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Introduction: Altitude exposes humans to stressors including hypobaric hypoxia, cold, solar radiation and prolonged cognitive effort. This study aimed to explore the individual and combined effects of mental fatigue and hypoxia on physical and cognitive performance. **Method:** Following ethical approval from Loughborough University, 15 healthy males (mean ± SD; 24.2 ± 3.27 years) completed one familiarisation session and six experimental trials, including: 1) normoxia (0.209 FiO_2) and no mental fatigue; 2) normoxia (0.209 FiO_2) with mental fatigue; 3) low normobaric hypoxia (0.13 FiO_2) and no mental fatigue; 4) low normobaric hypoxia (0.13 FiO_2) with mental fatigue; 5) high normobaric hypoxia (0.10 FiO_2) and no mental fatigue; 6) high normobaric hypoxia (0.10 FiO_2) with mental fatigue. All conditions were completed at 21°C with 50% relative humidity. Mental fatigue was induced using a 16-min individualised cognitive test. Each condition included a 15-min self-paced time trial on an arm bike, followed by a 60-s isometric maximal voluntary contraction (MVC) of the biceps brachii. Supramaximal nerve stimulation was used to quantify central and peripheral fatigue with voluntary activation (VA%) calculated using the twitch interpolation method. Following each time trial, participants performed the Tower of Hanoi (TOH) cognitive test. Subjective measures of mental fatigue (VASF) and mood (BRUMS) were assessed. **Results:** A main effect of hypoxia was observed on average power output, oxygen consumption and muscle oxygenation ($P \leq 0.004$), with no effect of mental fatigue, ($P \geq 0.599$). VA% of the biceps brachii was reduced in hypoxia, (68.42 ± 5.64%, $P = 0.039$). Time to completion in the TOH was significantly increased in all conditions (+14.74 ± 6.99-s, $P \leq 0.041$) however no effect of mental fatigue or hypoxia was observed on cognitive performance, ($P \geq 0.138$). **Conclusions:** Hypoxia impacted physical performance whilst mental fatigue had no effect on physical or cognitive performance.