RESEARCH ARTICLE

RUNNING HEAD: Exogenous Ketosis Counters Hypoxia-Induced Neural Changes

Exogenous ketosis mitigates hypoxia-induced neural signaling alterations and cerebral oxygenation decline at rest in healthy males

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ABSTRACT

Intensive exercise and high-altitude exposure can disrupt neural activity and impair cognitive functioning. Previous research suggests that ketone ester (KE) ingestion may counteract cognitive impairments, however, its impact on neural activity during exercise and hypoxia remains unclear. Therefore, we investigated the impact of KE on electroencephalography (EEG) patterns and cognition during hypoxia and exercise. Twelve healthy males completed three randomized crossover sessions: i) normoxia + placebo, ii) hypoxia + placebo, and iii) hypoxia + KE. Each session included normoxic endurance ($ET_{120'}$) and high-intensity interval training ($HIIT_{80'}$), followed by a 16-h period including sleep in either normoxia or hypoxia. The next day, participants performed a normoxic 30-min all-out time-trial ($TT_{30'}$). EEG was recorded during rest and exercise, while cerebral tissue oxygenation index (cTOI) and cognitive performance were evaluated during rest. At rest, KE attenuated hypoxia-induced increases in alpha and beta power and cTOI declines. Nonetheless, cognitive performance remained unaffected. Brain activity rose throughout $ET_{120'}$ and normalized during recovery, while $HIIT_{80'}$ elicited a fluctuating neural response but normalized during recovery. Following $TT_{30'}$, theta, alpha, and gamma power remained elevated during recovery. Altogether, these data, obtained in healthy males, show the potential of KE to stabilize resting-state EEG patterns in hypoxia. Moreover, they shed light on how EEG patterns vary with exercise intensity, with sustained post-exercise increases in theta, alpha, and gamma power following high-intensity efforts. These findings suggest that KE can help to preserve neural stability under hypoxia and highlight EEG's potential for monitoring fatigue and tailoring training or recovery strategies.

NEW & NOTEWORTHY

This study is the first to demonstrate the effects of ketone ester ingestion on hypoxia-induced neural alterations. Moreover, it uniquely combines measurements of cerebral oxygenation, cognitive performance, and electroencephalography (EEG) across low-, high-, and all-out exercise intensities, as well as during rest. Potentially highlighting EEG as a valuable tool for monitoring fatigue and optimizing training strategies.

Keywords: Brain activity; EEG; exercise; hypoxia; ketones

INTRODUCTION

Both exercise and environmental hypoxia are well-known stressors that can reduce blood and tissue oxygen availability (1–6). Under these stressors, sustained mental or physical effort can lead to (mental) fatigue, subsequently impairing cognitive (7, 8) and physical (8–12) performance. Accordingly, (mental) fatigue poses a critical risk for high-altitude expeditions and may increase athlete's susceptibility to injuries. However, the assessment of mental fatigue is often subjective and prone to misclassification (13), underscoring the need for more objective measures.

Interestingly, electroencephalography (EEG) has emerged as a promising tool to objectively evaluate mental fatigue (14), providing more insights than a cognitive test alone, with different frequency bands reflecting distinct cognitive states (15). While the precise impact of the various frequency bands remains to be determined, earlier studies indicated that delta and theta waves are typically observed during sleep and quiet focus states (15), while alpha waves constitute the most prominent brainwave band during wakefulness (16). Furthermore, alpha peak frequency (APF) has been proposed as a reliable indicator of cognitive preparedness (17–19), with higher values associated with faster reaction times (20), improved working memory (21, 22), and enhanced memory performance (23). Beta waves have also been shown to reflect mental alertness and active concentration (24), while gamma waves are positively associated with consciousness, perception, and awareness (25, 26). Although high-density EEG systems remain the gold standard, practical alternatives such as wearable EEG devices (*e.g.*, the Muse) have recently emerged. As such, EEG-derived markers are a promising tool to objectively evaluate cognitive state and fatigue, and their impact on cognitive and physical performance.

Various stressors are known to affect cognitive functioning, with strenuous exercise as a prime example. In general, the impact of exercise on cognitive function strongly varies with exercise intensity and the applied protocol (27, 28). More precisely, acute moderate intensities

(~70% LT) have been shown to elicit positive effects on psychocognitive functioning (29, 30), and acute high-intensity interval training has been associated with improved working memory and inhibitory control (31–33). In contrast, exhausting exercise (*i.e.*, 60 min ergometer cycling at 90% ventilatory threshold) has been shown to impair cognitive performance (33). Remarkably, similar conclusions appear regarding the impact of exercise on EEG patterns. Several studies report increased theta, alpha, and beta power during cycling at power outputs of 140 W and above (34–36). Conversely, a decrease in alpha power spectral density has been reported at intensities as low as 50 W (37). To date, gamma power has not been extensively studied concerning power output during cycling; however, an upward trend was observed over time during all-out cycling (38). Altogether, neural responses across three of the most commonly employed exercise intensity modalities (*i.e.*, prolonged low-intensity exercise, high-intensity interval exercise, and all-out efforts, such as time trials) remain poorly understood. Another infamous cognition-impairing stressor is exposure to hypoxia, with a recent meta-analysis indicating that hypoxia-induced cognitive impairments mostly become significant above 2,500 m (39). This is primarily reflected by impaired executive control, attention, psychomotor skills, and perceptual processing, resulting in, among others, impaired reaction times (40) and visual information processing (41), which may be particularly detrimental for acute high-altitude activities such as rescue missions and military operations, but also for athletes competing or residing at altitude (39, 42, 43). Remarkably, hypoxia-induced alterations in cerebral oxygenation are also known to disrupt spectral power and EEG patterns, although findings are often contradictory and the underlying mechanisms remain unknown (44). For instance, previous research combining EEG and near-infrared spectroscopy (NIRS) during a simple motor task reported a negative association between oxyhemoglobin (*i.e.*, as index of cerebral tissue oxygenation, cTOI) and alpha and beta rhythms, whereas an opposite relationship was observed for cTOI and deoxyhemoglobin (45). Furthermore, an inverse

relation between resting alpha-frequency and the amplitude of cerebro-vascular responses, defined as changes in cerebral deoxygenated hemoglobin, was reported (46). Previous research has reported that moderate hypoxia (SpO_2 75–90%) is associated with increased alpha activity, whereas severe hypoxia (SpO_2 <75%) is linked to decreased activity although the underlying mechanisms remain unknown (44). In general, theta, beta, and gamma (spectral) power are believed to increase with exposure to hypoxia (44, 47–50), and these effects may persist after termination of hypoxic exposure. Nevertheless, the limited number of studies available presented a large methodological heterogeneity, resulting in equivocal findings and conclusions. Since previous research has indicated that exogenously increasing blood ketone bodies has no beneficial (51–55) or even slightly negative effects (56, 57) on high-intensity endurance performance, the post-exercise intake of ketone supplements, like ketone monoesters (KE), is currently recommended to enhance post-exercise recovery and to promote adaptive responses to exercise (58–60). Interestingly, earlier studies from our and other laboratories indicated that ketone supplementation may counteract the negative impact of exercise and hypoxia on cognitive function (7, 51, 61–63), although not all studies report this effect (64–66). The underlying mechanism remain elusive, but may be related to the potential of ketosis to i) provide ketone bodies that can act as an alternative energy substrate for cerebral metabolism (67), ii) increase circulating concentrations of brain-derived neurotrophic factor (68), and dopamine (7), iii) enhance cerebral blood flow (63), and/or iv) improve the stability of brain networks (69). However, KE supplementation seems ineffective to upregulate normal cognitive function or to mitigate cognitive impairments induced by mild exercise or moderate hypoxia (39, 42), raising the question of whether it might still attenuate more subtle disruptions in EEG patterns or mental fatigue (39, 42). For instance, ingestion of KE during a 100-km ultra-endurance exercise negated the exercise-induced impairment in reaction time, movement time, and response latency (7). Besides, ingestion of KE during acute exposure to severe hypoxia

129 (FiO_2 = 9.7%, simulated altitude of 9,096 m) counteracted a hypoxia-induced decline in
130 cognitive efficiency (61), whereas no effects of either hypoxia or KE were observed under
131 milder hypoxia (FiO_2 = 12.7%, simulated altitude of 4,000 m) (65). As such, the impact of KE
132 on EEG patterns both in the context of exercise and hypoxia remains to be determined.

133 Therefore, we aimed to investigate the potential of KE to modulate dysregulations
134 induced by hypoxia and diverse exercise intensities (endurance, high-intensity interval, and all-
135 out effort) on EEG patterns and cognitive function. Since prior studies have not examined EEG,
136 we include it as an objective marker of brain function in addition to the cognitive tests used in
137 previous research, while assessing cerebral oxygenation as a potential mechanistic contributor
138 to these EEG responses. Therefore, we hypothesize that, under the mild conditions used in this
139 study, ingestion of KE does not affect cognitive function but may mitigate the dysregulations
140 caused by exercise and hypoxia.

METHODS

Ethical approval and participants.

This research is part of a larger project (70) that was pre-registered at www.clinicaltrials.gov (NCT06060093) and approved by the Ethics Committee Research UZ/KU Leuven (B3222022001041). All participants were young (18-35 yo), healthy, Western European males with a BMI of 18 to 25 $kg.m^{-2}$, who were active in either cycling, endurance running, or triathlon and classified as tier 2 (trained/developmental) according to the Participant Classification Framework (71). Exclusion criteria included exposure to altitudes >1,500 m within 3 months prior to the study, smoking, a history of altitude-sensitive pathologies, as well as participants working in late-night shifts, and those with extreme morning and evening chronotypes as determined by the Horne-Östberg questionnaire (72). Written informed consent was received from every participant. Of the thirteen participants initially included, one withdrew due to a COVID-19 infection. Consequently, data analyses were conducted on 12 participants [age: 25 ± 4 yr; height: 180.4 ± 7.0 cm; body mass: 72.4 ± 9.0 kg; physical activity: 9 ± 3 $h.week^{-1}$, $\dot{V}O_2peak$: 62.6 ± 8.2 $mL.kg^{-1}.min^{-1}$ (mean ± SD)].

General study design.

This study was performed in the context of a larger research project, of which the details have been reported previously (70). This study involved a randomized, double-blind, placebo-controlled, cross-over design consisting of three experimental sessions. Blinding was assured by assigning the randomization process to an individual who was uninvolved in the experimental testing. Each experimental session included a normoxic training program involving a 2-h endurance training session ($ET_{120'}$) in the morning and an 80-min high-intensity interval training ($HIIT_{80'}$) 1.5 h after lunch. After completion of the $HIIT_{80'}$, participants spent the night either in i) normoxia (FiO_2 = 20.9%) with placebo (PL) supplements (N_{PL}), or at a simulated altitude of 3,000 m (normobaric hypoxia; FiO_2 = 14.5% O_2) with either ii) PL

supplements (H_{PL}) or iii) ketone ester (H_{KE}) supplements (See Figure 1). In accordance with current recommendations (73) and common athlete practice, altitudes of 2,500-3,000 m are typically used to induce sufficient desaturation to promote physiological adaptation while preventing excessive sleep disruption. After returning to normoxia the next morning, participants performed a 30-min all-out time-trial ($TT_{30'}$). All experimental sessions took place in a normobaric hypoxic facility (Van Amerongen CA Technology, Tiel, The Netherlands) located at the Bakala Athletic Performance Center (Leuven, Belgium). The sessions were separated by a 1-week washout period, with identical protocols and timing applied across all three sessions. EEG was recorded during each resting measurement and exercise bout, while cognitive function was assessed at baseline and post-sleep (full details below).

Preliminary testing and familiarization sessions.

Two weeks prior to the first experimental session, participants completed a preliminary session that included two graded exercise tests on a cycling ergometer (Avantronic Cyclus II, Leipzig, Germany). These tests were performed separately to determine lactate threshold (LT) and peak oxygen uptake rate ($\dot{V}O_2peak$), as these assessments target distinct physiological responses and therefore require different testing protocols (74). For the LT test, the initial workload was set at 70 W and increased by 40 W every 8 min. These longer stages have been shown to provide higher test-retest reliability than shorter stages (*e.g.*, 4 min) (75) and reduce the likelihood of LT overestimation (76). Conversely, extending this 8-min protocol to determine $\dot{V}O_2peak$ would result in exhaustingly prolonged protocol, influencing $\dot{V}O_2peak$ by altered substrate utilization, dehydration, participant discomfort, and ventilatory muscle fatigue. Therefore, in accordance with recommendations that $\dot{V}O_2peak$ tests last approximately 8-12 min (77), the $\dot{V}O_2peak$ protocol employed in the present study had a mean duration of 453 ± 64 s (7 min 33 s ± 1 min 4 s). Capillary blood samples were collected every 4 min to measure blood lactate concentration (Lactate Pro2; Arkray, Amstelveen, The Netherlands). The LT was

191 defined as the lowest workload resulting in a 1 mM increase in blood lactate concentration
192 within the same stage (78–80). Following 15 min of active recovery at 70 W, participants
193 commenced a second incremental cycling test, starting at 100 W and increasing by 25 W every
194 30 s until volitional exhaustion. During this test, oxygen consumption ($\dot{V}O_2$) and carbon dioxide
195 production ($\dot{V}CO_2$) rates were continuously monitored using indirect calorimetry (Cortex
196 Metalyzer 3B, Cortex, Leipzig, Germany). $\dot{V}O_2$peak was determined as the highest mean $\dot{V}O_2$
197 recorded over a 30-s period.

198 In the two weeks leading up to the first experimental session, participants completed the
199 full experimental sleep and exercise protocols twice, and the cognitive test battery and resting
200 measurement twice in normoxia to get familiarized and eliminate learning effects.

201 *Experimental sessions.*

202 Participants arrived at the testing facility in a fasted state between 7:00 and 9:00 AM
203 (exact timings were replicated for each session). Approximately 2.5 h after consuming a
204 standardized breakfast (see *Dietary standardization* below), they completed a 2-h endurance
205 training session ($ET_{120'}$) on a cycling ergometer (Tacx Neo Smart, Wassenaar, The
206 Netherlands), which comprised eight consecutive 15-min intervals with workloads alternating
207 between 60% and 80% of their LT. Participants consumed a standardized lunch (see *Dietary*
208 *standardization* below) 1.5 h before performing an 80-min high-intensity interval training
209 ($HIIT_{80'}$) on a cycling ergometer (Avantronic Cyclus II, Leipzig, Germany). $HIIT_{80'}$ included a
210 10-min warm up at 70% of LT, followed by 10 repetitions of 3-min cycling at 120% of LT,
211 each separated by 4 min of active recovery at 50% of LT (81). This protocol balances high
212 metabolic demand with strategic recovery, ensuring the intensity remains sufficient to elicit
213 robust aerobic adaptations (82). Thirty minutes after completing $HIIT_{80'}$ (*i.e.*, 5 h before sleep-
214 time), participants entered their designated 'hotel room', which was set at either hypoxia
215 (H_{PL} and H_{KE}) or normoxia (N_{PL}). As previously indicated (70), nocturnal hypoxic exposure

substantially hampered participants' sleep quality, evidenced by a 3% reduction in both total sleep time (N_{PL}: 487 ± 23 min *vs*. H_{PL}: 472 ± 31 min, p = 0.042) and sleep efficiency (*i.e.*, total sleep time/time in bed; N_{PL}: 95.0 ± 2.0% *vs*. H_{PL}: 92.5 ± 4.3%, p = 0.037), mostly mediated through a doubling in wakefulness after the onset of sleep (N_{PL}: 17 ± 8 min *vs*. H_{PL}: 34 ± 26 min, p = 0.049), accompanied by a 22% fall in slow wave sleep duration (N_{PL}: 101 ± 20 min *vs*. H_{PL}: 79 ± 11 min, p = 0.002). Notably, KE intake did not alter any of these hypoxia-induced disruptions. After 16 h in either hypoxic or normoxic conditions, participants returned to normoxia and completed $TT_{30'}$ 3.5 h later. $TT_{30'}$ was performed on a cycling ergometer (Avantronic Cyclus II, Leipzig, Germany) and preceded by a 15-min warming up at 70% of LT. The initial workload of $TT_{30'}$ was fixed as the mean power output obtained during the second familiarization session (103 ± 8% of LT). After 5 min, participants were allowed to adjust the workload voluntarily every 5 min during the first 25 min and every min during the final 5 min, and instructed to maximize their average power output. As previously reported (70), mean power outputs throughout $TT_{30'}$ were similar in all conditions (~285 W, p = 0.454), and power output during the final minute was ~122 ± 18% of LT. Furthermore, resting measurements were conducted at four time points, in order to evaluate resting EEG: i) prior to $ET_{120'}$ (PRE; 0 h), ii) after 2 h in hypoxia or the equivalent duration in normoxia (+10 h), iii) immediately upon waking (+23 h), and iv) 2 h after re-exposure to normoxia (+27 h). Cognitive function was assessed during the first (PRE) and final (+27 h) resting measurements. The respective time points (0 h, +2 h, +4 h, +6 h, ~7.5 h, +10 h, +23 h, and +27 h) are defined relative to the start of the experimental session.

Supplementation protocol.

In a randomized order, participants received either 25 g of a KE (H_{KE}) or PL (N_{PL} and H_{PL}) drink immediately after i) $ET_{120'}$, and ii) $HIIT_{80'}$, as well as iii) after 1.5 h in hypoxia (or an equivalent period in normoxia), and iv) 30 min before sleep. Hence, participants in the H_{KE}

group received a cumulative dose of 100 g KE [(R)-3-hydroxybutyl (R)-3-hydroxybutyrate, KetoneAid Inc., Falls Church, VA, USA] to intermittently elevate blood ketone levels post-exercise and throughout the early part of the night. Participants in the N_{PL} and H_{PL} groups were provided with a total of 100 g of a taste- and viscosity-matched PL drink consisting of 12.5% w/v collagen (6d Sports Nutrition, Antwerpen, Belgium) and 1 mM bitter sucrose octaacetate (Sigma-Aldrich, Bornem, Belgium) dissolved in water. The total caloric intake from the KE supplements was approximately ~1,960 kJ *vs*. ~190 kJ for the placebo supplements. Randomization was performed by a researcher who was otherwise not involved in the study.

Dietary standardization.

On the evening prior to each experimental session, participants consumed a standardized, carbohydrate-rich dinner at home (~5,600 kJ; 69% carbohydrate, 16% fat, 15% protein). Water was permitted *ad libitum* until they arrived at the facility the following morning, and was replicated consistently for each session. Upon arrival in a fasted state, participants consumed a standardized breakfast (~4,200 kJ; 68% carbohydrate, 21% fat, 11% protein). 1 h before the $ET_{120'}$ exercise session, participants received a carbohydrate-rich snack (~660 kJ; 92% carbohydrate, 3% fat, 5% protein) and consumed 60 g of carbohydrates per hour during $ET_{120'}$ through isotonic drinks and carbohydrate-rich snacks (6d Sports Nutrition, Antwerpen, Belgium). A light lunch (~4,150 kJ; 74% carbohydrate, 25% fat, 14% protein) was provided 1.5 h before the $HIIT_{80'}$ session. Immediately after $HIIT_{80'}$, participants received a high-carbohydrate, high-protein recovery shake containing 60 g of carbohydrates and 30 g of protein (6d Sports Nutrition, Antwerpen, Belgium). After 30 min in either hypoxia or normoxia, participants were served a standardized dinner (~3,250 kJ; 69% carbohydrate, 5% fat, 26% protein) and a light snack (~1,700 kJ; 69% carbohydrate, 15% protein, 16% fat) 2 h before bedtime to prevent hunger overnight. The total caloric intake on the first day, excluding the KE supplements, was approximately 15,020 kJ. The following morning, participants received the

same standardized breakfast as on the first day, along with a carbohydrate-rich snack (as provided before $ET_{120'}$) 30 min prior to $TT_{30'}$.

Experimental measurements

Electroencephalography measurements

EEG data were recorded at rest and during exercise using the Muse 2 headband (InterAxon Inc., Toronto, ON, Canada), at a sampling rate of 256 Hz, not to be confused with high-density EEG. The Muse EEG system includes electrodes located at positions analogous to Fpz, AF7, AF8, TP9, and TP10, with electrode Fpz utilized as the reference electrode during recording. Data were collected through a Bluetooth connection between a Lenovo tablet and the Muse 2 headband (InterAxon Inc., Toronto, ON, Canada) and stored offline for later analysis in MATLAB (MathWorks, Natick, USA). EEG artifacts were removed using adaptive filtering based on general linear models, using the script available in the *Supplementary Materials*. First, linear trends were removed using MATLAB's built-in detrend function. EEG signals were band-pass filtered (1-50 Hz) to attenuate slow drifts (<1 Hz) and high-frequency noise (>50 Hz) outside conventional EEG frequency ranges. Generalized linear models were used to attenuate movement-related artifacts (83). Effectiveness of artifact attenuation was verified by a cross-correlation analysis with head velocity and acceleration data ($|r| = 0.006$ and $|r| = 0.011$, resp.). Additionally, 1-s segments of EEG power (expressed in μV^2) were analyzed using a threshold-based approach for the detection of ocular movement and muscular artifacts. On average, less than ~13 % of epochs were rejected due to artifacts. The mean signal-to-noise ratio was 12.82 ± 15.83 dB, which is consistent with the expected quality for low-density EEG during cycling (84). Finally, the APF (expressed in Hz) was calculated.

EEG at rest. During the resting measurements, participants rested in a supine position in a dark room with eyes closed for at least 10 min before the EEG assessment and were instructed to relax yet stay awake. Subsequently, data were collected over 5 min and presented

as the mean values obtained during this time. Changes in EEG power (Δtheta, Δalpha, ΔAPF, Δbeta and Δgamma) were analyzed relative to baseline across all rest timepoints.

EEG during exercise. Immediately before and after each exercise bout ($ET_{120'}$, $HIIT_{80'}$, and $TT_{30'}$), participants remained seated on their bike during a 5-min period to respectively assess baseline (BL; ET_{BL}, $HIIT_{BL}$, and TT_{BL}, resp.) and recovery values (REC; ET_{REC}, $HIIT_{REC}$, and TT_{REC}, resp.), which were averaged over the respective 5-min intervals. Subsequently, the data obtained throughout the warm-up ($HIIT_{WU}$ and TT_{WU}, resp.) were averaged over their respective durations (*i.e.*, 10 min, and 15 min, resp.). Throughout $ET_{120'}$, data were collected during – and averaged over – the final 5 min of i) the first low-intensity bout (*i.e.*, between 10-15 min, ET_{L1}), ii) the first high-intensity bout (*i.e.*, between 25-30 min, ET_{H1}), iii) the last low-intensity bout (*i.e.*, between 100-105 min, ET_{L4}), and iv) the last high-intensity bout (*i.e.*, between 115-120 min, ET_{H4}). Throughout $HIIT_{80'}$, data were collected during each interval and averaged over its duration for i) the first high-intensity bout (*i.e.*, between 10-13 min, $HIIT_{H1}$), ii) the first low-intensity bout (*i.e.*, between 13-17 min, $HIIT_{L1}$), iii) the last high-intensity bout (*i.e.*, between 73-76 min, $HIIT_{H10}$), and iv) the last low-intensity bout (*i.e.*, between 76-80 min, $HIIT_{L10}$). Throughout $TT_{30'}$, data were averaged in 5-min time chunks for the first segment ($TT_{0'-5'}$), and in 1-min time chunks for the final segment ($TT_{29'-30'}$).

Cerebral oxygenation.

cTOI was evaluated during the resting measurement bouts using NIRS, as previously reported (70). Within this previous publication, sleep quality was defined as the primary outcome, and one participant was excluded from all analyses due to a baseline sleep efficiency (78%) below our predefined inclusion criteria (*i.e.*, sleep efficiency of 85% as defined by the National Sleep Foundation). Given that this rationale for exclusion was no longer justified in the current manuscript, this participant was included for all data analyses, resulting in slightly

different results for cTOI (see *'Statistical analyses'*). Changes in cerebral tissue oxygenation (ΔcTOI) were analyzed relative to baseline across all rest timepoints.

Cognitive test battery

Cognitive performance was assessed during PRE and +27 h resting measurement bouts using the Cambridge Neuropsychological Test Automated Battery (CANTAB; Cambridge Cognition, Cambridge, UK), comprising two validated tests to measure: i) reaction time (RT) and ii) rapid visual information processing (RVP). The cognitive assessments were administered on a tablet device (Lenovo Tab M10 FHD Plus, Lenovo, Hong Kong, China), which was securely positioned on an inclined stand. Participants remained seated in a comfortable chair, facing a wall to ensure a distraction-free testing environment. They were instructed to complete all tasks using the index finger of their dominant hand and to inform the research team upon finishing the assessments. A comprehensive description of the test procedures can be accessed at www.cambridgecognition.com/cantab/cognitive-tests/. The primary outcome measures for each test were as follows: RT, median reaction time (RT-MRT), median movement time (RT-MMT), and total errors out of 30 trials (RT-E); RVP, mean response latency (RVP-MRL), number of correct responses (hits) out of 54 trials (RVP-H), and false alarms out of 54 trials (RVP-FA).

Statistical analyses and sample size calculation.

Statistical analyses were conducted using suitable parametric and non-parametric methods with GraphPad Prism version 10.4.1. Prior to conducting statistical analyses, the normality of the EEG data for $ET_{120'}$, $HIIT_{80'}$, and $TT_{30'}$ was assessed and verified using the D'Agostino-Pearson test. To examine differences between conditions at a single time point, a one-way analysis of variance (ANOVA) was applied. For data obtained across multiple time points within the same session, a two-way repeated measures ANOVA was employed. When the assumption of sphericity was not met (Mauchly's test, JASP version 0.18.1; JASP Team,

Amsterdam, the Netherlands), the Geisser-Greenhouse correction was implemented. Significant main or interaction effects were followed up with post hoc tests using Šidák's correction. Reported p-values correspond to post-hoc comparisons unless otherwise stated, in which case they refer to the main effects. Results are expressed as mean ± standard deviation (SD), and statistical significance was set at $p < 0.05$. The data used for correlation analysis did not meet the assumptions required for Pearson's correlation, therefore Spearman's rank was performed. An a-priori sample size calculation was performed with a focus on the primary outcome of the larger project; to explore the effects of KE intake on sleep efficiency in hypoxia. As elaborately described in Stalmans et al. (85), this power calculation was based on an earlier study from our laboratory, which reported the effect of KE during sleep in normoxia (78), and indicated that a sample size of 6 is required to establish a significant effect on sleep efficiency (η_p^2: 0.395; effect size f = 0.81; α error: 0.05; power: 0.80; number of groups: 3; number of measurements: 3; correlation among repeated measures: 0.5; nonsphericity correction: 1; ANOVA: repeated measures, within factors). Conversely, the current article hypothesizes that KE intake may prevent hypoxia-induced EEG pattern dysregulations. Given the lack of prior data regarding the effects of KE on resting EEG patterns, a secondary power calculation was aimed to guarantee sufficient statistical power to identify a moderate effect (moderate effect size f: 0.25; α error: 0.05; power: 0.80; number of groups: 3; number of measurements: 4; repeated measures ANOVA), which indicated a required sample size of n = 10.

RESULTS

KE ingestion increased blood βHB concentrations.

As reported earlier (70), blood [ßHB] was low (~0.4 mM) at baseline in all conditions and increased 30 min after each KE supplement to 2-3 mM, while remaining low (0.4-0.5 mM) in N_{PL} and H_{PL} ($p < 0.001$ for time x condition effect).

Neither KE nor hypoxia altered cognitive performance

Neither KE supplementation nor hypoxia influenced median movement time, median reaction time, or errors made during the reaction time task ($p > 0.113$, Fig 3A-C). Similarly, mean response latency, number of correct hits, and false alarms remained unaffected in all conditions ($p > 0.07$, Fig 3E-F).

EEG at rest – KE ingestion negated a hypoxia-induced increase in alpha and beta power

Resting theta power was similar at all timepoints and in each session ($p > 0.239$, Fig. 4A). Alpha (Fig. 4B) and beta (Fig. 4D) power exhibited a time x condition effect ($p = 0.004$ and $p = 0.029$, resp.). Power of both waves increased upon early exposure to hypoxia (*i.e.*, +10 h) (alpha: $p = 0.005$, beta: $p = 0.011$, both for H_{PL} *vs.* N_{PL}), yet had returned to baseline values at 23 h (alpha: $p = 0.904$, beta: $p = 0.907$, both for H_{PL} *vs*. N_{PL}). Interestingly, KE ingestion inhibited the hypoxia-induced increase in both alpha ($p = 0.005$ for H_{KE} *vs.* H_{PL} and $p > 0.999$ for H_{KE} *vs*. N_{PL}) and beta ($p = 0.022$ for H_{KE} *vs.* H_{PL} and $p = 0.999$ for H_{KE} *vs*. N_{PL}) power at the 10 h timepoint. APF was unaffected throughout the protocol ($p > 0.285$, Fig. 4C). Neither APF (Fig. 4C) nor gamma (Fig. 4E) power was affected by time (all $p > 0.226$), condition (all $p > 0.136$), or their interaction (all $p > 0.507$).

EEG during endurance exercise ($ET_{120'}$) – EEG power rises during endurance exercise and normalizes after recovery.

A main time effect was observed for all frequency bands throughout $ET_{120'}$ (theta: $p < 0.001$, Fig. 5A; alpha: $p < 0.001$, Fig. 5B; APF: $p = 0.019$, Fig. 5C; beta: $p < 0.001$, Fig. 5D; and gamma: $p = 0.002$, Fig. 5E). Theta and alpha power were elevated throughout $ET_{120'}$ compared to ET_{BL} ($p < 0.006$ and $p < 0.020$, resp.) but returned to baseline at ET_{REC} ($p = 0.280$ and $p = 0.734$, resp.). Alpha power was ~31% lower during ET_{H4} compared to ET_{H1} ($p = 0.031$ for ET_{H4} vs ET_{H1}) but was unchanged across low-intensity stages ($p > 0.973$). While APF showed a main time effect ($p = 0.019$), post-hoc analyses failed to reach significance between isolated timepoints ($p > 0.084$ vs. ET_{BL}). Beta power was elevated at ET_{L1} and ET_{L4} *vs.* ET_{BL} ($p = 0.004$ and $p = 0.007$), but not during ET_{H1}, ET_{H4}, and ET_{REC} ($p > 0.170$). Gamma power was similar to baseline throughout $ET_{120'}$, except for a ~63% increase at ET_{L4} ($p = 0.001$ for ET_{L4} *vs.* ET_{BL}, $p > 0.520$ for all other timepoints *vs.* ET_{BL}). Notably, gamma power increased by ~71% from ET_{H1} to E_{TL4} ($p < 0.001$) but later decreased by ~39% from ET_{L4} to ET_{H4} ($p = 0.001$).

EEG during interval training ($HIIT_{80'}$) – EEG power fluctuates during interval training but normalizes after recovery

A main effect of time was observed for all frequency bands throughout $HIIT_{80'}$, except for APF (theta: $p < 0.001$, Fig 6A; alpha: $p < 0.001$, Fig 6B; APF: $p > 0.079$, Fig 6C; beta: $p < 0.001$, Fig 6D; and gamma: $p = 0.002$, Fig 6E). Compared to $HIIT_{BL}$, theta power increased at all high- and low-intensity intervals ($p < 0.003$), while returning to baseline at $HIIT_{REC}$ ($p > 0.951$). Relative to $HIIT_{WU}$, theta power was higher during $HIIT_{H10}$ and $HIIT_{L10}$ ($p = 0.001$ and $p = 0.015$, resp.), but not throughout $HIIT_{H1}$ and $HIIT_{L1}$ ($p > 0.321$). Alpha power was elevated at $HIIT_{H1}$, $HIIT_{H10}$, and $HIIT_{L10}$ compared to $HIIT_{BL}$ ($p = 0.008$, $p < 0.001$, and $p = 0.005$, resp.),

but remained stable at $HIIT_{WU}$, $HIIT_{L1}$, and $HIIT_{REC}$ ($p > 0.212$). Beta power increased above baseline during $HIIT_{WU}$ ($p = 0.046$) and both high-intensity intervals ($p = 0.019$ for $HIIT_{H1}$ and $p = 0.002$ for $HIIT_{H10}$, resp.) but not during both low-intensity intervals ($p > 0.586$) and upon $HIIT_{REC}$ ($p = 0.999$). Gamma power was elevated at $HIIT_{H10}$ ($p = 0.005$) compared to $HIIT_{BL}$ but further remained unaffected (all $p > 0.690$).

EEG during time trial performance ($TT_{30'}$) – EEG power increases during the time trial and peaks upon completion

Throughout $TT_{30'}$, theta, alpha, beta, and gamma power, but not APF, showed a main time effect (theta: $p < 0.001$, Fig. 7A; alpha: $p < 0.001$, Fig 7B; APF: $p > 0.634$, Fig 7C; beta: $p = 0.002$, Fig 7D; and gamma: $p = 0.038$, Fig 7E). Theta and alpha power increased during $TT_{0'-5'}$ and $TT_{29'-30'}$ compared to TT_{BL} (theta: $p < 0.016$ and alpha: $p < 0.033$), and remained elevated at TT_{REC} ($p < 0.001$ vs. TT_{BL} for both). Intriguingly, both theta and alpha power increased by ~60% between the start and the end of $TT_{30'}$ (theta: $p = 0.032$, alpha: $p = 0.027$, both for $TT_{0'-5'}$ *vs.* $TT_{29'-30'}$). Beta power only increased above baseline at $TT_{29'-30'}$ ($p = 0.001$), resulting in a ~83% increase throughout $TT_{30'}$ ($p = 0.014$ for $TT_{0'-5'}$ *vs*. $TT_{29'-30'}$). Gamma power remained stable throughout $TT_{30'}$ ($p > 0.465$ *vs*. TT_{BL}) but increased during TT_{REC} above TT_{BL} ($p = 0.008$). An overview of all changes in EEG power per exercise intensity is provided in Table 1.

KE ingestion increased cerebral oxygenation in hypoxia.

A time x condition effect ($p < 0.001$) indicated that hypoxia reduced cTOI at both hypoxic timepoints (10 h: $p < 0.001$ and 23 h: $p = 0.006$ for H_{PL} *vs*. N_{PL}, Figure 2). Ingestion of KE counteracted this hypoxia-induced drop in cTOI at 10 h ($p = 0.019$ for H_{KE} *vs*. H_{PL}).

Cerebral tissue oxygenation does not correlate with EEG power.

No correlations were observed between ΔcTOI and changes in EEG power during the resting measurements (Δtheta: r = -0.201, p = 0.068; Δalpha: r = -0.117, p = 0.265; ΔAPF: r = 0.165, p = 0.092; Δbeta: r = -0.143, p = 0.173; and Δgamma: r = -0.118, p = 0.251; data not shown).

DISCUSSION

This study demonstrates the potential of KE to counteract hypoxia-induced disruptions in EEG power at rest. Additionally, KE mitigated the hypoxia-induced decline in cTOI, thereby preserving cerebral oxygenation. Neither KE nor hypoxia significantly affected cognitive performance. Although cognitive outcomes were not directly altered, the modulation of EEG spectral power by KE may still indicate improved neural efficiency and adaptability. Furthermore, our data indicate that EEG responses to exercise are intensity dependent, as we observed distinct EEG patterns at low, high, and all-out exercise. Transitioning from rest to exercise at 60% of LT increased theta, alpha, and beta power, whereas only beta power increased at 70% of LT. Notably, EEG power further increased during subsequent efforts at ~100% of LT ($TT_{0'\text{-}5'}$) and 120% of LT ($HIIT_{H1}$). On the contrary, APF and gamma power remained relatively stable across all transitions from rest to exercise. While EEG power returned to baseline following $ET_{120'}$ and $HIIT_{80'}$, theta, alpha, and gamma power remained elevated after $TT_{30'}$, suggesting that maximal, all-out exercise may induce prolonged mental and physical fatigue. Although validation studies reported high correlations between research-grade EEG systems (32/64 electrodes) and the 4-electrode Muse device for several frequency bands, agreement for gamma activity is only moderate, warranting cautious interpretation (122). These EEG changes could reflect preserved cortical stability and resilience to hypoxic stress, even in the absence of overt behavioral effects. Nonetheless, these findings should be interpreted cautiously, given the multifactorial influence of exercise and hypoxia on EEG outcomes.

Effects of ketone ester ingestion on EEG under hypoxia

Despite the inherent variability associated with the Muse 2 headband, our findings suggest that KE ingestion protected against acute hypoxia-induced increases in alpha and beta power. While the underlying mechanisms remain poorly understood, earlier data indicated that

an increase in alpha and beta (spectral) power at altitude results from the drop in either blood oxygen saturation (SpO_2) (49, 86, 87) or cerebral oxygenation (88). Although blood SpO_2 remained unaffected by KE ingestion at this particular timepoint [see data previously reported in Stalmans et al (70)], KE increased cerebral oxygenation. Such an increase in cTOI without apparent changes in SpO_2 is consistent with earlier data from our group showing that KE ingestion increased prefrontal cortex oxygenation but not SpO_2 after 4 h at a simulated altitude of 4,000 m (89). However, ΔcTOI was not correlated with changes in EEG band power (Δ's), implying that the observed increases in alpha and beta power were likely independent of cTOI variations. As previously described, this discrepancy between blood and tissue oxygenation most likely results from the lower pO_2 and higher pCO_2 in brain/muscle tissue compared to blood (90, 91), accommodating a location in the steep part of the oxyhemoglobin dissociation curve. Consequently, the small increase in pO_2 with KE ingestion, as reported earlier (70), may augment cerebral oxygenation despite similar SpO_2 levels.

Beyond the potential of KE to impact EEG power in hypoxia via increased cerebral oxygenation, other potential mechanisms include the ability of ketone bodies to reduce spontaneous neuronal firing by modulating K-ATP channels (92, 93), as well as reducing GABA levels in the cingulate cortex (94). While the direct relationship between GABA and EEG patterns remains unclear, a recent review indicated that GABAergic medications may both increase or decrease alpha power (95). Moreover, $GABA_B$ agonist administration has been shown to increase beta power up to 80% in mice, while antagonist administration reduced beta power (96). As such, a KE-mediated reduction in [GABA] may have contributed to its ability to prevent hypoxia-induced EEG pattern disruptions.

From an applied perspective, the ability of KE to increase cTOI while preventing hypoxia-induced alterations in EEG power may be particularly relevant for high-altitude

expeditions and other hypoxic operational settings. In these environments, preserving cerebral oxygenation and optimal neural functioning is critical, as disturbances can impair judgment and risk-related decision-making (97, 98). This relationship is relevant because our observations show that KE attenuate hypoxia-induced disruptions in alpha and beta activity, frequencies that have previously been associated with cognitive processing and working memory (99, 100). Unfortunately, cognitive performance was not assessed at the time point where KE stabilized EEG patterns, and neither hypoxic exposure nor KE ingestion throughout day 1 of the protocol altered next-day cognitive performance. This is in accordance with available literature, indicating that mild hypoxic exposure (101–103) or subtle sleep disruptions (85, 104, 105) do not substantially impair next-day cognitive performance or EEG patterns. Altogether, these data suggest that exogenous ketosis may only beneficially affect cognition (*i.e.*, as evidenced in earlier but not the present studies) whenever more drastic cognitive declines are apparent (7, 51). Alternatively, cognitive performance was assessed approximately 17 h after the final KE supplement, at a timepoint where participants were no longer in a state of ketosis, suggesting that similar hypothetically beneficial effects of KE may be temporally restricted to the state of ketosis.

EEG responses during the transition from rest to exercise

Besides the ability of KE to prevent hypoxia-induced disruptions in resting EEG patterns, our data provide novel insight into the impact of different exercise modalities and intensities on EEG patterns, while acknowledging the inherent variability associated with the use of a low-density, wearable EEG system. With the transition from rest to low-intensity exercise (*i.e.*, 60% of LT during $ET_{120'}$), theta, alpha, and beta power increased, which has been suggested to respectively reflect increased mental engagement (34, 37), cardiovascular regulation (106–108), and power output modulation (109). Conversely, theta and alpha power

did not increase during the 70% of LT warm-up of $HIIT_{80'}$ and $TT_{30'}$. While it cannot be excluded that this difference results from the 10% intensity difference, it more likely reflects alterations in exercise duration, as $HIIT_{WU}$ and TT_{WU} values were averaged over the entire WU (*i.e.,* 10- and 15-min, resp.), while ET_{L1} disregards the initial 10 min at 60% of LT. Indeed, when isolating the final minute of both WU periods, theta power increased compared to the respective rest periods, while alpha power remained similar (data not shown). Concerning beta power, an increase was observed with the transition from rest to exercise for HIIT and ET, yet not for $TT_{30'}$, likely reflecting increased arousal or focus with regard to the upcoming time-trial. On the contrary, APF and gamma power did not change upon the transition from rest to low-, medium-, or high-intensity exercise, which is also in line with previous reports (110).

EEG patterns across exercise intensity and recovery

EEG patterns throughout exercise showed distinct behavior for the different exercise protocols (see Table 1). Throughout $ET_{120'}$, alpha power decreased in line with earlier findings observed during 40 minutes of low-effort cycling (70 W) (35), which has been linked to diminished demand of cerebral associations required by the low-effort nature of such low-intensity exercise. Interestingly, gamma brain power increased by ~71% from ET_{H1} towards ET_{L4} and then declined by ~39% from ET_{L4} towards ET_{H4}. Although not previously reported in this context, these data suggest that gamma power reflects the mental effort related to low *vs*. high intensity cycling. Throughout $HIIT_{80'}$, no changes were observed between corresponding first and last repetitions of high- or low-intensity stages, suggesting that participants did not develop mental fatigue throughout $HIIT_{80'}$ or that this was not reflected in their EEG patterns. Nonetheless, theta power substantially increased in the last high-intensity stage of $HIIT_{80'}$ compared to $HIIT_{WU}$, suggesting the development of fatigue throughout $HIIT_{80'}$. This aligns

with earlier findings linking elevated frontal theta power to fatigue during high-cadence, fixed-resistance cycling (38).

Remarkably, theta, alpha, and beta power substantially increased at $TT_{29'-30'}$ compared to $TT_{0'-5'}$, likely reflecting both physical and mental exertion. These findings are consistent with previous studies, identifying theta power as a reliable indicator of mental fatigue (111, 112). This increased power upon exhaustion likely results from enhanced intracortical connectivity that is mediated by an increase in neural workload, leading to improved sensorimotor integration and elevated communication within the motor cortex (113). Nevertheless, this increased power may also simply reflect the higher power outputs during the final minutes (*i.e.*, 122% of LT) compared to the initial phase (*i.e.*, 103% of LT) or result from the expected increase in body temperature (114). Finally, participants were required to actively change their power output at regular timepoints throughout $TT_{30'}$. This cognitive engagement may have further augmented theta, alpha, and beta power throughout $TT_{30'}$, but not $HIIT_{90'}$, where such decision-making efforts were absent.

Immediately following $ET_{120'}$ and $HIIT_{80'}$, EEG power across all frequency bands returned to baseline levels. This pattern is consistent with previous findings reporting an immediate normalization of EEG signals following cessation of low- and moderate-to-high intensity exercise (20%-80% $\dot{V}O_2max$) (115). Conversely, during recovery following $TT_{30'}$, theta, alpha, and gamma power remained elevated, suggesting that the physical and mental fatigue induced by such all-out, maximal intensity exercise persists post-exercise. This finding is consistent with previous research, reporting post-exercise increases in theta and alpha power (34, 116), although such elevations typically dissipate within 10 minutes (34). While the post-exercise gamma response remains largely underreported, a sustained post-exercise elevation following $TT_{30'}$ may reflect the high 'active' exercise load induced by $TT_{30'}$. No changes were

observed for APF, which contrasts with earlier findings showing increased APF following exhaustive cycling at ~192 W (110). As APF is associated with arousal, attention (110), and cognitive processing speed (117), its stability throughout $TT_{30'}$ may reflect differences in task demands or measurement conditions. Nonetheless, these outcomes warrant careful interpretation, as exercise duration and intensity are known to strongly modulate post-exercise EEG responses. Moreover, the inclusion of KE supplementation and hypoxia exposure adds an additional layer of physiological complexity, which may influence EEG-recovery dynamics during and after $HIIT_{80'}$ and $TT_{30'}$, even in the absence of interaction effects. Therefore, subtle or transient effects of KE and hypoxia on EEG outcomes cannot be excluded despite the observation of only main effects of time.

Methodological considerations and limitations

Several methodological considerations must be acknowledged. First, no female participants were included in this protocol, as sleep quality and architecture (*i.e.*, the primary outcomes of the larger research project) substantially vary with hormonal fluctuations (118, 119). Besides, sex primarily affects EEG patterns (120), underpinning the importance of controlled research with minimal variation. Nevertheless, this limitation hampers the generalization of our findings. Another limitation is the absence of a KE condition under normoxia. Including such a condition would have allowed the isolation of the specific effects of KE independent of hypoxia. However, this has already been studied in earlier research from our group (78), and was not the primary focus of our research. Therefore, we did not include a fourth session to minimize participant burden and to reduce study costs. Notably, while EEG is a valuable technique to objectively evaluate mental load and fatigue, it is highly dependent on the adopted protocol and circumstances. For instance, cycling cadence may directly affect cortical parameters, and increases from 60 to 120 rpm have been shown to significantly elevate spectral EEG power in the alpha and beta frequency ranges, while reductions in cadence yield

585 the opposite effect (121). Although our participants were instructed to maintain a cycling
586 cadence around 90 rpm, this was not strictly maintained during each stage of *e.g.*, $HIIT_{80'}$.
587 Moreover, the dry-electrode nature of the Muse 2 headband is more prone to motion artifacts
588 (122) and exhibits higher test-retest variation than medical-grade EEG systems (123).
589 Nevertheless, previous validation studies have reported strong correlations between Muse and
590 research-grade EEG for theta, alpha, and beta frequency bands (r = 0.73-0.87), with only
591 moderate agreement for gamma activity (122). In the present study, EEG signals were band-
592 pass filtered (1-50 Hz), thereby attenuating high-frequency noise and reducing the influence of
593 the gamma band. Despite the application of artifact-mitigation procedures, residual movement-
594 related noise during exercise cannot be fully excluded. Furthermore, the minimal use of only 4
595 electrodes with one additional reference electrode in the Muse 2 headband affects reliability,
596 since previous studies indicated that at least 35 electrodes are required to obtain reliable results
597 in mobile brain imaging (124). Intra-individual EEG variability across the three $ET_{120'}$ sessions
598 was relatively high (coefficient of variation = 0.312 ± 0.203). This is broadly consistent with
599 prior EEG literature (125, 126), and likely attributable to physiological fluctuations and the
600 low-density electrode configuration. Nonetheless, due to its practical, user-friendly design, the
601 Muse 2 device remains valuable in certain situations. Additionally, the relationship between
602 exercise intensity and EEG power is believed to be non-linear. Previous studies have reported
603 reductions in brain activity at the end of incremental exercise testing (127, 128), potentially due
604 to cerebral deoxygenation and the resultant inhibitory processes in the prefrontal cortex at
605 intensities above the ventilatory threshold or respiratory compensation point (129).
606 Furthermore, the conditions under which EEG was recorded during exercise bouts may have
607 influenced the results, as we did not provide standardized instructions regarding eye state during
608 exercise. However, we standardized this (eyes-closed) during resting measurements. Notably,
609 alpha power has been shown to respond differently depending on whether the eyes are open or

closed; studies have reported decreased alpha power during eyes-open hypoxia (47), while a transient increase has been observed under eyes-closed conditions (49). Lastly, core temperature is known to impact the alpha/beta-index, typically increasing due to reduced beta power or amplitude, as temperature rises (130, 131). The controlled environment in the testing facility minimized temperature variations across sessions; however, subtle changes may have persisted and affected EEG outcomes at rest and during exercise.

Conclusions

Our data obtained in healthy males demonstrates, for the first time, that KE ingestion can mitigate hypoxia-induced increases in resting-state EEG power, particularly within the alpha and beta frequency bands. These findings suggest that KE may help modulate neurophysiological responses to hypoxia, potentially contributing to prevention of cognitive decline at the level of EEG dynamics, and supporting both physical performance and cerebral health. Nonetheless, this stabilizing effect of KE on EEG patterns did not translate to improved cognitive function on the next day. While neither KE nor hypoxia affected EEG responses during exercise, our data clearly show that different exercise modalities evoke distinct EEG patterns, with high-intensity efforts producing sustained post-exercise elevations in theta, alpha, and gamma power. Overall, these results highlight the potential of KE to preserve neural stability under hypoxic conditions and underscore EEG's sensitivity to exercise-induced mental and physical fatigue. Moreover, the observation that exercise intensity modulates EEG responses suggests that EEG metrics could provide valuable insights for athlete monitoring and for optimizing training and recovery strategies in both athletic and clinical populations.

ADDITIONAL INFORMATION

Supplementary materials

The MATLAB script used for GLM-based adaptive filtering is available at https://doi.org/10.5281/zenodo.18487316 (archived release of the GitHub repository: https://github.com/sv-rgb-code/GLM-Based-Adaptive-Filtering-of-Muse-2-Electroencephalography-data)

Data availability

Deidentified data will be made available upon reasonable request.

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Disclosures

The authors declare that they have no competing interests.

Author contributions

All experiments were performed within the Exercise Physiology Research Group and the Bakala Academy-Athletic Performance Center at the KU Leuven, Belgium. Conception and design of the study: DM, TD, CP, MS. Data collection and/or data analyses: NV, SV, DT, WL,

RR, MS. Interpretation of the data and manuscript drafting: NV, SV, CP, MS. All authors critically revised the manuscript and approved the final version of the manuscript.

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Figure 1. Schematic visualization of the experimental protocol.

In a double-blind, randomized, crossover design, 12 participants completed three experimental sessions each involving a two-day protocol. On day 1, participants performed a 120-min endurance training ($ET_{120'}$) and an 80-min high-intensity interval training ($HIIT_{80'}$) in normoxia, followed by a night either in normoxia (N) or at a simulated altitude of 3,000 m (hypoxia, H). After each training session, after hypoxic entry, and before sleep, participants received either a placebo (PL, $N_{PL,}$ and H_{PL}) or ketone ester (KE, H_{KE}) drink. On the second day, exercise performance was evaluated through a 30-min all-out time trial ($TT_{30'}$). Electroencephalography (EEG) was assessed at rest and during exercise by a Muse 2 headband, cerebral oxygenation was evaluated at rest using near-infrared spectroscopy, performed i) 0 h, ii) +10 h, iii) +23 h, and iv) +27 h, and cognitive function was evaluated at rest using a cognitive test battery, at i) 0 h and ii) +27 h. Created in BioRender. https://BioRender.com/wu8aidf.

Figure 2. The effects of hypoxia and ketone ester intake on cognitive function.

Data are presented as means (bar plots) ± SD (whisker), as well as individual values (n = 12) for reaction time (RT) outcomes including A) mean movement time (RT-MMT), B) mean reaction time (RT-MRT), and C) number of errors (RT-E), as well as rapid visual information processing (RVP) outcomes including D) median reaction latency (RVP-MRL), E) number of false alarms (RVP-FA), and F) number of hits (RVP-H). After performing a 2-h endurance training ($ET_{120'}$) and an 80-min high-intensity interval training ($HIIT_{80'}$), participants completed a 16-h recovery period, including the night in normoxia (N) or at a simulated altitude of 3,000 m (hypoxia, H). After each training session, after 1.5 h in normoxic/hypoxic recovery, and 30 min before sleep, participants received either a placebo (PL; $N_{PL,}$ and H_{PL}) or ketone ester (KE, H_{KE}) drink. Cognitive function was evaluated using a Cambridge Neuropsychological Test Automated Battery at rest before $ET_{120'}$ (PRE; 0 h relative to start of the experimental session) and 2 h after re-exposure to normoxia (POST: +27 h relative to start of the experimental session or +2 h relative to end of hypoxia). Data were analyzed using a two-way repeated measures ANOVA.

Figure 3. The effects of hypoxia and ketone ester intake on resting EEG power.

Data of electroencephalography (EEG) measurements during rest are presented as means (bar plots) ± SD (whisker), as well as individual data points (n = 12) for A) theta power, B) alpha power, C) alpha peak frequency

(APF), D) beta power, and E) gamma power. After performing a 2-h endurance training ($ET_{120'}$) and an 80-min high-intensity interval training ($HIIT_{80'}$), participants completed a 16-h recovery period, including the night in normoxia (N) or at a simulated altitude of 3,000 m (hypoxia, H). After each training session, after 1.5 h in normoxic/hypoxic recovery, and 30 min before sleep, participants received either a placebo (PL; N_{PL} and H_{PL}) or ketone ester (KE, H_{KE}) drink. Rest measurements were taken i) prior to $ET_{120'}$ (PRE, 0 h), ii) after 2 h in hypoxia or the equivalent duration in normoxia (+10 h), iii) immediately upon waking (+23 h), and iv) 2 h after re-exposure to normoxia (POST, +27 h). Data were analyzed using a two-way repeated measures ANOVA. §, $p < 0.05$ vs N_{PL}; *, $p < 0.05$ for H_{KE} *vs.* H_{PL}.

Figure 4. The effects of endurance training on EEG power.

Data of electroencephalography (EEG) measurements during a 120-min endurance training ($ET_{120'}$) are presented as means (bar plots) ± SD (whisker), as well as individual data points (n = 12) for A) theta power, B) alpha power, C) alpha peak frequency (APF), D) beta power, and E) gamma power. After performing $ET_{120'}$ and an 80-min high-intensity interval training ($HIIT_{80'}$), participants completed a 16-h recovery period, including the night in normoxia (N) or at a simulated altitude of 3,000 m (hypoxia, H). After each training session, after 1.5 h in normoxic/hypoxic recovery, and 30 min before sleep, participants received either a placebo (PL; N_{PL} and H_{PL}) or ketone ester (KE, H_{KE}) drink. Data were analyzed using a two-way repeated measures ANOVA. a, $p < 0.05$ *vs.* ET_{BL}; b, $p < 0.05$ *vs.* ET_{L1}; c, $p < 0.05$ *vs.* ET_{H1}; d, $p < 0.05$ *vs.* ET_{L4}.

Figure 5. The effect of high-intensity interval training on EEG power.

Data of electroencephalography (EEG) measurements during an 80-min high-intensity interval training ($HIIT_{80'}$) are presented as means (bar plots) ± SD (whisker), as well as individual data points (n = 12) for A) theta power, B) alpha power, C) alpha peak frequency (APF), D) beta power, and E) gamma power. After performing a 2-h endurance training ($ET_{120'}$) and $HIIT_{80'}$, participants completed a 16-h recovery period, including the night in normoxia (N) or at a simulated altitude of 3,000 m (hypoxia, H). After each training session, after 1.5 h in normoxic/hypoxic recovery, and 30 min before sleep, participants received either a placebo (PL; N_{PL} and H_{PL}) or ketone ester (KE, H_{KE}) drink. Data were analyzed using a two-way repeated measures ANOVA. a, $p < 0.05$ *vs.* $HIIT_{BL}$; b, $p < 0.05$ *vs.* $HIIT_{WU}$; c, $p < 0.05$ *vs.* $HIIT_{H1}$; d, $p < 0.05$ *vs.* $HIIT_{L1}$; e, $p < 0.05$ *vs.* $HIIT_{H10}$; f, $p < 0.05$ *vs.* $HIIT_{L10}$.

Figure 6. The effect of an all-out time trial on EEG power.

Data of electroencephalography (EEG) measurements during a 30-min time trial ($TT_{30'}$) are presented as means (bar plots) ± SD (whisker), as well as individual data points (n = 12) for A) theta power, B) alpha power, C) alpha peak frequency (APF), D) beta power, and E) gamma power. After performing a 2-h endurance training ($ET_{120'}$) and an 80-min high-intensity interval training ($HIIT_{80'}$), participants completed a 16-h recovery period, including the night in normoxia (N) or at a simulated altitude of 3,000 m (hypoxia, H), whereafter they performed $TT_{30'}$. After each training session, after 1.5 h in normoxic/hypoxic recovery, and 30 min before sleep, participants

received either a placebo (PL; N_{PL} and H_{PL}) or ketone ester (KE, H_{KE}) drink. Data were analyzed using a two-way repeated measures ANOVA. a, $p < 0.05$ *vs.* TT_{BL}; b, $p < 0.05$ *vs.* TT_{WU}; c, $p < 0.05$ *vs.* $TT_{5'\text{-}10'}$.

Table 1. Overview: changes in EEG power during transitions in different exercise bouts

Exercise onset = Transition from baseline to exercise; Recovery = Transition from exercise to recovery

Overview of changes in EEG power [Theta, Alpha, Alpha Peak Frequency (APF), Beta, and Gamma] measured by electroencephalography (EEG) during different exercise bouts: i) endurance training ($ET_{120'}$), ii) high-intensity interval training ($HIIT_{80'}$), and iii) time trial ($TT_{30'}$). Each exercise bout is represented across three stages: i) exercise compared to baseline, ii) change during exercise, and iii) recovery compared to exercise. Arrows indicate the direction of change: increase (↑), decrease (↓), bidirectional changes (↑|↓), and compared to baseline ($\uparrow_{BL}$).

Figure 7. Effect of nocturnal hypoxia and ketone ester (KE) ingestion on cerebral oxygenation.

During a randomized, cross-over trial, participants (n = 12) received either ketone ester (KE) or placebo (PL) supplements, while performing their post-exercise recovery period either in normoxia (N_{PL}) or at a simulated altitude of 3,000 m (H_{PL} and H_{KE}). Participants' cerebral tissue oxygenation index (cTOI) was evaluated using near-infrared spectroscopy at baseline (0 h relative to the start of the experimental session), after 2 h in normoxia/hypoxia (+10 h relative to the start of the experimental session), on the next morning in normoxia/hypoxia (+ 23 h relative to the start of the experimental session), and 2 h after returning to normoxia (+27 h relative to the start of the experimental session). Data were analyzed using a two-way repeated measures ANOVA. §, $p < 0.05$ vs. N_{PL}; *, $p < 0.05$ for H_{KE} vs. H_{PL}.