features in healthy controls and mitoD participants. Intrinsic functional coherence was assessed using Regional Homogeneity (ReHo); averaged canonical resting-state networks specified a priori: visual, somatomotor, attention, limbic, default mode, and frontoparietal networks. Structural features were evaluated using measures of cortical thickness and gray matter volume (Figure 8A).

Across all participants, Clock Speed showed no significant relationship with intrinsic coherence. In contrast, higher Variation was consistently associated with greater intrinsic coherence within higher order cognitive networks (Figure 8B). Group-wise comparisons revealed the group difference in Clock Speed–coherence associations, in which healthy controls showed a negative association and mitoD participants showed the opposite, was specific to transmodal networks (default mode, frontoparietal, and limbic), with no such group difference observed in unimodal networks (visual and somatomotor). By comparison, associations between Variation and intrinsic coherence were similar across groups (Figure 8B).

Structurally, mitoD participants exhibited differences in brain morphology. Group comparisons showed reduced mean cortical thickness ($p = 0.036$, $g = 0.47$; Figure 8C) and a trend toward lower gray matter volume ($p = 0.08$, $g = 0.45$; Figure 8D) compared to controls. Across all participants, greater gray matter volume was associated with lower Variation ($r = -0.23$, $p = 0.041$; Figure S8D). When analyzed by group, gray matter volume showed a significant inverse relationship with Variation ($r = -0.33$, $p = 0.015$; Figure 8E) in controls. In contrast, these

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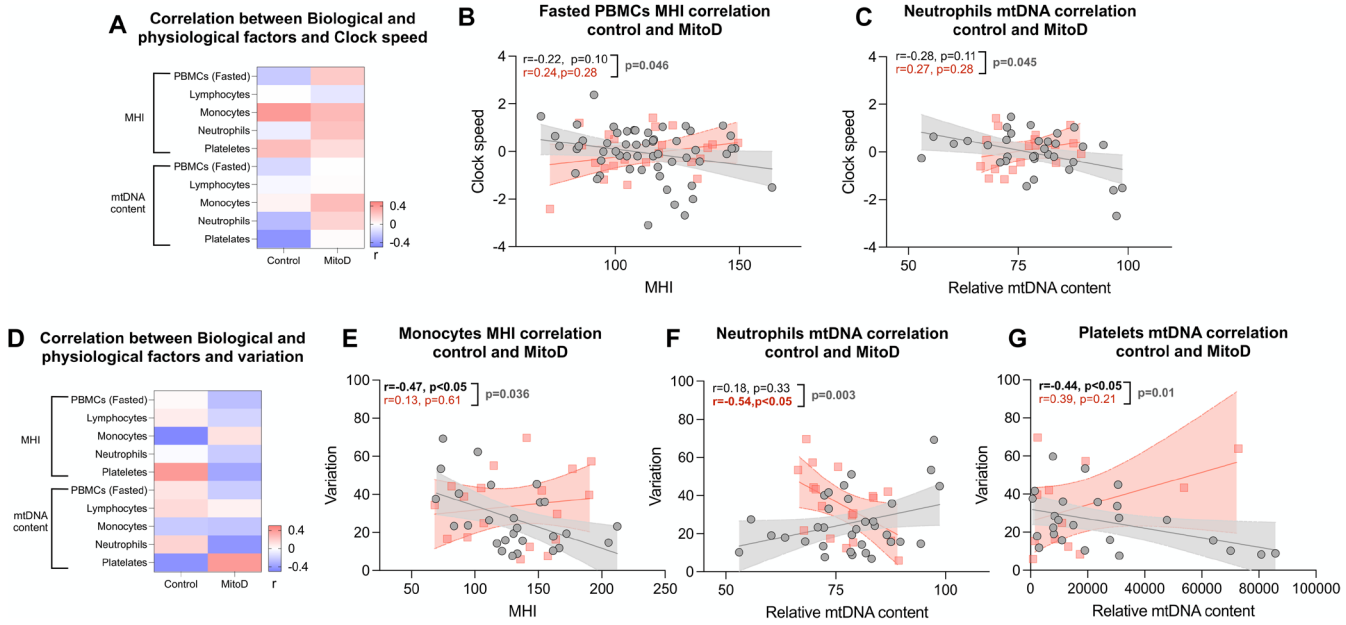

FIGURE 5 | Mitochondrial OxPhos dysfunction modulates the relationship between time perception and mitochondrial bioenergetic health in peripheral immune cells. (A) Heatmap showing group-specific correlations between Clock Speed scores and mitochondrial biomarkers, including the mitochondrial health index (MHI) and mitochondrial DNA content (mtDNAcn) measured in peripheral blood mononuclear cells (PBMCs) and sorted immune cell subtypes. Data are stratified by group (control vs. mitochondrial disease). Stronger associations in the control group suggest that intact mitochondrial function supports internal clock regulation, whereas these relationships appear attenuated or disrupted in individuals with mitochondrial OxPhos defects. (B, C) Scatter plots illustrating representative correlations: (B) MHI measured from fasted PBMCs and Clock Speed, (C) mtDNAcn in neutrophils and Clock Speed. (D) Heatmap showing group-specific correlations between Variation and mitochondrial biomarkers, paralleling Panel A but focused on variation. (E–G) Representative scatter plots of associations with variation in time perception: (E) MHI in monocytes, (F) mtDNAcn in neutrophils, and (G) mtDNAcn in platelets. Together, these findings suggest that mitochondrial bioenergetic capacity in monocytes, neutrophils, and platelets is linked to both the Clock Speed and variation of subjective time perception. In the presence of mitochondrial disease, these associations are distinct from those in control, potentially reflecting systemic energetic dysregulation or altered neuroimmune signaling that disrupts the integration of physiological states into time perception.

relationships were largely absent in the mitoD group. Notably, no group differences in structural associations were noted for Clock Speed (Figure S8).

Together, these findings indicate that both intrinsic coherence and cortical structure relate to time perception in healthy individuals, but account for only a small fraction of variance. However, in the context of mitoD, some of these brain–behavior relationships are altered.

4 | Discussion

In this study, we examined how subjective time perception, operationalized through two dimensions, Clock Speed and Variation, relates to physiological, cognitive, and psychological measures in both healthy adults and individuals with mitochondrial oxidative phosphorylation disorders (mitoD), using data from the MiSBIE cohort.

Although no significant group-level differences between control and mitoD participants emerged, we observed broad inter-individual variability in both Clock Speed and Variation. The correlates of these two dimensions diverged substantially. In healthy individuals, faster Clock Speed was associated with better working memory performance ($r = 0.31$, $p = 0.017$), and showed trend-level associations with higher resting energy expenditure ($p = 0.05$) and lower serum norepinephrine ($p = 0.08$). After Benjamini–Hochberg correction, the working-memory link was the association that remained robust, whereas the metabolic and autonomic couplings were attenuated to trend level ($q \approx 0.10–0.13$) and should be regarded as suggestive. This pattern is consistent with the subjective pace of time being coupled to energetic metabolism in general, autonomic tone, and cognitive efficiency (Bueti and Macaluso 2011). Because extreme Clock Speeds co-occurred with higher trial-to-trial variability, these relationships may reflect a tradeoff between pacemaker rate and temporal precision. Interestingly, while acute stress and heightened catecholaminergic states are typically associated with distortion of subjective time, prior studies have reported inconsistent results, with some showing compression of perceived time under stress and others showing dilatation (Vignaud et al. 2025). We interpret this apparent tension as a distinction between two regimes of the same noradrenergic system rather than a genuine contradiction. Our serum measure indexes tonic, resting noradrenergic tone, whereas classic timing paradigms manipulate acute, phasic sympathetic arousal. Baseline catecholamine levels are better understood as a regulatory set-point, shaped by homeostatic downregulation and chronic load, than as an index of momentary arousal. Consistent with adaptive-gain accounts of the locus coeruleus–norepinephrine system (Aston-Jones and Cohen 2005), tonic and phasic noradrenergic modes carry distinct, and at

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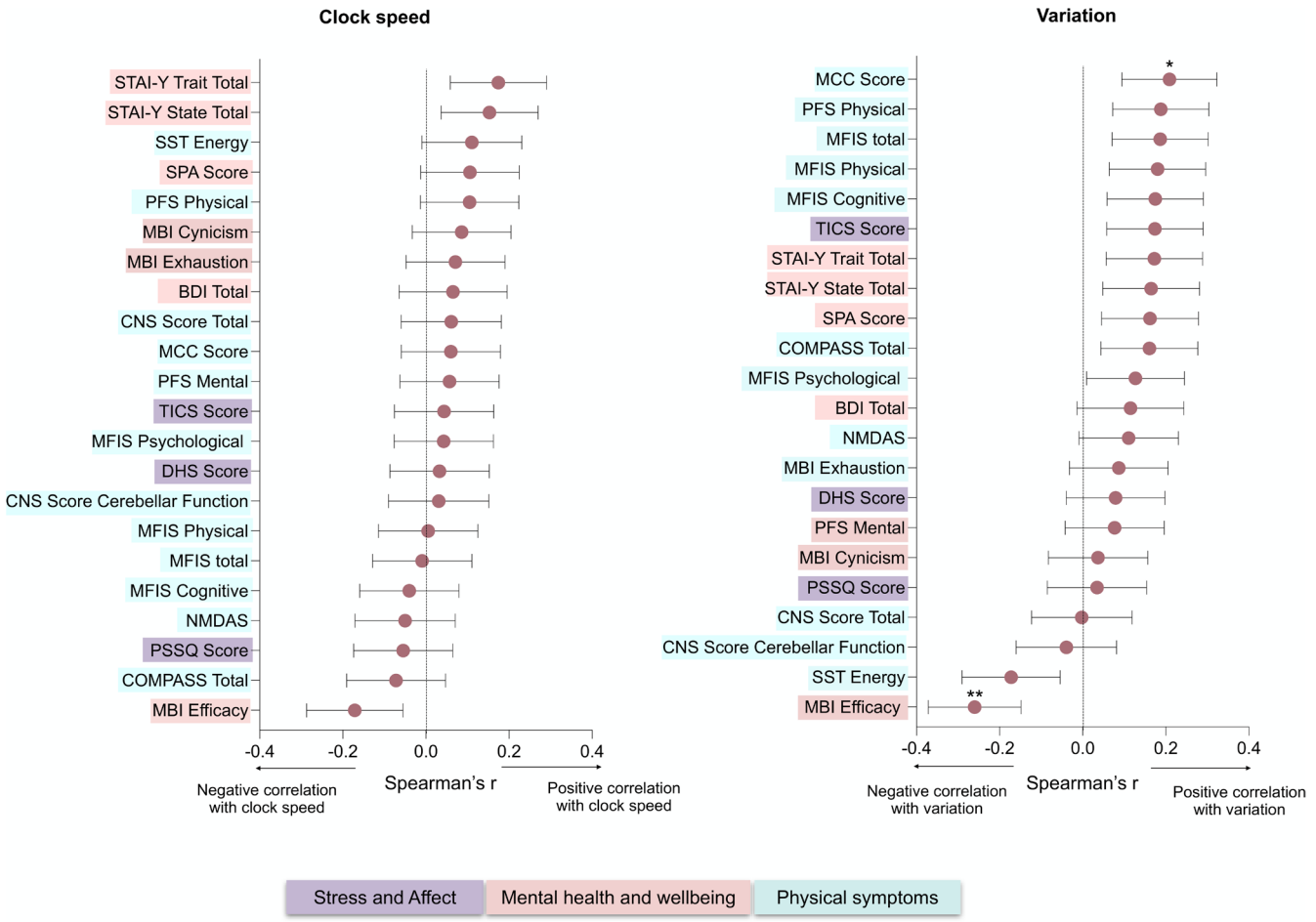

FIGURE 6 | Time perception: Clock speed and variation may be influenced by neurological and psychosocial factors. Forest plots showing the correlation between Clock speed and variation in time perception with psychological assessments of stress and affect, mental health and wellbeing, and physical symptoms. Positive *r* values indicate a positive correlation between clock speed or variation and questionnaire scores. These results suggest that subjective time perception is shaped by interactions with affective state, cognitive load, and physical symptomatology. $^{**}p < 0.01$, $^{*}p < 0.05$.

times opposing, behavioral signatures, and arousal relates to performance along an inverted-U rather than monotonically. Within this framework, a negative association between resting norepinephrine and Clock Speed is not necessarily in conflict with acute time-dilation findings, but may instead reflect a high-tonic, low-phasic regime of the same circuit. We therefore hypothesize rather the possibility that elevated tonic norepinephrine acts as a physiological "brake" that slows the internal pacemaker. This interpretation should be regarded as preliminary: the serum norepinephrine–Clock Speed association was weak and did not survive correction for multiple comparisons (Benjamini–Hochberg $q \approx 0.13$). It nonetheless aligns with observations from stressful waiting periods, where slow time perception amplifies distress and further decelerates perceived time, creating a bidirectional downward spiral (Rankin et al. 2019).

In contrast to Clock Speed, the second dimension of Variation showed trend-level associations (exploratory, uncorrected) with fatigue, perceived stress, and somatic symptom burden across groups, pointing to the stability of time perception as a candidate marker of psychosomatic load. Notably, the biological substrates of Variation, including associations with mitochondrial enzyme activities of immune cells and gray matter volume, differed depending on mitochondrial health status in exploratory analyses. Critically, while overall behavioral outputs, including the actual speed and precision of time perception, remained similar between groups, the physiological framework supporting these processes appeared altered in mitoD participants. In healthy controls, Clock Speed was positively coupled with energetic capacity (adjusted REE) and negatively with autonomic tone (serum NE). These normative relationships were absent or reversed in individuals with mitochondrial OxPhos defects. This indicates that mitochondria may not moderate time perception output directly, but rather moderate the integration of metabolic and neurochemical signals into the internal clock. The maintenance of "normal" behavior despite these shifts suggests that individuals with mitochondrial disease may utilize alternative neural or cognitive pathways to stabilize their sense of time in the face of bioenergetic constraints. These patterns highlight how Clock Speed and Variation reflect distinct yet complementary aspects of subjective time perception, and their correlates may shift under conditions of mitochondrial OxPhos defects.

Diagnostic category alone may be a limited lens for understanding individual differences in time perception. Metabolic capacity varies substantially within the mitoD group, which may explain why group-level comparisons yielded no significant differences

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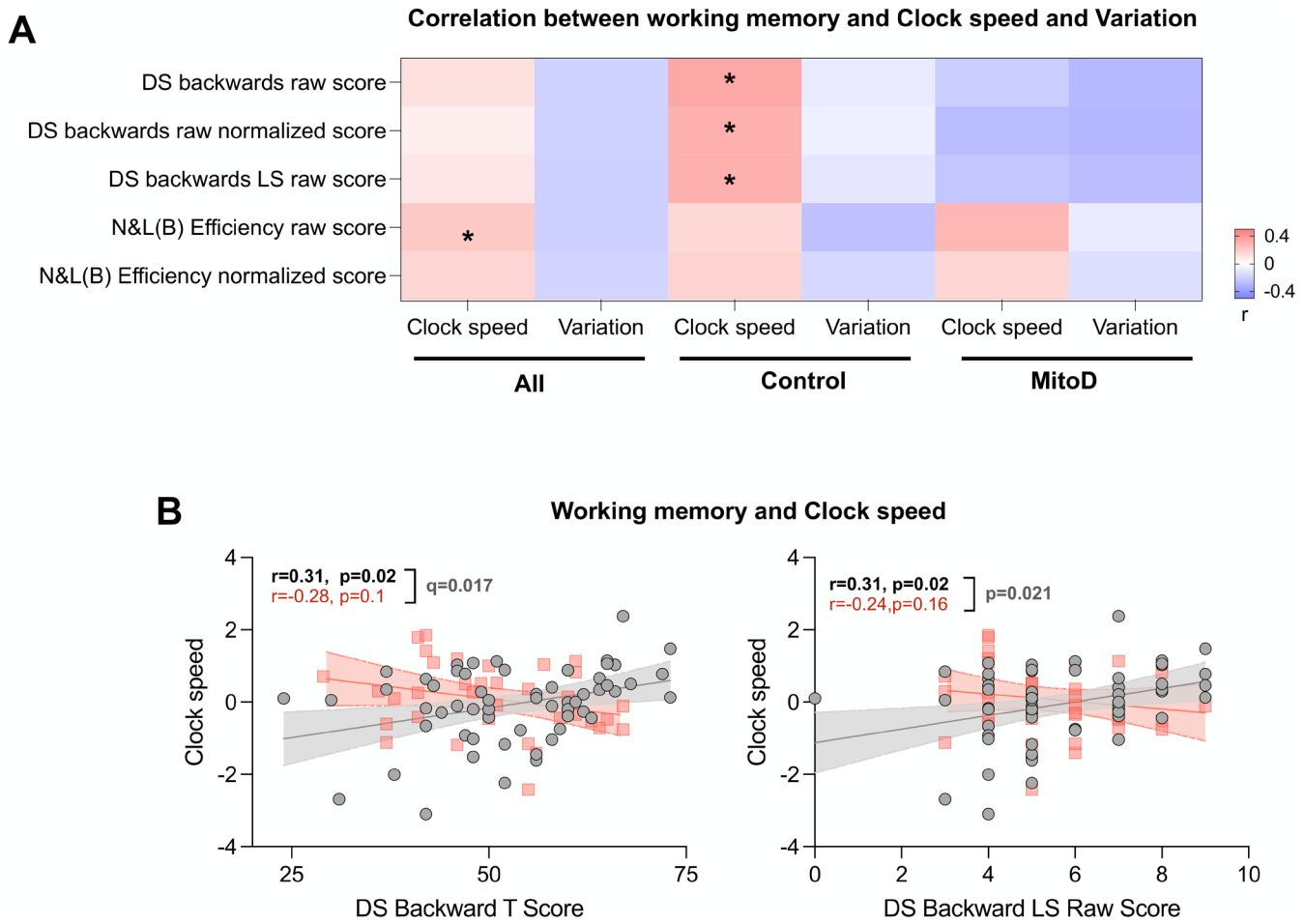

FIGURE 7 | Mitochondrial OxPhos dysfunction alters the relationship between working memory and prospective time perception. (A) Heatmap showing group-wise correlations between time perception metrics and working memory performance, contrasting control participants and individuals with mitochondrial OxPhos defects. Clock Speed and Variation are assessed in relation to composite working memory scores derived from Digit Span and N&L (B) scores. (B) Scatter plot illustrating the association between working memory performance and Clock Speed across control and mitoD participants. In healthy controls, greater working memory capacity is associated with faster clock speed, which appears attenuated or absent in individuals with mitochondrial OxPhos dysfunction. $^{*}p < 0.05$.

despite clear shifts in the physiological coupling patterns underlying them. Proximal metabolic measures may therefore be more informative than diagnostic status. However, even proximal signals must be interpreted within their metabolic context. In healthy controls, higher resting energy expenditure was associated with faster Clock Speed and elevated serum NE with slower Clock Speed at trend level, but neither relationship held in mitoD participants. The same physiological signal can thus carry different functional meaning depending on the individual's broader metabolic state, arguing for an interpretive framework that treats biomarkers as context-dependent rather than fixed indicators.

These findings should be interpreted considering several important caveats. First, we adopted a two-tiered inferential approach: a small, prespecified confirmatory set of hypothesis-driven tests was corrected for multiple comparisons using the Benjamini–Hochberg false-discovery-rate procedure within families defined by test type and time-perception dimension, while all remaining analyses were treated as exploratory and are reported with uncorrected *p*-values and labeled accordingly. After correction, most confirmatory associations were attenuated to trend level; the group × working-memory interaction on Clock Speed and, within controls, the coupling of Variation to resting energy expenditure and urinary norepinephrine were the effects that survived FDR. We therefore anchor our strongest claims to these results and treat the remaining associations as hypothesis-generating, acknowledging the elevated risk of false positives. Second, while our behavioral measures were designed to capture individual differences in time perception, they likely reflect overlapping contributions from attention, memory, and motor control. Third, the neuroimaging analysis focused on regional homogeneity, a measure of intrinsic coherence within networks, which does not directly index between-network functional connectivity. Fourth, peripheral mitochondrial measures were derived from multiple immune cell types, and we observed that MHI and its associations with time perception metrics varied by cell type, indicating cell type specificity in how bioenergetic status relates to both Clock Speed and Variation. Importantly, peripheral blood cells are unlikely to harbor detectable deletions due to rapid turnover and mitophagy. As a result, MHI measured in immune cells may appear normal and may not reflect mitochondrial adaptations in post-mitotic tissues such as brain and muscle. This limitation should be considered when interpreting MHI-related findings in

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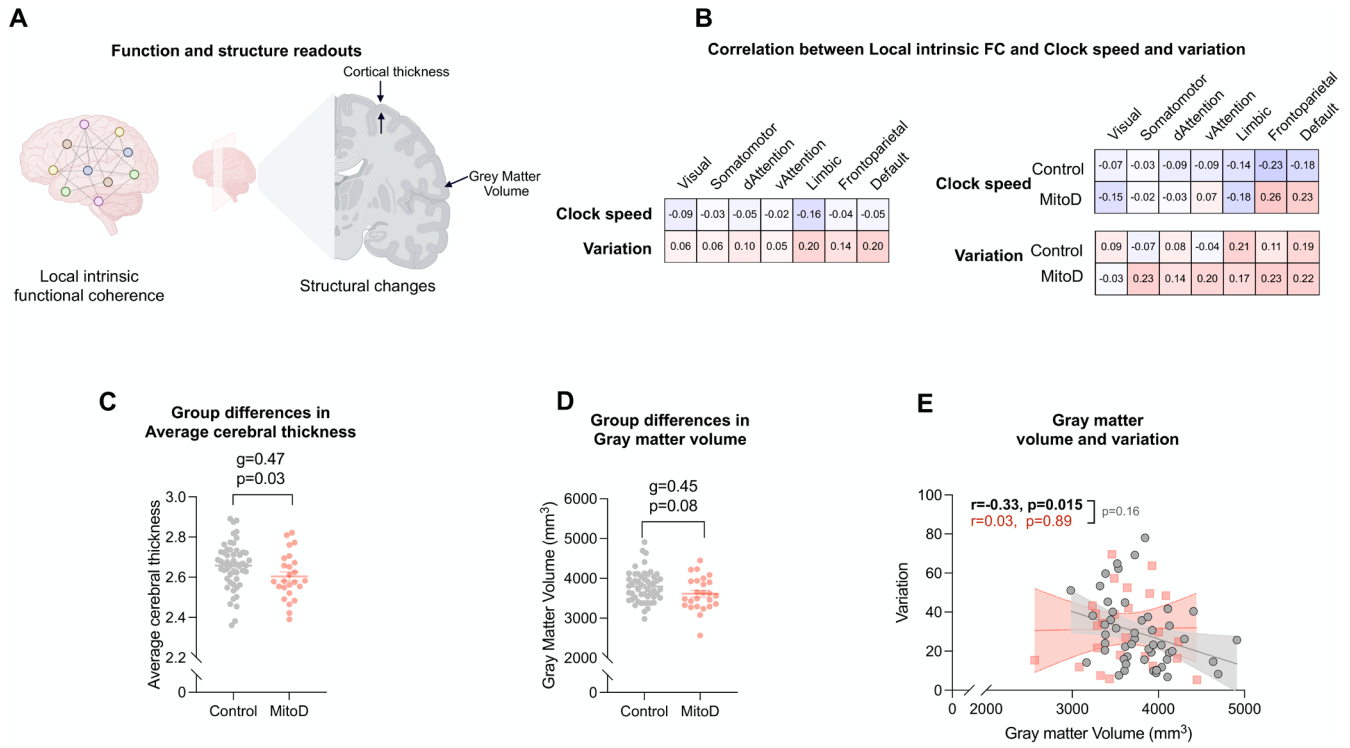

FIGURE 8 | Mitochondrial OxPhos dysfunction may alter the neural correlates of prospective time perception. (A) Functional and structural readouts. Functional measures reflect local intrinsic connectivity or synchrony (FC, functional coherence) indexed by regional homogeneity (ReHo), summarized within canonical large-scale brain networks including visual, somatomotor, dorsal and ventral attention, limbic, default mode, and frontoparietal networks. Structural measures include cortical thickness and gray matter volume. (B) Heatmap showing group-stratified correlations between time perception metrics and resting-state functional connectivity across canonical brain networks. (C) Group comparison of average cortical thickness reveals ($p = 0.03$), potentially reflecting neurodegenerative or neurodevelopmental effects of impaired oxidative metabolism. (D) Group comparison of total gray matter volume, showing ($p = 0.08$), with implications for structural integrity in networks subserving cognitive timing. (E) Scatter plot illustrating the association between gray matter volume and Variation. In control participants, greater gray matter volume is associated with more consistent (less variable) time estimates.

the mitoD group. Finally, our mitoD cohort included participants with diverse genotypes and clinical phenotypes, which may have diluted group-level effects or introduced variability in physiological coupling patterns.

In summary, our findings offer preliminary and partial support for a psychophysiological framework of time perception in which internal Clock Speed and Variation are likely shaped by a combination of metabolic parameters, cognitive control, and brain function. While both healthy and mitochondrial-impaired individuals exhibit broad variability in time perception, the coupling between timing and its biological correlates appears altered in the context of mitochondrial OxPhos defects. The most robust, correction-surviving signal of this mitochondrial dependence was the reversal of the working-memory–Clock Speed coupling in mitoD participants. We regard this as the primary finding, and the coupling of Variation to energetic capacity (resting energy expenditure) and catecholamine turnover (urinary NE) in healthy individuals as the main psychobiological findings to be replicated in future work. The differential associations between our MitoD and control groups suggest that depending on proximal metabolic state and the bioenergetic constraints they impose on the brain or other parts of the organism, the drivers of time perception could differ between individuals. These results underscore the importance of considering energetic and cognitive constraints on subjective time. This motivates future research that moves beyond phenomenology to a more mechanistic understanding of how the brain–body unit and the energy metabolism that animates it jointly construct time perception.

Author Contributions

Darshana Kapri: methodology, software, investigation, validation, formal analysis, writing – original draft, writing – review and editing, data curation, visualization. **Gabriel Sturm:** conceptualization, methodology, writing – review and editing. **Michio Hirano:** conceptualization, methodology, resources, writing – review and editing. **Tor D. Wager:** conceptualization, project administration, writing – review and editing. **Cynthia C. Liu:** methodology, investigation, data curation, validation, formal analysis. **Caroline Trumpff:** conceptualization, writing – review and editing, methodology, resources. **Ke Bo:** methodology, investigation, validation, formal analysis, data curation, writing – review and editing, writing – original draft. **Catherine Kelly:** investigation, methodology, data curation, writing – review and editing. **Martin Picard:** conceptualization, writing – review and editing, writing – original draft, resources, supervision, project administration, funding acquisition.

Funding

This work was supported by the National Institutes of Health under grants RF1AG076821, R01MH137190, R37MH076136, R21MH113011, and R01MH122706; the Seed Grant Program for MR

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Studies of the Zuckerman Mind Brain Behavior Institute at Columbia University; the Robert N. Butler Columbia Aging Center Fellowship Program at the Mailman School of Public Health; the National Center for Advancing Translational Sciences (UL1TR001873) and the National Cancer Institute (P30CA013696); the Columbia Irving Institute Scholars Program; the Nathaniel Wharton Fund; and the Baszucki Group (to M.P.).

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** Quantifying inter-individual differences in prospective time perception. (A, B) Line plots showing raw data for time estimation and time production tasks across multiple durations for each participant, illustrating within-subject performance and between-subject variability. (C, D) Ratio plots showing proportional deviation of estimated or produced time relative to probed durations; ratios >1 indicate faster perceived time (overestimation/underproduction), ratios <1 indicate slower perceived time. (E) Scatter plot showing average estimation and production ratios for each participant, highlighting the reciprocal relationship between tasks. (F) Correlation plot showing an inverse relationship between average estimation and production scores. (G) Scatter plot showing the association between Clock Speed and intra-individual Variation, indicating that individuals with more extreme Clock Speeds (faster or slower) tend to exhibit greater timing variability. **Figure S2:** Factor analysis for time perception score. Schematic representation of loadings for time perception score from relative time estimation and time production scores of each trial. **Figure S3:** Relationship between resting energy expenditure, body composition, and time perception. (A) Scatter plot showing a strong positive correlation between resting energy expenditure (REE) and fat-free mass (FFM) across all participants, consistent with established metabolic physiology indicating that REE is largely determined by lean body mass. (B, C) Scatter plots illustrating the association between REE and time perception metrics: (B) Clock Speed and (C) Coefficient of Variation. These plots explore the link between systemic metabolic rate and prospective timing performance. Greater REE is associated with faster clock speed and lower variability. **Figure S4:** Sex-specific differences in the association between prospective time perception and biological and physiological factors. (A, B) Participants ranked by their composite Clock Speed score and Variation. (A) Clock Speed and (B) Coefficient of Variation plotted separately for males and females. (C) Heatmap showing sex-stratified correlations between time perception metrics (Clock Speed and variation) and systemic physiological and cellular bioenergetic markers. Factors include mitochondrial health index (MHI) and mitochondrial DNA content across peripheral immune cell subtypes (e.g., PBMCs, neutrophils, monocytes, and platelets), as well as age, resting heart rate, resting energy expenditure (REE), and catecholaminergic signaling (serum and urine norepinephrine levels). **Figure S5:** Population distribution by group for time perception metrics. (A, B) Histograms illustrating the percentage distribution of control and mitoD participants: (A) Clock Speed and (B) variation in time perception. These histograms show the distribution in time perception across the two groups, highlighting potential shifts between control and mitoD participants. (C) Scatter plot showing the relationship between variation and absolute Clock Speed between control and mitoD groups. **Figure S6:** Differences in correlations between time perception

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and neurotransmitter content. (A) Heatmap showing correlations between time perception metrics (Clock Speed and Variation) and urine and serum neurotransmitter levels across all participants. (B) Heatmap showing group-wise correlations between time perception metrics (Clock Speed and Variation) and neurotransmitter levels in urine and serum, stratified by control and mitochondrial disease (mitoD) groups. Group-specific differences in neurotransmitter content and their association with time perception metrics are highlighted, suggesting potential modulatory effects of mitochondrial OxPhos dysfunction on neurotransmitter systems involved in time perception. $^{**}p < 0.01$, $^{*}p < 0.05$. **Figure S7:** Differences in correlations between time perception and psychological readouts in control and mitoD participants. Heatmap showing group-wise correlations between time perception metrics (Clock Speed and Coefficient of Variation) and neurological and psychosocial factors, stratified by control and mitochondrial disease (mitoD) groups. This heatmap displays the correlations between individual differences in time perception and a range of psychological and physiological measures, including neurological (e.g., cognitive function), and psychosocial factors (e.g., stress, mood, and well-being). **Figure S8:** Mitochondrial OxPhos dysfunction alters associations between prospective time perception and brain structure. (A–D) Scatter plots showing the association between (A) mean cortical thickness and Clock Speed, (B) mean cortical thickness and Variation, (C) gray matter volume and Clock Speed, and (D) gray matter volume and Variation. (E–G) Group-wise scatter plots showing the relationship between (E) mean cortical thickness and Clock Speed, (F) mean cortical thickness and Variation, and (G) gray matter volume and Clock Speed in control and mitochondrial disease (mitoD) participants. **Table S1:** Multiple correction false discovery rate testing for designated Hypothesis 1–4.

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