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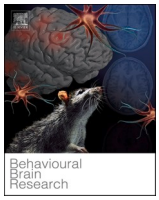

Creatine supplementation research fails to support the theoretical basis for an effect on cognition: Evidence from a systematic review

Terry McMorris [a,b,*], Beverley J. Hale [a], Beatrice S. Pine [a], Thomas B. Williams [b]

[a] Institue of Sport, Nursing and Allied Health, University of Chichester, College Lane, Chichester PO19 6PE, United Kingdom
[b] Department of Sport and Exercise Science, University of Portsmouth, Spinnaker Building, Cambridge Road, Portsmouth PO12ER, United Kingdom

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ABSTRACT

Creatine supplementation has been put forward as a possible aid to cognition, particularly for vegans, vegetarians, the elderly, sleep deprived and hypoxic individuals. However, previous narrative reviews have only provided limited support for these claims. This is despite the fact that research has shown that creatine supplementation can induce increased brain concentrations of creatine, albeit to a limited extent. We carried out a systematic review to examine the current state of affairs. The review supported claims that creatine supplementation can increases brain creatine content but also demonstrated somewhat equivocal results for effects on cognition. It does, however, provide evidence to suggest that more research is required with stressed populations, as supplementation does appear to significantly affect brain content. Issues with research design, especially supplementation regimens, need to be addressed. Future research must include measurements of creatine brain content.

1. Introduction

Creatine supplementation is widely used as an aid to physical performance, as it facilitates the maintenance of adenosine triphosphate (ATP) homeostasis in muscle [37,42,71]. The majority of creatine is synthesized in the liver and kidneys but a small amount is formed in the brain [146]. This has led several authors to examine the possibility of creatine supplementation having an effect on cognition. While authors have put forward convincing rationales for such an effect, narrative reviews of this work have shown somewhat equivocal results [11,108, 114,120]. Some argued that the equivocality of the results may be due to the heterogeneity of the nature of the participants - vegans, vegetarians, elderly and healthy young adults [114,120]. The fact that in several studies, the participants were in some way stressed, i.e. sleep deprived or hypoxic, has also been posited as a possible factor [120,85]. Task type, executive function versus attention, perception or memory tasks, has also been put forward as a credible reason for the equivocal nature of the results [11,85]. Other recent reviews [32,53] have focused primarily on research examining creatine supplementation by the pathologically stressed as opposed to heathy groups. Therefore, we decided to carry out a systematic review of the literature examining the effect of creatine supplementation on cognitive performance by healthy individuals. We expected to find that healthy individuals in non-stressed situations would not benefit from supplementation but that performance in stressful conditions may be facilitated by creatine supplementation. Moreover, we examined the effects of different task types, executive functions versus attention, perception and memory tasks combined. Given the equivocal nature of the results of previous literature reviews, we decided to critique the rationales for a creatine supplementation effect on cognition, in order to determine whether results were due to poor research designs and/or weak rationales. This is as recommended in research methods texts (e.g., [50]). We begin with a brief outline of the effects of creatine in the healthy brain.

1.1. Outline of the role of creatine in the brain

Creatine (α-N-methylguanidino acetic acid) is a nitrogenous organic amino acid, which is taken up from meat, fish and dairy products [12,5]. Synthesis begins in the kidney with the conversion of arginine and glycine to form guanidinoacetate and ornithine, catalyzed by L-arginine: glycine amidinotransferase (AGAT). Guanidinoacetate is released from the kidney and taken up by the liver, where glycine N-methyltransferase (GAMT) recruits S-adenosylmethionine to methylate guanidinoacetate to form creatine and S-adenylhomocysteine [2,24], although see [146].

* Correspondence to: 228 Hartfields Manor, Hartlepool TS26 0NW, United Kingdom.
E-mail address: t.mcmorris@chi.ac.uk (T. McMorris).

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However, creatine is also synthesized endogenously from the amino acids arginine, glycine and methionine in the kidneys, liver and pancreas [5,146]. Endogenous synthesis is also thought to occur in the brain, as AGAT and GAMT are expressed in brain neurons and oligodendrocytes [25]. Also, creatine is transferred from blood plasma across cellular membranes by the sodium and chloride-dependent creatine transporter 1 (CT1: [60,125]).

Once creatine enters the cell, it is transformed by phosphorylation into phosphocreatine by the enzyme creatine kinase. Phosphocreatine is stored as an energy reserve, which can quickly replenish ATP when demand requires. In those situations, creatine kinase catalyzes the transfer of the phosphate group from phosphocreatine to adenosine diphosphate (ADP) to form ATP. Important to note is that phosphocreatine is the rate-limiter in this rapid resynthesis of ATP [147,2]. This process is reversible in order to maintain phosphocreatine resources. Furthermore, the creatine/phosphocreatine system can also act to shuttle high-energy phosphates from mitochondria to cytoplasmic sites of utilization [12,59]. Thus, the main role of creatine in the brain is to provide the energy necessary to carry out brain activity, including neurotransmission, intracellular signaling and, axonal and dendritic transport [12,4,80].

Of great importance to the effects of creatine supplementation to brain activation is the role of CT1 in facilitating creatine crossing the blood-brain barrier. CT1 is found at the blood-brain barrier, expressed by neurons and oligodendrocytes but not by the astrocyte feet lining the microcapillary endothelial cells [22,26,23]. That CT1 is not expressed in these astrocytes means that supplementation will have a limited effect [101,22]. However, in stressful situations which induce increases in blood ammonia, CT1 is expressed in astrocytes, thus facilitating creatine entry into the brain [21].

1.2. Summary

From the previous sub-section, we can see that creatine plays a significant role in the provision of energy to the brain. This led researchers to hypothesize that creatine supplementation might affect cognition especially among vegans, vegetarians, the elderly and, mentally fatigued and physiologically stressed individuals, who may be lacking in brain concentrations of creatine [109,138,143,92,91,88]. This depletion may be permanent, in the case of the vegans, vegetarians and the elderly; or transient, in the case of the physiologically stressed and mentally fatigued. The idea that simply using supplementation may aid cognitive performance in healthy young people has also been hypothesized [20,64,93]. The conclusions reached by the narrative reviewers suggest that the state of physiological stress and task type may act as moderators. Based on these reviews, we hypothesized that creatine supplementation would have a positive effect on cognition. We, also, hypothesized that comparatively complex, executive function tasks would be more beneficially affected by creatine supplementation than attention, perception and memory tests. Furthermore, we hypothesized that stressed groups would benefit more from creatine supplementation than unstressed groups.

This last hypothesis is based on arguments that in normal healthy individuals with balanced diets, there is no deficit in brain creatine levels [110,85], therefore supplementation has no beneficial effect. However, it has been argued that stressed individuals show decreases in brain creatine and, therefore, benefit from supplementation [110,114,85]. The stressors we examined were diet (vegans and vegetarians), ageing, hypoxia, sleep deprivation and mental fatigue, as research has been undertaken using these stressors.

2. Method

A systematic literature search, using the databases PubMed and SCOPUS, was undertaken, following the preferred reporting items for systematic reviews. Each database was searched from their earliest available record up to April 2023. Key words used in the searches were “creatine supplementation” coupled with each of the following separately, “cognition”, “executive function”, “attention”, “perception” and “memory”. In addition, reference lists from empirical reports and reviews were examined and screened for eligibility.

2.1. Selection of studies

Two of the authors (TM and BSP) selected articles for inclusion. The titles and abstracts of publications obtained by the search strategy were screened. All trials classified as relevant by any of the authors were retrieved. Based on the information within the full reports, we used a standardized form to select the trials eligible for inclusion in the review. There was no blinding to study author, institution or journal at this stage.

Studies were included if they were written in English and provided information concerning (a) the dosage and duration of ingestion of the supplement, (b) utilized a placebo, (c) were double blind, (d) did not contain another variable which might compromise the results, (e) cognitive tests were objective and (f) evidence was presented to show that there were no significant pre-treatment differences in cognitive performance between groups and/or Δ values for each group were provided.

3. Results and discussion

Fig. 1 outlines the stages of the literature search and choice of studies to be included. Only 15 studies with N = 500, met all of the criteria for inclusion, this is similar to previous systematic reviews, with only a few additional studies included [11,114,120]. Table 1 shows the N, age, type of supplementation, dosage, cognitive tasks used in each of the studies and results.

As can be seen from Table 1, the results are somewhat equivocal. This not only applies between studies but also within studies, where some variables demonstrate significant improvements, while others show no significant effects. However, it should be noted that only one study provides an example of a negative result [14]. These results are consistent with previous reviews [11,114,120].

Some previous reviewers [11,85] have suggested that task type (executive function versus attention, perception and memory tasks

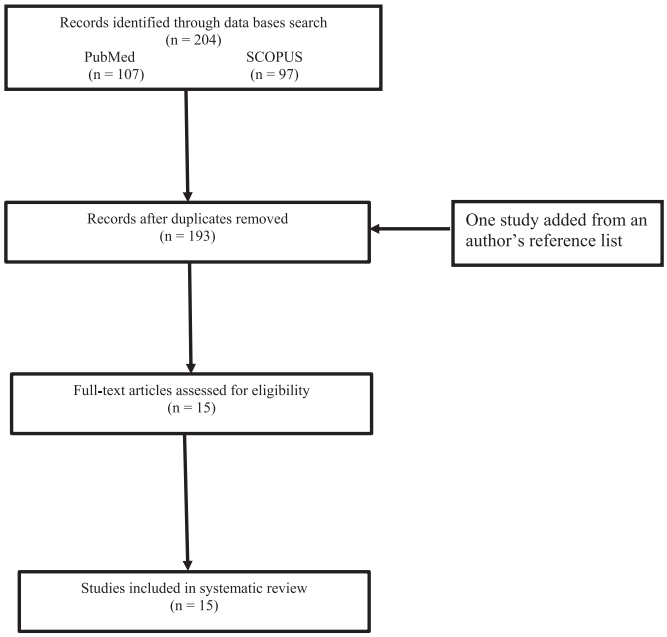

Fig. 1. Outline of literature search.

Table 1
Outline of studies selected for inclusion in meta-analysis.

Author(s)	N (F)	Age (SD)	Cre suppl type	Dosage	Cognitive tasks	Results
Alves et al. [3]	28 (F 28)	66.8 (NR)	monohyd	4×5g/d 5 days; 1×5g/d 163 days	MMSE; Stroop; Trail Making A; Digit Span; Delayed Recall	3 EF → 4 APM →
Benton & Donohoe [14]	121 (F 121)	20.3 (23.1)	monohyd	4×5g/d 5 days	Memory recall; Jensen RT test; Vigilance; COWAT	1 EF → 1 APM ↑ 1 APM →
Borchio et al. [20]	20 (F 0)	29.5 (9.3)	monohyd	4×5g/d 7 days	Go/NoGo; Visual RT	2 EF ↑ 1 APM ↑ 2 APM →
Hammett et al., [64]	22 (F NR)	Cr group (n=11) 30.18 (8.37) Plac group (n=11) 25.0 (4.82)	monohyd	2×10g/d 5 days 1×5g/day 2 days	BDS RAPM	1 EF ↑ 1 EF →
Ling et al. [76]	34 (F 12)	21 (1.38)	ethyl ester	1×5g/d 15 days	Memory scanning; Number pair-matching; Sustained attention; Flanker task	1 EF ↑ 1 EF → 2 APM →
Merege-Filho et al. [93]	67 (F 29)	11.6 (0.9)	monohyd	4×0.3 g/kg body weight 7 days	Stroop; RAVLT; Trail Making A & B	3 EF → 1 APM →
McMorris et al. [92]	19 (F 3)	21.11 (1.85)	monohyd	4×5g/d 7 days	RMG; Verbal fwd & bwd recall; Spatial fwd & bwd recall; Choice RT	1 EF ↑ 2 EF → 1 APM ↑ 2 APM →
McMorris et al. [91]*	20 (F 0)	21.11 (1.85)	monohyd	4×5g/d 7 days	Fwd number recall; Choice RT	1 EF ↑ 1 EF → 4 APM →
McMorris et al. [88]	32 (F 16)	76.4 (8.48)	monohyd	4×5g/d 7 days	RNG; Verbal fwd & bwd recall; Spatial fwd & bwd recall; LTM	3 EF ↑ 1 EF → 1 APM ↑ 1 APM →
Pires et al. [103]	26 (F 26)	24.9 (4.6)	monohyd	1×3g/d 28 days	Visual RT; Auditory RT: Go/No Go; Corsi block test fwd & bwd; DDT; Visual memory fwd; Flanker tas	4 EF → 5 APM →
Rae et al., [109]	45 (F 33)	24.9 (NR)	monohyd	1×5g/d 42 days	RAPM; Digit span bwd	2 EF ↑
Rawson et al. [115]	22 (F 9)	20.8 (2.15)	monohyd	1×0.03 g/kg 42 days	Visual RT; Sternberg task; 1-back test; STM	3 EF → 4 APM →
Turner et al. (2015)	15 (F 5)	31 (NR)	monohyd	4×5g/d 7 days	Stroop; Sustained attention; Verbal & visual STM	3 EF ↑ 3 EF → 3 APM →
Van Cutsem et al., [138]	14 (F 4)	24 (3)	monohyd	4×5g/ 7 days	Visuomotor flanker	1 EF → 1 APM →
Watanabe et al. [143]	24 (F 5)	24.39 (9.11)	monohyd	4×8g/d 5 days	Math	1 EF ↑

*These authors included other tests but did not provide enough information for them to be included in meta-analysis.
→ non-significant ($p > .05$); ↑ significant ($p < .05$); APM attention, perception and memory; bwd backward; COWAT controlled oral word association test; Cre creatine; DTT differentiation task test; EF executive function; F female: wd forward; g/d grams per day; LTM long-term memory; MMSE mini-mental state examination; monohyd monohydrate; NR not reported; RAPM Raven's advanced progessive matrices; RAVLT Rey auditory verbal learning test; RMG random movement generation; RNG random number generation; RT reaction time; SD standard deviation; STM short-term memory; suppl supplement.

combined) may be a moderator. However, when we compare the results for executive functions (n = 10: [3,14,20,76,92,88,93,103,109,136] with those for the attention, perception and memory tasks (n = 10: [3,14,20,76,92,91,88,93,103,115]), there is no convincing evidence for any difference between outcomes for the different task types. In fact, results show that in many of the studies, there is inconsistency even within task types (e.g., [92,88,136]).

With regard to the effects of stressed versus unstressed groups, observation of the unstressed group (n = 6; [20,93,64,76,103,115]) demonstrated an inconclusive pattern with no strong support for a significant effect of creatine supplementation on cognition. This is consistent with previous reviews [11,114,120]. A similar pattern emerged with the stressed group (n = 7: [3,92,91,88,109,136,138,143]). However, previous reviewers (Avgerinos, 2018; [114,120]) have argued for something of an interaction effect, with a tendency for the stressed groups to show more positive effects during executive functions than during non-executive tasks. We would concur with this to some extent, but it is important to note that in most of the studies, not all executive functions demonstrated significant effects.

In order, to examine these results in a meaningful way, we need to investigate the theoretical underpinnings for the rationales more closely, as well as scrutinizing the experimental designs. Evidence that supplementation actually results in increased brain creatine content is the first issue that requires verification. We follow this by examining the

rationale for executive functions being more positively affected by supplementation than simpler tasks; differences between stressed and unstressed individuals following supplementation; and finally, the interaction between task types and stress level. We also examine criticisms of research designs. In each case, we comment on the extent to which the research supports the rationales and discuss the implications for future research.

3.1. Evidence for supplementation increasing brain creatine content

In order for creatine supplementation to affect cognition, it must obviously cross into the brain. As we saw earlier, creatine can be transported across the blood-brain barrier by CT1, also known as SLC6A8, but the process is not efficient. Although CT1 is expressed in microcappilary cells at the blood-brain barrier, it is not expressed in astrocytes, this causes low permeability of the blood-brain barrier for creatine, but does not exclude entry into the brain [101,24,51]. In normal cicrcumstances the brain appears to be self-sufficient with regard to the processes of creatine synthesis. Braissant et al. [24], working with rats, found that AGAT and GAMT were expressed in central nervous system neurons and glia. They showed that messenger ribonucleic acid gene expression of L-arginine–glycine amidinotransferase and *S*-adenosyl-L-methionine–*N*-guanidinoacetate methyltransferase are also found in the brain. Hence everything necessary for the synthesis of creatine is present. As a results, it is thought that in the brain, endogenous creatine is of far more importance than exogenous [12,24], but supplementation will have some effect. Thus, the use of exogenous creatine by the brain is not ideal, but would appear to be viable.

Despite the limitations of creatine crossing the blood-brain barrier, studies in humans have demonstrated the potential of creatine monohydrate supplementation in raising brain creatine content [130,131,16,41] but not unequivocally [126,145,93]. Moreover, it appears that separate brain regions are affected differently [126,41], while there are large inter-individual differences in responses [41]. The situation is made more confusing by the fact that very different dosages and durations of supplementation have been used in the research (see Table 1). Dolan et al. (2019) pointed out that often researchers would utilize daily intakes and/or durations of treatment similar to those used to increase muscle creatine content. They argued that given the poor permeability of the blood-brain barrier to creatine, higher daily intakes and/or longer durations of treatment than are commonly used for increases in muscle creatine, are probably necessary for increasing brain content. These issues have not yet been resolved.

There has been an attempt to solve the blood-brain barrier permeability issue by the use of creatine ethyl ester as a supplement rather than creatine monohydrate [76]. Creatine ethyl ester is creatine monohydrate with an extra ester bond attached to its molecular structure [76], It is more lipophilic than creatine monohydrate and, as such, should cross the blood-brain barrier more easily, even without the presence of CT1 [52,76]. However, Fons et al. [52] found no significant effect of one year's administration of 0.4 g/kg/day, taken in two divided doses, of creatine ethyl ester in patients with CT1 deficiency. They explained their results by the fact that creatine ethyl ester is susceptible to hydrolysis in gastric acidic conditions and, as such, could be quickly converted to creatine and then creatinine, with little crossing the blood-brain barrier [128]. We should note that Ling et al. [76] did show some positive effects of 15 days of 5 g/day creatine supplementation on cognitive performance. Unfortunately, no measures of brain creatine content were undertaken.

Overall, it would appear that creatine does cross the blood-brain barrier but that this process is not efficient and the brain is more likely to rely on the synthesis and release of endogenous creatine. However, in this review, we also asked whether this conclusion only applies to unstressed individuals and possibly even only to simple tasks. These issues are covered in the following sub-sections.

3.2. Do executive functions benefit from creatine supplementation more than other tasks?

The rationale for executive functions benefitting from creatine supplementation more than for other tasks is based on the belief that these tasks are more complex than attention, perception and memory tests, and as a result, they require more energy. Miyake and associates [94] described executive functions as involving several processes including shifting between tasks or mental sets, updating and monitoring working memory representations, inhibition of prepotent responses, planning, and the coordination of multiple tasks. Leh et al. [74] provided other examples, e.g. abstract thinking, cognitive flexibility and selecting relevant sensory information.

These tasks are undoubtedly more difficult than simple attention, perception and memory tests, but there is no evidence to suggest that in normal circumstances, the brain is incapable of producing sufficient energy to ensure optimal performance of such tasks. However, some authors have argued that creatine supplementation may have a positive effect on cognition in stressful situations [110,85]. Moreover, there is empirical support for this, albeit somewhat limited [109,136,92,91]. The rationale for an interaction is based on the fact that executive functions activate frontoparietal networks, with the prefrontal cortex playing the major role, whereas attention, perception and short-term memory tasks activate the relevant primary sensory regions of the brain. While declarative, long-term memory requires activation of the hippocampus [18]. The prefrontal cortex is seen as being most readily affected by stress due to the demands placed on it [7]. These issues are discussed in the following sections.

3.3. Stress and the effects of creatine supplementation on cognition

Consistent with previous research [92,91,109], the results of our review provide weak support for the possibility that stressed individuals benefit more from creatine supplementation than unstressed people. Before discussing the results of the review, we should point out that someone undertaking a cognitive test is de facto under some level of stress. In this study, we have used the term unstressed, as the only stressors facing this group were the tests themselves, while the stressed individuals had additional stressors.

The rationale for an effect of creatine supplementation on cognition in healthy, unstressed individuals appears to be that extra creatine will result in more efficient brain functioning. However, as we have seen above, the main role of creatine during cognition is to provide the energy necessary for neurotransmission, intracellular signaling and, axonal and dendritic transport [12,4,80]. A typical diet along with a normal synthesis and release of endogenous creatine ensures sufficient energy in healthy, unstressed people. Adding more creatine via supplementation does not appear to affect cognition. Indeed, supplementation can lead to a transient lowering of the synthesis and release of endogenous creatine (Dolan et al., 2010), probably because it is redundant. Moreover, Raichle [111,112] has shown that in normal circumstances, healthy humans do not display deficiencies in brain energy supplies including ATP. Furthermore, there is very little difference between brain metabolic rates when humans are completely passive and resting, and when they are observably doing something [113], as demonstrated by activation of the default mode network [27].

Although undertaken with children aged 10 – 12 years, the study of Merege-Filho et al. [93], is of particular relevance to the viability of supplementation in unstressed participants. The authors showed no significant effect of 7-days of creatine supplementation on performance of a memory test and executive function tasks. More importantly, measurement of creatine content in the dorsolateral prefrontal cortex, left hippocampus, and occipital lobe by proton magnetic resonance spectroscopy (^{1}H-MRS) technique demonstrated no significant differences between a creatine supplementation group and a placebo group. The authors pointed out that it is possible that their results may only

apply to this specific population.

Another study of interest, with regard to measures of brain function in unstressed individuals during cognition following supplementation, is that of Hammett et al. [64]. Participants (N = 22) were divided into a creatine monohydrate supplementation group (n = 11; mean age 30.18, SD 8.37) and a placebo group (n = 11, mean age 25.00, SD 4.82). The supplementation group received 20 g/day of creatine monohydrate for five days, followed by 5 g/day for 2 days. They undertook the Backwards Digit Span (BDS) and Raven's Advanced Progressive Matrices (RAPM) tests before and after the supplementation period. Creatine supplementation had a significant effect on BDS but not RAPM. Although the authors did not measure brain creatine, they did measure blood oxygen level dependent (BOLD) response in the primary visual cortex (V1), using functional magnetic resonance imaging (fMRI). They found that creatine supplementation resulted in a decrease of 16% in BOLD response in V1, which is purportedly indicative of metabolic demand and neural activity [56]. The authors present a number of possible reasons for creatine supplementation resulting in a decrease in BOLD. In conclusion, they tentatively supported the argument that creatine enhances the normal relatively low uptake of available oxygen, reducing the ratio of oxy- to deoxy-hemoglobin. They stated that this may lead to an increase in the cerebral metabolic rate of oxygen by providing a pool for oxidative glycolysis, as had been shown for muscle [36]. This would reduce oxygen levels and therefore the BOLD response. However, we should note that BOLD does not measure brain activity directly and can provide misleading data with regard to brain activation [83]. The lack of a direct measure of brain creatine, unlike in the Merege-Filho et al. [93] study, makes it difficult to compare the two studies. The failure to show a significant effect on RAPM performance also raises questions.

The effect of creatine supplementation on cognitive performance of unstressed individuals is undoubtedly somewhat dubious. The creatine/phosphocreatine system is designed to ensure that phosphocreatine is stored as an energy reserve, which can quickly replenish ATP when demand requires. Therefore, brain energy supplies should remain intact in unstressed populations and, as a result, one would not expect any significant effect of supplementation. The Merege-Filho et al. [93] study really questions the beneficial value of supplementation on the brain regions involved in cognition. However, the Hammett et al. [64] study suggests possible increased activation of V1, during a visual task, but with limited effect on behavior.

Given the weak rationale for unstressed groups benefitting from creatine supplementation, it is not surprising to find that empirical research shows somewhat equivocal results for both executive functions and non-executive functions. We should note, however, that no studies demonstrate negative effects, they are either positive or non-significant, with a slight bias towards the latter. Observation of the findings of this review for stressed individuals also shows only limited support for a positive effect of supplementation. In order to better understand the results for the stressed people, we need to look more closely at each of the stressors individually, especially with regard to how each of them is thought to affect cognition.

3.3.1. Vegans and vegetarians

As we saw in Section 1.1, exogenous creatine derives from the consumption of meat, fish and dairy products [12,5], which led some authors to suggest that vegans and vegetarians might demonstrate deficits in creatine in the body [105,127,144] and brain [109]. Thus, supplementation might benefit cognition in these people. Research has shown that creatine supplementation does result in greater increases in muscle and blood creatine in vegetarians compared to omnivores [127,144]. However, this is not the case with the brain.

Solis and colleagues [126,127] found no differences in brain creatine content between vegetarians and omnivores. The authors pointed out that their results may have been affected by the differences in diet within the vegetarian group. The vegetarians in the first study included lacto-ovo-vegetarians (n = 10), ovo-vegetarians (n = 2) and vegans (n = 2). In the 2017 study, the vegetarians were lacto-ovo-(n = 9), ovo- (n = 1) and vegans (n = 4). Lacto-ovo-vegetarians eat dairy products and eggs but no red meat, poultry or fish: ovo-vegetarians eat eggs but no red meat, poultry, fish or dairy products: while the vegan diet consists of only plant-based foods [105]. Given that creatine is found in meat, fish and dairy products ([5]; Beard & [21]), the vegetarians in these studies will have some exogenous intake of creatine. We should note that there are other types of vegetarians, lacto-vegetarians, who eat dairy products, but no red meat, poultry, fish or eggs: pesco-vegetarians, who eat fish, but no red meat, poultry, dairy products or eggs: and pesco-lacto-ovo-vegetarians, who eat fish, dairy products and eggs but no red meat or poultry. Some of these sub-groups could have intakes of creatine not very dissimilar to that of omnivores [105]. To summarize, we can say that the evidence from research into the effects of creatine supplementation on brain creatine content of vegetarians and omnivores suggests that vegetarianism does not affect brain creatine content very much, if at all, when compared to omnivores. However, there seems to be little doubt that vegans do not intake sufficient (if any) exogenous creatine to ensure the levels necessary for maintaining optimal cognitive output.

Rae et al. [109] examined the effect of creatine monohydrate on the performance of executive functions by a group (N = 45) made up of vegans (n = 18) and vegetarians (n = 27). They demonstrated significant positive effects on executive functions (they did not examine non-executive functions). However, Benton and Donohoe [14] found no significant differences between omnivores and vegetarians following supplementation. As a result, they collapsed their data and did not provide results for the vegetarians alone. They did, however, point out that vegetarians taking creatine supplementation showed better results in a memory recall test than did omnivores taking the same supplement. Strangely, following creatine supplementation, omnivores actually performed worse on a short-term memory task than they did at baseline. This is very difficult to explain. It is important to remember that overall, there were no significant differences between omnivores and vegetarians in that study.

3.3.2. The elderly

As with vegans and vegetarians, research with the elderly has regularly shown lower concentrations of total creatine in muscle compared to younger adults [116,127,55,58]. However, with regard to the brain, longitudinal and cross-section studies show that total brain creatine content increases with age [54,66]. It has been claimed that this is to compensate for decreases in brain morphology and functions during ageing [102,75]. In order to understand the claims outlined above with regard to the necessity for creatine supplementation by the elderly, we need to examine the empirical evidence concerning the interaction between brain health and cognition in the elderly. Evidence exists to show that the elderly brain demonstrates decreases in structure; volume; size; white matter integrity; functional connectivity; number of dopaminergic receptors [102,75]; decrease in the number of mitochondria; changes in the size, shape and structural composition of mitochondria; a reduction in mitochondrial oxygen consumption and the ability to synthesize ATP [15].

Moreover, in older adults, neural activity also becomes less localized in some brain regions, particularly the prefrontal cortex [29,6]. Cabeza et al. [30] found that prefrontal activity during cognitive performances tends to be less lateralized in older adults than in younger adults and proposed the hemispheric asymmetry reduction in older adults (HAROLD) model. Furthermore, research has shown that older individuals, who activate both hemispheres of the prefrontal cortex, perform cognitive tasks better than those who demonstrate asymmetry [29]. There is evidence to show that the elderly also utilize symmetry in the parietal and temporal cortices [57], However, Cabeza [29] argues that the number of studies that have shown age-related asymmetry reductions in the parietal and temporal cortices is too small to justify the generalization of the HAROLD model beyond the prefrontal cortex. We

should note that age-related asymmetry reductions have typically been observed in groups of 60–80-year-olds. In fact, Nielson et al. [98] discovered that age-related changes consistent with the HAROLD model, were found in "old-old" (M = 74.5 years) participants but not in "young-old" (M = 63.2 years) participants.

There is also evidence to show that the elderly demonstrate increased prefrontal cortex activation in tasks in which other brain regions are normally more dominant [102,61]. Moreover, research shows age-related decreases in many tasks, e.g. episodic memory, semantic memory, working memory, perception and inhibition (Adulrahman et al., 2014; [29]).

Thus, it would appear that despite increased endogenous total creatine concentrations in the elderly brain, there is probably a necessity for supplementation. We should take into account the very high likelihood that there are large inter-individual differences in age-related changes in brain creatine content, as humans do not age at the same rate. As a result, we cannot use chronological age as a marker for the need for creatine supplementation. Researchers should measure total creatine brain content in their participants to determine their requirement for supplementation.

Only two studies have examined the effects of supplementation in the elderly. McMorris et al. [88] found significant improvements in three executive functions and one non-executive function but two non-significant effects for other non-executive function tasks. Alves et al. [3] demonstrated no significant effects on any variables (three executive functions and four non-executive functions). There were large differences in treatments. McMorris et al. prescribed 4 ×5 g/day for 7 days, while Alves et al.'s participants received 4 ×5 g/day for 5 days followed by 1 ×5 g/day for 163 days. This would suggest that Alves et al.'s participants should have shown the greater positive effect [42]. However, ages also differed. McMorris et al.'s group had a mean age of 76.4 (SD 8.8) years, while Alves et al.'s participants had a mean age of 66.8 with a range of 60 – 80 years. Both of these factors may have affected results but to re-state, we really need to know total brain creatine content in order to explain differences in the two studies.

3.3.3. Hypoxia

The importance of oxygen to all aspects of behavior and, indeed to staying alive, cannot be exaggerated. It is not surprising then to find that hypoxia can hinder cognitive performance. However, narrative [132, 140] and meta-analytic [89] reviews have shown that the negative effects on cognition are not as devastating as one might expect. McMorris et al. found that it was not until partial pressure of arterial oxygen (P_aO_2) fell below ~ 60 mmHg that a decline in performance was initiated. However, as P_aO_2 levels continue to fall, cognition deteriorates further.

The initial decline is attenuated by actions of the interoceptive system. When oxygen levels fall, chemoreceptors in the carotid body sense the fall and feedback, via the glossopharyngeal nerve, to the nucleus tractus solitarii (NTS), where they activate the tyrosine hydroxylase (TH)-containing noradrenergic neurons, A1 and A2. The NTS projects to the ventrolateral medulla (VLM), where the adrenergic neurons C1 are activated. C1, A1 and A2 neurons project to the hypothalamus, which initiates the release of norepinephrine from the locus coeruleus. C1 neurons also project directly to the locus coeruleus ([1,62]; King et al., 2013; [119]). This increases Ca^{2+} signaling in astrocytes, which is associated with the release of vasodilatory astroglial messengers, dilatation of brain microvessels and, hence, increases in cerebral blood flow (CBF) [134]. Similarly, during hypoxia, feedback to the NTS from visceral afferents and carotid body arterial chemoreceptors has been shown to activate non-TH-containing neurons. These non-catecholaminergic neurons project to the rostral VLM [62] and, also, stimulate the brain's response to hypoxia.

Moreover, adenosine, which is released from the carotid body during hypoxia, plays a role in increasing CBF by stimulating the release of nitric oxide (NO) from vascular endothelium vessels [117]. NO, mediated by its second messenger cyclic guanosine monophosphate, plays a major role in vasodilation during hypoxia [137]. In other words, increased CBF during hypoxia compensates for lower P_aO_2. However, several authors have questioned the ability of increases in hypoxia-induced CBF to ensure a sufficient supply of oxygen for proficient performance of many tasks, including cognitive functions [100,99, 17]. It is generally agreed that as P_aO_2 falls even further there becomes a point where even these interoceptive responses cannot maintain the quality of cognitive performance. Indeed, the brain prioritizes the cardiorespiratory system, which is vital for survival, rather than areas of the brain involved in cognition [141].

As P_aO_2 falls, one of the first processes to be affected is the production of ATP (Ashcroft & Ashcroft, 1990; [72,97]). However, ATP can be synthesized anaerobically when creatine kinase catalyzes the reversible transfer of phosphate between phosphocreatine and ATP [72]. Thus, while phosphocreatine levels are preserved, it is possible for cognitive performance to be maintained. Moreover, in vitro studies have shown that preincubation of brain slices with creatine, increased tissue phosphocreatine levels and prevented depletion of intracellular ATP, attenutaed the failure of synaptic transmission in hippocampal [33] and neocortical neurons [77], and increased firing in locus coeruleus neurons [67]. Furthermore, Turner et al. [135] showed that 50 mins of breathing a gas mixture containing 10% oxygen, which reduced arterial oxygen saturation by 20%, resulted in significantly lower cognitive performance than in a sham condition (inhaling a gas mixture with 21% oxygen).

In the one study which has examined the effect of creatine supplementation on cognition during hypoxia [136], participants inhaled a gas mixture with an inspired oxygen fraction of 0.1 for 90 mins. According to Marshall et al. (1995), this would induce a P_aO_2 of ~ 60 mmHg, the level below which a deterioration in cognitive functioning can be expected [89]. We must be cautious with this conclusion as no actual measures of $P_aO_2$were taken.

The creatine treatment was 4×5 g/day for 7 days. The authors demonstrated positive significant effects on three executive functions but not for all dependent variables. Although, it should be noted that some non-significant results were approaching significance and may have failed to reach that level due to low power. Moreover, using magnetic resonance stimulation, the authors demonstrated that total creatine in the hand knob of the left precentral gyrus (primary motor cortex: Brodmann area 4), following supplementation, demonstrated a significant increase in content. However, the density of gray and white matter in this region did not differ between treatments. With regard to cognition, this region is probably not of great importance. On the other hand, the dosage may not have been sufficient to induce large enough changes in total creatine.

3.3.4. Sleep deprivation

Evidence that sleep deprivation results in reduced cognitive performance has been demonstrated in humans [19,129]. Moreover, indirect support for loss of energy during deprivation being the cause of this decline in cognition has been shown by a 44% reduction in the cerebral metabolic rate (CMR) of glucose [81] and a 25% reduction in the CMR of oxygen [79]. However, the situation is not straightforward, and data for reduced brain total creatine content are not only very weak but actually total creatine may well increase during sleep deprivation [110]. In order to make sense of this, we need to look more closely at the research into sleep deprivation and brain energy supplies.

Dworak et al. [45] found that in rats, sleep deprivation resulted in greater neuronal activation and a significant decrease in brain phosphocreatine levels than during sleep. They argued that this suggests rapid mobilization of high-energy phosphates from phosphocreatine to prevent ATP depletion. Moreover, when sleep deprived animals, including humans, undertake restorative sleep, there is a decrease in metabolic expenditure relative to wakefulness, which is thought to restore brain energy metabolites to baseline levels [121,13]. Thus, there is a post-deprivation increase in total creatine in the brain [45,139].

Another indicator of the stress placed on energy consumption during sleep deprivation is the breakdown of ATP to adenosine. Adenosine is formed from adenosine monophosphate catalyzed intracelluarly by the enzyme 50-nucleotidase and extracellularly by the enzyme ecto-50-nucleotidase [44]. Tonic adenosine activation of A1 and A2A adenosine receptors in extracellular space has an inhibitory effect on brain activation and promotes a desire for sleep [106,43].

It is important to note that the research reviewed above, simply examined ATP and total creatine or phosphocreatine following sleep deprivation but not during cognitive performance following sleep deprivation. Posada-Quintero et al. [107] compared cognitive performance post-sleep deprivation to baseline using electroencephalography (EEG) and showed that there was evidence for sleep deprivation having a detrimental effect on vigilant attention and that this was related to changes in EEG measures, which supported a fall in brain energy supplies.

There is another interesting aspect of the effects of sleep deprivation and adenosine. In striatopallidal neurons, adenosine A2A receptors are co-expressed with dopaminergic D_2 receptors. When adenosine concentrations are increased, D_2 activation is decreased. Moreover, striatal adenosine A1 receptors have been shown to have an antagonistic effect on dopamine D_1 receptors [124]. This occurs due to receptor-receptor crosstalk and interactions at the intercellular second messenger systems [31,95]. This lowering of brain dopamine concentrations may inhibit motivation, resulting in poorer cognitive performance.

Only one study has measured the effect of creatine supplementation on brain creatine and/or phosphocreatine content following sleep deprivation and that was with rats [45]. However, the authors did make some interesting findings, which have implications for future research. They found that 6 hours of sleep deprivation showed a tendency for increased phosphocreatine and a decrease in cellular ATP levels in the brains of the supplemented rats but not in the control group. The supplemented group also demonstrated an attenuated increase in extracellular adenosine. Dworak et al. [45] argued that increased phosphocreatine levels following supplementation "shifted the equilibrium in the creatine kinase reaction ($Cr + ATP \leftrightarrow PCr + ADP + H^+$) toward the right" (p. 7: Cr creatine, PCr phosphocreatine), which results in decreased intracellular ATP and extracellular adenosine production. This, they claimed, facilitates activation of the phosphocreatine/creatine kinase system, which is an efficient phosphoryl transfer network that ensures energetic homeostasis under stress [46,104].

Similar changes in brain energy systems have been shown in healthy humans under normal conditions by Lyoo et al., [78], who demonstrated a reduction in cellular ATP, increased brain creatine and an increase in inorganic phosphate levels. According to Dworak et al. [45] their results indicate a reduced need for sleep and the maintenance of homeostasis in brain energy in the creatine supplemented rats. Furthermore, they pointed out that under normal circumstances, intracellular ATP levels remain constant, but under situations, which are likely to increase neuronal activity, such as sleep deprivation, ATP and adenosine concentrations vary and can affect cognitive performance. This could affect cellular signalling by the ATP purinergic receptors, P2X and P2Y, and adenosine receptors [28,65].

Despite the processes outlined above, the two studies, examining the effect creatine supplementation on cognition following sleep deprivation, provide somewhat equivocal results. McMorris et al. [92] examined participants following 24 hours of sleep deprivation, while McMorris et al. [91] tested participants following 24 and 36 hours deprivation. In the 2006a study, they found significant positive effect of supplementation in one executive function and one non-executive function, but no significant effect in two executive tasks and two non-executive tasks. McMorris et al. [91] showed a significant positive effect on an executive function but no effect on two non-executive functions at 36 hours but none of the results at 24 hours reached significance. Thus, it is difficult to draw conclusions from these studies.

It should be noted that in both of these studies, participants undertook intermittent physical activity, but at low intensities so that it would not affect cognition, as we know that moderate intensity exercise facilitates cognition, while heavy exercise has varying effects [87,86]. Moreover, durations were short and there were long rest periods. However, from a translational perspective, the physical activity carried out by individuals experiencing sleep deprivation may be a very important factor. The physical work that is undertaken by first responders and the military, as well as shift workers, would put stress on the individuals' bodies. Creatine supplementation has a positive effect on physical performance, which may affect psychological well-being, e.g. induce positive emotions and motivation [39,47]. In these situations, feedback from the periphery to the brain via the interoceptive system activates the insula cortex, anterior cingulate cortex, orbitofrontal cortex and lateral prefrontal cortex, which may facilitate cognition even under stress [86]. Moreover, the lateral prefrontal cortex and orbitofrontal cortex induce activation of the ventral striatum, which could result in increased motivation [86]. Thus, there is the possibility that maintenance of cognitive performance during sleep deprivation may be due to peripheral effects of creatine supplementation having a positive psychological effect rather than an increase in brain creatine content. Indeed, McMorris et al. [92] found that in the supplementation condition, perceptions of fatigue and vigor were less affected by 24 hours sleep deprivation than in a placebo condition. However, McMorris et al. [91] failed to support these data. The possibility that a similar effect may occur with vegans and the elderly can not be ruled out.

3.3.5. *Mental fatigue*

The idea that continuous performance of cognitive tasks leads to mental fatigue and inhibits the performance of subsequent cognitive tests, is controversial, with some supporting an effect [63], while others [34] question its validity. Arguments that undertaking continuous cognitive tasks would lead to depletion of brain resources have, in particular, been questioned ([84]; McMorris, 2020; [90]). As we saw in Section 3.3, [111,112,113] has shown that under normal circumstances, the brain can easily provide the necessary energy for the completion of cognitive tasks. However, this does not mean that continuous performance of a cognitive test does not negatively affect the performance of a subsequent undertaking, indeed reviews provide support for such effects (Brown et al., 2020; [90]). It has been argued that repeating the initial cognitive task results in a lowering of motivation to perform the subsequent task and that the individual perceives themselves as no longer having sufficient resources to maintain the same level of performance as in the control condition [84,90]. However, it is difficult to see how creatine supplementation would help the person maintain motivation and perception of effort costs.

Two studies [138,143] examined the effect of creatine monohydrate supplementation on mental fatigue. Watanabe et al.'s participants (N= 24, 5 female, mean age 24.39 years, SD 9.1) were divided into an experimental group (n = 12) and a control group (n = 12). The experimental group received 4×8 g/day of creatine monohydtrate for 5 days and were examined on the Uchida-Kraepelin task [73], a serial mathematical calculation test. Following treatment, the experimental group's performance was significantly better than that of the control group. Moreover, the creatine group demonstrated a significantly reduced increase in task-evoked cerebral oxygenated hemoglobin as measured by near infra-red spectroscopy. According to the authors, this is indicative of increased utilization of oxygen in the brain [118,68].

In the Van Cutsem et al. [138] study, participants (N = 14, 4 female, mean age 24 years, SD 3) undertook a mentally fatiguing task following creatine supplementation and placebo, using a counterbalanced, crossover, double-blinded design. They were then tested on a visuomotor task and the flanker task [48]. In the supplementation condition, participants took 4×5g/day of creatine monohydrate for 7 days. Supplementation did not affect performance on the visuomotor or flanker task. Supplementation did improve accuracy on the mentally fatiguing task (Stroop test) but these data included the early part of the test before mental

fatigue could have set in. Reaction time was not affected. It should be noted that Van Cutsem et al. also measured handgrip endurance before and after treatment, and demonstrated a significant positive effect of creatine supplementation.

That the two studies should result in different effects could be due to differences in creatine dosage and duration of the supplementation, but differences are very small, therefore an unlikely cause. They could also be due to the fact that Van Cutsem et al.'s (2020) study utilized a within subjects design while Watanabe et al.'s (2002) used a between subjects design. Van Cutsem et al. showed that in the supplementation condition, participants motivation levels were higher than in the control condition and they perceived themselves as feeling more vigorous in this condition. This does not appear to have had a large impact on the results.

3.3.6. Is there an stress-task type interaction?

The hypothesis that executive functions are more readily affected by stress than other tasks is based on the notion that they rely heavily on prefrontal cortex activation and that the prefrontal cortex is readily affected by stress, and may even close down in stressful situations. However, this hypothesis is primarily the result of studies with rodents, which have used far greater stressors than are used in human studies [7,8]. Moreover, we have shown in previous reviews that other physiological stressors, severe acute exercise [86] and hypoxia [89], do not affect executive functions differently than they do other tasks. In the present review, we found little support for differences between task types. However, there are questions over the reliability of some of the tests of executive functions, particularly in test re-test situations, and also the actual task difficulty [70]. Just because a task activates the prefrontal cortex, does not mean that it is difficult nor does it exempt it from becoming autonomous [9]. This is supported by the fact that we see so few errors of accuracy in most of these tasks [87]. Task difficulty may well be the more important issue.

Furthermore, the test re-test reliability has been seriously questioned [49,123], although it should be noted that most researchers found some variables to present satisfactory reliability. Of importance for our study, is the fact that although these tasks can be sub-divided into a number of latent variables, these variables only correlate weakly with one another, and can, and do, operate separately from one another [133,94]. We may need to treat these tasks as separate and not forming a specific task type. All of these factors may well have affected the results.

3.3.7. Summary

Overall, the results for the stressed group suggest that creatine supplementation has a moderate effect on cognition but observation of the data for vegans/vegetarians, the elderly, hypoxic, sleep deprived and mentally fatigued individuals suggests that there may be differences depending on the stressor. There are serious doubts about whether or not some of the stressors examined actually do result in reduced brain creatine content. Vegetarians may well have sufficient exogenous creatine from their diets. However, this is less likely with vegans. Rae et al.'s (2003) study, which included a large number of vegans, provides strong evidence fo a significant effect but the results of the Benton and Donohoe [14] study cast some doubt on whether or not supplementation has any effect on cognition in these groups. There is also some question over brain creatine content in the elderly. Evidence exists for age-related increases in total brain creatine content, and there is undoubtedly structural deterioration and a change in hemispheric asymmetry. Both of these could seriously affect the need for greater levels of brain creatine than are present in a normal diet. The two studies examining effects on the elderly provide contradictory results. Only one study examined the effects of hypoxia [136]. There is a logical rationale for creatine supplementation aiding hypoxic individuals. If P_aO_2 falls below ~ 60 mmHg, we are very likely to see a detrimental effect on cognition [89]. Given that creatine can synthesize ATP anaerobically, one might expect supplementation to have a positive effect. With regard to sleep deprivation, it would appear that it does result in increased brain activity but whether it is sufficient to require creatine supplementation in order to maintain energy supplies is not so clear. The two mental fatigue studies [138,143] also show mixed results with some significant variables but most not so. The role of brain energy supplies has been questioned and the claim that motivation and perception of effort are the more likely explanations for the phenomenon have been proffered [84,90]. Finally, the review does not supply strong support for an interaction between stress and task type. This may be because one does not exist but could also be affected by questions of reliability and task difficulty in the executive function tests. Undoubtedly, far more research is required but greater control over the research is essential if we are to move towards making definitive statements on the effects of creatine supplementation on cognition.

3.4. Future research

Probably the most important factor for future research is the necessity to measure brain creatine content before and after supplementation. This should be undertaken by ^{1}H-MRS or, in the case of phosphocreatine, phosphorous ^{31}P-magnetic resonance spectroscopy. Measures of ATP in the relevant cognitive brain networks would also provide valuable information. In vegetarian studies, there is a need to also undertake dietary information from the participants. While asymmetry could be measured in elderly participants. Moreover, we should note that stressful situations, such as sleep deprivation, hypoxia and aging [35,69,82], induce increases in blood ammonia. In such cases, it has been shown that CT1 is expressed in astrocytes, which facilitates creatine entry into the brain [21]. The possibility that other stressors have a similar effect requires to be examined.

There is also a major necessity to determine the optimal supplementation regimen - dosage and duration. This will almost certainly be dependent on the type and intensity of the stressor thought to be inducing the need for creatine supplementation. Not only is it possible that specific stressors have different effects, but variations in intensities and/or durations of the same stressor, could induce contrasting results. Hypoxia, for example, may have a threshold effect. Similarly, the effect of sleep deprivation of different lengths should be examined, while deprivation need not always be total, having intermittent breaks in sleep may have disparate effects compared to total deprivation.

Two factors that have received very little attention are motivation and perception of effort costs. These could particularly affect results in research into sleep deprivation, the elderly and during/following mental fatigue. Consistent with the theories of Aston-Jones et al., [10], and Craig [38], McMorris [86], examining the effect of acute exercise on cognition, argued that when an individual perceives effort cost as being unable to be met by the perceived resources available and motivation is low, the person will under-perform. However, if effort costs are seen to be within the available resources and motivation is high, performance is likely to, at least, remain at baseline level. Thus, measures of motivation, perception of effort costs and perception of available resources should be taken. While these factors would be measured by self-report, motivation could also be examined using pupillometry, which provides a biomarker of brain dopamine levels [142,96].

Although executive functions have been measured, no research has examined task difficulty. This could be done by using a task like the n-back test, which can easily be presented at different levels of difficulty. Other tasks may take some ingenuity from the researchers but there are examples, e.g. Scharinger et al. [122] used a combined n-back/flanker task in a non-creatine supplementation study.

4. Conclusion

In line with narrative revies [11,114,120], our findings suggest that creatine supplementation has no significant effect on young healthy participants in unstressed situations. Moreover, the review show mixed results for stressed groups (vegans/vegetarians, the elderly, the sleep

deprived, hypoxic and mentally fatigued participants). However, we differ from previous reviews in that we present no support for an effect of task type on cognition. Closer examination of the findings, taking into account the effects of the individual stressors on brain creatine content and the results of supplementation on total brain creatine levels, suggests that there may be more positive outcomes of supplementation than the research so far provides. More research is needed but research which takes into account pre- and post-supplementation brain creatine content. Furthermore, it is necessary to determine the most appropriate dosage and duration of treatment. Factors such as motivation, perception of effort costs and perception of resources avilable would also provide interesting information with regard to, not only, the outcomes but also the mechanisms involved. As people live for longer, and veganism and vegetarianism are being promoted to reduce greenhouse gasses, there may be a greater need for creatine supplementation in the future. Similarly, the use of creatine for individuals with chronic obstructive pulmonary disease should be ascertained. Furthermore, creatine supplementation as a treatment for degenerative diseases such as Parkinson's, Alzheimer's and similar diseases have been posited (see [2], for a review). Finally, the interaction between the positive effects of creatine supplementation on muscle and cognition also requires study. No-one has examined this, yet modern theories of interoception [38,40] would suggest possible, if not probable, interactions.

CRediT authorship contribution statement

Terry McMorris: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Beverley J. Hale:** Methodology, Formal analysis, Data curation. **Beatrice S. Pine:** Data curation. **Thomas B. Williams:** Formal analysis.

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