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Creatine supplementation on cognitive performance following exercise in female Muay Thai athletes

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Introduction

Muay thai, also known as Thai Boxing, is one of the most popular sports in Thailand and is growing in popularity worldwide. The International Federation of Muay thai includes members from 110 countries with 5 continental federations (Crisafulli et al., 2009). Muay thai utilizes 8 points of contact including left and right fists, elbows, knees, and feet, and encompasses a variety of fighting techniques such as punches, elbow and knee strikes, kicks, and grappling (Crisafulli et al., 2009). Physiologically, Muay thai involves repeated bursts of explosive dynamic movements and requires well-developed oxidative and non-oxidative energy systems (Crisafulli et al., 2009), as well as high levels of muscular strength and power. Further, Muay thai athletes require enhanced cognitive performance due to the strategic and technical demands of the sport, similar to other tactical sports such as soccer (Vestberg et al., 2017). Emerging research suggest that nutritional strategies or dietary supplements (i.e. nootropics) may augment cognitive performance (Meeusen & Decroix, 2018).

The brain is a highly metabolically active organ, requiring 20% of basal metabolism despite only accounting for 2% of total body mass (Allen, 2012). Neurons require high amounts and a constant supply of adenosine triphosphate (ATP) for several cellular processes, including maintaining ion gradients, neurotransmitter exocytosis, and synaptic functioning (Snow et al., 2018). Creatine is an important molecule associated with maintaining cellular ATP, particularly during times of high demand (e.g., exhaustive exercise, mental fatigue, and sleep deprivation) (Forbes et al., 2021; Ricci et al., 2020; Roschel et al., 2021). Creatine can be synthesized endogenously in the brain or exogenously ingested through the diet (e.g., red meat, seafood, and poultry) or as a dietary supplement (Forbes & Candow, 2018; Forbes et al., 2021; Paiva et al., 2020). Creatine supplementation increases brain creatine content and the phosphocreatine (PCr)/ATP ratio (Dechent et al., 1999; Pan & Takahashi, 2007). Creatine and ATP are converted to PCr and adenosine diphosphate (ADP) in a reversible reaction catalyzed by creatine kinase (Wyss & Kaddurah-Daouk, 2000). PCr functions as a high-energy molecule capable of regenerating ATP significantly faster than oxidative phosphorylation and glycolysis (Wallimann et al., 1998; Wyss & Kaddurah-Daouk, 2000). Supplementing with creatine monohydrate increases brain creatine stores by 5-10% (i.e. PCr and Cr) (Dechent et al., 1999; Dolan et al., 2019; Pan & Takahashi, 2007) leading to accelerated high-energy phosphate metabolism and ATP re-synthesis.

Presently, a limited number of studies have investigated the neurobehavioral effects of creatine supplementation (for review see Dolan et al., 2019, Roschel et al., 2021, and Forbes et al., 2021). For example, creatine supplementation (20 g/day for 7 days) increases corticomotor excitability and attenuated the rate of decline in attention following short-term exposure to hypoxia in healthy adults (10 males, 5 females) (Turner et al., 2015), improved mood and psychomotor function among sleep-deprived subjects (17 males, 3 females) (McMorris et al., 2006), improved general intellectual ability and working memory (5 g/day for 6 weeks; 12 males, 33 females) (Rae et al., 2003), and reduced mental fatigue and cerebral oxygenated hemoglobin in young healthy participants (8 g/day for 5 days; 19 males, 5 females) (Watanabe et al., 2002). Furthermore, creatine enhanced the accuracy of sport-specific passing performance in sleep deprived male rugby players (50 and 100 mg/kg) (Cook et al., 2011) and improved some indices of cognitive function in semi-professional male mountain bikers (20 g/day) (Borchio et al., 2020). In contrast, Cox et al. (2002) and Mohebbi et al. (2012) found no effect from creatine supplementation (20 g/day for 6-7 days) in soccer players. Collectively, these preliminary studies provide some evidence that creatine supplementation can have favorable effects on measures of cognitive performance which appear to be more robust during times of stress.

Despite the growing body of literature involving combat athletes and creatine supplementation (Meeusen & Decroix, 2018; Ricci et al., 2020), the effects of creatine supplementation following exhaustive exercise on cognitive performance is unknown. Exhaustive exercise increases metabolic demands in the brain and impairs cognitive performance (Lambourne & Tomporowski, 2010), which may be attenuated with creatine supplementation. Thus, the purpose of this study was to determine the effects of creatine supplementation on tasks of cognitive performance immediately following exhaustive exercise in trained Muay Thai female athletes compared to placebo. We hypothesized that creatine monohydrate supplementation would attenuate the cognitive decline associated with exhaustive exercise compared to placebo.

Methods

Participants

Twenty six female Muay Thai athletes (age: 25.9 ± 4.6 years; body mass: 65.1 ± 6.6 kg; height: 162 ± 5 cm; body mass index: 24.7 ± 2.4 kg/m^2; training experience: 2.6 ± 0.6 years, as shown in table 1) volunteered. Participants were excluded from the study if they: i) were taking medications that could impact muscle or brain biology and function, ii) had ingested creatine monohydrate within 4 weeks prior to the start of the study, iii) were vegetarian or vegan, or iv) had pre-existing kidney or liver abnormalities. Throughout the duration of the study, participants were instructed not to change their habitual diet or engage in additional physical activity. All participants trained at the same club under the guidance of the same coach. The study was approved by the Research Ethics Board at the University of Itaperuna and is in accordance with the code of ethics of the World Medical Association (Declaration of Helsinki). Participants were informed of the risks, potential benefits and purposes of the study before written consent was obtained.

Experimental Design, Supplementation, and Testing

The study was a double-blind, repeated measures, randomized placebo-controlled trial. Participants were randomized using a computer random number generator (Graphpad software) to one of two groups: creatine (CR: n=13; 3.0 g/day of creatine monohydrate [Creatine Powder; Midway, Santos-SP, Brazil]) or placebo (PLA: n=13; 3.0 g/day of dextrose [New Millen Ltda, Cajamar-SP, Brazil]) for 28 consecutive days. Three g/day for 28 days is an effective strategy to raise creatine tissue levels (Hultman et al., 1996). Importantly, creatine and placebo were similar in colour, texture and appearance. Participants were instructed to consume the supplement with ~400-600 mL of water after breakfast. Information on food consumption with creatine was recorded to estimate the amount of creatine ingested independent of supplementation. Anthropometrics including height (to the nearest 0.1 cm) and body mass (to the nearest 0.1 kg) were assessed using a calibrated scale (Health O Meter, USA), as well as participant age. Before and after 28 days of supplementation, participants completed a Muay Thai exhaustive training session which consisted of a 10 minute warm-up, followed by 40 minutes of technical training and 30 minutes of intensive fighting. Immediately following the bout of exercise, participants completed a series of standardized cognitive performance tests.

Table 1 – Participant Baseline Characteristics

	Creatine (n=13)	Placebo (n=13)	P-value
Age (years)	25.8 ± 4.9	26.1 ± 4.5	0.435
Height (cm)	162 ± 4	163 ± 5	0.250
Body Mass (kg)	64.5 ± 8.0	65.6 ± 5.0	0.340
Training Experience (years)	2.7 ± 0.6	2.5 ± 0.5	0.159

Cognitive Performance

Cognitive testing was performed immediately following exercise and included a visual reaction time (VRT) test, a visual GO/NO-GO reaction time (GNGVRT) test, an auditory reaction time (ART) test, a GO/NO-GO auditory reaction time (GNGART) test, a differentiation task (DTT) test, an Eriksen Flanker test (EFT), a Corsi block test (CBT), a reverse Corsi block test (RCBT), and a visual forward digit span test (VFDS), assessed in order. Protocols have been previously described (Borchio et al., 2020) and are available online at http://cognitivefun.net/. Briefly, the VRT is a reaction time test that prompted the participant to push a button when a green dot appeared in the frame and was used to measure processing speed. The GNGVRT was similar to the VRT with the addition of a patterned dot that was intentionally ignored. The auditory reaction time (ART) test required the participant to push a button when they heard the sound. The GO/NO GO auditory reaction time (GNGART) was similar to the ART but the participant only pushed a button when the sound was higher or lower than a reference sound. The DTT was a variation of the consonant span task aimed to evaluate character recognition and memory with limited phonological activation, whereby participants selected the correct answer from three distractors. The EFT required participants to quickly and accurately match a directional key displayed on the center of a computer screen. The CBT was a variation of the Corsi block tapping test that evaluated memory recall and reproduction of screen block position sequences, whereas the reverse Corsi block test (RCBT) was similar to the CBT but participants reproduced the sequences in reverse (last to first). The visual forward digit span (VFDS) test is often used to measure short-term memory via the phonological loop, with the objective to remember as many digits as possible.

Adverse Events Assessment

In the case of an adverse event or discomfort, participants were instructed to notify the researcher.

Statistics

Datum is reported as mean ± standard deviation. Statistical analyses were performed using a 2 (CR vs. PLA) x 2 (time: before vs. after) repeated measures ANOVA to compare all outcome variables. If a significant interaction was found an LSD post hoc analysis was performed. Significance was set at $p \leq 0.05$, however, due to the exploratory nature of the study p values approaching significance (i.e. 0.05>p<0.10) were also discussed. Further, absolute change (95% confidence intervals) for each outcome variable (post mean – pre mean) were assessed using an independent samples t-test. The magnitude of the difference between the means was determined by eta squared (η^2). This is a measure of the effect size and therefore of the proportion of the total variance that can be explained by the effects of the treatment. A η^2 value of 0.15 represents large differences, 0.06 represents medium differences, and 0.01 represents small differences. All statistical analyses were analyzed using Statistica software (Version 13).

Results

Participant Characteristics

A consort flow diagram is shown in Figure 1. There were no adverse events associated with the testing or supplementation. There were no significant differences between groups at baseline for age, height, body mass, and Muay thai experience, as shown in table 1. There was a significant group x time interaction for body mass ($p = 0.033$, $\eta^2 = 0.18$) with the creatine group increasing over time (pre = 64.5 ± 8.0, post = 65.2 ± 8.0, $p = 0.007$), with no change in the placebo group (pre = 65.6 ± 5.0, post = 65.6 ± 4.8, $p = 0.816$).

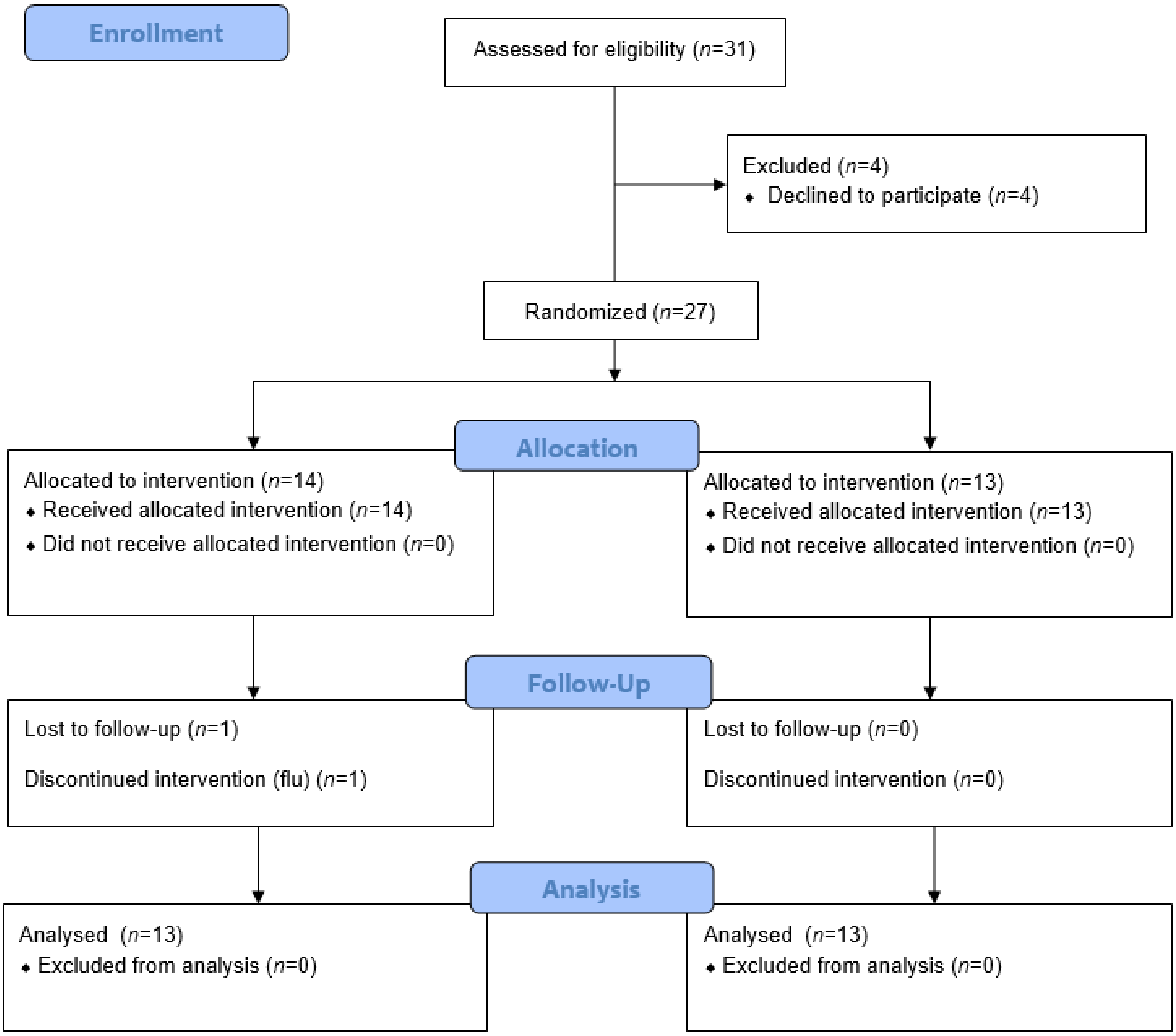

Figure 1: Consort flow diagram.

Cognitive Performance

Pre and post (mean ± SD) cognitive performance scores are shown in table 2. There was a trend for group x time interactions for visual reaction time (p = 0.067, η^2 = 0.13), GO/NO GO reaction time (p = 0.087, η^2 = 0.10) and the Erikson Flanker task (time in ms: p = 0.06, η^2 = 0.10; percentage correct: p = 0.09, η^2 = 0.11). Forced *post hoc* analyses showed a significant decrease in visual reaction time (p = 0.01) and GO/NO GO reacton time (p = 0.017) and an increase in the Erikson Flanker task performance (p = 0.05) with no changes observed in the placebo group (visual: p = 0.98; GO/NO GO: p = 0.97; The Erikson Flanker task: p = 0.46). Furthermore, there was a time main effect for auditory reaction time (p = 0.035, η^2 = 0.17) with no group differences.

Absolute changes in cognitive performance are shown in table 3, there were no significant differences between groups for any outcome variable.

Table 2 – Cognitive performance following creatine or placebo supplementation.

	Creatine		*Placebo*	
	Pre	***Post***	***Pre***	***Post***
Visual Reaction Time (ms)#	391±93	376±89*	419±48	419±60
Go/No Go Visual Reaction Time (ms)#	381±66	361±60*	487±60	487±61
Auditory Reaction Time (ms)(main effect)*	398±105	370±101	417±99	410±101
Go/No Go Auditory Reaction Time (ms)	450±80	437±84	492±66	490±56
Corsi Block Test (%)	98.7±2.4	99.5±1.5	98.3±3.5	99.6±1.5
Reverse Corsi Block Test (%)	98.4±2.6	99.6±1.5	98.7±3.3	98.7±3.3
Differentiation Test (%)	94.1±7.8	95.4±7.2	94.9±10.5	95.9±8.0
Visual Forward Digit Span (%)	94.6±4.5	97.9±3.6	95.9±5.2	96.4±4.7
EFT-Arrows in same direction (ms)#	451±107	387±106*	450±71	474±65
EFT-Arrows in opposite direction (ms)	475±120	434±120	483±67	466±72
EFT-% correct answers same direction (%)#	90.1±5.0	94.4±4.7	93.1±6.1	93.1±6.7
EFT-% correct answers opposite directions (%)	90.2±7.4	94.6±5.3	87.2±12.3	87.4±9.4

EFT = Erikson Flanker Task. # = trend ($0.05<p<0.1$). * = significant change over time.

Table 3 – Absolute changes (95% confidence intervals) in cognitive perofrmance.

	Creatine	*Placebo*	*P*
Visual Reaction Time	-15.5 (-25.6, -5.3)	-0.1 (-12.1, 11.9)	0.068
Go/No Go Visual Reaction Time	-20.1 (-36.7, -3.5)	-0.3 (-14.3, 13.6)	0.087
Auditory Reaction Time	-27.8 (-46.8, -8.7)	-7.5 (-32.1, 17.0)	0.214
Go/No Go Auditory Reaction Time	-11.8 (-32.1, 8.4)	-1.5 (-19.1, 16.0)	0.458
Corsi Block Test	0.9 (-0.8, 2.5)	1.3 (-0.9, 3.5)	0.764
Reverse Corsi Block Test	1.2 (-0.5, 3.0)	0.0 (-2.8, 2.8)	0.472
Differentiation Test	1.3 (-2.6, 5.2)	1.0 (-3.0, 5.1)	0.933
Visual Forward Digit Span	3.4 (1.1, 5.6)	0.5 (-3.3, 4.3)	0.219
EFT-Arrows in same direction	-63.9 (-137.6, 9.8)	23.5 (-23.8, 70.7)	0.062
EFT-Arrows in opposite direction	-41.7 (-114.4, 31.0)	-16.4 (-65.6, 32.8)	0.577
EFT-% correct answers same direction	4.3 (1.5, 7.1)	0.0 (-3.8, 3.8)	0.091
EFT-% correct answers opposite directions	4.4 (0.7, 8.2)	0.2 (-6.3, 6.7)	0.283

EFT = Erikson Flanker Task

Discussion

This was the first study to determine the effects of creatine supplementation on measures of cognitive performance following exhaustive exercise in trained female Muay Thai athletes. We hypothesized that creatine would enhance cognitive performance compared to placebo. Results showed that 3 g/day of creatine supplementation over 28 days appeared to improve processing speed (visual reaction time and visual go/no-go reaction time) and selective attention and executive function (Erikson Flanker Task), while no other effects were found for other cognitive domains. Practically, enhanced processing speed and decision making following exhaustive exercise may be advantageous for Muay Thai fighters due to the physical, technical and tactical demands, particularly in the later rounds of a fight.

Mechanistically, the brain requires a constant energy supply for several cellular processes, including maintaining ion gradients, neurotransmitter exocytosis, and synaptic functioning (Snow et al., 2018). Creatine is important for maintaining ATP levels during times of high demand (i.e., exercise). This is associated with PCr which functions as a high-energy molecule capable of regenerating ATP significantly faster than oxidative phosphorylation and through glycolysis (Wallimann et al., 1998). In the present study, we did not directly measure brain creatine levels, however, others have shown that supplementing with creatine increases total brain creatine stores 5-10% (i.e. PCr and Cr) (Dechent et al., 1999; Dolan et al., 2019; Pan & Takahashi, 2007). Importantly, others found no increases in brain creatine content following supplementation despite using similar methodologies (Merege-Filho et al., 2017; Wilkinson et al., 2006). Results of the present study suggest that creatine supplementation can have some cognitive performance benefits following exhaustive exercise. These results are further supported by other studies which have shown positive effects from creatine supplementation during times of stress (i.e. sleep deprivation, hypoxia, and mental fatigue). For example, creatine supplementation (20 g/day for 7 days) increased corticomotor excitability and attenuated the decline in attention that occurs during short-term hypoxia in healthy adults (10 males, 5 females) (Turner et al., 2015). Further, creatine improved mood and psychomotor function among sleep-deprived subjects (17 males, 3 females) (McMorris et al., 2006) and enhanced the accuracy of sport-specific passing performance in sleep deprived male rugby players (50 and 100 mg/kg) (Cook et al., 2011). In addition, Van Cutsem et al. (2020) found that creatine (20 g/day for 7 days) attenuated the decline in stroop (executive function) following a mentally fatiguing task, however there was no effect on a sport-specific psychomotor task or Flanker performance. Lastly, creatine (20 g/day for 7 days) has been shown to improve cognitive performance (go-no-go reaction time, Erikson Flanker task, and Corsi block test) in semi-professional male mountain bikers (Borchio et al., 2020). Interestingly, the present study used a low dose of creatine (3 g/day) over 28 days whereas most other studies used a higher dose (20 g/day) (Roschel et al., 2021). In support of our findings, Ling et al. (2009) and Rae and Broer (2015) both found improvements in cognitive function using a lower dose of creatine (5 g/day over 15 days and 6 weeks, respectively). Future research examining the dose response relationship with brain creatine levels and cognitive function are urgently needed, however, our research suggests that a low dose of creatine provided over 28 days appears to alter cognitive performance following exhaustive exercise.

Furthermore, body mass increased to a greater extent following creatine supplementation. These findings are in support of previous research (Candow et al., 2014; Candow et al., 2019; Chilibeck et al., 2017; Forbes et al., 2021; Kreider et al., 2017; Sarshin et al., 2021) and are likely due to an increase in muscle mass (Kreider et al., 2017) and may be associated with intracellular water retention (Antonio et al., 2021), however, no measure of body composition was assessed in the present study. Practically, an increase in body mass may be an important considerations for weight based athletes (Ricci et al., 2020).

Limitations

Our results have several other limitations worth noting. First, possibly due to the relatively small sample size or low dose of creatine, we only found trends when examining the interaction effects, which were subsequently explored with forced post-hocs, thus caution is warranted. Secondly, we did not directly measure brain creatine content or evaluate any possible mechanisms of action. As such, future research is required to confirm our findings. In addition, we did not monitor or control menstrual cycle and there was no sex based comparisons. Previous research has suggested that creatine may affect the brain in females differently than males in clinical or diseased populations, such as depression (Allen et al., 2012; Bakian et al., 2020). These sex based differences may be associated with the effects of estrogen or estrogen metabolites on creatine kinase (Allen et al., 2015). Lastly, the order of the tests may have influenced the results, however, the order of the tests was consistent pre to post testing.

Conclusions

Overall, it appears that creatine supplementation (3 g/day) for 28 days appears to have a small but positive effect on cognitive performance (i.e., increasing processing speed and executive function) in trained female Muay Thai fighters following exhaustive exercise compared to placebo. Beyond the known benefits of creatine to enhance muscle performance, creatine also appears to improve brain function following exercise in athletes.

Acknowledgements
NA

Conflicts of interest

DGC has conducted industry sponsored research involving creatine supplementation, received creatine donation for scientific studies and travel support for presentations involving creatine supplementation at scientific conferences. In addition, DGC serves on the Scientific Advisory Board for Alzchem (a company which manufactures creatine). SCF has served as a scientific advisor for a company that sells creatine products. LAMP and MM declare no competing interests.

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