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Effects of serotonergic pharmacological manipulation on exercise performance and central fatigue: a systematic review and three-level meta-analysis

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ABSTRACT

Background: Exercise-induced fatigue is a complex, non-pathological state that acutely limits physical performance, and the serotonergic (5-HT) system has been proposed as an important modulator of its central components. This systematic review and meta-analysis aimed to clarify the effects of serotonergic pharmacological manipulation on exercise-related outcomes.

Methods: Following PRISMA guidelines, we systematically searched PubMed, Scopus, Web of Science, Cochrane Central, and SportDiscus from inception to August 2025. Randomized controlled trials examining the effects of serotonergic pharmacological manipulation on exercise-related outcomes in healthy adults were included. Study selection, data extraction, and risk-of-bias assessment using RoB 2.0 were conducted independently. Pooled effects were synthesized using three-level random-effects models, and the certainty and robustness of the evidence were examined in additional analyses.

Results: Twenty-one randomized controlled trials involving 248 healthy adults were included in the systematic review, of which 19 studies involving 229 participants were included in the meta-analysis. In the primary models, serotonergic pharmacological manipulation was associated with small reductions in evoked motor response (Hedges' g = −0.24, 95% CI −0.46 to −0.02), time-domain EMG (Hedges' g = −0.18, 95% CI −0.33 to −0.02), heart rate (Hedges' g = −0.17, 95% CI −0.34 to −0.01), and blood glucose (Hedges' g = −0.50, 95% CI −0.89 to −0.11). Voluntary activation showed a borderline negative pooled estimate (Hedges' g = −0.20, 95% CI −0.40 to 0), whereas ratings of perceived exertion showed a positive but statistically uncertain pooled estimate (Hedges' g = 0.63, 95% CI −0.01 to 1.28). Resting twitch torque showed a small positive pooled effect (Hedges' g = 0.12, 95% CI 0.04 to 0.19), whereas superimposed twitch torque, maximal voluntary contraction, prolactin, lactic acid, and time to task failure did not show clear overall effects.

Conclusions: Overall, this meta-analysis indicates that serotonergic pharmacological manipulation has outcome-specific effects on exercise-related fatigue rather than a single uniform influence across domains. The most consistent primary-model signals were found for evoked motor response, time-domain EMG, heart rate, and blood glucose, whereas overt performance and perceptual outcomes remained more variable. By integrating evidence across different serotonergic interventions and exercise paradigms, these findings improve our understanding of how 5-HT-related mechanisms may contribute to central fatigue during exercise.

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KEYWORDS
5-HT; pharmacological manipulation; exercise performance; central fatigue; meta-analysis

1. Introduction

Exercise-induced fatigue is a transient, non-pathological state that limits physical performance and increases the perceived effort required to sustain exercise. It refers to an acute impairment of exercise performance that includes both an increased perceived effort to produce a given force or power and the eventual inability to produce that force or power output [1]. Fatigue is best viewed as a multifactorial condition, influenced by an

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interplay of both peripheral and central mechanisms [2]. Peripheral fatigue is a decline in force-generating capacity due to processes at or distal to the neuromuscular junction, essentially reflecting fatigue within the muscle. It arises from factors such as impaired neuromuscular transmission, substrate depletion, acidosis, and altered sarcoplasmic reticulum Ca^{2+} handling, which together reduce muscle power output [3]. The mechanisms of peripheral fatigue are now well delineated; however, central fatigue presents a greater challenge, with many questions regarding its fundamental mechanisms still unresolved. One current and widely held hypothesis of central fatigue is the neurotransmitter hypothesis, in which the balance of neurotransmitters (serotonin [5-hydroxytryptamine; 5-HT], dopamine [DA], and norepinephrine [NE]) influences thermoregulation, motor impulses, and sensations of fatigue, thus contributing to central control of the duration and intensity of exercise [2,4]. Of these neurotransmitters, 5-HT has been the most studied with specific reference to central fatigue, and numerous studies have explored its involvement in regulating perceived exertion, motor performance, and the development of fatigue during exercise [3,5].

The 5-HT has been suggested as an important modulator of mood, emotion, sleep, and appetite [6,7]. The central fatigue hypothesis suggests that an increase in central serotonergic activity is detrimental to the performance of prolonged exercise [4]. This occurs because sustained physical activity alters circulating substrate concentrations, which increases tryptophan availability and amplifies central 5-HT activity, ultimately heightening perceived exertion and hastening fatigue onset. Previous work in the animal models has elucidated a potential cellular mechanism of central fatigue whereby 5-HT modulates motoneuron excitability [8]. During muscle activation, brief focal stimulation promotes the release of 5-HT onto motoneurons, which subsequently enhances motoneuron excitability by activating excitatory 5-HT2 receptors (5-HT2R), thereby facilitating neuronal firing [9]. However, when stimulation is prolonged to mimic sustained exercise, high 5-HT levels spill over and activate inhibitory 5-HT1A receptors (5-HT1AR) at the axon initial segment, where their activation inhibits the Na^+ current responsible for spike initiation and consequently reduces motoneuron output [10].

The contribution of serotonergic manipulation to the regulation of exercise performance and fatigue has been investigated in humans using pharmacological tools. It was demonstrated that acute enhancement of 5-HT via selective serotonin reuptake inhibitors (SSRIs) (paroxetine, fluoxetine, and citalopram) or a 5-HT receptor agonist (buspirone) often failed to improve endurance performance, while in several cases, a reduction in time to exhaustion or maximal exercise tolerance has been observed, despite unchanged peripheral metabolic responses [11–14]. Some SSRI ingestion altered endocrine profiles [15,16], but these shifts rarely aligned with exercise performance. Moreover, reducing 5-HT level, such as blocking 5-HT2A/2C (ritanserin and pizotifen), did not reliably prolong cycling performance, though modest thermoregulatory and endocrine shifts were observed [17–19]. Research extended beyond endurance performance to investigate the effects of serotonergic modulation on central motor drive and contractile function. In brief isometric tasks, paroxetine suppressed physiological tremor and improved force steadiness at multiple intensities [20] and did not affect peak maximal voluntary contraction (MVC) torque [21]. 5-HT2R antagonist cyproheptadine reduced motor-unit discharge rate and rate of torque development [22]. During sustained and moderate intensity isometric contractions, paroxetine did not change torque or voluntary activation (VA) but increased perceived fatigue and shortened the TMS silent period [23]; conversely, cyproheptadine reduced superimposed twitch amplitude [24]. Under submaximal and maximal isometric contractions, paroxetine reduced VA and shortened the silent period [20], and decreased maximal voluntary torque and increased the rating of perceived exertion (RPE) [25]. Across agents and protocols, findings were mixed, with some trials reporting performance decrements and many showing no significant change, leaving the utility of pharmacologically altering 5-HT availability for improving exercise performance uncertain.

Therefore, our aim in this systematic review and meta-analysis is to evaluate how serotonergic manipulation influences endurance performance, neuromuscular outcomes, and perceived fatigue by synthesising effect sizes across studies, quantifying between-study heterogeneity, and examining prespecified moderators (e.g. drug, exercise type, protocol, and contraction intensity or duration). Specifically, we aimed to integrate data on endurance performance (e.g. time to task failure), muscular contraction function (e.g. MVC and VA), perceptual responses (e.g. RPE), and endocrine markers. To our knowledge, this is the first study to systematically integrate evidence across serotonergic pharmacological manipulations and multiple exercise tasks, providing a more comprehensive understanding of how 5-HT–related mechanisms may influence exercise performance and exercise-induced central fatigue.

2. Methods

We conducted and reported this systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The completed PRISMA 2020 checklist can be found in Table S1. The study has been a priori registered in PROSPERO (CRD420251125795).

2.1. Information sources and search strategy

A systematic literature search was conducted independently by two researchers (Guan and Han) until August 4th, 2025, in the following electronic databases: PubMed, Scopus, Web of Science, Cochrane Central, and SportDiscus. Our search strategy is described in detail in Table S2. In addition, we screened the reference lists of the selected articles as well as the authors' bibliographies. Finally, we searched Google Scholar with the same search terms in order to control for potentially overlooked relevant articles.

2.2. Eligibility criteria

Inclusion criteria were established using the PICOS model (Population, Intervention, Comparison, Outcome, Study type) [26]. Thus, articles were included if they met the following criteria: (a) included human adults (≥18 years) who are free from diagnosed neurological, psychiatric, cardiovascular, or musculoskeletal disorders that could affect exercise performance or fatigue; (b) orally administered a drug that acts on the serotonin system or a placebo before the formal experiment began;(c) measured exercise performance and central fatigue by rating of perceived exertion (RPE), time to task failure, muscle maximal voluntary contraction (MVC), voluntary activation (VA), resting twitch torque, superimposed twitch torque, time-domain electromyogram (EMG), evoked motor response, heart rate, prolactin, lactic acid, or blood glucose; (d) the full text was available in English; and (e) were RCTs. Reviews, conference abstracts, and editorials were not included. Studies that did not meet these criteria were excluded.

2.3. Selection process and data collection

Selected search terms related to '5-HT', 'fatigue', and 'exercise' were combined in Boolean logic. The articles identified in each source were combined in a single database, and duplicates were eliminated with EndNote X9 software (Clarivate, The EndNote Team, Pennsylvania, USA). The article selection process was carried out independently by two reviewers (Guan and Han), and any discrepancies were resolved by consulting a third reviewer (Fan). Initially, the titles and abstracts were all screened, and studies that clearly did not meet the inclusion criteria were discarded. The remaining studies were then retrieved from the full text, and finally, those meeting the inclusion criteria were included.

From the included studies, the following data were independently extracted by two authors (Guan and Han), and any discrepancies were resolved by consulting a third reviewer (Fan): general information (e.g. first author's name and year), participants (e.g. number of subjects and age), intervention (e.g. drug type and dosage), measurement methods (e.g. device, time, and sample rate), and outcomes (RPE, time to task failure, MVC, VA, resting twitch torque, superimposed twitch torque, time-domain EMG, evoked motor response, heart rate, prolactin, lactic acid, or blood glucose). Time-domain EMG refers only to voluntary surface electromyography recorded during active contractions, including amplitude-based measures (e.g. RMS EMG, EMG amplitude, normalised EMG amplitude) and integrated measures (e.g. EMG area). Evoked motor response refers to stimulation-evoked measures of corticospinal or motoneuronal excitability, including TMS-derived motor evoked potentials (MEPs) and cervicomedullary motor evoked potentials (CMEPs). For data extraction, if data were missing or only presented graphically, authors were contacted to request the necessary information. If this contact attempt was unsuccessful, and the data were available only in graphical form, relevant data were extracted using GetData Graph Digitiser.

2.4. Assessment of certainty of evidence

Two researchers (Guan and Han) independently conducted a quality assessment, following the Cochrane Collaboration's tool for assessing the risk of bias (RoB 2.0 tool) [27]. Any disagreement was resolved through discussion, and if a consensus could not be reached, a third reviewer (Fan) was consulted. The RoB 2.0 tool covers bias in six domains: randomisation process, bias arising from period and carryover effects, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Overall, a trial was considered at 'low risk of bias' if all domains were judged as 'low risk', 'some concerns' if there was at least one domain rated as having 'some concerns', and 'high risk of bias' if there was at least one domain judged as 'high risk'. Certainty of evidence was also assessed using the GRADE framework across the domains of risk of bias, inconsistency, indirectness, imprecision, and publication bias. Starting from high certainty for randomised trials, ratings were downgraded when concerns were identified in one or more of these domains. These assessments were conducted independently by two reviewers (Han and Guan), with any discrepancies resolved through discussion.

2.5. Statistical analysis

2.5.1. Effect measure

As all studies included in this meta-analysis used a crossover design, effect sizes were calculated as standardised mean changes (SMC) in R with the metafor package [28] using measure = "SMCC". This metric is suitable for paired or repeated-measures data because it standardises the mean difference between the experimental and control conditions by the standard deviation of the within-subject change scores [29].

To account for small sample bias, Hedges' g was calculated as [29,30]:

$$\text{Hedges' } g = \frac{M_{exp} - M_{con}}{SD_{change}} \times \left(1 - \frac{3}{4(n-1)-1}\right)$$

where M_{exp} and M_{con} are the means of the experimental and control conditions, respectively, n is the sample size, and SD_{change} is the standard deviation of the within-participant difference scores, calculated as [31]:

$$SD_{change} = \sqrt{SD_1^2 + SD_2^2 - 2rSD_1SD_2}$$

where SD_1 and SD_2 are the standard deviations of the two conditions and r is the within-subject correlation coefficient. Under the SMCC approach, r affects both the effect size estimate and its sampling variance. Because most studies did not report sufficient information to derive the standard deviation of the paired differences, r was imputed following the Cochrane Handbook guidance for approximate analyses of crossover trials. The primary analysis assumed $r = 0.8$, and sensitivity analyses using alternative plausible values were conducted to examine the robustness of the results.

Hedges' g was categorised as trivial (0–0.19), small (0.2–0.49), moderate (0.50–0.79), and large (≥ 0.80) [32].

2.5.2. Data synthesis

Because all included studies employed a crossover design, participants contributed data under multiple interventions, yielding multiple effect sizes per study. Conventional meta-analytic models assume independence among effect sizes; therefore, treating multiple comparisons from the same study as independent may lead to double-counting of some participants and consequently bias the pooled estimates [33]. Accordingly, multilevel meta-analysis was conducted using the metafor package in R to account for within-study dependence when synthesising outcomes [28]. In the three-level random-effects model, variance was partitioned into three components: sampling error (Level 1), within-study variance (Level 2), and between-study variance (Level 3). Parameters were estimated using restricted maximum likelihood (REML). Pooled effects were reported as point estimates with 95% confidence intervals, and statistical significance was set at $p < 0.05$.

To characterise heterogeneity, we calculated total I^2 and its level-specific components (within-study and between-study) as descriptive indices of variance partitioning. Because I^2 does not directly quantify the absolute dispersion of true effects, we did not interpret I^2 using fixed thresholds such as low, moderate, or high heterogeneity. Instead, prediction intervals (PI) were reported and used as the primary basis for interpreting heterogeneity, as they indicate the range of plausible true effects across comparable studies and whether that range crosses the null [34,35].

2.5.3. Moderator analyses

To investigate potential sources of heterogeneity, moderator analyses were performed using subgroup analyses for categorical variables and meta-regression for continuous variables.

For neuromuscular outcomes with sufficient methodological detail, namely evoked motor response, voluntary activation (VA), time-domain electromyography (EMG), superimposed twitch torque, maximal voluntary contraction (MVC), and resting twitch torque, subgroup analyses were conducted according to drug category, exercise-performance type, participants' training level, stimulation modality, task intensity, and muscle group.

For heart rate, prolactin, blood glucose, time-based endurance performance outcomes, rating of perceived exertion (RPE), and lactic acid, subgroup analyses were limited to drug category, exercise-performance type, and participants' training level, because stimulation modality, task intensity, and muscle group were either not consistently applicable or not extractable across these outcomes.

Because several included studies involved repeated within-session trials, we defined a variable termed *relative trial position (%)* as a potential moderator. To improve comparability across studies with different numbers of trials, this variable was normalised within each study as $(k/K) \times 100\%$, where k is the trial number and K is the total number of trials; studies including only a single trial without repeated measurements were coded as 0%. A mixed-effects meta-regression was then conducted using REML, with Hedges' g as the dependent variable and within-session trial position (%) as a fixed-effect moderator. Regression coefficients and their 95% confidence intervals were reported, and Wald tests were used to assess statistical significance ($p < 0.05$). In addition, marginal R^2 and conditional R^2 were calculated using the orchard package to quantify the variance explained by the moderator and by the full model, respectively [36].

2.5.4. Publication bias and sensitivity analyses

Potential publication bias was assessed using contour-enhanced funnel plots and a multilevel Egger-style regression test [37–39]. Funnel plot asymmetry was evaluated by visual inspection. Because multiple effect sizes were nested within studies, the regression-based test for small-study effects was implemented within a three-level mixed-effects meta-regression framework, with a sample-size-based precision term included as the predictor and random effects specified at the study and effect-size levels [38,39]. A statistically significant regression coefficient ($p < 0.05$) was interpreted as evidence of potential small-study effects.

Sensitivity analyses were conducted using three complementary approaches. First, potential outliers were identified at the effect-size level. At the effect-size level, externally studentized residuals were calculated for each effect size, and effect sizes with $|z| > 1.96$ were considered potential outliers [40]. Second, a meta-analytic analogue of the non-affirmative studies approach was performed [41]. The direction of the pooled standardised mean change from the main three-level meta-analysis was first used to define the hypothesised effect direction. Effect sizes were classified as affirmative if they were statistically significant ($p < 0.05$) and in the same direction as the pooled main effect, whereas all remaining effect sizes were classified as non-affirmative. The three-level meta-analytic model was then refitted using only the non-affirmative effect sizes. This analysis was performed only when at least two non-affirmative effect sizes from at least two studies were available. Third, a publication-bias-adjusted Bayesian multilevel meta-analysis was conducted using the RoBMA package [42]. Observed effect sizes and their corresponding standard errors were entered into the model, with study specified as the clustering variable to account for dependence among multiple effect sizes from the same study. Posterior estimates of the overall effect and prediction interval from the adjusted model were reported.

Finally, additional sensitivity analyses were conducted using SMCC with alternative assumed within-subject correlation coefficients ($r = 0.2$ and $r = 0.5$) to examine the robustness of the results to different

correlation assumptions. In addition, robust variance estimation (RVE) [43] models were fitted using alternative working within-study correlation parameters ($\rho = 0.2$, 0.5, and 0.8) to evaluate the robustness of the pooled estimates to different assumptions about effect-size dependence.

3. Results

3.1. Study selection

Our search produced 2408 records (Figure 1), of which 1050 duplicates were removed, resulting in 1358 potentially relevant articles to be identified. After applying the inclusion criteria to titles and abstracts, we reviewed 51 full-text articles, 14 of which were review articles. We excluded these from data extraction, as with 16 other articles, which were excluded for various reasons such as animal studies, inappropriate population, pharmacological interventions containing non-serotonin drugs, or studies containing no drugs. Finally, 21 intervention trials were included in this study (Table 1). Two studies (No.12 and No.20) were excluded from the meta-analysis because the required outcome data were not reported despite our attempts to contact them, and could not be obtained by using GetData Graph Digitiser.

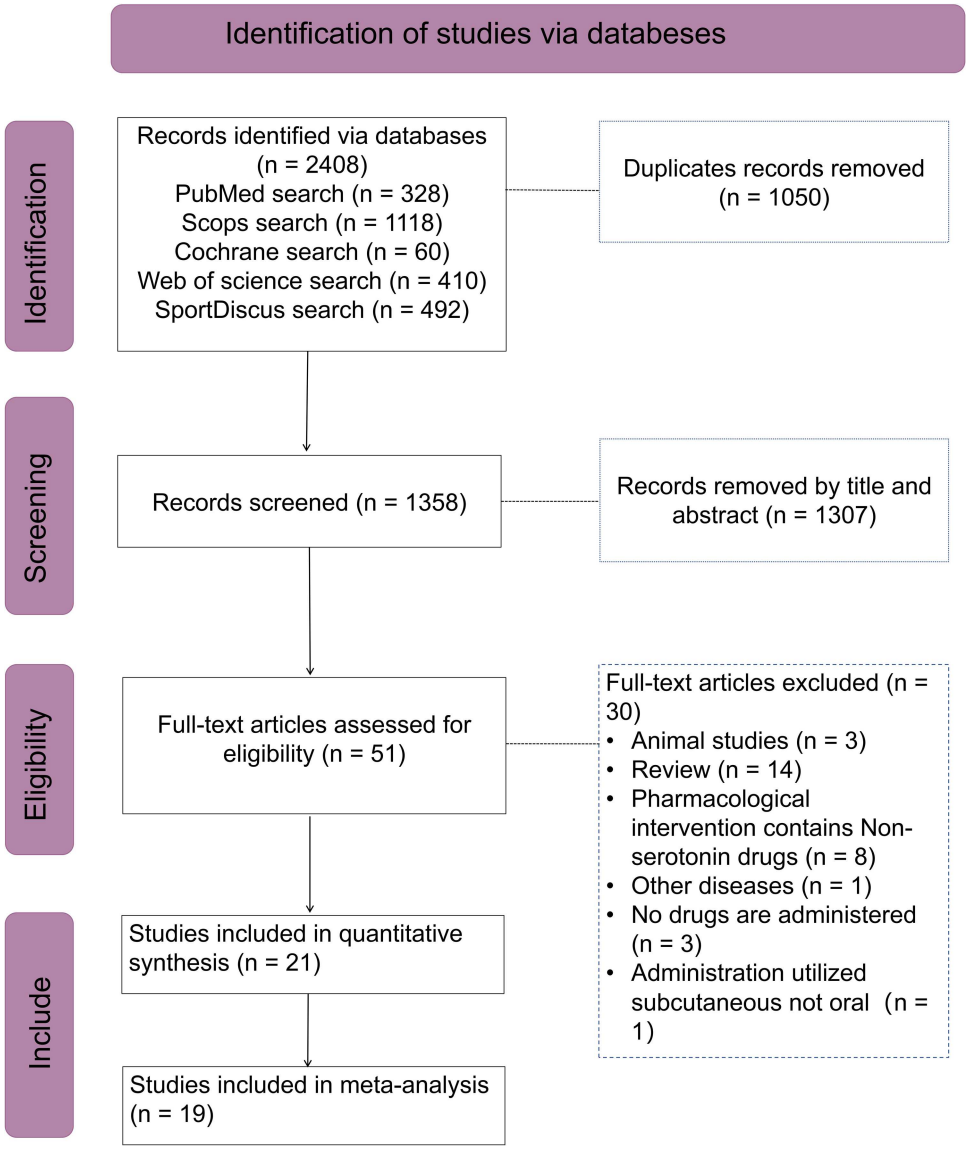

Figure 1. Flow diagram of study selection process for meta-analysis.

Table 1. Characteristics of included studies in the meta-analysis.

No.	Author	Population	Pharmacology	Protocol	Outcomes
1	G. Marvin et al. [13]	13 active males (Age: 23 ± 6)	Selective partial agonist for the 5-HT1AR (Buspirone, 45 mg)	Electrically braked cycle ergometer at 80% VO_2max until volitional fatigue	Time-trial performance; RPE; Serum prolactin; Heart rate; Lactic acid; Glucose
2	J. M. D'Amico et al. [44]	10 healthy adults (4 females, Age: 33 ± 12)	Selective partial agonist for the 5-HT1AR (Buspirone, 20 mg)	Maximal effort elbow flexions and brief elbow flexions at 20%, 40%, 60%, and 80% of peak MVC torque (5 contractions were performed for each contraction intensity)	CMEPs
3	J. J. Kavanagh et al. [25]	15 healthy individuals (7 female, Age: 24 ± 7)	SSRI (Paroxetine, 20 mg)	Exp. 1: 12 sub maximal isometric elbow flexions separated by 40-s rests; Exp. 2: 12 maximal isometric elbow flexions separated by 40-s rest	Peak MVC torque; Motor point resting twitch; The areas of MEP; Superimposed twitch
4	B. Roelands et al. [47]	11 healthy, trained male cyclists or triathletes (Age: 23 ± 5)	SSRI (Citalopram, 20 mg)	18 °C & 30 °C: 60 min constant load cycling at 55% Wmax, Immediately followed by a time trial to complete a fixed amount of work (Equivalent to 30 min at 75% Wmax) as fast as possible	Heart rate; Cortisol; Prolactin; β-endorphin; RPE
5	F. Teixeira-Coelho et al [14].	16 healthy physically active young men (Age: 24 ± 1)	SSRI (Paroxetine, 10, 20, or 40 mg)	Cycling at 60% of maximal power output until volitional fatigue (Unable to maintain power, RPE = 20, or request to stop)	Total exercise time; Core temperature; Skin temperature; Lactic acid; Glucose; Serum prolactin; RPE
6	J. L. Pannier et al. [18]	8 healthy young men (Age:22 ± 1)	5-HT2R antagonist (Pizotifen, 1 mg)	Treadmill running at a constant intensity corresponding to 70% of maximal oxygen uptake (VO_2max) until volitional exhaustion	Time to exhaustion; Heart rate; Lactic acid; Glucose; Amino acids; Ammonia; Haematocrit; RPE
7	D. Dwyer et al. [48]	20 sedentary young men (Age: 20–30)	5-HT agonist (Buspirone hydrochloride, 60 mg)	3 × 30 min/week cycling at 70% VO_2peak	Peak oxygen Consumption; Prolactin; Endurance time
8	A. T. Strachan [19]	7 endurance-trained individuals (6 males, 1 female, Age: 33 ± 9)	5-HT2R antagonist (Pizotifen, 1.5 mg)	40-km cycling time trial on a static ergometer in a climatic chamber to complete the distance as fast as possible (35.5 °C, 32% relative humidity).	Time-trial performance; Rectal temperature; Serum prolactin; Cortisol; Plasma glucose; Lactate; RPE
9	G. Parise et al. [45]	23 healthy, college-aged male athletes (Age:21.6 ± 3.6)	SSRI (Fluoxetine, 40 mg)	Cycle ergometer test at 80%-90% of VO_2max until exhaustion	MVC; Evoked peak twitch torque; Time to exhaustion; Wingate test performance;
10	A. T. Strachan [46]	8 active male cyclists (Age: 38 ± 3)	SSRI (Paroxetine, 20 mg)	Cycling in a climatic chamber at 32 °C, 60% humidity. Intensity set at 60% of VO_2max until volitional fatigue (Inability to continue or maintain > 60 rpm)	Heart rate; Serum prolactin; Cortisol; Plasma glucose; Lactic acid; RPE
11	M. F. Piacentini et al. [16]	7 healthy well-trained male cyclists (Age: 23 ± 1.7)	Selective serotonin/noradrenaline reuptake inhibitor (Venlafaxine, 75 mg)	Cycling time-trial to complete a fixed "target work" (≈ Equivalent to-90 min at 65% Wmax) as fast as possible	Time-trial performance; RPE; Lactic acid; Heart rate; Adrenocorticotropic hormone/β-endorphin/cortisol; Prolactin
12	H. K. Strüder et al. [12]	10 endurance-trained male cyclists (Age: 25.5 ± 2.1)	SSRI (Paroxetine, 20 mg)	Cycled to exhaustion on an ergometer at a fixed workload (256 ± 19.5W, corresponding to 2.0 mmol/L blood lactate from prior incremental test)	Time to exhaustion; Heart rate; Lactic acid; Glucose; Prolactin; Norepinephrine; Epinephrine
13	H. Weicker et al. [49]	10 endurance-trained male cyclists (Age: 25.5 ± 2.1)	SSRI (Paroxetine, 20 mg)	Cycling to exhaustion at fixed workload (256 ± 19.5 W, corresponding to 2.0 mmol/L blood lactate)	Time-to-exhaustion; Kullback-Leibler divergence scores
14	R. Meeusen et al. [15]	8 well-trained male cyclists (Age: 22.1 ± 2.7)	SSRI (Fluoxetine hydrochloride, 40 mg)	90-minute cycling time trial at 65% of maximal power output	Time to complete the preset amount of work; Prolactin; Cortisol; Glucose; RPE
15	W. M. Wilson et al. [11]	7 active male athletes (Age: 43 ± 6)	SSRI (Paroxetine, 20 mg)	Cycling on an ergometer at 70% of VO_2max until volitional exhaustion	Time to exhaustion; RPE;
16	J. R Thorstensen et al. [23]	10 healthy adults (4 female, Age: 22.3 ± 2.1)	SSRI (Paroxetine, 20 mg)	Isometric elbow-flexor model with two blocks: (Exp1) unfatigued baseline assessments; (Exp2) a sustained 30-min elbow flexion at 15% MVC with repeated brief MVCs and recovery testing	Torque; Biceps/Triceps electromyography (Root mean square); MEP; Transcranial magnetic stimulation-evoked Silent Period; VA

(*Continued*)

Table 1. (*Continued*)

No.	Author	Population	Pharmacology	Protocol	Outcomes
17	T. Henderson et al. [20]	12 healthy individuals (5 females, Age: 24 ± 3) 10 healthy individuals (2 females, Age: 27 ± 5)	SSRI (Paroxetine, 20 mg)	Isometric elbow flexion. Exp 1: brief 10% & 60% MVC, brief MVC, sustained MVC to 60% MVC; Exp 2: twelve 2-min contractions at 20% MVC with brief MVCs between blocks	Physiological tremor (8–12 Hz peak power); Coefficient of variation (CV) of force/ steadiness; EMG; Maximal torque
18	R. Meeusen et al. [17]	7 moderately trained male (Age: 21.4 ± 2.5)	5-HT2A/2CR antagonist (Ritanserin, 0.3 mg/kg)	Three exhaustive cycling trials at 65% Wmax	Time to exhaustion; Resting heart rate; Lactate; Growth hormone; Glucose; Haematocrit; RPE
19	J. R. Thorstensen et al. [24]	10 healthy adults (2 female, Age: 24.2 ± 1.9)	5-HT2R antagonist (Cyproheptadine, 8 mg)	Exp1: stimulus-response curves during very weak elbow flexions (10% of maximal). Exp2: TMS at a fixed intensity during elbow flexions of 20%, 40%, 60%, 80%, and 100% of maximal.	MEP amplitude; Maximal torque; Silent period; Superimposed twitch; MEP amplitude during voluntary contractions
20	B. I. Goodlich et al. [22]	9 healthy adults (4 female, Age: 23.7 ± 2)	5-HT2R antagonist (Cyproheptadine, 8 mg)	Maximally dorsiflex until their torque declined to 60% of their baseline MVC	Rate of torque development; Motor unit discharge rate
21	T. Henderson et al. [21]	17 healthy individuals (3 females, Age: 26 ± 4)	SSRI (Paroxetine, 20 mg)	Exp1: steady contractions at 10%, 60%, MVC, and sustained MVC. Exp2: repeated 2-min contractions at 20% MVC with brief MVCs between blocks.	Peak MVC torque; Motor cortical/ point superimposed twitch; Motor cortical/point VA

3.2. Study characteristics

The 21 included studies had a publication date range of 1992–2022. All of the included studies were crossover, randomised designs. The extracted data from the included studies are presented in Table 1. 248 healthy participants were involved in the 21 trials, comprising 32 women and 216 men. The sample size ranged from 7 to 23 participants per study. 13 studies consisted entirely of male participants, and 8 studies consisted of both males and females. 3 studies used 5-HT receptor agonist and 13 studies used 5-HT reuptake inhibitor to enhance serotonergic drive, 5 studies used 5-HT receptor antagonist to inhibit/block 5-HT signalling. 14 studies evaluated endurance performance and motor-output/control, and 8 centred on corticospinal excitability.

To characterise the effects of different serotonin drugs for healthy adults, this study conducted a meta-analysis of the following outcome measures. Across the trials, evoked motor response was obtained at rest and/or during low-to-moderate isometric elbow-flexor contractions to quantify changes in corticospinal or motoneuronal excitability under 5-HT manipulation [21,23,24,44]. Across the trials that reported VA [21,23,25,45], VA was estimated from twitch interpolation during brief maximal elbow-flexor contractions to quantify 5-HT–dependent changes in central motor drive. Across the time-domain EMG-reporting trials [20,21,23–25], time-domain EMG from the muscle was recorded during brief maximal and sustained submaximal isometric contractions, then rectified and averaged (RMS) to quantify changes in muscle activation under different 5-HT manipulations. In the included neurophysiological trials [21,23–25,45], superimposed twitch torque was elicited by transcranial magnetic stimulation of the motor cortex and/ or electrical stimulation of the brachial plexus or motor point during brief maximal voluntary contractions. In the trials that reported MVC [20,21,23–25,45], MVC torque of the elbow flexors was assessed during brief maximal isometric efforts to quantify changes in overall force-generating capacity under different 5-HT manipulations. In the trials that reported resting twitch torque [21,23,25,45], brief electrically or TMS-evoked twitches of the relaxed elbow flexors (or twitches estimated from the interpolation procedure) were used to derive an estimated resting twitch, which served to calculate VA and to help distinguish central from peripheral components of fatigue under 5-HT manipulation. In the endurance trials that reported heart rate [16,17,19,46,47], heart rate was monitored continuously or at fixed intervals during exercise and analysed as mean or peak values to assess the chronotropic response under different 5-HT manipulations. Across the included trials [11,16–19,44,46–48], prolactin, blood glucose, and lactic acid were assessed from venous blood samples collected at rest, during exercise, and/or during post-exercise recovery to characterise endocrine and metabolic responses to 5-HT–modulating interventions. In the trials that reported RPE

[13,15,16,18,19,25,46], RPE was assessed using the Borg scale and recorded at fixed intervals during exercise (and, in some studies, at task termination) to quantify subjective effort under different 5-HT manipulations. Across the included endurance trials [11,14,17,25,45,49], exercise tolerance was quantified as time to task failure or time to exhaustion during constant-load cycling or running, or as the completion time of a fixed-distance time trial.

3.3. Assessment of certainty of evidence

The domain-level RoB 2 assessment showed that the risk of bias was not evenly distributed across the six assessed domains (Figure 2). The domains of randomisation process (D1), bias arising from period and carryover effects (DS), deviations from the intended interventions (D2), and missing outcome data (D3) were judged most favourably, with all included studies rated as low risk in these domains. By contrast, concerns were concentrated in measurement of the outcome (D4), in which three studies were judged to be at high risk, whereas the remaining studies were rated as low risk. In addition, selection of the reported result (D5) was judged as presenting some concerns in all 21 studies, indicating a consistent limitation related to outcome reporting across the evidence base. Consistent with these findings, the GRADE assessment (Table S3) showed that the certainty of evidence was predominantly low to very low across outcomes. Certainty was rated as moderate only for resting

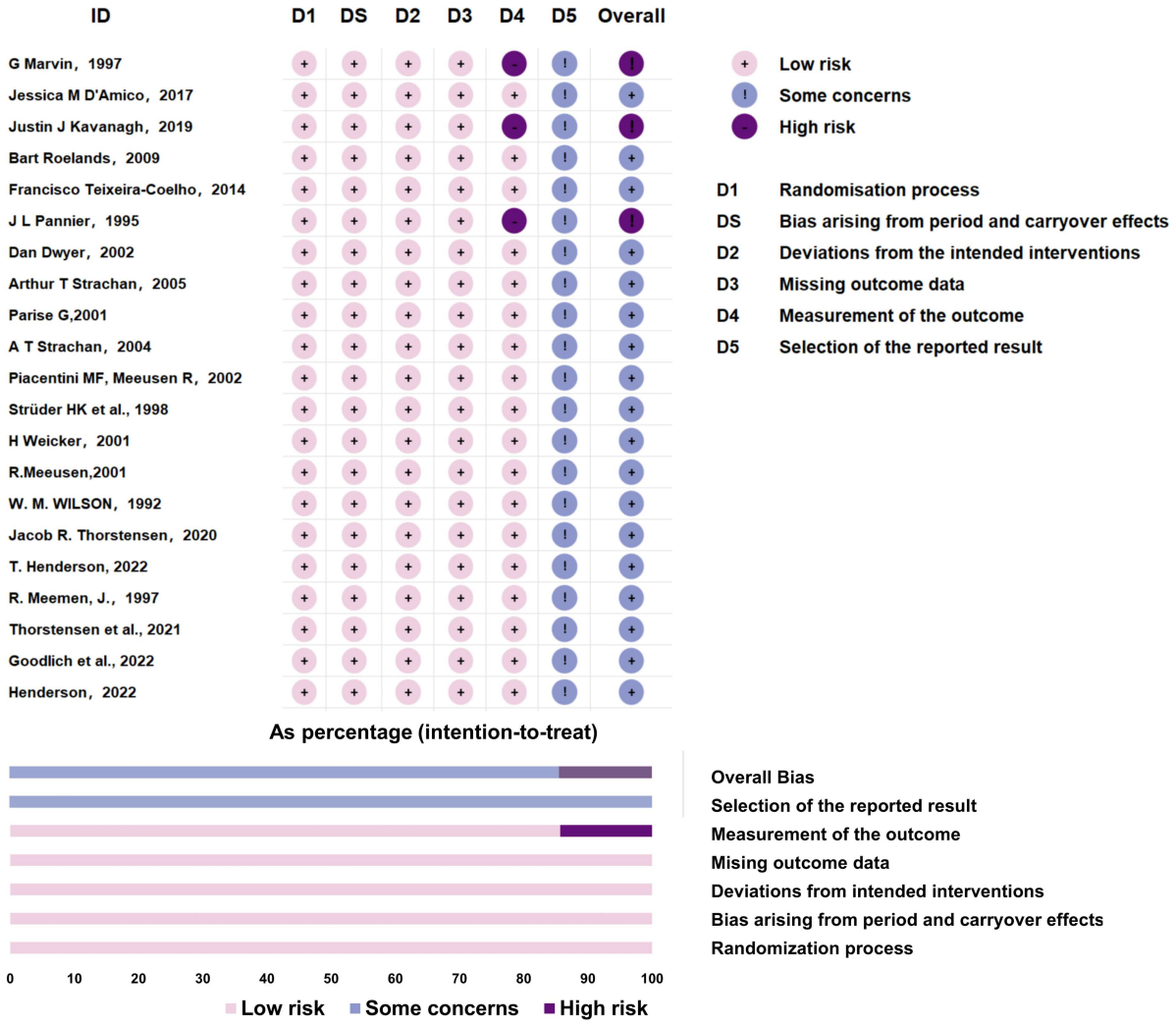

Figure 2. Risk of bias domains and overall risk of bias for included studies.

twitch torque; as low for superimposed twitch torque, MVC, time to task failure, and lactic acid; and as very low for evoked motor response, VA, time-domain EMG, heart rate, prolactin, blood glucose, and RPE, mainly because of study limitations, inconsistency, imprecision, and, for some outcomes, potential publication bias. We calculated the current statistical power and the true effect sizes needed to reach 80% power under the present evidence conditions using the POMADE framework [50] (Fig. S1-S2).

3.4. Meta-analysis

In the primary three-level models, serotonergic pharmacological manipulation showed small but outcome-specific effects across the 12 pooled outcomes (Figures 3–4) including: (1) evoked motor response; (2) VA; (3) time-domain EMG; (4) superimposed twitch torque; (5) MVC; (6) resting twitch torque; (7) heart rate; (8) prolactin; (9) blood glucose; (10) time to task failure; (11) RPE, and (12) lactic acid. The individual results for each of these 12 outcome measures are presented in Fig. S3-S14.

Among the neurophysiological outcomes, evoked motor response showed a small negative pooled effect (Hedges' g = −0.24, 95% CI −0.46 to −0.02, $p = 0.031$; PI −0.73 to 0.25; I^2total = 33.60%), and time-domain EMG also showed a modest negative effect (Hedges' g = −0.18, 95% CI −0.33 to −0.02, $p = 0.023$; PI −0.66 to 0.30; I^2total = 36.18%). VA showed a borderline negative estimate (Hedges' g = −0.20, 95% CI −0.40 to 0.00, $p = 0.050$; PI −1.07 to 0.67; I^2total = 66.90%). Superimposed twitch torque did not show a clear pooled effect (Hedges' g = 0.15, 95% CI −0.08 to 0.38, $p = 0.189$; PI −0.46 to 0.77; I^2total = 50.30%), and MVC remained close to the null (Hedges' g = −0.12, 95% CI −0.37 to 0.14, $p = 0.381$; PI −0.78 to 0.55; I^2total = 52.10%). By contrast, resting twitch torque showed a small positive pooled effect (Hedges' g = 0.12, 95% CI 0.04 to 0.19, $p = 0.002$; PI 0.04 to 0.19; I^2total = 0.00%).

For systemic and metabolic outcomes, heart rate showed a small negative pooled effect (Hedges' g = −0.17, 95% CI −0.34 to −0.01, $p = 0.040$; PI −0.40 to 0.05; I^2total = 4.16%), and blood glucose showed a moderate negative pooled effect (Hedges' g = −0.50, 95% CI −0.89 to −0.11, $p = 0.012$; PI −1.32 to 0.32; I^2total = 43.35%). In contrast, prolactin remained close to the null (Hedges' g = −0.04,

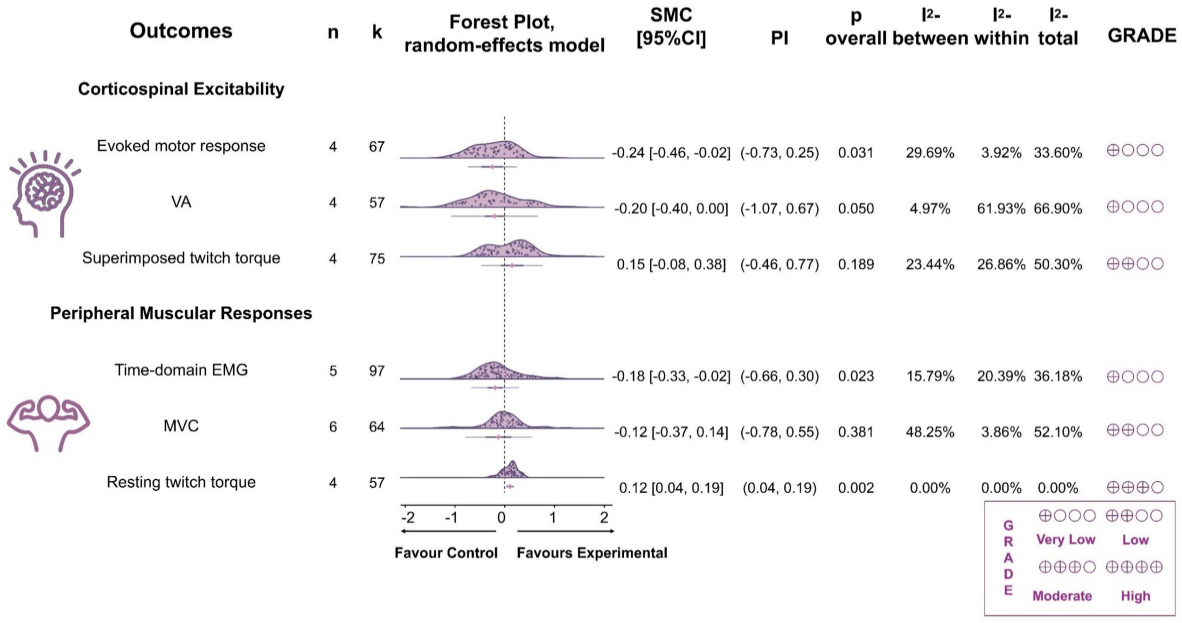

Figure 3. Forest plot showing the effect of serotonergic pharmacological manipulations on neurophysiological and neuromuscular outcomes. VA, voluntary activation; EMG, electromyogram; MVC, maximal voluntary contraction; n, number of studies; K, number of effect sizes; SMC, standardized mean change; CI, confidence interval; PI, prediction interval; I^2 between, between-study heterogeneity; I^2 within, within-study heterogeneity; I^2 total, total heterogeneity.

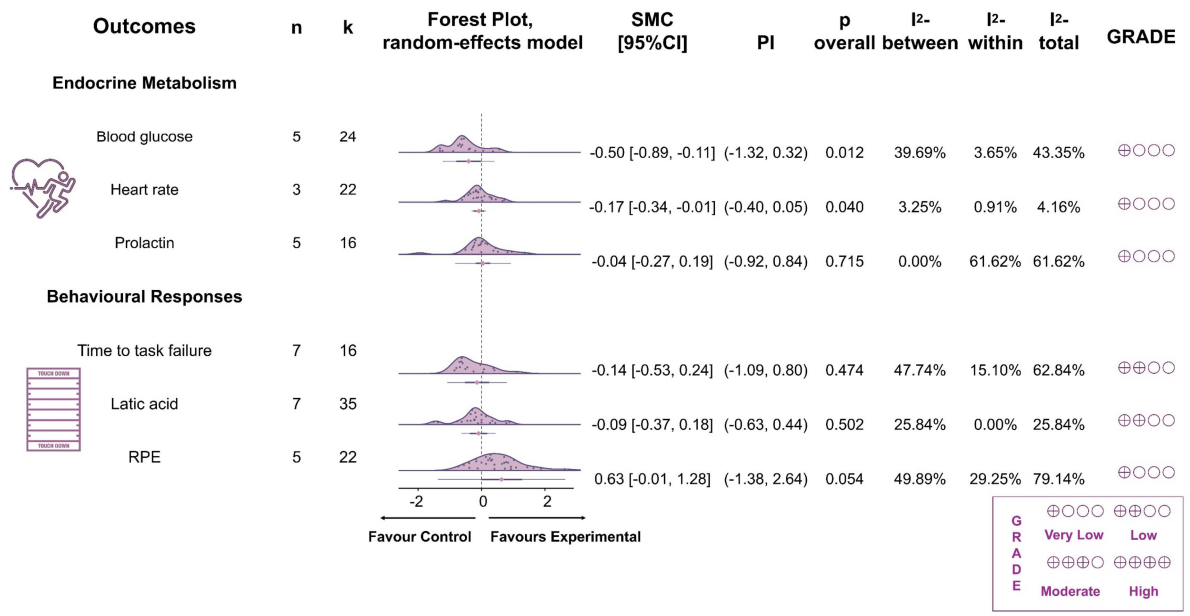

Figure 4. Forest plot showing the effect of serotonergic pharmacological manipulations on systemic, metabolic, and behavioural outcomes. RPE, rating of perceived exertion; n, number of studies; K, number of effect sizes; SMC, standardized mean change; CI, confidence interval; PI, prediction interval; I^2 between, between-study heterogeneity; I^2 within, within-study heterogeneity; I^2 total, total heterogeneity.

95% CI −0.27 to 0.19, $p = 0.715$; PI −0.92 to 0.84; I^2total = 61.62%), and lactic acid also showed no clear pooled effect (Hedges' g = −0.09, 95% CI −0.37 to 0.18, $p = 0.502$; PI −0.63 to 0.44; I^2total = 25.84%). Behavioural outcomes were more heterogeneous. RPE showed a positive but statistically uncertain pooled estimate (Hedges' g = 0.63, 95% CI −0.01 to 1.28, $p = 0.054$; PI −1.38 to 2.64; I^2total = 79.14%), whereas time to task failure remained small and non-significant overall (Hedges' g = −0.14, 95% CI −0.53 to 0.24, $p = 0.474$; PI −1.09 to 0.80; I^2total = 62.84%). Taken together, the primary analyses indicated small negative effects for selected neurophysiological and systemic outcomes, while several other outcomes remained heterogeneous or statistically uncertain.

Subgroup analyses showed significant moderator effects for task intensity in VA and time-domain EMG, muscle group in time-domain EMG, stimulation mode and task intensity in superimposed twitch torque, stimulation mode in MVC, drug category in blood glucose and RPE, and training status in RPE and lactic acid (Table 2; full results in Table S4). For VA, the pooled effect shifted from positive at baseline to negative at high intensity ($p < 0.001$). For time-domain EMG, both task intensity ($p = 0.042$) and muscle group ($p < 0.001$) were significant moderators: negative pooled effects were observed at low intensity and in biceps-derived measures, whereas the triceps subgroup showed a positive estimate. Superimposed twitch torque varied by both stimulation mode ($p = 0.035$) and task intensity ($p = 0.016$), with a clearer positive effect under peripheral stimulation and progressively more positive subgroup estimates from baseline to high intensity. MVC was also moderated by stimulation mode ($p = 0.026$), with the peripheral-stimulation subgroup showing the most negative estimate. Among the systemic and perceptual outcomes, drug category significantly moderated blood glucose ($p = 0.006$) and RPE ($p = 0.002$), while training status significantly moderated RPE ($p = 0.004$) and lactic acid ($p = 0.017$). Reuptake inhibitors showed a clearer negative pooled effect on blood glucose than antagonists, whereas the largest positive RPE estimate was observed in the agonist subgroup and in untrained participants.

3.5. Meta-regression

To examine whether the observed effects varied according to measurement timing within the task, we performed meta-regression analyses using normalised time position as a continuous moderator

Table 2. Key subgroup results for outcomes with statistically significant moderator effects.

Outcome	Moderator	Subgroup *p*	Subgroup	Studies	Effects	Hedges' g (95% CI)	PI	*p* overall	I^2 between	I^2 within	I^2 total
Time-domain EMG	Task intensity	0.042	Baseline	2	8	0.18 [−0.03, 0.40]	(−0.06, 0.43)	0.097	3.18	0.00	3.18
			Low intensity	4	59	−0.15 [−0.24, −0.06]	(−0.46, 0.16)	<0.001	0.00	18.90	18.90
			High intensity	3	30	−0.07 [−0.58, 0.44]	(−1.10, 0.96)	0.790	65.44	5.32	70.76
	Muscle group	<0.001	Biceps	5	77	−0.22 [−0.32, −0.11]	(−0.54, 0.11)	<0.001	5.83	15.32	21.15
			Triceps	2	20	0.19 [0.02, 0.37]	(−0.30, 0.68)	0.031	0.00	34.65	34.65
Superimposed twitch torque	Stimulation mode	0.035	Motor-cortical	3	48	0.05 [−0.30, 0.40]	(−0.63, 0.73)	0.772	50.63	0.00	50.63
			Peripheral	3	27	0.23 [0.09, 0.38]	(−0.28, 0.75)	0.001	0.00	43.86	43.86
	Task intensity	0.016	Baseline	3	6	−0.23 [−0.50, 0.05]	(−0.68, 0.23)	0.106	0.00	30.32	30.32
			Low intensity	3	30	0.01 [−0.36, 0.38]	(−0.73, 0.74)	0.971	45.60	8.60	54.20
			High intensity	4	39	0.28 [−0.01, 0.57]	(−0.41, 0.97)	0.059	34.99	20.13	55.12
VA	Task intensity	<0.001	Baseline	3	6	0.36 [0.10, 0.63]	(−0.06, 0.78)	0.008	0.00	24.35	24.35
			Low intensity	2	20	−0.00 [−0.21, 0.20]	(−0.74, 0.73)	0.982	0.00	58.91	58.91
			High intensity	2	28	−0.51 [−0.95, −0.07]	(−1.42, 0.39)	0.023	30.16	34.66	64.82
MVC	Stimulation mode	0.026	Motor-cortical	3	41	0.01 [−0.26, 0.28]	(−0.50, 0.52)	0.934	36.33	0.00	36.33
			Peripheral	2	8	−0.55 [−0.91, −0.19]	(−1.44, 0.34)	0.003	0.00	64.39	64.39
			No stimulation	1	15	0.16 [0.00, 0.32]	(0.00, 0.32)	0.048	0.00	0.00	0.00
Blood glucose	Drug category	0.006	Reuptake inhibitor	2	8	−0.91 [−1.21, −0.61]	(−1.21, −0.61)	<0.001	0.00	0.00	0.00
			Antagonist	3	8	−0.27 [−0.62, 0.09]	(−0.89, 0.35)	0.142	9.18	20.83	30.01
RPE	Drug category	0.002	Reuptake inhibitor	4	24	0.24 [−0.23, 0.71]	(−0.76, 1.24)	0.315	60.69	0.00	60.69
			Agonist	1	8	2.90 [1.47, 4.33]	(−1.15, 6.95)	<0.001	0.00	85.96	85.96
			Antagonist	2	3	0.67 [−0.26, 1.61]	(−0.96, 2.31)	0.156	0.00	67.81	67.81
	Training status	0.004	Trained	5	19	0.11 [−0.09, 0.32]	(−0.30, 0.52)	0.286	2.92	14.12	17.04
			Untrained	2	16	1.76 [0.10, 3.41]	(−1.73, 5.24)	0.038	44.34	42.94	87.28
Lactic acid	Training status	0.017	Trained	5	7	0.07 [−0.40, 0.54]	(−0.87, 1.01)	0.770	55.20	0.00	55.20
			Untrained	2	9	−0.50 [−0.75, −0.25]	(−1.02, 0.02)	<0.001	0.00	36.34	36.34

Abbreviations: CI, confidence interval, PI, prediction interval; I^2 between, between-study heterogeneity; I^2 within, within-study heterogeneity; I^2 total, total heterogeneity; EMG, electromyogram; VA, voluntary activation; MVC, maximal voluntary contraction; RPE, rating of perceived exertion. *p* values are reported as generated in the analysis output, including values shown as <0.001.

(Figures 5–6). No outcome showed a statistically significant time-dependent association. Specifically, no significant associations with within-task time were observed for evoked motor response ($\beta = -0.207$, $p = 0.413$), VA ($\beta = -0.883$, $p = 0.081$), time-domain EMG ($\beta = 0.096$, $p = 0.603$), superimposed twitch torque ($\beta = 0.418$, $p = 0.054$), MVC ($\beta = 0.065$, $p = 0.658$), resting twitch torque ($\beta = 0.121$, $p = 0.226$), heart rate ($\beta = 0.056$, $p = 0.889$), prolactin ($\beta = -0.198$, $p = 0.562$), blood glucose ($\beta = 0.379$, $p = 0.411$), time to task failure ($\beta = 0.264$, $p = 0.304$), RPE ($\beta = -1.155$, $p = 0.235$), or lactic acid ($\beta = 0.132$, $p = 0.454$). Although VA and superimposed twitch torque showed the largest time-related trends, neither reached statistical significance. Overall, these analyses do not support a consistent time-dependent modulation of the pooled effects across outcomes.

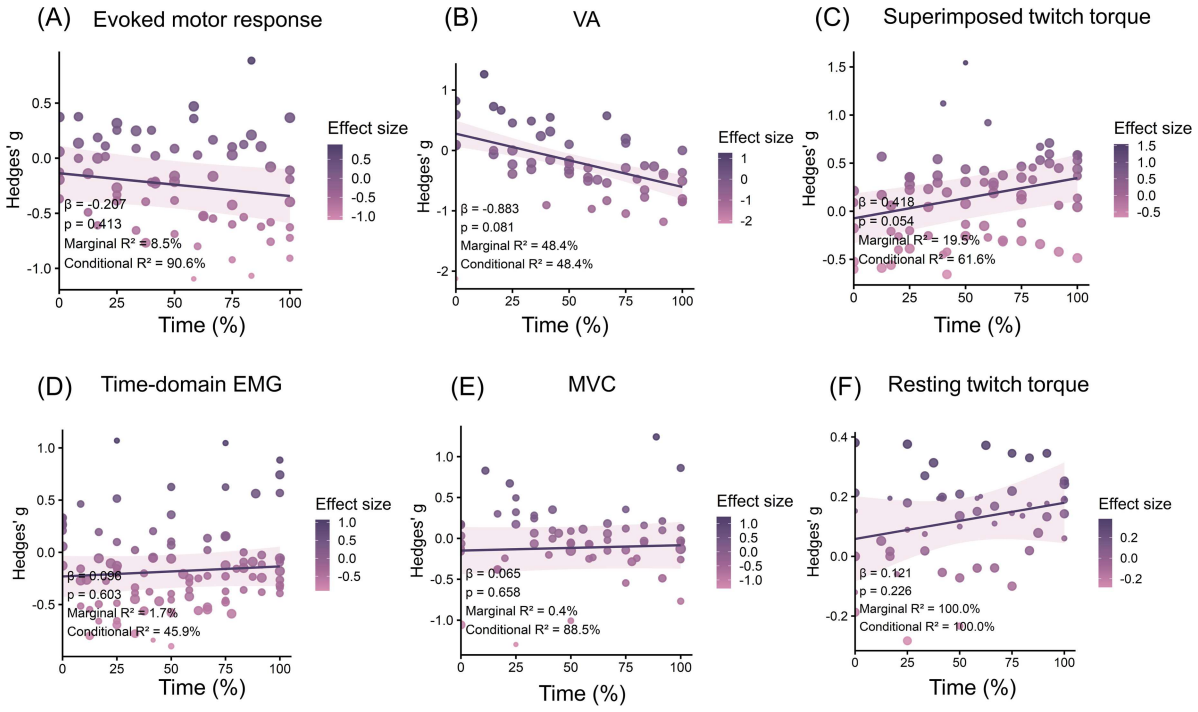

Figure 5. Meta-regression plots showing the relationship between normalised within-task time and the effect size of serotonergic pharmacological manipulations across outcomes. Panels illustrate evoked motor response (A), VA (B), superimposed twitch torque(C), time-domain EMG (D), MVC (E), and resting twitch torque (F). β = regression coefficient; marginal R^2 = variance explained by the moderator; conditional R^2 = variance explained by the full model.

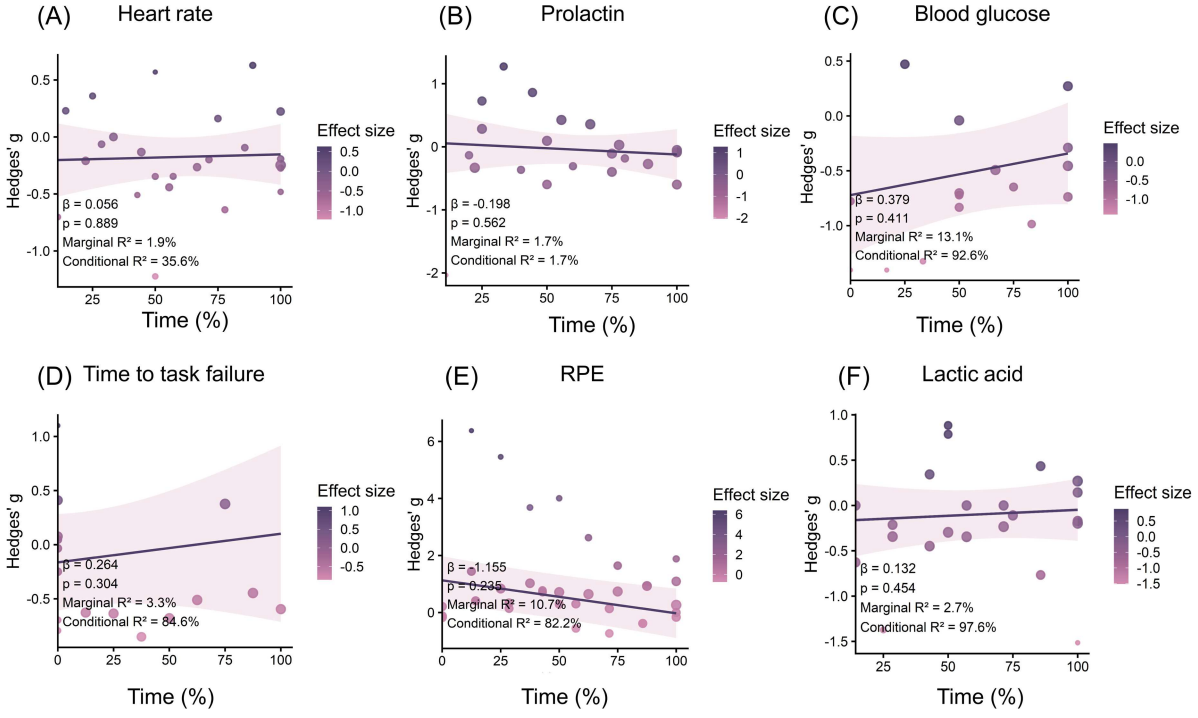

Figure 6. Meta-regression plots showing the relationship between normalised within-task time and the effect size of serotonergic pharmacological manipulations across outcomes. Panels illustrate heart rate (A), prolactin (B), blood glucose (C), time to task failure (D), RPE (E), and lactic acid (F). β = regression coefficient; marginal R^2 = variance explained by the moderator; conditional R^2 = variance explained by the full model.

3.6. Publication bias

Contour-enhanced funnel plots were visually inspected (Fig. S15-S16), and potential small-study effects were further examined using multilevel Egger-style regression. Statistically significant small-study-effect signals were observed for blood glucose and RPE, whereas heart rate showed a borderline pattern; no clear regression-based evidence was observed for the remaining outcomes. However, the practical impact of potential bias differed across outcomes when bias-corrected analyses were considered. Evoked motor response, VA, and time-domain EMG all showed attenuation after non-affirmative-studies correction, and their Bayesian-adjusted credible intervals included or reached the null. Heart rate also moved closer to zero after correction. Blood glucose showed the most stable negative systemic signal, remaining negative after non-affirmative-studies correction, although its Bayesian-adjusted interval still touched zero. By contrast, the positive primary estimate for RPE was markedly reduced after non-affirmative-studies correction and remained highly uncertain in the Bayesian-adjusted model. Superimposed twitch torque, MVC, resting twitch torque, prolactin, lactic acid, and time to task failure did not show robust evidence of an effect after correction. Taken together, these findings suggest that publication-bias concerns are most relevant for blood glucose and RPE, while several other outcomes also appear sensitive to correction procedures.

3.7. Sensitivity analyses

Sensitivity analyses showed that the robustness of the pooled effects differed substantially across outcomes. As shown in Table 3 and Table S5, evoked motor response, time-domain EMG, and blood glucose showed the most consistent directional effects across alternative specifications, whereas VA, heart rate, resting twitch torque, and RPE were more sensitive to influence analysis, non-affirmative-studies correction, or Bayesian adjustment. Evoked motor response remained directionally negative in the effect-size influence analysis (Hedges' g = −0.25, 95% CI −0.46 to −0.04), but the estimate was attenuated after non-affirmative-studies correction (Hedges' g = −0.16, 95% CI −0.35 to 0.03) and the Bayesian-adjusted credible interval included zero (−0.164, 95% CrI −0.45 to 0). Time-domain EMG showed a similar pattern: the negative pooled estimate became slightly stronger after excluding influential effect sizes (Hedges' g = −0.24, 95% CI −0.37 to −0.11), but weakened after non-affirmative-studies correction (Hedges' g = −0.11, 95% CI −0.24 to 0.02), and the Bayesian-adjusted credible interval also reached the null (−0.16, 95% CrI −0.34 to 0). Blood glucose showed the most stable negative systemic signal, remaining negative in the primary model (Hedges' g = −0.50, 95% CI −0.89 to −0.11) and after non-affirmative-studies correction (Hedges' g = −0.37, 95% CI −0.66 to −0.07), although the Bayesian-adjusted interval still touched zero (−0.47, 95% CrI −0.817 to 0).

By contrast, several outcomes appeared more sensitive to analytical assumptions. VA became significant after the effect-size influence analysis (Hedges' g = −0.18, 95% CI −0.30 to −0.06), but was attenuated after non-affirmative-studies correction (Hedges' g = −0.02, 95% CI −0.14 to 0.10) and remained uncertain in the Bayesian-adjusted model (−0.109, 95% CrI −0.48 to 0.04). Heart rate showed a small negative pooled effect in the primary model (Hedges' g = −0.17, 95% CI −0.34 to −0.01), but this weakened after non-affirmative-studies correction (Hedges' g = −0.13, 95% CI −0.28 to 0.02) and Bayesian adjustment (−0.08, 95% CrI −0.32 to 0). RPE also appeared unstable: the positive pooled estimate remained after the effect-size influence analysis (Hedges' g = 0.43, 95% CI 0.05 to 0.81), but disappeared after non-affirmative-studies correction (Hedges' g = 0.09, 95% CI −0.08 to 0.25), and the Bayesian-adjusted interval was wide and crossed zero (0.44, 95% CrI −0.07 to 1.11). Resting twitch torque showed a small positive primary effect (Hedges' g = 0.12, 95% CI 0.04 to 0.19), but the Bayesian-adjusted estimate was close to zero (−0.004, 95% CrI −0.1 to 0.02).

The remaining outcomes remained small and statistically uncertain across specifications. Superimposed twitch torque, MVC, prolactin, lactic acid, and time to task failure did not show robust evidence of an effect after correction procedures. Additional analyses using alternative within-subject correlation assumptions and RVE models did not materially alter the overall pattern: evoked motor response, time-domain EMG, and blood glucose remained directionally negative, whereas VA, heart rate, and RPE were more sensitive to analytical choices.

Table 3. Robustness of pooled effects across sensitivity and bias-correction analyses.

Outcome	Primary model (Hedges' g, 95% CI)	Primary model PI	Outlier-removed model (Hedges' g, 95% CI)	Outlier-removed model PI	Non-affirmative-studies correction model (Hedges' g, 95% CI)	Non-affirmative-studies correction model PI	Bayesian-corrected model (95% CrI)	Bayesian-corrected PI
1.Evoked motor response	−0.24 [−0.46, −0.02]	(−0.73, 0.25)	−0.25 [−0.46, −0.04]	(−0.69, 0.20)	−0.16 [−0.35, 0.03]	(−0.54, 0.23)	−0.164 [−0.45, 0]	[−0.24, 0.28]
2. VA	−0.20 [−0.40, 0.00]	(−1.07, 0.67)	−0.18 [−0.30, −0.06]	(−0.89, 0.53)	−0.02 [−0.14, 0.10]	(−0.60, 0.55)	−0.109 [−0.48, 0.04]	[−0.97, 0.59]
3.Time-domain EMG	−0.18 [−0.33, −0.02]	(−0.66, 0.30)	−0.24 [−0.37, −0.11]	(−0.53, 0.05)	−0.11 [−0.24, 0.02]	(−0.34, 0.15)	−0.16 [−0.34, 0.000]	[−0.40, 0.11]
4.Superimposed twitch torque	0.15 [−0.08, 0.38]	(−0.46, 0.77)	0.11 [−0.08, 0.31]	(−0.41, 0.64)	0.06 [−0.11, 0.23]	(−0.26, 0.39)	0.12 [−0.01, 0.41]	[−0.43, 0.36]
5.MVC	−0.12 [−0.37, 0.14]	(−0.78, 0.55)	−0.08 [−0.24, 0.09]	(−0.45, 0.30)	0.01 [−0.15, 0.17]	(−0.35, 0.36)	−0.01 [−0.21, 0.09]	(−0.32, 0.25)
6.Resting twitch torque	0.12 [0.04, 0.19]	(0.04, 0.19)	–	–	0.12 [0.04, 0.19]	(0.04, 0.19)	−0.004 [−0.1, 0.02]	(−0.14, 0.07)
7.Heart rate	−0.17 [−0.34, −0.01]	(−0.40, 0.05)	−0.16 [−0.32, −0.01]	(−0.32, −0.01)	−0.13 [−0.28, 0.02]	(−0.28, 0.02)	−0.08 [−0.32, 0]	(−0.37, 0.14)
8.Prolactin	−0.04 [−0.27, 0.19]	(−0.92, 0.84)	−0.03 [−0.20, 0.14]	(−0.50, 0.44)	0.02 [−0.20, 0.25]	(−0.63, 0.70)	0 [−0.17, 0.153]	(−0.83, 0.67)
9.Blood glucose	−0.50 [−0.89, −0.11]	(−1.32, 0.32)	–	–	−0.37 [−0.66, −0.07]	(−0.84, 0.11)	−0.47 [−0.82, 0.000]	(−0.85, 0.4)
10.Lactic acid	−0.09 [−0.37, 0.18]	(−0.63, 0.44)	0.02 [−0.28, 0.32]	(−0.58, 0.61)	0.02 [−0.28, 0.32]	(−0.58, 0.61)	−0.03 [−0.28, 0.03]	(−0.33, 0.5)
11.RPE	0.63 [−0.01, 1.28]	(−1.38, 2.64)	0.43 [0.05, 0.81]	(−0.62, 1.48)	0.09 [−0.08, 0.25]	(−0.08, 0.25)	0.44 [−0.07, 1.11]	(−0.64, 0.57)
12.Time to task failure	−0.14 [−0.53, 0.24]	(−1.09, 0.80)	−0.26 [−0.58, 0.06]	(−0.98, 0.45)	−0.07 [−0.36, 0.21]	(−0.8, 0.65)	−0.054 [−0.39, 0.1]	(−0.94, 0.39)

Abbreviations: CI, confidence interval; PI, prediction interval; CrI, credible interval; VA, voluntary activation; EMG, electromyogram; MVC, maximal voluntary contraction; RPE, rating of perceived exertion.

4. Discussion

This meta–analysis aimed to determine whether pharmacological manipulation of the serotonergic pathway influences exercise performance, fatigue–related responses, and neuromuscular outcomes in humans. Based on the updated three-level models, serotonergic manipulation appears to exert small but selective effects rather than a single, uniform influence across all outcomes. In the primary analyses, evoked motor response and time-domain EMG showed modest negative pooled effects, and blood glucose and heart rate also tended to decrease. By contrast, VA, superimposed twitch torque, prolactin, and behavioural outcomes showed greater uncertainty, either because the pooled effects were statistically weak, highly heterogeneous, or sensitive to robustness and bias-correction analyses. Overall, the pattern of findings is more consistent with a limited and outcome-specific modulatory role of 5-HT in exercise-related fatigue than with a broad and stable suppression of performance.

4.1. Serotonergic pharmacological manipulation may reduce central motor drive and corticospinal excitability

At the central level, one of the clearest primary neurophysiological signals was observed for evoked motor response, suggesting that serotonergic manipulation may influence voluntary neural drive or motor-output-related activation in some paradigms. However, the evidence was less stable for VA and superimposed twitch torque. VA showed only borderline support in the primary model and weakened further in several sensitivity analyses, whereas superimposed twitch torque remained directionally positive but statistically uncertain. Accordingly, the central findings should not be interpreted as uniformly convergent across all neurophysiological markers. Instead, they suggest that serotonergic manipulation can alter selected indices of central motor output, but with effect sizes that are generally small and not equally robust across measures.

Under serotonergic pharmacological manipulation, the decline in evoked motor response may reflect reduced corticospinal and/or motoneuronal excitability, demonstrating that the transmission of neural impulses from the motor cortex to the spinal motoneuron pool is weakened [51,52]. The borderline negative VA estimate may be compatible with incomplete recruitment or reduced motoneuron firing during maximal efforts [53]. An increase in the magnitude of the superimposed twitch directly reveals incomplete motor unit recruitment or suboptimal firing rates to achieve fused contractions at the time of stimulation [54], reflecting central fatigue. These observed deficits align with mechanistic research highlighting the specific inhibitory role of 5-HT via 5-HT1AR in motor control. During sustained or high-drive motor tasks, prolonged serotonergic activity is thought to promote activation of inhibitory 5-HT1ARs located on motoneurons and presynaptic structures [10,55]. Specially, animal studies indicate that 5-HT can directly inhibit motoneuron excitability via 5-HT1AR localised at the axon initial segment—the site of action potential initiation due to a high density of voltage-gated Na^+ channels—by suppressing the Ca^{2+} current responsible for spike generation, consequently decreasing motoneuron output [10,56,57]. Taken together, these findings are compatible with the possibility that serotonergic manipulation influences central motor pathways, particularly under sustained or demanding motor tasks. However, because the pooled effects were small and not equally stable across evoked motor response, VA, and superimposed twitch outcomes, the mechanistic interpretation should remain cautious.

4.2. Peripheral neuromuscular responses to serotonergic pharmacological manipulation are small and non-robust

Compared with the central findings, the peripheral neuromuscular results were less consistent and less robust. Time-domain EMG showed a small negative pooled effect in the primary model, indicating that serotonergic manipulation may modestly alter voluntary muscle activation signals under some task conditions. MVC, however, remained close to the null across the primary and sensitivity analyses, indicating no convincing overall effect on maximal force output. Resting twitch torque showed a small positive pooled effect in the primary model, but this finding did not remain stable after bias correction. Therefore, the peripheral neuromuscular outcomes do not support a simple conclusion of either clear impairment or no

effect. Instead, they suggest that some peripheral or output-related measures may shift modestly, but these effects are less consistent and generally less robust than the central findings.

Several physiological factors may explain why the peripheral outcomes yielded weak or null effects despite the clearer central changes. From a mechanistic perspective, acute serotonergic pharmacology is primarily expected to act at the level of the brainstem and spinal cord, modulating motoneuron excitability and synaptic drive [58], whereas the intrinsic contractile properties of the muscle fibres themselves are relatively insensitive to short term changes in 5-HT signalling [59,60]. This interpretation is consistent with previous experimental studies on serotonergic agents, which reported alterations in central activation indices without consistent reductions in measures associated with peripheral fatigue. These measurements include maximal torque or resting twitch responses, particularly when the interventions are acute and the tasks are of limited duration [23,25,45]. This pattern is broadly consistent with the view that acute serotonergic pharmacology is more likely to modify neural drive and task-dependent activation than to induce large, reproducible changes in intrinsic muscle contractile function.

4.3. Systemic autonomic and endocrine metabolic adjustments under serotonergic manipulation

At the systemic level, the updated results suggest a differentiated rather than uniform physiological response to serotonergic manipulation. Heart rate showed a small negative pooled effect in the primary model, although this effect moved closer to zero in several sensitivity analyses, indicating limited robustness. Blood glucose showed the clearest and most consistent systemic signal, with a moderate negative pooled effect that remained directionally stable across multiple analytical specifications. In contrast, prolactin no longer showed a clear pooled reduction in the primary model, and the estimate remained unstable after robustness and bias-correction analyses. Thus, among the systemic outcomes, blood glucose appears to provide the strongest evidence for a serotonergic effect, whereas heart rate is modest and influence-sensitive, and prolactin should be interpreted as uncertain.

These relatively clear systemic effects are compatible with the known role of 5-HT in regulating autonomic output and neuroendocrine function. Serotonergic projections from the brainstem raphe nuclei to cardiovascular control centres can modulate sympathetic and parasympathetic balance and regulate heart rate [61,62], and animal experiments have shown that intracerebroventricular administration of serotonergic agents can alter heart rate [63,64]. Similarly, central 5-HT pathways influence hypothalamic–pituitary activity and metabolic control [65]; pharmacological manipulation of 5-HT receptors can alter prolactin release and glucose homoeostasis through changes in hypothalamic drive, insulin sensitivity, and hepatic glucose output [66,67]. Consistent with this mechanism, these findings suggest that serotonergic manipulation may alter selected autonomic and metabolic responses to exercise, but the evidence does not support a broad and consistent suppression of all endocrine or systemic markers.

4.4. Behavioural and metabolic fatigue outcomes show weak and heterogeneous effects under serotonergic manipulation

Behavioural outcomes remained the most heterogeneous and least stable part of the evidence base. Time to task failure outcomes showed no clear pooled effect, with wide confidence intervals and substantial between-study variability, indicating that any true effect is likely to be small and easily obscured by protocol differences. RPE differed from the previous version of the manuscript in that the primary model yielded a positive pooled estimate; however, this result was accompanied by very high heterogeneity and weakened noticeably in the sensitivity analyses. Accordingly, RPE should not be interpreted as showing a stable serotonergic effect, but rather as an outcome that may be highly context-dependent and particularly sensitive to study design, task characteristics, and participant background.

These behavioural and perceptual findings are also consistent with evidence from other supplements. Our null finding for time to task failure is consistent with previous meta-analytic work on sodium bicarbonate [68], caffeine [69], and *N*-acetylcysteine [70], where time to task failure tests also showed at most small and imprecise drug–placebo differences, suggesting that either the effect of these supplements on time to task failure is genuinely small, or that the experimental paradigms used to assess time to task failure are not sufficiently sensitive or reliable to detect meaningful changes. The uncertain RPE finding in

the present analysis is also consistent with the broader literature showing that perceived exertion is highly context-sensitive and may vary according to exercise mode, fatigue state, and environmental conditions. In this sense, behavioural endpoints such as time to task failure and RPE may be less reliable indicators of acute serotonergic modulation than selected central or systemic physiological markers. The lack of a robust serotonergic effect on RPE in our analysis aligns with evidence that perceived exertion is highly variable and sensitive to contextual influences, as illustrated by caffeine studies showing RPE reductions only under certain hypoxic [71] or post high intensity fatigue [72]. As a result, behavioural endpoints, particularly time to task failure and RPE, are less sensitive and less reliable indicators of acute serotonergic modulation compared with central and systemic physiological markers.

5. Conclusion

Taken together, the updated findings suggest that acute serotonergic pharmacological manipulation does not exert a single, uniform effect on exercise fatigue outcomes, but instead produces small and outcome-specific changes across central, systemic, and behavioural domains. In the primary analyses, the clearest signals were modest reductions in evoked motor response, time-domain EMG, heart rate, and blood glucose, although robustness varied across outcomes. By contrast, VA, superimposed twitch torque, resting twitch torque, prolactin, and RPE showed greater uncertainty because their pooled effects were weakened by heterogeneity, influence analyses, or bias-correction procedures. MVC, lactic acid, and time to task failure did not show clear overall effects. Overall, the present meta-analysis demonstrates that serotonergic mechanisms play an important role in exercise fatigue, especially in neurophysiological responses, thereby enhancing current understanding of serotonergic involvement in exercise central fatigue.

5.1. Limitations

Despite the strengths of the present three-level meta-analytic approach and the additional robustness analyses, several limitations should be acknowledged. First, most included trials were small, acute pharmacological studies conducted under controlled laboratory conditions, which limits the generalisability of the findings to real-world exercise settings and to chronic serotonergic modulation. Second, the current evidence base was likely underpowered to detect small true effects, as also suggested by the simulation-based power analyses; therefore, null or weak pooled estimates should be interpreted cautiously and should not be taken as strong evidence of no effect. Third, although central and selected systemic markers were relatively well represented, behavioural outcomes and peripheral neuromuscular measures remained highly heterogeneous in both methodology and reporting, reducing the precision and comparability of pooled estimates. Fourth, the included interventions targeted different components of the serotonergic system—including reuptake inhibition, receptor agonism, and receptor blockade—and in several cases may also have co-modulated other monoaminergic pathways such as dopamine and norepinephrine, making it difficult to isolate receptor-specific contributions. Finally, we did not fit multivariable moderator models including multiple predictors simultaneously. Future research should therefore prioritise larger, preregistered trials with harmonised protocols and clearer pharmacological targeting to improve mechanistic resolution and the estimation of small but potentially meaningful effects.

Author contributions

CRediT: **Lulu Guan:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Supervision, Visualization, Writing – original draft, Writing – review & editing; **Linhang Han:** Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Supervision, Visualization, Writing – review & editing; **Yu Zou:** Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Writing – review & editing; **Dushuo Feng:** Investigation, Methodology, Supervision, Writing – review & editing; **Pengxuan Xia:** Investigation, Methodology, Supervision, Visualization, Writing – review & editing; **Yuxin Peng:** Formal analysis, Investigation, Methodology, Software, Supervision, Writing – review & editing; **Ziqi Fan:** Conceptualization, Formal analysis, Methodology, Software, Supervision, Visualization, Writing – original draft, Writing – review & editing.

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Data availability statement

All data analysed in this study are derived from published studies, which are cited in the reference list and available through the publicly accessible journals or databases (PubMed, Scopus, Web of Science, Cochrane Central, and SportDiscus).

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