DR SOICHI ANDO (Orcid ID : 0000-0003-0896-7008)

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The interactive effects of acute exercise and hypoxia on cognitive performance: a narrative review

Running head: Effects of exercise and hypoxia on cognition

Soichi Ando[1*], Takaaki Komiyama[2], Mizuki Sudo[3], Yasuki Higaki[4], Koji Ishida[5], Joseph T. Costello[6], & Keisho Katayama[5]

[1]Graduate School of Informatics and Engineering, The University of Electro-Communications, Tokyo, 182-8585, Japan
[2]Center for Education in Liberal Arts and Sciences, Osaka University, Osaka, Japan
[3]Meiji Yasuda Life Foundation of Health and Welfare, 192-0001, Tokyo, Japan
[4]Faculty of Sports Science, Fukuoka University, Fukuoka, 814-0180, Japan
[5]Research Center of Health, Physical Fitness and Sports, Nagoya University, 464-8601, Nagoya, Japan
[6]Extreme Environments Laboratory, Department of Sport and Exercise Science, University of Portsmouth, United Kingdom

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*All correspondence to Soichi Ando (soichi.ando@uec.ac.jp)

Graduate School of Informatics and Engineering, The University of Electro-Communications, 1-5-1 Chofugaoka, Chofu, Tokyo 182-8585, Japan; E-mail: soichi.ando@uec.ac.jp, Tel.: +81-42-443-5583

Abstract

Acute moderate intensity exercise has been shown to improve cognitive performance. In contrast, hypoxia is believed to impair cognitive performance. The detrimental effects of hypoxia on cognitive performance are primarily dependent on the severity and duration of exposure. In this review, we describe how acute exercise under hypoxia alters cognitive performance, and propose that the combined effects of acute exercise and hypoxia on cognitive performance are mainly determined by interaction among exercise intensity and duration, the severity of hypoxia, and duration of exposure to hypoxia. We discuss the physiological mechanism(s) of the interaction and suggest that alterations in neurotransmitter function, cerebral blood flow, and possibly cerebral metabolism are the primary candidates that determine cognitive performance when acute exercise is combined with hypoxia. Furthermore, acclimatization appears to counteract impaired cognitive performance during prolonged exposure to hypoxia although the precise physiological mechanism(s) responsible for this amelioration remain to be elucidated. This review has implications for sporting, occupational, and recreational activities at terrestrial high altitude where cognitive performance is essential. Further studies are required to understand physiological mechanisms that determine cognitive performance when acute exercise is performed in hypoxia.

Keywords: arterial oxygen saturation, neurotransmitter(s), cerebral blood flow, metabolism

1 Introduction

Cognitive function refers processes such as memory, attention, language, problem solving, and planning [1]. Executive function is a higher-order cognitive ability that controls purposeful and goal-directed behaviour [2] and includes sophisticated function specific to humans (e.g. decision making). Since many sports are performed in a dynamic environment, athletes are required to make decisions quickly and accurately under psychophysiological stress, including various extreme environmental conditions. Hence, considerable attention has been devoted to examining cognitive performance under physiological stressors (e.g. exercise) and various environmental challenges (e.g. exposure to hypoxia, heat, and cold).

Acute exercise has both beneficial and detrimental effects on cognitive performance, and there is a growing body of evidence to suggest that acute exercise at moderate intensity improves cognitive performance [3,4]. Among environmental challenges, hypoxia is defined as reduced partial pressure of oxygen [5]. Oxygen is critical for normal cellular function, as it is part of the electron transport chain for energy production in cells [6]. Hence, sufficient delivery and perfusion of oxygen to the brain tissue are critical for avoiding life-threatening conditions [7]. In acute hypoxia, cardiac output is increased to maintain systemic oxygen delivery [8] and cerebral blood flow (CBF) also increases to maintain oxygen delivery to the brain [9-11]. However, hypoxia may still have detrimental effects on the central nervous system and cause neurological deficits and structural damage to the brain tissue [12]. It is perhaps not surprising that cognitive performance is impaired under hypoxia at rest [12-14]. As moderate exercise and hypoxia have contrasting effects on cognitive performance, the question arises as to how cognitive performance is affected when acute exercise is combined in acute hypoxia.

The independent effects of acute exercise [3,4,15,16] and hypoxia [12-14,17-19] on cognitive performance have been reviewed extensively elsewhere. However, to our knowledge, this is the first review which has sought to examine the interactive effects of acute exercise and hypoxia on cognitive performance. In the current review, we describe how acute exercise under hypoxia may alter cognitive performance, and propose that the combined effects of acute exercise and hypoxia on cognitive performance are mainly determined by the interaction of exercise intensity and duration, the severity of hypoxia, and duration of exposure to hypoxia. In an attempt to understand this interaction, we also explore the potential physiological mechanism(s) which determine cognitive performance. This review has implications for sporting, occupational, and recreational activities at

high altitude where high cognitive demands are required (e.g. team sports, military operations, trekking, and mountaineering).

2 Combined effects of acute exercise and hypoxia

In the current review, studies were sourced from electronic databases and reference lists of relevant articles were screened. The majority of studies examined the effects of acute exercise on cognitive performance in acute hypoxia (~several hours) within a laboratory setting. Then, we briefly summarized evidence from high-altitude expeditions or prolonged exposure to simulated high altitude (~weeks or months) to gain insights into the combined effects of acute exercise and prolonged hypoxia. The effects of chronic hypoxia (e.g. immigrants to high altitude or high altitude natives) on cognitive performance are beyond the topic of the current review and we did not discuss this in the current review.

2.1 Laboratory setting

Ando and colleagues [20] were the first to examine the combined effects of acute exercise and hypoxia on cognitive performance. Subsequently, several others have also studies this area (see Table 1). Ando et al. [20] indicated that cognitive performance in the Go/No-Go (GNG) task improved during moderate exercise in moderate hypoxia. In follow-up studies, Komiyama et al. [21] reported cognitive improvement in the GNG and spatial delayed response tasks during moderate exercise in moderate hypoxia and severe hypoxia [22]. Seo and colleagues [23-25]. examined the combined effects of moderate exercise and in severe hypoxia in both male [23,24] and female [23,25] participants. The same group reported cognitive improvement in memory [23-25] and mathematical performance [23], but not in the GNG task [24]. Lei et al. [26] showed cognitive improvement in GNG task during moderate exercise under severe hypoxia in females. de Aquino-Lemos et al. [27] reported an improvement in cognitive performance in the GNG task after moderate exercise following prolonged exposure to hypoxia for 28 hours, which suggests that acute exercise has the potential to improve cognitive performance during prolonged exposure to hypoxia.

In contrast, several studies demonstrated that cognitive performance was impaired during, or after, exercise in acute hypoxia [28-31]. Dobashi et al. [29] reported impaired color-word Stroop task (CWST) performance after four bouts of moderate exercise in moderate hypoxia. Ochi et al. [31] indicated that CWST performance was impaired after moderate exercise in moderate hypoxia. Lefferts et al.

[30] reported impaired performance in the memory recognition and flanker task, but not in the N-tack task, during exercise in severe hypoxia. Bouak et al. [28] examined delayed matching-to-sample test, N-back and Stroop tasks after exercise under hypoxia at four different levels, and cognitive impairment was observed in all tasks under the most severe hypoxic environment. Furthermore, Shannon et al. [32] reported that attention switching and rapid visual information processing tasks performance was impaired during or after exercise under severe, compared with moderate, hypoxia. In contrast, spatial span task performance was not impaired in the present study. The results of Bouak et al. [28] and Shannon et al. [32] suggest that the severity of hypoxia is one of the factors that affect the combined effects of acute exercise and hypoxia on cognitive performance.

Kim et al. [33] reported that trail making test (TMT) performance was not affected after moderate exercise during prolonged exposure to severe hypoxia. Kammerer et al. [34] also reported TMT, target reaction test, and sorting reaction test remained unaffected following alternate cycling and walking in moderate hypoxia. However, the number of participants in these studies were small (7 and 8 participants) and the absence of statistical significance could be, at least in part, ascribed to low statistical power. Sun et al. [35] examined the effects of high-intensity interval exercise on cognitive performance under moderate hypoxia. They indicated that high-intensity interval exercise impaired accuracy of the GNG task, but moderate hypoxia had no effects on cognitive performance.

Among these laboratory studies, most studies used cognitive tasks to assess executive function (see details in Table 1). Further studies are required to understand which kinds of cognitive performance are more susceptible to acute exercise and hypoxia (see *"3.4 Type of cognitive task"*). In addition, the participants were primarily young or middle-aged males. Therefore, the impact of age and sex on cognitive performance when acute exercise is combined with hypoxia is unclear. Nevertheless, the role of sex differences may not be important as Seo and colleagues [24,25] have previously reported similar results in both male and female participants. Collectively, the present findings regarding the effects of exercise under hypoxia on cognitive performance are inconsistent. Methodological differences and experimental designs are most likely responsible for these inconsistent findings. It is plausible that the heterogeneous findings are derived from differences in physiological alterations in response to acute exercise and hypoxia. We discuss the cause of heterogeneity later in this article.

Insert Table 1 about here

2.2 High altitude expeditions or prolonged exposure to hypoxia

Evidence from studies during high-altitude expeditions or prolonged exposure to simulated high altitude are useful in attempting to understand the combined effects of acute exercise and hypoxia on cognitive performance. Several studies have reported that cognitive performance is impaired at simulated high-altitude [36-38] or during expedition (5-21 days) to altitudes (3,700-6,542 m) [39-41]. In contrast, other studies suggest that prolonged exposure to hypoxia has no, or only temporary, effects on cognitive performance [42-45]. Davranche et al. [42] examined changes in the Simon task when participants were transported to a high altitude via helicopter. Cognitive impairment was observed in the early hours of exposure (day 0), but after two days no impairment in response speed was detected (days 2 & 4), although the error rate remained high [42]. Hu et al. [43] reported that digit symbol substitution test performance was impaired during the first three days at high altitude (4,400m). However, cognitive performance was restored after one and three months [43]. Pagani et al. [44] suggested that acclimatization leads to improved cognitive performance at altitude of 5,350 m. Pun et al. [45] indicated that impaired cognitive performance was restored after acclimatization. Collectively, these findings suggest that prolonged hypoxia (a few days to weeks), in most cases, impairs cognitive performance. We suggest that some adaptive processes (i.e. acclimatization) potentially counteract impaired cognitive performance during prolonged exposure to hypoxia for weeks and perhaps a few months. Interestingly, Møller et al. reported that simple reaction time at rest and during exercise was unaltered before and after high altitude acclimatization at 5,260 m [46]. In general, there is a brevity of studies examining the effects of exercise on cognitive performance during prolonged exposure. Additional studies are required to explore how acute exercise alters cognitive performance following high altitude acclimatization.

3 Acute exercise, Severity and Duration of Hypoxia

Several reviews have extensively described the effects of acute exercise on cognitive performance [3,4,15,16,47]. Narrative [12,14,18,19] and systematic [13] reviews have also concluded that hypoxia has detrimental effects on cognitive performance. In this section, we summarize factors that potentially affect cognitive performance when acute exercise is performed in hypoxia. We also

discuss plausible physiological mechanisms that alter cognitive performance based on the available literature.

3.1 Acute exercise: intensity, duration, and physiological mechanism(s)

It has been suggested that the effects of acute exercise on cognitive performance are primarily dependent on exercise intensity and duration. [3,4,15,16,47]. In general, moderate intensity is defined at between 40/50% and 79% maximal oxygen uptake [48]. Acute moderate intensity exercise has been shown to improve cognitive performance [3,4,47]. A meta-analytic review indicated that, although effect sizes are small, exercise at low intensity may have the potential to lead to beneficial effects on cognitive performance [3]. In contrast, the effects of high-intensity and exhaustive exercise (>80% maximal oxygen uptake) on cognitive performance are inconsistent [49-56], and impaired cognitive performance was observed during high intensity and exhaustive exercise [53,54]. A meta-analysis also suggested that moderate exercise for a duration of greater than 20 min appears to improves cognitive performance [3]. However, this is not always the case [20,57]. Further, given that the beneficial effects disappear as the duration of exercise is prolonged (>2h) [58], the optimal exercise duration may exist for cognitive improvement during/after exercise, probably dependent on experimental conditions.

Many studies have attempted to explore the physiological mechanism(s) underlying cognitive improvement during/after acute exercise. For example, arousal level has been suggested to be associated with cognitive performance [3,4,47,59]. Previous studies using electroencephalogram suggest increases in arousal level following aerobic exercise at moderate intensity [60,61]. Although it has been widely accepted that moderate exercise increases arousal to an optimal level and thus improves cognitive performance [3,4], neural substrates of increased arousal level have not been elucidated. The prefrontal cortex subserves the highest-order cognitive abilities [62] and neural network of cognitive control involves the lateral prefrontal cortex [1]. Previous studies have indicated that acute exercise enhanced activations in the left dorsolateral prefrontal cortex (DLPFC) using functional near infrared spectroscopy (fNIRS) [57,63]. Notably, Byun et al. [57] indicated that enhanced activations in the left DLPFC and left frontopolar area corresponded with both cognitive improvements and increased arousal levels. This study empirically demonstrates that cognitive improvements are mediated by the exercise-induced arousal system, and that the prefrontal activations are closely associated with the increased arousal. Nevertheless, it remains unclear how acute exercise activates the prefrontal cortex and other brain regions associated with

cognitive improvement. The dopaminergic system, originating from the ventral tegmental area, has projection to the prefrontal cortex [64,65]. The noradrenergic system, originating from the locus coeruleus, also has extensive projections to the prefrontal cortex [64,66]. Dopamine and noradrenaline mediate the strength of the prefrontal cortex network connections, and precise regulation of both dopamine and noradrenaline is required for appropriate prefrontal cognitive performance [67]. Given that exercise alters brain circuits involving a number of neurotransmitters including dopamine and noradrenaline [4], it is plausible that the dopaminergic and noradrenergic systems play a key role in activation in the prefrontal cortex and cognitive improvements induced by acute exercise.

One may argue that increased CBF contributes to cognitive improvement induced by acute exercise. However, several studies indicated that increases in middle cerebral artery (MCA) blood flow mean velocity, measured by transcranial Doppler, is not related to changes in cognitive performance [22,68-70]. Although changes in MCA diameter under hypocapnic and hypercapnic conditions [71,72] might skew these results, it is likely that alterations in CBF are not directly associated with such improvements [15]. Nevertheless, given that CBF contributes to the increase in cerebral oxygen delivery during exercise, the absence of an association does not mean that increased CBF is not somewhat responsible for cognitive improvements.

At rest, blood glucose is the primary source of energy for the brain. Nevertheless, cognitive performance improves during exercise even after skipping breakfast [73], which suggests that other energy substrates compensate for the reduced availability of blood glucose. The brain utilizes lactate as an energy source [74]. Hence, increases in blood lactate appear to provide energy that contributes to improvements in cognitive performance. Recent studies suggest that increases in blood lactate provide energy that contributes to cognitive improvement after high intensity exercise [75,76]. These findings imply that enhanced lactate metabolism also contributes to cognitive improvement induced by acute exercise, particularly at high intensity exercise.

Collectively, there is consensus that acute exercise at moderate intensity potentially improves cognitive performance. The catecholamine hypothesis [4] is intriguing and promising, but the specific mechanism(s) by which it impacts cognitive performance remains ambiguous. Especially, understanding of the relationship between the central neurochemical changes, mainly described in rodents, and behavioural changes in humans is an open question [77]. Exercise indices a plethora of physiological changes in the brain and the beneficial effects of acute exercise on cognitive performance are multifaceted and probably determined by the integration of several of these physiological changes.

3.2 Severity of hypoxia

Narrative reviews consistently suggest that cognitive performance is impaired as the severity of hypoxia increases [12,14,18,19]. A recent systematic review using meta-regression analysis demonstrated that low (35–60 mmHg) arterial partial pressure of oxygen (PaO_2) is the key predictor of cognitive impairment [13]. The PaO_2 level (<60 mmHg) is below the threshold where the carotid body starts to respond to the lowering of PaO_2 [6]. Hence, McMorris and colleagues [13] suggested that impaired cognitive performance may occur below the threshold at which organism perceives the necessity for action to attempt to maintain homeostasis. Ochi et al. [78] indicated that peripheral oxygen saturation (SpO_2) was associated with cognitive performance in hypoxia. These findings indicate that the severity of hypoxia is associated with impairment in cognitive performance. As the severity of hypoxia increases, PaO_2 and arterial saturation of O_2 (SaO_2) decreases [79]. Arterial desaturation and the resultant biological processes are probably responsible for impairments in cognitive performance, although the physiological mechanism(s) underpinning this are not well understood.

CBF increases in response to hypoxia to maintain cerebral oxygen delivery [9-11]. Nevertheless, extra-mitochondrial cellular processes are sensitive to hypoxia even when cerebral oxygen delivery is sufficient to maintain overall metabolism and energetics [80]. In particular, the synthesis of enzymes and related neurotransmitters is sensitive to oxygen [81,82] and neurotransmitter dysfunction may occur even during subtle hypoxic challenge [80]. Indeed, neurotransmitters such as dopamine and noradrenaline are believed to be associated with cognitive performance [4,67]. It is likely that neurotransmitter dysfunction is exacerbated as the severity of hypoxia increases, which may lead to cognitive impairment under more severe hypoxic conditions. Recently, Williams et al. [83] have reported that although cognitive performance at rest in hypoxia was associated with reduction in both SpO_2 and cerebral oxygenation, plasma adrenaline, noradrenaline, cortisol or copeptin was not. However, in general, empirical evidence is largely absent in the hypoxia and cognition literature.

Although cerebral oxygen delivery to the brain is maintained under hypoxia [9-11], CBF is unevenly distributed in response to severe hypoxia [84,85]. Binks et al. [84] indicated that greater blood flow is directed to phylogenetically older parts of the brain, possibly to maintain essential homeostatic functions even at the cost of impaired cognitive performance. Lawley et al. [85] demonstrated that CBF is reduced in the brain areas associated with cognitive performance during acute and

prolonged exposure to severe hypoxia. These findings suggest that reduced regional CBF and oxygen delivery may not be sufficient to meet regional metabolic demands in the brain areas involved in cognitive performance under severe hypoxia. Hence, the heterogeneous distribution of CBF may be responsible for impaired cognitive performance during severe hypoxia. Furthermore, reduced regional CBF during prolonged exposure to hypoxia may reflect reduced regional cerebral metabolism [85]. Regional cerebral metabolism may also be reduced, and may be responsible, at least in part, for impaired cognitive performance under severe hypoxia. Turner and colleagues demonstrated that creatine supplementation for 7-days prevented impairments in cognitive performance under severe hypoxia [86], and suggested that the creatine supplementation increased energy availability and maintained appropriate neural membrane potential when cellular energy provision was compromised. This study lends additional support to the notion that impaired cerebral metabolism is associated with cognitive impairments during severe hypoxia. Recently, Ogoh et al. [87] reported that cognitive performance remained unaffected by impaired dynamic cerebral autoregulation during cognitive activity in both normoxic and hypoxic conditions. This suggests that impaired dynamic cerebral autoregulation is not responsible for cognitive impairment in acute hypoxia.

3.3 Duration of exposure to hypoxia

In the "*Severity of hypoxia*" section, we identified neurotransmitter dysfunction, heterogeneous CBF distribution, and possibly impaired regional cerebral metabolism as the primary candidates for impaired cognitive performance. Despite the need for experimental evidence, it is plausible that prolonged hypoxia exacerbates these physiological changes. For example, a reduction in CBF in the brain areas associated with cognitive performance was found to be more pronounced after prolonged (10 h) compared to acute (2 h) hypoxic exposure [85], which implies that prolonged hypoxia may reduce regional cerebral metabolism in the brain areas related to cognitive performance.

There are other candidates that potentially impair cognitive performance during prolonged exposure to hypoxia. First, free radical formation increases under hypoxia [88,89]. It has recently been suggested that systemic oxidative-inflammatory-nitrosative stress in high-altitude residents is associated with accelerated cognitive decline [90]. Furthermore, peripheral blood hypersensitive C-reaction protein, which is a biomarker of inflammation, is correlated with cognitive impairments during high-altitude expeditions [43]. Thus, oxidative stress and inflammation seem to impair

cognitive performance during prolonged exposure to hypoxia, and it is plausible that oxidative stress and inflammation are mutually interactive and would alter cognitive performance in a synergistic manner.

Acute mountain sickness (AMS) is a syndrome of non-specific symptoms including headache, nausea, malaise, dizziness, and difficulty of sleep [91,92]. Kramer et al. [93] reported there was no association between AMS severity and cognitive performance, and AMS should be distinguished from concurrent neuropsychological or behavioural alterations [14]. In contrast, AMS symptoms are reported to be associated with cognitive performance [94,95]. As summarized by Yan [19], effects of AMS on cognitive performance are controversial. Nevertheless, given that AMS symptom develops from several hours to 5 days following hypoxic exposure [92], AMS may contribute to cognitive impairment during prolonged exposure without acclimatization. Furthermore, exposure to hypoxia (hours to days) can lead to cerebral edema [96,97]. Cerebral edema is the excess accumulation of fluid in the intracellular or extracellular regions of the brain, which is also known as brain swelling. Cerebral venous congestion occurs after exposure to hypoxia for 3 hours [98], and cerebral edema is exacerbated following prolonged exposure [97,99]. The association between cerebral edema and AMS remain uncertain and controversial [12,97,99,100], and there is no direct evidence showing that cerebral edema is associated with cognitive impairment. Nevertheless, we cannot rule out the possibility that cerebral edema and an increase in intracranial pressure may somehow, directly or indirectly (e.g. via AMS), influence the brain regions involved in cognitive performance during hypoxia.

3.4 Type of cognitive task

Type of cognitive task is one of the factors that affect cognitive performance during/after exercise [3,16]. In a meta-analysis review, Chang et al. [3] reported that executive function was improved during/after acute exercise in normoxia. A recent review also highlighted the beneficial effects of acute exercise on executive function [77]. There are numerous studies that examined cognitive performance in response to hypoxia. Despite the fact that some narrative reviews[14,18] suggest that central executive tasks (e.g. executive function) tend to be more negatively impacted by hypoxia compared with non-executive task (e.g. perception, attention, and short-term memory tasks), a meta-regression analysis by McMorris et al. [13] suggested that the effects of hypoxia on cognitive performance are not different between executive and non-executive tasks. As noted by Petrassi et al. [17], cognitive and psychomotor deficits from moderate hypoxia are difficult to quantify, often

not reproducible, and sometimes conflicting. Interestingly, rodent studies indicated that the hippocampus is more sensitive to hypoxia-mediated oxidative stress and subsequent hypoxia-ischaemic injury than the cortex [101,102]. Prolonged exposure to hypoxia reduces cerebral perfusion in the posterior cingulate and cuneal cortex that are assumed to play a role in declarative and procedural memory [85]. Hence, it is plausible that the vulnerability of the hippocampus to hypoxia and/or reduced regional cerebral perfusion leads to the vulnerability of hippocampus dependent memory (e.g., short-term memory) to hypoxia. However, it is still unclear whether combined effects of acute exercise and hypoxia are dependent on type of cognitive task studies. Further empirical evidence is warranted to clarify which cognitive domains are most susceptible to exercise in hypoxia.

Finally, we briefly describe other factors that affect exercise-cognition interaction. Previous reviews have suggested that the effects of acute exercise on cognitive performance are affected by timing of cognitive task (i.e. during or after exercise), type of exercise, and physical fitness level of participants [3,16]. For example, although many studies indicated cognitive improvement during exercise, a meta-analysis reported negative effects on cognitive performance during exercise [16]. In contrast, positive effects were observed following exercise [16]. Treadmill running appears to be susceptible to cognitive impairment compared to cycling [16]. Individuals with lower aerobic capacities also appear most susceptible to cognitive impairments, assessed via coefficient of variability, as compared with individuals with higher aerobic capacities [53]. However, it remains to be elucidated if these factors affect cognitive performance when acute exercise is performed in hypoxia.

4 Discussion

The effects of acute exercise on cognitive performance appear to be dependent on the intensity and duration of exercise, and moderate exercise has beneficial effects. In contrast, the detrimental effects of hypoxia on cognitive performance are dependent on the severity and duration of exposure. Hence, we can assume that the combined effects of acute exercise and hypoxia are mainly determined by interaction between the beneficial and detrimental effects. Although current findings regarding the combined effects of acute exercise and acute/prolonged exposure to hypoxia on cognitive performance are limited and inconsistent, we illustrate, based on the available literature, how cognitive performance is altered when acute exercise is undertaken in a hypoxic environment (Figure 1). The figure reflects the current knowledge regarding the

combined effects of acute exercise and hypoxia. Cognitive performance is progressively impaired as exposure duration to hypoxia is prolonged for at least the first few days. The severity of hypoxia determines the degree of cognitive impairment. The vertical arrows indicate that cognitive performance is altered within the range when acute exercise is performed in hypoxia. For example, in the case of moderate exercise and/or brief exposure to hypoxia, the beneficial effects of acute exercise outweigh the detrimental effects of hypoxia. Indeed, when duration of exposure to hypoxia is relatively short (~105min), cognitive improvements are frequently observed during exercise [20-22,24-26]. In contrast, in the case of severe and/or prolonged exposure to hypoxia, the beneficial effects of acute exercise appear to be negated by the detrimental effects of hypoxia, or are unable to override the detrimental effects. The effects of acute exercise on cognitive performance depend on exercise intensity and duration, while the severity and duration of exposure to hypoxia are crucial for the detrimental effects on cognitive performance. Hence, we propose that the combined effects of acute exercise and hypoxia on cognitive performance are mainly determined by interaction among exercise intensity and duration, the severity of hypoxia, and duration of exposure to hypoxia. Whether the interaction is additive or interactive warrants further investigation. The extent of cognitive impairment in response to hypoxia may be (cognitive) task-specific: hippocampus dependent memory (e.g., short-term memory) could be more susceptible. The combined effects of acute exercise and hypoxia on cognitive performance may also be affected by timing of the cognitive assessment, type of exercise, and training status of an individual. This is applicable during acute and prolonged exposure to hypoxia before acclimatization.

Insert Figure 1 about here

Exercise in hypoxia leads to cerebral perturbations [103]. A meta-analysis study [13] indicated that arterial desaturation is the key predictor of cognitive impairment under hypoxia at rest. Given that acute exercise under hypoxia induces progressive brain desaturation [104-107], cognitive improvements may be attenuated as brain desaturation proceeds during exercise under hypoxia. Indeed, cognitive improvements during exercise under hypoxia were attenuated in individuals exhibiting a greater decrease in SpO_2 [22]. Thus, the notion that decreased arterial desaturation is responsible for cognitive impairment appears to be extended to exercising under hypoxia. Both Bouak et al. [28] and Shannon et al. [32] have previously indicated that cognitive performance was

impaired during/after exercise under severe hypoxia, but not moderate hypoxia [28,32]. These findings suggest that the severity of hypoxia is a critical factor in determining cognitive performance when acute exercise is performed in hypoxia.

The synthesis of several neurotransmitters/modulators is regulated by O_2 requiring rate-limiting enzymes [81]. Perturbations in O_2 homeostasis under hypoxia may affect neural activation by altering neurotransmitter synthesis [81], which may impair cognitive performance [13]. Accordingly, neurotransmitter dysfunction is likely to occur even when cerebral oxygen delivery is maintained under hypoxia [80]. In contrast, moderate exercise is thought to have beneficial effects on brain circuits involving a number of neurotransmitters [4]. Indeed, rodent studies have shown that acute exercise increases neurotransmitters [108]. Therefore, when acute exercise is combined with hypoxia, neurotransmitter function is likely to be determined by the interaction between the detrimental effects of hypoxia and the beneficial effects of exercise, which would affect neural activation associated with cognitive performance.

A previous study indicated that alteration in CBF, assessed by MCA blood flow velocity, was not directly associated with alteration in cognitive performance during exercise under hypoxia [22,23]. However, CBF is heterogeneously distributed in the brain under severe hypoxia [84,85]. In contrast, during exercise, increases in cerebral metabolism increase CBF to maintain oxygen delivery for aerobic metabolism [109]. Acute exercise activates brain regions including motor and sensory cortices, insular cortex, and cerebellum [110,111], which suggests that neural activation in response to acute exercise is not uniform across the brain. Therefore, acute exercise under hypoxia is likely to further accentuate the heterogeneous distribution of CBF, particularly during prolonged exposure to severe hypoxia. Hence, although global CBF increases to maintain oxygen delivery during exercise under severe hypoxia [112], regional CBF and oxygen delivery may be compromised in the brain regions involved in cognitive performance. The heterogeneous distribution of CBF and possibly impaired regional cerebral metabolism may compromise cognitive performance when acute exercise and hypoxia are combined.

Acute exercise further promotes free radical formation under hypoxia [89,113]. Acute exercise also seems to exacerbate AMS [40,91,114] and cerebral edema [97,100] under hypoxia. Prolonged hypoxia causes increase in oxidative stress [115] as well as progress of AMS [92] and cerebral edema [97,99]. Hence, although acute exercise *per se* has a beneficial effect on cognitive performance, increases in oxidative stress, inflammation, AMS and cerebral edema, may augment the detrimental effects on cognitive performance during prolonged exposure to hypoxia.

Figure 2 illustrates how combined effects of acute exercise and hypoxia are determined. When acute exercise and hypoxia are combined, neurotransmitter function, CBF, and cerebral metabolism are altered. The interaction is the primary candidates that affect neural activation involved in cognitive performance. Regardless of the mechanistic pathways by which acute exercise and hypoxia interact, neural activation involved in cognitive performance appears to be exacerbated as the duration of exposure is prolonged. As noted, current findings concerning the combined effects of acute exercise and hypoxia are inconsistent. Given that physiological alterations in response to acute exercise and hypoxia are dependent on experimental study designs, differences in physiological alterations may account for these heterogeneous findings.

Insert Figure 2 about here

Despite our proposal that the combined effects of acute exercise and hypoxia are determined by the interaction, neural correlates responsible for cognitive improvement or impairment remain to be elucidated. A neuroimaging study revealed that cognitive impairment after exercise under hypoxia was associated with reduction in task-related activation in the left DLPFC using fNIRS [31]. This suggests that the DLPFC is responsible for cognitive impairment after exercise in hypoxia, and that activation in the DLPFC plays a crucial role in cognitive performance when acute exercise and hypoxia are combined. Nevertheless, this is the only study that examined neural correlates and additional empirical evidence is required to support these initial findings. Furthermore, fNIRS measurements are limited to only the superficial layers of the cerebral cortex. Investigations into the combined effects of exercise and prolonged exposure to hypoxia on cognitive performance using sophisticated neuroimaging methods (e.g. functional MRI, positron emission tomography) are necessary to fully elucidate the physiological interaction(s).

Based on data demonstrating that acclimatization probably counteracts the detrimental effects on cognitive performance during high-altitude expeditions [42-45], some adaptive processes appear to attenuate or diminish these detrimental effects. However, the physiological mechanisms underlying the adaptation are unclear. During prolonged exposure to hypoxia, the increase in CBF peaks after 1-2 days followed by a slow and progressive decline towards sea level baseline [116,117]. Møller et al. [46] reported that CBF and cerebral metabolism were unaltered after high-altitude acclimatization for 5 weeks. Maintaining CBF and cerebral metabolism may serve to attenuate or diminish cognitive impairment after prolonged exposure to hypoxia or acclimatization during

high-altitude expeditions. Pun et al. [45] suggested that changes in SpO_2 during acclimatization may affect cognitive performance, which is in line with the previous study showing that short term pre-acclimatization to hypoxia was beneficial to cognitive performance [118]. Future studies are needed to understand the neurophysiological adaptations following prolonged exposure to hypoxia. Given that exercise at high altitude still induces profound arterial hypoxemia after acclimatization [91,119], it is imperative to accumulate empirical evidence investigating how acute exercise alters cognitive performance under hypoxia after acclimatization.

5. Perspectives

This review suggests that the combined effects of acute exercise and hypoxia on cognitive performance are mainly determined by interaction among exercise intensity and duration, the severity of hypoxia, and duration of exposure to hypoxia. It is of practical importance that adaptive processes appear to counteract impaired cognitive performance during prolonged exposure to hypoxia. Given that frequent high altitude climbing induces ventilatory and muscular adaptation in response to hypoxia [120], it is worth investigating whether some adaptation affects cognitive performance in response to hypoxia following repeated or prolonged exposure. This review also highlights the neurotransmitter function, cerebral blood flow, and cerebral metabolism as primary candidates responsible for cognitive performance. Further studies are warranted to investigate the physiological mechanism(s) that determine cognitive performance during exercise in hypoxic environments.

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Figure Captions

Figure 1: Illustration of the combined effects of acute exercise and hypoxia on cognitive performance and factors that affect the combined effects. Solid horizontal line represents the baseline (rest under normoxia). Dashed line represents cognitive performance without exercise. The vertical arrows indicate that cognitive performance is altered within the range when acute exercise is performed in hypoxia. Note that this is applicable during acute and prolonged exposure to hypoxia before acclimatization.

Figure 2: Illustration of how the combined effects of acute exercise and hypoxia determine cognitive performance. White broad arrow leads to cognitive improvement. Black broad arrows lead to cognitive impairment. See details in the text.

Table 1. Studies investigating the combined effects of acute exercise and hypoxia on cognitive performance in the laboratory settings.

Authors	Participants	Cognitive task(s)	Environmental conditions	Hypoxia (FIO_2)	Exposure duration	Exercise mode, intensity and duration	Timing of cognitive task	Main findings
Ando et al. 2013 (20)	N = 12 healthy males age 23±2	GNG task*	Normoxia (rest & exercise) vs. hypoxia (rest & exercise), counterbalanced	0.180 or 0.150	30 min	Cycling 60% $\dot{V}O_{2peak}$ 10 min	Rest & during exercise	During exercise RT↑
Komiyama et al. 2015 (21)	N = 16 healthy males age 23±2	GNG task* SDR task*	Normoxia (rest & exercise) vs. hypoxia (rest & exercise), counterbalanced	0.150	50 min	Cycling Constant HR at 140 bpm. 30 min	Rest & during exercise	During exercise GNG task: RT↑ SDR task ≈
Kim et al. 2015 (33)	N = 8 healthy males age 41±2	TMT*	Hypoxia (rest) vs. hypoxia (rest & exercise), counterbalanced	0.125	300 min	Cycling 50% altitude adjusted $\dot{V}O_{2max}$ 1 hour	Rest & immediately, 1h, and 2h after exercise	After exercise TMT≈

Seo et al. 2015 (24)	N = 16 healthy males age 24±4	GNG task* RMCPT*	Normoxia (rest) followed by hypoxia (rest & exercise), single session	0.125	105 min	Cycling 40% or 60% altitude adjusted VO_{2max} 15 min × 2	Rest & during exercise	During exercise GNG task≈ RMCPT: RT↑ score↑
Lefferts et al. 2016 (30)	N = 30 healthy males & females age 22±4	Memory recognition# Flanker task* N-back task*	Normoxia (rest & exercise) vs. hypoxia (rest & exercise), counterbalanced	0.125	145 min	Cycling 55% age-predicted HRmax 25 min	Rest & during exercise	During exercise Memory recognition: RT↓ Flanker task: RT↓ N-back task≈
Dobashi et al. 2016 (29)	N = 9 healthy males age 24±2	CWST*	Normoxia (rest & exercise) vs. hypoxia (rest & exercise), counterbalanced	0.141	240 min	Cycling 50% VO_{2peak} 30 min × 4	Rest & immediately after exercise and post 1h	Post 1h number of correct response↓
de Aquino-Lemos et al.	N = 40 (38 completed) healthy males	Simple reaction time (GNG task*)	Normoxia (N) group, Exercise under N group, Hypoxia (H) group, Exercise under H	0.135	28 hours + 10min	Running 50% VO_{2max} 60 min × 2 (3 & 27 hours	Immediately after exercise (28 hours after	After exercise RT↑

2016 (27)	age 20-30		group, randomized			after the exposure)	the exposure)	
Seo et al. 2017 (25)	N = 16 healthy females age 24±4	RMCPT*	Normoxia (rest) followed by hypoxia (rest & exercise), single session	0.125	105 min	Cycling 40% or 60% altitude adjusted VO_{2max} 15 min × 2	Rest & during exercise	During exercise score↑
Shannon et al. 2017 (32)	N = 10 healthy males age 23±3	AST* RVP# SST*	Moderate hypoxia (rest & exercise) vs. severe hypoxia (rest & exercise), nitrate supplementation & placebo, counterbalanced	0.140 or 0.117	150 min	Walking 30% VO_{2max} 45 min Simulated altitude hiking 3 km time-trial 10% gradient, 10 kg backpack	Rest, during and 5 min after exercise	During exercise AST: number of correct response↓ response time↓ RVP: response time↓ severe vs. moderate hypoxia SST≈ After exercise AST: response time↓

								RVP: number of correct response↓ response time↓ number of false alarm↓ SST≈ severe vs. moderate hypoxia
Komiyama et al. 2017 (22)	N = 13 healthy males age 22±4	GNG task* SDR task*	Normoxia (rest & exercise) vs. hypoxia (rest & exercise), counterbalanced	0.120 or 0.130	30 min	Cycling 50% VO_{2peak} 15 min	Rest & during exercise	During exercise GNG task: RT↑ SDR task ≈
Stavres et al. 2017 (23)	N = 18 healthy males age (22±3) and females age (23±2)	MATH* RMCPT*	Normoxia (rest & exercise) vs. hypoxia (rest & exercise), counterbalanced	0.125	105 min	Cycling 60% VO_{2max} 20 min	Rest, during exercise & immediately, 15, 30, & 45 min after exercise.	During exercise & recovery MATH↑ Rest, during exercise, & recovery

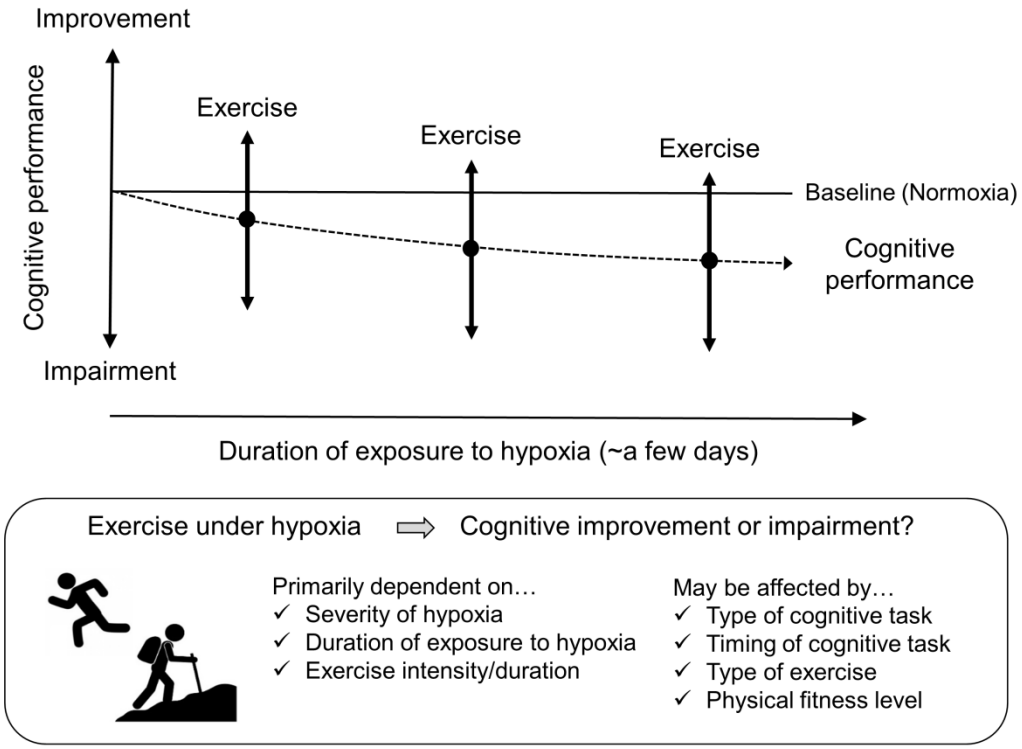
								RMCPT↑
Ochi et al. 2018 (31)	N = 14 (Exp1) healthy males & a female age 23±2 N = 15 (Exp2) healthy males & females age 21±2	CWST*	Exp1: Normoxia (rest & exercise) vs. hypoxia (rest & exercise), counterbalanced Exp2: Hypoxia (rest vs. rest & exercise), counterbalanced	0.135	48 min	Cycling 50% VO_{2peak} 10 min	Rest & 15 min after exercise	Exp1 & Exp2 After exercise Stroop interference↓ under hypoxia
Bouak et al. 2018 (28)	N = 16 healthy males (military helicopter pilots) age 33±11	dMTS test# N-back test* Stroop task*	Hypoxia at 4 different levels (exercise), counterbalanced	0.154, 0.143, 0.132, or 0.123	1 hour	Cycling 30W & 60W 7 min × 3 times	Immediately after exercise	dMTs↓ N-back test↓ Stroop task: accuracy↓ at lowest FIO_2 (0.123) vs. higher FIO_2 level(s)

Kammerer et al. 2018 (34)	N = 7 (additional experiment) healthy males & females age 36±4	TMT* tRT† sRT#	Hypoxia (rest vs. exercise), counterbalanced (vs. expedition to high altitude)	0.131	4 hours	Alternate cycling and walking mean HR: 133 ± 17 during exercise 2 hours 15% slope	Rest & immediately after exercise	After exercise TMT≈ tRT≈ sRT≈
Sun et al. 2019 (35)	N = 20 healthy males & females age 24±3	GNG task*	Normoxia (rest & exercise) vs. hypoxia (rest & exercise), counterbalanced	0.154	~40 min	10 repetition of 6 s High intensity cycling with 30 s recovery	Rest & immediately after exercise	After exercise under normoxia & hypoxia GNG task: accuracy↓
Lei et al. 2019 (26)	N =30 healthy females age 23±3	GNG task*	Normoxia (rest & exercise) vs. hypoxia (rest & exercise), counterbalanced	0.12	22 min	Cycling 45% PPO	Rest & during exercise	During exercise GNG task: RT↑

N: number of participants; GNG task: Go/No-Go task; SDR task: spatial delayed response task;

TMT: trail making test; RMCPT: running memory continuous performance task; CWST: color-word Stroop task; AST: attention switching task; RVP: rapid visual information processing task; SST: spatial span task; MATH: mathematical performance; dMTS: delayed matching-to-sample test;

tRT: target reaction test; sRT: sorting reaction test; VO2: oxygen uptake; HR: heart rate. PPO: peak power output. RT: reaction time. ↑improvement in cognitive performance, ↓impairment in cognitive performance, ≈no effect. *executive function task, #memory task. †simple reaction task



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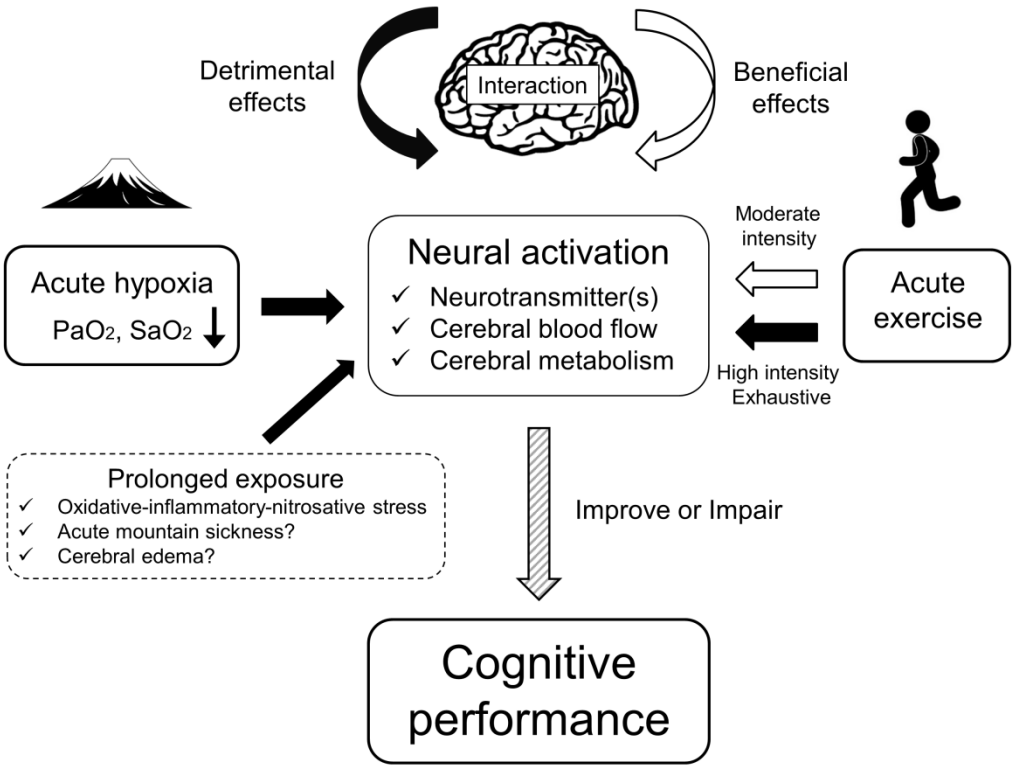

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